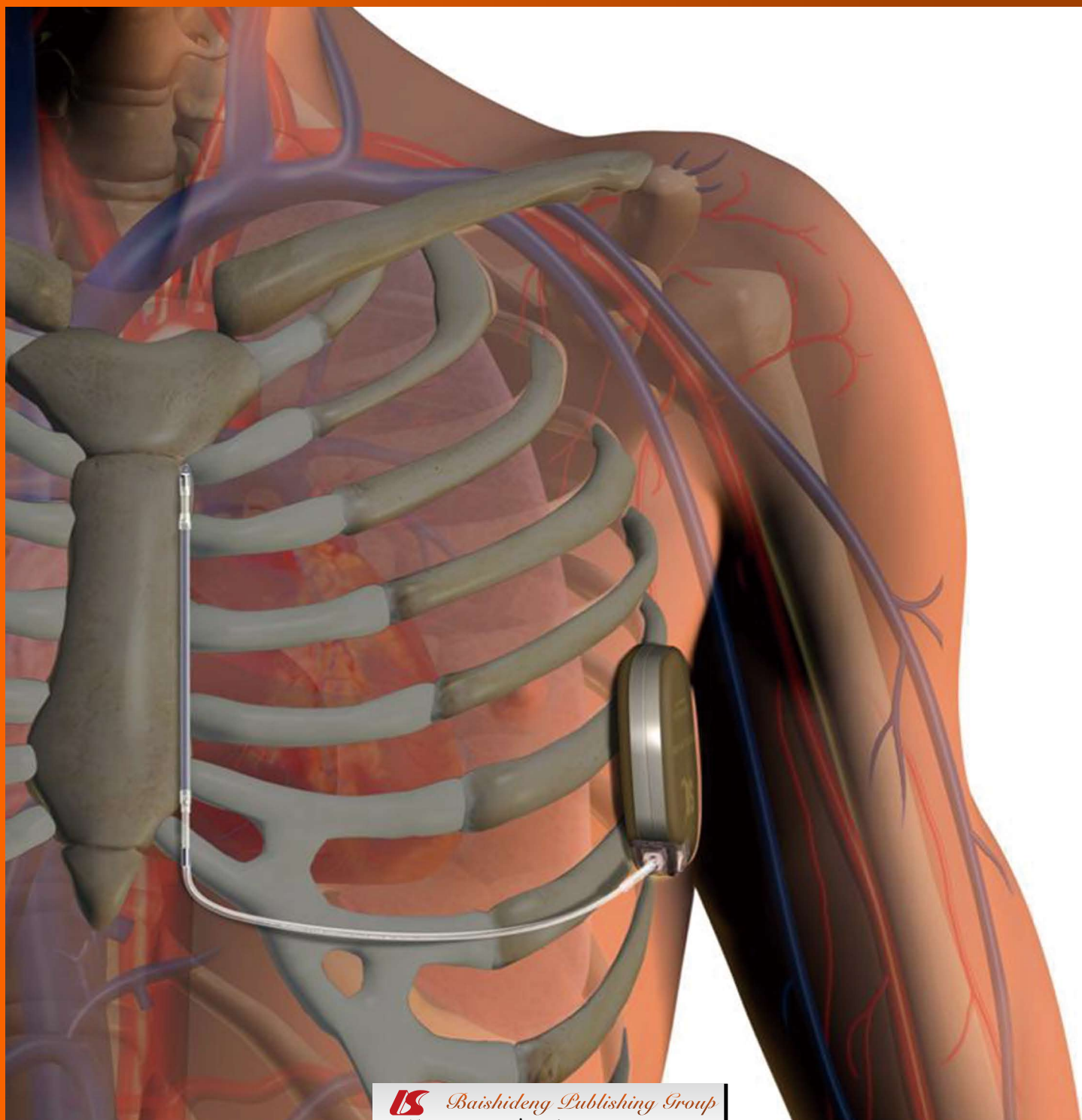


World Journal of *Cardiology*

World J Cardiol 2013 September 26; 5(9): 317-374





Editorial Board

2009-2013

The *World Journal of Cardiology* Editorial Board consists of 362 members, representing a team of worldwide experts in cardiology. They are from 43 countries, including Argentina (4), Australia (9), Belgium (2), Brazil (5), Canada (24), Chile (1), China (18), Colombia (1), Czech (1), Denmark (4), France (3), Germany (32), Greece (14), Hungary (2), India (8), Iran (2), Ireland (1), Israel (2), Italy (44), Japan (24), Kosovo (1), Lebanon (1), Malaysia (1), Mexico (1), Morocco (1), Netherlands (9), Nigeria (1), Oman (1), Pakistan (1), Poland (3), Portugal (1), Russia (1), Singapore (1), Slovenia (2), South Africa (2), South Korea (6), Spain (10), Switzerland (1), Thailand (1), Turkey (8), United Kingdom (14), United States (93), and Uruguay (1).

EDITORS-IN-CHIEF

Raúl Moreno, *Madrid*
Victor L Serebruany, *Baltimore*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF

Amitesh Aggarwal, *Delhi*
Imtiaz S Ali, *Halifax*
Giuseppe Biondi-Zoccai, *Turin*
AC Campos de Carvalho, *Rio de Janeiro*
Serafino Fazio, *Naples*
Steven Joseph Haas, *Melbourne*
Masoor Kamalesh, *Indianapolis*
Peter A McCullough, *Royal Oak*
Giuseppe Mulé, *Palermo*
Mamas A Mamas, *Manchester*
Shinro Matsuo, *Kanazawa*
Prashanth Panduranga, *Muscat*
Rui A Providência, *Coimbra*
Seung-Woon Rha, *Seoul*
Manel Sabaté, *Barcelona*
SAM Said, *Hengelo*

GUEST EDITORIAL BOARD MEMBERS

Shih-Tai Chang, *Chua-Yi Shien*
Mien-Cheng Chen, *Kaohsiung*
Ming-Jui Hung, *Keelung*
Pi-Chang Lee, *Taipei*
Hung-Jung Lin, *Tainan*
Shoa-Lin Lin, *Kaohsiung*
Chin-San Liu, *Changhua*
Wei-Chuan Tsai, *Tainan*
Chin-Hsiao Tseng, *Taipei*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Tomás F Cianciulli, *Buenos Aires*

José Milei, *Buenos Aires*
Alfredo E Rodriguez, *Buenos Aires*
Gaston A Rodriguez-Granillo, *Buenos Aires*



Australia

Yuri V Bobryshev, *Kensington*
Gavin Lambert, *Melbourne*
Peter J Little, *Melbourne*
Ralph Nigel Martins, *Nedlands*
Trevor A Mori, *Perth*
Jason N Peart, *Brisbane*
Joseph B Selvanayagam, *Adelaide*
Zhonghua Sun, *Perth*



Belgium

Bernhard L Gerber, *Woluwe St. Lambert*
Paul Vermeersch, *Antwerp*



Brazil

Luiz César Guarita-Souza, *Curitiba Pr*
CA Mandarim-de-Lacerda, *Rio de Janeiro*
Cristiane Pulz, *Code*
Jose E Tanus-Santos, *Ribeirao Preto*



Canada

Rodrigo Bagur, *Quebec*
Olivier F Bertrand, *Quebec*
MG Bourassa, *Quebec*
Mohamed Chahine, *Québec*
Michael CY Chan, *Edmonton*
Clara Chow, *Sydney*
Paul Farand, *Sherbrooke*
R Michael Giuffre, *Alberta*
Haissam Haddad, *Ontario*

Pavel Hamet, *Québec*
Francois Harel, *Montreal*
Ismail Laher, *Vancouver*
Frans HH Leenen, *Ontario*
Gordon Moe, *Ontario*
Kambiz Norozi, *London*
Louis P Perrault, *Quebec*
Philippe Pibarot, *Quebec*
Shirya Rashid, *Hamilton*
Robert Roberts, *Ottawa*
Grzegorz Sawicki, *Saskatoon*
Chantale Simard, *Québec*
Jack CJ Sun, *Hamilton*
Anthony S Tang, *Victoria*



Chile

Xavier F Figueroa, *Santiago*



China

Shao-Liang Chen, *Nanjing*
Lan Huang, *Chongqing*
En-Zhi Jia, *Nanjing*
Bin Jiang, *Beijing*
Man-Hong Jim, *Hong Kong*
Jian-Jun Li, *Beijing*
Tong Liu, *Tianjin*
Yong Xu, *Nanjing*
Xiao-Ming Zhang, *Hangzhou*



Colombia

Patricio Lopez-Jaramillo, *Santander*



Czech

Jan Sochman, *Prague*

**Denmark**

Morten Grunnet, *Ballerup*
 Won Yong Kim, *Aarhus*
 Ole Dyg Pedersen, *Copenhagen*
 Jacob Tfelt-Hansen, *Copenhagen*

**France**

Philippe Commeau, *Ollioules*
 Yves D Durandy, *Massy*
 Thierry Lefèvre, *Massy*

**Germany**

Ferruh Artunc, *Tübingen*
 Muhammet A Aydin, *Hamburg*
 Alexander Bauer, *Heidelberg*
 Peter Bernhardt, *Ulm*
 Torsten Bossert, *Jena*
 Marcus Dörr, *Greifswald*
 Holger Eggebrecht, *Essen*
 Tommaso Gori, *Mainz*
 Dariusch Haghi, *Mannheim*
 Stefan E Hardt, *Heidelberg*
 Klaus Hertting, *Hamburg*
 Thomas Jax, *Neuss*
 Thorsten Kälisch, *Mannheim*
 Klaus Kettering, *Frankfurt*
 Grigorios Korosoglou, *Heidelberg*
 Horst J Kuhn, *Planegg*
 Lorenz H Lehmann, *Heidelberg*
 Huige Li, *Mainz*
 Veselin Mitrovic, *Bad Nauheim*
 Ulrich Nellesen, *Stendal*
 Guenter Pilz, *Hausham*
 Peter W Radke, *Lübeck*
 Obaida Rana, *Aachen*
 Tienush Rassaf, *Düsseldorf*
 Oliver Ritter, *Wuerzburg*
 Erol Saygili, *Aachen*
 Dirk Skowasch, *Bonn*
 Tim Süselbeck, *Mannheim*
 Dirk Taubert, *Cologne*
 Theodor Tirilomis, *Goettingen*
 Stephen Wildhirt, *Ulm*
 Thomas Zeller, *Bad Krozingen*

**Greece**

Yiannis S Chatzizisis, *Thessaloniki*
 Moses S Elisaf, *Ioannina*
 Gerasimos Filippatos, *Athens*
 Panagiotis Korantzopoulos, *Ioannina*
 Nicholas G Kounis, *Patras*
 Antigone Lazou, *Thessaloniki*
 Konstantinos P Letsas, *Athens*
 Athanassios N Manginas, *Athens*
 Lampros Michalis, *Ioannina*
 Serafim Nanas, *Athens*
 Loukianos S Rallidis, *Athens*
 Georgios I Tagarakis, *Thessaloniki*
 Dimitrios Tziakas, *Alexandroupolis*
 Theodoros Xanthos, *Athens*

**Hungary**

Gergely Feher, *Pecs*

Albert Varga, *Szeged*

**India**

MPS Chawla, *Roorkee*
 S Dwivedi, *Delhi*
 Rajeev Gupta, *Jaipur*
 Deepak Kaul, *Chandigarh*
 Prabhakaran Prabhakaran, *New Delhi*
 KV Pugalendi, *Tamilnadu*
 Rajesh Vijayvergiya, *Chandigarh*

**Iran**

VR Dabbagh Kakhki, *Mashhad*
 Roya Kelishadi, *Isfahan*

**Ireland**

Jonathan D Dodd, *Dublin*

**Israel**

Jacob George, *Tel Aviv*
 E Goldhammer, *Haifa*

**Italy**

Maria Grazia Andreassi, *Massa*
 Giuseppe Barbaro, *Rome*
 Riccardo Bigi, *Milan*
 Tonino Bombardini, *Pisa*
 Filippo Cademartiri, *Parma*
 Alessandro Capucci, *Piacenza*
 Sergio Coccheri, *Bologna*
 Antonio Colombo, *Milan*
 Alberto Cuocolo, *Napoli*
 Roberto De Ponti, *Varese*
 Gianluca Di Bella, *Messina*
 Giovanni Fazio, *Palermo*
 Vittorio Fineschi, *Foggia*
 Antonio F Folino, *Padova*
 Gabriele Fragasso, *Milano*
 Carmine Gazzaruso, *Vigevano*
 Massimo Imazio, *Torino*
 Federico Lombardi, *Milan*
 Roberto Marchioli, *Santa Maria Imbaro*
 Giovan Giuseppe Mattera, *Pomezia*
 Germano Melissano, *Milano*
 Pietro A Modesti, *Florence*
 Eraldo Occhetta, *Novara*
 Pasquale Pagliaro, *Orbassano*
 Emilio Maria G Pasanisi, *Pisa*
 Vincenzo Pasceri, *Rome*
 Salvatore Patanè, *Messina*
 Nunzia Rosa Petix, *Florence*
 Eugenio Picano, *Pisa*
 Rita Rezzani, *Brescia*
 Manfredi Rizzo, *Palermo*
 Gian Paolo Rossi, *Padua*
 Speranza Rubattu, *Rome*
 Andrea Rubboli, *Bologna*
 Rosa Sicari, *Pisa*
 Giuseppe Tarantini, *Padua*
 Luigi Tavazzi, *Cotignola*
 Luca Testa, *Milan*
 Maurizio Turiel, *Milan*
 Cristina Vassalle, *Pisa*
 Massimo Volpe, *Rome*

**Japan**

Yoshifusa Aizawa, *Niigata*
 Junichiro Hashimoto, *Sendai*
 Hajime Kataoka, *Oita*
 Akinori Kimura, *Tokyo*
 Sei Komatsu, *Amagasaki*
 Ikuo Fukuda, *Hiroaki*
 Satoshi Kurisu, *Hiroshima*
 Yoshihiro Matsumoto, *Shizuoka*
 Tetsuo Minamino, *Osaka*
 Yoko Miyasaka, *Osaka*
 Kenichi Nakajima, *Kanazawa*
 Mashio Nakamura, *Tsu*
 Kazuaki Nishio, *Tokyo*
 Koichi Sakabe, *Kagawa*
 Masataka Sata, *Tokushima*
 Shinji Satoh, *Fukuoka*
 Yoshihide Takahashi, *Kanagawa*
 Masamichi Takano, *Chiba*
 Kengo Tanabe, *Tokyo*
 Hiroki Teragawa, *Hiroshima*
 Hiroyasu Ueda, *Osaka*
 Takanori Yasu, *Okinawa*
 Hiroshi Yoshida, *Chiba*

**Kosovo**

Gani Bajraktari, *Prishtina*

**Lebanon**

Habib A Dakik, *Beirut*

**Malaysia**

Eric Tien Siang Lim, *Johor*

**Mexico**

Enrique Vallejo, *Mexico*

**Morocco**

Abdenasser Drighil, *Casablanca*

**Netherlands**

Folkert Wouter Asselbergs, *Groningen*
 Jeroen J Bax, *Leiden*
 JJ Brugts, *Rotterdam*
 Peter W de Leeuw, *AZ Maastricht*
 Corstiaan A Den Uil, *Rotterdam*
 PA Doevendans, *Utrecht*
 D Poldermans, *Rotterdam*
 PW Serruys, *Rotterdam*

**Nigeria**

OS Ogah, *Ibadan*

**Pakistan**

Fahim H Jafary, *Karachi*



Poland

Pawel Buszman, *Katowice*
 Maciej Kurpisz, *Poznan*
 Sebastian Szmít, *Warsaw*



Russia

Nadezda Bylova, *Moscow*



Singapore

Jinsong Bian, *Singapore*



Slovenia

Mitja Lainscak, *Golnik*
 Matej Podbregar, *Ljubljana*



South Africa

Benjamin Longo-Mbenza, *Pretoria*
 JP Smedema, *Capetown*



South Korea

Jang-Ho Bae, *Daejeon*
 Young-Guk Ko, *Seoul*
 Sang-Hak Lee, *Seoul*
 Pil-Ki Min, *Seoul*
 Seung-Jung Park, *Seoul*



Spain

Miguel A Arias, *Toledo*
 Antoni Bayés-Genís, *Barcelona*
 Alberto Dominguez-Rodriguez, *Tenerife*
 Lorenzo Facila, *Castellon*
 José Luis Pérez-Castrillon, *Valladolid*
 Jesus Peteiro, *Coruña*
 Pedro L Sánchez, *Madrid*
 José L Zamorano, *Madrid*



Switzerland

Paul Erne, *Luzern*



Thailand

Nipon Chattipakorn, *Chiang Mai*



Turkey

Turgay Çelik, *Etilik-Ankara*

Yengi U Celikyurt, *Kocaeli*
 Hamza Duygu, *Yesilyurt*
 Cemil Gürgün, *İzmir*
 T Fikret İlgenli, *Kocaeli*
 Ergün Barış Kaya, *Ankara*
 Mehmet Ozaydin, *Isparta*
 Mustafa Yildiz, *Istanbul*



United Kingdom

AD Blann, *Birmingham*
 Geoffrey Burnstock, *London*
 John GF Cleland, *Kingston upon Hull*
 Armen Yuri Gasparyan, *Dudley*
 Derek J Hausenloy, *London*
 Farhad Kamali, *Newcastle upon Tyne*
 Juan Carlos Kaski, *London*
 Rajesh G Katare, *Bristol*
 Sohail Q Khan, *Manchester*
 Khalid Rahman, *Liverpool*
 Alexander M Seifalian, *London*
 Mark Slevin, *Manchester*
 Anastasis Stephanou, *London*



United States

Kamran Akram, *Omaha*
 Arshad Ali, *Ashland*
 Mouaz Al-Mallah, *Detroit*
 Naser M Ammash, *Rochester*
 Vignendra Ariyarah, *Philadelphia*
 Wilbert S Aronow, *Valhalla*
 S Serge Barold, *Tampa*
 Gregory W Barsness, *Rochester*
 Daniel S Berman, *Los Angeles*
 John F Beshai, *Chicago*
 William E Boden, *Buffalo*
 Somjot S Brar, *Los Angeles*
 David W Brown, *Decatur*
 Lu Cai, *Louisville*
 Christopher Paul Cannon, *Boston*
 Ricardo Castillo, *Brooklyn*
 Jun R Chiong, *Loma Linda*
 Steven G Chrysant, *Oklahoma*
 Timm Dickfeld, *Baltimore*
 Dayue Darrel Duan, *Reno*
 Rosemary B Duda, *Boston*
 Michael E Farkouh, *New York*
 Arthur Michael Feldman, *Philadelphia*
 Ronald Freudenberger, *Allentown*
 Jalal K Ghali, *Detroit*
 Lev G Goldfarb, *Bethesda*
 Samuel Z Goldhaber, *Boston*
 Hitinder S Gurm, *Ann Arbor*
 Julia H Indik, *Tucson*
 Antony Leslie Innasimuthu, *Pittsburgh*
 Ami E Iskandrian, *Birmingham*
 Rovshan M Ismailov, *Pittsburgh*
 Diwakar Jain, *Philadelphia*
 Shahrokh Javaheri, *Mason*
 Jacob Joseph, *West Roxbury*
 Bobby V Khan, *Atlanta*
 Christopher M Kramer, *Charlottesville*
 Rakesh C Kukreja, *Richmond*
 Roberto M Lang, *Chicago*
 Marzia Leacche, *Nashville*
 Jingping Lin, *Bethesda*
 Yi-Hwa Liu, *New Haven*
 Angel López-Candales, *Pittsburgh*
 Frank Marcus, *Tucson*
 Malek G Massad, *Chicago*
 Jawahar L Mehta, *Little Rock*
 Robert M Mentzer Jr, *Detroit*
 J Gary Meszaros, *Rootstown*
 Michael Miller, *Baltimore*
 Emile R Mohler III, *Philadelphia*
 Patrick M Moriarty, *Kansas City*
 Jeffrey W Moses, *New York*
 Mohammad-Reza Movahed, *Tucson*
 Gerald V Naccarelli, *Hershey*
 Andrea Natale, *Austin*
 Tien MH Ng, *Los Angeles*
 Steven Nissen, *Cleveland*
 Gian M Novaro, *Weston*
 Brian Olshansky, *Iowa*
 Robert Lee Page II, *Aurora*
 Weihong Pan, *Baton Rouge*
 Linda Pauliks, *Hershey*
 Philip Jack Podrid, *Boston*
 Vikas K Rath, *Midlothian*
 Jun Ren, *Laramie*
 Harmony R Reynolds, *New York*
 Clive Rosendorff, *Bronx*
 Samir Saba, *Pittsburgh*
 Rajesh Sachdeva, *Little Rock*
 Sandeep A Saha, *Spokane*
 Tiziano M Scarabelli, *Detroit*
 Robert H Schneider, *Maharishi Vedic*
 Frank W Sellke, *Providence*
 Samin K Sharma, *New York*
 Jamshid Shirani, *Danville*
 Boris Z Simkhovich, *Los Angeles*
 Krishna Singh, *Johnson City*
 Laurence S Sperling, *Atlanta*
 Jonathan S Steinberg, *New York*
 Ernst R von Schwarz, *Los Angeles*
 Richard Gary Trohman, *Chicago*
 Tong Tang, *San Diego*
 Qing Kenneth Wang, *Cleveland*
 Yi Wang, *Wilmington*
 Adam Whaley-Connell, *Columbia*
 Bruce L Wilkoff, *Cleveland*
 Qinglin Yang, *Birmingham*
 Xing Sheng Yang, *Atlanta*
 Yucheng Yao, *Los Angeles*
 Midori A Yenari, *San Francisco*
 Cuihua Zhang, *Columbia*



Uruguay

Juan C Grignola, *Montevideo*



Contents

Monthly Volume 5 Number 9 September 26, 2013

REVIEW

- 317 Hyponatremia in patients with heart failure
Filippatos TD, Elisaf MS
- 329 Coronary-cameral fistulas in adults (first of two parts)
Said SAM, Schiphorst RHM, Derksen R, Wagenaar L
- 337 Relationship between vitamin D deficiency and cardiovascular disease
Ku YC, Liu ME, Ku CS, Liu TY, Lin SL

MINIREVIEWS

- 347 Subcutaneous implantable defibrillator: State-of-the art 2013
Akerström F, Arias MA, Pachón M, Puchol A, Jiménez-López J

CASE REPORT

- 355 Cardiac resynchronization therapy in acute pulmonary edema: A case report
Barsoum EA, Bhat T, Asti D, Kowalski M, Vazzana T
- 359 Exercise-induced left bundle branch block: an infrequent phenomenon: Report of two cases
Said SAM, Bultje-Peters M, Nijhuis RLG
- 364 Complete regression of cardiac involvement associated with lymphoma following chemotherapy
Vinicki JP, Cianciulli TF, Farace GA, Saccheri MC, Lax JA, Kazelian LR, Wachs A
- 369 Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery
Teragawa H, Sueda T, Fujii Y, Takemoto H, Toyota Y, Nomura S, Nakagawa K

LETTERS TO THE EDITOR 373

- Persistent left superior vena cava and pacemaker implantation
Pontillo D, Patruno N

APPENDIX I-V Instructions to authors**ABOUT COVER**

Akerström F, Arias MA, Pachón M, Puchol A, Jiménez-López J. Subcutaneous implantable defibrillator: State-of-the art 2013. *World J Cardiol* 2013; 5(9): 347-354

<http://www.wjgnet.com/1949-8462/full/v5/i9/347.htm>

<http://dx.doi.org/10.4330/wjc.v5.i9.347>

AIM AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Cardiology is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

FLYLEAF**I-III Editorial Board****EDITORS FOR THIS ISSUE**

Responsible Assistant Editor: *Xin-Xin Che*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Cui*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Raúl Moreno, MD, Director of Interventional Cardiology, Interventional Cardiology, Hospital La Paz, Paseo La Castellana, 261, 28041 Madrid, Spain

Victor L Serebruany, MD, PhD, Associate Professor, Johns Hopkins University School of Medicine, President, HeartDrug™ Research Laboratories, Osler Medical Center, 7600 Osler Drive, Suite 307, Towson, MD 21204, United States

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Cardiology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjc@wjgnet.com
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza, 315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
<http://www.wjgnet.com>

PUBLICATION DATE
September 26, 2013

COPYRIGHT
© 2013 Baishideng. Articles published by this Open Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Hyponatremia in patients with heart failure

Theodosios D Filippatos, Moses S Elisaf

Theodosios D Filippatos, Moses S Elisaf, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece

Author contributions: Filippatos TD wrote the review, Elisaf MS edited and supervised the manuscript.

Correspondence to: Moses S Elisaf, MD, FRSH, FASA, FISA, Professor, Department of Internal Medicine, School of Medicine, University of Ioannina, Staurou Niarchou Avenue, 45110 Ioannina, Greece. egepi@cc.uoi.gr

Telephone: +30-26510-07509 Fax: +30-26510-07016

Received: June 23, 2013 Revised: July 30, 2013

Accepted: August 16, 2013

Published online: September 26, 2013

© 2013 Baishideng. All rights reserved.

Key words: Heart failure; Hyponatremia; Sodium; Vasopressin; Vasopressin-receptor antagonists; Tolvaptan; Conivaptan; Lixivaptan

Core tip: Patients with heart failure and hyponatremia have increased morbidity and mortality compared with subjects with normal sodium levels. Established treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. Arginine vasopressin (AVP)-receptor antagonists increase sodium levels and exhibit beneficial effects on hemodynamic variables in patients with heart failure. However, double-blind, placebo-controlled trials examining the effects of AVP-receptor antagonists on mortality, quality of life and length of hospital stay in patients with heart failure and hyponatremia are missing.

Abstract

The present review analyses the mechanisms relating heart failure and hyponatremia, describes the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and presents treatment options focusing on the role of arginine vasopressin (AVP)-receptor antagonists. Hyponatremia is the most common electrolyte disorder in the clinical setting and in hospitalized patients. Patients with hyponatremia may have neurologic symptoms since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with major neurologic complications. Patients with heart failure often develop hyponatremia owing to the activation of many neurohormonal systems leading to decrease of sodium levels. A large number of clinical studies have associated hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure. Treatment options for hyponatremia in heart failure, such as water restriction or the use of hypertonic saline with loop diuretics, have limited efficacy. AVP-receptor antagonists increase sodium levels effectively and their use seems promising in patients with hyponatremia. However, the effects of AVP-receptor antagonists on hard outcomes in patients with heart failure and hyponatremia have not been thoroughly examined.

Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. *World J Cardiol* 2013; 5(9): 317-328 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/317.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.317>

INTRODUCTION

Hyponatremia is defined as a serum sodium concentration lower than 136 mmol/L^[1]. It is recognized as the most common electrolyte disorder both in the clinical setting and in hospitalized patients^[2,3]. The prevalence of hyponatremia in hospitalized patients varies depending on the sodium level used to define the condition and the patient population^[4-13]. Patients with hyponatremia may suffer major neurologic complications since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with increased morbidity and mortality^[14-18]. It should be mentioned that elderly women and subjects who also have hypokalemia

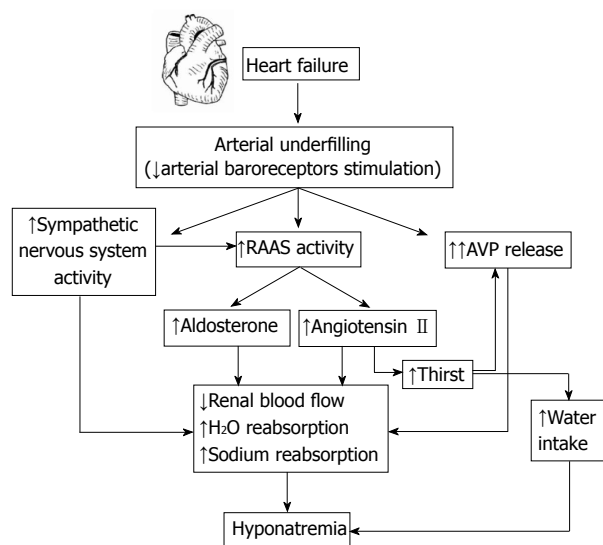


Figure 1 Mechanisms of hyponatremia in patients with heart failure. RAAS: Renin-angiotensin-aldosterone system; AVP: Arginine-vasopressin.

are characterized by an increased risk for neurologic complications following rapid correction of hyponatremia^[19-24]. The mortality rates associated with hyponatremia range from 5% to 50% depending on severity and acuity of onset^[25].

Heart failure is a disabling and growing disease associated with high morbidity and mortality rates and with annually increasing costs^[26-29]. Hyponatremia is often encountered in patients with heart failure^[30-33]. In a study of our group, 33.7% of patients with congestive heart failure had hyponatremia, which was the most common electrolyte abnormality in the study population^[34]. Aim of the present review is to demonstrate the mechanisms relating heart failure and hyponatremia, to present the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and to describe treatment options focusing on the role of arginine-vasopressin (AVP)-receptor antagonists.

A PubMed/Scopus search was performed up to June 2013 using combinations of “heart failure” with the following keywords: sodium, hyponatremia, vasopressin, aldosterone, diuretics, morbidity, mortality, hospital stay, water restriction, vaptans, vasopressin-receptor antagonists, tolvaptan, conivaptan, lixivaptan, electrolyte. Randomised controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

MECHANISMS OF HYPONATREMIA IN PATIENTS WITH HEART FAILURE

Neurohormonal mechanisms

Many factors are implicated in the pathogenesis of hyponatremia in patients with heart failure (Figure 1)^[6]. Heart failure reduces cardiac output and results in arterial underfilling, which induces the activation of the sym-

thetic nervous system (SNS). This leads to peripheral and renal vasoconstriction and decreases glomerular filtration rate, effects that combined with arterial underfilling result in increased reabsorption of sodium and water and induce the activation of the renin-angiotensin-aldosterone system (RAAS)^[31,32,35]. The subsequent increase of angiotensin II results in peripheral and renal vasoconstriction and induces aldosterone release from the adrenal gland causing further sodium retention^[36-43]. Arterial underfilling and the activation of both SNS and RAAS lead to increased release of AVP. Angiotensin II also stimulates the thirst center of the brain and increases water intake and the release of AVP^[44-46]. AVP binds to the vasopressin-2 (V2) receptor subtype and increases the number of aquaporin-2 water channels, leading to increased permeability of water in the collecting duct and enhanced free water retention^[47-50]. Aquaporin water channels consist of six membrane-spanning domains that form water channels within collecting duct membranes^[50-52].

In agreement with the above mechanisms patients with heart failure and hyponatremia have higher levels of plasma renin, angiotensin II, aldosterone, epinephrine, norepinephrine, and dopamine compared with patients with normal sodium levels^[40,53,54]. It has been shown that heart failure patients exhibit increased AVP production and generally a dysregulation of AVP characterised by an elevation of its levels despite the presence of volume overload, atrial distension and low plasma osmolality^[55-61]. Furthermore, the urinary excretion of aquaporin-2 is increased in heart failure patients with elevated AVP^[48]. Notably, the elevated plasma AVP levels are not appropriately reduced even with acute water loading in hyponatremic patients with advanced heart failure^[62]. These observations led to the hypothesis that hyponatremia may be a marker of neurohormonal activation that reflects the severity of heart failure^[63].

AVP plays an important role in the development of hyponatremia in heart failure but unfortunately it cannot reliably be determined by the current laboratory methods. Copeptin, the C-terminal part of the AVP precursor peptide, is secreted in an equimolar ratio to AVP and is a sensitive and stable surrogate marker for its release^[64]. Copeptin levels have been used as a prognostic marker in patients with acute diseases such as lower respiratory tract infection, heart disease and stroke. Copeptin is also a promising marker in the differential diagnosis of hyponatremia^[64]. In a study plasma copeptin and N-terminal pro-B-type natriuretic peptide were evaluated in 340 patients with left ventricular systolic dysfunction, who were divided into 3 groups according to copeptin tertiles and followed for 55 mo^[65]. Copeptin, although it did not predict the future development of hyponatremia, was a significant predictor of hospitalization or death (HR = 1.4, 95%CI: 1.1-1.9, $P < 0.019$) even after adjustment for plasma sodium, loop diuretic dose, and N-terminal pro-B-type natriuretic peptide levels^[65]. However, a secondary analysis of three prospective studies of patients with lower respiratory tract infections and acute cerebrovascu-

Table 1 Treatment options in patients with heart failure and hyponatremia

| Indication | Intervention | Comments | Citations |
|--|---|--|--|
| Acute symptomatic hyponatremia with severe neurologic symptoms | Infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L per hour until symptoms subside | The rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-h period. | Adrogué <i>et al</i> ^[1] Ghali <i>et al</i> ^[54] Fraser <i>et al</i> ^[114] |
| Chronic hyponatremia (the rate of correction of sodium levels should not exceed 8 mEq/L per hour the first 24 h, in order to avoid central pontine myelinolysis) | Fluid restriction (< 800-1000 mL/d) | The least expensive option. Many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction. | Adrogué <i>et al</i> ^[1] Fraser <i>et al</i> ^[114] Ghali <i>et al</i> ^[54] Albert <i>et al</i> ^[123] |
| | Loop diuretics | The mainstay of treatment in patients with heart failure with fluid overload. The combination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia. | Chow <i>et al</i> ^[71] Dzau <i>et al</i> ^[124] Elisaf <i>et al</i> ^[125] |
| | Infusion of hypertonic saline (e.g., 150 mL 1.4%-4.6% NaCl in 30 min for 6 to 12 d) combined with high-dose diuretics (furosemide 500 to 1000 mg) | Two studies (167 patients with heart failure) showed increased serum sodium levels, improvement in symptoms, decreased length of stay and re-admissions compared with furosemide infusion alone. | Paterna <i>et al</i> ^[126] Licata <i>et al</i> ^[127] |
| | Tolvaptan | Oral, selective V2-receptor blocker. Many studies showed efficacy in increasing serum sodium levels and improving heart failure symptoms. The drug should be initiated in hospital for safety reasons. It should not be administered for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death. | Berl <i>et al</i> ^[140] Gheorghiade <i>et al</i> ^[145] Gheorghiade <i>et al</i> ^[146] Rossi <i>et al</i> ^[147] Udelson <i>et al</i> ^[148] Gheorghiade <i>et al</i> ^[150] Konstam <i>et al</i> ^[151] Hauptman <i>et al</i> ^[152] |
| | Lixivaptan | Oral, highly selective V2-receptor antagonist. Studies have shown improvement of heart failure symptoms. | Ghali <i>et al</i> ^[154] Abraham <i>et al</i> ^[155] Ghali <i>et al</i> ^[156] |
| | Conivaptan | Only intravenous administration. The drug is both V1A- and a V2-receptor blocker, but the aquaretic effect is due to antagonism of the V2 receptor. Studies have shown significant increase in urine volumes in the first 48 h. It is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4. | Ali <i>et al</i> ^[158] Yatsu <i>et al</i> ^[159] Verbalis <i>et al</i> ^[160] Udelson <i>et al</i> ^[166] Goldsmith <i>et al</i> ^[167] Goldsmith <i>et al</i> ^[168] |

V2: Vasopressin-2; V1A: Vasopressin-1A.

lar events showed that plasma copeptin levels did not add significant information to the investigation of sodium imbalance states in hospitalized patients^[66]. It should be mentioned that this analysis was based on a small sample size and did not focus on patients with heart failure^[66].

Another molecule that may play role in the development of hyponatremia in patients with heart failure is apelin, which is an endogenous ligand of the orphan APJ receptor. Apelin has a wide tissue distribution and is implicated in the regulation of body fluid homeostasis, cardiovascular functions, glucose homeostasis, cell proliferation, and angiogenesis^[67]. Apelin has diuretic properties and it has been shown that it is regulated in opposite directions with AVP to maintain body fluid homeostasis^[67,68]. There is evidence of apelin dysregulation in patients with cardiac failure since it has been shown that the observed increase in plasma apelin cannot compensate for the higher levels of AVP and may contribute to the corresponding water metabolism defect^[69].

Diuretics

Diuretics are one of the most common causes of drug-induced hyponatremia^[70,71]. The great majority of cases

of diuretic-induced hyponatremia are caused by thiazide diuretics, which act solely in the distal tubules and do not interfere with urinary concentration and the ability of AVP to promote water retention^[24,70,72,73]. Thiazide-induced hyponatremia is usually mild, but acute severe hyponatremia is occasionally developed as an idiosyncratic reaction^[70,72,74].

It should also be mentioned that the hydrochlorothiazide and amiloride combination appears to increase the risk of hyponatremia. This increment is probably because of the direct effect of amiloride on the collecting tubule increasing sodium loss^[75-77]. Moreover, amiloride spares potassium and, hence, aggravates thiazide-induced hyponatremia as a consequence of potassium retainment by exchanging it for sodium in the distal tubule. Indapamide administration has also been associated with hyponatremia^[78-80].

EFFECTS OF HYPONATREMIA IN THE PROGNOSIS OF PATIENTS WITH HEART FAILURE

A large number of clinical studies have confirmed the

association of hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure^[10,11,42,81-94]. A recent meta-analysis that included 14766 patients from 22 studies and used as endpoint the death from any cause at 3 years showed that the risk of death is linearly increasing with serum sodium levels < 140 mmol/L^[95]. Moreover, hyponatremia was predictive of death in both patients with reduced or preserved ejection fraction^[95]. Another recent study, which enrolled 1000 consecutive patients with heart failure of any cause and severity for a median duration of 5.1 years, showed that hyponatremia was associated with a significantly increased mortality risk (HR = 2.10, 95%CI: 1.60-2.77)^[96]. Notably, it was shown that serum sodium within the reference range has a U-shaped association with mortality risk; specifically, sodium levels of 135-139 mmol/L indicated an increased mortality risk, whereas sodium levels of 140-145 mmol/L were associated with the best prognosis^[96]. Hyponatremia has also been found to be an important predictor of survival in several risk models in patients with heart failure^[83,84,97-101].

Hyponatremia is associated with increased rate of re-hospitalization^[102], increased length of stay^[10,84,103], increased hospital resource use^[104], increased complications^[81,105] and increased costs^[106-108]. Furthermore, the presence of hyponatremia in patients with acute ST-elevation myocardial infarction is associated with the development of acute heart failure and with in-hospital adverse outcomes^[109]. Moreover, the risk of in-hospital mortality was associated with the severity of hyponatremia in patients with acute ST-elevation myocardial infarction^[109,110].

Recent studies have also shown the role of copeptin in the prognosis of heart failure. In the Biomarkers in Acute Heart Failure trial, which enrolled 1641 patients with acute dyspnea, of whom 557 patients had acute heart failure, copeptin concentrations in the highest quartile were associated with increased 90-d mortality (HR = 3.85, $P < 0.001$)^[111]. The combination of elevated copeptin and hyponatremia was associated with a higher risk of 90-d mortality (HR = 7.36, $P < 0.001$). Of note, no correlation was found between copeptin and sodium concentration^[111]. Similarly, marked elevations of copeptin were independent predictors of poor outcomes in a cohort of 157 patients with class III or IV heart failure prospectively evaluated for 2 years^[112]. Furthermore, the combination of increased copeptin levels with hyponatremia was a stronger predictor^[112].

TREATMENT OF ACUTE SYMPTOMATIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In acute symptomatic hyponatremia serum sodium concentrations decrease rapidly resulting in the appearance of neurologic symptoms^[25,113]. These neurologic symptoms are due to brain edema resulting from fluid shifts from the hypotonic extracellular fluid into the more

hypertonic brain^[1]. In acute symptomatic hyponatremia with severe neurologic symptoms (for example seizures and/or obtundation) immediate treatment is required to reduce the risk of neurologic complications^[1,114]. The proposed treatment for symptomatic hyponatremia is the infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L per hour until symptoms subside^[54]. After this emergency intervention, the treatment should continue with the measures that are analysed below for the correction of chronic hyponatremia. Notably, in any case the rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-h period.

TREATMENT OF CHRONIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In patients with chronic hyponatremia the rate of correction of sodium levels should not exceed the rate of 8 mEq/L per day in any 24-h period^[115,116]. A more rapid correction increases the danger of central pontine myelinolysis^[1,117,118]. Central pontine myelinolysis is a neurological disease caused by the rapid rise in serum sodium levels during treatment in individuals with hyponatremia. It is characterised by severe damage of the myelin sheath of nerve cells in the pons area in the brainstem, leading to confusion, horizontal gaze paralysis, spastic quadriplegia, dysphagia, dysarthria and other neurological symptoms. The neurologic deterioration occurs 48-72 h after the rapid correction of hyponatremia. Death is common, but if the patient survives chronic neurologic deficits including locked-in syndrome and spastic quadriparesis are usually observed^[117-120]. Brain magnetic resonance imaging is used to reveal the demyelination in the brainstem pons^[121,122].

Fluid restriction

Fluid is restricted to amounts less than 800-1000 mL/d in order to achieve a negative water balance^[54]. It is the least expensive treatment option. In a randomized study, patients with hyponatremia (serum sodium ≤ 137 mg/dL) received usual care ($n = 26$) or 1000 mL/d fluid restriction ($n = 20$) at discharge^[123]. After 60 d patients in the group of fluid restriction had significantly better scores of symptom burden, total symptoms and overall quality of life. In this study there were no differences in thirst or adherence to fluid restriction between groups^[123]. However, many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction^[54].

Diuretics

The use of diuretics is the mainstay of treatment in patients with heart failure with fluid overload. Loop diuretics are preferred because they increase electrolyte-free water clearance^[71]. It has been shown that the addition of a loop diuretic to an angiotensin-converting enzyme inhibitor reversed hyponatremia in heart failure patients^[124]. Furthermore, a study of our group showed that the com-

bination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia^[125]. Specifically, six patients with congestive heart failure and serum sodium of 125-128 mmol/L treated with furosemide received captopril in progressively increasing doses. The addition of captopril resulted in clinical improvement and induced a significant increase in serum sodium levels, which was associated with a rise in the diluting ability of the kidney^[125].

It has also been shown that the infusion of hypertonic saline combined with high-dose diuretics was associated with increase in serum sodium levels and a potential improvement in outcomes in heart failure patients^[126,127]. One study enrolled 60 patients with New York Heart Association Class IV heart failure, who received infusion of furosemide (500 to 1000 mg) plus hypertonic saline (150 mL 1.4%-4.6% NaCl) in 30 min for 6 to 12 d. The combination of furosemide and hypertonic saline increased serum sodium levels and decreased length of stay and re-admissions compared with furosemide infusion alone^[126]. In a larger study, which enrolled 107 patients with heart failure, the infusion of furosemide plus hypertonic saline was associated with improvement in symptoms and reduction of re-admissions and mortality^[127].

AVP-receptor antagonists

AVP has three different receptor subtypes^[128]. V1A receptors are found in vascular smooth muscle and cardiac myocytes causing vasoconstriction and hypertrophy, as well as in platelets and hepatocytes regulating platelet aggregation and glycogen metabolism^[129-135]. V1B receptors are found in the anterior pituitary gland and are associated with adrenocorticotrophic hormone and b-endorphin release^[136]. Interestingly, these receptor subtypes have been also linked to the regulation of glucose homeostasis^[137]. V2 receptors are found on the renal collecting ducts and cause free-water reabsorption leading to increased water retention^[50,51,138]. V2 receptors are mainly linked to the development of hyponatremia in heart failure patients.

The central role of AVP in hyponatremia is targeted with the AVP-receptor antagonists (vaptans) conivaptan, tolvaptan and lixivaptan, which differ in their affinity for the V1A and V2 receptor^[139].

Tolvaptan: Tolvaptan is an orally active, selective V2-receptor blocker. It is recommended to initiate the drug in hospital for safety reasons, although patients have been receiving tolvaptan safely as long as 3 years^[140].

Tolvaptan has been extensively studied in patients with heart failure. The administration of tolvaptan at a single oral dose (15, 30 or 60 mg) in 181 patients with advanced heart failure on standard therapy resulted in favourable changes in filling pressures and a significant increase in urine output^[141]. The low-dose (7.5 mg/d) tolvaptan for seven days improved hemodynamic parameters and resulted in significant fluid removal in 22 patients with chronic heart failure^[142]. Tolvaptan administration for 7 consecutive days reduced body weight and improved symptoms

compared with placebo in patients with heart failure and volume overload despite the use of conventional diuretics^[143,144]. Tolvaptan administration in 254 stable patients with heart failure decreased body weight and increased urine volume^[145]. Similarly, in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial tolvaptan administration in hospitalized patients with systolic heart failure ($n = 319$) resulted in a significant decrease in body weight at 24 h without any changes in heart rate or blood pressure or increase in the rates of hypokalemia or worsening renal function^[146]. Of note, a lower 60-d mortality was observed in post hoc analyses in patients with renal dysfunction or severe systemic congestion^[146,147]. In the Multicenter Evaluation of Tolvaptan Effect on Remodeling (METEOR) study tolvaptan for 54 wk did not show any beneficial or detrimental effects on remodeling compared with placebo in 240 patients with stable systolic heart failure^[148]. Moreover, tolvaptan administration prevented the worsening of renal function compared with conventional therapy in patients with acute decompensated heart failure and high risk of renal failure^[149].

The larger trial of tolvaptan is the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), which enrolled 4133 patients hospitalized with systolic heart failure. A significant reduction in body weight on day 7 after discharge was demonstrated^[150]. During a median follow-up of 9.9 mo a significant increase in sodium levels was observed in patients with hyponatremia^[151]. However, tolvaptan had no effect on long-term mortality or heart failure-related morbidity. Specifically, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (HR = 0.98, 95%CI: 0.87-1.11, $P = 0.68$). The composite of cardiovascular death or hospitalization for heart failure occurred in 42% of patients receiving tolvaptan and 40.2% of patients receiving placebo (HR = 1.04, 95%CI: 0.95-1.14, $P = 0.55$)^[151]. It should be mentioned that EVEREST did not enrol solely patients with heart failure and hyponatremia, who in theory could benefit from the administration of tolvaptan. A recent analysis of patients with hyponatremia from the EVEREST trial ($n = 475$) showed that tolvaptan was associated with greater likelihood of normalization of serum sodium, greater weight reduction and greater relief of dyspnea at discharge than placebo (all $P < 0.05$)^[152]. Tolvaptan did not reduce long-term outcomes compared with placebo among all patients with hyponatremia. However, the administration of tolvaptan in patients with pronounced hyponatremia (< 130 mEq/L; $n = 92$) resulted in a significant reduction in cardiovascular morbidity and mortality after discharge ($P = 0.04$)^[152].

A recent study showed that the use of a single dose tolvaptan in pediatric patients with heart failure ($n = 28$) significantly increased serum sodium concentration ($P < 0.001$)^[153]. Furthermore, urine output was significantly increased at 24 h ($P < 0.001$).

Lixivaptan: Lixivaptan is an oral, highly selective V2-

receptor antagonist^[154]. The administration of lixivaptan in 42 patients with mild to moderate heart failure was associated with significant increases in urine volume and solute-free water excretion without any significant change in plasma renin, norepinephrine, aldosterone, atrial natriuretic peptide and endothelin-1 levels^[155]. Treatment with lixivaptan 100 mg/d for 8 wk (in addition to standard therapy) in outpatients with heart failure and volume overload significantly reduced body weight and improved dyspnea and orthopnea^[156]. Lixivaptan was generally well tolerated but thirst and polyuria occurred more frequently in the active drug group compared with the placebo group^[156].

The effectiveness and safety of lixivaptan for 60 d in patients with heart failure and hyponatremia are being evaluated in a double-blind, placebo-controlled study, the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) study^[157]. Primary endpoint is the effect of lixivaptan on serum sodium in patients hospitalized with worsening heart failure (target $n = 650$), signs of congestion and serum sodium concentrations < 135 mEq/L. Other endpoints include assessment of dyspnea, body weight, cognitive function and days of hospital-free survival^[157].

Conivaptan: Conivaptan is both a V1A- and a V2-receptor blocker; the aquaretic effect is due to antagonism of the V2 receptor^[158-161]. The drug is a substrate and potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may result in significant drug-drug interactions^[158]. The drug is given only intravenously (20 mg bolus, then continuous infusion 20-40 mg/24 h) over up to 4 d in hospital^[139]. It has been shown that volume status or the presence of congestive heart failure do not alter the pharmacokinetics of conivaptan 20 or 40 mg/d^[162].

The effects of conivaptan in hyponatremia of various origin were evaluated in 3 randomized double-blind, controlled studies which showed significant improvement in serum sodium levels^[163-165]. The acute hemodynamic effects of conivaptan (single intravenous dose of 10, 20 or 40 mg) in heart failure were examined in 142 patients with symptomatic heart failure (New York Heart Association class III and IV)^[166]. The administration of conivaptan resulted in favourable changes in hemodynamic variables and urine output without affecting blood pressure or heart rate^[166]. In a double-blind trial, which randomised 170 patients hospitalized for worsening heart failure receiving standard therapy to conivaptan (20 mg loading dose followed by 2 successive 24-h continuous infusions of 40, 80, or 120 mg/d) or placebo, conivaptan significantly increased urine output at 24 h compared with placebo (1-1.5 L difference, $P \leq 0.02$ for all doses)^[167]. Body weight was decreased with the 40 and 80 mg/d dose in parallel with the increase in urine output but this reduction was not significant. Global and respiratory status at 48 h did not differ significantly between conivaptan and placebo groups. Conivaptan was well tolerated with the most common adverse events being infusion-site reac-

tions^[167]. Another study assessed the role of conivaptan, furosemide or their combination in 8 patients with chronic stable heart failure on standard medical treatment^[168]. Both conivaptan and furosemide monotherapy increased urine volume, but the combination treatment significantly augmented this effect. Although conivaptan did not increase urinary sodium excretion compared with furosemide, the combination led to a greater urinary sodium excretion compared with furosemide monotherapy. There were no significant effects of conivaptan, furosemide or their combination on heart rate, arterial pressure, systemic vascular resistance, cardiac output, glomerular filtration rate, renal blood flow, plasma catecholamines, renin activity, AVP and B-type natriuretic peptide levels^[168].

Other considerations: Fluid should not be restricted in patients with hyponatremia who start AVP-receptor antagonists and serum sodium concentration should be monitored every 6-8 h in order to avoid rapid correction of sodium levels^[139]. Although osmotic demyelination has not been reported with the use of AVP-receptor antagonists in studies with heart failure patients, a warning letter was recently published concerning the occurrence of neurological sequelae in some patients treated with tolvaptan in whom the correction of serum sodium exceeded the suggested rate^[169].

AVP-receptor antagonists should not be used in patients with hypovolemic hyponatremia, who should instead be treated with isotonic saline. Adverse effects of AVP-receptor antagonists include dry mouth, thirst and increased urination in most patients. These agents may not be effective in patients with advanced acute or chronic renal failure^[139]. Furthermore, the United States Food and Drug Administration based on a recent large clinical trial of tolvaptan in patients with autosomal dominant polycystic kidney disease^[170] has recently determined that tolvaptan should not be administered for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death^[171].

CONCLUSION

Many patients with heart failure have decreased sodium levels due to neurohormonal mechanisms. Patients with heart failure and hyponatremia have increased morbidity and worse prognosis compared with subjects with normal sodium levels. Treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. AVP-receptor antagonists increase effectively sodium levels and their use seems promising in patients with hyponatremia. However, it is not clear whether normalization of serum sodium also leads to an improved prognosis. Furthermore, the effects of AVP-receptor antagonists on the mortality, quality of life and length of hospital stay, as well as their cost-effectiveness, have not been thoroughly examined in double-blind,

placebo-controlled trials in patients with heart failure and hyponatremia.

REFERENCES

- 1 Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581-1589 [PMID: 10824078 DOI: 10.1056/NEJM200005253422107]
- 2 Siragy HM. Hyponatremia, fluid-electrolyte disorders, and the syndrome of inappropriate antidiuretic hormone secretion: diagnosis and treatment options. *Endocr Pract* 2006; **12**: 446-457 [PMID: 16901803 DOI: 10.4158/EP.12.4.446]
- 3 Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. *CMAJ* 2002; **166**: 1056-1062 [PMID: 12002984]
- 4 Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med* 2006; **119**: S30-S35 [PMID: 16843082 DOI: 10.1016/j.amjmed.2006.05.005]
- 5 Oren RM. Hyponatremia in congestive heart failure. *Am J Cardiol* 2005; **95**: 2B-7B [PMID: 15847851 DOI: 10.1016/j.amjcard.2005.03.002]
- 6 Bettari L, Fiuzat M, Felker GM, O'Connor CM. Significance of hyponatremia in heart failure. *Heart Fail Rev* 2012; **17**: 17-26 [PMID: 20838881 DOI: 10.1007/s10741-010-9193-3]
- 7 Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin North Am* 2003; **32**: 459-81, vii [PMID: 12800541 DOI: 10.1016/S0889-8529(03)00004-5]
- 8 Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003; **337**: 169-172 [PMID: 14568195 DOI: 10.1016/j.cccn.2003.08.001]
- 9 Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009; **122**: 857-865 [PMID: 19699382 DOI: 10.1016/j.amjmed.2009.01.027]
- 10 Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007; **28**: 980-988 [PMID: 17309900 DOI: 10.1093/eurheartj/ehl542]
- 11 Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006; **27**: 1207-1215 [PMID: 16603579 DOI: 10.1093/eurheartj/ehl845]
- 12 Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003; **24**: 442-463 [PMID: 12633546 DOI: 10.1016/S0195-668X(02)00823-0]
- 13 Filippatos TD, Milionis HJ, Elisaf MS. Alterations in electrolyte equilibrium in patients with acute leukemia. *Eur J Haematol* 2005; **75**: 449-460 [PMID: 16313256 DOI: 10.1111/j.1600-0609.2005.00547.x]
- 14 Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986; **314**: 1529-1535 [PMID: 3713746 DOI: 10.1056/NEJM198606123142401]
- 15 Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 1976; **55**: 121-129 [PMID: 1256311]
- 16 Gross P, Palm C. Thiazides: do they kill? *Nephrol Dial Transplant* 2005; **20**: 2299-2301 [PMID: 16115842 DOI: 10.1093/ndt/gfi109]
- 17 Reynolds RM, Seckl JR. Hyponatraemia for the clinical endocrinologist. *Clin Endocrinol (Oxf)* 2005; **63**: 366-374 [PMID: 16181228 DOI: 10.1111/j.1365-2265.2005.02318.x]
- 18 Gross SG, Bell RD. Central pontine myelinolysis and rapid correction of hyponatremia. *Tex Med* 1982; **78**: 59-60 [PMID: 7147196]
- 19 Verbalis JG, Martinez AJ. Neurological and neuropathological sequelae of correction of chronic hyponatremia. *Kidney Int* 1991; **39**: 1274-1282 [PMID: 1895679 DOI: 10.1038/ki.1991.161]
- 20 Ayus JC, Arieff AI. Hyponatremia and myelinolysis. *Ann Intern Med* 1997; **127**: 163 [PMID: 9230010 DOI: 10.7326/0003-4819-127-2-199707150-00016]
- 21 Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Engl J Med* 1987; **317**: 1190-1195 [PMID: 3309659 DOI: 10.1056/NEJM198711053171905]
- 22 Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. *Am J Med* 1994; **96**: 408-413 [PMID: 8192171 DOI: 10.1016/0002-9343(94)90166-X]
- 23 Lien YH. Role of organic osmolytes in myelinolysis. A topographic study in rats after rapid correction of hyponatremia. *J Clin Invest* 1995; **95**: 1579-1586 [PMID: 7706464 DOI: 10.1172/JCI117831]
- 24 Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. *Int J Clin Pract* 2008; **62**: 1572-1580 [PMID: 18822027 DOI: 10.1111/j.1742-1241.2008.01860.x]
- 25 Fall PJ. Hyponatremia and hypernatremia. A systematic approach to causes and their correction. *Postgrad Med* 2000; **107**: 75-82; quiz 179 [PMID: 10844943 DOI: 10.3810/pgm.2000.5.1.1068]
- 26 Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: 143-152 [PMID: 23283859 DOI: 10.1161/CIR.0b013e318282ab8f]
- 27 Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012; **125**: 188-197 [PMID: 22215894 DOI: 10.1161/CIR.0b013e3182456d46]
- 28 Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wyllie-Rosett J. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: e46-e215 [PMID: 20019324 DOI: 10.1161/CIRCULATIONAHA.109.192667]
- 29 Filippatos TD, Mikhailidis DP. Statins and heart failure. *Angiology* 2008; **59**: 58S-61S [PMID: 18508847 DOI: 10.1177/000319708319643]

- 30 **Fried LF**, Palevsky PM. Hyponatremia and hypernatremia. *Med Clin North Am* 1997; **81**: 585-609 [PMID: 9167647 DOI: 10.1016/S0025-7125(05)70535-6]
- 31 **Farmakis D**, Filippatos G, Parissis J, Kremastinos DT, Gheorghiade M. Hyponatremia in heart failure. *Heart Fail Rev* 2009; **14**: 59-63 [PMID: 18758941 DOI: 10.1007/s10741-008-9109-7]
- 32 **Sica DA**. Hyponatremia and heart failure--pathophysiology and implications. *Congest Heart Fail* 2005; **11**: 274-277 [PMID: 16230871 DOI: 10.1111/j.1527-5299.2005.04180.x]
- 33 **Klein L**, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF, Califf RM, Gheorghiade M. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005; **111**: 2454-2460 [PMID: 15867182 DOI: 10.1161/01.CIR.0000165065.82609.3D]
- 34 **Milionis HJ**, Alexandrides GE, Liberopoulos EN, Bairaktari ET, Goudevenos J, Elisaf MS. Hypomagnesemia and concurrent acid-base and electrolyte abnormalities in patients with congestive heart failure. *Eur J Heart Fail* 2002; **4**: 167-173 [PMID: 11959045 DOI: 10.1016/S1388-9842(01)00234-3]
- 35 **Schrier RW**. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med* 2006; **119**: S47-S53 [PMID: 16843085 DOI: 10.1016/j.amjmed.2006.05.007]
- 36 **Hasking GJ**, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986; **73**: 615-621 [PMID: 3948363 DOI: 10.1161/01.CIR.73.4.615]
- 37 **DiBona GF**, Herman PJ, Sawin LL. Neural control of renal function in edema-forming states. *Am J Physiol* 1988; **254**: R1017-R1024 [PMID: 3381907]
- 38 **Schrier RW**, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**: 577-585 [PMID: 10451464 DOI: 10.1056/NEJM199908193410806]
- 39 **Schuster VL**, Kokko JP, Jacobson HR. Angiotensin II directly stimulates sodium transport in rabbit proximal convoluted tubules. *J Clin Invest* 1984; **73**: 507-515 [PMID: 6699174 DOI: 10.1172/JCI11237]
- 40 **Lilly LS**, Dzau VJ, Williams GH, Rydstedt L, Hollenberg NK. Hyponatremia in congestive heart failure: implications for neurohumoral activation and responses to orthostasis. *J Clin Endocrinol Metab* 1984; **59**: 924-930 [PMID: 6384261 DOI: 10.1210/jcem-59-5-924]
- 41 **Dzau VJ**, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure. Relation to activation of the renin-angiotensin system and hyponatremia. *N Engl J Med* 1984; **310**: 347-352 [PMID: 6361570 DOI: 10.1056/NEJM198402093100603]
- 42 **Lee WH**, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986; **73**: 257-267 [PMID: 3002660 DOI: 10.1161/01.CIR.73.2.257]
- 43 **Weber KT**. Aldosterone in congestive heart failure. *N Engl J Med* 2001; **345**: 1689-1697 [PMID: 11759649 DOI: 10.1056/NEJMra000050]
- 44 **Brooks VL**, Keil LC, Reid IA. Role of the renin-angiotensin system in the control of vasopressin secretion in conscious dogs. *Circ Res* 1986; **58**: 829-838 [PMID: 3521934 DOI: 10.1161/01.RES.58.6.829]
- 45 **Mitchell LD**, Barron K, Brody MJ, Johnson AK. Two possible actions for circulating angiotensin II in the control of vasopressin release. *Peptides* 1982; **3**: 503-507 [PMID: 7122277 DOI: 10.1016/0196-9781(82)90116-4]
- 46 **Sica DA**. Pharmacotherapy in congestive heart failure: angiotensin II and thirst: therapeutic considerations. *Congest Heart Fail* 2001; **7**: 325-328 [PMID: 11828179]
- 47 **Schrier RW**, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979; **236**: F321-F332 [PMID: 373467]
- 48 **Funayama H**, Nakamura T, Saito T, Yoshimura A, Saito M, Kawakami M, Ishikawa SE. Urinary excretion of aquaporin-2 water channel exaggerated dependent upon vasopressin in congestive heart failure. *Kidney Int* 2004; **66**: 1387-1392 [PMID: 15458431 DOI: 10.1111/j.1523-1755.2004.00902.x]
- 49 **Kumar S**, Rubin S, Mather PJ, Whellan DJ. Hyponatremia and vasopressin antagonism in congestive heart failure. *Clin Cardiol* 2007; **30**: 546-551 [PMID: 17847041 DOI: 10.1002/clc.18]
- 50 **Nielsen S**, Kwon TH, Christensen BM, Promeneur D, Frøkier J, Marples D. Physiology and pathophysiology of renal aquaporins. *J Am Soc Nephrol* 1999; **10**: 647-663 [PMID: 10073616 DOI: 10.1016/S1095-6433(00)80217-2]
- 51 **Kwon TH**, Hager H, Nejsum LN, Andersen ML, Frøkier J, Nielsen S. Physiology and pathophysiology of renal aquaporins. *Semin Nephrol* 2001; **21**: 231-238 [PMID: 11320486 DOI: 10.1053/snep.2001.21647]
- 52 **Nielsen S**. Renal aquaporins: an overview. *BJU Int* 2002; **90** Suppl 3: 1-6 [PMID: 12445090 DOI: 10.1046/j.1464-410X.90.s3.1.x]
- 53 **Packer M**, Medina N, Yushak M. Relation between serum sodium concentration and the hemodynamic and clinical responses to converting enzyme inhibition with captopril in severe heart failure. *J Am Coll Cardiol* 1984; **3**: 1035-1043 [PMID: 6323565 DOI: 10.1016/S0735-1097(84)80364-2]
- 54 **Ghali JK**, Tam SW. The critical link of hypervolemia and hyponatremia in heart failure and the potential role of arginine vasopressin antagonists. *J Card Fail* 2010; **16**: 419-431 [PMID: 20447579 DOI: 10.1016/j.cardfail.2009.12.021]
- 55 **Anderson RJ**, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985; **102**: 164-168 [PMID: 3966753 DOI: 10.7326/0003-4819-102-2-164]
- 56 **Lee CR**, Watkins ML, Patterson JH, Gattis W, O'Connor CM, Gheorghiade M, Adams KF. Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003; **146**: 9-18 [PMID: 12851603 DOI: 10.1016/S0002-8703(02)94708-3]
- 57 **Kalra PR**, Anker SD, Coats AJ. Water and sodium regulation in chronic heart failure: the role of natriuretic peptides and vasopressin. *Cardiovasc Res* 2001; **51**: 495-509 [PMID: 11476740 DOI: 10.1016/S0008-6363(01)00297-8]
- 58 **Isnard R**, Pousset F, Trochu J, Chapirovskaia O, Carayon A, Golmard J, Lechat P, Thomas D, Bouhour J, Komajda M. Prognostic value of neurohormonal activation and cardiopulmonary exercise testing in patients with chronic heart failure. *Am J Cardiol* 2000; **86**: 417-421 [PMID: 10946035 DOI: 10.1016/S0002-9149(00)00957-7]
- 59 **Francis GS**, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990; **82**: 1724-1729 [PMID: 2146040 DOI: 10.1161/01.CIR.82.5.1724]
- 60 **Goldsmith SR**. Congestive heart failure: potential role of arginine vasopressin antagonists in the therapy of heart failure. *Congest Heart Fail* 2002; **8**: 251-256 [PMID: 12368587 DOI: 10.1111/j.1527-5299.2002.01158.x]
- 61 **Goldsmith SR**, Francis GS, Cowley AW, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1983; **1**: 1385-1390 [PMID: 6343460 DOI: 10.1016/S0735-1097(83)80040-0]
- 62 **Goldsmith SR**, Francis GS, Cowley AW. Arginine vasopres-

- sin and the renal response to water loading in congestive heart failure. *Am J Cardiol* 1986; **58**: 295-299 [PMID: 3739918 DOI: 10.1016/0002-9149(86)90065-2]
- 63 **De Luca L**, Klein L, Udelson JE, Orlandi C, Sardella G, Fedele F, Gheorghiadu M. Hyponatremia in patients with heart failure. *Am J Cardiol* 2005; **96**: 19L-23L [PMID: 16399089 DOI: 10.1016/j.amjcard.2005.09.066]
 - 64 **Nickel CH**, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. *BMC Med* 2012; **10**: 7 [PMID: 22264220 DOI: 10.1186/1741-7015-10-7]
 - 65 **Balling L**, Kistorp C, Schou M, Egstrup M, Gustafsson I, Goetze JP, Hildebrandt P, Gustafsson F. Plasma copeptin levels and prediction of outcome in heart failure outpatients: relation to hyponatremia and loop diuretic doses. *J Card Fail* 2012; **18**: 351-358 [PMID: 22555263 DOI: 10.1016/j.cardfail.2012.01.019]
 - 66 **Nigro N**, Müller B, Morgenthaler N, Fluri F, Schütz P, Neidert S, Stolz D, Bingisser R, Tamm M, Christ-Crain M, Katan M. The use of copeptin, the stable peptide of the vasopressin precursor, in the differential diagnosis of sodium imbalance in patients with acute diseases. *Swiss Med Wkly* 2011; **141**: w13270 [PMID: 21990032 DOI: 10.4414/ smw.2011.13270]
 - 67 **Galanth C**, Hus-Citharel A, Li B, Llorens-Cortès C. Apelin in the control of body fluid homeostasis and cardiovascular functions. *Curr Pharm Des* 2012; **18**: 789-798 [PMID: 22236125 DOI: 10.2174/138161212799277770]
 - 68 **Llorens-Cortes C**, Moos F. Apelin and vasopressin: two work better than one. *J Neuroendocrinol* 2012; **24**: 1085-1086 [PMID: 22712789 DOI: 10.1111/j.1365-2826.2012.02316.x]
 - 69 **Blanchard A**, Steichen O, De Mota N, Curis E, Gauci C, Frank M, Wuerzner G, Kamenicky P, Passeron A, Azizi M, Llorens-Cortes C. An abnormal apelin/vasopressin balance may contribute to water retention in patients with the syndrome of inappropriate antidiuretic hormone (SIADH) and heart failure. *J Clin Endocrinol Metab* 2013; **98**: 2084-2089 [PMID: 23515451 DOI: 10.1210/jc.2012-3794]
 - 70 **Liamis G**, Milonion H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008; **52**: 144-153 [PMID: 18468754 DOI: 10.1053/j.ajkd.2008.03.004]
 - 71 **Chow KM**, Szeto CC, Wong TY, Leung CB, Li PK. Risk factors for thiazide-induced hyponatraemia. *QJM* 2003; **96**: 911-917 [PMID: 14631057 DOI: 10.1093/qjmed/hcg157]
 - 72 **Spital A**. Diuretic-induced hyponatremia. *Am J Nephrol* 1999; **19**: 447-452 [PMID: 10460932 DOI: 10.1159/000013496]
 - 73 **Miltiadous G**, Mikhailidis DP, Elisaf M. Acid-base and electrolyte abnormalities observed in patients receiving cardiovascular drugs. *J Cardiovasc Pharmacol Ther* 2003; **8**: 267-276 [PMID: 14740076 DOI: 10.1177/107424840300800404]
 - 74 **Liamis G**, Christidis D, Alexandridis G, Bairaktari E, Madias NE, Elisaf M. Uric acid homeostasis in the evaluation of diuretic-induced hyponatremia. *J Investig Med* 2007; **55**: 36-44 [PMID: 17441410 DOI: 10.2310/6650.2007.06027]
 - 75 **van Assen S**, Mudde AH. Severe hyponatraemia in an amiloride/hydrochlorothiazide-treated patient. *Neth J Med* 1999; **54**: 108-113 [PMID: 10189785 DOI: 10.1016/S0300-2977(98)00153-3]
 - 76 **Fidler HM**, Goldman J, Bielawska CA, Rai GS, Hoffbrand BI. A study of plasma sodium levels in elderly people taking amiloride or triamterene in combination with hydrochlorothiazide. *Postgrad Med J* 1993; **69**: 797-799 [PMID: 8290411 DOI: 10.1136/pgmj.69.816.797]
 - 77 **Strykers PH**, Stern RS, Morse BM. Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984; **252**: 389 [PMID: 6737629 DOI: 10.1001/jama.1984.03350030057021]
 - 78 Hypokalaemia and hyponatraemia due to indapamide. *Prescrire Int* 2002; **11**: 183 [PMID: 12472097]
 - 79 **Chapman MD**, Hanrahan R, McEwen J, Marley JE. Hyponatraemia and hypokalaemia due to indapamide. *Med J Aust* 2002; **176**: 219-221 [PMID: 11999238]
 - 80 **Mathew TH**, Boyd IW, Rohan AP. Hyponatraemia due to the combination of hydrochlorothiazide and amiloride (Moduretic): Australian spontaneous reports 1977-1988. *Med J Aust* 1990; **152**: 308-309 [PMID: 2314335]
 - 81 **Chin MH**, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; **156**: 1814-1820 [PMID: 8790075 DOI: 10.1001/archinte.1996.00440150068007]
 - 82 **Chen MC**, Chang HW, Cheng CI, Chen YH, Chai HT. Risk stratification of in-hospital mortality in patients hospitalized for chronic congestive heart failure secondary to non-ischemic cardiomyopathy. *Cardiology* 2003; **100**: 136-142 [PMID: 14631134 DOI: 10.1159/000073931]
 - 83 **Felker GM**, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF, Gheorghiadu M, O'Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004; **10**: 460-466 [PMID: 15599835 DOI: 10.1016/j.cardfail.2004.02.011]
 - 84 **Lee DS**, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003; **290**: 2581-2587 [PMID: 14625335 DOI: 10.1001/jama.290.19.2581]
 - 85 **Packer M**, Lee WH, Kessler PD, Medina N, Yushak M, Gottlieb SS. Identification of hyponatremia as a risk factor for the development of functional renal insufficiency during converting enzyme inhibition in severe chronic heart failure. *J Am Coll Cardiol* 1987; **10**: 837-844 [PMID: 2821091 DOI: 10.1016/S0735-1097(87)80278-4]
 - 86 **Velavan P**, Khan NK, Goode K, Rigby AS, Loh PH, Komajda M, Follath F, Swedberg K, Madeira H, Cleland JG. Predictors of short term mortality in heart failure - insights from the Euro Heart Failure survey. *Int J Cardiol* 2010; **138**: 63-69 [PMID: 18789548 DOI: 10.1016/j.ijcard.2008.08.004]
 - 87 **Wong PS**, Davidsson GK, Timeyin J, Warren A, Watson DJ, Vincent R, Davidson C. Heart failure in patients admitted to hospital: mortality is still high. *Eur J Intern Med* 2002; **13**: 304-310 [PMID: 12144909 DOI: 10.1016/S0953-6205(02)00086-9]
 - 88 **Bettari L**, Fiuzat M, Shaw LK, Wojdyla DM, Metra M, Felker GM, O'Connor CM. Hyponatremia and long-term outcomes in chronic heart failure--an observational study from the Duke Databank for Cardiovascular Diseases. *J Card Fail* 2012; **18**: 74-81 [PMID: 22196845 DOI: 10.1016/j.cardfail.2011.09.005]
 - 89 **Schou M**, Valeur N, Torp-Pedersen C, Gustafsson F, Køber L. Plasma sodium and mortality risk in patients with myocardial infarction and a low LVEF. *Eur J Clin Invest* 2011; **41**: 1237-1244 [PMID: 21554269 DOI: 10.1111/j.1365-2362.2011.02532.x]
 - 90 **Gheorghiadu M**, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007; **167**: 1998-2005 [PMID: 17923601 DOI: 10.1001/archinte.167.18.1998]
 - 91 **Baldasseroni S**, Urso R, Orso F, Bianchini BP, Carbonieri E, Cirò A, Gonzini L, Leonardi G, Marchionni N, Maggioni AP. Relation between serum sodium levels and prognosis in outpatients with chronic heart failure: neutral effect of treatment with beta-blockers and angiotensin-converting enzyme inhibitors: data from the Italian Network on Congestive Heart Failure (IN-CHF database). *J Cardiovasc Med (Hagerstown)* 2011; **12**: 723-731 [PMID: 21873881 DOI: 10.2459/JCM.0b013e32834ae87e]
 - 92 **Sato N**, Gheorghiadu M, Kajimoto K, Munakata R, Minami Y, Mizuno M, Aokage T, Asai K, Sakata Y, Yumino D, Mizuno K, Takano T. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). *Am J Cardiol* 2013; **111**: 1019-1025 [PMID: 23312128 DOI: 10.1016/j.amjcard.2012.12.019]

- 93 **Lee SE**, Choi DJ, Yoon CH, Oh IY, Jeon ES, Kim JJ, Cho MC, Chae SC, Ryu KH, Oh BH. Improvement of hyponatraemia during hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry. *Heart* 2012; **98**: 1798-1804 [PMID: 23125248 DOI: 10.1136/heartjnl-2012-302334]
- 94 **Kearney MT**, Fox KA, Lee AJ, Brooksby WP, Shah AM, Flapan A, Prescott RJ, Andrews R, Batin PD, Eckberg DL, Gall N, Zaman AG, Lindsay HS, Nolan J. Predicting sudden death in patients with mild to moderate chronic heart failure. *Heart* 2004; **90**: 1137-1143 [PMID: 15367507 DOI: 10.1136/hrt.2003.021733]
- 95 **Rusinaru D**, Tribouilloy C, Berry C, Richards AM, Whalley GA, Earle N, Poppe KK, Guazzi M, Macin SM, Komajda M, Doughty RN. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis(†): Meta-Analysis Global Group in Chronic heart failure (MAGGIC). *Eur J Heart Fail* 2012; **14**: 1139-1146 [PMID: 22782968 DOI: 10.1093/eurjhf/hfs099]
- 96 **Deubner N**, Berliner D, Frey A, Güder G, Brenner S, Fenske W, Alolio B, Ertl G, Angermann CE, Störk S. Dysnatraemia in heart failure. *Eur J Heart Fail* 2012; **14**: 1147-1154 [PMID: 22820314 DOI: 10.1093/eurjhf/hfs115]
- 97 **Aaronson KD**, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; **95**: 2660-2667 [PMID: 9193435 DOI: 10.1161/01.CIR.95.12.2660]
- 98 **Kearney MT**, Nolan J, Lee AJ, Brooksby PW, Prescott R, Shah AM, Zaman AG, Eckberg DL, Lindsay HS, Batin PD, Andrews R, Fox KA. A prognostic index to predict long-term mortality in patients with mild to moderate chronic heart failure stabilised on angiotensin converting enzyme inhibitors. *Eur J Heart Fail* 2003; **5**: 489-497 [PMID: 12921810 DOI: 10.1016/S1388-9842(03)00053-9]
- 99 **Levy WC**, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006; **113**: 1424-1433 [PMID: 16534009 DOI: 10.1161/CIRCULATIONAHA.105.584102]
- 100 **Vazquez R**, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, Gonzalez-Juanatey JR, Cubero JM, Pastor L, Ordonez-Llanos J, Cinca J, de Luna AB. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J* 2009; **30**: 1088-1096 [PMID: 19240065 DOI: 10.1093/eurheartj/ehp032]
- 101 **O'Connor CM**, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fiuzat M, Rogers JG, Leier CV, Stevenson LW. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol* 2010; **55**: 872-878 [PMID: 20185037 DOI: 10.1016/j.jacc.2009.08.083]
- 102 **Rich MW**, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995; **333**: 1190-1195 [PMID: 7565975 DOI: 10.1056/NEJM199511023331806]
- 103 **Krumholz HM**, Chen YT, Bradford WD, Ceresse J. Variations in and correlates of length of stay in academic hospitals among patients with heart failure resulting from systolic dysfunction. *Am J Manag Care* 1999; **5**: 715-723 [PMID: 10538451]
- 104 **Amin A**, Deitelzweig S, Christian R, Friend K, Lin J, Lowe TJ. Healthcare resource burden associated with hyponatremia among patients hospitalized for heart failure in the US. *J Med Econ* 2013; **16**: 415-420 [PMID: 23336297 DOI: 10.3111/13696998.2013.766615]
- 105 **Konishi M**, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, Ashikaga T, Isobe M. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. *J Card Fail* 2012; **18**: 620-625 [PMID: 22858077 DOI: 10.1016/j.cardfail.2012.06.415]
- 106 **Callahan MA**, Do HT, Caplan DW, Yoon-Flannery K. Economic impact of hyponatremia in hospitalized patients: a retrospective cohort study. *Postgrad Med* 2009; **121**: 186-191 [PMID: 19332977 DOI: 10.3810/pgm.2009.03.1991]
- 107 **Shea AM**, Hammill BG, Curtis LH, Szczeh LA, Schulman KA. Medical costs of abnormal serum sodium levels. *J Am Soc Nephrol* 2008; **19**: 764-770 [PMID: 18216314 DOI: 10.1681/ASN.2007070752]
- 108 **Zilberberg MD**, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, Shorr AF. Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr Med Res Opin* 2008; **24**: 1601-1608 [PMID: 18426691 DOI: 10.1185/03007990802081675]
- 109 **Tada Y**, Nakamura T, Funayama H, Sugawara Y, Ako J, Ishikawa SE, Momomura S. Early development of hyponatremia implicates short- and long-term outcomes in ST-elevation acute myocardial infarction. *Circ J* 2011; **75**: 1927-1933 [PMID: 21617327 DOI: 10.1253/circj.CJ-10-0945]
- 110 **Tang Q**, Hua Q. Relationship between hyponatremia and in-hospital outcomes in Chinese patients with ST-elevation myocardial infarction. *Intern Med* 2011; **50**: 969-974 [PMID: 21532218 DOI: 10.2169/internalmedicine.50.4703]
- 111 **Maisel A**, Xue Y, Shah K, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand IS, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. Increased 90-day mortality in patients with acute heart failure with elevated copeptin: secondary results from the Biomarkers in Acute Heart Failure (BACH) study. *Circ Heart Fail* 2011; **4**: 613-620 [PMID: 21765124 DOI: 10.1161/CIRCHEARTFAILURE.110.960096]
- 112 **Miller WL**, Grill DE, Struck J, Jaffe AS. Association of hyponatremia and elevated copeptin with death and need for transplantation in ambulatory patients with chronic heart failure. *Am J Cardiol* 2013; **111**: 880-885 [PMID: 23276468 DOI: 10.1016/j.amjcard.2012.11.053]
- 113 **Goh KP**. Management of hyponatremia. *Am Fam Physician* 2004; **69**: 2387-2394 [PMID: 15168958]
- 114 **Fraser CL**, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997; **102**: 67-77 [PMID: 9209203 DOI: 10.1016/S0002-9343(96)00274-4]
- 115 **Assadi F**. Hyponatremia: a problem-solving approach to clinical cases. *J Nephrol* 2012; **25**: 473-480 [PMID: 22307436 DOI: 10.5301/jn.5000060]
- 116 **Pfennig CL**, Slovis CM. Sodium disorders in the emergency department: a review of hyponatremia and hypernatremia. *Emerg Med Pract* 2012; **14**: 1-26 [PMID: 23114652]
- 117 **Karp BI**, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine (Baltimore)* 1993; **72**: 359-373 [PMID: 8231786 DOI: 10.1097/00005792-199311000-00001]
- 118 **Kumar S**, Fowler M, Gonzalez-Toledo E, Jaffe SL. Central pontine myelinolysis, an update. *Neurol Res* 2006; **28**: 360-366 [PMID: 16687066 DOI: 10.1179/016164106X110346]
- 119 **Laureno R**, Karp BI. Myelinolysis after correction of hyponatremia. *Ann Intern Med* 1997; **126**: 57-62 [PMID: 8992924 DOI: 10.7326/0003-4819-126-1-199701010-00008]
- 120 **Martin RJ**. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 2004; **75** Suppl 3: iii22-iii28 [PMID: 15316041 DOI: 10.1136/jnnp.2004.045906]
- 121 **Graff-Radford J**, Fugate JE, Kaufmann TJ, Mandrekar JN,

- Rabinstein AA. Clinical and radiologic correlations of central pontine myelinolysis syndrome. *Mayo Clin Proc* 2011; **86**: 1063-1067 [PMID: 21997578 DOI: 10.4065/mcp.2011.0239]
- 122 **Hart BL**, Eaton RP. Images in clinical medicine. Osmotic myelinolysis. *N Engl J Med* 1995; **333**: 1259 [PMID: 7566003 DOI: 10.1056/NEJM199511093331905]
 - 123 **Albert NM**, Nutter B, Forney J, Slifcak E, Tang WH. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *J Card Fail* 2013; **19**: 1-9 [PMID: 23273588 DOI: 10.1016/j.cardfail.2012.11.007]
 - 124 **Dzau VJ**, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100**: 777-782 [PMID: 6372563 DOI: 10.7326/0003-4819-100-6-777]
 - 125 **Elisaf M**, Theodorou J, Pappas C, Siamopoulos K. Successful treatment of hyponatremia with angiotensin-converting enzyme inhibitors in patients with congestive heart failure. *Cardiology* 1995; **86**: 477-480 [PMID: 7585758 DOI: 10.1159/000176926]
 - 126 **Paterna S**, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, Giubilato A, Licata G. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2**: 305-313 [PMID: 10938493 DOI: 10.1016/S1388-9842(00)00094-5]
 - 127 **Licata G**, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomondo A, Paterna S. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003; **145**: 459-466 [PMID: 12660669 DOI: 10.1067/mhj.2003.166]
 - 128 **Thibonnier M**, Conarty DM, Preston JA, Wilkins PL, Bertin-Mattera LN, Mattera R. Molecular pharmacology of human vasopressin receptors. *Adv Exp Med Biol* 1998; **449**: 251-276 [PMID: 10026814 DOI: 10.1007/978-1-4615-4871-3_34]
 - 129 **Wallace AW**, Tunin CM, Shoukas AA. Effects of vasopressin on pulmonary and systemic vascular mechanics. *Am J Physiol* 1989; **257**: H1228-H1234 [PMID: 2801982]
 - 130 **Xu YJ**, Gopalakrishnan V. Vasopressin increases cytosolic free [Ca²⁺] in the neonatal rat cardiomyocyte. Evidence for V1 subtype receptors. *Circ Res* 1991; **69**: 239-245 [PMID: 2054937 DOI: 10.1161/01.RES.69.1.239]
 - 131 **Goldsmith SR**. The role of vasopressin in congestive heart failure. *Cleve Clin J Med* 2006; **73** Suppl 3: S19-S23 [PMID: 16970149 DOI: 10.3949/cjcm.73.Suppl_3.S19]
 - 132 **Nakamura Y**, Haneda T, Osaki J, Miyata S, Kikuchi K. Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin V(1A) receptor. *Eur J Pharmacol* 2000; **391**: 39-48 [PMID: 10720633]
 - 133 **Fukuzawa J**, Haneda T, Kikuchi K. Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. *Mol Cell Biochem* 1999; **195**: 93-98 [PMID: 10395073]
 - 134 **Thibonnier M**, Coles P, Thibonnier A, Shoham M. The basic and clinical pharmacology of nonpeptide vasopressin receptor antagonists. *Annu Rev Pharmacol Toxicol* 2001; **41**: 175-202 [PMID: 11264455 DOI: 10.1146/annurev.pharmtox.41.1.175]
 - 135 **Howl J**, Ismail T, Strain AJ, Kirk CJ, Anderson D, Wheatley M. Characterization of the human liver vasopressin receptor. Profound differences between human and rat vasopressin-receptor-mediated responses suggest only a minor role for vasopressin in regulating human hepatic function. *Biochem J* 1991; **276** (Pt 1): 189-195 [PMID: 2039469]
 - 136 **Tanoue A**, Ito S, Honda K, Oshikawa S, Kitagawa Y, Koshimizu TA, Mori T, Tsujimoto G. The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. *J Clin Invest* 2004; **113**: 302-309 [PMID: 14722621 DOI: 10.1172/JCI19656]
 - 137 **Nakamura K**, Aoyagi T, Hiroshima M, Kusakawa S, Mizutani R, Sanbe A, Yamauchi J, Kamohara M, Momose K, Tanoue A. Both V(1A) and V(1B) vasopressin receptors deficiency result in impaired glucose tolerance. *Eur J Pharmacol* 2009; **613**: 182-188 [PMID: 19375419 DOI: 10.1016/j.ejphar.2009.04.008]
 - 138 **Xu DL**, Martin PY, Ohara M, St John J, Pattison T, Meng X, Morris K, Kim JK, Schrier RW. Upregulation of aquaporin-2 water channel expression in chronic heart failure rat. *J Clin Invest* 1997; **99**: 1500-1505 [PMID: 9119993 DOI: 10.1172/JCI119312]
 - 139 **Schrier RW**, Sharma S, Shchekochikhin D. Hyponatraemia: more than just a marker of disease severity? *Nat Rev Nephrol* 2013; **9**: 37-50 [PMID: 23165296 DOI: 10.1038/nrne-ph.2012.246]
 - 140 **Berl T**, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 2010; **21**: 705-712 [PMID: 20185637 DOI: 10.1681/ASN.2009080857]
 - 141 **Udelson JE**, Orlandi C, Ouyang J, Krasa H, Zimmer CA, Frivold G, Haught WH, Meymandi S, Macarie C, Raef D, Wedge P, Konstam MA, Gheorghiade M. Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: an international, multicenter, randomized, placebo-controlled trial. *J Am Coll Cardiol* 2008; **52**: 1540-1545 [PMID: 19007589 DOI: 10.1016/j.jacc.2008.08.013]
 - 142 **Watanabe K**, Dohi K, Sugimoto T, Yamada T, Sato Y, Ichikawa K, Sugiura E, Kumagai N, Nakamori S, Nakajima H, Hoshino K, Machida H, Okamoto S, Onishi K, Nakamura M, Nobori T, Ito M. Short-term effects of low-dose tolvaptan on hemodynamic parameters in patients with chronic heart failure. *J Cardiol* 2012; **60**: 462-469 [PMID: 23068288 DOI: 10.1016/j.jicc.2012.09.002]
 - 143 **Matsuzaki M**, Hori M, Izumi T, Fukunami M. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). *Cardiovasc Drugs Ther* 2011; **25** Suppl 1: S33-S45 [PMID: 22120092 DOI: 10.1007/s10557-011-6304-x]
 - 144 **Fukunami M**, Matsuzaki M, Hori M, Izumi T. Efficacy and safety of tolvaptan in heart failure patients with sustained volume overload despite the use of conventional diuretics: a phase III open-label study. *Cardiovasc Drugs Ther* 2011; **25** Suppl 1: S47-S56 [PMID: 22120093 DOI: 10.1007/s10557-011-6348-y]
 - 145 **Gheorghiade M**, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, Orlandi C. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation* 2003; **107**: 2690-2696 [PMID: 12742979 DOI: 10.1161/01.CIR.0000070422.41439.04]
 - 146 **Gheorghiade M**, Gattis WA, O'Connor CM, Adams KF, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004; **291**: 1963-1971 [PMID: 15113814 DOI: 10.1001/jama.291.16.1963]
 - 147 **Rossi J**, Bayram M, Udelson JE, Lloyd-Jones D, Adams KF, O'Connor CM, Stough WG, Ouyang J, Shin DD, Orlandi C, Gheorghiade M. Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. *Acute Card Care* 2007; **9**: 82-86 [PMID: 17573581 DOI: 10.1080/17482940701210179]
 - 148 **Udelson JE**, McGrew FA, Flores E, Ibrahim H, Katz S, Koshkarian G, O'Brien T, Kronenberg MW, Zimmer C, Orlandi C, Konstam MA. Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. *J Am Coll Cardiol* 2007; **49**: 2151-2159 [PMID: 17543634 DOI: 10.1016/

- j.jacc.2007.01.091]
- 149 **Matsue Y**, Suzuki M, Seya M, Iwatsuka R, Mizukami A, Nagahori W, Ohno M, Matsumura A, Hashimoto Y. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure in high-risk population. *J Cardiol* 2013; **61**: 169-174 [PMID: 23159210 DOI: 10.1016/j.jcc.2012.08.020]
- 150 **Gheorghiade M**, Konstam MA, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, Udelsion JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007; **297**: 1332-1343 [PMID: 17384438 DOI: 10.1001/jama.297.12.1332]
- 151 **Konstam MA**, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, Udelsion JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007; **297**: 1319-1331 [PMID: 17384437 DOI: 10.1001/jama.297.12.1319]
- 152 **Hauptman PJ**, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, Krasa HB, Maggioni A, Ouyang J, Swedberg K, Zannad F, Zimmer C, Udelsion JE. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail* 2013; **19**: 390-397 [PMID: 23743487 DOI: 10.1016/j.cardfail.2013.04.001]
- 153 **Regen RB**, Gonzalez A, Zawodniak K, Leonard D, Quigley R, Barnes AP, Koch JD. Tolvaptan increases serum sodium in pediatric patients with heart failure. *Pediatr Cardiol* 2013; **34**: 1463-1468 [PMID: 23463133 DOI: 10.1007/s00246-013-0671-y]
- 154 **Ghali JK**, Zmily HD, Farah JO, Daifallah S. Lixivaptan, a non-peptide vasopressin V2 receptor antagonist for the potential oral treatment of hyponatremia. *IDrugs* 2010; **13**: 782-792 [PMID: 21046526]
- 155 **Abraham WT**, Shamshirsaz AA, McFann K, Oren RM, Schrier RW. Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol* 2006; **47**: 1615-1621 [PMID: 16630999 DOI: 10.1016/j.jacc.2005.11.071]
- 156 **Ghali JK**, Orlandi C, Abraham WT. The efficacy and safety of lixivaptan in outpatients with heart failure and volume overload: results of a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. *Eur J Heart Fail* 2012; **14**: 642-651 [PMID: 22510424 DOI: 10.1093/eurjhf/hfs051]
- 157 **Abraham WT**, Aranda JM, Boehmer JP, Elkayam U, Gilbert EM, Gottlieb SS, Hasenfuss G, Kukin M, Lowes BD, O'Connell JB, Tavazzi L, Feldman AM, Ticho B, Orlandi C. Rationale and design of the treatment of hyponatremia based on lixivaptan in NYHA class III/IV cardiac patient evaluation (THE BALANCE) study. *Clin Transl Sci* 2010; **3**: 249-253 [PMID: 20973922 DOI: 10.1111/j.1752-8062.2010.00217.x]
- 158 **Ali F**, Raufi MA, Washington B, Ghali JK. Conivaptan: a dual vasopressin receptor v1a/v2 antagonist [corrected]. *Cardiovasc Drug Rev* 2007; **25**: 261-279 [PMID: 17919259 DOI: 10.1111/j.1527-3466.2007.00019.x]
- 159 **Yatsu T**, Tomura Y, Tahara A, Wada K, Kusayama T, Tsukada J, Tokioka T, Uchida W, Inagaki O, Iizumi Y, Tanaka A, Honda K. Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V1A and V2 receptor antagonist, in dogs with pacing-induced congestive heart failure. *Eur J Pharmacol* 1999; **376**: 239-246 [PMID: 10448882 DOI: 10.1016/S0014-2999(99)00379-9]
- 160 **Verbalis JG**, Zeltser D, Smith N, Barve A, Andoh M. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvoletic hyponatremia: subgroup analysis of a randomized, controlled study. *Clin Endocrinol (Oxf)* 2008; **69**: 159-168 [PMID: 18034777 DOI: 10.1111/j.1365-2265.2007.03149.x]
- 161 **Chatterjee K**. Hyponatremia in heart failure. *J Intensive Care Med* 2009; **24**: 347-351 [PMID: 19850560 DOI: 10.1177/0885066609344941]
- 162 **Mao ZL**, Stalker D, Keirns J. Pharmacokinetics of conivaptan hydrochloride, a vasopressin V(1A)/V(2)-receptor antagonist, in patients with euvoletic or hypervolemic hyponatremia and with or without congestive heart failure from a prospective, 4-day open-label study. *Clin Ther* 2009; **31**: 1542-1550 [PMID: 19695403 DOI: 10.1016/j.clinthera.2009.07.011]
- 163 **Zeltser D**, Rosansky S, van Rensburg H, Verbalis JG, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvoletic and hypervolemic hyponatremia. *Am J Nephrol* 2007; **27**: 447-457 [PMID: 17664863 DOI: 10.1159/000106456]
- 164 **Annane D**, Decaux G, Smith N. Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvoletic or hypervolemic hyponatremia. *Am J Med Sci* 2009; **337**: 28-36 [PMID: 19057376 DOI: 10.1097/MAJ.0b013e31817b8148]
- 165 **Ghali JK**, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long WA, Smith N. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvoletic or hypervolemic hyponatremia. *J Clin Endocrinol Metab* 2006; **91**: 2145-2152 [PMID: 16522696 DOI: 10.1210/jc.2005-2287]
- 166 **Udelsion JE**, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, Ghali JK, Selaru P, Chanoine F, Pressler ML, Konstam MA. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001; **104**: 2417-2423 [PMID: 11705818 DOI: 10.1161/hc4501.099313]
- 167 **Goldsmith SR**, Elkayam U, Haught WH, Barve A, He W. Efficacy and safety of the vasopressin V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure: a dose-ranging pilot study. *J Card Fail* 2008; **14**: 641-647 [PMID: 18926434 DOI: 10.1016/j.cardfail.2008.06.003]
- 168 **Goldsmith SR**, Gilbertson DT, Mackedanz SA, Swan SK. Renal effects of conivaptan, furosemide, and the combination in patients with chronic heart failure. *J Card Fail* 2011; **17**: 982-989 [PMID: 22123359 DOI: 10.1016/j.cardfail.2011.08.012]
- 169 Direct Healthcare Professional Communication on the risk of increases in serum sodium with tolvaptan (Samsca). Available from: URL: <http://www.cbg-meb.nl/NR/rdonlyres/BC53C10C-62AF-44B3-A43A-CE7A39A231B4/0/120326DHPCSamscaEN.pdf>. Accessed at 08-06-2013
- 170 **Torres VE**, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407-2418 [PMID: 23121377 DOI: 10.1056/NEJMoa1205511]
- 171 U.S. Food and Drug Administration. Drug Safety Communication 30-4-2013. Available from: URL: <http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm>. Accessed at 24-07-2013

P- Reviewers Esposito P, Giuffrè M, Liu T **S- Editor** Wen LL
L- Editor A **E- Editor** Wang CH



Coronary-cameral fistulas in adults (first of two parts)

Salah AM Said, Rikke HM Schiphorst, Richard Derksen, Lodewijk Wagenaar

Salah AM Said, Department of Cardiology, Hospital Group Twente, 7555 DL Hengelo, The Netherlands

Rikke HM Schiphorst, Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, 7513 ER Enschede, The Netherlands

Richard Derksen, Department of Cardiology, Rijnstate Hospital, 6815 AD Arnhem, The Netherlands

Lodewijk Wagenaar, Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, 7513 ER Enschede, The Netherlands

Author contributions: Said SAM, Schiphorst RHM and Derksen R contributed to this paper; Schiphorst RHM collected the data; Derksen R provided the case with coronary cameral fistula; Said SAM prepared the manuscript and the literature review; Wagenaar L revised the manuscript; All authors have approved the final review of the paper.

Correspondence to: Salah AM Said, MD, PhD, FESC, Department of Cardiology, Hospital Group Twente, Geerdinksweg 141, 7555 DL Hengelo, The Netherlands. samsaid@home.nl
Telephone: +31-74-2905286 Fax: +31-74-2905289

Received: May 24, 2013 Revised: July 5, 2013

Accepted: August 28, 2013

Published online: September 26, 2013

Abstract

This is a case series and review of the literature adding 11 new cases. Coronary-cameral fistulas (CCFs) are infrequent anomalies which are in general co-incidentally found during diagnostic coronary angiography (CAG). To delineate the characteristics of congenital and acquired CCFs in adults, we performed a PubMed search for papers dealing with congenital or acquired CCFs in adults. Publications on coronary-vascular fistulas or paediatric subjects were not included. From the world literature, a total of 243 adult patients were identified who had congenital (65%) or acquired (35%) CCFs. In this review, which is part one of a two-part series on CCFs, we describe and discuss the congenital fistulas, give an overview on the published literature and report details of our own series of 11 patients with MMFs and solitary macro CCFs. Of the congenital group, 85% were small or large solitary macro CCFs (cut-off

1.5 mm) and 15% were coronary artery-ventricular multiple micro-fistulas (MMFs). Apical hypertrophic cardiomyopathy was reported in some of the reviewed subjects with MMFs (3/24 = 13%) but not was seen in our own series. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators (ICD) were implanted in 2/24 (8%) of subjects, especially when extensive micro-fistulisations were involved. None of the patients of our own series required an ICD, as the MMFs were of limited size. Congenital or acquired CCFs in adults are infrequent anomalies having a wide spectrum of clinical presentation may varies from asymptomatic to severely devastating states requiring different treatment modalities.

© 2013 Baishideng. All rights reserved.

Key words: Congenital heart defect; Congenital coronary artery-ventricular multiple micro-fistulas; Congenital coronary-cameral fistulas; Coronary angiography

Core tip: A case series and review of the literature adding 11 new cases. A total of 243 adult patients were identified who had congenital (65%) or acquired (35%) coronary-cameral fistulas. Of the congenital group, 56% were small or large solitary macro CCFs (cut-off 1.5 mm) and 9% were coronary artery-ventricular multiple micro-fistulas (MMFs). T-waves were inverted in the anterior precordial leads in 38% and apical hypertrophic cardiomyopathy was reported in 13% of the subjects. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators were implanted in 8% of subjects, especially when extensive micro-fistulisations were involved.

Said SAM, Schiphorst RHM, Derksen R, Wagenaar L. Coronary-cameral fistulas in adults (first of two parts). *World J Cardiol* 2013; 5(9): 329-336 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/329.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.329>

INTRODUCTION

Coronary-cameral fistulas (CCFs) are defined as single or multiple, small or large direct communications that arise from one or more coronary arteries and enter into one of the four cardiac chambers (right atrium (RA) and ventricle (RV) and left atrium (LA) and ventricle (LV))^[1,2]. These arterio-venous or arterio-arterial connection, giving rise to left-right or left-left shunts, respectively. In general, CCFs are invariably congenital^[3,4], but they may also have an acquired etiology^[5] which will be addressed in the second part of this review. The congenital entity can be distinguished into coronary artery-ventricular multiple micro-fistulas^[2,6-9] or small or large solitary macro fistulas^[1], the latter making up the vast majority^[10].

Eleven adult patients with congenital multiple micro-fistulas (MMFs) and solitary macro CCFs from our own patient population are presented and discussed. The present part I of the review is confined to congenital CCFs discusses development, clinical presentation, diagnosis and therapy of this infrequent entity and finally review the published literature.

LITERATURE RESEARCH

PubMed was searched for the terms "CCFs", "congenital" and "acquired" combined with "adult". English and non-English publications were screened for both types of congenital and acquired CCFs in an adult population. The definitions used for congenital and acquired traumatic accidental or iatrogenic CCFs were adopted from previous publications^[1,11,12]. The following criteria were stipulated to include homogenous subsets for analysis: congenital solitary macro (small and large) coronary cameral fistulas or coronary artery-ventricular multiple micro-fistulas MMFs (first part) and acquired traumatic accidental, iatrogenic or spontaneous CCFs (second part). Manuscripts were checked for completeness and a meticulous search was performed for fistula termination into any of the cardiac chambers. Review subjects were tabulated according to the etiology, age, gender, clinical presentations, complications and management. Patients with coronary-vascular fistulas (CVFs) and publications considering a paediatric population were not included. Data of 11 adult patients with congenital MMFs and solitary macro CCFs are presented (Table 1).

Definitions

The definitions offered by Chiu *et al.*^[1] and Gupta-Malhotra^[12] were applied.

Congenital coronary-cameral fistulas: Small or large, single or multiple fistulous connections originating from any of the coronary arteries and terminating into any of the cardiac chambers (RA, RV, LA and LV)^[1,12,13].

Solitary macro-fistulas: These are single or multiple, small (< 1.5 mm) or large fistulas (> 1.5 mm), originating mainly from the proximal segment of a coronary artery

and entering into a cardiac chamber^[1,10,11].

Coronary artery-left: Ventricular MMFs: These are multiple small channels originating from the mid or distal part of one or more coronary arteries fistulating more often into the left than the right ventricular cavity^[2,6-9].

Statistical analysis

Continuous variables are expressed as means and ranges and categorical variables were presented as percentages.

RESULTS

From the published literature, 243 adult patients were selected with 65% congenital (159/243) and 35% acquired (84/243) CCFs. Of the congenital group, 56% (135/243) were solitary macro (large or small) coronary artery-cameral fistulas and 9% (24/243) coronary artery-ventricular multiple micro-fistulas. The congenital subgroup will be presented here (first part). This review focuses on and pertains to different aspects with regard to etiology, clinical presentation and management (Tables 2 and 3).

Literature review

Congenital coronary artery-cameral fistulas: Sixty-five percent ($n = 159$) of the 243 CCFs were congenital^[9,13-32]. Fifteen percent (24/159) of whom, (15 females, 63%) had multiple micro-fistulas (MMFs). The mean age was 62.7 years (range 39-85); 9 patients had known hypertension and 2 diabetes mellitus. The origin of the fistulas was the left coronary artery (LCA) in 23, the right coronary artery (RCA) in 8 and from the left sinus of Valsalva in 1 of the fistulas. Unilateral fistulas were present in 15, bilateral fistulas in 8 and multilateral fistulas in 1 of the patients. Origin from the distal segment of the involved coronary artery was documented in 5 of the subjects. The fistulas terminated into the LV in 24 patients and into the RV in 1 patient.

The main clinical presentations were angina pectoris ($n = 10$), chest pain ($n = 10$), dyspnoea ($n = 4$), supra-ventricular tachycardia ($n = 3$), acute coronary syndrome ($n = 3$), ventricular fibrillation ($n = 1$), syncope ($n = 3$), fatigue ($n = 1$), congestive heart failure ($n = 1$), family history of sudden death ($n = 1$) and abnormal ECG ($n = 1$). Among the diagnostic modalities implemented were besides ECG and conventional coronary angiography, ambulatory Holter ECG monitoring ($n = 4$), exercise tolerance testing ($n = 7$) (1 was non-diagnostic and 6 were positive for ischemia), transthoracic echocardiography ($n = 17$), cardiovascular magnetic resonance (CMR) ($n = 4$), myocardial perfusion test ($n = 11$) (5 were negative and 6 were positive for ischemia) and multi-detector computed tomography (MDCT) ($n = 1$). Sinus rhythm was demonstrated in 22, atrial flutter in 1 and supraventricular tachycardia in 2 of the patients. Significant coronary artery disease was present in only 2 patients. Dilated and tortuous coronary arteries were reported in 6 (25%) subjects.

The major treatment modality was conservative medi-

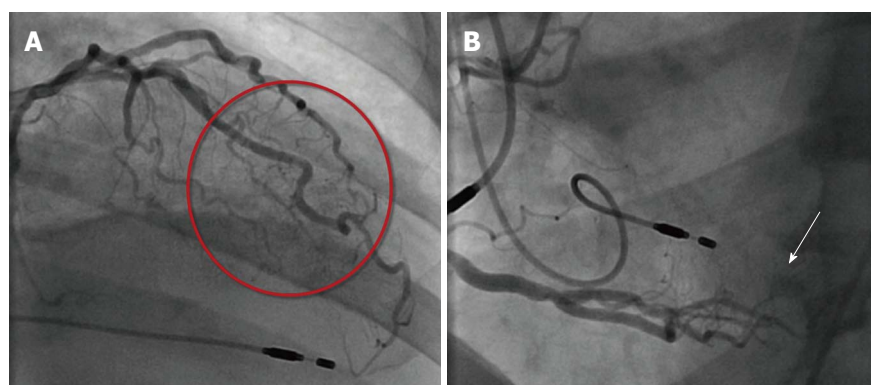


Figure 1 From the distal segment. A: The left anterior descending coronary artery/diagonal branch multiple micro-fistulas (red circle) to the left ventricle (LV) lumen are visible; B: The right coronary artery multiple fistulas (arrow) to the LV cavity. Dual endocardial pacing leads are appreciated.

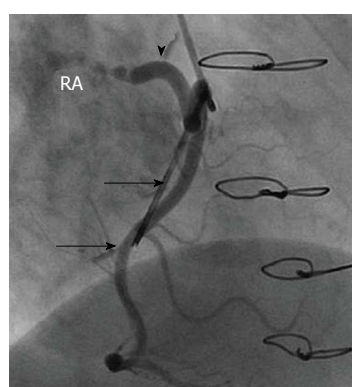


Figure 2 Dilated fistulous vessel (arrow head) originating from the proximal segment of the right coronary artery (solid arrow) and terminating into the right atrium. The mitral valve ring is visible (hollow arrow). RA: Right atrium.

cal management (CMM) with pharmacological agents including β -blockers ($n = 14$), angiotensin converting enzyme inhibitors ($n = 6$), calcium channel blockers ($n = 5$), aspirin ($n = 4$), nitrates ($n = 5$), oral anticoagulants ($n = 2$), lipid lowering agent ($n = 2$), angiotensin-receptor blocker ($n = 1$), clopidogrel ($n = 1$) and Ivabradine ($n = 1$). In two patients successful percutaneous coronary intervention (PCI) procedures for fistula-bearing and non-fistula-bearing vessels were performed for the relief of complaints. In another 2 of the 3 patients presented with syncope, with extensive MMFs, a prophylactic implantable cardioverter-defibrillator (ICD) was implanted. One patient refused further treatment. Concomitant congenital anomalies were single coronary artery ($n = 1$) and cor triatriatum ($n = 1$) as well as apical hypertrophic cardiomyopathy ($n = 3$).

Solitary macro-fistulas CCFs^[11,33-35]: A total of 135 patients with solitary congenital small or large CCFs (135/159; 85%) were reviewed and included. They were part of a previous publication^[11]. Mean age of these patients was 46.2 years (range 18-85), and 50% were females. CCFs with single (unilateral) origin were 87% and CCFs with multiple (bilateral and multilateral) in 13% of subjects. In fistulas with single or multiple origins, the share from the RCA or LCA to the fistula formation was equally distributed.

Fistula-related complications such as aneurysmal formation (18.2%), infective endocarditis (8%) and pericar-

dial effusion (2.9%) were reported. None of the patients with CCFs developed a myocardial infarction (MI). It was observed that the presence of CCFs predisposed to the development of infective endocarditis as compared to the patients with CVFs.

Current own series

There were 11 patients with congenital MMFs mean age of 61.5 years (range 44-79) (6 females) having 16 MMFs (Figure 1A and B) and 1 patient with congenital solitary *macro* CCF (Table 1) (Figure 2). The clinical presentations were chest pain ($n = 4$), angina pectoris ($n = 4$), non-ST elevation MI ($n = 1$) and dyspnoea on exertion ($n = 2$). None of the patients had an infective endocarditis. The concomitant disorders and risk factors were transient ischemic attack ($n = 2$), sick sinus syndrome ($n = 1$), aortic and mitral regurgitation ($n = 2$), previous MI ($n = 3$), diabetes mellitus ($n = 1$), chronic obstructive pulmonary disease ($n = 2$), arterial hypertension ($n = 3$), obstructive sleep apnoea syndrome ($n = 1$), glomerulonephritis ($n = 1$), coronary artery disease ($n = 3$) [coronary artery bypass grafting ($n = 1$), percutaneous coronary intervention ($n = 1$)] and aortic or mitral valve replacement ($n = 2$). The ECG depicted sinus rhythm in 10 and atrial fibrillation in 1 patient without T wave inversion in the anterior chest leads.

Transthoracic ($n = 10$) and transesophageal ($n = 2$) echocardiography were performed. Of these, 6 were normal, 1 showed left ventricular hypertrophy, 1 demonstrated moderate LV systolic function, 1 had severe mitral regurgitation and 1 showed hypokinesia of the inferior wall. Three patients underwent myocardial perfusion tests (1 was negative and 2 were positive for ischemic changes). MDCT was performed in 1 patient and revealed normal coronary arteries without identification of the MMFs. Bilateral fistulas were seen in 6 and unilateral fistulas in 5 patients. They originated from the RCA ($n = 7$) and from the left coronary artery ($n = 9$) and terminated into the left ventricle in 15 and the right ventricle in 1 of the fistulas. In 1 patient the CCF originated from the RCA and terminated into the right atrium. He underwent mitral valve repair and surgical ligation of the fistula. Significant coronary artery disease was found in 3 subjects, of whom 2 had one vessel disease (VD) and 1 had 3-VD, while 8 were free of atherosclerotic lesions.

Conservative medical management was applied in all

Table 1 Data of adult patients with congenital coronary artery-ventricular multiple micro-fistulas and solitary macro fistulas

| Case Age/gender | Clinical presentation | Previous history | Concomitant disorders | MMFs fistula | ECG | Echocardiography | Myocardial perfusion test | Management |
|--------------------|--------------------------|------------------------------|----------------------------|--|------------|---|------------------------------|-----------------|
| 1, 44M | CP | TIA/Lyme disease | - | D-LV Unilateral 0-VD | SR | N | - | CMM |
| 2, 73M | CP | SSS | COPD/RR/GN | D-LV dRCA-LV Bilateral 0-VD (Figure 1 A and B) | SR | N | Apical ischemic changes | CMM, DDDR |
| 3, 62F | NSTEMI | - | - | D-LV dRCA-LV Bilateral 0-VD | SR | N | - | CMM |
| 4, 45F | CP | - | RR | D-LV dRCA-LV Bilateral 0-VD | SR | N | - | CMM |
| 5, 65F | AP | Old IMI/ breast carcinoma | COPD/RR/ hypothyroidism | Cx-LV dRCA-LV Bilateral 1-VD | SR old IMI | Hypokinesia inferior | Mid baso-inferior EF 60% | CMM, PCI RCA |
| 6, 62M | AP | - | RR | D-LV Unilateral 3-VD | SR | Anterolateral hypokinesia and apical akinesia | - | CMM, CABG |
| 7, 70F | CP | TIA | - | AL-LV Unilateral 0-VD | SR | N | Negative | CMM |
| 8, 65M | AP | Old IMI | DM/OSAS | RCA-RV Unilateral 1-VD | SR icRBBB | N | - | CMM |
| 9, 79F | AP | - | RR | LAD-LV RCA-LV Bilateral 0-VD | SR LVH | LVH | - | CMM |
| 10, 64F | DOE | Old ILMI | AF/AR/epilepsy | Cx-LV RCA-LV Bilateral 0-VD | AF LBBB | Moderate LV systolic function | - | CMM, AVR |
| 11, 52M | DOE | MR/MVP/PAF | RR | Solitary macro CCF RCA-RA | SR RBBB | Severe MR | - | MVR/PVI/SL |

AR: Aortic regurgitation; AL: Anterolateral branch; AP: Angina pectoris; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CP: Chest pain; CMM: Conservative medical management; COPD: Chronic obstructive pulmonary disease; Cx: Circumflex coronary artery; d: Distal; D: Diagonal branch; DM: diabetes mellitus; DOE: Dyspnoea on exertion; EF: Ejection fraction; F: Female; GN: Glomerulonephritis; ic: Incomplete; ILMI: Inferolateral myocardial infarction; IMI: Inferior myocardial infarction; LAD: Left anterior descending coronary artery; LBBB: Left bundle branch block; LV: Left ventricle; LVH: Left ventricular hypertrophy; M: Male; MMFs: Coronary artery-ventricular multiple micro-fistulas; MR: Mitral regurgitation; MVP: Mitral valve plasty; MVR: Mitral valve replacement; N: Normal; NSTEMI: Non-ST elevation myocardial infarction; OSAS: Obstructive sleep apnoea syndrome; PCI: Percutaneous coronary intervention; PAF: Paroxysmal atrial fibrillation; PVI: Pulmonary vein isolation; RA: Right atrium; RBBB: Right bundle branch block; RCA: Right coronary artery; RR: Hypertension; SL: Surgical ligation; SR: Sinus rhythm; SSS: Sick sinus syndrome; TIA: Transient ischemic attack; VD: Vessel disease.

patients, which consisted of aspirin ($n = 9$), lipid lowering drug ($n = 6$), β -blocker ($n = 5$), angiotensin-receptor blocker ($n = 5$), calcium channel blocker ($n = 2$), angiotensin-converting enzyme inhibitor ($n = 3$) and an oral anticoagulant ($n = 1$).

COMMENTS

Congenital coronary cameral fistulas encompass a group of solitary macro (small or large) or multiple micro coronary cameral communications that are increasingly recognized due to sophistication and wide spread application of non-invasive and invasive angiographic imaging modalities^[10,30,36]. Both entities, solitary macro and multiple micro coronary cameral fistulas, have rarely been reported in a single symptomatic patient^[37]. Congenital CCFs may develop due to a disturbance of embryonic development with partial persistence of the embryonic intertrabecular vascular network^[9,38]. Congenital MMFs terminate mainly into the LV, and in congenital solitary macro CCFs the outflow sites are the right atrium, coronary sinus, right ventricle, left atrium and left ventricle^[11]. Congenital coronary cameral fistulas vary widely in their clinical presentation. While most patients are asymp-

tomatic or have non-specific complaints, bilateral MMFs draining into the LV may remain clinically silent^[39] or may produce diastolic murmur^[40] and diastolic volume overload, mimicking aortic valve insufficiency.

Congenital coronary artery-ventricular multiple micro-fistulas

Among the reviewed subjects, only a single asymptomatic patient with (silent MMFs) was assessed because of an abnormal ECG at rest (1/24; 4%). Moreover, the clinical diagnosis of congenital MMFs can be difficult because as laboratory tests and ECG manifestations are non-specific and the imaging modalities may sometimes be non-interpretable. Moreover, the diagnostic capabilities of CMR and MDCT have failed to demonstrate congenital MMFs^[22,24]. On the contrary, MDCT is a readily valuable tool for the detection of congenital solitary macro CCFs^[41].

ECG findings

Of great interest are the ECG findings in the 24 literature review subjects, of whom sinus rhythm was depicted in the majority of cases (23/24; 96%) and atrial flutter in a single patient (4%), T-waves were inverted in the anterior

Table 2 Results of literature review of 243 subjects with coronary-cameral fistulas (65% congenital and 35% acquired)

| Condition | <i>n</i> (%) female % | Mean age /range yr | Etiology | Management |
|-----------|----------------------------|--------------------|----------------------------------|--|
| MMFs | 24 (15) Female 63% | 62.7 (39-85) | Congenital part I | CMM 100% |
| CCFs | 135 (85) Female 50% | 46.2 (18-85) | Congenital part I | CMM 22%, SL 56%, PTE 22% |
| CCFs | 7 (3) Female 0% | 24.1 (17-38) | Accidental part II | Emergent surgical intervention 100% |
| CCFs | 8 (3.3) Female 38% | 55.8 (46-73) | Iatrogenic (pacing) part II | CMM Spontaneous resolution |
| CCFs | 7 (3) Female 29% | 66.5 (58-75) | Iatrogenic (PCI) part II | CMM |
| CCFs | 25 (10.3) Female 22% | 50.8 (43-64) | Iatrogenic (EMB) part II | CMM Spontaneous resolution 27% |
| CCFs | 5 (2.1) Female 20% | 61 (40-78) | Iatrogenic (surgery) part II | CMM |
| CCFs | 20 (8.2) Female unknown | 45 (32-74) | Iatrogenic (SM) part II | CMM 11%, PTE 11% Spontaneous resolution 78% |
| CCFs | 12 (5) Female 0% | 61 (29-75) | Spontaneous (post-MI) part II | CMM 60%, SL 30% Spontaneous resolution 10% |

CCFs: Coronary cameral fistulas; CMM: Conservative medical management; EMB: Endomyocardial biopsy; MI: Myocardial infarction; MMFs: Coronary artery-ventricular multiple micro-fistulas; PCI: Percutaneous coronary intervention; PTE: Percutaneous therapeutic embolization; SL: Surgical ligation; SM: Septal myectomy.

Table 3 Fistula characteristics in congenital and acquired coronary-cameral fistulas in adults

| | Congenital CCFs (0.07%) ^[1] | | | Acquired CCFs | | | |
|-------------------------|---|---|---|---------------------------------|------------------------------|------------------------|--------------------------------|
| | Solitary Macro CCFs (large ≥ 1.5 mm) | Solitary Macro CCFs (small ≤ 1.5 mm) | Multiple Micro MMFs | Post-SM | Post-EMB | Post-pacing | Blunt or sharp chest trauma |
| Prevalence/incidence | 0.03% ^[1] | 0.04% ^[1] | 0.09% ^[1] | 19%-23% ^[5,56] | 28%-23.2% ^[57-60] | Unknown | Unknown |
| Fistula characteristics | | | | | | | |
| Origin | Proximal segment of coronary arteries | | Distal segment of coronary arteries LV > RV | Septal perforator LV | RCA>LAD> Cx RV | LCA | RCA or LAD |
| Termination | Any cardiac chamber | | | | | Any cardiac chamber | RV or LV |
| Management | CMM/SL/PTE | | CMM (100%) Incidentally ICD | SC (78%)/ CMM 11% PTE 11% | SC (27%) | CMM/SC | Surgical repair (100%) |

CMM: Conservative medical management; EMB: Endomyocardial biopsy; LA: Left atrium; LAD: Left anterior descending artery; LCA: Left coronary artery; LV: Left ventricle; PTE: Percutaneous therapeutic embolization; RA: Right atrium; RCA: Right coronary artery; RV: Right ventricle; SC: Spontaneous closure; SL: Surgical ligation; SM: Septal myectomy; CCFs: Coronary-cameral fistulas.

precordial leads in 9 (38%) subjects, and 3 of them had LVH and apical hypertrophic cardiomyopathy (AHCM). Therefore, congenital MMFs may be included in the differential diagnosis of anterior precordial T-wave inversion. Reversible^[42] or permanent^[43] T-wave inversions either associated with multilateral or unilateral congenital MMFs have been reported. However, in our own series, none of the patients showed T-wave inversion in the precordial leads and T-wave inversions in the anterior chest wall leads were absent in patients with solitary macro CCFs.

Shunt characteristics

The magnitude of the shunt of MMFs may be considerable. In MMFs, Cottier *et al*^[44], measured a reduction of

28% of total coronary blood flow during recumbent bicycle exercise whereas greater cardiac vein flow increased by 66% in the presence of typical anginal pain and ischemic LV dysfunction. Furthermore, Meissner *et al*^[45] measured coronary artery flow velocity with intravascular Doppler guide wire for hemodynamic quantification of shunt flow, which revealed a left-to-left shunt of 23% of the total LV output. Oh *et al*^[43] assessed the hemodynamic significance of unilateral MMFs by fractional flow reserve (FFR) and found no evidence of hemodynamic compromise. These investigations may provide interesting data but were not performed either in the reviewed subjects (*n* = 24) or in our own current series (*n* = 11). Non-invasive, myocardial perfusion tests may, incidental-

ly, demonstrate reversible perfusion defects in congenital MMFs^[46] as was depicted in 2 patients of our own series and in 6 of the reviewed subjects.

Incidence of congenital MMFs

The angiographic incidence of congenital MMFs in the Chinese adult population is estimated at 0.09% with slight female predominance (58%) as was found in the review subjects (63%) and in our own series (60%). Origin from mid or distal segment of the LAD is highly prevalent, occurring in 88% of patients. Symptoms ensued in the 6th decade of life. Our findings were similar and in accordance with the findings of others^[1]. The mean age in the reviewed subjects was 62.7 years and, in our own series of 10 patients with MMFs, it was 69.1 years.

Associated disorders

Concomitant AHCM was detected in 13% of the reviewed MMFs subjects and was not observed in any of the solitary CCFs patients^[23-25]. AHCM, a variant of hypertrophic cardiomyopathy, is rare among Caucasians but more common in the Asian population, especially in the Japanese^[25]. This association between MMFs has recently been observed not only with AHCM^[47,48] but also with non-compaction cardiomyopathy (NCCM)^[49]. Alternatively, one can assume and may speculate that an early common pathway may exist, yet not detected, for their development. In addition, pre-existent congenital multilateral fistulas (from all 3 epicardial coronary arteries) have been reported in a heart transplant recipient, which were detected after transplantation during routine coronary angiography^[50].

Autopsy findings

Autopsy of patients with congenital multilateral MMFs to both ventricles depicted insignificant atherosclerotic coronary artery disease, cardiac dilatation and hypertrophy, and dilated coronary arteries with histologically, numerous small vessels of various diameters across the myocardium with patchy subendocardial fibrosis^[51,52]. This was in accordance with the necropsy findings of Honey and Lau in solitary *macro* congenital CCFs^[53,54], the only difference being the presence of a single fistulous vessel.

Congenital solitary macro coronary-cameral fistulas

On the other hand, congenital solitary *macro* coronary-cameral fistulas (small and large)^[11,33-35] showed an incidence of 0.07%. Of these, 0.03% were large and 0.04% were small CCFs^[1]. CCFs with single (unilateral) origin presented 87% and CCFs with multiple (bilateral and multilateral) origin 13% of subjects. Fistula-related complications such as aneurysmal formation (18.2%), infective endocarditis (8%) and pericardial effusion (2.9%) were reported. None of the CCFs patients developed MI, however, and subjects with CCFs were susceptible for the development of infective endocarditis compared to

the group presented with coronary-vascular fistulas^[11]. In bilateral CCFs, hemodynamic significance was assessed by FFR and ischemia was ruled out^[43]. In our patient with congenital solitary macro fistula from RCA to RA, the fistulous vessel was surgically ligated during redo of mitral valve repair for mitral valve prolapse accompanied with symptomatic severe mitral regurgitation.

Supraventricular (SV) and ventricular arrhythmias have been associated with coronary cameral fistulas (solitary or MMFs). In our own series ($n = 11$), atrial fibrillation/flutter (AF) was present in only 1 patient (10%), and AF and supraventricular tachycardia were present in 2 of the MMFs reviewed subjects (8%). However, neither ventricular arrhythmias nor infective endocarditis were reported in the MMFs subjects.

Myocardial infarction

In the absence of atherosclerosis, MI may develop in the presence of MMFs originating from all 3 coronary arteries terminating into both ventricles^[55]. One patient of our own series (1/10; 10%) sustained inferior wall MI, in which the fistula-bearing RCA was involved.

Management

In all 24 reviewed subjects, conservative medical management was conducted including β -blockers^[17], calcium channel blockers^[18] and sotalol^[19] as was previously reported^[1]. While congenital MMFs are generally treated conservatively, congenital solitary CCFs may undergo percutaneous occlusion or surgical ligation in the presence of substantial significant shunts. Only in few of the reviewed subjects, having morphologically extensive MMFs, a prophylactic ICD was implanted (8%). None of the patients in our own series required an ICD as the MMFs were not widespread.

CONCLUSION

In almost 40% of the reviewed subjects with congenital coronary artery-ventricular multiple micro-fistulas, T-wave inversion was present in the precordial leads of the electrocardiogram in association with or without apical hypertrophic cardiomyopathy. For adult patients with congenital coronary artery-ventricular multiple micro-fistulas, conservative medical management is the treatment of choice. Due to the multiplicity of the fistulas, they are inaccessible for percutaneous or surgical intervention which may be considered in large solitary coronary-cameral macro fistulas with hemodynamically significant shunts. Limited data were reported on adult patients with solitary CCFs. Within the entity of CCFs, each subtype has its own specific characteristics such as origin, termination of fistulas and treatment options. In addition, there were few reports on the implantation of an ICD in patients with extensive congenital MMFs in association with syncope.

ACKNOWLEDGEMENTS

During the preparation of the manuscript, the assistance of the librarian, Mrs. A. Geerdink, and Mr. D. Maas of hospital group Twente is gratefully acknowledged. The authors thank Prof. dr. Clemens von Birgelen, Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands for his intellectual suggestions for the manuscript.

REFERENCES

- 1 Chiu CZ, Shyu KG, Cheng JJ, Lin SC, Lee SH, Hung HF, Liou JY. Angiographic and clinical manifestations of coronary fistulas in Chinese people: 15-year experience. *Circ J* 2008; **72**: 1242-1248 [PMID: 18654007 DOI: 10.1253/circj.72.1242]
- 2 Said SA, van der Werf T. Dutch survey of congenital coronary artery fistulas in adults: coronary artery-left ventricular multiple micro-fistulas multi-center observational survey in the Netherlands. *Int J Cardiol* 2006; **110**: 33-39 [PMID: 16181690 DOI: 10.1016/j.ijcard.2005.07.009]
- 3 Brito FS, Vianna CB, Caixeta AM, Rati MA, Perin MA, Ramires JA, Martinez Filho EE. Single coronary arteries: two cases with distinct and previously undescribed angiographic patterns. *J Invasive Cardiol* 1999; **11**: 430-434 [PMID: 10745567]
- 4 Reeder GS, Tajik AJ, Smith HC. Visualization of coronary artery fistula by two-dimensional echocardiography. *Mayo Clin Proc* 1980; **55**: 185-189 [PMID: 7354655]
- 5 Sgalambro A, Olivotto I, Rossi A, Nistri S, Baldini K, Baldi M, Stefano P, Antonucci D, Garbini F, Cecchi F, Yacoub MH. Prevalence and clinical significance of acquired left coronary artery fistulas after surgical myectomy in patients with hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg* 2010; **140**: 1046-1052 [PMID: 20471659 DOI: 10.1016/j.jtcvs.2010.02.020]
- 6 Chia BL, Chan AL, Tan LK, Ng RA, Chiang SP. Coronary artery-left ventricular fistula. *Cardiology* 1981; **68**: 167-179 [PMID: 7317886 DOI: 10.1159/000173278]
- 7 Nawa S, Miyachi Y, Shiba T, Toshino N, Hayashi K, Tamesue K, Yamamoto H, Ota T, Shimizu N. Clinical and angiographic analysis of congenital coronary artery fistulae in adulthood. Is there any new trend? *Jpn Heart J* 1996; **37**: 95-104 [PMID: 8632629 DOI: 10.1536/ihj.37.95]
- 8 Stierle U, Giannitsis E, Sheikhzadeh A, Potratz J. Myocardial ischemia in generalized coronary artery-left ventricular micro-fistulae. *Int J Cardiol* 1998; **63**: 47-52 [PMID: 9482144 DOI: 10.1016/S0167-5273(97)00280-5]
- 9 Cartoni D, Salvini P, De Rosa R, Cortese A, Nazzaro MS, Tanzi P. Images in cardiovascular medicine. Multiple coronary artery-left ventricle micro-fistulae and spongy myocardium: the eagerly awaited link? *Circulation* 2007; **116**: e81-e84 [PMID: 17638934 DOI: 10.1161/CIRCULATIONAHA.106.684811]
- 10 Zenooz NA, Habibi R, Mammen L, Finn JP, Gilkeson RC. Coronary artery fistulas: CT findings. *Radiographics* 2009; **29**: 781-789 [PMID: 19448115 DOI: 10.1148/rg.293085120]
- 11 Said SA. Current characteristics of congenital coronary artery fistulas in adults: A decade of global experience. *World J Cardiol* 2011; **3**: 267-277 [PMID: 21876777 DOI: 10.4330/wjc.v3.i8.267]
- 12 Gupta-Malhotra M. Coronary artery fistulas. Available from: URL: <http://emedicine.medscape.com/article/895749-overview>, 2010
- 13 Papazoglou PD, Mitsibounas D, Nanas JN. Left anterior descending coronary artery-left ventricular fistula presenting as unstable angina and syncope. *Int J Cardiol* 2004; **96**: 121-122 [PMID: 15203273 DOI: 10.1016/j.ijcard.2003.04.057]
- 14 Iadanza A, del Pasqua A, Fineschi M, Pierli C. Three-vessel left-ventricular micro-fistulization syndrome: a rare case of angina. *Int J Cardiol* 2004; **96**: 109-111 [PMID: 15203269 DOI: 10.1016/j.ijcard.2003.04.052]
- 15 Cakar MA, Tatli E. Coronary-cameral fistula with angina pectoris. *Case Rep Med* 2010; **2010**: 362532 [PMID: 21209744 DOI: 10.1155/2010/362532]
- 16 Brueck M, Bandorski D, Vogt PR, Kramer W, Heidt MC. Myocardial ischemia due to an isolated coronary fistula. *Clin Res Cardiol* 2006; **95**: 550-553 [PMID: 16830266 DOI: 10.1007/s00392-006-0418-3]
- 17 Durán A, Michelis V, Díaz P, Lujambio M, Kuster F, Lluberas R, Romero C. Evaluación de pacientes portadores de fistulas coronario-ventriculares múltiples. *Revista Médica del Uruguay* 2003; **19**: 237-241
- 18 Macfadyen RJ, Varma C, Anderson RH. Multiple microvessels extending from the coronary arteries to the left ventricle in a middle aged female presenting with ischaemic chest pain: a case report. *J Med Case Rep* 2007; **1**: 177 [PMID: 18067687 DOI: 10.1186/1752-1947-1-177]
- 19 Sambu N, Sharma R, Kalra PR. Multiple coronary to left ventricular fistulae. *Eur J Echocardiogr* 2009; **10**: 352 [PMID: 18755698 DOI: 10.1093/ejehocard/jen229]
- 20 Jang SN, Her SH, Do KR, Kim JS, Yoon HJ, Lee JM, Jin SW. A case of congenital bilateral coronary-to-right ventricle fistula coexisting with variant angina. *Korean J Intern Med* 2008; **23**: 216-218 [PMID: 19119260 DOI: 10.3904/kjim.2008.23.4.216]
- 21 Lozano I, Batalla A, Rubin J, Avanzas P, Martin M, Moris C. Sudden death in a patient with multiple left anterior descending coronary artery fistulas to the left ventricle. *Int J Cardiol* 2008; **125**: e37-e39 [PMID: 17391787 DOI: 10.1016/j.ijcard.2006.11.247]
- 22 Uechi Y, Higa K. [Single left coronary artery with micro-fistula communicating with the left ventricle: a case report]. *J Cardiol* 2007; **50**: 199-203 [PMID: 17941196]
- 23 Hong GR, Choi SH, Kang SM, Lee MH, Rim SJ, Jang YS, Chung NS. Multiple coronary artery-left ventricular micro-fistulae in a patient with apical hypertrophic cardiomyopathy: a demonstration by transthoracic color Doppler echocardiography. *Yonsei Med J* 2003; **44**: 710-714 [PMID: 12950129]
- 24 Dresios C, Apostolakis S, Tzortzis S, Lazaridis K, Gardikiotis A. Apical hypertrophic cardiomyopathy associated with multiple coronary artery-left ventricular fistulae: a report of a case and review of the literature. *Eur J Echocardiogr* 2010; **11**: E9 [PMID: 19995797 DOI: 10.1093/ejehocard/jep196]
- 25 Alyan O, Ozeke O, Golbasi Z. Coronary artery-left ventricular fistulae associated with apical hypertrophic cardiomyopathy. *Eur J Echocardiogr* 2006; **7**: 326-329 [PMID: 15994129 DOI: 10.1016/j.euje.2005.06.006]
- 26 Rana O, Swallow R, Senior R, Greaves K. Detection of myocardial ischaemia caused by coronary artery-left ventricular fistulae using myocardial contrast echocardiography. *Eur J Echocardiogr* 2009; **10**: 175-177 [PMID: 18682407 DOI: 10.1093/ejehocard/jen215]
- 27 Arat N, Gurel OM, Biyikoglu FS, Duru E. Coronary artery to left ventricular fistula demonstrated by transthoracic echocardiography. *Eur J Echocardiogr* 2008; **9**: 121-122 [PMID: 17604226]
- 28 Padfield GJ. A case of coronary cameral fistula. *Eur J Echocardiogr* 2009; **10**: 718-720 [PMID: 19414488 DOI: 10.1093/ejehocard/jep049]
- 29 Caliskan K, Balk AH, Wykrzykowska JJ, van Geuns RJ, Seruys PW. How should I treat an unusual referral for heart transplantation? *EuroIntervention* 2010; **5**: 861-865 [PMID: 20142204 DOI: 10.4244/EIJV5I7A144]
- 30 Heper G, Kose S. Increased myocardial ischemia during nitrate therapy: caused by multiple coronary artery-left

- ventricle fistulae? *Tex Heart Inst J* 2005; **32**: 50-52 [PMID: 15902822]
- 31 **Nabais S**, Salomé N, Brandão A, Simões A, Marques J, Costa J, Basto L, Costeira A, Correia A. Coexistence of coronary cameral fistulae and cor triatriatum sinister in an elderly patient. *Eur J Echocardiogr* 2008; **9**: 712-715 [PMID: 18490293 DOI: 10.1093/ejehoccard/jen140]
 - 32 **Hartmann M**, van Es J, Galjee MA, van der Burgh PH, de Bruin WI, Said SA, von Birgelen C. Cardiac imaging in a symptomatic patient with multiple coronary artery-left ventricular microfistulae. *Heart Vessels* 2007; **22**: 428-431 [PMID: 18044003 DOI: 10.1007/s00380-007-0992-y]
 - 33 **Kadir I**, Ascione R, Linter S, Bryan AJ. Intraoperative localisation and management of coronary artery fistula using transesophageal echocardiography. *Eur J Cardiothorac Surg* 1999; **16**: 364-366 [PMID: 10554861 DOI: 10.1016/S1010-7940(99)00209-2]
 - 34 **Brussee H**, Gasser R. Images in clinical medicine. Fistula connecting the left main coronary artery with the right atrium in a marathon runner. *N Engl J Med* 2002; **346**: 904 [PMID: 11907290 DOI: 10.1056/NEJMcim980664]
 - 35 **Hamada M**, Kubo H, Matsuoka H, Kokubu T, Oosuga Y, Joh T. Myocardial infarction complicating surgical repair of left coronary-right ventricular fistula in an adult. *Am J Cardiol* 1986; **57**: 372-374 [PMID: 3946242 DOI: 10.1016/0002-9149(86)90935-5]
 - 36 **Choi SI**, Kim SK, Shin JH, Lee JU, Kim KS, Lim HK, Kim JH, Lee BH. A case of coronary-artery-left ventricular microfistulae demonstrated by transthoracic Doppler echocardiography. *J Cardiovasc Ultrasound* 2006; **4**: 157-160
 - 37 **van de Water JM**, van Houwelingen KG, von Birgelen C. [Multiple rare causes of typical angina pectoris in a single patient]. *Rev Esp Cardiol* 2007; **60**: 196 [PMID: 17338884 DOI: 10.1157/13099466]
 - 38 **Black IW**, Loo CK, Allan RM. Multiple coronary artery-left ventricular fistulae: clinical, angiographic, and pathologic findings. *Cathet Cardiovasc Diagn* 1991; **23**: 133-135 [PMID: 2070401 DOI: 10.1002/ccd.1810230216]
 - 39 **Martens J**, Haseldonckx C, Van de Werf F, De Geest H. Silent left and right coronary artery - left ventricular fistulas: an unusual prominent Thebesian system. *Acta Cardiol* 1983; **38**: 139-142 [PMID: 6603087]
 - 40 **Yokawa S**, Watanabe H, Kurosaki M. Asymptomatic left and right coronary artery-left ventricular fistula in an elderly patient with a diastolic murmur only. *Int J Cardiol* 1989; **25**: 244-246 [PMID: 2807616 DOI: 10.1016/0167-5273(89)90117-4]
 - 41 **Tan KT**, Chamberlain-Webber R, McGann G. Characterisation of coronary artery fistula by multi-slice computed tomography. *Int J Cardiol* 2006; **111**: 311-312 [PMID: 16256220 DOI: 10.1016/j.ijcard.2005.07.070]
 - 42 **Jung Y**, Kim HJ, Yoon CH. Severe form of persistent thebesian veins presenting as ischemic heart disease. *Korean Circ J* 2012; **42**: 714-717 [PMID: 23170102 DOI: 10.4070/kcj.2012.42.10.714]
 - 43 **Oh JH**, Lee HW, Cha KS. Hemodynamic significance of coronary cameral fistula assessed by fractional flow reserve. *Korean Circ J* 2012; **42**: 845-848 [PMID: 23323123 DOI: 10.4070/kcj.2012.42.12.845]
 - 44 **Cottier C**, Kiowski W, von Bertrab R, Pfisterer M, Burkart F. Multiple coronary arteriocameral fistulas as a cause of myocardial ischemia. *Am Heart J* 1988; **115**: 181-184 [PMID: 3336972 DOI: 10.1016/0002-8703(88)90537-6]
 - 45 **Meissner A**, Lins M, Herrmann G, Simon R. Multiple coronary artery-left ventricular fistulae: haemodynamic quantification by intracoronary Doppler ultrasound. *Heart* 1997; **78**: 91-93 [PMID: 9290410]
 - 46 **Suchon E**, Kostkiewicz M, Szot W. Left coronary arteriovenous malformation with fistulous connections to the left and right ventricles. *Nucl Med Rev Cent East Eur* 2012; **15**: 80-82 [PMID: 23047578 DOI: 10.5603/NMR.2012.0014]
 - 47 **Yılmaz S**, Uçar FM, Gölbaş 1 Z, Tüfekçioğlu O. Coronary artery-left ventricular micro-fistulas associated with apical hypertrophic cardiomyopathy. *Anadolu Kardiyol Derg* 2012; **12**: E28 [PMID: 22728741]
 - 48 **Roubille F**, Micheau A, Vernhet-Kovacsik H. Multiple coronary-left ventricular fistulae associated with apical hypertrophic cardiomyopathy: coronary angiogram compared to coronary scan and cardiac magnetic resonance scan. *Cardiol J* 2011; **18**: 702-703 [PMID: 22113763 DOI: 10.5603/CJ.2011.0039]
 - 49 **Wilhelm J**, Heinroth K, Stoevesandt D, Werdan K, Plehn A. Non-compaction cardiomyopathy with diffuse left coronary artery fistulae as a rare cause of congestive heart failure. *Eur Heart J* 2013; **34**: 12 [PMID: 22719021 DOI: 10.1093/eurheartj/ehs178]
 - 50 **Vermeulen T**, Haine S, Paelinck BP, Rodrigus IE, Vrints CJ, Conraads VM. Coronary artery-pulmonary artery fistula in a heart-transplanted patient. *Eur J Echocardiogr* 2010; **11**: 80-81 [PMID: 19749198 DOI: 10.1093/ejehoccard/jep113]
 - 51 **Shiota K**, Kinoshita M, Kimura N, Kurosu H, Kuwahara K, Mori C. Multiple fistulae of coronary arteries to both ventricles. *Jpn Heart J* 1988; **29**: 741-746 [PMID: 3221449 DOI: 10.1536/ihj.29.741]
 - 52 **Rose AG**. Multiple coronary arterioventricular fistulae. *Circulation* 1978; **58**: 178-180 [PMID: 647882 DOI: 10.1161/01.CIR.58.1.178]
 - 53 **Honey M**. Coronary arterial fistula. *Br Heart J* 1964; **26**: 719-722 [PMID: 14213035 DOI: 10.1136/hrt.26.5.719]
 - 54 **Lau G**. Sudden death arising from a congenital coronary artery fistula. *Forensic Sci Int* 1995; **73**: 125-130 [PMID: 7797185 DOI: 10.1016/0379-0738(95)01721-T]
 - 55 **McLellan BA**, Pelikan PC. Myocardial infarction due to multiple coronary-ventricular fistulas. *Cathet Cardiovasc Diagn* 1989; **16**: 247-249 [PMID: 2706682 DOI: 10.1002/ccd.1810160408]
 - 56 **Chenzbraun A**, Pinto FJ, Meyer B, Stinson EB, Popp RL. Frequency of acquired coronary-cameral fistula after ventricular septal myectomy in hypertrophic cardiomyopathy. *Am J Cardiol* 1993; **71**: 1244-1246 [PMID: 8480661 DOI: 10.1016/0002-9149(93)90661-U]
 - 57 **Sandhu JS**, Uretsky BF, Zerbe TR, Goldsmith AS, Reddy PS, Kormos RL, Griffith BP, Hardesty RL. Coronary artery fistula in the heart transplant patient. A potential complication of endomyocardial biopsy. *Circulation* 1989; **79**: 350-356 [PMID: 2644055 DOI: 10.1161/01.CIR.79.2.350]
 - 58 **Fitchett DH**, Forbes C, Guerraty AJ. Repeated endomyocardial biopsy causing coronary arterial-right ventricular fistula after cardiac transplantation. *Am J Cardiol* 1988; **62**: 829-831 [PMID: 3048074 DOI: 10.1016/0002-9149(88)91237-4]
 - 59 **Gascuña R**, de Lombera F, Fernández S, Santos M, Delgado J, Escribano P, Gómez MA. Left circumflex coronary artery-to-left atrium fistulas detected by transesophageal echocardiography in heart transplant recipients. *Echocardiography* 2000; **17**: 443-445 [PMID: 10979018 DOI: 10.1111/j.1540-8175.2000.tb01161.x]
 - 60 **Saraiva F**, Matos V, Gonçalves L, Antunes M, Providência LA. Complications of endomyocardial biopsy in heart transplant patients: a retrospective study of 2117 consecutive procedures. *Transplant Proc* 2011; **43**: 1908-1912 [PMID: 21693299 DOI: 10.1016/j.transproceed.2011.03.010]

P- Reviewer Pauliks L S- Editor Wen LL L- Editor A
E- Editor Lu YJ



Relationship between vitamin D deficiency and cardiovascular disease

Yan-Chiou Ku, Mu-En Liu, Chang-Sheng Ku, Ta-Yuan Liu, Shoa-Lin Lin

Yan-Chiou Ku, Nursing Department, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

Mu-En Liu, Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

Chang-Sheng Ku, Division of Cardiology, Kaohsiung Veterans General Hospital-Tainan Branch, Tainan 710, Taiwan

Ta-Yuan Liu, Ta Yuan Polyclinic, Taipei 106, Taiwan

Shoa-Lin Lin, Division of Cardiology, Department of Internal Medicine, Yuan's General Hospital, Kaohsiung 802, Taiwan

Shoa-Lin Lin, National Defense Medicine Center, Taipei 114, Taiwan

Author contributions: Lin SL and Ku YC planned the structure of the article and were the primary writers; Liu ME and Ku CS contributed to the development and editing of the manuscript; Da-Yuan Liu assisted in data collection and prepared figure 1.

Supported by (in part) the Kaohsiung Veterans General Hospital, No. VGHKS100-032

Correspondence to: Shoa-Lin Lin, MD, Division of Cardiology, Department of Internal Medicine, Yuan's General Hospital, No.162, Cheng-Gong 1st Rd., Lingya District, Kaohsiung 802, Taiwan. lingoodman@yahoo.com.tw

Telephone: +886-7-73351121 Fax: +886-7-73505220

Received: June 24, 2013 Revised: August 26, 2013

Accepted: September 3, 2013

Published online: September 26, 2013

mentation can reduce cardiovascular risk. Given the low cost, safety, and demonstrated benefit of higher 25-hydroxyvitamin D levels, vitamin D supplementation should become a public health priority for combating common and costly chronic cardiovascular diseases.

© 2013 Baishideng. All rights reserved.

Key words: Cardiovascular disease; Morbidity; Mortality; Review; Vitamin D

Core tip: We performed an extensive review to determine whether vitamin D supplementation reduces cardiovascular risk. Only double-blind, placebo- and randomized-controlled trials were included. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are underway to address this issue. These results from these studies will likely not be available for another 3-5 years. At this stage, we propose recommendations for preventing of vitamin D deficiency and conclude that there is a benefit to vitamin D supplementation.

Abstract

Epidemiological studies have found that low 25-hydroxyvitamin D levels may be associated with coronary risk factors and adverse cardiovascular outcomes. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. In this review, we analyze the association between vitamin D supplementation and the reduction in cardiovascular disease. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are needed to investigate whether oral vitamin D supple-

Ku YC, Liu ME, Ku CS, Liu TY, Lin SL. Relationship between vitamin D deficiency and cardiovascular disease. *World J Cardiol* 2013; 5(9): 337-346 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/337.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.337>

INTRODUCTION

Vitamin D is likely one of the oldest hormones, having existed for at least 750 million years^[1]. Studies have demonstrated that low levels of vitamin D represent a problem of global dimensions^[2-13]. A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that approximately 50% and 60% of the elderly in

North America and the rest of the world, respectively, do not have satisfactory vitamin D levels^[14]. The situation is similar in younger subjects. Reasons for this widespread deficiency remain unclear but are likely related to factors such as urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decreases in the cutaneous production of vitamin D with age. Epidemiological pooled analysis of prospective observational studies of diverse populations demonstrates that hypovitaminosis D is associated with a modest risk of cardiovascular events^[15-20]. The amount of vitamin D obtained from dietary sources is generally viewed as too low in many regions of the world to have an effect on the vitamin D status at the population level^[14]. This review introduces the general concept of vitamin D, defines vitamin D deficiency, evaluates the relationship between vitamin D deficiency and cardiovascular disease, proposes a recommendation for preventing vitamin D deficiency and offers conclusions.

NATURE OF VITAMIN D

There are 2 major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in plants and can be consumed in fortified foods or as a supplement. Vitamin D3 is obtained from either dietary sources or through the conversion of 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation^[10,21]. Vitamin D3 from the skin is bound to the vitamin D-binding protein, whereas vitamin D2 and vitamin D3 from diet are bound to vitamin D-binding protein and lipoproteins. Both forms are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D; D represents D2 or D3]. However, 25(OH)D is inactive and requires hydroxylation in the kidney to form 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol]. Calcitriol [1,25(OH)2D] maintains calcium in the blood and has an array of effects on the body's organs. Calcitriol acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton^[10,19,22,23]. Although 1,25(OH)2D is considered to be the active form of vitamin D, its levels in the serum do not correlate with overall vitamin D status, whereas the 25(OH)D levels is a more clinically relevant marker^[24]. Vitamin D activity is measured in μg of 25(OH)D (1 μg = 40 International Units, IU). The minimum desirable serum level of 25(OH)D has been suggested to be 20-30 ng/mL according to the consensus conference^[14].

Dietary sources of vitamin D are limited to fatty fish (wild or farm salmon, mackerel, tuna fish, sardines, and cod liver oil) and products fortified with vitamin D, which include dairy products, cereals, margarine, flour, and orange juice^[24,25].

DEFINITION OF VITAMIN D DEFICIENCY

Several measures have been used to define vitamin D

deficiency, insufficiency, and adequacy. A 25(OH)D of < 20 ng/mL is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D^[26]. Parathyroid hormone levels begin to reach their nadir when the 25(OH)D levels are > 30 ng/mL^[27,28]. Intestinal calcium absorption in adults is maximized when 25(OH)D is > 30 ng/mL^[29]. Thus, many experts define vitamin D deficiency, insufficiency, and sufficiency as levels of < 20, 21 to 29, and > 30 ng/mL, respectively. To achieve these levels, a minimum of 1000 IU of vitamin D2 or vitamin D3 is needed daily when sun exposure is either unavailable or inadequate for producing vitamin D3, such as during the winter or when a sunscreen is used^[30,31].

In the United States, Europe, India, Asia, Middle East, New Zealand, and Australia, vitamin D deficiency is common in pregnant women, newborns, young and adolescent children, and the elderly^[32-37]. Serum vitamin D levels are lower in European young adults than in North American young adults during winter^[37]. Vitamin D deficiency is especially common in people of color or who avoid sunlight^[38].

RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Numerous studies have found high rates of CV diseases among patients with lower levels of vitamin D. More recently, low levels of 25(OH)D have been linked to the presence of cardiovascular disease, hypertension, and the metabolic syndrome^[39-42]. It is still unclear whether supplementation with vitamin D is beneficial to cardiovascular health. To this end, we have performed an extensive survey of published studies. Only double-blinded and randomized controlled trials (RCT) were included. The databases searched include MEDLINE, EMBASE, and PUBMED from January 1966 to May 2013. We selected search terms that capture generic and specific words relevant to the exposure and outcome on the basis of Medical Subject Heading terms and text words from a priori identified key articles. The terms selected for vitamin D were the following: "vitamin D intake, vitamin D supplement, calcidiol, calcitriol, cholecalciferol, and ergocalciferol". The terms selected for cardiovascular disease (CVD) were the following: "cardiovascular disease, ischemic heart disease, coronary artery disease, cardiovascular mortality, myocardial infarction, and stroke". We restricted the search to articles published in English and studies of humans that double-blinded and RCT. We applied the same search strategy to each database. Because of the limitations in assessing cause-effect relationships, we excluded ecological, cross-sectional, and retrospective case-control studies. By screening abstracts, we also excluded case reports, studies of vitamin D combination treatment (*e.g.*, combined vitamin D + calcium supplementation), and studies that did not assess the use of

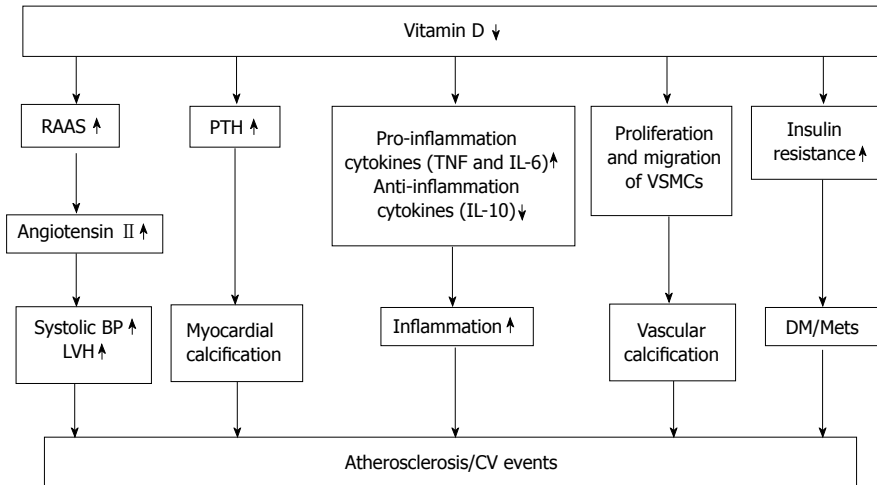


Figure 1 Potential mechanisms for cardiovascular effects of vitamin D deficiency. The data were modified from References 51, 52, and 54. RAAS: Renin-angiotensin-aldosterone system; PTH: Parathyroid hormone; BP: Blood pressure; LVH: Left ventricular hypertrophy; TNF: Tumor necrosis factor; IL-6: Interleukin-6; VSMCs: Vascular smooth muscle cells; DM: Diabetes mellitus; MetS: Metabolic syndrome; CV: Cardiovascular.

vitamin D supplementations. We retrieved articles that passed the abstract screening test for a full-text review, and we further excluded review articles, editorials, or letters to editors as well as studies lacking a comparison between participants who received vitamin D supplementation and non-recipients.

After the abstract screening and full-text review, we selected 19 eligible articles. Ten articles favored beneficial cardiovascular effects after supplementation with vitamin D (Table 1)^[43-52]. A trial in the United States randomly assigned 283 African American subjects into a 4-arm, double-blind trial of placebo, 1000, 2000, or 4000 IU of oral cholecalciferol per day. At baseline and 3 mo, the systolic and diastolic pressure and 25(OH)D were measured. This study found that although cholecalciferol supplementation did not affect the diastolic pressure ($P = 0.37$), the difference in systolic pressure between baseline and 3 mo was +1.7 mmHg for those receiving placebo, -0.66 mmHg for 1000 U/d, -3.4 mmHg for 2000 U/d, and -4.0 mmHg for 4000 U/d of cholecalciferol (-1.4 mmHg for each additional 1000 U/d of cholecalciferol; $P = 0.04$). For each 1-ng/mL increase in the plasma 25(OH)D, there was a significant 0.2-mmHg reduction in the systolic pressure ($P = 0.02$)^[43]. Larsen *et al.*^[45] investigated the effect of 3000 IU vitamin D per day for 20 wk in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients residing in Denmark. Vitamin D supplementation reduced the systolic pressure significantly. In a post-hoc subgroup analysis of 92 subjects with baseline p-25(OH)D levels < 32 ng/mL, significant decreases in the 24-h systolic and diastolic BP were observed in response to cholecalciferol supplementation^[45]. Similar reports^[44,46-52] relevant to “vitamin D supplementation produces beneficial cardiovascular effects” are summarized in Table 1.

In contrast, the remaining nine articles did not find a cardioprotective effect of vitamin D supplementation (Table 2)^[53-61]. In Ireland, 202 healthy adults (20-40 years

old) and 192 healthy elders (≥ 64 years old) were recruited and received vitamin D supplementation at a dosage of 0, 200, 400, or 600 IU for 22 wk. Serum 25(OH)D, intact parathyroid hormone, systolic and diastolic blood pressure, fasting lipids, glucose and insulin, high-sensitivity CRP, matrix metalloproteinase-9, and its inhibitor (tissue inhibitor metalloproteinase-1) were measured at baseline and 22 wk later, which was the endpoint. This study revealed that there were no significant effects of supplementation on the CVD risk biomarkers in either age group^[56]. Wood *et al.*^[60] conducted a parallel-group, double-blind, placebo- and randomized-controlled trial in 305 healthy postmenopausal women to test whether daily doses of vitamin D3 at 400 or 1000 IU/d for 1 year affected the conventional markers of cardiovascular disease risk. The serum lipid profile (total, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides; and apolipoproteins A-1 and B100), insulin resistance (homeostatic model assessment), inflammatory biomarkers (high-sensitivity C-reactive protein, IL-6, and soluble intracellular adhesion molecule-1), and blood pressure were studied. They found that dietary vitamin D supplementation is unlikely to reduce CVD risk factors, such as serum lipid profile, insulin resistance, inflammatory biomarkers, and blood pressure^[60]. Additional reports that did not find a cardioprotective effect of vitamin D supplementation are summarized in Table 2^[53-55,57-59,61].

MECHANISMS FOR THE CARDIOVASCULAR EFFECTS OF VITAMIN D DEFICIENCY

The results of recent nationwide investigations showed an association between low 25(OH)D levels and important cardiovascular risk factors^[40,62], and further supported the findings of preclinical and clinical investigations that demonstrated positive effects of vitamin D and its

Table 1 Double-blind, placebo- and randomized-controlled trials that favor supplement with vitamin D may have a beneficial cardiovascular effects

| Ref. | Country | Participants | Intervention | Duration of follow-up | Results |
|--|----------------|---|--|-----------------------|--|
| Forman <i>et al</i> ^[43] | United States | 283 African-American subjects | Oral vitamin D3 (cholecalciferol, 1000, 2000, or 4000 IU), or placebo per day for 3 mo | 6 mo | Reduction in systolic pressure. |
| Harris <i>et al</i> ^[44] | United States | 45 African-American adults | 60000 IU monthly oral vitamin D(3) or placebo for 16 wk | 16 wk | Effective at improving vascular endothelial function |
| Larsen <i>et al</i> ^[45] | Denmark | 112 Hypertensive patients | 75 µg (3000 IU) cholecalciferol per day or placebo for 20 wk | 20 wk | Significant decreases in systolic blood pressure |
| Lind <i>et al</i> ^[46] | Sweden | 65 subjects with impaired glucose tolerance | Alphacalcidol (0.75 microgram daily) or placebo over 12 wk | 12 wk | Significant reduction of blood pressure |
| Lind <i>et al</i> ^[47] | Sweden | 65 Hypertensive patients with primary hyperparathyroidism | Alphacalcidol, (1 microgram daily) or placebo over 6 mo | 6 mo | Significant reduction of blood pressure |
| Longenecker <i>et al</i> ^[48] | United States | 45 HIV-infected individuals with vitamin D deficiency | Vitamin D3 4000 IU daily or placebo for 12 wk | 12 wk | Modestly improved cholesterol |
| Salehpour <i>et al</i> ^[49] | Iran. | 77 healthy premenopausal overweight and obese women | Vitamin D (25 µg/d as cholecalciferol) or the placebo group for 12 wk | 12 wk. | Significantly improvement of HDL-cholesterol, apoA-I concentrations and LDL-cholesterol: apoB-100 ratio. |
| Shedeed ^[50] | Egypt | 80 infants with CHF | Vitamin D(3) oral drops or placebo oral drops for 12 wk | 12 wk | Significant improvement of HF score, LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction%, and myocardial performance index. |
| Witham <i>et al</i> ^[51] | United Kingdom | 58 stroke patients | 100000 units of a single oral dose of vitamin D2 or placebo | 16 wk | Short-term improvement in endothelial function (Flow mediated dilatation was significantly higher in the intervention group at 8 wk) |
| Zittermann <i>et al</i> ^[52] | Germany | 200 healthy overweight subjects in a weight-reduction program | Vitamin D (83 microg/d) or placebo for 12 mo | 12 mo | Significant improvement of cardiovascular disease risk markers |

LV: Left-ventricular; CHF: Congestive heart failure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; IU: International units.

analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth^[63-69]. Together, these findings strongly suggest that 25(OH)D has beneficial effects, some involving the cardiovascular system, that are independent of calcium metabolism. Several mechanisms might be responsible for the protective effect of calcitriol on atherosclerotic lesions and vascular calcification (Figure 1). First, vascular smooth cells express vitamin D receptors. Calcitriol inhibits proliferation of these cells with an acute influx of calcium into the cells^[69]. Second, a lack of calcitriol results in an increase in the serum parathyroid hormone (PTH) levels. Excess PTH levels may at least in part promote cardiovascular disease by increased the cardiac contractility and myocardial calcification^[70]. Third, experimental studies have shown that calcitriol suppresses the release of the inflammatory cytokines such as tissue necrosis factor- α (TNF- α), IL-6, and IL-10. There is now increasing evidence that inflammatory processes play an important role in the development of a vascular insult^[71-88]. Fourth, calcitriol is a negative endocrine regulator of the rennin-angiotensin-aldosterone system (RAAS) The RAAS plays a central role in the regulation of blood pressure, electrolytes, and volume hemostasis. Calcitriol treatment reduces blood pressure, plasma rennin activity and angiotensin II levels^[89]. Fifth, vascular smooth muscle cell proliferation

and migration, as well as the osteogenic processes may contribute to the vascular calcification, which may eventually cause the thrombogenesis^[90]. Sixth, vitamin D plays a role in the insulin sensitivity, which has a role in diabetes and in metabolic syndrome^[78,90].

Essential hypertension is related to several disturbances in the systemic and cellular calcium metabolism. Extracellular ionized or ultrafiltrable calcium levels are decreased while intracellular cytosolic calcium concentrations are increased. Dietary calcium intake is often lower and renal calcium loss is higher in hypertensive than in normotensive subjects. Epidemiologic studies have demonstrated an inverse association between serum 25(OH)D levels and diastolic blood pressure^[91]. Moreover, Afro-Americans have a significantly higher prevalence of diastolic hypertension and have lower 25(OH)D levels compared with white Americans^[88,92,93]. In clinical trials, the daily administration of 5 µg of vitamin D showed no effects on blood pressure in normotensive subjects. However, some studies have demonstrated a blood pressure lowering effect with 0.75 or 1.0 µg vitamin D/d in hypertensive patients^[94]. Short-term supplementation with 20 µg of vitamin D/d significantly reduced diastolic blood pressure. A reduction in the diastolic and systolic blood pressure was observed in mildly hypertensive patients after 6 wk of UV-B exposure^[88,94]. A normalization

Table 2 Double-blind, placebo- and randomized-controlled trials that do not favor supplementation with vitamin D

| Ref. | Country | Participants | Intervention | Duration of follow-up | Results |
|--|----------------|---|--|-----------------------|---|
| Gepner <i>et al</i> ^[53] | United States | 114 post-menopausal women | Vitamin D3 2500 IU or placebo, daily for 4 mo | 4 mo | No significant effects of vitamin D supplementation to reduce cardiovascular disease risk |
| Jorde <i>et al</i> ^[54] | Norway | 330 overweight or obese subjects | Vitamin D [cholecalciferol, vitamin D(3)] 40000 IU, vitamin D 20000 IU, or placebo per week for 1 yr | 1 yr | No significant effect of vitamin D on glucose tolerance, blood pressure or serum lipids |
| Marckmann <i>et al</i> ^[55] | Denmark | 52 chronic kidney disease patients with vitamin D deficiency | 40000 IU of cholecalciferol orally per week for 8-wk | 8 wk | No significant impact on functional markers and plasma concentrations of biomarkers related to cardiovascular disease |
| Muldowney <i>et al</i> ^[56] | Ireland | 394 healthy participants | Cholecalciferol at doses of 0, 5, 10, or 15 µg/d (0-600 IU) for 22 wk | 22 wk | No significant effects of supplementation on CVD risk biomarkers |
| Scragg <i>et al</i> ^[57] | United Kingdom | 95 elderly adults | A single oral dose of 2.5 mg cholecalciferol or placebo | 5 wk | No significant effect of vitamin D supplementation to change blood pressure or serum cholesterol |
| Stricker <i>et al</i> ^[58] | Switzerland | 62 peripheral arterial disease patients with vitamin D deficiency | A single, oral supplementation of 100000 IU vitamin D3 or placebo | 1 mo | Unlikely to influence endothelial function, arterial stiffness, coagulation and inflammation |
| Thadhani <i>et al</i> ^[59] | United States | 227 patients with chronic kidney disease | Paricalcitol or placebo over 48 wk | 48 wk | Unlikely to alter left ventricular mass index or improve certain measures of diastolic dysfunction |
| Wood <i>et al</i> ^[60] | United Kingdom | 305 healthy postmenopausal women | A daily capsule of 400 or 1000 IU vitamin D(3) or placebo for 12 mo | 12 mo | Unlikely to reduce CVD risk factors |
| Yiu <i>et al</i> ^[61] | Hong Kong | 100 patients with type 2 DM | Oral vitamin D (5000 IU/d) or placebo per day for 12 wk | 12 wk | No significant effect on vascular function or serum biomarkers of inflammation and oxidative stress |

CVD: Cardiovascular disease; IU: International units; DM: Diabetes mellitus.

of the enhanced intracellular calcium levels seems to be an important measure for reducing blood pressure, which can explain the therapeutic effects of calcium-channel blockers in hypertensive patients^[95,96]. Low adenylate cyclase activity can result in a decreased calcium re-uptake into the sarcoplasmic reticulum and can contribute to an accumulation of intracellular free calcium and to an increase in vascular reactivity and blood pressure^[97]. Activity of the intracellular adenylate cyclase is calcitriol-dependent and improvement of the activity of this enzyme may thus reduce free cellular calcium concentrations.

Hyperlipidemia, diabetic mellitus, and an increase in blood coagulation factors, blood viscosity, and leukocyte counts are important risk factors for the development of arteriosclerosis. There is now increasing evidence that arteriosclerosis is a low-grade systemic inflammatory disease. An increase in serum C-reactive protein levels is an important indicator of inflammatory reactions and also of the risk of developing arteriosclerosis^[98]. The synthesis of C-reactive protein is regulated by IL-6 and IL-10 as well as TNF- α ^[73,99]. Animal studies have demonstrated that IL-6 and IL-10 accelerate arteriosclerosis^[100]. Calcitriol can suppress the secretion of TNF- α and IL-6 *in vitro* in a dose-dependent manner^[101]. A recent study identified an inverse association between TNF- α and 25(OH)D levels in human subjects^[102].

PREVENTION OF VITAMIN D INSUFFICIENCY

Preventive measures must take into account that there is a high risk of vitamin D insufficiency in the whole population during winter and that the elderly population, especially institutionalized subjects, are at an increased risk for vitamin D insufficiency or even deficiency. There are two prevention models available: increased exposure to ultraviolet light and increased oral vitamin D intake. Sunlight provides the most potent source of vitamin D, with approximately 3000 IU vitamin D3 for 5 to 10 min of mid-day, mid-year exposure of the arms and legs for a light-skinned Caucasian^[10]. Adequate daily oral vitamin D intake could be an easy and effective measure for maintaining a physiological vitamin D status. In November 2010, the Institute of Medicine of the National Academies of United States provided an update to the recommended intakes of calcium and vitamin D. For vitamin D intake, the committee assumed that North Americans need on average 400 IU of vitamin D daily; people 71 years old and older may require as much as 800 IU per day^[103]. However, nutrition experts have suggested that vitamin D intake of 800 to 2000 IU daily may be needed. These doses are quite difficult to obtain without routine supplementation, particularly in areas with extreme win-

ter climates and higher latitudes^[104]. The United States Food and Drug Administration reported that a dose of 2000 IU daily is safe^[21]. The Institute of Medicine of the National Academies has recently suggested a new tolerable upper intake level of only 4000 IU of vitamin D per day for the general adult population^[103] because of the concern about potential toxicity at higher levels of 25(OH)D^[103-106]. However, currently there is no recommended daily intake dose for vitamin D. For a practical approach, maintenance therapy can be continued by routine sunlight exposure or by administering vitamin D supplements, 800 to 2000 IU vitamin D3 daily or 50000 IU of either D2 or D3 every 2 wk^[10,21,107].

RECOMMENDATIONS

It is still unproven whether supplementation with vitamin D reduces the cardiovascular risks. Autier *et al.*^[108] analyzed 18 independent randomized controlled trials of more than 57000 participants with mean follow-up of 5.7 years. Although there was considerable variability in the dose of vitamin D administered (from 300 to 2000 IU daily), the summary relative risk for all-cause mortality was reduced by 7% with vitamin D therapy^[109]. Wang *et al.*^[106] performed a meta-analysis of 8 randomized trials, showing a slight, but statistically nonsignificant, 10% reduction in CV disease risk with vitamin D supplementation at moderate to high doses (approximately 1000 IU daily). Another meta-analysis evaluated the relationship between vitamin D levels and cardiovascular risk and reported that vitamin D was associated with nonsignificant effects on the patients' death, myocardial infarction and stroke rates^[109]. However, this study did not focus on the effect of vitamin D supplementation in the reduction of cardiovascular risks. At the present stage, we still feel confident that the benefits of vitamin D will likely outweigh the risks. A large double-blind randomized placebo-controlled trial (Vitamin D and Omega-3 Trial, VITAL) sponsored by the National Institutes of Health and run by Harvard Medical School and the Brigham and Women's Hospital is underway^[110]. This study should help to determine whether increasing low vitamin D levels will reduce the risk of CV events, depression, and death. O'Keefe *et al.*^[111] have claimed that several large scale trials have just started but the results of these trials will not be available for another 3-5 years or more; in the meantime, they recommend a daily intake of 1500 to 2000 IU of vitamin D3 for most American adults.

CONCLUSION

On the basis of this review, hypovitaminosis D has been observed worldwide, and many studies have demonstrated a strong association between vitamin D status and cardiovascular disease risk factors, including hypertension, diabetes, metabolic syndrome and inflammation. In the meantime, health professionals should be aware of the potential negative implications of vitamin D insufficiency

and make recommendations for their patients to improve their vitamin D status. We suggest that to maintain health in younger and older adults and prevent hypertension, chronic heart diseases, and cardiovascular events, an increase in the current recommended intake of vitamin D is warranted. However, definitive randomized controlled trials are still needed to determine whether vitamin D therapy is beneficial to preventing cardiovascular disease. Given the low cost, safety, and demonstrated benefits of higher 25(OH)D concentration, vitamin D supplementation should become a public health priority to combat these common and costly chronic cardiovascular diseases.

REFERENCES

- 1 Holick MF. Vitamin D and sunlight: strategies for cancer prevention and other health benefits. *Clin J Am Soc Nephrol* 2008; **3**: 1548-1554 [PMID: 18550652 DOI: 10.2215/CJN.01350308]
- 2 Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* 2000; **11**: 847-852 [PMID: 11075874]
- 3 Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; **84**: 18-28 [PMID: 16825677]
- 4 Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, Giovannucci EL. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1502-1508 [PMID: 15342452]
- 5 Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. The role of vitamin D in cancer prevention. *Am J Public Health* 2006; **96**: 252-261 [PMID: 16380576 DOI: 10.2105/AJPH.2004.045260]
- 6 Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006; **98**: 451-459 [PMID: 16595781 DOI: 10.1093/jnci/djj101]
- 7 Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF. Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol* 2005; **97**: 179-194 [PMID: 16236494 DOI: 10.1016/j.jsbmb.2005.06.018]
- 8 Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81**: 353-373 [PMID: 16529140 DOI: 10.4065/81.3.353]
- 9 Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006; **116**: 2062-2072 [PMID: 16886050 DOI: 10.1172/JCI29449]
- 10 Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462 DOI: 10.1056/NEJMra070553]
- 11 Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003; **78**: 1463-1470 [PMID: 14661675 DOI: 10.4065/78.12.1463]
- 12 Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998; **338**: 777-783 [PMID: 9504937 DOI: 10.1056/NEJM199803193381201]
- 13 Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, Holick MF, Hollis BW, Lamberg-Allardt C, McGrath JJ, Norman AW, Scragg R, Whiting SJ, Willett WC, Zittermann A. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007;

- 85: 649-650 [PMID: 17344484]
- 14 **Norman AW**, Bouillon R, Whiting SJ, Vieth R, Lips P. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; **103**: 204-205 [PMID: 17234402 DOI: 10.1016/j.jsbmb.2006.12.071]
- 15 **Fleck A**. Latitude and ischaemic heart disease. *Lancet* 1989; **1**: 613 [PMID: 2564129 DOI: 10.1016/S0140-6736(89)91634-6]
- 16 **Kristal-Boneh E**, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. *Hypertension* 1997; **30**: 1289-1294 [PMID: 9369290 DOI: 10.1161/01.HYP.30.5.1289]
- 17 **Poole KE**, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA. Reduced vitamin D in acute stroke. *Stroke* 2006; **37**: 243-245 [PMID: 16322500 DOI: 10.1161/01.STR.0000195184.24297.c1]
- 18 **Scragg R**, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol* 1990; **19**: 559-563 [PMID: 2262248 DOI: 10.1093/ije/19.3.559]
- 19 **Sokol SI**, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. *Cardiol Rev* 2011; **19**: 192-201 [PMID: 21646873 DOI: 10.1097/CRD.0b013e31821da9a5]
- 20 **Watson KE**, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 1997; **96**: 1755-1760 [PMID: 9323058 DOI: 10.1161/01.CIR.96.6.1755]
- 21 **Lüderitz B**, Holmes DR, Harold J. The history of the German Cardiac Society and the American College of Cardiology and their two founders. *J Am Coll Cardiol* 2013; **61**: 802-807 [PMID: 23428213 DOI: 10.1016/j.jacc.2012.11.043]
- 22 **Bouillon R**, Okamura WH, Norman AW. Structure-function relationships in the vitamin D endocrine system. *Endocr Rev* 1995; **16**: 200-257 [PMID: 7781594 DOI: 10.1210/er.16.2.200]
- 23 **DeLuca HF**. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; **80**: 1689S-1696S [PMID: 15585789]
- 24 **Mosekilde L**. Vitamin D requirement and setting recommendation levels: long-term perspectives. *Nutr Rev* 2008; **66**: S170-S177 [PMID: 18844845 DOI: 10.1111/j.1753-4887.2008.00103.x]
- 25 **Holden JM**, Lemar LE. Assessing vitamin D contents in foods and supplements: challenges and needs. *Am J Clin Nutr* 2008; **88**: 551S-553S [PMID: 18689400]
- 26 **Malabanan A**, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998; **351**: 805-806 [PMID: 9519960 DOI: 10.1016/S0140-6736(05)78933-9]
- 27 **Chapuy MC**, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997; **7**: 439-443 [PMID: 9425501 DOI: 10.1007/s001980050030]
- 28 **Holick MF**, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005; **90**: 3215-3224 [PMID: 15797954 DOI: 10.1210/jc.2004-2364]
- 29 **Heaney RP**, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003; **22**: 142-146 [PMID: 12672710 DOI: 10.1080/07315724.2003.10719287]
- 30 **Webb AR**, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab* 1988; **67**: 373-378 [PMID: 2839537 DOI: 10.1210/jcem-67-2-373]
- 31 **Matsuoka LY**, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab* 1987; **64**: 1165-1168 [PMID: 3033008 DOI: 10.1210/jcem-64-6-1165]
- 32 **Lee JM**, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr (Phila)* 2007; **46**: 42-44 [PMID: 17164508 DOI: 10.1177/0009922806289311]
- 33 **Marwaha RK**, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, Saluja B, Ganie MA, Singh S. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 2005; **82**: 477-482 [PMID: 16087996]
- 34 **Bodnar LM**, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab* 2007; **92**: 3517-3522 [PMID: 17535985 DOI: 10.1210/jc.2007-0718]
- 35 **Bakhtiyarova S**, Lesnyak O, Kyznesova N, Blankenstein MA, Lips P. Vitamin D status among patients with hip fracture and elderly control subjects in Yekaterinburg, Russia. *Osteoporos Int* 2006; **17**: 441-446 [PMID: 16328605 DOI: 10.1007/s00198-005-0006-9]
- 36 **McKenna MJ**. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 1992; **93**: 69-77 [PMID: 1385673 DOI: 10.1016/0002-9343(92)90682-2]
- 37 **Chapuy MC**, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992; **327**: 1637-1642 [PMID: 1331788]
- 38 **Sedrani SH**. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Ann Nutr Metab* 1984; **28**: 181-185 [PMID: 6610383 DOI: 10.1159/000176801]
- 39 **Zittermann A**. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; **92**: 39-48 [PMID: 16600341 DOI: 10.1016/j.pbiomolbio.2006.02.001]
- 40 **Martins D**, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2007; **167**: 1159-1165 [PMID: 17563024 DOI: 10.1001/archinte.167.11.1159]
- 41 **Forman JP**, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; **49**: 1063-1069 [PMID: 17372031 DOI: 10.1161/HYPERTENSIONAHA.107.087288]
- 42 **Lee JH**, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008; **52**: 1949-1956 [PMID: 19055985 DOI: 10.1016/j.jacc.2008.08.050]
- 43 **Forman JP**, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, Bennett GG, Chandler PD, Hollis BW, Emmons KM, Giovannucci EL, Fuchs CS, Chan AT. Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension* 2013; **61**: 779-785 [PMID: 23487599 DOI: 10.1161/HYPERTENSIONAHA.111.00659]
- 44 **Harris RA**, Pedersen-White J, Guo DH, Stallmann-Jorgensen IS, Keeton D, Huang Y, Shah Y, Zhu H, Dong Y. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *Am J Hypertens* 2011; **24**: 557-562 [PMID: 21311504 DOI: 10.1038/ajh.2011.12]
- 45 **Larsen T**, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens* 2012; **25**: 1215-1222 [PMID: 22854639 DOI: 10.1038/ajh.2012.111]

- 46 **Lind L**, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alfacalcidol. A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. *Acta Med Scand* 1988; **223**: 211-217 [PMID: 3281411 DOI: 10.1111/j.0954-6820.1988.tb15789.x]
- 47 **Lind L**, Wengle B, Wide L, Sörensen OH, Ljunghall S. Hypertension in primary hyperparathyroidism—reduction of blood pressure by long-term treatment with vitamin D (alfacalcidol). A double-blind, placebo-controlled study. *Am J Hypertens* 1988; **1**: 397-402 [PMID: 3063290 DOI: 10.1093/ajh/1.4.397]
- 48 **Longenecker CT**, Hileman CO, Carman TL, Ross AC, Seydankan S, Brown TT, Labbato DE, Storer N, Tangpricha V, McComsey GA. Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial. *Antivir Ther* 2012; **17**: 613-621 [PMID: 22293363 DOI: 10.3851/IMP1983]
- 49 **Salehpour A**, Shidfar F, Hosseiniapanah F, Vafa M, Razaghi M, Hoshirrad A, Gohari M. Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr* 2012; **108**: 1866-1873 [PMID: 22317756 DOI: 10.1017/S0007114512000098]
- 50 **Shedeed SA**. Vitamin D supplementation in infants with chronic congestive heart failure. *Pediatr Cardiol* 2012; **33**: 713-719 [PMID: 22349668 DOI: 10.1007/s00246-012-0199-6]
- 51 **Witham MD**, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients - a randomised controlled trial. *Nutr Metab Cardiovasc Dis* 2012; **22**: 864-870 [PMID: 21194910 DOI: 10.1016/j.numecd.2010.11.001]
- 52 **Zittermann A**, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr* 2009; **89**: 1321-1327 [PMID: 19321573 DOI: 10.3945/ajcn.2008.27004]
- 53 **Gepner AD**, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One* 2012; **7**: e36617 [PMID: 22586483 DOI: 10.1371/journal.pone.0036617]
- 54 **Jorde R**, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. *J Intern Med* 2010; **267**: 462-472 [PMID: 20141565 DOI: 10.1111/j.1365-2796.2009.02181.x]
- 55 **Marckmann P**, Agerskov H, Thineshkumar S, Bladbjerg EM, Sidelmann JJ, Jespersen J, Nybo M, Rasmussen LM, Hansen D, Scholze A. Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. *Nephrol Dial Transplant* 2012; **27**: 3523-3531 [PMID: 22822092 DOI: 10.1093/ndt/gfs138]
- 56 **Muldowney S**, Lucey AJ, Hill TR, Seamans KM, Taylor N, Wallace JM, Horgan G, Barnes MS, Bonham MP, Duffy EM, Strain JJ, Cashman KD, Kiely M. Incremental cholecalciferol supplementation up to 15 µg/d throughout winter at 51-55 ° N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. *J Nutr* 2012; **142**: 1519-1525 [PMID: 22739371 DOI: 10.3945/jn.111.154005]
- 57 **Scragg R**, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr* 1995; **49**: 640-646 [PMID: 7498100]
- 58 **Stricker H**, Tosi Bianda F, Guidicelli-Nicolosi S, Limoni C, Colucci G. Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial disease: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg* 2012; **44**: 307-312 [PMID: 22831874 DOI: 10.1016/j.ejvs.2012.06.023]
- 59 **Thadhani R**, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, Bhan I, Agarwal R, Zoccali C, Wanner C, Lloyd-Jones D, Cannata J, Thompson BT, Andress D, Zhang W, Packham D, Singh B, Zehnder D, Shah A, Pachika A, Manning WJ, Solomon SD. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA* 2012; **307**: 674-684 [PMID: 22337679 DOI: 10.1001/jama.2012.120]
- 60 **Wood AD**, Secombes KR, Thies F, Aucott L, Black AJ, Mavroeidi A, Simpson WG, Fraser WD, Reid DM, Macdonald HM. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab* 2012; **97**: 3557-3568 [PMID: 22865902 DOI: 10.1210/jc.2012-2126]
- 61 **Yiu YF**, Yiu KH, Siu CW, Chan YH, Li SW, Wong LY, Lee SW, Tam S, Wong EW, Lau CP, Cheung BM, Tse HF. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis* 2013; **227**: 140-146 [PMID: 23298824 DOI: 10.1016/j.atherosclerosis.2012.12.013]
- 62 **Chonchol M**, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int* 2007; **71**: 134-139 [PMID: 17082756 DOI: 10.1038/sj.ki.5002002]
- 63 **Dobnig H**, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008; **168**: 1340-1349 [PMID: 18574092 DOI: 10.1001/archinte.168.12.1340]
- 64 **Pacifico L**, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, Chiesa C. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol* 2011; **165**: 603-611 [PMID: 21753070 DOI: 10.1530/EJE-11-0545]
- 65 **London GM**, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, Métivier F. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol* 2007; **18**: 613-620 [PMID: 17202417 DOI: 10.1681/ASN.2006060573]
- 66 **Michos ED**, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 7-12 [PMID: 18090651 DOI: 10.1097/MCO.0b013e3282f2f4dd]
- 67 **Mitsushashi T**, Morris RC, Ives HE. 1,25-dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. *J Clin Invest* 1991; **87**: 1889-1895 [PMID: 1645744 DOI: 10.1172/JCI115213]
- 68 **Schleithoff SS**, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2006; **83**: 754-759 [PMID: 16600924]
- 69 **Wu-Wong JR**, Nakane M, Ma J, Ruan X, Kroeger PE. Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. *Atherosclerosis* 2006; **186**: 20-28 [PMID: 16095599 DOI: 10.1016/j.atherosclerosis.2005.06.046]
- 70 **Rostand SG**, Drüeke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999; **56**: 383-392 [PMID: 10432376 DOI: 10.1046/j.1523-1755.1999.00575.x]
- 71 **de Boer OJ**, Hirsch F, van der Wal AC, van der Loos CM, Das PK, Becker AE. Costimulatory molecules in human atherosclerotic plaques: an indication of antigen specific T lymphocyte activation. *Atherosclerosis* 1997; **133**: 227-234 [PMID: 9298683 DOI: 10.1016/S0021-9150(97)00135-4]
- 72 **Breithaupt-Faloppa AC**, Vitoretto LB, Cavriani G, Lino-dos-Santos-Franco A, Sudo-Hayashi LS, Oliveira-Filho RM, Vargaftig BB, Tavares-de-Lima W. Intestinal lymph-borne factors induce lung release of inflammatory mediators and expression of adhesion molecules after an intestinal ischemic insult. *J Surg Res* 2012; **176**: 195-201 [PMID: 21872880]

- DOI: 10.1016/j.jss.2011.06.074]
- 73 **Canning MO**, Grotenhuis K, de Wit H, Ruwhof C, Drexhage HA. 1- α ,25-Dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes. *Eur J Endocrinol* 2001; **145**: 351-357 [PMID: 11517017 DOI: 10.1530/eje.0.1450351]
 - 74 **Dirksen MT**, van der Wal AC, van den Berg FM, van der Loos CM, Becker AE. Distribution of inflammatory cells in atherosclerotic plaques relates to the direction of flow. *Circulation* 1998; **98**: 2000-2003 [PMID: 9808596 DOI: 10.1161/01.CIR.98.19.2000]
 - 75 **Fukuo K**, Nakahashi T, Nomura S, Hata S, Suhara T, Shimizu M, Tamatani M, Morimoto S, Kitamura Y, Ogihara T. Possible participation of Fas-mediated apoptosis in the mechanism of atherosclerosis. *Gerontology* 1997; **43 Suppl 1**: 35-42 [PMID: 9187937 DOI: 10.1159/000213884]
 - 76 **Goon PK**, Boos CJ, Lip GY. Circulating endothelial cells: markers of vascular dysfunction. *Clin Lab* 2005; **51**: 531-538 [PMID: 16285476]
 - 77 **Kohchi K**, Takebayashi S, Hiroki T, Nobuyoshi M. Significance of adventitial inflammation of the coronary artery in patients with unstable angina: results at autopsy. *Circulation* 1985; **71**: 709-716 [PMID: 3971540 DOI: 10.1161/01.CIR.71.4.709]
 - 78 **Lavie CJ**, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? *J Am Coll Cardiol* 2011; **58**: 1547-1556 [PMID: 21958881 DOI: 10.1016/j.jacc.2011.07.008]
 - 79 **Lendon CL**, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophages density is increased. *Atherosclerosis* 1991; **87**: 87-90 [PMID: 1872926 DOI: 10.1016/0021-9150(91)90235-U]
 - 80 **Mach F**, Schönbeck U, Sukhova GK, Bourcier T, Bonnefoy JY, Pober JS, Libby P. Functional CD40 ligand is expressed on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for CD40-CD40 ligand signaling in atherosclerosis. *Proc Natl Acad Sci U S A* 1997; **94**: 1931-1936 [PMID: 9050882 DOI: 10.1073/pnas.94.5.1931]
 - 81 **Magnus T**, Wiendl H, Kleinschmitt C. Immune mechanisms of stroke. *Curr Opin Neurol* 2012; **25**: 334-340 [PMID: 22547104 DOI: 10.1097/WCO.0b013e328352ede6]
 - 82 **Pasterkamp G**, Schoneveld AH, van der Wal AC, Hijnen DJ, van Waveren WJ, Plomp S, Teepen HL, Borst C. Inflammation of the atherosclerotic cap and shoulder of the plaque is a common and locally observed feature in unruptured plaques of femoral and coronary arteries. *Arterioscler Thromb Vasc Biol* 1999; **19**: 54-58 [PMID: 9888866 DOI: 10.1161/01.ATV.19.1.54]
 - 83 **Polverini PJ**, Cotran PS, Gimbrone MA, Unanue ER. Activated macrophages induce vascular proliferation. *Nature* 1977; **269**: 804-806 [PMID: 927505 DOI: 10.1038/269804a0]
 - 84 **Signore A**, Annovazzi A, Corsetti F, Capriotti G, Chianelli M, De Winter F, Scopinaro F. Biological imaging for the diagnosis of inflammatory conditions. *BioDrugs* 2002; **16**: 241-259 [PMID: 12196038 DOI: 10.2165/00063030-200216040-00002]
 - 85 **Sullivan GW**, Sarembock IJ, Linden J. The role of inflammation in vascular diseases. *J Leukoc Biol* 2000; **67**: 591-602 [PMID: 10810997]
 - 86 **Tenaglia AN**, Buda AJ, Wilkins RG, Barron MK, Jeffords PR, Vo K, Jordan MO, Kusnick BA, Lefer DJ. Levels of expression of P-selectin, E-selectin, and intercellular adhesion molecule-1 in coronary atherectomy specimens from patients with stable and unstable angina pectoris. *Am J Cardiol* 1997; **79**: 742-747 [PMID: 9070552 DOI: 10.1016/S0002-9149(96)00861-2]
 - 87 **Uyemura K**, Demer LL, Castle SC, Jullien D, Berliner JA, Gately MK, Warrier RR, Pham N, Fogelman AM, Modlin RL. Cross-regulatory roles of interleukin (IL)-12 and IL-10 in atherosclerosis. *J Clin Invest* 1996; **97**: 2130-2138 [PMID: 8621803 DOI: 10.1172/JCI118650]
 - 88 **Zittermann A**, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr* 2005; **94**: 483-492 [PMID: 16197570 DOI: 10.1079/BJN20051544]
 - 89 **Li YC**, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; **110**: 229-238 [PMID: 12122115]
 - 90 **Gunta SS**, Thadhani RI, Mak RH. The effect of vitamin D status on risk factors for cardiovascular disease. *Nat Rev Nephrol* 2013; **9**: 337-347 [PMID: 23609564 DOI: 10.1038/nrneph.2013.74]
 - 91 **McCarron DA**, Morris CD, Bukoski R. The calcium paradox of essential hypertension. *Am J Med* 1987; **82**: 27-33 [PMID: 3544831 DOI: 10.1016/0002-9343(87)90268-3]
 - 92 **MacGregor GA**, Cappuccio FP. The kidney and essential hypertension: a link to osteoporosis? *J Hypertens* 1993; **11**: 781-785 [PMID: 8228200 DOI: 10.1097/00004872-199308000-00003]
 - 93 **Strauzzullo P**. The renal calcium leak in primary hypertension: pathophysiological aspects and clinical implications. *Nutr Meta Cardiovasc Dis* 1991; **1**: 98-103
 - 94 **Scragg R**, Holdaway L, Jackson R, Lim T. Plasma 25-hydroxyvitamin D3 and its relation to physical activity and other heart disease risk factors in the general population. *Ann Epidemiol* 1992; **2**: 697-703 [PMID: 1342321 DOI: 10.1016/1047-2797(92)90014-H]
 - 95 **Dustan HP**. Obesity and hypertension in blacks. *Cardiovasc Drugs Ther* 1990; **4 Suppl 2**: 395-402 [PMID: 2271401 DOI: 10.1007/BF02603183]
 - 96 **Harris SS**, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr* 1998; **67**: 1232-1236 [PMID: 9625098]
 - 97 **Zittermann A**. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89**: 552-572 [PMID: 12720576 DOI: 10.1079/BJN2003837]
 - 98 **Van Lente F**. Markers of inflammation as predictors in cardiovascular disease. *Clin Chim Acta* 2000; **293**: 31-52 [PMID: 10699421 DOI: 10.1016/S0009-8981(99)00236-3]
 - 99 **Mendall MA**, Patel P, Asante M, Ballam L, Morris J, Strachan DP, Camm AJ, Northfield TC. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* 1997; **78**: 273-277 [PMID: 9391290]
 - 100 **Huber SA**, Sakkinen P, Conze D, Hardin N, Tracy R. Interleukin-6 exacerbates early atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 1999; **19**: 2364-2367 [PMID: 10521365 DOI: 10.1161/01.ATV.19.10.2364]
 - 101 **Müller K**, Haahr PM, Diamant M, Rieneck K, Kharazmi A, Bendtzen K. 1,25-Dihydroxyvitamin D3 inhibits cytokine production by human blood monocytes at the post-transcriptional level. *Cytokine* 1992; **4**: 506-512 [PMID: 1337987]
 - 102 **Zittermann A**, Schleithoff SS, Tenderich G, Berthold HK, Körfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol* 2003; **41**: 105-112 [PMID: 12570952 DOI: 10.1016/S0735-1097(02)02624-4]
 - 103 **Wang TJ**, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117**: 503-511 [PMID: 18180395 DOI: 10.1161/CIRCULATIONAHA.107.706127]
 - 104 **Melamed ML**, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008; **168**: 1629-1637 [PMID: 18695076 DOI: 10.1001/archinte.168.15.1629]
 - 105 **Wang L**, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152**: 315-323 [PMID: 20194238 DOI: 10.7326/0003-4819-152-5-201003020-00010]

- 106 Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Report of the Institute of Medicine of the National Academies, Washington, DC: The National Academies Press, 2011
- 107 **Heaney RP**, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003; **77**: 204-210 [PMID: 12499343]
- 108 **Autier P**, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; **167**: 1730-1737 [PMID: 17846391 DOI: 10.1001/archinte.167.16.1730]
- 109 **Elamin MB**, Abu Elnour NO, Elamin KB, Fatourehchi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH, Montori VM. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96**: 1931-1942 [PMID: 21677037 DOI: 10.1210/jc.2011-0398]
- 110 Vitamin D and Omega-3 Trial (VITAL). ClinicalTrials.gov ID: NCT01169259. Cited 2013-08-21. Available from: URL: <http://clinicaltrials.gov/show/NCT01169259>
- 111 **O'Keefe JH**, Patil HR, Lavie CJ. Can vitamin D deficiency break your heart? *Mayo Clin Proc* 2012; **87**: 412-413; author reply 413 [PMID: 22469354 DOI: 10.1016/j.mayocp.2011.12.013]

P- Reviewers Georgescu A, Su H **S- Editor** Song XX
L- Editor A **E- Editor** Lu YJ



Subcutaneous implantable defibrillator: State-of-the art 2013

Finn Akerström, Miguel A Arias, Marta Pachón, Alberto Puchol, Jesús Jiménez-López

Finn Akerström, Miguel A Arias, Marta Pachón, Alberto Puchol, Jesús Jiménez-López, Cardiac Arrhythmia and Electrophysiology Unit, Department of Cardiology, Hospital Virgen de la Salud, 45004 Toledo, Spain

Author contributions: All authors contributed to the paper.

Correspondence to: Dr. Miguel A Arias, MD, PhD, Cardiac Arrhythmia and Electrophysiology Unit, Department of Cardiology, Hospital Virgen de la Salud, Avda, Barber 30, Planta Semisótano, 45004 Toledo, Spain. maapalomares@secardiologia.es

Telephone: +34-92-5265492 Fax: +34-92-5265492

Received: June 26, 2013 Revised: August 1, 2013

Accepted: August 16, 2013

Published online: September 26, 2013

Abstract

The subcutaneous implantable cardioverter-defibrillator (S-ICD) has recently been approved for commercial use in Europe, New Zealand and the United States. It is comprised of a pulse generator, placed subcutaneously in a left lateral position, and a parasternal subcutaneous lead-electrode with two sensing electrodes separated by a shocking coil. Being an entirely subcutaneous system it avoids important periprocedural and long-term complications associated with transvenous implantable cardioverter-defibrillator (TV-ICD) systems as well as the need for fluoroscopy during implant surgery. Suitable candidates include pediatric patients with congenital heart disease that limits intracavitary lead placements, those with obstructed venous access, chronic indwelling catheters or high infection risk, as well as young patients with electrical heart disease (*e.g.*, Brugada Syndrome, long QT syndrome, and hypertrophic cardiomyopathy). Nevertheless, given the absence of intracavitary leads, the S-ICD is unable to offer pacing (apart from short-term post-shock pacing). It is therefore not suitable in patients with an indication for antibradycardia pacing or cardiac resynchronization therapy, or with a history of repetitive monomorphic ventricular tachycardia that would benefit from antitachycardia pacing. Current data from initial clinical studies and post-commercialization

"real-life" case series, including over 700 patients, have so far been promising and shown that the S-ICD successfully converts induced and spontaneous ventricular tachycardia/ventricular fibrillation episodes with associated complication and inappropriate shock rates similar to that of TV-ICDs. Furthermore, by using far-field electrograms better tachyarrhythmia discrimination when compared to TV-ICDs has been reported. Future results from ongoing clinical studies will determine the S-ICD system's long-term performance, and better define suitable patient profiles.

© 2013 Baishideng. All rights reserved.

Key words: Implantable cardioverter-defibrillator; Subcutaneous; Sudden death; Ventricular tachycardia; Ventricular fibrillation

Core tip: The subcutaneous implantable cardioverter-defibrillator (S-ICD) has recently been commercialized in Europe, New Zealand and the United States and implanted in over 2000 patients so far worldwide. It represents an important innovation in the field of device therapy since it avoids the potential periprocedural and long-term complications associated with endovascular leads used with conventional transvenous ICDs. Future studies will better define patient target groups and thereby establish the therapeutic potential of this new device technology.

Akerström F, Arias MA, Pachón M, Puchol A, Jiménez-López J. Subcutaneous implantable defibrillator: State-of-the art 2013. *World J Cardiol* 2013; 5(9): 347-354 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/347.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.347>

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) effec-

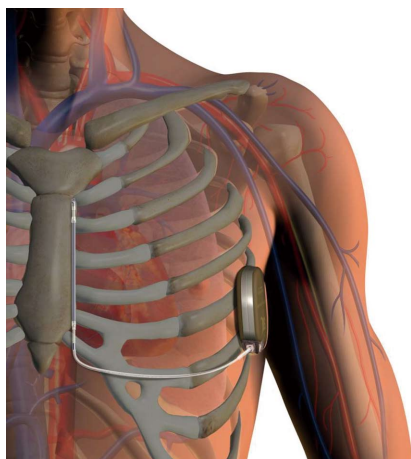


Figure 1 The subcutaneous implantable cardioverter-defibrillator system with the pulse generator implanted subcutaneously in a left lateral position, and the parasternal lead-electrode positioned parallel to and 1 to 2 cm to the left of the sternal midline. The lead-electrode contains two sensing electrodes separated by an 8 cm shocking coil.

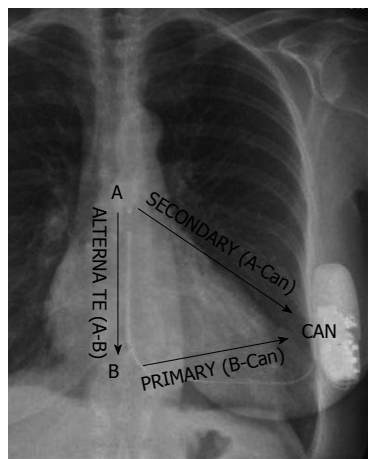


Figure 2 Chest X-ray of a patient with a subcutaneous implantable cardioverter-defibrillator system. The cardiac rhythm is detected by 1 of the 3 available vectors, formed between the 2 sensing electrodes and the pulse generator: B-Can, A-Can, and A-B. B-Can: Proximal-to-can; A-Can: Distal-to-can; A-B: Distal to proximal.

tively prevents sudden cardiac death, when used both in primary^[1,2] and secondary prevention^[3]. To date the vast majority of implanted systems utilize a conventional design, consisting of a transvenous lead for arrhythmia detection and treatment (antitachycardia pacing or defibrillation) positioned in the right ventricle. Nevertheless, transvenous ICD (TV-ICD) is associated with significant periprocedural and long-term complications. A recent observational large-scale study reported 1.5% major complications (in-hospital death, cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, hemothorax, pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, cardiac tamponade, and arterial-venous fistula)^[4]. Over time, the incidence of intrinsic lead defects, mainly due to insulation defects, invariably increases with a reported annual failure rate at 10-year-old leads of up to 20%^[5]. Furthermore, the problem of defibrillation lead recalls is frequent and relevant^[6] and revision or extraction of a chronic indwelling lead is frequently a difficult procedure with significant associated morbidity and mortality^[7]. Therefore, although the TV-ICD is highly effective in treating ventricular arrhythmias its associated adverse effects are of relevance. A non-TV-ICD system is therefore an attractive option that would overcome many of these problems. Recently, a dedicated entirely subcutaneous ICD (S-ICD, Cameron Health, Inc, San Clemente, California, United States) system has been developed and recently approved for commercial use in Europe, New Zealand, and the United States with more than 2000 successful device implants so far worldwide.

IMPLANTATION, OPERATING AND PROGRAMMING FEATURES

The S-ICD system is comprised of a pulse generator, subcutaneous electrode, electrode insertion tool, and de-

vice programmer. The pulse generator has an estimated longevity of 5 years, is slightly larger and weighs approximately the double (145 g) of a modern TV-ICD generator. It provides high-energy defibrillation shocks (80 J) therapy through the use of a constant tilt biphasic waveform, and is capable of delivering post-shock bradycardia pacing at 50 impulses per minute, using a 200 mA biphasic transthoracic pulse for a period of up to 30 s if > 3.5 s of post-shock asystole is detected. Since implantation is guided by anatomic landmarks, fluoroscopy is unnecessary and the operator and patient radiation exposure is subsequently avoided. The generator is placed subcutaneously in a left lateral position over the 6th rib between the midaxillary and anterior axillary lines. *Via* two parasternal incisions, a 3 mm tripolar parasternal electrode (polycarbonate urethane) is positioned parallel to and 1 to 2 cm to the left of the sternal midline with the distal sensing electrode localized adjacent to the manubriosternal junction and the proximal sensing electrode positioned adjacent to the xiphoid process. The 8 cm shocking coil is found between the two sensing electrodes (Figure 1). The cardiac rhythm is detected by the use of 1 of the 3 vectors, which are formed between the sensing electrodes and the pulse generator (proximal-to-can, distal-to-can, and distal to proximal) (Figure 2). The S-ICD automatically selects the most suitable vector for rhythm detection with a satisfactory R-wave/T-wave ratio, in order to minimize the risk for oversensing. In addition, the manufacture recommends carrying out a screening ECG template to confirm a satisfactory R-wave/T-wave ratio in at least 1 of the 3 available sensing configurations pre-implantation. During device insertion effective conversion of induced similar to ventricular fibrillation (VF) using 65 J is tested, nevertheless once implanted, the S-ICD only delivers a non-programmable 80 J shock to ensure a 15 J safety margin^[8]. Noteworthy, since the device safety and effectiveness data comes from studies that utilized defibrillation testing this constitutes an obligatory step during

TREATED EPISODE 007:03/29 12:01:52 AM 25 mm/s 2.5 mm/mV
SHOCK IMPEDANCE = 79 Ohms FINAL SHOCK POLARITY = STD



Figure 3 Subcutaneous implantable cardioverter-defibrillator electrogram showing a sustained monomorphic ventricular tachycardia that is terminated by a shock (lightning symbol). The subcutaneous implantable cardioverter-defibrillator (S-ICD) system uses an 18/24 interval criterion for tachycardia detection (T) which is reconfirmed after capacitor charging (C), but before shock delivery, to exclude the presence of non-sustained tachyarrhythmias. S: Sensed event not classified as tachycardia.

implantation of the S-ICD, as opposed to the TV-ICD system where this is no longer considered necessary^[8,9].

The S-ICD system calculates the heart rate as the average of the last 4 intervals, and performs tachycardia analysis using an 18/24 duration criteria. Tachycardia is reconfirmed after capacitor charging (average time of 14 ± 2 s) but before shock delivery to exclude the presence of non-sustained tachyarrhythmias^[8]. Apart from a shock zone [VF zone in TV-ICDs], the device offers an optional conditional discrimination zone that involves 3 distinct rhythm analyses to distinguish atrial from ventricular tachyarrhythmia and avoid inappropriate shocks of the former: (1) Correlation waveform analysis of up to 41 points of each ventricular complex comparing the current tachycardia beat with the stored template acquired at rest. More than 50% of correlation is considered normal activity and suggests an atrial tachyarrhythmia; (2) Beat-to-beat analysis that evaluates monomorphic or polymorphic beat relationships. In the case of a polymorphic relationship, ventricular tachyarrhythmia is suspected and in the case of monomorphic relationship the algorithm continues; (3) QRS width analysis, using the baseline template, that indicate ventricular tachycardia (VT) if the QRS complex is wide and if the beat-to-beat analysis registered a monomorphic relationship. If the QRS complex is narrow, atrial tachyarrhythmia is assumed^[8]. If ventricular tachyarrhythmia is confirmed the device is able to deliver up to 5 shocks of 80 J with shock polarity reversed if the first shock is unsuccessful (Figure 3). A total of 24 episodes can be stored with a maximum of 120 s of recorded electrograms per event. A software update, aimed at reducing the incidence of inappropriate shocks due to oversensing, was introduced in October 2009^[8].

The programming of the S-ICD is simple since almost all device settings are automated apart from shock

Table 1 Subcutaneous implantable cardioverter-defibrillator programming

| Device options | Nominal settings |
|---|---------------------|
| Shock therapy ("ON/OFF") | ON |
| Post shock pacing ("ON/OFF") | ON |
| Conditional discrimination zone ("ON/OFF"; rate cutoff: 170 to 250 bpm) | ON (200 to 220 bpm) |

therapy (on/off), pacing after shock (on/off), and conditional discrimination zone (on/off) with a programmable rate cutoff between 170 to 250 bpm^[8] (Table 1). The device is not adequate for patients with symptomatic bradycardia and/or frequent ventricular tachycardia episodes likely to benefit from antitachycardia pacing (ATP), or concurrent use of unipolar pacemakers (that would interfere with the S-ICD arrhythmia detection).

EARLY CLINICAL STUDIES: VALIDATING DEVICE SAFETY AND EFFICACY

The results of 4 small non-randomized initial studies using the S-ICD system in patients with standard indication for ICD implantation were published in 2010 by Bardy *et al.*^[8]. The first short-term study determined the best electrode configuration in a total of 78 patients, and led to the selection of the shock configuration currently available for clinical use. Subsequently, using the best shock configuration previously determined, a second short-term study compared defibrillation thresholds between S-ICD and TV-ICD systems that were simultaneously implanted in 49 patients. The mean defibrillation threshold was 11.1 ± 8.5 J with the TV-ICD and 36.6 ± 19.8 J with the S-ICD ($P < 0.001$). In one patient the S-ICD failed to defibrillate the induced VF, however this was due to incorrect electrode positioning, approximately 6 cm to the left of the sternum. Following this, two clinical studies evaluated the performance of permanently implanted S-ICD, in 6 patients from New Zealand and 55 from Europe, respectively. Those with a history of VT < 170 bpm, and documented VT known to be reliably terminated with ATP were excluded. The primary endpoint was successful conversion of 2 subsequent episodes of induced VF at 65 J out of 4 attempts. In the pilot trial, consisting of 6 patients, all 18 episodes of induced VF were appropriately detected and defibrillated, and after 16 mo follow-up there were no occurrence of VT/VF episodes, device-related complications or inappropriate shocks. In the European cohort, there were a total of 137 induced VF episodes, all appropriately detected by the S-ICD, and in 98% of the tested patients, the 2 consecutive VF episodes were successfully converted at 65 J. Mean time to shock delivery was 14.0 ± 2.5 s. In one patient (2%) defibrillation was achieved during the first induction but not during the second induction, and received as per protocol a TV-ICD. After a 10 mo follow-up 12 episodes of spontaneous VT were detected and successfully treated

in 3 patients. Five patients presented minor complications (pocket infections, parasternal subcutaneous lead dislodgement). Oversensing occurred in 5 patients [muscle noise ($n = 3$), inadequate electrode placement ($n = 1$), and rate-dependent right bundle branch block ($n = 1$)], in all instances resolved by device reprogramming. There were no inappropriate shocks due to atrial tachyarrhythmias when such episodes occurred above > 170 bpm. Following these positive results the S-ICD was approved for commercial use in the European Union and New Zealand (June 2009).

The Subcutaneous versus Transvenous Arrhythmia Recognition Testing (START) study^[10] further evaluated the accuracy of rhythm confirmation and discrimination algorithms of the S-ICD system in a prospective, multicenter, head-to-head comparison with conventional TV-ICDs from three device manufactures. Atrial and ventricular arrhythmias were induced and simultaneously recorded by transvenous and cutaneous electrodes, in 64 patients with standard indication for dual-chamber ICD or cardiac resynchronization therapy defibrillator implantation. Cutaneous electrodes were placed on the patient's skin at locations that represented the subcutaneous position of the S-ICD system's implanted electrode and hence simulated the 3 previously mentioned sensing vectors. A test library was developed based on data from induced atrial arrhythmias with duration ≥ 30 s and ventricular response > 170 bpm ($n = 50$), and ventricular arrhythmias with duration ≥ 10 s and rates > 170 bpm ($n = 46$). Sensitivity performance for appropriate detection of ventricular tachyarrhythmias was first assessed by comparing single-chamber TV-ICDs with S-ICD using a single-zone (VF ≥ 170 bpm) configuration, and subsequently repeated using a dual-zone (VF ≥ 240 bpm; VT ≥ 170 bpm) in order to test the impact of discrimination algorithms on the detection of ventricular arrhythmias. The dual-zone S-ICD was subsequently compared to dual-chamber TV-ICDs, in order to assess whether the addition of atrial lead information would impact on arrhythmia detection sensitivity. Finally, specificity performance for discrimination of supraventricular tachycardias of the S-ICD and single- and dual-chamber TV-ICDs was undertaken. All ventricular tachyarrhythmias were detected in all systems using a single-zone configuration, and with the dual zone configuration all but one episode were detected (a single-chamber TV-ICD failed to detect one of the ventricular episodes). There was no significant difference in the sensitivity performance to detect ventricular tachyarrhythmias between the S-ICD and the single- and dual-chamber TV-ICDs. However, specificity for supraventricular arrhythmias was significantly superior for the S-ICD when compared to 2 of the 3 TV-ICDs, and when compared to the composite of the 3 TV-ICDs [98.0% (S-ICD) *vs* 76.7% (single-chamber TV-ICDs) *vs* 68.0% (dual-chamber TV-ICDs); $P < 0.001$]. No clear benefit of dual-chamber over single-chamber TV-ICDs was observed. Therefore, the results of the START study not only confirm the accuracy of ventricular tachyar-

rhythmia detection but also suggest a potential reduction in inappropriate therapies when compared to TV-ICDs. It should be noted however, that the START study included a limited number of patients, only evaluated induced arrhythmias and that most of the atrial tachyarrhythmias were atrial fibrillation. Furthermore, given that 3 different TV-ICD systems were included, comparison of the composite performance of these systems *vs* S-ICD should be interpreted with caution since their arrhythmia detection algorithms are not identical.

Following the initial clinical study by Bardy *et al*^[8] and the European commercialization, the prospective, multicenter, international S-ICD System Clinical Investigation study [the investigational device exemption (IDE) study]^[9] was commenced in order to gain approval of the Food and Drug Administration in the United States. The primary endpoints of the study were complication-free rate at 180 d post-implant of $\geq 79\%$ and induced VF conversion rate of $\geq 88\%$. Chronic performance of the S-ICD was also evaluated. The (unpublished) study results were presented at the Heart Rhythm Society conference in May 2012^[9]. A total of 321 patients were included in the safety cohort and of those 92% had met the procedure-related complication-free rate at 180 d. Complications included (number of patients) system infections (4), sub-optimal pulse generator and and/or electrode position (4), lead dislodgement (2), oversensing (3), inappropriate shock (3) and premature battery depletion (2). In 10 patients the device was explanted due to system infection (4), oversensing (2), pre-mature battery depletion (1), CRT indication (1), need for ATP (1), and elective due to patient request (1). The device successfully converted 100% of the induced VF episodes. During the total follow-up of a mean 321 d, 16 patients presented a total of 109 spontaneous VT/VF episodes, all of which were successfully converted with 80 J or spontaneously converted. Thirty-eight patients received inappropriate shocks (15 = atrial tachyarrhythmias with rates $>$ discrimination zone; 24 = oversensing). On the basis of the results from the IDE study the FDA subsequently approved the S-ICD for commercial use in September 2012.

POST COMMERCIALIZATION CASE SERIES: THE INITIAL EUROPEAN EXPERIENCE

Since the European approval 6 early "real-life experience" case series have been reported from Germany^[11,12], the Netherlands^[13,14], and the United Kingdom^[15,16] (Table 2). These studies include a total of 354 patients (32 and 41 patients with appropriate and inappropriate episodes respectively), the majority diagnosed with ischemic cardiomyopathy or idiopathic dilated cardiomyopathy and a primary prevention ICD indication^[17]. Overall, the results confirm that the S-ICD effectively converts both induced and spontaneous VT/VF episodes, and indicate that complication rates and inappropriate shock (mainly due to

Table 2 Clinical subcutaneous implantable cardioverter-defibrillator case series *n* (%)

| | Bardy <i>et al.</i> ^[8] (2010) | Jarman <i>et al.</i> ^[15] (2012) | Aydin <i>et al.</i> ^[11] (2012) | Olde Nordkamp <i>et al.</i> ^[14] (2012) | Köbe <i>et al.</i> ^[12] (2013) | Jarman <i>et al.</i> ^[16] (2013) | Burke <i>et al.</i> ^[9] (ongoing, initial results) |
|---|--|---|--|---|--|--|--|
| Number of patients | 55 | 16 | 40 | 118 | 69 | 111 | 304 |
| Male | 80% | 56% | 70% | 75% | 73% | N/A | 74% |
| Age [median (range)/ mean \pm SD] | 56 \pm 13 | 23 (10-48) | 42 \pm 15 | 50 \pm 15 | 46 \pm 16 | 33 (10-87) | 52 \pm 16 |
| Primary prevention | 78% | N/A | 44% | 60% | 59% | 50% | 79% |
| Secondary prevention | 22% | N/A | 56% | 40% | 41% | 50% | 21% |
| Underlying pathology | | | | | | | |
| Ischemic cardiomyopathy or idiopathic dilated cardiomyopathy | 85% | 0% | 45% | 57% | 52% | 19% | 52% |
| Hypertrophic cardiomyopathy | N/A | 0% | 13% | N/A | 15% | 20% | 9% |
| Congenital heart disease | 4% | 25% | 3% | 1% | 4% | 12% | N/A |
| Electrical heart disease ¹ | N/A | 75% | 33% | 26% | 20% | 43% | 12% |
| Others | 11% | 0% | 6% | 16% | 10% | 7% | 27% |
| Follow-up | | | | | | | |
| Mean/median follow-up (mo) | 10 | 9 | 8 | 18 | 7 | 13 | N/A |
| Patients with re-interventions | 6 (11) | 3 (19) | 5 (13) | 16 (14) | 3 (4) | 19 (17) | 92% procedure-related complication-free rate at 180 d |
| Patients with inappropriate shocks | 5 (9) | 4 (25) | 2 (5) | 15 (13) | 3 (4) | 17 (15) | 38 (13) |
| Patients with appropriate shocks | 3 (5) | 4 (25) | 4 (10) | 8 (7) | 3 (4) | 13 (12) | 16 (5) |
| Spontaneous VT/VF episode successfully converted by S-ICD or spontaneously converted | 100% | 100% [2 VF episodes with prolonged time (24 and 27 s) to therapy] | 96% (1 episode of electrical storm was terminated by external shocks) | 100% | 100% | 96% (1 death, see text for details) | 100% |

¹Brugada syndrome; long QT syndrome; catecholamine polymorphic ventricular tachycardia; idiopathic ventricular fibrillation. N/A: Data not available; S-ICD: Subcutaneous implantable cardioverter-defibrillator; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

T-wave oversensing) rates are similar to that of previous TV-ICD studies^[11,18]. An interesting observation in some of the studies was that more complications occurred with the first implants, suggesting a physician-related learning curve^[14,16]. The 2 United Kingdom registries by Jarman *et al.*^[15,16] from 2012 and 2013 that included 16 and 111 patients respectively, are of particular interest since they report on a different patient profile - younger individuals (23 and 33 years) with a higher prevalence of electrical inherited heart diseases (43 and 75%) and congenital structural heart diseases (12 and 25%). Both registries informed a higher rate of re-operations (17 and 19%) and inappropriate shocks (15 and 25%) than the other 4 case series. These findings were in part related to the greater incidence of T-wave oversensing (10% and 25%), since this not only caused inappropriate shocks but also led to device-explantation (0 and 5%) when present in multiple vectors. Therefore and with the study limitations (retrospective case series) in mind, it seems like T-wave oversensing may be a greater problem in young patients. As suggested by the authors, this could be ameliorated by increasing the pre-implantation requisite of satisfactory R-wave/T-wave ratio templates to > 1 in the three available sensing configurations (the manufacture currently recommends 1 satisfactory template). Furthermore, screening during exercise may be useful to assess for R-wave/T-wave ratio template changes during exertion^[15,16].

Finally, one arrhythmic death has so far been re-

ported, however without evidence of device malfunction since the lowest detection rate was programmed to 180 bpm, and a monomorphic VT was appropriately detected at first but later fell below 180 bpm and therapy was subsequently aborted with the VT continued for a significant amount of time below the programmed rate limit. The VT later degenerated into VF, which was appropriately detected and shocked into a slow ventricular escape rhythm that did not respond to post-shock pacing^[16].

ONGOING CLINICAL STUDIES

There are currently several ongoing clinical studies that shall help to provide more information on the safety and effectiveness of S-ICD, and importantly, compare its performance to the conventional TV-ICD system. Two important studies are the Evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry (NCT01085435)^[19], and the Prospective randomized comparison of subcutaneous and transvenous implantable cardioverter-defibrillator therapy (PRAETORIAN) trial (NCT01296022)^[20].

The EFFORTLESS S-ICD Registry^[19] is an observational, nonrandomized study assessing the standard of care in approximately 50 investigational centers in Europe and New Zealand where the device had been approved for commercial use at the start of the study. The endpoints of the main registry, with an estimated target

Table 3 Subcutaneous implantable cardioverter-defibrillator patient suitability

| Suitable | Unsuitable |
|-------------------------------------|---|
| Young and active | Present (or high risk of) AV conduction loss requiring pacing |
| No venous access | Recurrent monomorphic VT |
| Permanent indwelling catheters | CRT indication |
| High infection risk | |
| Electrical heart disease | |
| Congenital structural heart disease | |

AV: Atrioventricular; CRT: Cardiac resynchronization therapy; VT: Ventricular tachycardia.

sample size of 1000 patients and at least 60 mo' follow-up, are perioperative (30 d post-implant) complication-free rate, 360-d complication free-rate, and proportion of inappropriate shocks for atrial tachyarrhythmias. The study will also enroll 250 patients from the main registry to the PRO substudy (12 mo follow-up) that will evaluate the patient perspective (*e.g.*, quality of life) and hospital personnel implant and follow-up experience with the S-ICD. Initial results from the EFFORTLESS S-ICD Registry were presented in June 2012 by which time 219 patients had been enrolled^[21]. Fourteen patients had experienced 19 VT/VF episodes with successful conversion in all instances. In addition, the proportion of device-related complications and inappropriate shocks were lower than previously reported in the IDE trial^[10].

For the first time, in the randomized prospective PRAETORIAN trial^[20] which aims to recruit 700 patients from various centers from the Netherlands with class I or II a ICD indication^[17] and without indication for pacing therapy, the S-ICD is being compared against conventional TV-ICD systems. The primary study objective is to demonstrate non-inferiority of the S-ICD to the TV-ICD in terms of the composite of inappropriate shocks and ICD-related complications. The follow-up is estimated to a median of 30 mo. The S-ICD will be programmed with the conditional zone activated with the discriminator rate cutoff between 180 and 250 bpm. The TV-ICDs will be programmed with a monitor zone (> 167 bpm), fast VT zone (> 182 bpm) with 1 sequence of ATP followed by shocks, and a VF zone with high-energy shocks only (> 250 bpm).

WHAT PATIENTS SHOULD RECEIVE A SUBCUTANEOUS CARDIAC DEFIBRILLATOR?

Given the lack of long-term data on the S-ICD safety and performance in comparison with the conventional TV-ICDs, one can only speculate on different patient group's suitability for the subcutaneous system (Table 3). Nevertheless, patients with pacing indication (bradycardia pacing, CRT, and ATP for recurrent monomorphic VTs) should not receive an S-ICD since this feature is not offered. Furthermore patients with documented slow VTs

(< 170 bpm) represent another patient group unsuitable for the S-ICD since the VT rate would fall below the programmable VT zone (minimum of 170 bpm) and subsequently not be treated. On the contrary, in certain patient groups (congenital heart disease, indwelling catheters, or immunocompromised), where implantation of the TV-ICD system is either technically difficult (or even impossible) and/or is associated with increased procedural risk, the S-ICD represents an attractive and suitable therapeutic option. Moreover, in young and active patients with a long life expectancy, a TV-ICD is associated with significant risk of lead failure and need for reinterventions. Thus, young patients with electrical heart diseases (*e.g.*, Brugada syndrome, long QT syndrome, and hypertrophic cardiomyopathy) with low risk of bradycardia and monomorphic VT, theoretically constitute another group where the S-ICD may be the preferred device. However, caution in this patient group is at present warranted since the S-ICD system longevity (including the subcutaneous leads) is currently unknown, and initial data indicate a higher rate of inappropriate shocks due to T-wave oversensing in younger individuals^[15,16].

Nonetheless, in real life clinical practice the majority of patients with ICD indication have ischemic cardiomyopathy or idiopathic dilated cardiomyopathy and they do not belong to any of the previously discussed groups. The initial clinical studies showed that the S-ICD was safe and effective in this patient profile, however long-term prospective data evaluating important aspects like the development of a pacing indication is missing. Nevertheless, this issue has been addressed by a recently published single-center retrospective analysis of 2712 patients that received an ICD during 2002 and 2011^[22]. Half of the patients had a pacing indication and were excluded from the analysis, and of the remaining 1345 patients, the majority with ischemic cardiomyopathy, the combined endpoint (necessity for cardiac pacing, appropriate ATP without subsequent shock or device upgrade) was reached in 34% after a median follow-up of 3.4 years. Secondary prevention, NYHA class III/IV, QRS duration were independent determinants of future unsuitability for the S-ICD. Despite its obvious limitations, the study provides data from a real-life cohort, which shows that a large proportion of patients could represent potential suitable S-ICD candidates.

CONCLUSION

The S-ICD represents an important innovation that has recently gained approval for commercial use in Europe, New Zealand and the United States. Compared to the conventional TV-ICD it avoids the potential risks associated with the periprocedural and long-term complications associated with endovascular leads. Currently ongoing clinical studies shall help to establish the S-ICD system's long-term performance, including subcutaneous lead longevity, better define optimal patient groups that would benefit more, and offer prospective comparisons against

the conventional TV-ICD system, thereby determine the therapeutic potential of this new device technology.

REFERENCES

- Bardy GH**, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225-237 [PMID: 15659722 DOI: 10.1056/nejmoa043399]
- Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877-883 [PMID: 11907286 DOI: 10.1056/nejmoa013474]
- Connolly SJ**, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; **21**: 2071-2078 [PMID: 11102258 DOI: 10.1053/ehj.2000.2476]
- Curtis JP**, Luebbert JJ, Wang Y, Rathore SS, Chen J, Heidenreich PA, Hammill SC, Lampert RI, Krumholz HM. Association of physician certification and outcomes among patients receiving an implantable cardioverter-defibrillator. *JAMA* 2009; **301**: 1661-1670 [PMID: 19383957 DOI: 10.1001/jama.2009.547]
- Kleemann T**, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of ≥ 10 years. *Circulation* 2007; **115**: 2474-2480 [PMID: 17470696 DOI: 10.1161/circulationaha.106.663807]
- Arias MA**, Domínguez-Pérez L, Toquero J, Jiménez-Candil J, Olagüe J, Díaz-Infante E, Tercedor L, Valverde I, Castro J, García-Fernández FJ, Rodríguez-Padial L. Sprint fidelis defibrillation lead: a nine-center experience in Spain. *Rev Esp Cardiol* 2011; **64**: 312-318 [PMID: 21377260 DOI: 10.1016/j.recesp.2010.11.008]
- Eckstein J**, Koller MT, Zabel M, Kalusche D, Schaer BA, Osswald S, Sticherling C. Necessity for surgical revision of defibrillator leads implanted long-term: causes and management. *Circulation* 2008; **117**: 2727-2733 [PMID: 18490526 DOI: 10.1161/circulationaha.107.740670]
- Bardy GH**, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010; **363**: 36-44 [PMID: 20463331 DOI: 10.1056/nejmoa0909545]
- Burke MC**. Safety and efficacy of a subcutaneous implantable defibrillator (S-ICD). Heart rhythm society 33rd annual scientific sessions; 2012 May 9-12; Boston, USA; 2012
- Gold MR**, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, Wood MA, Burke MC. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J Cardiovasc Electro-physiol* 2012; **23**: 359-366 [PMID: 22035049 DOI: 10.1111/j.1540-8167.2011.02199.x]
- Aydin A**, Hartel F, Schlüter M, Butter C, Köbe J, Seifert M, Gosau N, Hoffmann B, Hoffmann M, Vettorazzi E, Wilke I, Wegscheider K, Reichenspurner H, Eckardt L, Steven D, Willems S. Shock efficacy of subcutaneous implantable cardioverter-defibrillator for prevention of sudden cardiac death: initial multicenter experience. *Circ Arrhythm Electro-physiol* 2012; **5**: 913-919 [PMID: 22923274 DOI: 10.1161/circcep.112.973339]
- Köbe J**, Reinke F, Meyer C, Shin DI, Martens E, Kääh S, Löher A, Amler S, Lichtenberg A, Winter J, Eckardt L. Implantation and follow-up of totally subcutaneous versus conventional implantable cardioverter-defibrillators: a multicenter case-control study. *Heart Rhythm* 2013; **10**: 29-36 [PMID: 23032867 DOI: 10.1016/j.hrthm.2012.09.126]
- Dabiri Abkenari L**, Theuns DA, Valk SD, Van Belle Y, de Groot NM, Haitsma D, Muskens-Heemskerk A, Szili-Torok T, Jordaens L. Clinical experience with a novel subcutaneous implantable defibrillator system in a single center. *Clin Res Cardiol* 2011; **100**: 737-744 [PMID: 21416191 DOI: 10.1007/s00392-011-0303-6]
- Olde Nordkamp LR**, Dabiri Abkenari L, Boersma LV, Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA, Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. *J Am Coll Cardiol* 2012; **60**: 1933-1939 [PMID: 23062537 DOI: 10.1016/j.jacc.2012.06.053]
- Jarman JW**, Lascelles K, Wong T, Markides V, Clague JR, Till J. Clinical experience of entirely subcutaneous implantable cardioverter-defibrillators in children and adults: cause for caution. *Eur Heart J* 2012; **33**: 1351-1359 [PMID: 22408031 DOI: 10.1093/eurheartj/ehs017]
- Jarman JW**, Todd DM. United Kingdom national experience of entirely subcutaneous implantable cardioverter-defibrillator technology: important lessons to learn. *Europace* 2013; **15**: 1158-1165 [PMID: 23449924 DOI: 10.1093/europace/eut016]
- Epstein AE**, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008; **117**: e350-e408 [PMID: 18483207 DOI: 10.1161/circulationaha.108.189742]
- van Rees JB**, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ, Schalij MJ. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *J Am Coll Cardiol* 2011; **57**: 556-562 [PMID: 21272746 DOI: 10.1016/j.jacc.2010.06.059]
- Pedersen SS**, Lambiasi P, Boersma LV, Murgatroyd F, Johansen JB, Reeve H, Stuart AG, Adragao P, Theuns DA. Evaluation of Factors Impacting CLinical Outcome and Cost Effectiveness of the S-ICD: design and rationale of the EFFORTLESS S-ICD Registry. *Pacing Clin Electro-physiol* 2012; **35**: 574-579 [PMID: 22360677 DOI: 10.1111/j.1540-8159.2012.03337.x]
- Olde Nordkamp LR**, Knops RE, Bardy GH, Blaauw Y, Boersma LV, Bos JS, Delnoy PP, van Dessel PF, Driessen AH, de Groot JR, Herrman JP, Jordaens LJ, Kooiman KM, Maass AH, Meine M, Mizusawa Y, Molhoek SG, van Opstal J, Tijssen JG, Wilde AA. Rationale and design of the PRAETORIAN trial: a Prospective, RANdomizEd comparison of

- subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. *Am Heart J* 2012; **163**: 753-760.e2 [PMID: 22607851 DOI: 10.1016/j.ahj.2012.012]
- 21 **Lambiase P**, Barr CS, Knops RE, Murgatroyd F, Johansen JB, Boersma L. International Experience with a Subcutaneous ICD; Preliminary Results of the EFFORTLESS S-ICD Registry. *Cardiotim*; 2012 June 13-16; Nice, France; 2012
- 22 **de Bie MK**, Thijssen J, van Rees JB, Putter H, van der Velde ET, Schalij MJ, van Erven L. Suitability for subcutaneous defibrillator implantation: results based on data from routine clinical practice. *Heart* 2013; **99**: 1018-1023 [PMID: 23704324 DOI: 10.1136/heartjnl-2012-303349]

P- Reviewers De Ponti R, Kettering K, Steinberg JS
S- Editor Song XX **L- Editor** A **E- Editor** Wang CH



Cardiac resynchronization therapy in acute pulmonary edema: A case report

Emad A Barsoum, Tariq Bhat, Deepak Asti, Marcin Kowalski, Thomas Vazzana

Emad A Barsoum, Deepak Asti, Department of Medicine, Staten Island University Hospital, New York, NY 10305, United States

Tariq Bhat, Marcin Kowalski, Thomas Vazzana, Division of Cardiology, Staten Island University Hospital, New York, NY 10305, United States

Author contributions: All the authors contributed to this manuscript.

Correspondence to: Dr. Emad A Barsoum, MD, Department of Medicine, Staten Island University Hospital, 475 Seaview Ave, Staten Island, New York, NY 10305,

United States. emad_barsoum@siuh.com

Telephone: +1-347-6669321 Fax: +1-718-2268695

Received: July 14, 2013 Revised: August 14, 2013

Accepted: August 20, 2013

Published online: September 26, 2013

Abstract

We are reporting a case of 71-year old lady with a dual chamber demand pacemaker, who developed acute pulmonary edema due to an acute left ventricular (LV) dysfunction and worsening in mitral valve regurgitation after atrioventricular nodal ablation for uncontrolled atrial fibrillation. This was attributed to right ventricular apical pacing leading to LV dyssynchronization. Patient dramatically improved within 12-24 h after upgrading her single chamber pacemaker to biventricular pacing. Our case demonstrates that biventricular pacing can be an effective modality of treatment of acute congestive heart failure. In particular, it can be used when it is secondary to LV dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with atrioventricular nodal ablation for chronic atrial fibrillation.

© 2013 Baishideng. All rights reserved.

Key words: Acute congestive heart failure; Cardiac resynchronization therapy pacemaker; Pacing; Cardiac biventricular pacing

Core tip: Our case demonstrates that biventricular pacing (cardiac resynchronization therapy pacemaker, CRT-P) can be an effective modality of treatment in acute congestive heart failure. In particular, it can be used when it is secondary to left ventricular dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with atrioventricular (AV) nodal ablation for chronic atrial fibrillation. Our case matches recent update to guidelines that CRT can be useful in patients with atrial fibrillation and left ventricular ejection fraction (LVEF) $\leq 35\%$ if AV nodal ablation will allow ventricular pacing with CRT except our patient has LVEF $> 35\%$.

Barsoum EA, Bhat T, Asti D, Kowalski M, Vazzana T. Cardiac resynchronization therapy in acute pulmonary edema: A case report. *World J Cardiol* 2013; 5(9): 355-358 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/355.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.355>

INTRODUCTION

The detrimental effects of right ventricular apical (RVA) pacing on left ventricular (LV) hemodynamics have been well documented and a higher incidence of heart failure hospitalizations or death in patients with chronic RVA pacing has been attributed to the ventricular dyssynchronization^[1,2]. Theoretically, acute RVA pacing could induce discrepancy between electric and mechanical ventricular synchronization resulting in asynchronous left ventricular contraction and relaxation. However, the exact mechanisms of acute LV dysfunction after RVA pacing are not fully understood.

Biventricular pacing (BVP) in chronic heart failure patients within the New York Heart Association (NYHA) functional class III or IV with LV dysfunction and prolonged QRS duration have led to improvement in both

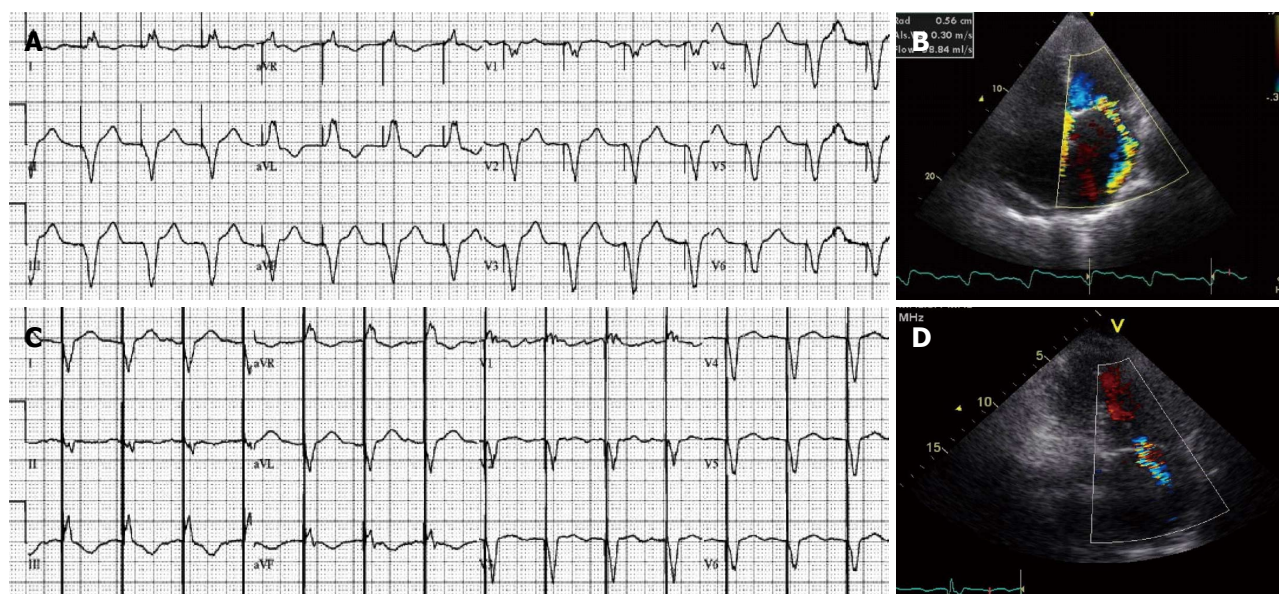


Figure 1 Electrocardiogram and echocardiographic examination. A: Twelve lead electrocardiogram after atrioventricular nodal ablation showing pacing rhythm by dual-chamber pacing pacemaker; B: Echocardiography showed moderate to severe mitral regurgitation before cardiac resynchronization therapy pacemaker (CRT-P); C: Twelve lead electrocardiogram after cardiac resynchronization therapy pacemaker; D: Echocardiography showed mild mitral regurgitation after CRT-P.

morbidity and mortality^[3-8]. In addition, cardiac resynchronization therapy (CRT) became the innovative treatment of congestive heart failure, and its use has been extended to patients with NYHA functional class I or II^[9-11].

In our case report, we address the benefit and therapeutic role of CRT pacing in patients who developed acute ventricular dysfunction and worsening in mitral regurgitation due to RVA pacing after atrio-ventricular node ablation for refractory atrial fibrillation.

CASE REPORT

A 71-year old woman presented to the emergency department with a chief complaint of worsening dyspnea and orthopnea for three days (NYHA class IV), she had an atrioventricular (AV) nodal ablation for refractory atrial fibrillation five days prior to presentation. Patient had a history of atrial fibrillation, mild mitral regurgitation, hypothyroidism, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, obstructive sleep apnea, chronic kidney disease, primary biliary cirrhosis. She had a history of permanent dual chamber pacemaker that was inserted two years ago for symptomatic bradycardia secondary to sick sinus syndrome after atrial fibrillation cardioversion.

On admission she was orthopneic, tachycardic and hypoxic that partially improved by using bi-level positive airway pressure. Physical exam revealed positive S1 and S2 heart sounds with a summation gallop, a grade 4/6 apical systolic murmur and a left parasternal systolic murmur that accentuates with inspiration. There was a jugular venous distention up to jaw line. On lung auscultation, there were bibasilar crackles heard. The patient also had bilateral pedal edema. An electrocardiogram (EKG) showed ventricular pacing with a rate of 90 beats per minute (bpm) and QRS duration of 200 ms with positive

R in Lead I (Figure 1A). Echocardiographic examination demonstrated decreased left ventricular function (40%), a LV end-diastolic volume (LVEDV) of 97 mL, markedly dilated left atrium (6.1 cm). There were moderate to severe mitral regurgitation (Figure 1B) and moderate to severe tricuspid regurgitation. Pacemaker interrogation showed that the pacemaker was programmed in a DDD mode with lower rate of 60 bpm and upper tracking rate of 120 bpm.

The patient was diagnosed as pulmonary edema and was admitted to the coronary care unit (CCU). She was placed on maximal medical therapy for five days without improvement. Acute ischemic event was ruled out by serial cardiac enzymes. The worsening symptoms and LV dysfunction were attributed to RVA pacing, which then was leading to dyssynchrony and worsening mitral regurgitation.

We decided to upgrade her pacemaker to biventricular (cardiac resynchronization therapy pacemaker, CRT-P), by adding new lead through the coronary sinus to accomplish left ventricular pacing. The old right atrial and right ventricular leads were connected to the CRT pacemaker. Immediately post operatively, the patient reported feeling better and her symptoms improved (NYHA class III). Follow up EKG showed ventricular pacing with a rate of 90 bpm with reduction in QRS duration to 156 ms with negative R in Lead I (Figure 1C). Forty-eight hours after surgery echocardiography demonstrated improvement in LV function (45%) with a reduction in LVEDV to 88 mL and improvement in mitral regurgitation (Figure 1D). The patient was discharged without complication from CCU.

DISCUSSION

Since the introduction of cardiac pacing five decades ago

as an effective treatment for symptomatic bradycardia, scientists have pursued the goal of better approximating the normal cardiac physiology leading to more highly sophisticated devices^[12,13]. BVP has been found to resynchronize ventricular contraction in heart failure patients with wide QRS complexes, leading not only to reversal of LV remodeling over time but also increased functional capacity with an improvement in mortality and quality of life^[14,15].

The main indication for CRT is congestive heart failure patients with wide QRS and left ventricular dysfunction (ejection fraction $\leq 35\%$), who are symptomatic even while on maximal medical therapy. Also, CRT can be useful in patients with atrial fibrillation and left ventricular ejection fraction $\leq 35\%$ if AV nodal ablation will allow ventricular pacing with CRT^[16]. According to recent guidelines from the European Society of Cardiology, CRT can be an alternative to traditional right ventricular pacing in patients with heart failure and LV dysfunction who have a standard indication for pacing^[17].

Although, biventricular pacing can reverse the dyssynchronization induced by RVA pacing and trials have shown the benefit of biventricular pacing in patients with symptomatic atrial fibrillation after AV nodal ablation^[18-20]. A recent meta-analysis of four trials did not demonstrate improvement in mortality with BVP in comparison with RVA pacing^[21].

Mitral regurgitation is common in patient with left ventricular dysfunction that negatively affect the survival of patients with congestive heart failure^[22], but CRT has been shown to reduce functional mitral regurgitation by optimizing the force balance acting on the mitral valve^[23].

Our patient developed acute pulmonary edema after two days of atrio-ventricular node ablation, mostly secondary to left ventricular dyssynchrony, which led to worsening of her mitral regurgitation. This in turn caused pulmonary edema. Despite optimization of medical treatment, her symptoms didn't improve for five days in CCU, the patient dramatically improved within hours of changing the right ventricular pacemaker to CRT-P. This improvement included a reduction in severity of the status of her mitral regurgitation as well as an alleviation of her symptoms.

Our case demonstrates that biventricular pacing (CRT-P) can be an effective modality of treatment of acute congestive heart failure. In particular, it can be used when it is secondary to LV dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with AV nodal ablation for chronic atrial fibrillation.

REFERENCES

- 1 **Tops LE**, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. *J Am Coll Cardiol* 2006; **48**: 1642-1648 [PMID: 17045901]
- 2 **Tse HF**, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002; **40**: 1451-1458 [PMID: 12392836]
- 3 **Sutton MG**, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchay E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* 2006; **113**: 266-272 [PMID: 16401777]
- 4 **Young JB**, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; **289**: 2685-2694 [PMID: 12771115]
- 5 **Abraham WT**, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; **346**: 1845-1853 [PMID: 12063368]
- 6 **Cazeau S**, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; **344**: 873-880 [PMID: 11259720]
- 7 **Auricchio A**, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schöndube F, Wolfhard U, Böcker D, Krahnefeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002; **39**: 2026-2033 [PMID: 12084604]
- 8 **Higgins SL**, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003; **42**: 1454-1459 [PMID: 14563591]
- 9 **Linde C**, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008; **52**: 1834-1843 [PMID: 19038680 DOI: 10.1016/j.jacc.2008.08.027]
- 10 **Tang AS**, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; **363**: 2385-2395 [PMID: 21073365 DOI: 10.1056/NEJMoa1009540]
- 11 **Moss AJ**, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**: 1329-1338 [PMID: 19723701 DOI: 10.1056/NEJMoa0906431]
- 12 **Jeffrey K**, Parsonnet V. Cardiac pacing, 1960-1985: a quarter century of medical and industrial innovation. *Circulation* 1998; **97**: 1978-1991 [PMID: 9609092]
- 13 **Trohan RG**, Kim MH, Pinski SL. Cardiac pacing: the state of the art. *Lancet* 2004; **364**: 1701-1719 [PMID: 15530632]
- 14 **Bristow MR**, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140-2150 [PMID: 15152059]

- 15 **Cleland JG**, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352**: 1539-1549 [PMID: 15753115]
- 16 **Tracy CM**, Epstein AE, Darbar D, Dimarco JP, Dunbar SB, Estes NA, Ferguson TB, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012; **60**: 1297-1313 [PMID: 22975230 DOI: 10.1016/j.jacc.2012.07.009]
- 17 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787-1847 [PMID: 22611136 DOI: 10.1093/eurheartj/ehs104]
- 18 **Leclercq C**, Cazeau S, Lellouche D, Fossati F, Anselme F, Davy JM, Sadoul N, Klug D, Mollo L, Daubert JC. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. *Pacing Clin Electrophysiol* 2007; **30** Suppl 1: S23-S30 [PMID: 17302711]
- 19 **Orlov MV**, Gardin JM, Slawsky M, Bess RL, Cohen G, Bailey W, Plumb V, Flathmann H, de Metz K. Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. *Am Heart J* 2010; **159**: 264-270 [PMID: 20152225 DOI: 10.1016/j.ahj.2009.11.012]
- 20 **Doshi RN**, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005; **16**: 1160-1165 [PMID: 16302897]
- 21 **Chatterjee NA**, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail* 2012; **14**: 661-667 [PMID: 22436544 DOI: 10.1093/eurjhf/hfs036]
- 22 **Trichon BH**, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003; **91**: 538-543 [PMID: 12615256]
- 23 **Solis J**, McCarty D, Levine RA, Handschumacher MD, Fernandez-Friera L, Chen-Tournoux A, Mont L, Vidal B, Singh JP, Brugada J, Picard MH, Sitges M, Hung J. Mechanism of decrease in mitral regurgitation after cardiac resynchronization therapy: optimization of the force-balance relationship. *Circ Cardiovasc Imaging* 2009; **2**: 444-450 [PMID: 19920042 DOI: 10.1161/CIRCIMAGING.108.823732]

P- Reviewers Chawla M, Durandy Y, Liu T, Petix N, Vermeersch P, Xanthos T **S- Editor** Gou SX **L- Editor** A **E- Editor** Wang CH



Exercise-induced left bundle branch block: an infrequent phenomenon: Report of two cases

Salah AM Said, Marisa Bultje-Peters, Rogier LG Nijhuis

Salah AM Said, Marisa Bultje-Peters, Rogier LG Nijhuis, Department of Cardiology, Hospital Group Twente, 555 DL Hengelo, The Netherlands

Author contributions: Said SAM, Bultje-Peters M and Nijhuis RLG contributed to this paper; all authors have approved the final version of the paper.

Correspondence to: Salah AM Said, MD, PhD, FESC, Department of Cardiology, Hospital Group Twente, Geerdinksweg 141, 7555 DL Hengelo, The Netherlands. samsaid@home.nl

Telephone: +31-74 -2905286 Fax: +31-74-2905289

Received: May 31, 2013 Revised: July 29, 2013

Accepted: August 17, 2013

Published online: September 26, 2013

described. The first patient with typical angina pectoris had significant obstructive coronary artery disease (CAD) requiring percutaneous coronary intervention of multiple lesions including placement of drug eluting stents. The second patient had atypical chest pain without signs of CAD at all. Both patients are discussed and the literature is reviewed.

Said SAM, Bultje-Peters M, Nijhuis RLG. Exercise-induced left bundle branch block: an infrequent phenomenon: Report of two cases. *World J Cardiol* 2013; 5(9): 359-363 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/359.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.359>

Abstract

Exercise-induced left bundle branch block (EI-LBBB) is infrequent phenomenon. We present two patients with angina pectoris who developed EI-LBBB during exercise tolerance test. The first patient with typical angina pectoris had significant obstructive coronary artery disease (CAD) requiring percutaneous coronary intervention of multiple lesions including placement of drug eluting stents. The second patient had atypical chest pain without signs of CAD at all. EI-LBBB occurred at a heart rate of 80 bpm and 141 bpm in the first and second patient, respectively. EI-LBBB remained visible through the test till the recovery period in the first patient at a heart rate of 83 bpm and disappeared at 96 bpm in the second patient. Both patients with this infrequent phenomenon are discussed and the literature is reviewed.

© 2013 Baishideng. All rights reserved.

Key words: Angina pectoris; Electrocardiography; Exercise tolerance test; Left bundle branch block; Coronary artery disease.

Core tip: Two patients who presented with angina pectoris and exercise-induced left bundle branch block are

INTRODUCTION

The estimated prevalence of permanent left bundle branch block (LBBB) in the general population is 1.5%^[1], 0.43% for men and 0.28% for women of middle age^[2]. Exercise-induced transient LBBB (EI-LBBB) is infrequent and occurs in 0.4%-0.5% of patients undergoing exercise tolerance tests (ETT)^[3-5]. Grady *et al*^[5] have shown that transient EI-LBBB is an independent predictor for major cardiovascular morbidity and mortality. A longitudinal study demonstrated that coronary artery disease and heart failure were more prevalent in patients with EI-LBBB^[4]. The mechanism of transient EI-LBBB remains unclear, it may reflect concomitant valvular heart disease, cardiomyopathy, congenital heart disease, conduction abnormalities or coronary artery disease (CAD). Generally, permanent LBBB may be associated with a deterioration of left ventricular function, mechanical dyssynchrony and heart failure^[6]. Furthermore, it has also been reported that transient EI-LBBB may result in reversible left ventricular dyssynchrony^[7].

In some patients, EI-LBBB may be the first manifestation of diffuse heart disease and its presence is associ-

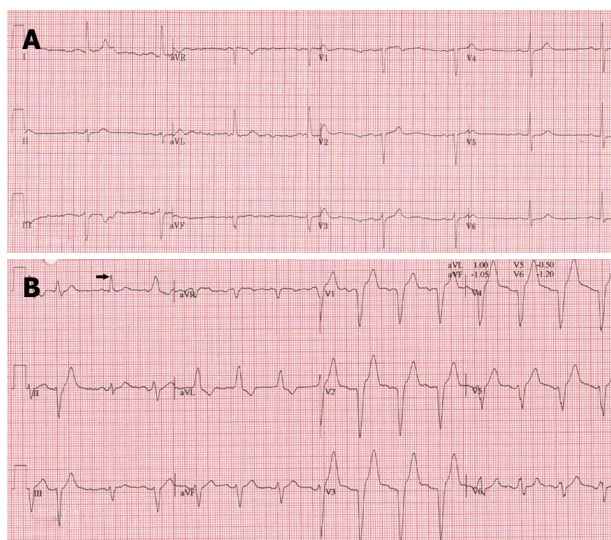


Figure 1 Resting electrocardiogram demonstrating sinus rhythm at 48 bpm with slow progression of R wave in the right precordial leads V₁-V₄ without delayed conduction (A) and during exercise tolerance testing at a heart rate of 80 bpm a left bundle branch block occurred which persisted into the recovery period (B).

ated with a poorer prognosis compared to normal intraventricular conduction and right bundle branch block (RBBB) without concomitant cardiac disorders^[8]. We present two adult patients with exercise-induced LBBB in the presence or absence of CAD and an attempt is made to review the international literature.

CASE REPORT

Case 1

An 80-year-old male with well treated hypertension and paroxysmal atrial fibrillation was evaluated for chest pain exaggerated by physical stress with a good reaction to sublingual nitroglycerin. On examination his body mass index (BMI) was 29 kg/m², rest blood pressure was 129/81 mmHg and rest heart rate of 60 bpm. Neither cardiac murmur or signs of congestive heart failure were present. The rest of the examination was normal. Resting electrocardiogram (ECG) depicted sinus rhythm (SR) with left axis deviation and slow progression of R-waves in V₁₋₄ (Figure 1A). Transthoracic echocardiography (TTE) revealed a normal left ventricle ejection fraction (LVEF) of 0.64, LV hypertrophy, inferior wall hypokinesia, bi-atrial dilatation, mild mitral and tricuspid regurgitation with normal estimated pulmonary artery pressure of 20 mmHg. On routine ETT 120% of target exercise tolerance was reached and 87% of the maximal heart rate. He developed EI-LBBB at frequency of 80 bpm (Figure 1B), which lasted, through the third minute of the recovery period, till the end of the test at a heart rate of 83 bpm. At coronary angiography, significant stenoses were found in the left anterior descending and circumflex coronary arteries. Percutaneous coronary intervention was performed and both lesions were dilated with placement of DES. Accordingly a drug therapy was started composed

of aspirin for 1 mo, clopidogrel for 1 year and oral anti-coagulant, lipid lowering drug, hydrochlorothiazide and irbesartan as a maintenance drug regimen.

Case 2

A 58-year-old female with known subclinical hypothyroidism without risk factors for CAD was analyzed for exercise-related oppressive chest pain. She had no previous history of cardiovascular disease. On physical examination, BMI was 21 kg/m², rest blood pressure of 117/70 mmHg and rest heart rate regular of 85 bpm, central venous pressure was not elevated and further physical examination was otherwise unremarkable. Resting ECG (Figure 2A) revealed SR with normal findings and biochemical values, all were within normal limits. Findings of TTE were all normal. On echocardiography no intraventricular dyssynchrony was observed as TTE was performed at rest during normal conduction. The LVEF was 0.65. Nuclear stress myocardial perfusion studies revealed no reversible or irreversible defects, but EI-LBBB developed during the exercise phase at a heart rate of 141 bpm (Figure 2B) and a QRS width of 138 ms which was accompanied with chest discomfort. EI-LBBB disappeared at a frequency of 96 bpm. Beta blocker was initiated and on repeated bicycle ergometer test performed one month later, EI-LBBB accompanied with chest pain occurred at a slower heart rate of 129 bpm (Figure 2C) which recovered at a rate of 100 bpm (Figure 2D). Due to persistence of the chest complaints and occurrence of EI-LBBB during myocardial perfusion test despite normal findings (resting ECG and failure to demonstrate any reversible/irreversible defects in the nuclear stress myocardial perfusion), a decision was made to perform CAG which revealed normal coronary arterial tree. The β -blocker therapy was discontinued. An explanation for the failure of beta-blocker to abolish EI-LBBB may be related to inappropriate dose of the drug used for an “unknown” substrate.

Definitions

Maximal heart rate: Was calculated as (220 - age), predicted maximal heart rate and directly measured maximal heart rate from the ECG.

Target heart rate: About 85% of the maximal heart rate, based on age, gender and length. Exercise tolerance test (ETT): were performed on a bicycle ergometer in accordance with the guidelines for exercise testing^[9]. All exercise tests were assessed by a cardiologist, specialized nurse and/or a nurse practitioner. Exercise test end points were defined by the following: (1) Positive: ECG evidence of myocardial ischemia, ≥ 1.0 mm horizontal shift of the ST segment at 80 ms after the J point in comparison with the baseline ECG and/or a 30 mmHg decrease in systolic blood pressure and/or ventricular arrhythmia and/or typical limiting anginal complaints; (2) Negative: in the absence of any of the above cited criteria; (3) Intermediate: < 1.0 mm ST segment depres-

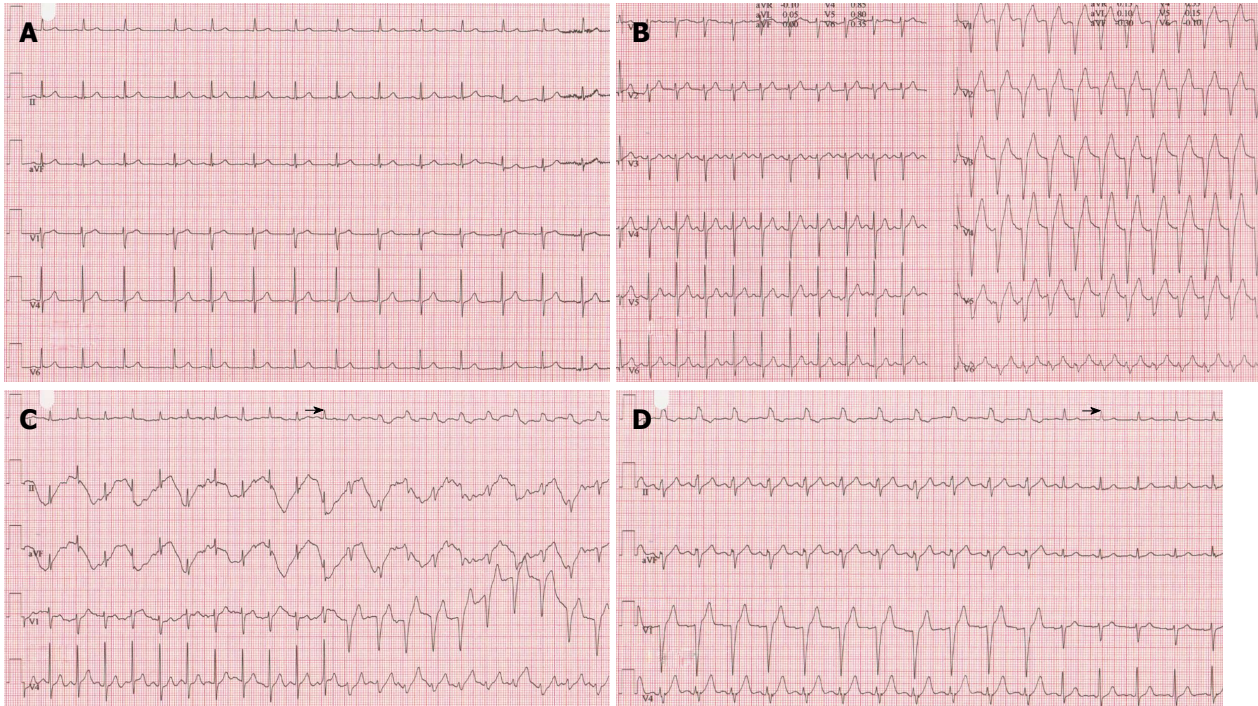


Figure 2 Resting electrocardiogram depicting normal sinus rhythm at a rate of 85 bpm with normal conduction (A), during exercise tolerance testing normal conduction till a frequency of 129 bpm (left panel) and at a heart rate of 141 bpm (right panel) a left bundle branch block occurred which recovered at a frequency of 96 bpm (not shown) (B), on repeat exercise tolerance tests, under β -blocker therapy, exercise-induced left bundle branch block occurred at a heart rate of 129 bpm (C) and disappeared at a frequency of 100 bpm (D). Black arrows indicate the transition from normal to abnormal conduction and vice versa.

sion as compared to baseline ECG and/or non-specific anigal complaints in the absence of ECG evidence of ischemia; and (4) Non-interpretable: if less than 85% of the target heart rate was reached and absence of the criteria of a positive test.

Left bundle branch block: The diagnosis of complete LBBB was made from the 12-lead ECG if all the following criteria were accordingly met: (1) a QRS duration ≥ 120 ms, (2) predominantly upright complexes with broad-slurred R waves in leads I and V_6 , (3) a QS or rS pattern in V_1 and (4) absence of q wave in leads I or V_6 .

DISCUSSION

Intermittent bundle branch block was first described by Lewis in 1913^[10]. Exercise-induced LBBB associated with angina pectoris in the presence of normal coronary arteries is infrequent but a well known clinical entity and has been reported earlier by Vieweg *et al*^[11] in 1976. It has been found in association with underlying structural heart disease^[12], slow arterial coronary flow^[13], coronary spasm^[14] and also in subjects without heart disease^[15]. Virtanen *et al*^[16] defined the chest complaints as atypical characterized by sudden onset, starting simultaneously with the appearance of EI-LBBB, not radiating and associated with palpitation and walk through phenomenon. EI-LBBB occurs when the frequency reaches or exceeds the refractory period of one of the bundles. Both transient RBBB and LBBB may be induced during exercise

tolerance test. On follow-up, significant CAD was detected in all patients with EI-RBBB and in only 70% of patients with EI-LBBB^[3]. EI-LBBB is more prevalent (74%) than RBBB (26%), with a heart rate at onset varying from 74 to 170 bpm and associated with high prevalence of significant CAD (70%)^[3]. In the first patient, EI-LBBB ensued at a heart rate of 94 bpm, later coronary angiography showed multi-vessel disease requiring percutaneous intervention which was successfully performed. In our second patient, EI-LBBB accompanied with chest pain started at a frequency of 141 bpm with a QRS width of 138 ms and following treatment with B-blocker, EI-LBBB occurred at a heart rate of 129 bpm without alteration of QRS width. An explanation for the failure of beta-blocker to abolish EI-LBBB may be related to inappropriate dose of the drug used for an “unknown” substrate.

In a study by Schultz *et al*^[17] in 1986, in 4 patients with EI-LBBB compared with normal controls, significant differences between the left and the right ventricle were observed in a mean phase imaging. When typical angina was present in association with EI-LBBB, abnormal myocardial perfusion scans were significantly frequent (68%) *vs* (25%) of atypical chest pain^[18]. In our second case, no abnormalities were depicted on stress myocardial perfusion test. Mechanism of rate-dependent-LBBB has been delineated by Neuss *et al*^[19] in 1974, they postulated that rate-dependent-LBBB during rapid atrial stimulation is due to increased recovery time of the involved bundle branch, failure of anticipated shortening of action poten-

tial with increasing heart rate and postdrive depression of conductivity. Another possible mechanism for EI-LBBB, is the presence of microcirculatory ischemia undetectable by coronary angiography as proposed by Loubeyre *et al*^[20]. Furthermore, paradoxical septal motion may be responsible for the chest discomfort in EI-LBBB^[16].

In 2011, Tanaka *et al*^[7] demonstrated in a case report that EI-LBBB occurring at a heart rate of 100 bpm during treadmill exercise testing is associated with significant left ventricular intraventricular mechanical dyssynchrony, confirmed by speckle tracking radial time strain which has resolved after pharmacological intervention with β -blocker and angiotensin II antagonist.

On the other hand, transient LBBB at a heart frequency of 100 bpm on a "resting" ECG and echocardiographic confirmation of interventricular dyssynchrony (80 ms difference in aortic and pulmonary preejection time) have been described in a patient with flecainide self intoxication, both have resolved after discontinuation of the drug^[21]. None of our patients was on flecainide therapy.

The prognostic significance of EI-LBBB has been variably reported^[22]. Grady *et al*^[5] have shown that EI-LBBB independently predicts a higher risk of death (29%) and major cardiac events (19%) compared with matched control group, (25%) and (10%), respectively. The total event rate was 76% for EI-LBBB (28/37) group versus 24% for the control group (9/37). In the study of Candell Riera *et al*^[15], they found that the prognosis of patients with EI-LBBB associated with chest pain and normal coronary arteries is favorable but on follow-up permanent LBBB developed (5 out of 8 patients) and atrioventricular block rarely occurred requiring pacemaker implantation (1 out of 8 patients)^[15]. Hertzeanu *et al*^[22] suggested that heart rate at which EI-LBBB is a prognostic factor, *i.e.*, the onset of EI-LBBB at a heart rate of ≤ 120 -125 bpm correlated with the occurrence of occlusive CAD, as was the case in our first patient, whereas subjects who develop EI-LBBB at a heart rate of ≥ 120 -125 bpm have a normal coronary arterial tree and a better prognosis which was demonstrated in our second patient. However, when coronary artery disease is the cause of asymptomatic (silent ischemia) EI-LBBB occurring even at a heart rate of 188 bpm, the overall prognosis tends to be poor^[12]. It has been suggested that the onset of EI-LBBB at a heart rate of ≥ 125 bpm is highly correlated with the presence of normal coronary arteries^[23], but in some cases it has been observed to occur at a lower heart rate of 105 bpm^[24]. Our second patient developed EI-LBBB at heart rate of 141 bpm without β -blocker and at 129 bpm under β -blocker therapy without evident significant CAD.

The importance of history taking regarding the nature of presenting chest pain, typical or atypical has been elaborated by Vasey *et al*^[23]; CAD was present in EI-LBBB with classic angina but otherwise absent when atypical chest pain was prevalent. In the eighties, in the study of Hardarson *et al*^[2], no increase in mortality rate due to CAD or hypertension was observed among subjects with permanent LBBB. Recently, it has been shown in phar-

macologically and invasively treated patients with permanent LBBB and high-risk myocardial perfusion SPECT, that cardiac deaths, mostly sudden, occurred in 18% of patients^[25]. These findings renders the current treatment policy of such group of patients to be revisited.

Not only EI-LBBB may be associated with CAD in 70% of patients but also CAD had been documented in 100% of patients with EI-RBBB^[3]. Recently, Bussink *et al*^[26], delineated that newly acquired RBBB in adult population is associated with increased risk of myocardial infarction and pacemaker implantation but not with chronic heart failure, atrial fibrillation or chronic obstructive pulmonary disease. On the contrary to the findings of Breithardt^[8], RBBB is found to be associated with increased cardiovascular risk and all-cause mortality in men and women. Thus even the development of RBBB in asymptomatic individuals should attract our attention for cardiovascular risk^[26].

ACKNOWLEDGEMENTS

During the preparation of the manuscript, the assistance of the librarian, Mrs. A. Geerdink and Mr. D. Maas of hospital group Twente is gratefully acknowledged.

REFERENCES

- 1 Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. *Circulation* 1998; **98**: 2494-2500 [PMID: 9832497 DOI: 10.1161/01.CIR.98.22.2494]
- 2 Hardarson T, Arnason A, Eliasson GJ, Pálsson K, Eyjólfsson K, Sigfússon N. Left bundle branch block: prevalence, incidence, follow-up and outcome. *Eur Heart J* 1987; **8**: 1075-1079 [PMID: 3678236]
- 3 Williams MA, Esterbrooks DJ, Nair CK, Sailors MM, Sketch MH. Clinical significance of exercise-induced bundle branch block. *Am J Cardiol* 1988; **61**: 346-348 [PMID: 3341213 DOI: 10.1016/0002-9149(88)90942-3]
- 4 Stein R, Ho M, Oliveira CM, Ribeiro JP, Lata K, Abella J, Olson H, Myers J, Froelicher V. Exercise-induced left bundle branch block: prevalence and prognosis. *Arq Bras Cardiol* 2011; **97**: 26-32 [PMID: 21552647 DOI: 10.1590/S0066-782X2011005000054]
- 5 Grady TA, Chiu AC, Snader CE, Marwick TH, Thomas JD, Pashkow FJ, Lauer MS. Prognostic significance of exercise-induced left bundle-branch block. *JAMA* 1998; **279**: 153-156 [PMID: 9440667 DOI: 10.1001/jama.279.2.153]
- 6 Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Køber L, Cazeau S, Ritter P, Maggioni AP, Ferrari R, Lechat P. Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail* 2007; **9**: 7-14 [PMID: 16890486 DOI: 10.1016/j.ejheart.2006.04.011]
- 7 Tanaka H, Hiraishi M, Miyoshi T, Tsuji T, Kaneko A, Ryo K, Yamawaki K, Fukuda Y, Norisada K, Tatsumi K, Matsu-moto K, Kawai H, Hirata K. Exercise-induced left bundle branch block and subsequent mechanical left ventricular dyssynchrony--resolved with pharmacological therapy. *Cardiovasc Ultrasound* 2011; **9**: 4 [PMID: 21294925 DOI: 10.1186/1476-7120-9-4]
- 8 Breithardt G, Breithardt OA. Left bundle branch block, an old-new entity. *J Cardiovasc Transl Res* 2012; **5**: 107-116 [PMID: 22258866 DOI: 10.1007/s12265-011-9344-5]
- 9 Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'

- Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; **106**: 1883-1892 [PMID: 12356646 DOI: 10.1161/01.CIR.0000034670.06526.15]
- 10 **Lewis T.** An Address ON CERTAIN PHYSICAL SIGNS OF MYOCARDIAL INVOLVEMENT: Delivered at the Opening of the North-East London Post-Graduate College. *Br Med J* 1913; **1**: 484-489 [PMID: 20766537 DOI: 10.1136/bmj.1.2723.484]
 - 11 **Vieweg WV, Stanton KC, Alpert JS, Hagan AD.** Rate-dependent left bundle branch block with angina pectoris and normal coronary arteriograms. *Chest* 1976; **69**: 123-124 [PMID: 1244271 DOI: 10.1378/chest.69.1.123]
 - 12 **Ferrer MI.** Interesting electrocardiogram: the appearance of left bundle branch block during treadmill testing--revisited. *J Insur Med* 2005; **37**: 63-65 [PMID: 15895700]
 - 13 **Ozcan F, Maden O, Ozlu MF, Ozeke O, Balbay Y.** Exercise induced left bundle branch block in a patient with slow coronary flow. *Abant Medical Journal* 2012; **1**: 156-158 [DOI: 10.5505/abantmedj.2012.75047]
 - 14 **García Pascual J, Méndez M, Gomez-Pajuelo C.** Exercise-induced left bundle branch block: resolution after calcium antagonist therapy. *Int J Cardiol* 1986; **13**: 243-246 [PMID: 3793281 DOI: 10.1016/0167-5273(86)90148-8]
 - 15 **Candell Riera J, Oller Martínez G, Vega J, Gordillo E, Ferreira I, Peña C, Castell J, Aguadé S, Soler Soler J.** Exercise-induced left bundle-branch block in patients with coronary artery disease versus patients with normal coronary arteries. *Rev Esp Cardiol* 2002; **55**: 474-480 [PMID: 12015926 DOI: 10.1016/S0300-8932(02)76638-4]
 - 16 **Virtanen KS, Heikkilä J, Kala R, Siltanen P.** Chest pain and rate-dependent left bundle branch block in patients with normal coronary arteriograms. *Chest* 1982; **81**: 326-331 [PMID: 7056108 DOI: 10.1378/chest.81.3.326]
 - 17 **Schultz DA, Wahl RL, Juni JE, Buda AJ, McMeekin JD, Struble LR, Tuscan MJ.** Diagnosis of exercise-induced left bundle branch block at rest by scintigraphic phase analysis. *Eur J Nucl Med* 1986; **11**: 434-437 [PMID: 3011436 DOI: 10.1007/BF00261005]
 - 18 **Moran JE, Scurlock B, Henkin R, Scanlon PJ.** The clinical significance of exercise-induced bundle branch block. *J Electrocardiol* 1992; **25**: 229-235 [PMID: 1645063 DOI: 10.1016/0022-0736(92)90008-N]
 - 19 **Neuss H, Thormann J, Schlepper M.** Electrophysiological findings in frequency-dependent left bundle-branch block. *Br Heart J* 1974; **36**: 888-898 [PMID: 4425603 DOI: 10.1136/hrt.36.9.888]
 - 20 **Loubeyre C, Tison E, Neuville C, Degroote P, Ducloux G.** [Painful left bundle-branch block during exertion]. *Ann Cardiol Angeiol (Paris)* 1991; **40**: 613-617 [PMID: 1781636]
 - 21 **El-Mourad M, Dedobbeleer C, Loiseau J, Correia H, Jottrand M, Unger P.** Transient dyspnea and left bundle branch block: a case of Munchausen syndrome. Sophia Antipolis: European Association of Echocardiography Clinical Case Portal, 2013
 - 22 **Hertzeanu H, Aron L, Shiner RJ, Kellermann J.** Exercise dependent complete left bundle branch block. *Eur Heart J* 1992; **13**: 1447-1451 [PMID: 1464333]
 - 23 **Vasey C, O'Donnell J, Morris S, McHenry P.** Exercise-induced left bundle branch block and its relation to coronary artery disease. *Am J Cardiol* 1985; **56**: 892-895 [PMID: 4061330 DOI: 10.1016/0002-9149(85)90777-5]
 - 24 **Michaelides AP, Kartalis AN, Aigyptiadou MN, Toutouzias PK.** Exercise-induced left bundle branch block accompanied by chest pain. Correlation with coronary artery disease. *J Electrocardiol* 2004; **37**: 325-328 [PMID: 15484163 DOI: 10.1016/j.jelectrocard.2004.07.007]
 - 25 **Ten Cate TJ, Kelder JC, Plokker HW, Verzijlbergen JF, van Hemel NM.** Patients with left bundle branch block pattern and high cardiac risk myocardial SPECT: does the current management suffice? *Neth Heart J* 2013; **21**: 118-124 [PMID: 21695525 DOI: 10.1007/s12471-011-0174-5]
 - 26 **Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E.** Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. *Eur Heart J* 2013; **34**: 138-146 [PMID: 22947613 DOI: 10.1093/eurheartj/ehs291]

P- Reviewers Kaski JC, Ueda H **S- Editor** Zhai HH
L- Editor A **E- Editor** Wang CH



Complete regression of cardiac involvement associated with lymphoma following chemotherapy

Juan Pablo Vinicki, Tomás F Cianciulli, Gustavo A Farace, María C Saccheri, Jorge A Lax, Lucía R Kazelian, Adolfo Wachs

Juan Pablo Vinicki, Gustavo A Farace, Adolfo Wachs, Department of Internal Medicine, Hospital of the Government of the City of Buenos Aires "Dr. Cosme Argerich", Buenos Aires, C1155AHD, Argentina

Tomás F Cianciulli, María C Saccheri, Jorge A Lax, Lucía R Kazelian, Department of Cardiology, Hospital of the Government of the City of Buenos Aires "Dr. Cosme Argerich", Buenos Aires, C1155AHD, Argentina

Author contributions: Wachs A, Vinicki JP and Farace GA attended the patient; Saccheri MC and Kazelian LR prepared the manuscript and figures; Lax JA and Cianciulli TF performed the echocardiographic images and participated in the design and review of the manuscript; all authors read and approved the final manuscript.

Correspondence to: Tomás F Cianciulli, Professor, MD, FACC, Department of Cardiology, Hospital of the Government of the City of Buenos Aires "Dr. Cosme Argerich", Pi y Margall 750, Capital Federal, Buenos Aires, C1155AHD, Argentina. tcianciulli@gmail.com

Telephone: +54-11-41210879 Fax: +54-11-48015510

Received: April 11, 2013 Revised: July 26, 2013

Accepted: August 8, 2013

Published online: September 26, 2013

Following the diagnosis and staging, chemotherapy was started. Twenty-two days after finishing the first cycle of chemotherapy, the ECG showed regression of T-wave changes in all leads and normalization of the ST-segment elevation in the inferior leads. A follow-up Two-dimensional echocardiography confirmed regression of the myocardial infiltration. This case report illustrates a lymphoma presenting with testicular mass, unilateral peripheral facial paralysis and myocardial involvement, and demonstrates that regression of infiltration can be achieved by intensive chemotherapy treatment. To our knowledge, there are no reported cases of T-LBL presenting as a testicular mass and unilateral peripheral facial paralysis, with complete regression of myocardial involvement.

© 2013 Baishideng. All rights reserved.

Key words: T-cell lymphoblastic lymphoma; Echocardiography; Myocardial involvement; Chemotherapy; Complete regression

Abstract

Cardiac involvement as an initial presentation of malignant lymphoma is a rare occurrence. We describe the case of a 26 year old man who had initially been diagnosed with myocardial infiltration on an echocardiogram, presenting with a testicular mass and unilateral peripheral facial paralysis. On admission, electrocardiograms (ECG) revealed negative T-waves in all leads and ST-segment elevation in the inferior leads. On two-dimensional echocardiography, there was infiltration of the pericardium with mild effusion, infiltrative thickening of the aortic walls, both atria and the interatrial septum and a mildly depressed systolic function of both ventricles. An axillary biopsy was performed and reported as a T-cell lymphoblastic lymphoma (T-LBL).

Core tip: In this report, we describe the case of a 26 year old man who was admitted with infiltration of the pericardium, aortic walls, both atria and the interatrial septum. An axillary biopsy was performed and reported as a T-cell lymphoblastic lymphoma (T-LBL). Following the diagnosis and staging, chemotherapy was started. Twenty-two days after finishing the first cycle of chemotherapy, a follow-up two-dimensional echo confirmed regression of the myocardial infiltration. We describe an unusual case of precursor T-LBL presenting with cardiac involvement and demonstrate that regression of myocardial infiltration can be achieved by intensive chemotherapy treatment.

Vinicki JP, Cianciulli TF, Farace GA, Saccheri MC, Lax JA, Kazelian LR, Wachs A. Complete regression of cardiac involvement associated with lymphoma following chemotherapy. *World J Cardiol*

2013; 5(9): 364-368 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/364.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.364>

INTRODUCTION

Gross tumor formation in any of the cardiac chambers is rare, particularly at the time of presentation and in cases of lymphoma^[1-4]. Symptoms are usually very subtle and non-specific, particularly in the setting of co-existing morbidities. We report an unusual case of a 26 year old man presenting with a gross intracardiac mass, testicular mass and unilateral peripheral facial paralysis, who was ultimately diagnosed with T-cell lymphoblastic lymphoma (T-LBL).

CASE REPORT

The patient is a 26-year-old man, presenting with a testicular tumor and peripheral facial paralysis noted 21 d before admission. Physical exam revealed a left peripheral facial paralysis and ipsilateral conjunctival congestion, bilateral supraclavicular and inguinal lymph nodes, left axillary nodes and a left testicular tumor measuring 7 cm × 5 cm, as well as signs consistent with bilateral (predominantly right sided) pleural effusion. On electrocardiograms (ECG), there was sinus tachycardia, ST-segment elevation in leads II, III and aVF and negative T waves in all leads except aVR. Laboratory values were remarkable for anemia (hematocrit 36%), leukocytosis (13000/mL), thrombocytosis (615000/mL) and lactate dehydrogenase of 1787 UI/L.

The computed tomography (CT) showed an orbit with diffuse thickening of the inferior, medial and lateral rectus muscles, a right maxillary sinus filled with a polypoid structure and soft tissue density, a cluster of lymph nodes in the mediastinum causing a mass effect in the adjacent vessels, pericardial thickening and another lymph node cluster in the abdomen involving areas of the aorta and its branches (celiac axis, left iliac artery and left renal artery). On 2-dimensional echocardiography (2D-echo) (Figures 1A and 2A), there was pericardial infiltration with very mild effusion, infiltrative thickening of the aortic walls, left atrium, right atrium, interatrial septum and the tricuspid annulus, and mildly depressed systolic function of both ventricles. The axillary biopsy revealed findings consistent with T-LBL.

Following diagnosis and staging, chemotherapy was started, according to the HyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone). Treatment consisted of IV cyclophosphamide and mesna during the first three days, combined with high dose dexamethasone 4 times a week during the first 15 d. Additionally, methotrexate, citarabine and dexamethasone were injected into the intrathecal space once a week during the first two weeks. Doxorubicin and vincristine were administered the day after discontinuing cyclophosphamide and on day 11 a new dose of the second agent was added.

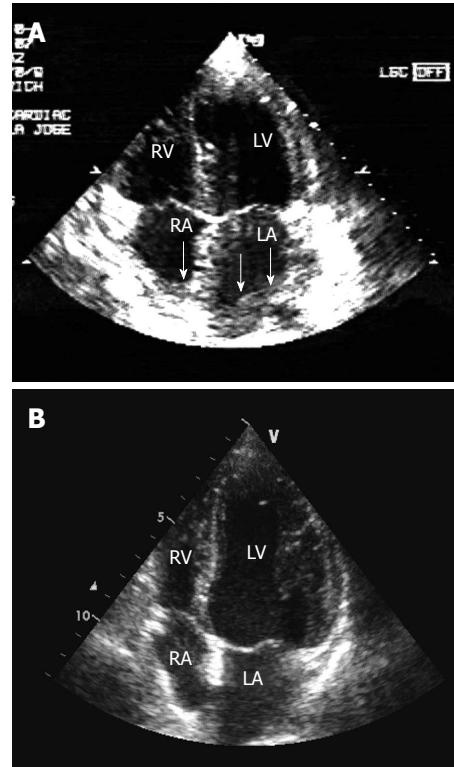


Figure 1 Two-dimensional echocardiography - 4-chamber view. A: Before chemotherapy, the echocardiogram showed tumor infiltration of the myocardium of both atria and the atrial septum (see arrow); B: After chemotherapy, the echocardiogram showed total regression of myocardial infiltration. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle.

Twenty-two days after finishing the first course of chemotherapy, the ECG showed significant regression of the negative T waves in all leads and of the ST segment elevation in the inferior leads. Follow-up 2D echo confirmed total regression of the cardiac and aortic infiltrate (Figures 1B and 2B).

The patient required multiple admissions due to progression of his baseline disease; dissemination was found in the bone marrow, nerve roots, meninges, cranial nerves and bone, with partial response to chemotherapy. Other regimens were tried and despite maximum support measures the patient died after the fourth hospital admission.

DISCUSSION

In our patient, cardiac involvement was not the main pathological process and the systemic component was quite evident. Hence, the case is consistent with a diffuse cardiac infiltration by lymphoma.

In the literature, the majority of patients reported present with various and non-specific symptoms, such as dyspnea, edema, arrhythmia, cardiac tamponade (metastatic tumors of the heart have also been associated with pericardial effusion, particularly hemorrhagic effusion), palpitations and congestive heart failure, and are related to the location and volume of the tumor as well as the functional status of the heart^[1,5-8]. In one large study, the incidence of signs and symptoms plus electro-

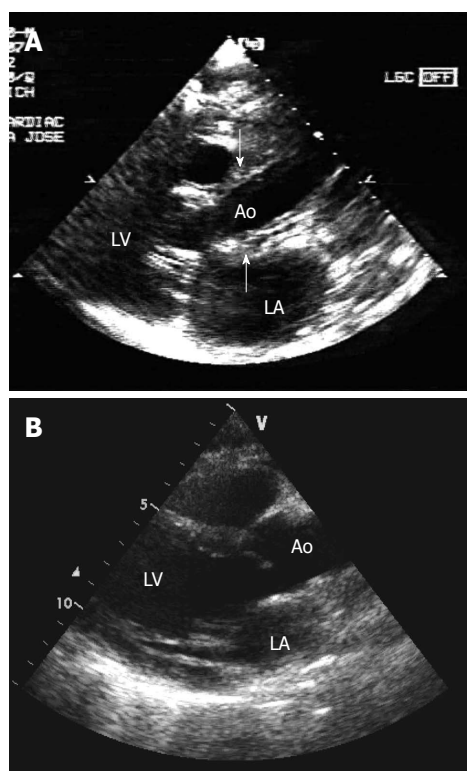


Figure 2 Two-dimensional echocardiography - parasternal long-axis view. A: Before chemotherapy, the echocardiogram showed tumor infiltration of the aorta (see arrows). B: After chemotherapy, the echocardiogram showed total regression of aortic infiltration. LA: Left atrium; LV: Left ventricle; Ao: Aorta.

cardiographic abnormalities in patients who died with malignant lymphoma was similar in those with cardiac metastases when compared to those without cardiac metastases^[9]. Scott *et al*^[10] stated that the most important sign of cardiac invasion in a patient with malignant disease is the onset of congestive heart failure without another apparent cause. The presence of cardiac arrhythmias under similar conditions is also suggestive.

Based upon the data of 22 large autopsy series, Reynen *et al*^[11] established that the frequency of primary cardiac tumors is approximately 0.02%, corresponding to 200 tumors in 1 million autopsies^[8]. Most of these primary cardiac tumors are intracavitary and preferentially develop in the left atrium, thereby leading to left ventricular inflow obstruction. Embolism is also common^[8]. Primary cardiac lymphoma, defined as a lymphoma involving only the heart and pericardium, is extremely rare, with a reported incidence ranging from 0.15% to 1%^[1,5]. Secondary cardiac infiltration from nodal lymphoma of the mediastinum appears to be more common with approximately 35%-40% of patients dying with malignant lymphomas reported to have myocardial involvement. The majority of reported cases were diagnosed at autopsy because of the rapid progression and non-specific clinical symptoms^[1-4]. In our case, this entity was prospectively diagnosed *in vivo* by two-dimensional echocardiography. We have found only 4 reports previous to the present case (Table 1)^[12-17] of metastatic cardiac lymphoma^[13-16].

Roberts *et al*^[9] carried out a necropsy study of 196 patients with malignant lymphoma and found cardiac disease in 48 cases. Among all lymphoma subtypes, cardiac infiltration was seen in 16% of patients with Hodgkin's lymphoma, 25% of patients with non-Hodgkin's lymphoma, and 33% of patients with mycosis fungoides. Of these 48 patients, lymphoma was identified grossly in the heart in 27 cases and found on microscopical examination alone in 21. The pericardium and epicardial fat, particularly in the atrioventricular sulci, were most commonly affected. Nodular deposits within the cardiac chambers were also found^[8,18,19]. According to a study of 25 autopsy cases, T-cell lymphomas, compared with B-cell lymphomas, invade the heart more frequently and aggressively and are associated with a variety of cardiac manifestations^[4].

Most cases of cardiac lymphoma are solid, infiltrative nodular tumors affecting 1 or several cardiac chambers^[13-17]. The right heart is the most common site of cardiac lymphoma. Lymphomatous infiltration of the pericardium is also seen in a number of cases. In contrast, cardiac valve involvement with hematogenous malignancies is uncommon and has been rarely reported to occur as a result of the direct extension of malignant lymphoma from extravascular lesions^[2]. In our patient, the initial description of the first 2D-echo in the clinical case showed severe thickening and infiltration of the myocardium and its subsequent regression after chemotherapy.

The method of choice to detect cardiac metastases and their complications is 2D-echo. It is a simple, safe and non-invasive method and can provide better anatomical details than other more invasive studies^[8,11,18,20].

The infiltrating masses have a peculiar, granular echocardiographic texture which is always different to normal myocardium. The ventricular walls appear thickened and hypokinetic or even akinetic in the area of infiltration. The transmural invasion modifies the epicardial and endocardial contours. All these aspects allow the differential diagnosis with thrombi or other masses, which can be adherent to the endocardium^[17].

Although cardiac metastases may rarely be the first presenting sign of an underlying malignancy, the presence of malignant disease elsewhere is an important clue to the etiology of an intracavitary infiltration^[11].

In 1992, Lestuzzi *et al*^[21] studied the usefulness of transesophageal echocardiography (TEE) performed on 70 patients for the evaluation of paracardiac neoplastic masses (26 patients had non-Hodgkin's lymphoma, 23 had Hodgkin's lymphoma and the rest corresponded to isolated cases of mediastinal tumors). Twenty-three patients underwent repeat TEE after medical or radiation therapy treatments: a total of 101 TEE examinations were performed. The TEE allowed better visualization of the mass, cardiac chambers and great vessels than transthoracic echocardiography in 68 of 101 examinations. Most of the patients underwent CT within 2 wk of TEE. The TEE and CT data were comparable in 58

Table 1 Characteristics of 7 reported cases of cardiac metastatic lymphoma

| Ref. | Age/sex | Symptoms | Type of lymphoma | Localization in heart | Diagnostic tools | Therapy and evolution |
|--|---------|--|--|--|------------------|---|
| Wiernik <i>et al</i> ^[12] | 42/M | Ureteral obstruction Acute myocardial infarction Heart failure | Lymphocytic lymphoma | Gross infiltration of the lateral wall of the left ventricle | Autopsy | Chemotherapy Radiotherapy Died 9 yr later |
| Lestuzzi <i>et al</i> ^[13] | 23/F | None | Lymphoblastic lymphoma | Cardiac apex | 2D-echo | Local radiotherapy Died 12 mo later |
| | 53/F | Dyspnea | Burkitt's lymphoma | Epicardium, posterior ventricular wall and interventricular septum | 2D-echo | Local radiotherapy Died 20 d later |
| Lynch <i>et al</i> ^[14] | NA | NA | NA | Pericardial and myocardial | NA | Chemotherapy |
| Cracowski <i>et al</i> ^[15] | 25/M | Dyspnea | High grade malignant lymphoma | Left ventricular hypertrophy with increased echogenicity of the myocardial walls and marked decrease in left ventricular ejection fraction | 2D-echo, EMB | Chemotherapy |
| Cho <i>et al</i> ^[16] | 39/F | Dyspnea and palpitation | Diffuse large cell type non-Hodgkin's lymphoma | Interventricular septum and left ventricular posterior wall | 2D-echo | Chemotherapy |
| Bergler-Klein <i>et al</i> ^[17] | 34/F | None | Burkitt's lymphoma | Asymmetric hypertrophy of the mid and distal septum with a speckled appearance of the myocardium and LV apical region | 2D-echo MRI, PET | Chemotherapy Died 9 mo later |
| Vinicki <i>et al</i> | 26/M | Testicular mass and unilateral peripheral facial paralysis | T-cell lymphoblastic lymphoma | Pericardial, aorta, both atrial and the interatrial septum | 2D-echo | Chemotherapy Died 4 mo later |

2D-echo: Two-dimensional echocardiography; EMB: Endomyocardial biopsy; F: Female; M: Male; MRI: Magnetic resonance imaging; NA: Not applied.

cases. In 14 of 58 cases, the anatomic data (site, size of the mass, cardiovascular infiltration) obtained by TEE fully corresponded to those obtained by CT. In 3 cases, TEE clearly demonstrated an intracardiac extension of the mass not detected by CT. In 30 cases in which CT was not diagnostic, TEE allowed diagnosis of or exclusion of the infiltration of cardiovascular structures. In 34 patients, TEE contributed additional hemodynamic data not obtained by any other imaging technique. As a conclusion, they consider that CT scan is less precise in defining highly mobile structures, does not provide real-time images, structures are shown on a smaller scale and transthoracic echocardiography is limited mostly to neoplasms of the anterior mediastinum. In contrast, TEE allows a better visualization of the mediastinum (albeit with “blind areas” due to the airway) which allows making the differential diagnosis between vascular and nonvascular lesions, assessing the superior vena cava and pulmonary vein flow, the infiltration of the descending thoracic aorta and the pulmonary artery and its branches^[21].

Compared to ultrasound, computed tomography and magnetic resonance imaging (MRI) provide tissue differentiation between solid, liquid, hemorrhagic and fatty lesions and myocardial metastases can be better delineated. The most compelling indication for MRI is pre-operative assessment of patients with known cardiac masses. According to Lund *et al*^[22], it helps to determine the need to operate and aided in surgical planning^[8,22,23].

Cardiac treatment is mostly confined to palliative measures. Surgical resection is only indicated in exceptional cases of solitary intracavitary heart metastases, leading to obliteration of cardiac chambers or valve obstruction if the tumor of origin was surgically resected *in toto* and the patient appears to have a good progno-

sis^[8,20,24,25]. Frequently, however, complete resection fails and postoperative mortality is high^[2,8]. Usually, cardiac infiltrates in leukemia and lymphoma respond well to radio- or chemotherapy^[1,7,8].

Here, we describe an unusual case of precursor T-LBL presenting with a testicular mass, unilateral peripheral facial paralysis and cardiac involvement, and demonstrate that regression of myocardial infiltration can be achieved by intensive chemotherapy treatment. The definitive diagnosis should have been made by myocardial biopsy, which was certainly not indicated in our patient given his severe systemic involvement.

Although the progression of the disease could be suppressed during chemotherapy, it relapsed early after completing the treatment cycles. Interestingly, although the relapse occurred at several sites different from the initial site of presentation, it did not involve the myocardium.

Secondary neoplastic myocardial infiltration, although frequent at autopsy, is rarely recognized *in vivo*. In our case, this entity was prospectively diagnosed *in vivo* by 2D-echo echocardiography. In addition, it allowed recognition of myocardial infiltration and definition of the location and size of metastases and it helped to decide the most appropriate therapy and to assess the results. Identification and treatment of all secondary neoplastic localizations, however, is important and of clinical relevance, mainly for tumors entailing a less guarded prognosis.

REFERENCES

- 1 Lee PW, Woo KS, Chow LT, Ng HK, Chan WW, Yu CM, Lo AW. Images in cardiovascular medicine. Diffuse infiltration of lymphoma of the myocardium mimicking clinical hypertrophic cardiomyopathy. *Circulation* 2006; 113: e662-e664 [PMID: 16567575 DOI: 10.1161/CIRCULA-

- 2 **Furihata M**, Ido E, Iwata J, Sonobe H, Ohtsuki Y, Takata J, Chikamori T, Doi Y. Adult T cell leukemia/lymphoma with massive involvement of cardiac muscle and valves. *Pathol Int* 1998; **48**: 221-224 [PMID: 9589491 DOI: 10.1111/j.1440-1827.1998.tb03896.x]
- 3 **Daisley H**, Charles W. Cardiac involvement with lymphoma/leukemia: a report of three autopsy cases. *Leukemia* 1997; **11** Suppl 3: 522-524 [PMID: 9209444]
- 4 **Chinen K**, Izumo T. Cardiac involvement by malignant lymphoma: a clinicopathologic study of 25 autopsy cases based on the WHO classification. *Ann Hematol* 2005; **84**: 498-505 [PMID: 15782345 DOI: 10.1007/s00277-005-1009-5]
- 5 **Ikeda H**, Nakamura S, Nishimaki H, Masuda K, Takeo T, Kasai K, Ohashi T, Sakamoto N, Wakida Y, Itoh G. Primary lymphoma of the heart: case report and literature review. *Pathol Int* 2004; **54**: 187-195 [PMID: 14989742 DOI: 10.1111/j.1440-1827.2003.01606.x]
- 6 **McDonnell PJ**, Mann RB, Bulkley BH. Involvement of the heart by malignant lymphoma: a clinicopathologic study. *Cancer* 1982; **49**: 944-951 [PMID: 7037154]
- 7 **Klatt EC**, Heitz DR. Cardiac metastases. *Cancer* 1990; **65**: 1456-1459 [PMID: 2306690]
- 8 **Reynen K**, Köckeritz U, Strasser RH. Metastases to the heart. *Ann Oncol* 2004; **15**: 375-381 [PMID: 14998838 DOI: 10.1093/annonc/mdh086]
- 9 **Roberts WC**, Glancy DL, DeVita VT. Heart in malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and mycosis fungoides). A study of 196 autopsy cases. *Am J Cardiol* 1968; **22**: 85-107 [PMID: 4873149 DOI: 10.1016/0002-9149(68)90250-6]
- 10 **Scott RW**, Garvin CF. Tumors of the heart and pericardium. *Am Heart J* 1939; **17**: 431-436
- 11 **Reynen K**. Frequency of primary tumors of the heart. *Am J Cardiol* 1996; **77**: 107 [PMID: 8540447 DOI: 10.1016/S0002-9149(97)89149-7]
- 12 **Wiernik PH**. Spontaneous regression of hematologic cancers. *Natl Cancer Inst Monogr* 1976; **44**: 35-38 [PMID: 1030780]
- 13 **Lestuzzi C**, Biasi S, Nicolosi GL, Lodeville D, Pavan D, Collazzo R, Guindani A, Zanuttini D. Secondary neoplastic infiltration of the myocardium diagnosed by two-dimensional echocardiography in seven cases with anatomic confirmation. *J Am Coll Cardiol* 1987; **9**: 439-445 [PMID: 3805532]
- 14 **Lynch M**, Cobbs W, Miller RL, Martin RP. Massive cardiac involvement by malignant lymphoma. *Cardiology* 1996; **87**: 566-568 [PMID: 8904687 DOI: 10.1159/000177155]
- 15 **Cracowski JL**, Trémeil F, Nicolini F, Bost F, Mallion JM. Myocardial localization of malignant non-Hodgkin lymphoma responsive to chemotherapy. *Arch Mal Coeur Vaiss* 1997; **90**: 1527-1531 [PMID: 9539827]
- 16 **Cho JG**, Ahn YK, Cho SH, Lee JJ, Chung IJ, Park MR, Kim HJ, Jeong MH, Park JC, Kang JC. A case of secondary myocardial lymphoma presenting with ventricular tachycardia. *J Korean Med Sci* 2002; **17**: 549-551 [PMID: 12172054]
- 17 **Bergler-Klein J**, Knoebl P, Kos T, Streubel B, Becherer A, Schwarzwinger I, Maurer G, Binder T. Myocardial involvement in a patient with Burkitt's lymphoma mimicking hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2003; **16**: 1326-1330 [PMID: 14652615 DOI: 10.1067/j.echo.2003.08.013]
- 18 **Allen DC**, Alderdice JM, Morton P, Mollan PA, Morris TC. Pathology of the heart and conduction system in lymphoma and leukaemia. *J Clin Pathol* 1987; **40**: 746-750 [PMID: 2957395 DOI: 10.1136/jcp.40.7.746]
- 19 **Bogren HG**, DeMaria AN, Mason DT. Imaging procedures in the detection of cardiac tumors, with emphasis on echocardiography: a review. *Cardiovasc Intervent Radiol* 1980; **3**: 107-125 [PMID: 6991115 DOI: 10.1007/BF02552329]
- 20 **DePace NL**, Soulen RL, Kotler MN, Mintz GS. Two dimensional echocardiographic detection of intraatrial masses. *Am J Cardiol* 1981; **48**: 954-960 [PMID: 7197875 DOI: 10.1016/0002-9149(81)90364-7]
- 21 **Lestuzzi C**, Nicolosi GL, Mimo R, Pavan D, Zanuttini D. Usefulness of transesophageal echocardiography in evaluation of paracardiac neoplastic masses. *Am J Cardiol* 1992; **70**: 247-251 [PMID: 1626515 DOI: 10.1016/0002-9149(92)91283-A]
- 22 **Lund JT**, Ehman RL, Julsrud PR, Sinak LJ, Tajik AJ. Cardiac masses: assessment by MR imaging. *AJR Am J Roentgenol* 1989; **152**: 469-473 [PMID: 2783798 DOI: 10.2214/ajr.152.3.469]
- 23 **Go RT**, O'Donnell JK, Underwood DA, Feiglin DH, Salcedo EE, Pantoja M, MacIntyre WJ, Meaney TF. Comparison of gated cardiac MRI and 2D echocardiography of intracardiac neoplasms. *AJR Am J Roentgenol* 1985; **145**: 21-25 [PMID: 3873848 DOI: 10.2214/ajr.145.1.21]
- 24 **Yoshikawa J**, Sabah I, Yanagihara K, Owaki T, Kato H, Tanemoto K. Cross-sectional echocardiographic diagnosis of large left atrial tumor and extracardiac tumor compressing the left atrium. Limitation of M mode echocardiography in distinguishing the two lesions. *Am J Cardiol* 1978; **42**: 853-857 [PMID: 707297 DOI: 10.1016/0002-9149(78)90107-8]
- 25 **Come PC**, Riley MF, Markis JE, Malagold M. Limitations of echocardiographic techniques in evaluation of left atrial masses. *Am J Cardiol* 1981; **48**: 947-953 [PMID: 7304443 DOI: 10.1016/0002-9149(81)90363-5]

P-Reviewer Hardt S S-Editor Zhai HH
L-Editor Roemmele A E-Editor Wang CH



Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery

Hiroki Teragawa, Takashi Sueda, Yuichi Fujii, Hiroaki Takemoto, Yasushi Toyota, Shuichi Nomura, Keigo Nakagawa

Hiroki Teragawa, Takashi Sueda, Yuichi Fujii, Hiroaki Takemoto, Yasushi Toyota, Shuichi Nomura, Department of Cardiovascular Medicine, Hiroshima General Hospital of West Japan Railway Company, Hiroshima 732-0057, Japan

Keigo Nakagawa, Department of Internal Medicine, Chuden Hospital, Hiroshima 730-8562, Japan

Author contributions: Teragawa H wrote the manuscript; Fujii Y, Takemoto H, Toyota Y and Nomura S collected data; Sueda T and Nakagawa K evaluated the study data and revised the manuscript.

Correspondence to: Hiroki Teragawa, MD, PhD, Department of Cardiovascular Medicine, Hiroshima General Hospital of West Japan Railway Company, 3-1-36 Futabanosato, Higashi-ku, Hiroshima 732-0057, Japan. hiroteraga71@gmail.com

Telephone: +81-82-262-1171 Fax: +81-82-262-1499

Received: May 3, 2013 Revised: July 25, 2013

Accepted: August 4, 2013

Published online: September 26, 2013

Abstract

We report a successful endovascular technique using a snare with a suture for retrieving a migrated broken peripherally inserted central catheter (PICC) in a chemotherapy patient. A 62-year-old male received monthly chemotherapy through a central venous port implanted into his right subclavian area. The patient completed chemotherapy without complications 1 mo ago; however, he experienced pain in the right subclavian area during his last chemotherapy session. Computed tomography on that day showed migration of a broken PICC in his left pulmonary artery, for which the patient was admitted to our hospital. We attempted to retrieve the ectopic PICC through the right jugular vein using a goose-neck snare, but were unsuccessful because the catheter was lodged in the pulmonary artery wall. Therefore, a second attempt was made through the right femoral vein using a snare with triple loops, but we could not grasp the migrated PICC. Finally, a string was tied to the

top of the snare, allowing us to curve the snare toward the pulmonary artery by pulling the string. Finally, the catheter body was grasped and retrieved. The endovascular suture technique is occasionally extremely useful and should be considered by interventional cardiologists for retrieving migrated catheters.

© 2013 Baishideng. All rights reserved.

Key words: Port catheter; Catheter migration; Endovascular suture technique

Core tip: Catheter migration has been reported as a delayed complication of peripherally inserted central catheter (PICC). Retrieval by the endovascular technique using a snare is usually attempted in cases of PICC migration, but there have been some difficulties in retrieving the broken catheter. We encountered a patient with an ectopic PICC in the left pulmonary artery; the ectopic PICC could not be retrieved by the usual method using a snare, but was successfully retrieved using a snare and suture technique. The endovascular suture technique is a useful method to retrieve a dislocated or broken catheter and should be considered by interventional cardiologists.

Teragawa H, Sueda T, Fujii Y, Takemoto H, Toyota Y, Nomura S, Nakagawa K. Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery. *World J Cardiol* 2013; 5(9): 369-372 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/369.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.369>

INTRODUCTION

Chemotherapy drug administration through a peripher-

ally inserted central catheter (PICC) has been widely used because of several advantages such as easier PICC insertion and improved patient satisfaction^[1]. The main complications of PICC are bloodstream infection and venous thrombosis^[1,2], although catheter migration has been reported as a delayed complication^[1,3,4]. In cases of PICC migration to the heart or pulmonary artery, retrieval by the endovascular technique using a snare is usually attempted^[4,5], but some difficulties have been reported and the procedure requires several devices and advanced techniques^[4-7]. We describe a patient with an ectopic PICC in the left pulmonary artery, which was successfully retrieved using a snare with a suture technique on the second attempt.

CASE REPORT

A 62-year-old male, who underwent surgeries for advanced colon cancer in November 2008 and for lung metastasis in February 2010, was receiving monthly chemotherapy through a central venous port to his right subclavian vein since March 2010. The last chemotherapy session was performed on November 22, 2010 and no problems occurred during this time. On December 20, 2010, he experienced pain in the right subclavian area during chemotherapy. Subsequent contrast-enhanced computed tomography (CT) showed an ectopic PICC in his left pulmonary artery (Figure 1); therefore, the patient was presented and admitted to our hospital for retrieval of the ectopic PICC on the same day. On admission, his vital signs were stable. Blood examination showed increase in D-dimer (3.6 mg/dL) and C-reactive protein (0.96 mg/dL) levels. In addition, he had poorly controlled diabetes mellitus, with hemoglobin A_{1c} level of 8.4%.

After informed consent was obtained, we attempted retrieval of the ectopic PICC through the right internal jugular vein using a 12-Fr sheath and 8-Fr guiding catheter. CT and pulmonary arteriography revealed that the distal end of the broken catheter was present in the left branch of the pulmonary artery and the proximal end was present in the left pulmonary artery trunk. Therefore, we decided to grasp the ectopic PICC from the proximal end of the catheter. Two goose neck snares (Amplatz GooseNeck, COVIDIEN) measuring 15 and 25 mm were used in our first attempt, but the PICC body could not be grasped because it was lodged in the pulmonary artery wall; we therefore discontinued the attempt because of the extended procedure time. The patient and his family were explained about the possible consequences of the presence of an ectopic PICC in the left pulmonary artery and they requested a second attempt at retrieval.

Three days later, the second retrieval attempt was made through the right femoral vein using 12 and 6-Fr long sheaths (Parent Plus, Medikit). At first, a balloon-occluded pulmonary arteriography (BOPA) was performed using a wedge balloon catheter (Selecon MP Catheter II, Terumo Clinical Supply), which showed

thrombosis of the arterial branch housing the distal end of the ectopic PICC. The proximal end of the ectopic PICC could not be grasped using a snare equipped with triple loops (En Snare, SHEEN MAN). Other catheters such as a 4-Fr Judkins right catheter and pig-tail catheter were inserted through the left femoral vein to lift the proximal end of PICC lodged in the pulmonary artery wall. However, these attempts failed to grasp the ectopic PICC. Finally, an endovascular suture technique was attempted. Several 2.0 sutures were tightly combined and tied to the bottom of the snare loops (Figure 2A) to guide the snare downward. The 6-Fr guiding catheter was switched for an 8-Fr guiding catheter because the 2.0 sutures could not be inserted into a 6-Fr sheath. After the snare was inserted into the left pulmonary artery, it was curved downward toward the pulmonary artery by pulling the string, thus allowing us to grasp the proximal end of the ectopic PICC (Figure 3) and retrieve it (Figure 2B). Two days later, the patient was discharged without any complications.

DISCUSSION

We encountered a patient with an ectopic PICC in the left pulmonary artery; the ectopic PICC could not be retrieved by the usual method using a snare, but was successfully retrieved using a snare/suture technique.

Although the main complications of PICC are bloodstream infection and venous thrombosis^[1,2,8], migration of a broken catheter has been reported as a delayed complication^[1,3]. Catheters can migrate at an estimated rate of 0%-3.1%^[9,10] within 1.5 years^[4]. The most common sign of catheter migration is irrigation resistance to infusion^[4], which indicates that a few weeks have elapsed since the onset of an ectopic PICC. Even in the present case, the exact time of the ectopic PICC migration was unknown, and a few weeks may have elapsed before it was detected. The delayed discovery of the ectopic PICC in our case and the use of a thicker catheter, may have caused the catheter to lodge in the pulmonary artery wall, thereby complicating the retrieval procedure.

In general, ectopic PICC management includes percutaneous transcatheter retrieval, open thoracotomy, and long-term anticoagulation therapy^[6]. However, cases of fatal cardiac tamponade following migration of a broken catheter have been reported^[2]; therefore, percutaneous transcatheter retrieval is usually performed as the first treatment. In the present case, an ectopic PICC extended from the left pulmonary artery trunk to the branch of the left pulmonary artery, in which a thrombosis occurred. Although, cardiac tamponade and pulmonary artery perforation seldom occur, an ectopic PICC may cause an increased incidence of thrombosis in the left pulmonary artery, which may cause clinical symptoms or may act as a source of potential infection. Therefore, after we considered the patient's requests and the possibility of complications, we attempted percutaneous transcatheter retrieval twice.

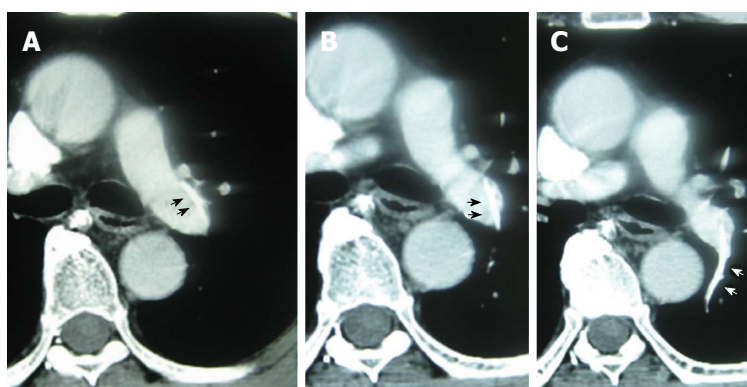


Figure 1 Contrast-enhanced computed tomography showing the proximal end of the catheter lodged in the wall of the left pulmonary artery trunk (A and B); the distal catheter end was in the small branch of left pulmonary artery (C). The broken catheter is indicated by arrows.

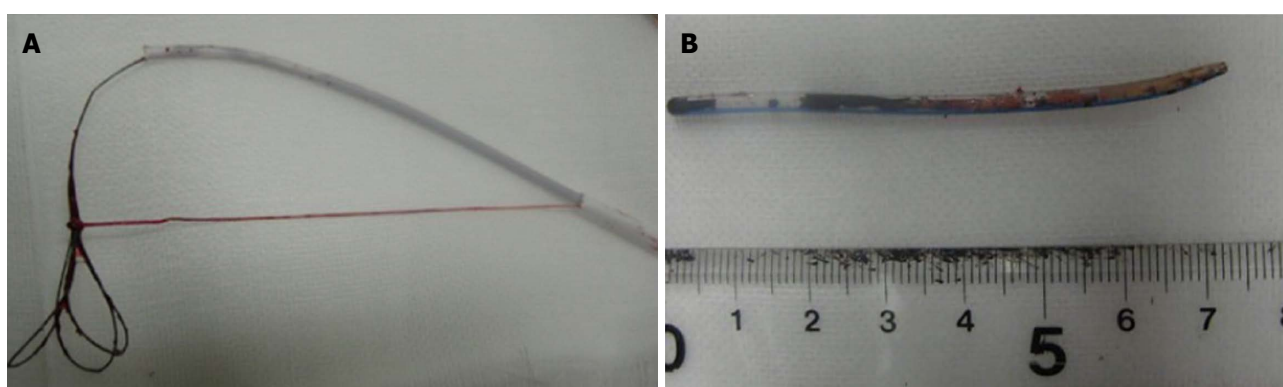


Figure 2 Snare with a suture technique and the retrieved catheter. A: A snare with a suture was curved downward by pulling the string; B: The retrieved catheter.

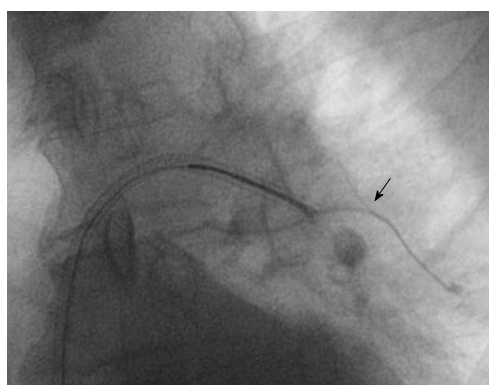


Figure 3 Image of the procedure. The second attempt using the snare with a suture technique was successful to grasp the body of broken catheter. The broken catheter is indicated by an arrow.

There have been several reported percutaneous trans-catheter retrieval techniques using a snare, basket catheter, pigtail catheter, or ablation catheter^[4-7]. However, it may be important to grasp the center of the catheter body to contain it within a guiding catheter or a long sheath. Contrast-enhanced CT and/or pulmonary arteriography, including BOPA, are useful to assist the surgeon in deciding the catheter end to be grasped. Furthermore, it may be more important to remove the end of catheter from the vessel wall or myocardium to enable the surgeon to grasp the catheter body using a snare. However, in the present case, other devices such as a pigtail catheter did not help to retrieve the broken catheter end

because it was lodged in the vessel wall. Therefore, we had to guide the snare downward toward the vessel wall and subsequently use the snare with an endovascular suture technique^[7]. The guidewire or catheter can be easily controlled by pulling the attached string. Although this technique is interesting and a useful method to control catheter movement, it may be associated with the risk of vascular injury and other unresolved problems such as the thickness and type of suture used.

In conclusion, the endovascular suture technique is occasionally an extremely useful method to retrieve a dislocated or broken catheter and should be considered by interventional cardiologists.

REFERENCES

- 1 **Chopra V**, Anand S, Krein SL, Chenoweth C, Saint S. Blood-stream infection, venous thrombosis, and peripherally inserted central catheters: reappraising the evidence. *Am J Med* 2012; **125**: 733-741 [PMID: 22840660 DOI: 10.1016/j.amjmed.2012.04.010]
- 2 **Amerasekera SS**, Jones CM, Patel R, Cleasby MJ. Imaging of the complications of peripherally inserted central venous catheters. *Clin Radiol* 2009; **64**: 832-840 [PMID: 19589422 DOI: 10.1016/j.crad.2009.02.021]
- 3 **Cheng CC**, Tsai TN, Yang CC, Han CL. Percutaneous retrieval of dislodged totally implantable central venous access system in 92 cases: experience in a single hospital. *Eur J Radiol* 2009; **69**: 346-350 [PMID: 17976941 DOI: 10.1016/j.ejrad.2007.09.034]
- 4 **Motta Leal Filho JM**, Carnevale FC, Nasser F, Santos AC, Sousa Junior Wde O, Zurstrassen CE, Affonso BB, Moreira

- AM. Endovascular techniques and procedures, methods for removal of intravascular foreign bodies. *Rev Bras Cir Cardio-vasc* 2010; **25**: 202-208 [PMID: 20802912]
- 5 **Kawata M**, Ozawa K, Matsuura T, Kuroda M, Hirayama Y, Adachi K, Matsuura A, Sakamoto S. Percutaneous interventional techniques to remove embolized silicone port catheters from heart and great vessels. *Cardiovasc Interv Ther* 2012; **27**: 196-200 [PMID: 22991143 DOI: 10.1007/s12928-012-0100-9]
- 6 **Cope C**. Novel Endovascular Suture Techniques for Aortic and Femoral Branch Arteries. *J Invasive Cardiol* 1998; **10**: 443-446 [PMID: 10973365]
- 7 **Liem TK**, Yanit KE, Moseley SE, Landry GJ, Deloughery TG, Rumwell CA, Mitchell EL, Moneta GL. Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. *J Vasc Surg* 2012; **55**: 761-767 [PMID: 22370026 DOI: 10.1016/j.jvs.2011.10.005]
- 8 **Kock HJ**, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access systems: experience in 1500 patients with totally implanted central venous port systems. *World J Surg* 1998; **22**: 12-16 [PMID: 9465755]
- 9 **Charvát J**, Linke Z, Horáèková M, Prausová J. Implantation of central venous ports with catheter insertion via the right internal jugular vein in oncology patients: single center experience. *Support Care Cancer* 2006; **14**: 1162-1165 [PMID: 16596418 DOI: 10.1007/s00520-006-0073-2]
- 10 **Orme RM**, McSwiney MM, Chamberlain-Webber RF. Fatal cardiac tamponade as a result of a peripherally inserted central venous catheter: a case report and review of the literature. *Br J Anaesth* 2007; **99**: 384-388 [PMID: 17611250 DOI: 10.1093/bja/aem181]

P-Reviewer Olsha O S-Editor Wen LL L-Editor A
E-Editor Lu YJ



Persistent left superior vena cava and pacemaker implantation

Daniele Pontillo, Nicolino Patruno

Daniele Pontillo, Division of Cardiology, Complesso Ospedaliero Belcolle, Padiglione di Montefiascone, Montefiascone (VT), 01027, Italy

Nicolino Patruno, Division of Cardiology, S. Giuseppe Hospital, ASL Roma H, Albano Laziale 00041, Italy

Author contributions: Daniele Pontillo conceived the clinical case and wrote the manuscript; Nicolino Patruno conceived the clinical case.

Correspondence to: Daniele Pontillo, MD, Division of Cardiology, Complesso Ospedaliero Belcolle, Padiglione di Montefiascone, Montefiascone Facility Via Donatori di Sangue snc, Montefiascone (VT), 01027, Italy. daniele.pontillo@gmail.com

Telephone: +39-33-83734157 Fax: +39-17-82716245

Received: May 25, 2013 Revised: August 6, 2013

Accepted: August 16, 2013

Published online: September 26, 2013

© 2013 Baishideng. All rights reserved.

Key words: Cardiovascular anatomy; Persistent superior vena cava; Pacemaker implantation; Coronary sinus; Echocardiography

Core tip: The letter focuses in detail on the noninvasive diagnosis of persistent superior left vena cava, which is mandatory before pacemaker implantation.

Pontillo D, Patruno N. Persistent left superior vena cava and pacemaker implantation. *World J Cardiol* 2013; 5(9): 373-374
Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i9/373.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i9.373>

Abstract

Our study group read with interest the paper from Vijayvergiya *et al* describing the implantation of an implantable cardioverter-defibrillator lead in the presence of the persistence of the left superior vena cava. The issue of the identification a persistent left superior vena cava is of paramount importance in interventional cardiology, being the most common venous anomaly of the thoracic distribution, and because it may create some problem to any physician while performing a pacemaker lead implantation. In our letter we underscore the specific issues related to pacemaker implantation while encountering a persistent left superior vena cava (and maybe the absence of the right vena cava) and the workup that should be performed to obtain the preoperative diagnosis of the venous anomaly. More specifically, we consider avoiding any kind of defibrillator lead implantation through the coronary sinus for safety issues, and underscore the straightforward transthoracic ultrasound approach to identify the left superior vena cava.

TO THE EDITOR

We have read with interest the contribution from Vijayvergiya *et al*^[1], who describe a tricky case of implantable cardioverter-defibrillator (ICD) implantation facing the persistence of the left superior vena cava (PLSVC).

A few years ago we experienced a similar situation with a VVI pacemaker implantation^[2]: nonetheless, we would like to underscore some peculiar and personal features we think should always be born in mind before a pacemaker is implanted. Firstly, a complete ultrasound examination should be obtained before implantation in order to rule out anatomical difficulties, *e.g.*, PLSVC. In our case we did not perform an echocardiogram because of the precipitating clinical situation, but in routine settings the EP physician should always be aware of detailed cardiac anatomy. Secondly, we discourage lead implantation-especially of an ICD lead, when the existence of a right vena cava has been proven even though the procedure has started with a left-side approach. Caution is needed when trying to place any kind of lead through the coronary sinus in order to avoid ominous tears or dissections^[3].

Moreover, as we describe in a previous paper regarding the diagnostic features of this venous anomaly, the evaluation of venae cavae anatomy with transthoracic echocardiography is not difficult^[4], and in the presence of a poor acoustic window a transesophageal approach may be helpful. The pre-operative diagnosis of PLSVC may be suspected whenever a dilated coronary sinus is identified at transthoracic echocardiography and it can be confirmed by sequential injection of agitated saline in both left and right arm veins, avoiding further invasive examinations and favoring a correct planning of the implantation technique.

PLSVC still remains a ghost-like entity, usually passing unobserved or diagnosed by chance. On the contrary, its recognition before invasive procedures is paramount to avoid medical errors, loss of time and suboptimal results.

REFERENCES

- 1 **Vijayvergiya R**, Shrivastava S, Kumar A, Otaal PS. Transvenous defibrillator implantation in a patient with persistent left superior vena cava. *World J Cardiol* 2013; **5**: 109-111 [PMID: 23675558 DOI: 10.4330/wjc.v5.i4.109]
- 2 **Pontillo D**, Turreni F, Patruno N, Serra F, Achilli A, Sassara M. [Persistent left superior vena cava. Follow the yellow brick road...]. *Ital Heart J Suppl* 2005; **6**: 821-823 [PMID: 16444926]
- 3 **Lin CT**, Kuo CT, Lin KH, Hsu TS. Superior vena cava syndrome as a complication of transvenous permanent pacemaker implantation. *Jpn Heart J* 1999; **40**: 477-480 [PMID: 10611913 DOI: 10.1536/jhj.40.477]
- 4 **Petronzelli S**, Patruno N, Pontillo D. Persistent left superior vena cava: diagnosis with saline contrast echocardiography. *Heart* 2008; **94**: 835 [PMID: 18552222 DOI: 10.1136/hrt.2007.120733]

P- Reviewers Hung MY, Lin SL **S- Editor** Qi Y **L- Editor** A
E- Editor Wang CH





GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

WJC is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial board members or peer reviewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJC* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer

to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers); (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, etc.; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in cardiology; (12) Brief Articles: To briefly report the novel and innovative findings in cardiology; (13) Meta-Analysis: Covers the systematic review, mixed treatment comparison, meta-regression, and overview of reviews, in order to summarize a given quantitative effect, e.g., the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of cardiology; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

Launch date

December 31, 2009

Frequency

Monthly

Instructions to authors

Editors-in-Chief

Raúl Moreno, MD, Director of Interventional Cardiology, Interventional Cardiology, Hospital La Paz, Paseo La Castellana, 261, 28041 Madrid, Spain

Victor L Serebruany, MD, PhD, Associate Professor, Johns Hopkins University School of Medicine, President, HeartDrug™ Research Laboratories, Osler Medical Center, 7600 Osler Drive, Suite 307, Towson, MD 21204, United States

Editorial office

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Cardiology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: wjc@wjgnet.com
<http://www.wjgnet.com>

Publisher

Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza, 315-321 Lockhart Road,
Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
<http://www.wjgnet.com>

Production center

Beijing Baishideng BioMed Scientific Co., Limited
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

Representative office

USA Office
8226 Regency Drive,
Pleasanton, CA 94588-3144, United States

Instructions to authors

Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

Indexed and Abstracted in

PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Redit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should

be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJC* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copyedit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and report-

ing of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is <http://www.clinicaltrials.gov> sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: <http://www.wjgnet.com/esps/>. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjcn@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be

provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/..."), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g., 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, etc., and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ... etc. It is our principle to publish high resolution-figures for the E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, etc., and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a

Instructions to authors

second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. ^a*P* < 0.05, ^b*P* < 0.01 should be noted (*P* > 0.05 should not be noted). If there are other series of *P* values, ^c*P* < 0.05 and ^d*P* < 0.01 are used. A third series of *P* values can be expressed as ^e*P* < 0.05 and ^f*P* < 0.01. Other notes in tables or under illustrations should be expressed as ¹F, ²F, ³F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, etc., in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability^[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references^[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Please provide PubMed citation numbers to the reference list, e.g., PMID and DOI, which can be found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed> and <http://www.crossref.org/SimpleTextQuery/>, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23243641.

The format for how to accurately write common units and quantum numbers can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: <http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15>

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The

revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system via the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1949-8462/g_info_20100312200118.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312195923.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

STATEMENT ABOUT ANONYMOUS PUBLICATION OF THE PEER REVIEWERS' COMMENTS

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

PUBLICATION FEE

WJC is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. All invited articles are published free of charge.



Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
<http://www.wjgnet.com>

