ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2016 August 26; 8(8): 436-495

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

A peer-reviewed, online, open-access journal of Cardiology

Editorial Board

2014-2017

The *World Journal of Cardiology* Editorial Board consists of 410 members, representing a team of worldwide experts in cardiology. They are from 46 countries, including Argentina (3), Australia (7), Austria (6), Belgium (2), Brazil (8), Canada (11), China (37), Croatia (1), Cuba (1), Cyprus (1), Czech Repoublic (2), Denmark (3), Egypt (1), Finland (3), France (3), Germany (31), Greece (10), Hungary (5), India (4), Iran (2), Ireland (1), Israel (4), Italy (61), Japan (32), Kosovo (1), Malaysia (1), Mexico (1), Morocco (1), Netherlands (9), New Zealand (1), Nigeria (2), Norway (2), Poland (8), Portugal (2), Saudi Arabia (2), Singapore (3), Slovenia (1), South Korea (9), Spain (14), Switzerland (2), Thailand (3), Turkey (13), United Arab Emirates (1), United Kingdom (20), United States (72), Uruguay (2), and Venezuela (1).

Masamichi Takano, *Inzai*
Hiroki Teragawa, *Hiroshima*
Hiroyasu Ueda, *Osaka*
Tadayuki Uetani, *Nagoya*
Sho-ichi Yamagishi, *Kurume*
Hideya Yamamoto, *Hiroshima*
Hiroshi Yoshida, *Kashiwa*

Kosovo

Gani Bajraktari, *Prishtina*

Malaysia

Harris A Ngow, *Kuantan*

Mexico

Erick Alexanderson, *Mexico City*

Morocco

Abdenasser Drighil, *Casablanca*

Netherlands

Pierfrancesco Agostoni, *Utrecht*
Christos V Bourantas, *Rotterdam*
Jasper J Brugts, *Rotterdam*
Filippo Cademartiri, *Rotterdam*
Henricus J Duckers, *Utrecht*
Guido Krenning, *Groningen*
Frans L Moll, *Utrecht*
Martijn C Post, *Nieuwegein*
Salah AM Said, *Hengelo*

New Zealand

Barry Palmer, *Christchurch*

Nigeria

Rufus A Adedoyin, *Ile-Ife*
Okechukwu S Ogah, *Ibadan*

Norway

Jonas Hallen, *Oslo*
Serena Tonstad, *Oslo*

Poland

Maciej Banach, *Lodz*
Iwona Cicha, *Erlangen*
Grzegorz Gajos, *Krakow*
Piotr Jankowski, *Kraków*
Maciej K Kurpisz, *Poznan*
Katarzyna M Mizia-Stec, *Katowice*
Jerzy Sacha, *Opole*
Sebastian Szmit, *Warsaw*

Portugal

Rui A Providência, *Coimbra*
Fernando Ribeiro, *Aveiro*

Saudi Arabia

T Albacker, *Riyadh*
Mouaz H Al-Mallah, *Riyadh*

Singapore

Koon-Hou Mak, *Singapore*
Kian Keong Poh, *Singapore*
Samuel SW Tay, *Singapore*

Slovenia

Mitja Lainscak, *Golnik*

South Korea

Kyung-Mook Choi, *Seoul*
Young-Hoon Jeong, *Jinju-si*
Hyo-Soo Kim, *Seoul*
Cheorl-Ho Kim, *Suwon*
Seong Hwan Kim, *Ansan*
Young-Guk Ko, *Seoul*
Gi-Byoung Nam, *Seoul*
Jong-Min Song, *Seoul*
Darren R Williams, *Gwangju*

Spain

Ezequiel Alvarez, *Santiago de Compostela*
Miguel A Arias, *Toledo*
Alberto B Berenguer, *Valencia*
Alberto Dominguez-Rodriguez, *Tenerife*
Julio J Ferrer-Hita, *La Laguna*
Joaquin De Haro, *Madrid*
Raul Moreno, *Madrid*
Ivan J Nunez-Gil, *Madrid*
Jesus Millan Nuuez-Cortes, *Madrid*
Jesus Peteiro, *A Coruna*
Aurelio Quesada, *Valencia*
Manel Sabate, *Barcelona*
Rocio Toro, *Cadiz*
Jose M Valdivielso, *Lleida*

Switzerland

Paul Erne, *Zurich*
Richard Kobza, *Luzern*

Thailand

Nipon Chattipakorn, *Chiang Mai*
Rungroj Krittayaphong, *Bangkok*
Yaowapa Maneerat, *Bangkok*

Turkey

Bahri Akdeniz, *Izmir*
Ismail Biyik, *Usak*
Murat Can, *Zonguldak*
Turgay Celik, *Ankara*
Yengi U Celikyurt, *Kocaeli*
Omer F Dogan, *Adana*
Dursun Duman, *Istanbul*
Nihan Erdogan, *Istanbul*
Tevfik F Ilgenli, *Konya*
Fehmi Kacmaz, *Sanliurfa*
Kaan Kirali, *Istanbul*
Mehmet Ozaydin, *Isparta*
Murat Ozeren, *Mersin*

United Arab Emirates

Nicolas Christoforou, *Abu Dhabi*

United Kingdom

Suneil K Aggarwal, *London*
Abdallah Al-Mohammad, *Sheffield*
Umberto Benedetto, *Papworth*
Christopher J Boos, *Poole*
Geoffrey Burnstock, *London*
Halina Dobrzynski, *Manchester*
Lyndon M Evans, *Cardiff*
Matthew Ginks, *Oxford*
Cathy M Holt, *Manchester*
Jamie Y Jeremy, *Bristol*
Muhammed Z Khawaja, *London*
Babu Kunadian, *Liverpool*
Najma Latif, *Harefield*
Saagar Mahida, *leeds*
Mamas Mamas, *Manchester*
Pankaj K Mishra, *Wolverhampton*
Shahzad G Raja, *London*
Sudhir Rathore, *Camberley*
Ganesh N Shivu, *Ravenshead*
Neil A Turner, *Leeds*

United States

Ola Akinboboye, *New York*
Arshad Ali, *North Platte*
Piero Anversa, *Boston*
Ehrin J Armstrong, *Denver*
Wilbert S Aronow, *Valhalla*
Basem Azab, *Staten Island*
Alison E Baird, *Brooklyn*
Saravanan Balamuthusamy, *Tucson*
Hendrick B Barner, *Saint Louis*
Marion A Hofmann Bowman, *Chicago*
Danny Chu, *Pittsburgh*
Undurti N Das, *Federal Way*
Jose M Dizon, *New York*
Khalid M Elased, *Dayton*
Sammy Elmariah, *Boston*
James D Fett, *Lacey*
Don A Gabriel, *Chapel Hill*
Nisha J Garg, *Galveston*
Cynthia J Girman, *North Wales*
Mardi Gomberg-Maitland, *Chicago*

WJC World Journal of Cardiology

Contents

Monthly Volume 8 Number 8 August 26, 2016

Contents

World Journal of Cardiology
Volume 8 Number 8 August 26, 2016

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
August 26, 2016

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

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

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.436

World J Cardiol 2016 August 26; 8(8): 436-446
ISSN 1949-8462 (online)

REVIEW

Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success

Karl Fengler, Karl Philipp Rommel, Thomas Okon, Gerhard Schuler, Philipp Lurz

Karl Fengler, Karl Philipp Rommel, Thomas Okon, Gerhard Schuler, Philipp Lurz, Department of Internal Medicine/Cardiology, University of Leipzig - Heart Center, 04289 Leipzig, Germany

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Philipp Lurz is consultant to ReCor Medical and Medtronic.

Manuscript source: Invited manuscript

Correspondence to: Philipp Lurz, MD, PhD, Department of Internal Medicine/Cardiology, University of Leipzig - Heart Center, Strümpellstraße 39, 04289 Leipzig, Germany. philipp.lurz@gmx.de
Telephone: +49-341-8651428
Fax: +49-341-8651461

Received: April 27, 2016
Peer-review started: April 28, 2016
First decision: June 16, 2016
Revised: June 21, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: August 26, 2016

Abstract

Many forms of human hypertension are associated with an increased systemic sympathetic activity. Especially the renal sympathetic nervous system has been found to play a prominent role in this context. Therefore, catheter-interventional renal sympathetic denervation (RDN) has been established as a treatment for patients suffering from therapy resistant hypertension in the past decade. The initial enthusiasm for this treatment was markedly dampened by the results of the Symplicity-HTN-3 trial, although the transferability of the results into clinical practice to date appears to be questionable. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, its effects on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Effects of RDN have been described on many levels in human trials: From altered systemic sympathetic activity across cardiac and metabolic alterations down to changes in renal function. Most of these changes could sustainably change long-term morbidity and mortality of the treated patients, even if blood pressure remains unchanged. Furthermore, a number of promising predictors for a successful treatment with RDN have been identified recently and further trials are ongoing. This will certainly help to improve the preselection of potential candidates for RDN and thereby optimize treatment outcomes. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Key words: Renal sympathetic denervation; Sympathetic nervous system; Predictors; Hypertension; Renal hypertension

Core tip: The initial enthusiasm for renal sympathetic denervation (RDN) has disappeared. However, the detailed effects of RDN on the complex pathophysiological

mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Moreover, a number of promising predictors for successful RDN treatment have been identified recently which could help to improve future trial design. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Fengler K, Rommel KP, Okon T, Schuler G, Lurz P. Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success. *World J Cardiol* 2016; 8(8): 436-446 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/436.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.436

BACKGROUND

Many forms of human hypertension are associated with an increased systemic sympathetic activity[1]. Especially the sympathetic nervous system of the kidney plays a key role in the pathogenesis and perpetuation of hypertension. An activation of efferent renal nerve fibers leads to salt and water retention *via* stimulation of α_{1B}-adrenoceptors, activation of the renin-angiotensin-aldosterone system *via* β_1-adrenoceptors causing thereby an increased systemic blood pressure (BP)[1,2]. The release of vasoactive peptides present in renal nerve fibers is also controlled by efferent sympathetic fibers[3,4]. *Via* afferent fibers, the kidney itself affects systemic sympathetic activity[1].

One option to reduce the systemic sympathetic activity is renal sympathetic denervation (RDN). Once introduced as a surgical treatment for hypertension in the past century[5,6], this interesting therapeutic approach lost clinical relevance since medical antihypertensive treatment was introduced to practice. As the burden of cardiovascular diseases associated with hypertension increased over the last decades, RDN experienced a renaissance, now as a catheter-based interventional treatment option[7]. After the first promising trial results, the initial enthusiasm for this therapy strategy was markedly dampened, when the results of the sham-controlled randomized Symplicity-HTN-3 trial did not show any significant effect on BP of RDN-treated *vs* sham-treated patients[8]. The results of this particular trial are part of an ongoing debate and further trials to allow definite conclusion on the effect of RDN on BP are on the way[9]. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, the detailed effects of RDN on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood.

In the following review we present a short overview of the manifold effects described for RDN so far (Table 1).

EFFECTS OF RDN

BP

The main indication for RDN in the past decade and in the past century has been therapy resistant hypertension. Therefore, BP as an end point has been included in nearly every single trial regarding RDN. In almost any trial, controlled, uncontrolled or sham-controlled, a significant BP reduction was found after RDN[7,10-14] (Table 2). However, the largest randomized sham-controlled trial to date, the Symplicity-HTN-3 trial, failed to show any superiority of RDN over sham-control, mostly through an unexpected drop in BP in the sham-treated arm of the trial[8].

Another sham-controlled randomized approach, excluding most of the confounding factors which might have blurred the results of Symplicity-HTN-3 by careful patient selection, the ongoing SPYRAL-HTN trial (NCT02439775), will hopefully give a definite answer to this issue soon.

It is of particular interest, that many of the effects attributed to RDN result in a reduced BP: A diminished systemic vascular tone leading to a reduced afterload, sympathetic mediated alterations in cardiac output, altered sodium- and volume-state or (*via* the renin-angiotensin-aldosterone axis) humoral-mediated changes. Which and how much these effects contribute to a RDN-induced BP drop and how they are counter-regulated remains an unresolved issue that needs to be clarified in future RDN-trials.

Besides other confounders, a constant observation in clinical trials is that a proportion of patients does not respond to RDN, which might in part contribute to the negative results in Symplicity-HTN3. Interestingly, the problem of non-responsiveness to renal denervation seems to be as old as the procedure itself: Even for surgical sympathectomy a high proportion of non-responders (ranging between 55% and 68%) has been described[5,6]. Despite that, a strong positive effect on long-term mortality was found in a large series of 1200 patients[5]. This leads to the question which other beneficial effects besides BP reduction RDN might have in humans, which might explain this discrepancy.

Renal function and sodium excretion

A potential deterioration of renal function - either by renal artery stenosis or by changes in intrarenal hemodynamics - is an often raised concern regarding RDN. On the contrary, as renal blood flow and salt/water retention is influenced by sympathetic activity[2], RDN might have nephroprotective effects.

Two larger non-randomized analyses found glomerular filtration rates (GFR) to be unchanged after RDN[15,16]. Interestingly, one trial could even show a decrease in albuminuria, consistent with an improvement of hypertension-induced end-organ damage[16]. In another study, examining the effects of RDN in patients with impaired renal function, the authors were able to show that the hypertension-related deterioration of renal

Table 1 Effects of renal sympathetic denervation

Ref.	Year	*n* (RDN/control)	Effector	Effect	Control
Ott *et al*[15]	2013	19/-	Renal blood flow	None	None
Pöss *et al*[19]	2015	137/-	Renal sodium excretion	Increased sodium excretion, less pronounced in responders	None
Mahfoud *et al*[24]	2014	55/17	Left ventricular mass	Reduced left ventricular mass after RDN	Medical therapy
Doltra *et al*[25]	2014	5/23			Medical therapy
McLellan *et al*[26]	2015	14/-			None
Lu *et al*[27]	2016	139/-			Meta-analysis
McLellan *et al*[26]	2015	14/-	Atrial conduction	Improved atrial conduction after RDN	None
Qiu *et al*[31]	2016	21/-	Persistent atrial fibrillation	Reduced heart rate after RDN	None
Armaganijan *et al*[36]	2015	10/-	Ventricular arrhythmia	Reduced frequency of ventricular arrhythmia episodes	None
Ott *et al*[15]	2013	19/-	Central hemodynamics	Reduced central BP and augmentation index after RDN	None
Brandt *et al*[38]	2012	110/10		Reduced aortic pulse pressure, pulse wave velocity and augmentation index	Medical
Mortensen *et al*[39]	2012	21/-			None
Hering *et al*[40]	2013	40/10		Reduced augmentation index	Medical
Okon *et al*[41]	2016	23/-		Unchanged invasive pulse wave velocity after RDN	None
Donazzan *et al*[51]	2015	11/-	Sympathetic activity	Reduced cardiac sympathetic activity after RDN	None
van Brussel *et al*[52]	2016	21/-		Unchanged cardiac sympathetic activity after RDN	None
Tsioufis *et al*[53]	2014	14/-		Reduced heart rate and arrhythmia burden and improved heart rate variability after RDN	None
Vink *et al*[55]	2014	13/-			None
Brinkmann *et al*[56]	2012	12/-		Unchanged muscle sympathetic nervous activity after RDN	None
Hering *et al*[57]	2013	10/25		Reduced muscle sympathetic nervous activity after RDN	Medical
Dörr *et al*[58,59]	2015	150/-		Reduced Neuropeptide Y and transiently reduced brain derived neutrophic factor after RDN	None
	2015	100/-			
Dörr *et al*[63]	2015	60/-	Inflammation	Reduced systemic inflammation after RDN	None
Mahfoud *et al*[65]	2011	37/13	Insulin sensitivity	Improved insulin sensitivity after RDN	Medical
Verloop *et al*[66]	2015	29/-		Unchanged insulin sensitivity	None
Ewen *et al*[71]	2014	50/10	Exercise testing	Reduced Exercise BP after RDN	Medical
Ukena *et al*[69]	2011	37/9			Medical
Fengler *et al*[70]	2016	22/26			Sham
Lenski *et al*[72]	2013	36	Orthostatic reaction	None	None

BP: Blood pressure; RDN: Renal sympathetic denervation.

function could be halted with RDN over a follow up of three years[17]. This suggests overall beneficial effects of RDN on renal function, especially in these patients who already suffer from hypertension-induced end-organ damage, which will clearly improve long-term mortality.

Despite the known vasoconstrictive effects of systemic sympathetic activity on the arterial vasculature[2] and significant alterations in an animal study[18], RDN does neither seem to improve nor deteriorate renal blood flow in humans[15]. Presumably, this can be explained by the auto-regulative capacities of the renal vessels outweighing any RDN-induced changes.

The putative effect of RDN on renal sodium excretion is a promising therapeutic goal. The only human trial investigating this hard-to-assess endpoint however showed mixed results, as patients with stronger BP response after RDN showed a diminished effect on sodium excretion compared to those with less BP changes[19]. To some extent this might be explained by a compensatory dietary sodium intake which was not assessed in the study. Therefore, this interesting aspect of RDN needs to be investigated thoroughly by additional rigorous assessment of dietary sodium intake. An additional MRI-based quantification of tissue sodium and water might be helpful here as elevated concentrations are observed in patients with essential hypertension. Sodium and water tissue content might therefore represent an interesting diagnostic and therapeutic goal[20,21].

Cardiac and hemodynamic changes

Left-ventricular-mass and fibrosis: An elevated left-ventricular mass is a frequent finding in hypertensive subjects[22]. Its presence and its regression through therapeutic interventions significantly affects patients' outcomes[22,23]. Therefore, it is a worthwhile therapeutic target in the treatment of human hypertension.

Several smaller studies and one recent meta-analysis describe a reduction of left-ventricular mass after RDN[24-27]. In one of them an additional improvement in left-ventricular strain and ejection fraction was observed in patients with reduced values at baseline[24]. Besides reversal of myocyte hypertrophy left-ventricular fibrosis might be altered by renal denervation, as the absolute extracellular volume was found to be reduced

Table 2 Blood pressure effects of renal sympathetic denervation

Ref.	Year	Control	*n* (RDN/control)	Systolic office BP (mmHg)	P-value	Systolic ambulatory BP (mmHg)	*P*-value
Krum *et al*[7]	2009	None	50	-22	< 0.001[a]	NA	NA
Esler *et al*[11]	2010	RDN *vs* medical	106 (52/54)	-32 *vs* 1	< 0.00001[b]	-11/-7 *vs* -3/-1	NA
Bhatt *et al*[8]	2014	RDN *vs* sham	535 (364/171)	-14 *vs* -12	0.26[b]	-6.8 *vs* -4.8	0.98[b]
Desch *et al*[10]	2015	RDN *vs* sham	71 (35/36, intention to treat) 63 (29/34, per protocol)	NA NA	NA NA	-8.5 *vs* -4.7 -8.3 *vs* -3.5	0.06[b] 0.04[b]
Rosa *et al*[13]	2015	RDN *vs* intensified medical treatment	106 (52/54)	-12 *vs* -14	< 0.001[a]/0.60[b]	-8.6 *vs* -8.1	< 0.001[a]/0.87[b]
Azizi *et al*[14]	2015	Stepped-care antihypertensive treatment with *vs* without RDN	106 (53/53)	-15 *vs* -9	0.15[b]	-15.8 *vs* -9.9	0.03[b]
Böhm *et al*[12]	2015	None	998	-12	< 0.00001[a]	-6.6	< 0.00001[a]

[a]*P*-value for within group change; [b]*P*-value for between group change. BP: Blood pressure; RDN: Renal sympathetic denervation; NA: Not available.

after RDN[25]. This finding might be supported by a reduced cellular matrix turnover assessed by collagen pro-peptides in patients after renal denervation in an upcoming laboratory study[28].

Atrial fibrillation: Associated with BP reduction, RDN has been shown to improve atrial conduction[26]. This might allow a look-out on renal denervation as an alternative or additional option for the treatment of symptomatic atrial fibrillation. This concept is supported by two recent animal studies in dogs, where RDN could impede the induction of atrial fibrillation[29,30]. Also, for persistent atrial fibrillation, RDN was found to reduce the heart rate in a small case-series of symptomatic patients[31]. Beyond this, several in-human trials regarding this issue are currently ongoing which will certainly help to improve our understanding of the intracardiac effects of RDN (NCT01635998, NCT01990911, NCT02064764).

Ventricular arrhythmia: As ventricular arrhythmias are more likely to occur under an elevated sympathetic activity, using RDN as a treatment for refractory ventricular arrhythmia seems a reasonable endeavor[32]. Animal studies show promising effects for RDN in ischemia-induced arrhythmias when compared to a sham procedure[33,34], while inducibility of ventricular arrhythmias cannot be prevented by RDN in healthy animals[35]. Also a first in-man cohort of 10 patients with mainly non-ischemic cardiomyopathies reveals a dramatic drop in arrhythmia burden after RDN[36]. Nonetheless, further prospective, randomized trials are needed to confirm this scope of application for RDN.

Hemodynamics and volume changes: Since the effects of RDN on renal water/sodium excretion and systemic vasculature are likely to be associated with changes in systemic volume status, it would be interesting to assess changes in intra-cardiac pressure and pressure-volume relations. Also, changes in central and peripheral hemodynamics in patients undergoing RDN are of particular interest, as they determine the incidence of heart failure and potentially the course of cardiovascular remodeling[37].

Several trials investigated central hemodynamics using non-invasive methods[15,38-40]. Herein, alterations of cardiac afterload, namely a significant reduction in central pulse pressure and aortic augmentation index after RDN could be demonstrated. Also, a reduction of non-invasively assessed pulse-wave velocity, indicating decreased arterial stiffness after RDN, was observed, even if this is conflicting with the results of a smaller cohort with unchanged invasively acquired pulse-wave-velocity 6 mo after RDN[41]. As arterial stiffness is - to some extent - a BP-dependent parameter, any changes observed after RDN have to be interpreted with caution.

An explicit effect of RDN on cardiac hemodynamics, including changes in preload, filling and contractility, has - to the present date - not been described. Assessment of hemodynamic changes can be achieved *via* echocardiography, which was part of virtually all protocols of bigger studies examining treatment effects of RDN. The paucity of published data regarding echocardiographically assessed hemodynamic changes in patients treated with RDN might imply negative findings (assuming a publication bias), might be a consequence of the limited sensitivity of echocardiography in detecting cardiac filling pressures or might just have been neglected so far. Therefore - besides invasive measurements - other non-invasive methods like MRI-based analyses (*e.g.*, the left atrial transit time) could provide additional information here[42].

Furthermore, given the described impact of RDN on the LV musculature and the arterial system, an improvement of ventricular-atrial coupling could be assumed after treatment.

However, as cardiac loading underlies marked intra-individual changes, reliable assessment of changes in central hemodynamics depend on testing of patients instantaneously under different physiologic conditions (such as rest and exercise) or under longitudinal observational trial settings.

Central and peripheral nervous changes

As illustrated above, mediated through afferent central nervous fibers RDN also affects the central nervous system. Interestingly, overall successful treatment of essential hypertension is associated with improved neuropsychological performance and to some extent with alterations in regional cerebral blood flow response to working memory tasks at short-term follow up[43]. To date, this has not been assessed for patients undergoing RDN but might be a promising task for future trials, especially since uncontrolled hypertension is a well-known risk factor for cerebrovascular diseases and might contribute to cognitive decline[44].

The link between central-nervous and peripheral sympathetic-nervous alterations in hypertensive patients could further be investigated in assessing to which extent central nervous changes are mediated indirectly by BP alterations or by increased sympathetic overdrive and afferent signaling itself.

The role of a potential sympathetic re-innervation after RDN[45,46] warrants further investigation as it might partly explain non-responsiveness and lead to negative trial results. However, BP reductions in response to effective RDN seems to be long-lasting in the data published so far[47-49].

Systemic sympathetic activity

Direct measurement of the systemic sympathetic activity is difficult to perform and is therefore underrepresented in clinical trials of RDN[50]. Indirect assessment, however, is feasible with different techniques and has been used in various trials.

Cardiac scintigraphy: Two small trials (including only 23 and 11 patients) examined alterations in the cardiac sympathetic nervous system activity after RDN using scintigraphy[51,52]. Their results were conflicting, as in one trial with only a non-significant BP drop in ambulatory BP-measurements in the RDN patients, no significant alterations in cardiac sympathetic activity were found. The other trial found a remarkable impact of RDN on ambulatory measured BP and also found a strong reduction in cardiac sympathetic activity. Since the results are inconclusive at present, further evaluation in larger, adequately powered cohorts is necessary.

Heart rate variability: Another way to measure systemic sympathetic activity is assessing heart rate variability (HRV). In a small case series, Tsioufis and coworkers were able to show RDN achieved a significant reduction in patient's HRV and arrhythmia burden, suggesting a reduced systemic sympathetic activity in the treated patients[53].

Muscle sympathetic nerve activity: Muscle sympathetic nerve activity is known to be elevated in hypertensive subjects[54], indicating a direct link to systemic sympathetic activity. Hence, direct intraneural recordings could be considered as a good marker for treatment success after RDN. So far this hypothesis has been investigated in two smaller case series which failed to show any alterations through RDN[55,56]. In contrast, a prospective controlled trial in 35 patients found significant alterations in single- and multi-unit muscle sympathetic nerve activity[57]. Despite the latter results, overall the role of muscle sympathetic activity as an outcome marker in RDN trials is not fully determined and warrants further research.

Laboratory markers: Dörr *et al*[58] investigated the role of Neuropeptide Y, a neurotransmitter that is co-released with norepinephrine and up-regulated during sympathetic activity. They were able to show a significant drop of Neuropeptide Y after RDN which can be interpreted as an expression of a reduced systemic sympathetic activity.

Successful RDN also leads to a transient down-regulation of serum brain-derived neurotrophic factor immediately after denervation[59]. Since brain-derived neurotrophic factor is a neuronal growth factor, this adds further evidence for true downregulation of the sympathetic nervous system on a neuronal base through RDN.

Overall, despite the lack of data for a direct assessment of systemic sympathetic activity in RDN-trials, indirect markers strongly indicate that RDN results in significant changes of systemic sympathetic activity.

Inflammation

Arterial hypertension is associated with chronic vascular inflammation and remodeling[60-62]. In a prospective analysis of 60 patients undergoing RDN, a significant reduction of pro-inflammatory cytokine interleukine-6 and high-sensitive C-reactive protein was achieved[63]. This is in particular encouraging, as it might be related to beneficial long-term effects of RDN. It has however to be debated, if the observed changes are rather related to the BP lowering effects of RDN, which might attenuate the pathologic immune response, rather than to RDN itself.

Metabolic effects

Insulin sensitivity: An elevated sympathetic activity seems to be associated with an altered insulin sensitivity[64]. Therefore, RDN might help to improve the glucose metabolism in patients with a high sympathetic overdrive. The first trial to investigate this relation, a pilot-study in 50 patients, found a significant change in glucose metabolism and insulin sensitivity[65]. Notably, only 40% of these patients were diagnosed with diabetes mellitus and only 36% had an impaired glucose tolerance at baseline. In contrast, a smaller, uncontrolled prospective trial did not find any changes in insulin sensitivity after a follow up of 12 mo in 29 patients with metabolic syndrome[66]. Therefore, the role of RDN for improvement of insulin sensitivity remains equivocal.

However, if an effect of RDN on this very relevant end point could be proven, it could tremendously affect patients' long-term prognosis.

Exercise testing: Exercise BP, an important risk factor for future cardiovascular events[67,68], was found to be reduced after RDN in two non-randomized studies and one sham-controlled trial[69-71]. Also beneficial effects for exercise capacity and duration are described for RDN without affecting chronotropic competence in treated patients[69,71].

Orthostatic effects: Safety concerns regarding potential unfavorable orthostatic effects of RDN can largely be ruled out due to the lack of the occurrence of orthostatic side effects in the large RDN treatment trials and a smaller trial which did not find any pathologic alterations in tilt table testing for RDN-treated patients[72].

Conclusion

Beyond the still debated effects of RDN on BP in hypertensive patients, a wide range of promising effects has been shown. Most of these changes could importantly change long-term morbidity and mortality of the treated subjects, even if their BP remained unchanged. To determine the value of non-BP effects of RDN for clinical practice, further long-term data with multiple cardiovascular endpoints is needed.

Until then, it seems prudent to optimize BP outcome in RDN trials through the identification of predictors for treatment success. In the following we will give a brief overview of such predictors that have been identified so far.

PREDICTORS FOR SUCCESSFUL RDN

Baseline BP

High BP prior to renal denervation has most frequently been described as the strongest predictor of BP reduction after RDN[12,73]. However, whether this is related to a higher sympathetic activity in patients with higher baseline BP or a manifestation of the regression to mean phenomenon remains controversial and is an unresolved issue to date[74]. Thus, other predictors for treatment success in RDN are needed.

Anatomy and technological aspects

Anatomy: The anatomy of the renal arteries seems to have considerable influence on the BP response to RDN. Importantly, the anatomy of human renal vessels shows a high variability[75]. Accessory renal arteries or an early bifurcation occurs in approximately one of three patients[75]. This is important, as the presence of accessory or early bifurcated vessels seems to influence outcome negatively[76]. In principle it seems prudent to exclude these patients from renal denervation. Nevertheless, in the ongoing SPYRAL-HTN trial (NCT02439775) denervation of accessories with a diameter above or equal 3 mm is planned. This will hopefully clarify the role of accessory arteries and early bifurcations soon.

As the sympathetic nerve fibers are closer to the lumen in the distal part of the renal vessel[77], ablation of the distal main artery or even the side branches are also thought to improve outcome[78,79].

Technological aspects: One of the major shortcoming of RDN is the lack of a direct feedback mechanism during intervention[50]. Despite many promising approaches, including direct intravascular and (sub-)cutaneous measurements of renal sympathetic activity, the challenging task of a direct *in-vivo* feedback for renal denervation success is still far away from clinical practice. Nevertheless, once a direct assessment method for renal sympathetic activity is established this will be a milestone in improving renal denervation success[50].

Another technological aspect for future trial designs is that denervation success seems to be dependent of the number of ablation points as well as the experience of the interventional physician[73]. Therefore, RDN should only be performed by trained interventionalists and as many ablations as possible should be delivered to optimize BP outcome.

Most clinical trials regarding RDN were carried out using radiofrequency based catheters. The role of other devices, like ultrasound-based[80-82] or chemical approaches[83,84], remain uncertain, as head-to-head comparisons of different techniques are lacking. Nevertheless, ultrasound treatment appears to be a promising treatment option, as recent work from our group suggests: Treatment of 24 non-responders to radiofrequency based RDN with an ultrasound denervation system significantly improved BP[85].

Obesity

Obesity seems to be associated with an elevated sympathetic activity, even in normotensive subjects[86]. Therefore, it might be a good predictor for BP responsiveness to RDN. In contrast, according to one singular study[87] obesity seems to be a predictor for non-responsiveness to RDN. The results of this trial are however somewhat questionable, as this constellation was neither found in any other trial[8,73] nor in the even large multicenter Global Simplicity Registry[12]. Moreover, in two smaller trials a higher body mass index was found to be a predictor for responsiveness to RDN[47,88]. To date, obesity should not be considered to have any predictive value for RDN success until reevaluation in larger, adequately powered cohorts has been performed.

Gender

So far the effect of RDN seems to be independent of gender. Nevertheless, due to the higher incidence of hypertension and therapy resistant hypertension in men, women are strongly underrepresented in any clinical trial regarding RDN. The percentage of women included in trials of renal denervation ranges between 23 and

Table 3 Predictors for blood pressure change after renal sympathetic denervation

Ref.	Year	Patients	Predictor
Böhm *et al*[12]	2015	998	Higher baseline BP predicts better BP response to RDN
Kandzari *et al*[73]	2015	364	
Id *et al*[76]	2013	74	Less BP response to RDN if accessories are present
Ewen *et al*[89]	2015	126	Better BP response in patients with combined vs isolated systolic hypertension
Okon *et al*[41]	2016	58	Lower pulse wave velocity predicts BP response
Zuern *et al*[88]	2013	40	Better BP response in patients with impaired baroreflex sensitivity

BP: Blood pressure; RDN: Renal sympathetic denervation.

41[8,10,13,14,47]. Realizing a meta-analysis of prospective trials could clarify the role of gender for RDN success.

Age

The age of the treated patients itself was not found to have a good predictive value for the success of RDN[73]. In contrast, considerable evidence was found for vascular aging and stiffening as a predictor for renal denervation over the last years[41,89].

Vascular aging and stiffness

Arterial stiffening is associated with a high cardiovascular mortality in hypertensive patients[90,91]. It also can be regarded as a cause for essential hypertension[92,93]. Ewen *et al*[89] found, that the presence of isolated systolic hypertension - characterized by increased aortic stiffness - is associated with a diminished response to RDN. In line with these data, our group also found an increased aortic stiffness, assessed by invasive pulse wave velocity, to be an independent predictor for poor BP response to renal denervation[41]. This is a promising finding, as isolated systolic hypertension and pulse wave velocity, among other markers of vascular aging and aortic stiffness, can easily be assessed non-invasively and thereby could help improving the preselection of patients available for renal denervation. To some extent, this might also explain why a trial by Vink *et al*[94] found the presence of cardiovascular diseases (a composite of stroke, transient ischemic attack and coronary artery disease), which are associated with increased vascular stiffness, to be a predictor for BP response to RDN.

Baroreflex

An impaired cardiac baroreflex occurs frequently in hypertensive subjects[95]. This might be explained by sympathetic overactivity[88]. Therefore, the presence of an impaired cardiac baroreflex as an indicator for high sympathetic overdrive could be a good predictor for renal denervation success. This hypothesis was already confirmed by a trial in 50 patients[88], but has not been applied in other prospective trials to date.

Renal function

Patients with renal diseases have often been excluded from clinical trials for safety reasons. Despite these considerations, patients with impaired renal function show an elevated sympathetic activity[96,97], and therefore might be good candidates for RDN. Consequently, Vink *et al*[94] found an inverse relation between the estimated GFR and the change in BP after RDN in a hypertensive population off antihypertensive medication. However, when analyzing patients on antihypertensive medication, no significant predictive value for estimated GFR was observed. These interesting findings warrant further investigation, as - besides enlightening the predictive role of renal function - they might partly explain why and how antihypertensive drugs interact with the effectiveness of RDN. Several trials investigating the effect of renal denervation in chronic kidney disease are currently recruiting patients (*e.g.*, NCT02002585, NCT01442883).

Conclusion

Despite the disappointing results of the SYMPLICITY-HTN3 trial, the canon of published data identifies RDN as a promising therapeutic option for hypertensive patients. Besides direct BP-lowering effects RDN has been shown to affect a broad range of pathophysiological mechanisms and might even be a viable treatment option for patients with other conditions such as heart failure or arrhythmias.

Although various predictors for the success of RDN have been identified (Table 3), an optimization for the prediction of RDN response is highly desired and several trials are ongoing which hopefully will improve treatment success and future RDN-trial design.

Verification of specific treatment effects of RDN in carefully and well-designed trials bare the hope to secure the role for RDN in treating arterial hypertension and ideally in reducing cardiovascular morbidity and mortality in the future.

REFERENCES

1 **Krum H**, Sobotka P, Mahfoud F, Böhm M, Esler M, Schlaich M. Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. *Circulation* 2011; **123**: 209-215 [PMID: 21242507 DOI: 10.1161/CIRCULATIONAHA.110.971580]

2 **DiBona GF**. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005; **289**: R633-R641 [PMID: 16105818 DOI: 10.1152/ajpregu.00258.2005]

3 **Reinecke M**, Forssmann WG. Neuropeptide (neuropeptide Y, neurotensin, vasoactive intestinal polypeptide, substance P, calcitonin gene-related peptide, somatostatin) immunohistochemistry and

ultrastructure of renal nerves. *Histochemistry* 1988; **89**: 1-9 [PMID: 2452814]
4 **Mione MC**, Ralevic V, Burnstock G. Peptides and vasomotor mechanisms. *Pharmacol Ther* 1990; **46**: 429-468 [PMID: 2188271]
5 **Smithwick RH**, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. *J Am Med Assoc* 1953; **152**: 1501-1504 [PMID: 13061307]
6 **Parkes WE**. Thoracolumbar sympathectomy in hypertension. *Br Heart J* 1958; **20**: 249-252 [PMID: 13523020]
7 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]
8 **Bhatt DL**, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370**: 1393-1401 [PMID: 24678939 DOI: 10.1056/NEJMoa1402670]
9 **Kandzari DE**, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, Townsend R, Weber MA, Böhm M. The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016; **171**: 82-91 [PMID: 26699604 DOI: 10.1016/j.ahj.2015.08.021]
10 **Desch S**, Okon T, Heinemann D, Kulle K, Röhnert K, Sonnabend M, Petzold M, Müller U, Schuler G, Eitel I, Thiele H, Lurz P. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015; **65**: 1202-1208 [PMID: 25824248 DOI: 10.1161/HYPERTENSIONAHA.115.05283]
11 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]
12 **Böhm M**, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich MP, Schmieder RE, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancia G. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015; **65**: 766-774 [PMID: 25691618 DOI: 10.1161/HYPERTENSIONAHA.114.05010]
13 **Rosa J**, Widimský P, Toušek P, Petrák O, Čurila K, Waldauf P, Bednář F, Zelinka T, Holaj R, Štrauch B, Šomlóová Z, Táborský M, Václavík J, Kociánová E, Branny M, Nykl I, Jiravský O, Widimský J. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015; **65**: 407-413 [PMID: 25421981 DOI: 10.1161/HYPERTENSIONAHA.114.04019]
14 **Azizi M**, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand PY, Lantelme P, Denolle T, Dourmap-Collas C, Trillaud H, Pereira H, Plouin PF, Chatellier G. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; **385**: 1957-1965 [PMID: 25631070 DOI: 10.1016/S0140-6736(14)61942-5]
15 **Ott C**, Janka R, Schmid A, Titze S, Ditting T, Sobotka PA, Veelken R, Uder M, Schmieder RE. Vascular and renal hemodynamic changes after renal denervation. *Clin J Am Soc Nephrol* 2013; **8**: 1195-1201 [PMID: 23559677 DOI: 10.2215/CJN.08500812]
16 **Ott C**, Mahfoud F, Schmid A, Ditting T, Veelken R, Ewen S, Ukena C, Uder M, Böhm M, Schmieder RE. Improvement of albuminuria after renal denervation. *Int J Cardiol* 2014; **173**: 311-315 [PMID: 24681017 DOI: 10.1016/j.ijcard.2014.03.017]
17 **Ott C**, Mahfoud F, Schmid A, Toennes SW, Ewen S, Ditting T, Veelken R, Ukena C, Uder M, Böhm M, Schmieder RE. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. *J Hypertens* 2015; **33**: 1261-1266 [PMID: 25923731 DOI: 10.1097/HJH.0000000000000556]
18 **DiBona GF**, Sawin LL. Effect of renal denervation on dynamic autoregulation of renal blood flow. *Am J Physiol Renal Physiol* 2004; **286**: F1209-F1218 [PMID: 14969998 DOI: 10.1152/ajprenal.00010.2004]
19 **Pöss J**, Ewen S, Schmieder RE, Muhler S, Vonend O, Ott C, Linz D, Geisel J, Rump LC, Schlaich M, Böhm M, Mahfoud F. Effects of renal sympathetic denervation on urinary sodium excretion in patients with resistant hypertension. *Clin Res Cardiol* 2015; **104**: 672-678 [PMID: 25715938 DOI: 10.1007/s00392-015-0832-5]
20 **Kopp C**, Linz P, Dahlmann A, Hammon M, Jantsch J, Müller DN, Schmieder RE, Cavallaro A, Eckardt KU, Uder M, Luft FC, Titze J. 23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. *Hypertension* 2013; **61**: 635-640 [PMID: 23339169 DOI: 10.1161/HYPERTENSIONAHA.111.00566]
21 **Kopp C**, Linz P, Wachsmuth L, Dahlmann A, Horbach T, Schöfl C, Renz W, Santoro D, Niendorf T, Müller DN, Neininger M, Cavallaro A, Eckardt KU, Schmieder RE, Luft FC, Uder M, Titze J. (23)Na magnetic resonance imaging of tissue sodium. *Hypertension* 2012; **59**: 167-172 [PMID: 22146510 DOI: 10.1161/HYPERTENSIONAHA.111.183517]
22 **Levy D**, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996; **275**: 1557-1562 [PMID: 8622246]
23 **Okin PM**, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlöf B. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343-2349 [PMID: 15547161 DOI: 10.1001/jama.292.19.2343]
24 **Mahfoud F**, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, Fries P, Dreysse S, Wellnhofer E, Schneider G, Buecker A, Schneeweis C, Doltra A, Schlaich MP, Esler MD, Fleck E, Böhm M, Kelle S. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. *Eur Heart J* 2014; **35**: 2224-231b [PMID: 24603307 DOI: 10.1093/eurheartj/ehu093]
25 **Doltra A**, Messroghli D, Stawowy P, Hassel JH, Gebker R, Leppänen O, Gräfe M, Schneeweis C, Schnackenburg B, Fleck E, Kelle S. Potential reduction of interstitial myocardial fibrosis with renal denervation. *J Am Heart Assoc* 2014; **3**: e001353 [PMID: 25516438 DOI: 10.1161/JAHA.114.001353]
26 **McLellan AJ**, Schlaich MP, Taylor AJ, Prabhu S, Hering D, Hammond L, Marusic P, Duval J, Sata Y, Ellims A, Esler M, Peter K, Shaw J, Walton A, Kalman JM, Kistler PM. Reverse cardiac remodeling after renal denervation: Atrial electrophysiologic and structural changes associated with blood pressure lowering. *Heart Rhythm* 2015; **12**: 982-990 [PMID: 25638699 DOI: 10.1016/j.hrthm.2015.01.039]
27 **Lu D**, Wang K, Liu Q, Wang S, Zhang Q, Shan Q. Reductions of left ventricular mass and atrial size following renal denervation: a meta-analysis. *Clin Res Cardiol* 2016; **105**: 648-656 [PMID: 26838292 DOI: 10.1007/s00392-016-0964-2]
28 **Dörr O**, Liebetrau C, Möllmann H, Gaede L, Troidl C, Morczeck K, Wiebe J, Hoffmann J, Voss S, Bauer T, Hamm C, Nef H. Influence of Renal Sympathetic Denervation on Cardiac Extracellular Matrix Turnover and Cardiac Fibrosis. *Am J Hypertens* 2015; **28**: 1285-1292 [PMID: 25767136 DOI: 10.1093/ajh/hpv020]
29 **Zhou Q**, Zhou X, TuEr-Hong ZL, Wang H, Yin T, Li Y, Zhang L, Lu Y, Xing Q, Zhang J, Yang Y, Tang B. Renal sympathetic denervation suppresses atrial fibrillation induced by acute atrial ischemia/infarction through inhibition of cardiac sympathetic activity. *Int J Cardiol* 2016; **203**: 187-195 [PMID: 26512836 DOI: 10.1016/j.ijcard.2015.10.120]
30 **Hou Y**, Hu J, Po SS, Wang H, Zhang L, Zhang F, Wang K, Zhou Q.

Catheter-based renal sympathetic denervation significantly inhibits atrial fibrillation induced by electrical stimulation of the left stellate ganglion and rapid atrial pacing. *PLoS One* 2013; **8**: e78218 [PMID: 24223140 DOI: 10.1371/journal.pone.0078218]

31 **Qiu M**, Shan Q, Chen C, Geng J, Guo J, Zhou X, Qian W, Tang L, Yin Y. Renal sympathetic denervation improves rate control in patients with symptomatic persistent atrial fibrillation and hypertension. *Acta Cardiol* 2016; **71**: 67-73 [PMID: 26853256 DOI: 10.2143/AC.71.1.3132100]

32 **Kosiuk J**, Hilbert S, Pokushalov E, Hindricks G, Steinberg JS, Bollmann A. Renal denervation for treatment of cardiac arrhythmias: state of the art and future directions. *J Cardiovasc Electrophysiol* 2015; **26**: 233-238 [PMID: 25231911 DOI: 10.1111/jce.12553]

33 **Linz D**, Wirth K, Ukena C, Mahfoud F, Pöss J, Linz B, Böhm M, Neuberger HR. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Heart Rhythm* 2013; **10**: 1525-1530 [PMID: 23851058 DOI: 10.1016/j.hrthm.2013.07.015]

34 **Huang B**, Yu L, He B, Lu Z, Wang S, He W, Yang K, Liao K, Zhang L, Jiang H. Renal sympathetic denervation modulates ventricular electrophysiology and has a protective effect on ischaemia-induced ventricular arrhythmia. *Exp Physiol* 2014; **99**: 1467-1477 [PMID: 25172887 DOI: 10.1113/expphysiol.2014.082057]

35 **Lubanda JC**, Kudlicka J, Mlcek M, Chochola M, Neuzil P, Linhart A, Kittnar O. Renal denervation decreases effective refractory period but not inducibility of ventricular fibrillation in a healthy porcine biomodel: a case control study. *J Transl Med* 2015; **13**: 4 [PMID: 25591755 DOI: 10.1186/s12967-014-0367-y]

36 **Armaganijan LV**, Staico R, Moreira DA, Lopes RD, Medeiros PT, Habib R, Melo Neto J, Katz M, Armaganijan D, Sousa AG, Mahfoud F, Abizaid A. 6-Month Outcomes in Patients With Implantable Cardioverter-Defibrillators Undergoing Renal Sympathetic Denervation for the Treatment of Refractory Ventricular Arrhythmias. *JACC Cardiovasc Interv* 2015; **8**: 984-990 [PMID: 26088516 DOI: 10.1016/j.jcin.2015.03.012]

37 **Chirinos JA**, Kips JG, Jacobs DR, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012; **60**: 2170-2177 [PMID: 23103044 DOI: 10.1016/j.jacc.2012.07.054]

38 **Brandt MC**, Reda S, Mahfoud F, Lenski M, Böhm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1956-1965 [PMID: 23062529 DOI: 10.1016/j.jacc.2012.08.959]

39 **Mortensen K**, Franzen K, Himmel F, Bode F, Schunkert H, Weil J, Reppel M. Catheter-based renal sympathetic denervation improves central hemodynamics and arterial stiffness: a pilot study. *J Clin Hypertens* (Greenwich) 2012; **14**: 861-870 [PMID: 23205753 DOI: 10.1111/j.1751-7176.2012.00704.x]

40 **Hering D**, Lambert EA, Marusic P, Ika-Sari C, Walton AS, Krum H, Sobotka PA, Mahfoud F, Böhm M, Lambert GW, Esler MD, Schlaich MP. Renal nerve ablation reduces augmentation index in patients with resistant hypertension. *J Hypertens* 2013; **31**: 1893-1900 [PMID: 23697964 DOI: 10.1097/HJH.0b013e3283622e58]

41 **Okon T**, Röhnert K, Stiermaier T, Rommel KP, Müller U, Fengler K, Schuler G, Desch S, Lurz P. Invasive Aortic Pulse Wave Velocity as a Marker for Arterial Stiffness Predicts Outcome of Renal Sympathetic Denervation. *EuroIntervention* 2016; In press

42 **Cao JJ**, Wang Y, McLaughlin J, Haag E, Rhee P, Passick M, Toole R, Cheng J, Berke AD, Lachman J, Reichek N. Left ventricular filling pressure assessment using left atrial transit time by cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging* 2011; **4**: 130-138 [PMID: 21262980 DOI: 10.1161/CIRCIMAGING.110.959569]

43 **Richard Jennings J**, Christie IC, Muldoon MF, Ryan CM, Price JC, Meltzer CC. Brain function, cognition, and the blood pressure response to pharmacological treatment. *Psychosom Med* 2010; **72**: 702-711 [PMID: 20639391 DOI: 10.1097/PSY.0b013e3181e7c1a2]

44 **Gąsecki D**, Kwarciany M, Nyka W, Narkiewicz K. Hypertension, brain damage and cognitive decline. *Curr Hypertens Rep* 2013; **15**: 547-558 [PMID: 24146223 DOI: 10.1007/s11906-013-0398-4]

45 **Booth LC**, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, May CN. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. *Hypertension* 2015; **65**: 393-400 [PMID: 25403610 DOI: 10.1161/HYPERTENSIONAHA.114.04176]

46 **Rodionova K**, Fiedler C, Guenther F, Grouzmann E, Neuhuber W, Fischer MJ, Ott C, Linz P, Freisinger W, Heinlein S, Schmidt ST, Schmieder RE, Amann K, Scrogin K, Veelken R, Ditting T. Complex reinnervation pattern after unilateral renal denervation in rats. *Am J Physiol Regul Integr Comp Physiol* 2016; **310**: R806-R818 [PMID: 26911463 DOI: 10.1152/ajpregu.00227.2014]

47 **Tsioufis CP**, Papademetriou V, Dimitriadis KS, Kasiakogias A, Tsiachris D, Worthley MI, Sinhal AR, Chew DP, Meredith IT, Malaiapan Y, Thomopoulos C, Kallikazaros I, Tousoulis D, Worthley SG. Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the EnligHTN I first-in-human study using a multi-electrode ablation system. *Int J Cardiol* 2015; **201**: 345-350 [PMID: 26301677 DOI: 10.1016/j.ijcard.2015.08.069]

48 **Mancia G**, Mahfoud F, Narkiewicz K, Ruilope LM, Schlaich MP, Schmieder RE, Williams B, Böhm M. 4A.01: long-term effects of renal artery denervation in real world patients with uncontrolled hypertension from the global symplicity registry. *J Hypertens* 2015; **33** Suppl 1: e49 [PMID: 26102834 DOI: 10.1097/01.hjh.0000467475.67073.7e]

49 **Hering D**, Marusic P, Walton AS, Lambert EA, Krum H, Narkiewicz K, Lambert GW, Esler MD, Schlaich MP. Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. *Hypertension* 2014; **64**: 118-124 [PMID: 24732891 DOI: 10.1161/HYPERTENSIONAHA.113.03098]

50 **Nair GK**, Massé S, Asta J, Sevaptisidis E, Azam MA, Lai PF, Veluppillaim A, Magtibay K, Jackson N, Nanthakumar K. The need for and the challenges of measuring renal sympathetic nerve activity. *Heart Rhythm* 2016; **13**: 1166-1171 [PMID: 26806582 DOI: 10.1016/j.hrthm.2016.01.018]

51 **Donazzan L**, Mahfoud F, Ewen S, Ukena C, Cremers B, Kirsch CM, Hellwig D, Eweiwi T, Ezziddin S, Esler M, Böhm M. Effects of catheter-based renal denervation on cardiac sympathetic activity and innervation in patients with resistant hypertension. *Clin Res Cardiol* 2016; **105**: 364-371 [PMID: 26493305 DOI: 10.1007/s00392-015-0930-4]

52 **van Brussel PM**, Eeftinck Schattenkerk DW, Dobrowolski LC, de Winter RJ, Reekers JA, Verberne HJ, Vogt L, van den Born BJ. Effects of renal sympathetic denervation on cardiac sympathetic activity and function in patients with therapy resistant hypertension. *Int J Cardiol* 2016; **202**: 609-614 [PMID: 26447672 DOI: 10.1016/j.ijcard.2015.09.025]

53 **Tsioufis C**, Papademetriou V, Tsiachris D, Dimitriadis K, Kasiakogias A, Kordalis A, Antonakis V, Kefala A, Thomopoulos C, Kallikazaros I, Lau EO, Stefanadis C. Drug-resistant hypertensive patients responding to multielectrode renal denervation exhibit improved heart rate dynamics and reduced arrhythmia burden. *J Hum Hypertens* 2014; **28**: 587-593 [PMID: 24621623 DOI: 10.1038/jhh.2014.14]

54 **Anderson EA**, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension* 1989; **14**: 177-183 [PMID: 2759678]

55 **Vink EE**, Verloop WL, Siddiqi L, van Schelven LJ, Liam Oey P, Blankestijn PJ. The effect of percutaneous renal denervation on muscle sympathetic nerve activity in hypertensive patients. *Int J Cardiol* 2014; **176**: 8-12 [PMID: 25027168 DOI: 10.1016/j.ijcard.2014.06.021]

56 **Brinkmann J**, Heusser K, Schmidt BM, Menne J, Klein G, Bauersachs J, Haller H, Sweep FC, Diedrich A, Jordan J, Tank J. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients:

prospective case series. *Hypertension* 2012; **60**: 1485-1490 [PMID: 23045466 DOI: 10.1161/HYPERTENSIONAHA.112.201186]
57 **Hering D**, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013; **61**: 457-464 [PMID: 23172929 DOI: 10.1161/HYPERTENSIONAHA.111.00194]
58 **Dörr O**, Ewen S, Liebetrau C, Möllmann H, Gaede L, Linz D, Hohl M, Troidl C, Bauer T, Böhm M, Hamm C, Mahfoud F, Nef H. Neuropeptide Y as an indicator of successful alterations in sympathetic nervous activity after renal sympathetic denervation. *Clin Res Cardiol* 2015; **104**: 1064-1071 [PMID: 26008896 DOI: 10.1007/s00392-015-0874-8]
59 **Dörr O**, Liebetrau C, Möllmann H, Gaede L, Troidl C, Haidner V, Wiebe J, Voss S, Bauer T, Hamm C, Nef H. Brain-derived neurotrophic factor as a marker for immediate assessment of the success of renal sympathetic denervation. *J Am Coll Cardiol* 2015; **65**: 1151-1153 [PMID: 25790889 DOI: 10.1016/j.jacc.2014.11.071]
60 **Virdis A**, Dell'Agnello U, Taddei S. Impact of inflammation on vascular disease in hypertension. *Maturitas* 2014; **78**: 179-183 [PMID: 24846805 DOI: 10.1016/j.maturitas.2014.04.012]
61 **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]
62 **Furumoto T**, Saito N, Dong J, Mikami T, Fujii S, Kitabatake A. Association of cardiovascular risk factors and endothelial dysfunction in japanese hypertensive patients: implications for early atherosclerosis. *Hypertens Res* 2002; **25**: 475-480 [PMID: 12135329]
63 **Dörr O**, Liebetrau C, Möllmann H, Mahfoud F, Ewen S, Gaede L, Troidl C, Hoffmann J, Busch N, Laux G, Wiebe J, Bauer T, Hamm C, Nef H. Beneficial effects of renal sympathetic denervation on cardiovascular inflammation and remodeling in essential hypertension. *Clin Res Cardiol* 2015; **104**: 175-184 [PMID: 25326158 DOI: 10.1007/s00392-014-0773-4]
64 **Masuo K**, Mikami H, Ogihara T, Tuck ML. Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, nonobese Japanese population. *Am J Hypertens* 1997; **10**: 77-83 [PMID: 9008251]
65 **Mahfoud F**, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; **123**: 1940-1946 [PMID: 21518978 DOI: 10.1161/CIRCULATIONAHA.110.991869]
66 **Verloop WL**, Spiering W, Vink EE, Beeftink MM, Blankestijn PJ, Doevendans PA, Voskuil M. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. *Hypertension* 2015; **65**: 751-757 [PMID: 25646297 DOI: 10.1161/HYPERTENSIONAHA.114.04798]
67 **Mundal R**, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. *Hypertension* 1994; **24**: 56-62 [PMID: 8021008]
68 **Fagard R**, Staessen J, Thijs L, Amery A. Prognostic significance of exercise versus resting blood pressure in hypertensive men. *Hypertension* 1991; **17**: 574-578 [PMID: 2013484]
69 **Ukena C**, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, Brandt MC, Hoppe UC, Krum H, Esler M, Sobotka PA, Böhm M. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2011; **58**: 1176-1182 [PMID: 21884958 DOI: 10.1016/j.jacc.2011.05.036]
70 **Fengler K**, Heinemann D, Okon T, Rohnert K, Stiermaier T, von Roder M, Besler C, Muller U, Hollriegel R, Schuler G, Desch S, Lurz P. Renal denervation improves exercise blood pressure: insights from a randomized, sham-controlled trial. *Clin Res Cardiol* 2016 [PMID: 26728060 DOI: 10.1007/s00392-015-0955-8]
71 **Ewen S**, Mahfoud F, Linz D, Pöss J, Cremers B, Kindermann I, Laufs U, Ukena C, Böhm M. Effects of renal sympathetic denervation on exercise blood pressure, heart rate, and capacity in patients with resistant hypertension. *Hypertension* 2014; **63**: 839-845 [PMID: 24420550 DOI: 10.1161/HYPERTE NSIONAHA.113.01985]
72 **Lenski M**, Mahfoud F, Razouk A, Ukena C, Lenski D, Barth C, Linz D, Laufs U, Kindermann I, Böhm M. Orthostatic function after renal sympathetic denervation in patients with resistant hypertension. *Int J Cardiol* 2013; **169**: 418-424 [PMID: 24157238 DOI: 10.1016/j.ijcard.2013.10.017]
73 **Kandzari DE**, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015; **36**: 219-227 [PMID: 25400162 DOI: 10.1093/eurheartj/ehu441]
74 **Howard JP**, Shun-Shin MJ, Hartley A, Bhatt DL, Krum H, Francis DP. Quantifying the 3 Biases That Lead to Unintentional Overestimation of the Blood Pressure-Lowering Effect of Renal Denervation. *Circ Cardiovasc Qual Outcomes* 2016; **9**: 14-22 [PMID: 26758193 DOI: 10.1161/CIRCOUTCOMES.115.002533]
75 **Ozkan U**, Oğuzkurt L, Tercan F, Kizilkiliç O, Koç Z, Koca N. Renal artery origins and variations: angiographic evaluation of 855 consecutive patients. *Diagn Interv Radiol* 2006; **12**: 183-186 [PMID: 17160802]
76 **Id D**, Kaltenbach B, Bertog SC, Hornung M, Hofmann I, Vaskelyte L, Sievert H. Does the presence of accessory renal arteries affect the efficacy of renal denervation? *JACC Cardiovasc Interv* 2013; **6**: 1085-1091 [PMID: 24156968 DOI: 10.1016/j.jcin.2013.06.007]
77 **Sakakura K**, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014; **64**: 635-643 [PMID: 25125292 DOI: 10.1016/j.jacc.2014.03.059]
78 **Mahfoud F**, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Böhm M, Melder RJ. Impact of Lesion Placement on Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation. *J Am Coll Cardiol* 2015; **66**: 1766-1775 [PMID: 26483099 DOI: 10.1016/j.jacc.2015.08.018]
79 **Henegar JR**, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-Based Radiofrequency Renal Denervation: Location Effects on Renal Norepinephrine. *Am J Hypertens* 2015; **28**: 909-914 [PMID: 25576624 DOI: 10.1093/ajh/hpu258]
80 **Rong S**, Zhu H, Liu D, Qian J, Zhou K, Zhu Q, Jiang Y, Yang G, Deng C, Zhang D, Zhou Q, Lei H, He TC, Wang Z, Huang J. Noninvasive renal denervation for resistant hypertension using high-intensity focused ultrasound. *Hypertension* 2015; **66**: e22-e25 [PMID: 26238444 DOI: 10.1161/HYPERTENSIONAHA.115.05754]
81 **Sakakura K**, Roth A, Ladich E, Shen K, Coleman L, Joner M, Virmani R. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. *EuroIntervention* 2015; **10**: 1230-1238 [PMID: 25349043 DOI: 10.4244/EIJY14M10_14]
82 **Mabin T**, Sapoval M, Cabane V, Stemmett J, Iyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. *EuroIntervention* 2012; **8**: 57-61 [PMID: 22580249 DOI: 10.4244/EIJV8I1A10]
83 **Fischell TA**, Fischell DR, Ghazarossian VE, Vega F, Ebner A. Next generation renal denervation: chemical "perivascular" renal denervation with alcohol using a novel drug infusion catheter. *Cardiovasc Revasc Med* 2015; **16**: 221-227 [PMID: 25979565 DOI: 10.1016/j.carrev.2015.04.008]
84 **Ricke J**, Seidensticker M, Becker S, Schiefer J, Adamchic I, Lohfink K, Kandulski M, Heller A, Mertens PR. Renal Sympathetic Denervation by CT-Guided Ethanol Injection: A Phase II Pilot Trial of a Novel Technique. *Cardiovasc Intervent Radiol* 2016; **39**: 251-260 [PMID: 26634740 DOI: 10.1007/s00270-015-1261-6]
85 **Stiermaier T**, Okon T, Fengler K, Mueller U, Hoellriegel R, Schuler G, Desch S, Lurz P. Endovascular ultrasound for renal

sympathetic denervation in patients with therapy-resistant hypertension not responding to radiofrequency renal sympathetic denervation. *EuroIntervention* 2016; **12**: e282-e289 [PMID: 27290688 DOI: 10.4244/EIJV12I2A43]

86 **Grassi G**, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, Giannattasio C, Brunani A, Cavagnini F, Mancia G. Sympathetic activation in obese normotensive subjects. *Hypertension* 1995; **25**: 560-563 [PMID: 7721398]

87 **Id D**, Bertog SC, Ziegler AK, Hornung M, Hofmann I, Vaskelyte L, Matic P, Gafoor S, Sievert H. Predictors of Blood Pressure Response: Obesity Is Associated With a Less Pronounced Treatment Response After Renal Denervation. *Catheter Cardiovasc Interv* 2015; **87**: E30-E38 [PMID: 26104216 DOI: 10.1002/ccd.26068]

88 **Zuern CS**, Eick C, Rizas KD, Bauer S, Langer H, Gawaz M, Bauer A. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2013; **62**: 2124-2130 [PMID: 23973686 DOI: 10.1016/j.jacc.2013.07.046]

89 **Ewen S**, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfeil S, Schmieder RE, Böhm M, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension* 2015; **65**: 193-199 [PMID: 25331843 DOI: 10.1161/HYPERTE NSIO NAHA.114.04336]

90 **Laurent S**, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236-1241 [PMID: 11358934]

91 **Maroules CD**, Khera A, Ayers C, Goel A, Peshock RM, Abbara S, King KS. Cardiovascular outcome associations among cardiovascular magnetic resonance measures of arterial stiffness: the Dallas heart study. *J Cardiovasc Magn Reson* 2014; **16**: 33 [PMID: 24886531 DOI: 10.1186/1532-429X-16-33]

92 **Pettersen KH**, Bugenhagen SM, Nauman J, Beard DA, Omholt SW. Arterial stiffening provides sufficient explanation for primary hypertension. *PLoS Comput Biol* 2014; **10**: e1003634 [PMID: 24853828 DOI: 10.1371/journal.pcbi.1003634]

93 **Kaess BM**, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; **308**: 875-881 [PMID: 22948697 DOI: 10.1001/2012.jama.10503]

94 **Vink EE**, Verloop WL, Bost RB, Voskuil M, Spiering W, Vonken EJ, Bots ML, Blankestijn PJ. The blood pressure-lowering effect of renal denervation is inversely related to kidney function. *J Hypertens* 2014; **32**: 2045-2053; discussion 2053 [PMID: 25023158 DOI: 10.1097/HJH.0000000000000282]

95 **Bristow JD**, Honour AJ, Pickering GW, Sleight P, Smyth HS. Diminished baroreflex sensitivity in high blood pressure. *Circulation* 1969; **39**: 48-54 [PMID: 4302539]

96 **Campese VM**. Pathophysiology of resistant hypertension in chronic kidney disease. *Semin Nephrol* 2014; **34**: 571-576 [PMID: 25416666 DOI: 10.1016/j.semnephrol.2014.08.011]

97 **Converse RL**, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912-1918 [PMID: 1454086 DOI: 10.1056/NEJM199212313272704]

P- Reviewer: Elisaf MS, Ong HT, Velasco M **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.447

World J Cardiol 2016 August 26; 8(8): 447-455
ISSN 1949-8462 (online)

12-lead electrocardiogram features of arrhythmic risk: A focus on early repolarization

Caterina Rizzo, Francesco Monitillo, Massimo Iacoviello

Caterina Rizzo, Francesco Monitillo, School of Cardiology, Department of Emergency and Organ Transplantation, University of Bari, 70124 Bari, Italy

Massimo Iacoviello, Cardiology Unit, Department of Cardiothoracic, Policlinic University Hospital, 70124 Bari, Italy

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Manuscript source: Invited manuscript

Correspondence to: Massimo Iacoviello, MD, PhD, FESC, FANMCO, Cardiology Unit, Department of Cardiothoracic, Policlinic University Hospital, Piazza Giulio Cesare 11, 70124 Bari, Italy. massimo.iacoviello@cardio.uniba.it
Telephone: +39-80-5478622
Fax: +39-80-5478796

Received: April 28, 2016
Peer-review started: April 30, 2016
First decision: May 17, 2016
Revised: June 6, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: August 26, 2016

Abstract

The 12-lead electrocardiogram (ECG) is still the most used tool in cardiology clinical practice. Considering its easy accessibility, low cost and the information that it provides, it remains the starting point for diagnosis and prognosis. More specifically, its ability to detect prognostic markers for sudden cardiac death due to arrhythmias by identifying specific patterns that express electrical disturbances of the heart muscle, which may predispose to malignant arrhythmias, is universally recognized. Alterations in the ventricular repolarization process, identifiable on a 12-lead ECG, play a role in the genesis of ventricular arrhythmias in different cardiac diseases. The aim of this paper is to focus the attention on a new marker of arrhythmic risk, the early repolarization pattern in order to highlight the prognostic role of the 12-lead ECG.

Key words: Ventricular repolarization; Cardiovascular diseases; Arrhythmic risk; Early repolarization; Arrhythmia

Core tip: By identifying specific patterns which are an expression of ventricular repolarization alterations, the 12-lead electrocardiogram plays an important role in the diagnosis of electrical disturbances and in the risk stratification of death due to arrhythmias. This review focuses the attention on the new early repolarization marker of arrhythmic risk and its prognostic implications.

Rizzo C, Monitillo F, Iacoviello M. 12-lead electrocardiogram features of arrhythmic risk: A focus on early repolarization. *World J Cardiol* 2016; 8(8): 447-455 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/447.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.447

INTRODUCTION

More than 100 years after its invention, the 12-lead electrocardiogram (ECG) is still the most used tool in cardiology clinical practice. Moreover, it represents the

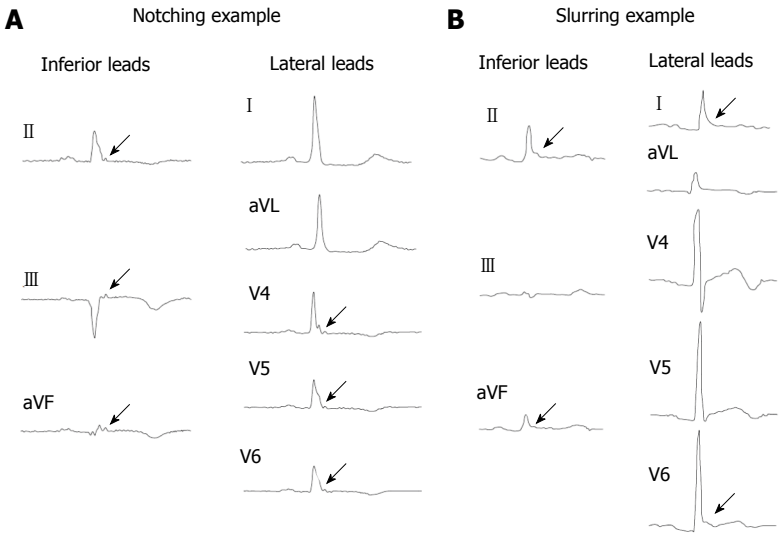

Figure 1 Notching and slurring example of early repolarization. A: Notching example; B: Slurring example.

starting point for diagnosis, given its easy accessibility and low cost.

Its ability to predict sudden cardiac death (SCD) due to arrhythmias by identifying specific patterns that express electrical disturbances of the heart muscle, which may predispose to malignant arrhythmias, is universally recognized.

On a surface 12-lead ECG it is possible to recognize a phase of ventricular depolarization, represented by the QRS complex, and a phase of ventricular repolarization (VR), that conventionally begins at the QRS wave and ends at the T waves. VR is made up of the J-wave, ST-segments and T-waves and U-waves[1,2]. Over the years several studies have analyzed the characteristics of VR and have recognized visible alterations as characteristic patterns on 12-lead ECG, emphasizing the role of the latter in the genesis of ventricular arrhythmias in different cardiac diseases[3-6].

From a pathophysiological point of view, it has been shown that changes in the process of VR can lead to malignant ventricular arrhythmias through abnormalities occurring in the action potential (AP) and in the refractory period of cardiac cells, thus leading to spatial heterogeneity and temporal fluctuations in repolarization, favoring the onset of arrhythmias[7,8].

However, an ECG can also be modulated by genetic factors which can determine an arrhythmogenic substrate that leads to an increased risk of SCD. This effect is particularly evident in inherited arrhythmogenic disorders such as long QT syndrome, short QT syndrome and Brugada syndrome, where the ECG can identify not only specific diagnostic alterations, but also prognostic indicators. This emphasizes the role of the ECG as an instrument not only for diagnostic but also for prognostic purposes[9].

The aim of this review is to focus the attention on a new marker of arrhythmic risk, *i.e.*, the early repolarization (ER) pattern. The notions presented in the literature will be revised and the prognostic and predictive role of the 12-lead ECG will be highlighted, by recognizing, characterizing and carefully studying VR disturbances in the context of the ER pattern.

DEFINITION AND FAMILY FORM OF ER, A NEW ELECTROCARDIOGRAPHIC MARKER OF ARRHYTHMIC RISK

The early ER pattern as a 12-lead ECG marker of arrhythmic risk is a more recent discovery. It is characterized by a J-point elevation of at least 1 mm in two contiguous leads with a "notching" type appearance, *i.e.*, a positive J-deflection inscribed in the S wave, or a "slurring", *i.e.*, a gradual transition of the QRS to the ST segment in the inferior, lateral or inferolateral leads, as defined by Haissaguerre in 2008[10] (Figure 1).

The J-point on the ECG waveform is historically defined as the junction between the end of the QRS complex and the beginning of the ST-segment[11].

In the 1953, Osborn[12] described the association between hypothermia and the appearance of positive deflections due to J-point elevation associated with VF. They were considered currents of injury. They became known as J-waves bearing his name (Osborn waves) and have become a generally accepted marker for clinical hypothermia.

In 1961, it was defined by Wasserburger *et al*[13] as an elevated take-off of the ST segment at the J-junction with downward concavity of the ST segment and symmetrical T waves. This elevation is manifested either as QRS slurring or notching in at least two inferior or lateral leads.

This definition remained in place until 2008 when Haissaguerre[10] shifted the focus from the ST-segment elevation to the J-point. J-point elevation was defined as being an elevation of at least 1 mm in two contiguous leads with a "notching" appearance, *i.e.*, a positive J-deflection inscribed in the S wave, or "slurring", *i.e.*, a gradual transition of the QRS to the ST segment in the inferior, lateral or infero-lateral leads. The simultaneous

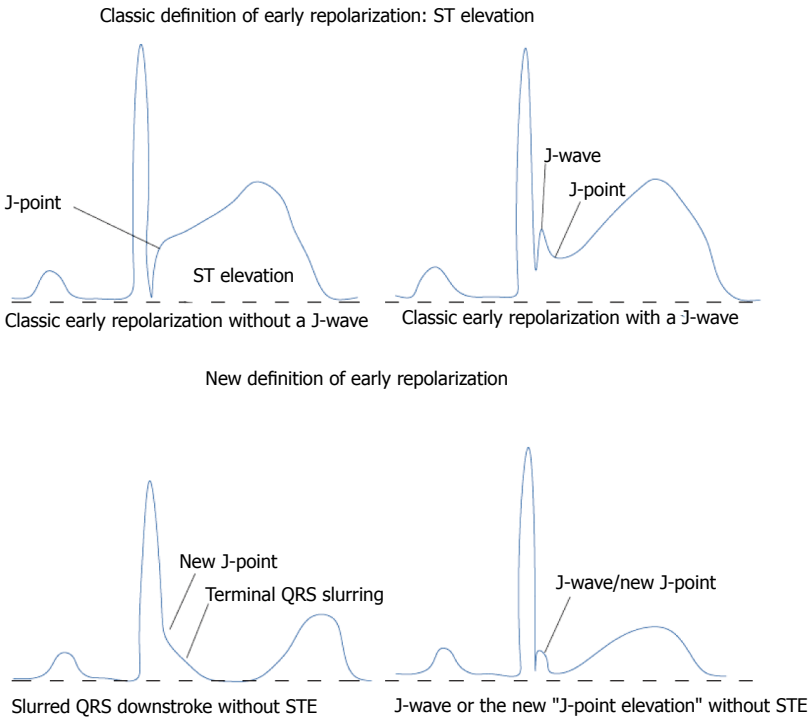

Figure 2 Old and new definition of early repolarization. STE: ST elevation.

presence of ST-segment elevation is not necessary for diagnosis (Figure 2).

ER was historically considered a benign ECG variant, commonly seen in the anterolateral leads of young male athletes of black ethnicity but also in adolescents, accentuated by vagal tone and hypothermia[14-18]. In effect, an increase in vagal activity is known to cause an ST-segment elevation whereas sympathetic agonists normalize the ST segment[19].

A prevalence of between 1% and 5% has been estimated in healthy adults[13,20-22]. Furthermore, an intermittent pattern of ER is commonly observed, being only rarely present in all the ECGs performed successively on the same patient. It then becomes less common with age[23]. This evidence could be explained by the direct correlation of ER pattern with elevated testosterone plasma levels, as it is observed in young males. This would also explain the absence of the ER in older subjects[24].

Although not considered a marker of cardiovascular disease, ER has a practical importance because it may mimic the ECG of acute myocardial infarction, pericarditis, ventricular aneurysm, hyperkalemia or hypothermia. A dilemma may occur when a patient with ST variant presents with chest pain and no prior available ECG[25-28]. Unnecessary or incorrect diagnostic tests, therapeutic decisions, including administration of thrombolytic drugs[29], and hospital admissions might result from misinterpretation.

The available literature also provides evidence of a possible hereditary pattern of ER. In particular, a study of 500 families showed that subjects with at least one parent with ER were twice as likely to have the same ECG alteration. Family transmission is more frequent when the mother has the ER pattern, both for notching forms and for those in the lower location[30]. Such families have been shown to have a high incidence of sudden death, probably linked to ER.

There are also very rare forms of autosomal dominant inheritance[31]. In this context it was suggested that the Valsalva maneuver can unmask forms of ER which are not spontaneous on the surface ECG. The sensitivity of this maneuver, however, is considered to be low.

The question of whether family forms have a worse prognosis than sporadic forms remains.

PATHOPHYSIOLOGICAL BACKGROUND OF J-WAVE AS AN ARRHYTHMIC MARKER

An ER pattern with the characteristics of the J-point elevation of at least 2 mm and a horizontal or descending pattern of the ST segment appears to increase the risk of developing ventricular arrhythmias, especially in structurally abnormal hearts. In fact, ER creates a kind of gradient of repolarization between adjacent areas that results in re-entry phenomena that cause the onset of arrhythmias.

The J-wave comes from an alteration of the AP involving the epicardial, but not the endocardial, cells during phase 1 of the AP. In this period (ER phase) there are two ion currents of repolarization: Potassium tends to leak out (current Ito) and chlorine tends to enter into the cell (current ICl) while the front sodium current (INa-late) is gradually attenuated until it disappears. As a result of the loss of positive charges (K^+) and the acquisition of negative charges (Cl^-), the transmembrane potential is reduced to less positive

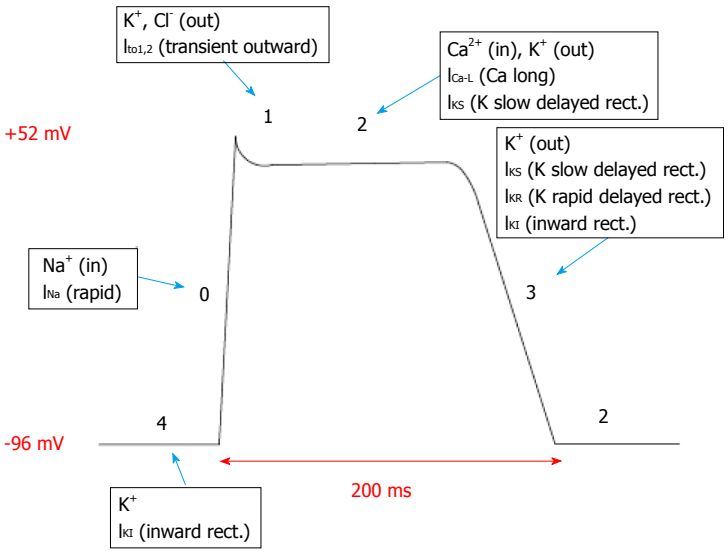

Figure 3 Action potential in physiological condition.

values, from +30 to approximately 0 mV. The incoming sodium current (INa-late) has the opposite effect to that of Ito and ICl and, by bringing positive charges within the cell, it slows down the repolarization. However, since it is quickly depleted, its importance is relatively modest in physiological conditions (Figure 3). In subjects who have the ER patterns, repolarization proceeds more quickly than normal during phase 1, with a rapid reduction in the potential which passes from +30 to 0 mV or negative values[32]. The imbalance between outward and inward positive currents during phase 1 of the AP and thus the propagation of the AP dome from sites where it is maintained and to sites at which it is lost, might lead to a local re-excitation *via* phase-2 re entry which, in turn, may facilitate the development of premature beats. An increase in transmural dispersion might facilitate transmural propagation of the extrasystole predisposing to the development of polymorphic VT and VF[33] (Figure 4).

CLINICAL EVIDENCES OF ER/J WAVE AS A MARKER OF ARRHYTHMIC RISK

It is important to identify ECG characteristics that differentiate the "benign ER" pattern from the "malignant ER"[34,35] (Table 1). In fact, for the first time, an English case-control study has demonstrated the arrhythmogenic potential of ER by putting in relation the ER with the idiopathic ventricular fibrillation (IVF). In fact 206 subjects under the age of 60 with IVF, were compared with a control group of 412 healthy patients. The results suggested a correlation between ER and sudden cardiac arrest. It was observed that most of the subjects with the characteristic patterns were young males, with a history of unexplained syncope or cardiac arrest during sleep. In addition, at baseline ECG, ER was present mainly in the inferior-lateral leads[10].

Tikkanen also considered the importance of defining a benign form of ER from a malignant one[35,36]. He studied a group of young athletes with ECG patterns of ER. Most of these presented an aspect of "rapidly ascending ST-segment blending with T-wave". Naturally, this has been regarded as the benign form of ER. On the other hand, a minority of the athletes showed a pattern with an ST segment that remained flat, horizontal, or even descending towards the T-wave. The authors considered this to be the malignant variant of ER which is associated with arrhythmic mortality during long-term follow up. Moreover, subjects with an elevation of at least 2 mm of the J-point in the inferior leads had an increased risk of cardiac death. The study showed a relationship between mortality and ER and revealed that the risk of death was influenced by the seat, more common in the inferior leads, and the amount of elevation of the J-point, for values greater than 2 mm. In addition, Tikkanen *et al*[35,36] demonstrated that benign ER (ascending/upsloping ST segment) is associated with a significantly shorter QTc interval compared to the malignant form (horizontal/descending ST segment) which is associated with a significantly longer QRS duration (a prolonged QTc interval was defined as at least 440 ms for men and at least 460 ms for women). Therefore, benign ER appears to reflect earlier onset of repolarization, but malignant ER may reflect abnormal depolarization, possibly with underlying subtle structural disease[35,36].

The supposition of Tikkanen was later supported by a study that compared 21 athletes with a history of previous cardiac arrest of unknown etiology with more than 300 healthy athletes[37]. The study proved that athletes with a horizontal pattern of ER and ST were 11 times more at risk of cardiac arrest. Furthermore, recent studies have shown that patients with an ER pattern have a higher risk of having ischemic events and ischemic VF[38-40]. More specifically, the ER pattern with a horizontal ST segment was an independent predictor of sudden death[41]. As regards the malignant form of ER, the pattern of ER in the inferior lateral leads must be

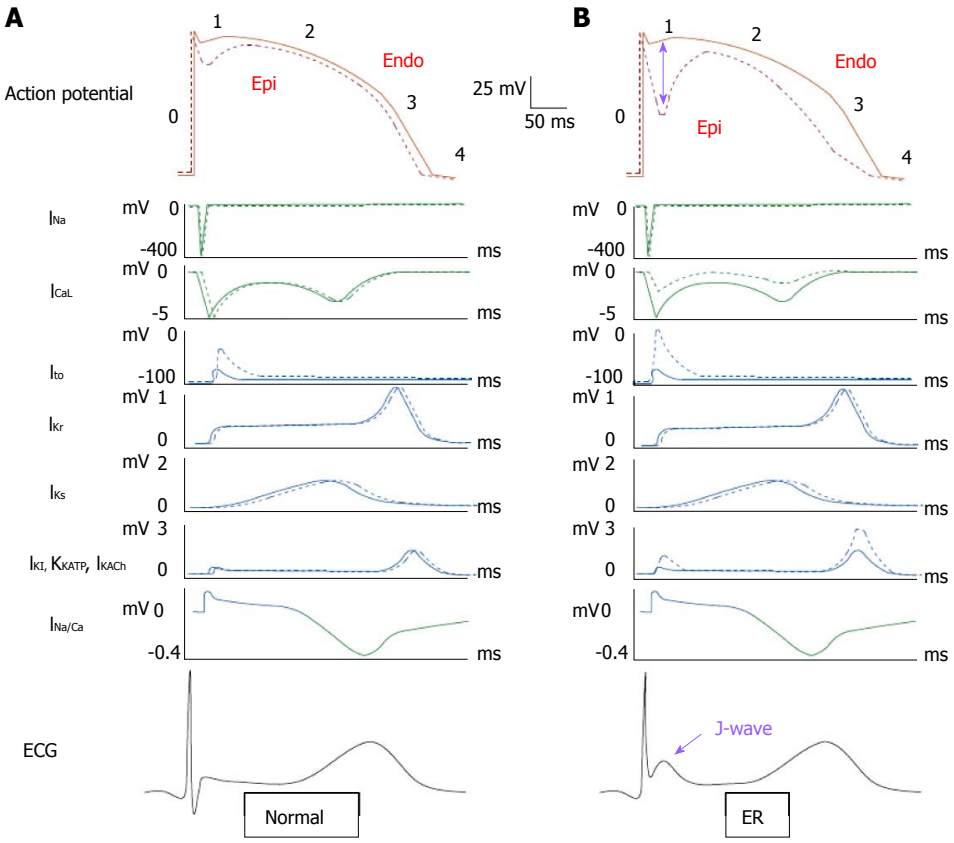

Figure 4 The pathophysiological background of J wave. A: The normal action potential, underlying currents and corresponding ECGs. Epicardial (Epi) action potential and current are shown by dotted lines and endocardial (Endo) by solid lines. Depolarizing currents are depicted downward in green and repolarizing currents upward in blue. The Epi action potential has a characteristic notch caused by larger phase -1 Ito compared with Endo; B: Exaggeration of the Epi notch results from enhancement of net outward current. Phase-1 current flow from Endo to Epi produces the J-wave. The various ionic mechanisms that are believed to produce ER are shown with purple stars. INa: Inward sodium current; ICaL: Inward calcium currents; INa/Ca: Sodium calcium exchange; Ito: Transient outward current; IKs: Slow delayed rectifier current; IKr: Rapid delayed rectifier current; IK1: Inward rectifier current; IKATP: Adenosine triphosphate-sensitive current; IKACh: Acetylcholine-activated current; ECG: Electrocardiogram.

carefully considered. It is characterized by a deflection in the R-wave (slurred pattern) descending in the terminal part of the QRS in at least two inferior leads (Ⅱ, Ⅲ, aVF), in two lateral leads (Ⅰ, aVL, V4-V6), or both. Numerous studies have demonstrated the association between a pattern of ER in these locations, especially in the inferior leads, and the presence of idiopathic VF (IVF)[26,29,42]. However, contrasting results in the available literature should be considered. In fact, in one study of nearly 30000 outpatients, with a mean follow up of 7 years, the negative prognostic effect of the ER patterns was not confirmed[43]. The only meta-analysis available of this emphasizes the correlation of ER with a higher risk of arrhythmic death but not of cardiac death or death from other causes[44].

In 1992 a Japanese study assessed the dynamicity of J-wave associated with idiopathic VF by analyzing its pause-dependent increase.

The J-wave amplitude was measured in the beat immediately after a pause and compared with the mean J-wave measured in almost three beats before the pause. The pause was considered as an abnormal sudden prolongation of the interval R-R, induced by arrhythmias such us sinus arrest, sinoatrial block, atrioventricular block, or atrial and ventricular premature beats.

It is interesting to note that the pause-dependent increase of J-wave was observed only in patients with idiopathic VF and in none of the control patients and this augmentation was associated with depression of the ST-segment or inversion of the T-waves. This dynamicity could be well explained by the pause-dependent augmentation in transient outward current (Ito) of the AP. In conclusion the authors suggested that the pausedependent augmentation was highly predictive of arrhythmic events and proposed a description of the characteristics of the "J-wave" potentially associated with IVF[45].

The same authors have further analyzed the J-wave dynamicity in the general patient population, with no symptoms and no history of IVF. They have observed an increase in amplitude of J-wave at high frequency but not at low frequencies and this may be due to a delay conduction[46].

So the analysis of the J-wave variations according to RR interval can be used to characterize the J-wave and use it for the arrhythmic risk stratification.

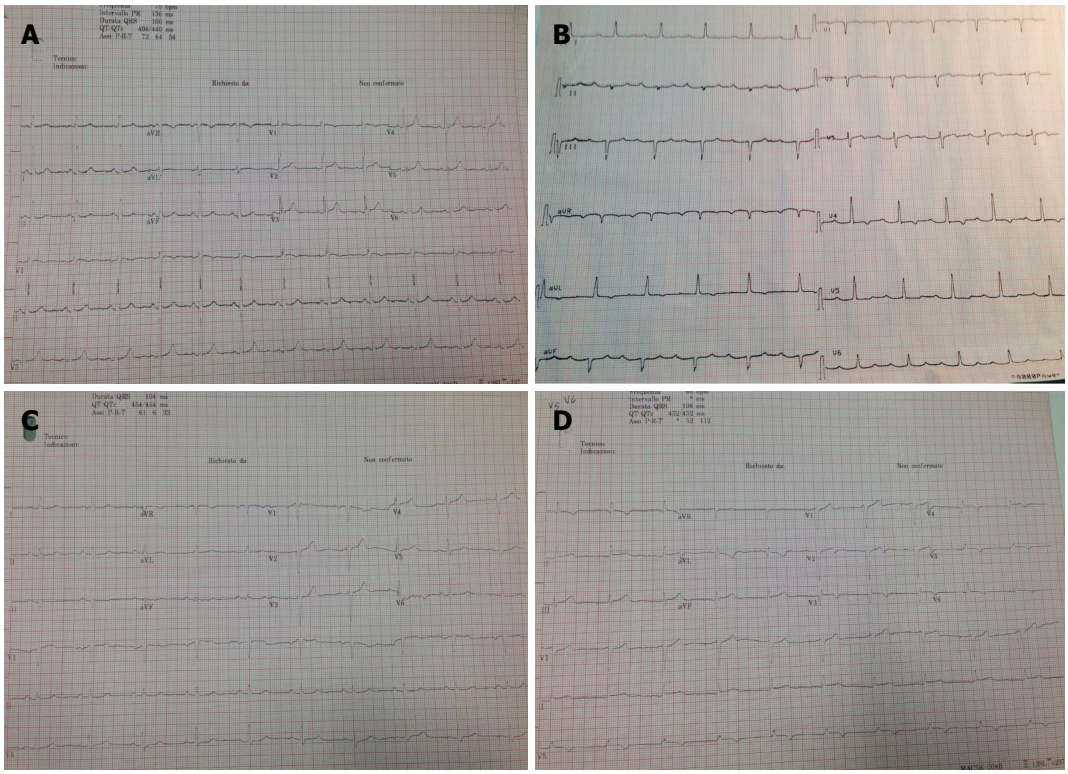

Figure 5 Early repolarization in clinical practice. A: Example of ER pattern "notching tipe" in Inferior-lateral leads (D2, D3, aVF, V5, V6). Width: 1 mm; B: Example of ER pattern "slurring tipe" in lateral leads (D1, aVL, V5, V6). Width: 1 mm; C: Example of ER pattern "notching tipe" in Inferior leads (D2, D3, aVF). Width: 1.5 mm; D: Example of ER pattern "notching tipe" in lateral leads (V5, V6). Width: 1.8 mm. ER: Early repolarization.

Focus on ECG features

Given the conflicting results between the different studies analyzed, possibly due to the non-uniformity of the case histories of patients treated, it is reasonable to think that, in addition to the seat and extent of the J-point changes, a key role is played by the characteristics of the segment elevation ST, as Tikkanen first demonstrated in his study, where the presence of a rapidly ascending ST was not associated with an increased risk of death from arrhythmia causes, unlike the detection of a horizontal or descending ST. The maximum risk was achieved by the combination of an ER pattern in the inferior leads with an ST-segment elevation at J-point greater than 2 mm and a horizontal-descending ST[35,36]. It is also interesting to note that patients with rapidly ascending ST were mostly young, had low blood pressure, and signs of left ventricular hypertrophy.

The literature shows that subjects with a good prognosis, who are young and athletic, with no evidence of structural heart disease have a high prevalence of an ER pattern with rapidly ascending ST elevation. Conversely, individuals with a poor prognosis, due to advanced age, and who have had a myocardial infarction with or without arrhythmic complications, have a high prevalence of an ER pattern with a horizontally-downward ST[47].

It is also important to evaluate the J-wave dynamicity in order to recognize ECG features predictive of arrhythmic risk, which are the pause dependent augmentation, the large amplitude and the concomitant horizontal-descending ST-segment[45].

CONCLUSION

In conclusion, there is a correlation between 12-lead ECG VR patterns and cardiac death due to arrhythmias, especially in inferior or inferolateral localized forms, associated with a J-point elevation of at least 2 mm and a horizontal ST pattern. This pattern is more common in a poor prognosis population, *i.e.*, in older subjects with a history of myocardial infarction or heart disease. Although ER is a common ECG finding, ER syndrome (ER with IVF) is rare[42].

Even in middle-aged individuals with an inferior ER of > 0.2 mV, the 3-fold increased SCD risk was not apparent until 10 years after the index ECG[35,36].

There have been no risk stratifies for asymptomatic ER subjects and, to date, no primary prevention strategy has been established. It is currently impossible to make recommendations based on this incidental ECG finding in an asymptomatic individual.

In fact, if it is simple and almost automatic to propose defibrillator implantation for a patient with a personal history of cardiac arrest and an ECG showing a typical framework, it is much less easy to take a decision if the same ECG is recorded by chance in an asymptomatic subject. The research carried out to date has highlighted some aspects of the problem but does not offer a one-size fits all approach. Moreover, it is not recommended

Table 1 The main studies evaluating the relationship between early repolarization pattern and death due to arrhythmia

Ref.	No. of patients	Study population	ER pattern	Results
Tikkanen *et al*[36], 2009	10.864	Community-based general population of middle-aged subjects	ER was stratified according to the degree of J-point elevation (> or = 0.1 mV or > 0.2 mV) in either inferior or lateral leads	ER pattern in the inferior leads is associated with an increased risk of death from cardiac causes in middle-aged subjects
Tikkanen *et al*[35], 2011	565 young healthy athletes-10 864 middle-aged subjects	565 young healthy athletes compared with ECGs from a general population of 10864 middle-aged subjects	ER pattern with horizontal/descending or rapidly ascending/upsloping	ST-segment morphology variants associated with ER separates subjects with and without an increased risk of arrhythmic death in middle-aged subjects. Rapidly ascending ST segments after the J- point, the dominant ST pattern in healthy athletes, seems to be a benign variant of ER
Uberoi *et al*[43], 2011	29281	Resting ambulatory ECGs	J-point elevation ⩾ 0.1 mV-notching and slurring type in at least 2 lateral or inferior-lateral leads	No significant association between any components of early repolarization and cardiac mortality
Haïssaguerre *et al*[10], 2008	206	Patients who were resuscitated after cardiac arrest due to IVF	Elevation of the QRS-ST junction of at least 0.1 mm inferior or lateral lead-QRS slurring or notching	Correlation between ER and sudden cardiac arrest
Nam *et al*[41], 2008	1410	1595 controls and 15 patients with IVF	J-point elevation ≥ 0.1 mV-notching and slurring type in at least 2 lateral or inferior leads	ER pattern is indicative of a highly arrhythmogenic substrate
Rosso *et al*[42], 2008	290	45 patients with idiopathic VF were compared with 124 age- and gender- matched control subjects and with 121 young athletes	J-point elevation ⩾ 0.1 mV-notching and slurring type in at least 2 lateral or inferior-lateral leads	J-point elevation is found more frequently among patients with idiopathic VF than among healthy control subjects. The frequency of J-point elevation among young athletes is intermediate
Rosso *et al*[29], 2011	8980	331 patients with IVF and 8.649 controls	J waves > 2 mm	The presence of J waves > 2 mm in amplitude in asymptomatic adults is associated with a threefold increased of arrhythmic death
Aizawa *et al*[45], 2012	116	Forty patients with J-wave-associated idiopathic VF compared with 76 non-VF patients	J-wave amplitude was measured in the beat immediately after a pause and compared with the mean J-wave measured in almost three beats before the pause. J waves were defined as those ⩾ 0.1 mV above the isoelectric line	Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification
Cappato *et al*[37], 2010	386	21 athletes with a history of previous cardiac arrest of unknown etiology compared with more than 300 healthy athletes	ER pattern with horizontal/descending or rapidly ascending/upsloping	Athletes with a horizontal pattern of ER and ST were 11 times more at risk of cardiac arrest
Naruse *et al*[38], 2012	220	patients with AMI	elevation of the QRS-ST junction of > 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	The presence of ER increased the risk of VF occurrences within 48 hours after the AMI onset
Rudic *et al*[40], 2012	60	Patients with AMI	J-point elevation ⩾ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior leads	Early repolarization pattern seems to be associated with ventricular tachyarrhythmias in the setting of acute myocardial infarction
Tikkanen *et al*[39], 2012	964	432 consecutive victims of SCD because of acute coronary event and 532 survivors of such an event	elevation of the QRS-ST junction of > 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	The presence of ER increases the vulnerability to fatal arrhythmia during acute myocardial ischemia
Wu *et al*[44], 2013		meta-analysis		Correlation of ER with a higher risk of arrhythmic death but not of cardiac death or death from other causes

ER: Early repolarization; IVF: Idiopathic ventricular fibrillation; AMI: Acute myocardial infarction; SCD: Sudden cardiac death.

that athletes should stop exercising or adopt specific preventive measures[48]. In addition, it should be noted that the usefulness of an electrophysiological study in these subjects is low considering that the inducibility of arrhythmias was observed in only 28% of cases[49]. In symptomatic subjects the etiology of symptoms should be evaluated. In cases of unexplained syncope with ER, an ECG may arouse suspicion if there is also a family history of sudden death or the occurrence of palpitations before syncope. Ventricular arrhythmias, if confirmed, clearly require the delivery of a defibrillation system in primary prevention[50]. It is still unclear if there is a different prognosis for patients presenting with notching or slurring patterns.

A greater characterization of the prognostic value of the ECG pattern of ER is necessary, but there is no doubt regarding the correlation between 12-lead ECG VR patterns and cardiac death due to arrhythmias and that the higher risk was achieved by the combination of an ER pattern in the inferior leads with an ST-segment elevation at J-point greater than 2 mm and a horizontal-descending ST. This pattern is also more common in a poor prognosis population, *i.e.*, in older subjects with a history of myocardial infarction or heart disease.

Conversely, subjects with a good prognosis, who are young and athletic, with no evidence of structural heart disease show a high prevalence of an ER pattern with rapidly ascending ST elevation.

Moreover, the evidence of pause-dependent increase in J-wave amplitude, highlighted in patients with idiopathic VF, has proved to be highly specific and high predictive of arrhythmic events. This simple phenomenon may be used for the stratification of arrhythmic risk in patients with J-wave.

So, in conclusion, given the increased risk of major arrhythmic events in these subjects, it becomes important for the cardiologist to recognize the "malignant ER" pattern in order to improve the risk stratification of these patients (Figure 5).

REFERENCES

1 **Yan GX**, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. *J Am Coll Cardiol* 2003; **42**: 401-409 [PMID: 12906963 DOI: 10.1016/S0735-1097(03)00713-7]

2 **Monitillo F**, Leone M, Rizzo C, Passantino A, Iacoviello M. Ventricular repolarization measures for arrhythmic risk stratification. *World J Cardiol* 2016; **8**: 57-73 [PMID: 26839657 DOI: 10.4330/wjc.v8.i1.000]

3 **Zareba W**, Moss AJ, le Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. *Am J Cardiol* 1994; **74**: 550-553 [PMID: 8074036]

4 **Ikeda T**, Sakata T, Takami M, Kondo N, Tezuka N, Nakae T, Noro M, Enjoji Y, Abe R, Sugi K, Yamaguchi T. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. *J Am Coll Cardiol* 2000; **35**: 722-730 [PMID: 10716476 DOI: 10.1016/S0735-1097(99)00590-2]

5 **Haigney MC**, Zareba W, Gentlesk PJ, Goldstein RE, Illovsky M, McNitt S, Andrews ML, Moss AJ. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2004; **44**: 1481-1487 [PMID: 15464332 DOI: 10.1016/j.jacc.2004.06.063]

6 **Iacoviello M**, Forleo C, Guida P, Romito R, Sorgente A, Sorrentino S, Catucci S, Mastropasqua F, Pitzalis M. Ventricular repolarization dynamicity provides independent prognostic information toward major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2007; **50**: 225-231 [PMID: 17631214 DOI: 10.1016/j.jacc.2007.02.071]

7 **Berger RD**, Kasper EK, Baughman KL, Marban E, Calkins H, Tomaselli GF. Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation* 1997; **96**: 1557-1565 [PMID: 9315547 DOI: 10.1161/01.CIR.96.5.1557]

8 **Turrini P**, Corrado D, Basso C, Nava A, Bauce B, Thiene G. Dispersion of ventricular depolarization-repolarization: a noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2001; **103**: 3075-3080 [PMID: 11425771 DOI: 10.1161/01.CIR.103.25.3075]

9 **Napolitano C**, Priori SG. [Role of standard resting ECG in the assessment of sudden cardiac death risk]. *G Ital Cardiol* (Rome) 2014; **15**: 670-677 [PMID: 25533116]

10 **Haïssaguerre M**, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008; **358**: 2016-2023 [PMID: 18463377 DOI: 10.1056/NEJMoa071968]

11 **Lepeschkin E**, Surawicz B. The measurement of the duration of the QRS interval. *Am Heart J* 1952; **44**: 80-88 [PMID: 14933310 DOI: 10.1016/0002-8703(52)90174-9]

12 **Osborn JJ**. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am J Physiol* 1953; **175**: 389-398 [PMID: 13114420]

13 **Wasserburger RH**, Alt WJ. The normal RS-T segment elevation variant. *Am J Cardiol* 1961; **8**: 184-192 [PMID: 13783301]

14 **Junttila MJ**, Sager SJ, Freiser M, McGonagle S, Castellanos A, Myerburg RJ. Inferolateral early repolarization in athletes. *J Interv Card Electrophysiol* 2011; **31**: 33-38 [PMID: 21161572 DOI: 10.1007/s10840-010-9528-y]

15 **Higgins JP**. Normal resting electrocardiographic variants in young athletes. *Phys Sportsmed* 2008; **36**: 69-75 [PMID: 20048474 DOI: 10.3810/psm.2008.12.14]

16 **Wellens HJ**. Early repolarization revisited. *N Engl J Med* 2008; **358**: 2063-2065 [PMID: 18463384 DOI: 10.1056/NEJMe0801060]

17 **Lazzoli JK**, Soares PP, da Nóbrega AC, de Araújo CG. Electrocardiographic criteria for vagotonia-validation with pharmacological parasympathetic blockade in healthy subjects. *Int J Cardiol* 2003; **87**: 231-236 [PMID: 12559544 DOI: 10.1016/S0167-5273(02)00330-3]

18 **Krantz MJ**, Lowery CM. Images in clinical medicine. Giant Osborn waves in hypothermia. *N Engl J Med* 2005; **352**: 184 [PMID: 15647581 DOI: 10.1056/NEJMicm030851]

19 **Kasanuki H**, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997; **95**: 2277-2285 [PMID: 9142005 DOI: 10.1161/01.CIR.95.9.2277]

20 **Goldman MJ**. Normal variants in the electrocardiogram leading to cardiac invalidism. *Am Heart J* 1960; **59**: 71-77 [PMID: 13850708]

21 **Gottschalk CW**, Craige E. A comparison of the precordial S-T and T waves in the electrocardiograms of 600 healthy young Negro and white adults. *South Med J* 1956; **49**: 453-457 [PMID: 13324429]

22 **Vacanti LJ**. [Thoracic pain and early repolarization syndrome at the cardiologic emergency unit]. *Arq Bras Cardiol* 1996; **67**: 335-338 [PMID: 9239869]

23 **Walsh JA**, Ilkhanoff L, Soliman EZ, Prineas R, Liu K, Ning H, Lloyd-Jones DM. Natural history of the early repolarization pattern in a biracial cohort: CARDIA (Coronary Artery Risk Development in Young Adults) Study. *J Am Coll Cardiol* 2013; **61**: 863-869 [PMID: 23428218 DOI: 10.1016/j.jacc.2012.11.053]

24 **Junttila MJ**, Tikkanen JT, Porthan K, Oikarinen L, Jula A, Kenttä T, Salomaa V, Huikuri HV. Relationship between testosterone level and early repolarization on 12-lead electrocardiograms in men. *J Am Coll Cardiol* 2013; **62**: 1633-1634 [PMID: 23916922 DOI: 10.1016/j.jacc.2013.07.015]

25 **Eastaugh JA**. The early repolarization syndrome. *J Emerg Med* 1989; **7**: 257-262 [PMID: 2745947]

26 **Brady WJ**, Chan TC. Electrocardiographic manifestations: benign early repolarization. *J Emerg Med* 1999; **17**: 473-478 [PMID: 10338242 DOI: 10.1016/S0736-4679(99)00010-4]

27 **Brady WJ**, Perron AD, Chan T. Electrocardiographic ST-segment elevation: correct identification of acute myocardial infarction (AMI) and non-AMI syndromes by emergency physicians. *Acad Emerg Med* 2001; **8**: 349-360 [PMID: 11282670 DOI: 10.1111/

j.1553-2712.2001.tb02113.x]
28 **Hollander JE**, Lozano M, Fairweather P, Goldstein E, Gennis P, Brogan GX, Cooling D, Thode HC, Gallagher EJ. "Abnormal" electrocardiograms in patients with cocaine-associated chest pain are due to "normal" variants. *J Emerg Med* 1994; **12**: 199-205 [PMID: 8207156]
29 **Rosso R**, Adler A, Halkin A, Viskin S. Risk of sudden death among young individuals with J waves and early repolarization: putting the evidence into perspective. *Heart Rhythm* 2011; **8**: 923-929 [PMID: 21295159 DOI: 10.1016/j.hrthm.2011.01.037]
30 **Reinhard W**, Kaess BM, Debiec R, Nelson CP, Stark K, Tobin MD, Macfarlane PW, Tomaszewski M, Samani NJ, Hengstenberg C. Heritability of early repolarization: a population-based study. *Circ Cardiovasc Genet* 2011; **4**: 134-138 [PMID: 21282333 DOI: 10.1161/CIRCGENETICS.110.958298]
31 **Gourraud JB**, Le Scouarnec S, Sacher F, Chatel S, Derval N, Portero V, Chavernac P, Sandoval JE, Mabo P, Redon R, Schott JJ, Le Marec H, Haïssaguerre M, Probst V. Identification of large families in early repolarization syndrome. *J Am Coll Cardiol* 2013; **61**: 164-172 [PMID: 23273290 DOI: 10.1016/j.jacc.2012.09.040]
32 **Oreto G**, Luzza F, Donato A, Carbone V, Satullo G, Calabrò MP. L'elettrocardiogramma: un mosaico a 12 tessere. Torino: Centro Scientifico Editore, 2009: 207-222
33 **Yan GX**, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999; **100**: 1660-1666 [PMID: 10517739 DOI: 10.1161/01.CIR.100.15.1660]
34 **Viskin S**, Rosso R, Halkin A. Making sense of early repolarization. *Heart Rhythm* 2012; **9**: 566-568 [PMID: 22120134 DOI: 10.1016/j.hrthm.2011.11.042]
35 **Tikkanen JT**, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, Sager SJ, Rissanen HA, Myerburg RJ, Reunanen A, Huikuri HV. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation* 2011; **123**: 2666-2673 [PMID: 21632493 DOI: 10.1161/CIRCULATIONAHA.110.01406]
36 **Tikkanen JT**, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009; **361**: 2529-2537 [PMID: 19917913 DOI: 10.1056/NEJMoa0907589]
37 **Cappato R**, Furlanello F, Giovinazzo V, Infusino T, Lupo P, Pittalis M, Foresti S, De Ambroggi G, Ali H, Bianco E, Riccamboni R, Butera G, Ricci C, Ranucci M, Pelliccia A, De Ambroggi L. J wave, QRS slurring, and ST elevation in athletes with cardiac arrest in the absence of heart disease: marker of risk or innocent bystander? *Circ Arrhythm Electrophysiol* 2010; **3**: 305-311 [PMID: 20511538 DOI: 10.1161/CIRCEP.110.945824]
38 **Naruse Y**, Tada H, Harimura Y, Hayashi M, Noguchi Y, Sato A, Yoshida K, Sekiguchi Y, Aonuma K. Early repolarization is an independent predictor of occurrences of ventricular fibrillation in the very early phase of acute myocardial infarction. *Circ Arrhythm Electrophysiol* 2012; **5**: 506-513 [PMID: 22534250 DOI: 10.1161/CIRCEP.111.966952]
39 **Tikkanen JT**, Wichmann V, Junttila MJ, Rainio M, Hookana E, Lappi OP, Kortelainen ML, Anttonen O, Huikuri HV. Association of early repolarization and sudden cardiac death during an acute coronary event. *Circ Arrhythm Electrophysiol* 2012; **5**: 714-718 [PMID: 22730409 DOI: 10.1161/CIRCEP.112.970863]
40 **Rudic B**, Veltmann C, Kuntz E, Behnes M, Elmas E, Konrad T, Kuschyk J, Weiss C, Borggrefe M, Schimpf R. Early repolarization pattern is associated with ventricular fibrillation in patients with acute myocardial infarction. *Heart Rhythm* 2012; **9**: 1295-1300 [PMID: 22406149 DOI: 10.1016/j.hrthm.2012.03.006]
41 **Nam GB**, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. *N Engl J Med* 2008; **358**: 2078-2079 [PMID: 18463391 DOI: 10.1056/NEJMc0708182]
42 **Rosso R**, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol* 2008; **52**: 1231-1238 [PMID: 18926326 DOI: 10.1016/j.jacc.2008.07.010]
43 **Uberoi A**, Jain NA, Perez M, Weinkopff A, Ashley E, Hadley D, Turakhia MP, Froelicher V. Early repolarization in an ambulatory clinical population. *Circulation* 2011; **124**: 2208-2214 [PMID: 21986288 DOI: 10.1161/CIRCULATIONAHA.111.047191]
44 **Wu SH**, Lin XX, Cheng YJ, Qiang CC, Zhang J. Early repolarization pattern and risk for arrhythmia death: a meta-analysis. *J Am Coll Cardiol* 2013; **61**: 645-650 [PMID: 23290543 DOI: 10.1016/j.jacc.2012.11.023]
45 **Aizawa Y**, Sato A, Watanabe H, Chinushi M, Furushima H, Horie M, Kaneko Y, Imaizumi T, Okubo K, Watanabe I, Shinozaki T, Aizawa Y, Fukuda K, Joo K, Haissaguerre M. Dynamicity of the J-wave in idiopathic ventricular fibrillation with a special reference to pause-dependent augmentation of the J-wave. *J Am Coll Cardiol* 2012; **59**: 1948-1953 [PMID: 22624834 DOI: 10.1016/j.jacc.2012.02.028]
46 **Aizawa Y**, Sato M, Kitazawa H, Aizawa Y, Takatsuki S, Oda E, Okabe M, Fukuda K. Tachycardia-dependent augmentation of "notched J waves" in a general patient population without ventricular fibrillation or cardiac arrest: not a repolarization but a depolarization abnormality? *Heart Rhythm* 2015; **12**: 376-383 [PMID: 25460863 DOI: 10.1016/j.hrthm.2014.11.010]
47 **Adler A**, Rosso R, Viskin D, Halkin A, Viskin S. What do we know about the "malignant form" of early repolarization? *J Am Coll Cardiol* 2013; **62**: 863-868 [PMID: 23770177 DOI: 10.1016/j.jacc.2013.05.054]
48 **Corrado D**, Pelliccia A, Heidbuchel H, Sharma S, Link M, Basso C, Biffi A, Buja G, Delise P, Gussac I, Anastasakis A, Borjesson M, Bjørnstad HH, Carrè F, Deligiannis A, Dugmore D, Fagard R, Hoogsteen J, Mellwig KP, Panhuyzen-Goedkoop N, Solberg E, Vanhees L, Drezner J, Estes NA, Iliceto S, Maron BJ, Peidro R, Schwartz PJ, Stein R, Thiene G, Zeppilli P, McKenna WJ. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J* 2010; **31**: 243-259 [PMID: 19933514 DOI: 10.1093/eurheartj/ehp473]
49 **Haïssaguerre M**, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clémenty J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol* 2009; **53**: 612-619 [PMID: 19215837 DOI: 10.1016/j.jacc.2008.10.044]
50 **Moya A**, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, van Dijk JG, Walma EP, Wieling W. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009; **30**: 2631-2671 [PMID: 19713422 DOI: 10.1093/eurheartj/ehp298]

P- Reviewer: Aizawa Y, Bonanno C, Jaroszynski A, Rauch B, Skobel E
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.456

World J Cardiol 2016 August 26; 8(8): 456-463
ISSN 1949-8462 (online)

MINIREVIEWS

Application of appropriate use criteria for percutaneous coronary intervention in Japan

Taku Inohara, Shun Kohsaka, Ikuko Ueda, Takashi Yagi, Yohei Numasawa, Masahiro Suzuki, Yuichiro Maekawa, Keiichi Fukuda

Taku Inohara, Department of Cardiology, Hiratsuka City Hospital, Hiratsuka 254-0065, Japan

Taku Inohara, Shun Kohsaka, Ikuko Ueda, Yuichiro Maekawa, Keiichi Fukuda, Department of Cardiology, Keio University School of Medicine, Tokyo 160-8582, Japan

Takashi Yagi, Yohei Numasawa, Masahiro Suzuki, Keio interhospital Cardiovascular Studies, Tokyo 160-8582, Japan

Author contributions: Inohara T and Kohsaka S contributed to draft of the manuscript; Inohara T, Kohsaka S, Ueda I, Yagi T, Numasawa Y, Suzuki M, Maekawa Y and Fukuda K contributed to critical revision of the manuscript for important intellectual content.

Supported by The Pfizer Health Research Foundation.

Conflict-of-interest statement: Dr. Kohsaka and Fukuda received unrestricted research grant for Department of Cardiology, Keio University School of Medicine from Bayer Pharmaceutical Co., Ltd. No other authors have any conflicts to disclose. The funders had no role in the conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation or approval of the manuscript.

Manuscript source: Invited manuscript

Correspondence to: Shun Kohsaka, MD, PhD, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. kohsaka@cpnet.med.keio.ac.jp
Telephone: +81-3-58436702
Fax: +81-3-53633875

Received: April 2, 2016
Peer-review started: April 6, 2016
First decision: May 17, 2016
Revised: June 7, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: August 26, 2016

Abstract

The aim of this review was to summarize the concept of appropriate use criteria (AUC) regarding percutaneous coronary intervention (PCI) and document AUC use and impact on clinical practice in Japan, in comparison with its application in the United States. AUC were originally developed to subjectively evaluate the indications and performance of various diagnostic and therapeutic modalities, including revascularization techniques. Over the years, application of AUC has significantly impacted patient selection for PCI in the United States, particularly in non-acute settings. After the broad implementation of AUC in 2009, the rate of inappropriate PCI decreased by half by 2014. The effect was further accentuated by incorporation of financial incentives (*e.g.*, restriction of reimbursement for inappropriate procedures). On the other hand, when the United States-derived AUC were applied to Japanese patients undergoing elective PCI from 2008 to 2013, about one-third were classified as inappropriate, largely due to the perception gap between American and Japanese experts. For example, PCI for low-risk non-left atrial ascending artery lesion was more likely to be classified as appropriate by Japanese standards, and anatomical imaging with coronary computed tomography angiography was used relatively frequently in Japan, but no scenario within the current AUC includes this modality. To extrapolate the current AUC to Japan or any other region outside of the United States, these local discrepancies must be taken into consideration, and scenarios should be revised to reflect

contemporary practice. Understanding the concept of AUC as well as its perception gap between different counties will result in the broader implementation of AUC, and lead to the quality improvement of patients' care in the field of coronary intervention.

Key words: Appropriate use criteria; Acute coronary syndrome; Percutaneous coronary intervention; Japan; Stable ischemic heart disease

Core tip: The concept of appropriate use criteria (AUC) regarding percutaneous coronary intervention (PCI) has significantly impacted patient selection for PCI in the United States, particularly in non-acute settings. In Japan, when the United States-derived AUC were applied to Japanese patients, about one-third of elective cases were classified as inappropriate. This is largely due to the perception gap between American and Japanese experts. To extrapolate the current AUC to Japan or any other regions outside of the United States, these local discrepancies must be taken into consideration, and scenarios should be revised to reflect contemporary practice.

Inohara T, Kohsaka S, Ueda I, Yagi T, Numasawa Y, Suzuki M, Maekawa Y, Fukuda K. Application of appropriate use criteria for percutaneous coronary intervention in Japan. *World J Cardiol* 2016; 8(8): 456-463 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/456.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.456

INTRODUCTION

To improve the quality of care, such as indications for and performance of various procedures, appropriate use criteria (AUC) have been developed. The concept of AUC has been widely accepted to aid in quantifying and improving the quality of care, and AUC have become available in various diagnostic and therapeutic modalities[1-3]. In the field of coronary intervention, the potential overutilization of percutaneous coronary intervention (PCI) has come under harsh criticism, particularly after the initial report of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[4]. In this setting, AUC for coronary revascularization were developed in 2009 and revised in 2012 in the United States[5,6].

In this review, we aimed to provide an overview of the concept of AUC for coronary revascularization and its impact on the selection of patients undergoing PCI in the United States. Furthermore, we sought to clarify the appropriate ratings of PCI indications in Japan based on the current United States-derived AUC. Finally, we discuss issues that remain to be resolved when extrapolating the current AUC to Japanese clinical practice and propose the future direction of this concept in Japanese cardiovascular society. This minireview will aid in the broader implementation of the concept of AUC in various countries outside of the United States, and will lead to improve the quality of care, especially patients' selection, in PCI.

ROLE OF CORONARY INTERVENTION IN STABLE ISCHEMIC HEART DISEASE

PCI providing emergent or urgent recanalization of acute thrombi has played a crucial role in treating patients with acute coronary syndrome (ACS). The so-called "open artery hypothesis" proposes that early reperfusion through infarcted coronary arteries leads to better clinical outcomes than nonreperfusion. Reopening an occluded coronary artery would minimize myocardial injury, preserves cardiac function, and may ultimately improve overall survival.

From the same scientific rationale for improving patient longevity, preventing future acute coronary syndrome, and relieving anginal symptoms, PCI was also widely implemented in stable ischemic heart disease (SIHD) patients for a fairly short time period. However, in the past decade, increasing scientific evidence has highlighted the unclear benefit of PCI on SIHD, and expectations for PCI have been tempered[7]. This issue was further underscored by the publication of the COURAGE trial[8], a multicenter study that recruited most of its patients from the Veterans Administration Hospital Network and failed to demonstrate clear benefits of PCI for hard endpoints (mortality and/or myocardial infarction) in comparison with optimized medical therapy alone in patients with SIHD. Concern towards overuse of PCI has emerged, and the above neutral results for PCI in the non-acute setting provoked a debate in the reconsideration of the indications for elective PCI.

Under these circumstances, 6 professional societies in the United States [American College of Cardiology Foundation (ACCF)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS)/American Association for Thoracic Surgery (AATS)/American Heart Association (AHA)/American Society of Nuclear Cardiology (ASNC)] have presented their own "appropriate use" provisions in order to solve this problem. The original criteria were developed in 2009, and the revised version was published in 2012[5,6].

DEVELOPMENT OF AUC

The process of evaluating appropriateness was based on the RAND approach, which blends scientific evidence, guidelines, and practical experience by engaging a technical panel in a modified Delphi exercise. In brief, nationally recognized experts were recruited, and the panel included interventional cardiologists, cardiovascular

surgeons, and general cardiologists. Over 200 clinical scenarios were prepared. Initially, the members independently rated the appropriateness of performing PCI in these clinical scenarios using a 9-point scale, with 1 point regarded as being the most inappropriate and 9 points as being the most appropriate, based on different combinations of the following items: (1) Anatomical information [left main trunk (LMT), 3-vessel disease (VD), 1- or 2-VD with/without proximal left anterior descending artery (LAD) involvement]; (2) Evaluation of the presence and severity of preoperative ischemia (treadmill, exercise myocardial scintigraphy, and stress echocardiography); (3) Presence and severity of symptoms [asymptomatic, Canadian Cardiovascular Society (CCS) scale 1-4]; and (4) Presence of optimal medical therapy. An example would be as follows.

Asymptomatic patient with diabetes; after screening electrocardiography performed at an annual health check-up revealed abnormalities, coronary computed tomography angiography (CCTA) findings indicated severe stenosis in the mid-right coronary artery; myocardial scintigraphy revealed mild ischemia in the relevant area, which was consistent with the finding of CCTA; drugs administered: Aspirin (100 mg), rosuvastatin (2.5 mg).

When this scenario is evaluated using the 4 evaluation points for AUC, the patient would be classified as having "asymptomatic single-vessel disease without proximal LAD involvement and mild ischemia, and no optimal medical therapy". According to the AUC, each evaluation committee member determines the appropriateness of PCI based on such a simplified scenario. The panel then met for a face-to-face discussion, and the panel members independently re-provided their final scores for each indication. Each panel member had equal weight in producing the final result. The median score was documented for each scenario. Based on the median score for each indication (range, 1-9), they were categorized as "appropriate" (median, 7-9), "uncertain" (4-6), or "inappropriate" (1-3).

CURRENT STATUS OF APPROPRIATE RATINGS IN THE UNITED STATES

A set of AUC was initially proposed to review clinical decisions made by medical teams in each facility. In addition, after its publication and initial phase of implementation, attempts have been made to assess the appropriateness of the indications for PCI in actual clinical practice by applying these AUC to large-scale registry data[9,10]. The results of the analysis of PCI appropriateness in the United States revealed that in acute settings, the procedure was generally adapted appropriately. By contrast, in non-acute settings, 11.6% of PCIs were deemed to be inappropriate (by 2009 AUC), and when using the revised 2012 AUC, as many as 26.2% of PCIs were evaluated as inappropriate, indicating the overuse of PCI for SIHD (Figure 1).

At the same time, the following changes were observed from 2009 to 2014[10], which were thought to popularize the concept of AUC: (1) The rates of patients with serious symptoms (CCS 3 or 4), patients with severe ischemia, and patients receiving optimal medical therapy increased; (2) The annual trend revealed that the rate of inappropriate PCI decreased from 26.2% to 13.3% (Figure 1), and the ratio of elective PCI patients decreased 30% overall; and (3) The variance of appropriateness among facilities also improved.

In the United States, on the basis of a study by Hachamovitch *et al*[11] demonstrating that PCI-related prognostic improvement could only be obtained in cases with > 10% ischemic area, pre-procedural evaluation of the extent of ischemia is deemed almost essential. Furthermore, reflecting the COURAGE trial, clinical guidelines also emphasize the use of optimal medical therapy prior to revascularization. From such evidence, PCI in cases of 1- or 2-VD without proximal LAD involvement and optimal medical therapy is not accepted regardless of patient symptoms. Additionally, coronary artery bypass graft (CABG) is considered to be a more appropriate therapeutic strategy than PCI for multivessel CAD, based on the findings of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial[12] and the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial[13].

Consequently, according to the CathPCI registry (National Cardiovascular Data Registry), there was a significant 33.8% reduction in the volume of non-acute PCI procedures from 2010 (89704) to 2014 (59375)[10]. Similarly, analysis of the Clinical Outcomes Assessment Program also demonstrated a 43% decline in the number of PCIs for elective indications (from 3818 in 2010 to 2193 in 2013)[14].

APPLICATION OF THE CURRENT AUC IN JAPAN

The number of PCI procedures has continued to increase in Japan. More than 250000 procedures in > 800 hospitals were performed in 2014, which is estimated to be > 14 times greater than the number of CABG procedures. The proportion of elective procedure accounts for < 40% of all PCI in the United States, and as many as three-fourths of PCIs are performed in non-acute settings in Japan[15,16].

To document the rate of appropriate vs. inappropriate PCI in Japanese practice, we applied US AUC scenario ratings to patients registered in the Japan Cardiovascular Database - Keio interhospital Cardiovascular Studies (JCD-KiCS). JCD-KiCS is an ongoing prospective multicenter registry built to collect clinical background and outcome data on consecutive PCI patients in 15 centers affiliated with Keio University Hospital (11258 patients registered from 2008 to 2013)[17-22].

Similar to the results in the United States, PCI was

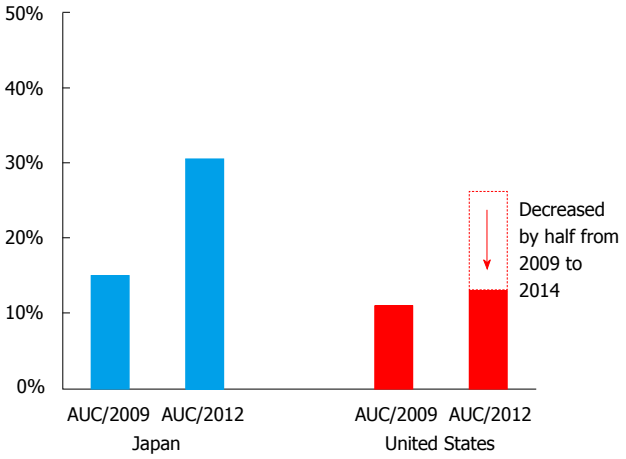

Figure 1 The rates of inappropriate percutaneous coronary intervention in non-acute settings in Japan and in the United States. In Japan, when evaluated under the original criteria developed in 2009 (AUC/2009), 15% of PCIs were categorized as inappropriate, and 30.7% of PCIs were classified as inappropriate under the revised criteria (AUC/2012) (blue bars). By contrast, in the United States, 11.6% of PCIs were deemed to be inappropriate by AUC/2009, and when using the AUC/2012, 26.2% of PCIs were classified as inappropriate (red bars). Additionally, the rates of inappropriate PCI decreased by half from 2009 to 2014, owing to the publication of AUC. PCI: Percutaneous coronary intervention; AUC: Appropriate use criteria.

generally performed appropriately in acute settings. However, in non-acute settings, 15% of PCI cases were classified as inappropriate under the 2009 AUC, and 30.7% of PCI cases were categorized as inappropriate under the revised 2012 AUC. As mentioned earlier, when the 2009 AUC was applied, the rate of inappropriate PCI in the United States was 11%, and when the revised 2012 AUC was used, the rate ranged from 13% to 26%; based on these findings, the rate of inappropriate PCI in Japan is high (Figure 1).

This higher rate of inappropriate PCIs in Japan compared with the United States is mostly driven by differences in the therapeutic strategy toward patients with low-risk ischemia. In contrast to the United States practice, where indications for PCI are strictly limited to cases with > 10% ischemia, PCI for low-risk patients is considered acceptable in Japan. The Japanese Stable Angina Pectoris (JSAP) trial evaluated the effectiveness of PCI for such stable low-risk CAD patients compared with medical therapy in Japan, and the results were strikingly different from those of the COURAGE trial. In the JSAP trial, the long-term benefit of PCI compared to conservative management was observed[23]. The JSAP trial enrolled 384 patients with low-risk CAD consisting of 1- or 2-VD from 78 institutions in Japan. This trial was conducted in a randomized fashion, and patients were randomly allocated to a medical therapy only group or PCI plus medical therapy group. The primary end point was the composite of all-cause death, ACS admission, cerebrovascular accidents, and emergency hospitalization. During the 3.3-year follow-up, the incidence of the primary composite end point was significantly lower in the PCI plus medical therapy group compared to the initial medical therapy-only group, which demonstrated the effectiveness of PCI for stable CAD patients at low-risk for cardiovascular events.

However, the JSAP trial had several concerns. First, the benefit of PCI was only recognized in the composite end point and disappeared for all-cause death. This discrepancy could obscure the prognostic impact of PCI for this low-risk population. Furthermore, in this trial, the medical therapy was not optimal in either group. The prescription rates of statin and beta-blocker were 45.2% and 51.6%, respectively, even in the medical therapy group. From the insight of the COURAGE trial[8], implementation of the optimal medical therapy was an equivalent therapeutic option for the management of low-risk CAD patients, and the findings of the JSAP trial should be cautiously interpreted.

We have also previously evaluated the appropriateness of PCI, based on both the United States and Japanese AUC, and compared the ratings[18]. Japanese AUC was developed in the line with the United States AUC; however, several issues have merged since the establishment of J-AUC. J-AUC was published in 2007, and this was before the publication of COURAGE trial. Therefore, the importance of optimal medical therapy was not highlighted in the clinical practice guidelines then. Furthermore, the J-AUC panel was weighted more toward coronary interventionists (7, in comparison to 2 cardiac surgeons). Thorough revision is needed for the application of J-AUC, but it reflected consensus toward the indication of PCI in Japan to some extent. Naturally, the rate of inappropriate PCI under J-AUC in JCD-KiCS was substantially lower (5.2%) than that using the US AUC (15%); the rating discrepancies between the US- and J-AUC were largely due to difference in the interpretation of revascularization in asymptomatic, low- or intermediate-risk patients without proximal LAD involvement. This discrepancy may be related to multiple factors including cultural differences and the unique Japanese healthcare system. It also underscores the need for revision of AUC according to their associated culture and healthcare system.

Lastly, the variability of the appropriate ratings among institutes is also an issue that remains to be resolved. When the current United States AUC was applied to our registered dataset (JCD-KiCS registry), the rate of inappropriate PCI varied across institutes, ranging from 17.5% to 50% (Figure 2). This finding suggests uneven care in the field of coronary intervention in Japan, which should be resolved to improve the quality of care. Hospital-level variation in the proportion of PCIs classified as inappropriate was also found in the United States. However, since the launch of the AUC in 2009, it has substantially improved[10]. The concept of AUC has tremendous potential to improve patient selection for PCI, and is expected to gain wider acceptance in Japanese clinical practice.

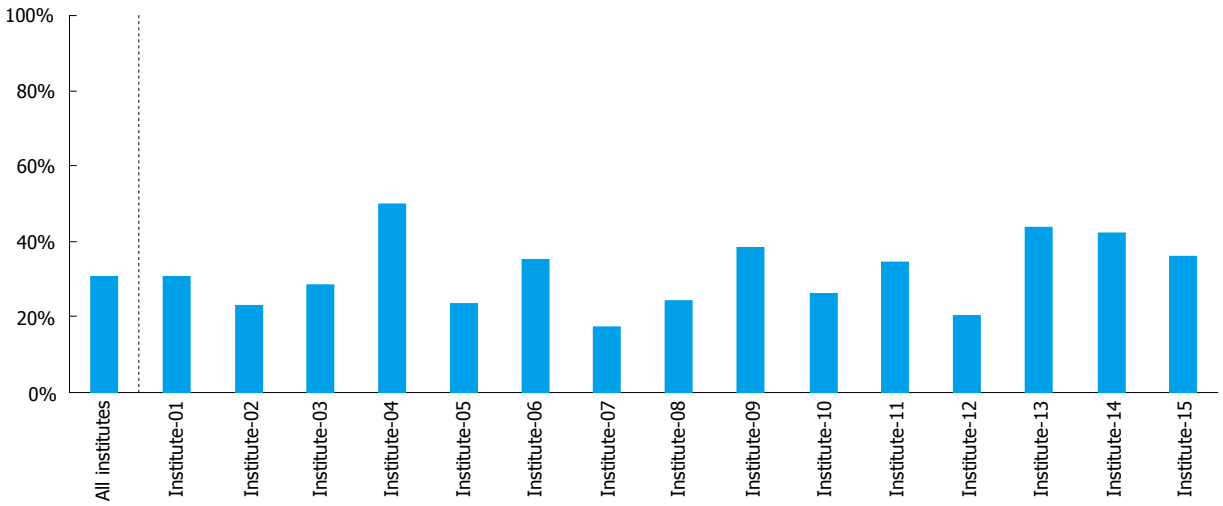

Figure 2 The variability of inappropriate ratings in elective percutaneous coronary interventions among institutes participating in the JCD-KiCS registry (15 centers). When the current AUC (developed in 2012) was applied to the JCD-KiCS registry, 30.7% of elective PCIs were classified as having inappropriate indications. This rate varied across institutes, ranging from 17.5% to 50%. AUC: Appropriate use criteria; PCI: Percutaneous coronary intervention.

PROBLEMS EXTRAPOLATING THE CURRENT AUC TO DAILY PRACTICE IN JAPAN

Can the current United States-derived AUC be directly applied to daily clinical practice in Japan? There are several problems concerning this issue. First, the modalities for evaluating CAD differ between the United States and Japan. In the United States, stress testing, including treadmill, myocardial scintigraphy, and stress echocardiography, is generally used to assess ischemia. However, in recent years, CCTA has become widespread in Japan, and fractional flow reserve (FFR) is often used to assess ischemia. Since appropriateness criteria assign high value to functional information, reflecting a strong tilt toward physiological assessment of ischemia in the United States, CCTA, which only provides anatomical information, is not recognized as one of the prior non-invasive tests under these criteria. We previously indicated that due to the popularity of CCTA and FFR, Japanese PCI cannot be adequately evaluated under the current AUC developed in the United States (Figure 3)[17], and an editorial published from the American perspective entitled "lessons learned from Japan" also mentions this problem[24].

Second, as quoted previously, the therapeutic strategy toward patients with low-risk ischemia differs greatly between the United States and Japan. Clearly, further studies involving the Japanese population are needed to close the perception gap for PCI indications that lack sufficient scientific underpinning.

Finally, there is room for improvement in the current AUC proposed in the United States. For example, clinical scenarios involving PCI for chronic total occlusion (CTO) are limited to "chronic total occlusion of 1 major epicardial coronary artery, without other coronary stenosis"; therefore other types of CTO-PCI cannot be accurately evaluated[5,6,19]. In addition, although the use of FFR is limited to cases with moderate stenosis, it should be widely accepted in evaluating various lesions. Based on the results of the FFR *vs* angiography for multi-vessel evaluation Ⅱ (FAME2) study[25], the prevalence of FFR-guided PCI substantially increased[17,26]. Because FFR enables the evaluation of the significance of CAD in the cardiac catheterization laboratory, pre-procedural tests might have been omitted in some patients; therefore, patients evaluated only by FFR are likely to be classified as having inappropriate PCI, unless such cases are properly assigned to FFR-related scenarios. However, in the current AUC, ischemic evaluation by FFR is accepted only for 1- or 2-vessel CAD with borderline stenosis of "50% to 60%", and the use of FFR in coronary artery stenosis greater than 60% was not adjudicated[5,6].

Previously, we discussed such issues concerning the current AUC with United States investigators in the form of correspondence to the paper by Inohara *et al*[27] and Brandley *et al*[14,28]. We mainly insisted on the validity of performing CCTA as a pre-procedural evaluation. However, although they agreed that AUC comprise a living document and require frequent revision to incorporate evolving evidence, they disagreed with our opinion, since pre-procedural evaluation using CCTA was performed in only 0.5% of all PCIs registered in their dataset. When considering such perception gaps, it is impractical to extrapolate the current AUC advocated in the United States to daily clinical practice in Japan. In order to popularize the concept of appropriate ratings in Japan, further effort is needed to refine and correct the disconnection between the current AUC and Japanese clinical practice.

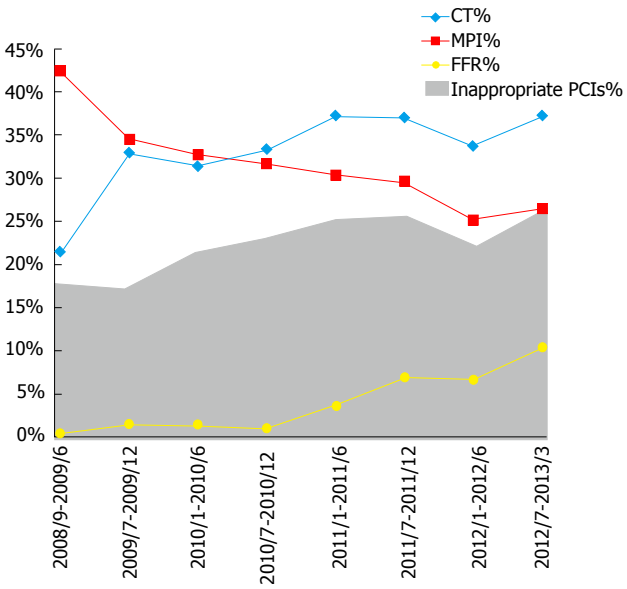

Figure 3 Association between temporal trends in non-invasive tests and frequency of inappropriate ratings. The proportion of patients evaluated with CCTA and FFR substantially increased (both *P* for trend < 0.001), which coincided with a decrease in utilization of stress myocardial perfusion imaging over the course of 5 years (*P* for trend < 0.001). Contemporaneously, the proportion of inappropriate PCIs increased (*P* for trend = 0.003) in parallel with the increase in utilization of CCTA. The gray area indicates the percentages of inappropriate procedures based on original appropriateness criteria (AUC/2009). From Inohara *et al*[17]. CCTA: Coronary computed tomography angiography; MPI: Myocardial perfusion imaging; FFR: Functional flow reserve.

TOWARDS THE INTERNATIONAL APPLICATION OF AUC

Although the revision of the current AUC in accordance with the daily clinical practice in Japan will require some effort, the effects that the concept of AUC brings are expected to be extremely large. As previously discussed, the application of AUC in the United States led to a reduction in the number of elective PCI by half.

A recent study by Chinese investigators demonstrated that the medical records of many patients undergoing PCI lacked documentation of important process measures needed to assess quality of care[29]. AUC can serve as a foundation to guide future efforts on quality improvement in the use of PCI in such cases. Variation in quality of care across hospitals has also been noted in European countries. In a hospital-level international comparison of patients with acute myocardial infarction admitted to hospitals in Sweden and the United Kingdom, inter-hospital variation in the use of primary PCI, antiplatelet treatment, and statin at discharge were important in explaining variation in 30-d mortality[30]. The results of this study suggest that more consistent adherence to new treatment guidelines across all hospitals would deliver improved outcomes, and standardizing the appropriateness of the revascularization procedures could aid in facilitating this adherence.

In Japan, the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) has developed a nationwide registry designed to collect clinical variables and outcome data on PCI patients (J-PCI), which is also linked to medical specialty boards. Therefore, it is feasible that the construction of a feedback system *via* such a registry will lead to the popularization and practical use of AUC in daily clinical practice in Japan. However, issues concerning the balance between the professionalism and autonomy of physicians are deeply involved, making it difficult to reach a conclusion regarding the role of physician discretion in the decision to perform PCI. Looking at various past examples in Japan, the Japanese public appears to have developed a negative attitude toward organizations, including specialized professional groups that have failed to perform self-auditing. For this reason, we believe that some sort of restriction toward the indication of PCIs such as AUC will be implemented in the near future.

CONCLUSION

The concept of AUC has shown great value as a quality measure and led to improved patient selection for PCI in the United States. Although several issues remain to be resolved in order to extrapolate the current AUC to Japanese clinical practice, this concept should be introduced to improve the quality of care in Japan and other countries.

ACKNOWLEDGMENTS

The authors appreciate the contributions of all the investigators and clinical coordinators involved in the JCD-KiCS registry.

REFERENCES

1 **Brindis RG**, Douglas PS, Hendel RC, Peterson ED, Wolk MJ, Allen JM, Patel MR, Raskin IE, Hendel RC, Bateman TM, Cerqueira MD, Gibbons RJ, Gillam LD, Gillespie JA, Hendel RC, Iskandrian AE, Jerome SD, Krumholz HM, Messer JV, Spertus JA, Stowers SA. ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association. *J Am Coll Cardiol* 2005; **46**: 1587-1605 [PMID: 16226194 DOI: 10.1016/j.jacc.2005.08.029]

2 **Hendel RC**, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Kramer CM, Lesser JR, Martin ET, Messer JV, Redberg RF, Rubin GD, Rumsfeld JS, Taylor AJ, Weigold WG, Woodard PK, Brindis RG, Hendel RC, Douglas PS, Peterson ED, Wolk MJ, Allen JM, Patel MR. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and

Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006; **48**: 1475-1497 [PMID: 17010819 DOI: 10.1016/j.jacc.2006.07.003]

3 **Douglas PS**, Khandheria B, Stainback RF, Weissman NJ, Brindis RG, Patel MR, Khandheria B, Alpert JS, Fitzgerald D, Heidenreich P, Martin ET, Messer JV, Miller AB, Picard MH, Raggi P, Reed KD, Rumsfeld JS, Steimle AE, Tonkovic R, Vijayaraghavan K, Weissman NJ, Yeon SB, Brindis RG, Douglas PS, Hendel RC, Patel MR, Peterson E, Wolk MJ, Allen JM. ACCF/ASE/ACEP/ASNC/SCAI/SCCT/SCMR 2007 appropriateness criteria for transthoracic and transesophageal echocardiography: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American Society of Echocardiography, American College of Emergency Physicians, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society for Cardiovascular Magnetic Resonance endorsed by the American College of Chest Physicians and the Society of Critical Care Medicine. *J Am Coll Cardiol* 2007; **50**: 187-204 [PMID: 17616306 DOI: 10.1016/j.jacc.2007.05.003]

4 **Borden WB**, Redberg RF, Mushlin AI, Dai D, Kaltenbach LA, Spertus JA. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. *JAMA* 2011; **305**: 1882-1889 [PMID: 21558519 DOI: 10.1001/jama.2011.601]

5 **Patel MR**, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009; **53**: 530-553 [PMID: 19195618 DOI: 10.1016/j.jacc.2008.10.005]

6 **Patel MR**, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012; **59**: 857-881 [PMID: 22296741 DOI: 10.1016/j.jacc.2011.12.001]

7 **Bangalore S**, Maron DJ, Hochman JS. Evidence-Based Management of Stable Ischemic Heart Disease: Challenges and Confusion. *JAMA* 2015; **314**: 1917-1918 [PMID: 26547460 DOI: 10.1001/jama.2015.11219]

8 **Boden WE**, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503-1516 [PMID: 17387127 DOI: 10.1056/NEJMoa070829]

9 **Chan PS**, Patel MR, Klein LW, Krone RJ, Dehmer GJ, Kennedy K, Nallamothu BK, Weaver WD, Masoudi FA, Rumsfeld JS, Brindis RG, Spertus JA. Appropriateness of percutaneous coronary intervention. *JAMA* 2011; **306**: 53-61 [PMID: 21730241 DOI: 10.1001/jama.2011.916]

10 **Desai NR**, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. *JAMA* 2015; **314**: 2045-2053 [PMID: 26551163 DOI: 10.1001/jama.2015.13764]

11 **Hachamovitch R**, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107**: 2900-2907 [PMID: 12771008 DOI: 10.1161/01.CIR.0000072790.23090.41]

12 **Serruys PW**, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**: 961-972 [PMID: 19228612 DOI: 10.1056/NEJMoa0804626]

13 **Farkouh ME**, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, Bertrand M, Fuster V. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367**: 2375-2384 [PMID: 23121323 DOI: 10.1056/NEJMoa1211585]

14 **Bradley SM**, Bohn CM, Malenka DJ, Graham MM, Bryson CL, McCabe JM, Curtis JP, Lambert-Kerzner A, Maynard C. Temporal Trends in Percutaneous Coronary Intervention Appropriateness: Insights From the Clinical Outcomes Assessment Program. *Circulation* 2015; **132**: 20-26 [PMID: 26022910 DOI: 10.1161/CIRCULATIONAHA.114.015156]

15 **The Japanese Circulation Society**. Jcs national survey on management of cardiovascular diseases: Annual report. 2014. Available from: URL: http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2014web.pdf

16 **Dehmer GJ**, Weaver D, Roe MT, Milford-Beland S, Fitzgerald S, Hermann A, Messenger J, Moussa I, Garratt K, Rumsfeld J, Brindis RG. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol* 2012; **60**: 2017-2031 [PMID: 23083784 DOI: 10.1016/j.jacc.2012.08.966]

17 **Inohara T**, Kohsaka S, Miyata H, Ueda I, Ishikawa S, Ohki T, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness ratings of percutaneous coronary intervention in Japan and its association with the trend of noninvasive testing. *JACC Cardiovasc Interv* 2014; **7**: 1000-1009 [PMID: 25234672 DOI: 10.1016/j.jcin.2014.06.006]

18 **Inohara T**, Kohsaka S, Miyata H, Ueda I, Noma S, Suzuki M, Negishi K, Endo A, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, Higashi T, Fukuda K. Appropriateness of coronary interventions in Japan by the US and Japanese standards. *Am Heart J* 2014; **168**: 854-861.e11 [PMID: 25458648]

19 **Inohara T**, Kohsaka S, Miyata H, Ueda I, Hayashida K, Maekawa Y, Kawamura A, Numasawa Y, Suzuki M, Noma S, Nishi Y, Fukuda K. Real-World Use and Appropriateness of Coronary Interventions for Chronic Total Occlusion (from a Japanese Multicenter Registry). *Am J Cardiol* 2015; **116**: 858-864 [PMID: 26183792 DOI: 10.1016/j.amjcard.2015.06.008]

20 **Inohara T**, Kohsaka S, Abe T, Miyata H, Numasawa Y, Ueda I, Nishi Y, Naito K, Shibata M, Hayashida K, Maekawa Y, Kawamura A, Sato Y, Fukuda K. Development and validation of a pre-percutaneous coronary intervention risk model of contrast-induced acute kidney injury with an integer scoring system. *Am J Cardiol* 2015; **115**: 1636-1642 [PMID: 25891989 DOI: 10.1016/j.amjcard.2015.03.004]

21 **Inohara T**, Miyata H, Ueda I, Maekawa Y, Fukuda K, Kohsaka S. Use of Intra-aortic Balloon Pump in a Japanese Multicenter Percutaneous Coronary Intervention Registry. *JAMA Intern Med* 2015; **175**: 1980-1982 [PMID: 26523549 DOI: 10.1001/jamainternmed.2015.5119]

22 **Kohsaka S**, Miyata H, Ueda I, Masoudi FA, Peterson ED, Maekawa Y, Kawamura A, Fukuda K, Roe MT, Rumsfeld JS. An international comparison of patients undergoing percutaneous coronary intervention: A collaborative study of the National Cardiovascular

Data Registry (NCDR) and Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies (JCD-KiCS). *Am Heart J* 2015; **170**: 1077-1085 [PMID: 26678628 DOI: 10.1016/j.ahj.2015.09.017]

23 **Nishigaki K**, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, Takekoshi N, Tomoike H, Hori M, Matsuzaki M, Takeshita A, Shimbo T, Fujiwara H. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease a randomized, comparative, multicenter study. *JACC Cardiovasc Interv* 2008; **1**: 469-479 [PMID: 19463347 DOI: 10.1016/j.jcin.2008.08.002]

24 **Hung OY**, Samady H, Anderson HV. Appropriate use criteria: lessons from Japan. *JACC Cardiovasc Interv* 2014; **7**: 1010-1013 [PMID: 25234673 DOI: 10.1016/j.jcin.2014.06.005]

25 **De Bruyne B**, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; **367**: 991-1001 [PMID: 22924638 DOI: 10.1056/NEJMoa1205361]

26 **Pothineni NV**, Shah NS, Rochlani Y, Nairooz R, Raina S, Leesar MA, Uretsky BF, Hakeem A. U.S. Trends in Inpatient Utilization of Fractional Flow Reserve and Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2016; **67**: 732-733 [PMID: 26868697 DOI: 10.1016/j.jacc.2015.11.042]

27 **Inohara T**, Kohsaka S, Fukuda K. Letter by Inohara et al Regarding Article, "Temporal Trends in Percutaneous Coronary Intervention Appropriateness: Insights From the Clinical Outcomes Assessment Program". *Circulation* 2016; **133**: e423 [PMID: 26927014 DOI: 10.1161/CIRCULATIONAHA.115.018106]

28 **Bradley SM**, Bohn CM, Malenka DJ, Graham MM, Bryson CL, McCabe JM, Curtis JP, Lambert-Kerzner A, Maynard C. Response to Letter Regarding Article, "Temporal Trends in Percutaneous Coronary Intervention Appropriateness: Insights From the Clinical Outcomes Assessment Program". *Circulation* 2016; **133**: e424 [PMID: 26927015 DOI: 10.1161/CIRCULATIONAHA.115.019554]

29 **Zheng X**, Curtis JP, Hu S, Wang Y, Yang Y, Masoudi FA, Spertus JA, Li X, Li J, Dharmarajan K, Downing NS, Krumholz HM, Jiang L. Coronary Catheterization and Percutaneous Coronary Intervention in China: 10-Year Results From the China PEACE-Retrospective CathPCI Study. *JAMA Intern Med* 2016; **176**: 512-521 [PMID: 26974883 DOI: 10.1001/jamainternmed.2016.0166]

30 **Chung SC**, Sundström J, Gale CP, James S, Deanfield J, Wallentin L, Timmis A, Jernberg T, Hemingway H. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. *BMJ* 2015; **351**: h3913 [PMID: 26254445 DOI: 10.1136/bmj.h3913]

P- Reviewer: Celik T, Xiao DL **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.464

World J Cardiol 2016 August 26; 8(8): 464-471
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan

Gen-Min Lin, Yi-Hwei Li, Chung-Jen Lee, Jeng-Chuan Shiang, Ko-Huan Lin, Kai-Wen Chen, Yu-Jung Chen, Ching-Fen Wu, Been-Sheng Lin, Yun-Shun Yu, Felicia Lin, Fung-Ying Su, Chih-Hung Wang

Gen-Min Lin, Yi-Hwei Li, Fung-Ying Su, Department of Public Health, Tzu-Chi University, Hualien 970, Taiwan

Gen-Min Lin, Jeng-Chuan Shiang, Ko-Huan Lin, Kai-Wen Chen, Yu-Jung Chen, Been-Sheng Lin, Yun-Shun Yu, Felicia Lin, Chih-Hung Wang, Department of Medicine, Hualien-Armed Forces General Hospital, Hualien 971, Taiwan

Gen-Min Lin, Chih-Hung Wang, Department of Medicine, Tri-Service General Hospital, and National Defense Medical Center, Taipei 114, Taiwan

Chung-Jen Lee, Department of Nursing, Tzu-Chi College of Technology, Hualien 970, Taiwan

Ching-Fen Wu, Department of Medicine, Mennonite Christian Hospital, Hualien 970, Taiwan

Author contributions: Lin GM and Wang CH contributed equally to conception and design of the study; Lin GM drafts the article; Li YH and Su FY analyze the data; all authors make critical revisions and make final approval of the version of the article to be published.

Supported by The Research Grants from the Hualien-Armed Forces General Hospital, No. 805-C105-10; and the Ministry of National Defense-Medical Affairs Bureau, No. MAB-106-124.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Mennonite Christian Hospital in Taiwan.

Informed consent statement: Participants were not required to give informed consent to this retrospective study since the analysis of baseline characteristics used anonymous clinical data that were obtained after each patient agreed to share with the results by written informed consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Gen-Min Lin, MD, MPH, Department of Medicine, Hualien-Armed Forces General Hospital, No. 630, Jiali Rd. Xincheng Township, Hualien 971, Taiwan. farmer507@yahoo.com.tw
Telephone: +886-38260601
Fax: +886-38261370

Received: May 23, 2016
Peer-review started: May 24, 2016
First decision: June 17, 2016
Revised: June 18, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: August 26, 2016

Abstract

AIM

To investigate the association between cardiorespiratory fitness and hospitalization events in a cohort of large voluntary arm forces in Taiwan.

METHODS

The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of more than 4000 professional military members aged 18-50 years in Eastern Taiwan. All participants received

history taking, physical examination, chest radiography, 12-lead electrocardiography, blood tests for cell counts and fasting glucose, lipid profiles, uric acid, renal function and liver function in the Hualien Armed Forces General Hospital during 2014. In addition, participants were required to undergo two indoor resistant exercise tests including 2-min push-up and 2-min sit-up, both scored by infrared sensing, and one outdoor endurance 3000-m none weight-bearing running test, the main indicator of cardiorespiratory fitness in the Military Physical Training and Testing Center in Eastern Taiwan in 2014.

RESULTS

Hospitalization events for cardiovascular disease, acute kidney injury, rhabdomyolysis, severe infectious disease, acute psychiatric illness, diabetes, orthopedic surgery and mortality will be identified in the National Insurance Research Database for 10 years.

CONCLUSION

CHIEF will be among the largest Eastern Asian armed forces cohort, in which physical status was strictly evaluated to follow up the hospitalization events for severe illness.

Key words: Cardiorespiratory fitness; Hospitalization; Voluntary armed forces

Core tip: Whether rigorous physical trainings including endurance and resistance exercises for professional young adults in armed forces associated with well or poor cardiovascular outcomes in their middle ages is unknown. In addition, several unhealthy factors such as cigarette smoking and depressive mood are prevalent among arm forces, which may affect the physical performance and increase the risk of hospitalization for severe illness. In this case, we will investigate the association of cardiorespiratory fitness with hospitalization events in a retrospective armed forces cohort consisting of about 4000 professional military members aged 18-50 years in Eastern Taiwan for more than 10 years.

Lin GM, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, Chen YJ, Wu CF, Lin BS, Yu YS, Lin F, Su FY, Wang CH. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol* 2016; 8(8): 464-471 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/464.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.464

INTRODUCTION

Professional military members are required to take regular rigorous physical trainings including endurance and resistance exercise to maintain their outstanding fitness. Frequent exercise training and well physical fitness have been associated with lower risk of cardiovascular disease and mortality in the general population[1-3]. However, current evidence showed conflicting results regarding the cardiovascular outcomes in those taking repetitive strenuous exercises[4,5]. For instance, cardiac remodeling such as left ventricular muscle hypertrophy, chamber dilatation, mitral valve regurgitation, and arrhythmia, which have been well regarded as poor prognostic predictors of acute cardiac events among patients with conventional atherosclerotic risk factors are commonly present in elite athletes[6-8]. Whether these physiological cardiac adaptations to repetitive vigorous training on future cardiovascular disease and mortality are beneficial or hazardous to armed forces remain unknown. In addition, several unhealthy behaviors and environments such as cigarette smoking, alcohol intake, stress, insomnia, and depressive mood are prevalent among arm forces, which may affect the physical performance by reducing cardiopulmonary function and increase the risk of hospitalization for acute illness[9,10]. However there were few studies using large military cohorts, particularly of Asian young adults, with detailed data of demographics, laboratory exams, and cardiopulmonary function evaluations at baseline, to follow up the incidence of cardiovascular disease and other severe illness events. Therefore the aim of our study is to retrospectively investigate the association between cardiorespiratory fitness and hospitalization events in a large voluntary arm forces cohort in Eastern Taiwan.

MATERIALS AND METHODS

Study population

The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of voluntary military members aged 18-50 years in Eastern Taiwan during 2014.

Measurements of the health examinations

All participants had to undergo physical examinations, anthropometric measurements for height, weight, and waist circumference at standing position, hemodynamic status including pulse rate and blood pressures, which were automatically measured by the PARAMA TECH FT-201 blood pressure monitor over right upper arm at sitting position, after taking rest for at least 15 min, chest radiography [posteroanterior (PA) standing view], 12-lead electrocardiography which was interpreted mainly according to the computerized Minnesota Code classification system[11], urinalysis, blood tests for cell counts and concentrations of fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, serum uric acid, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) which was defined on the basis of the Chronic Kidney Disease Epidemiology Collaboration equation[12], aspartate transaminase (AST), alanine transaminase (ALT), and surface antigen of

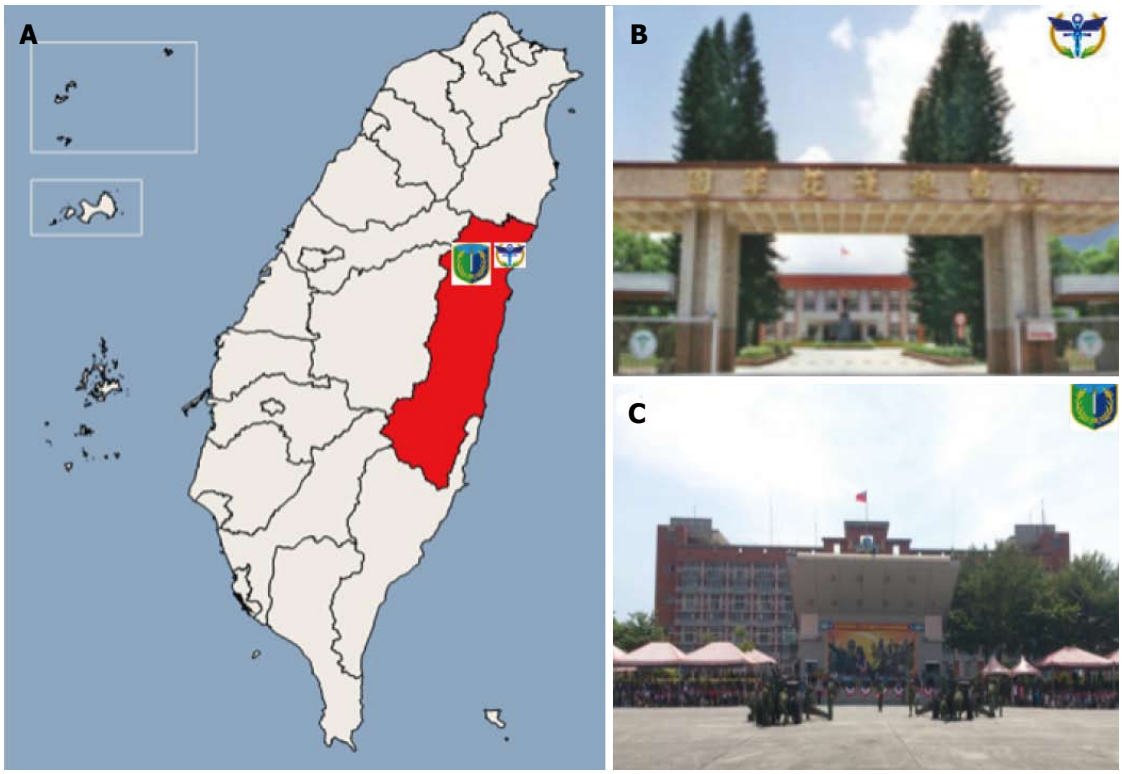

Figure 1 Geographic institutions of the cardiorespiratory fitness and hospitalization events in armed forces study performed. (A) The map of Hualien County in Taiwan is highlighted in red, and the symbols represent (B) the Hualien-Armed Forces General Hospital and (C) the Military Physical Training and Testing Center in the Army HuaDong Defense Command.

viral hepatitis B in the Hualien Armed Forces General Hospital where is the only military referral center for the professional armed forces in Hualien, Taiwan to perform the whole body health exams in 2014 (Figure 1). With regard to history taking, all participants were asked to self-report a questionnaire including demographic information, personal and third degree relatives medical history, current cigarette smoking status, current alcohol intake status, current betel chewing status, frequency of exercise persisting for at least 30 min in the past half year (never, occasionally, 0-1 time/wk, 3-5 times/wk), ever experienced any discomfort related to exercise (dizziness, chest tightness, dyspnea, or palpitation), and Brief Symptom Rating Score (BSRS-5)[13,14] which is a 5-item Likert scale [scores of 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (extremely severe)] for measurement of the severity of psychological distress. A higher score indicates poorer mental health[13]. The full scale contained the following five items of psychopathology: (1) feeling tense or keyed up (anxiety); (2) feeling low in mood (depression); (3) feeling easily annoyed or irritated (hostility); (4) feeling inferior to others (interpersonal hypersensitivity: Inferiority); and (5) having trouble falling asleep (insomnia); and an additional question, "do you have any suicide ideation?" was added at the end of the questionnaire.

Measurements of the physical fitness

In addition, participants were also required to undergo 2 indoor resistant exercise tests including 2-min push-up and 2-min sit-up and one outdoor endurance 3000-m none weight-bearing running exercise test, the main indicator of cardiorespiratory fitness in the Military Physical Training and Testing Center in Eastern Taiwan during 2014. Both 2-min push-up and 2-min sit-up contests were computerized scoring and whole courses were recorded by video. The procedure of 2-min push-up was scored only when the participants' body upward movement achieving the initial resting set height levels of shoulder and buttock simultaneously detected by infrared sensors (Figure 2A). The test would be early aborted once either elbows or knees touched down on the ground before time out. The procedure of 2-min sit-up was scored only if participants' body bended forward and elbows blew the touch sensors on both thighs (Figure 2B). With regard to 3000-m none weight-bearing running exercise test, whole course was recorded by video as well. All 3000-m none weight-bearing running tests were only allowed to be held at 16:00 pm when the risk coefficient of heat stroke, the product of outdoor temperature (℃) and relative humidity (%) × 0.1, was less than 40 or it was not raining.

Follow-up for the outcome of interests

After 2014, those retained in annual health or physical fitness exams will be followed up longitudinally. The outcome of interest will be the hospitalization events for cardiovascular disease, acute kidney injury, rhabdomyolysis, severe infectious disease, acute psychiatric illness, type 2 diabetes mellitus, orthopedic surgery, and mortality respectively. Hospitalization events will be identified in the National Insurance Research Data-

Figure 2 Illustrations of standardized procedure for push-up and sit-up tests in the cardiorespiratory fitness and hospitalization events in armed forces study, respectively. A: A participant prepared for the push-up test surrounded by four flared sensors and a computerized monitor was ahead of him. A supervisor squatted aside by him to watch for all his procedure; B: A participant prepared for the sit-up test with two touch sensors were bound on both thighs and a computerized monitor was opposite to him. A supervisor stood aside by him to watch for all his procedure.

base and followed up for at least 10 years. This study was approved by the Institutional Review Board of the Mennonite Christian Hospital in Hualien, Taiwan and written informed consent was obtained from all participants.

Statistical analysis

The armed forces in Eastern Taiwan who did not receive health examinations or undergo exercise tests in the index centers of Hualien during 2014 were excluded. Figure 3 shows the flow diagram to select the CHIEF study cohort. Demographic characteristics and exercise performances of men and women were reported as mean ± SD or percent for continuous and categorical variables, respectively. The analysis will use the time for follow-up at January 1, 2014 with censoring at first occurrence of hospitalization events for specific severe illness, death, or end of follow-up (December 31, 2024). Kaplan-Meier analysis will be used to assess the sex-specific association of each exercise test performances (2-min push-up, 2-min sit-up, and 3000-m none weight-bearing running) with incident hospitalization events for specific severe illness. Cox proportional hazard regression analyses will be used to assess the sex-specific multivariable association between each exercise test performance and incident hospitalization events, adjusting for potential confounders. A 2-tailed value of *P*-value < 0.05 will be considered significant.

RESULTS

The historical CHIEF cohort consists of 4080 participants who received both health exams and underwent at least one exercise test during 2014. The administrative rates for 2-min sit-up, 2-min push-up, and 3000-m none weight-bearing running test were 99.5%, 98.8% and 88.6%, respectively. The descriptive statistics of baseline profiles, medical and family history, laboratory and 12-lead electrocardiographic findings, BSRS scores, and each exercise test performance of men and women were shown in Tables 1-4 respectively. Of these participants, men accounted for about 89.9% and the mean age of men and women were about 29 and 28 years, respectively.

DISCUSSION

Previous studies have demonstrated the benefit of leisure time exercise which may reduce inflammatory response, viscosity, and the risk of cardiovascular disease in the general population[15-18]. However, it is not clear the relationship of what kinds of exercise, how the dosing of exercise, and the performance of physical fitness in young adults with future health status in their middle age. In addition, for a population with rigorous exercise training daily for work such as athletes and professional military members, the question of exercise training and physical fitness on the health status has not been answered yet, since there were too few large cohort studies to investigate the association. Therefore the CHIEF study will be one of the largest retrospective military cohort ever in the world to retrospectively follow up the severe illness events.

In CHIEF, the anthropometric profile of men was characterized by an average overweight value defined by the body mass index criteria for Eastern Asian individuals (> 24.0 kg/m^2), but within a non-obese waist circumference limit defined to be < 85 cm for Asian male populations[19,20]. This may reflect that muscle mass may account for a higher proportion of body weight in men, which was also supported by a higher proportion of electrocardiographic left ventricular hypertrophy (17%) in men. In contrast, both levels of body mass index and waist circumference in women were within non-obese levels suggested for Asian female populations[20]. Unlike elite athletes, many unhealthy behaviors such as cigarette smoking and alcohol consumption were prevalent in men (about 40%) and in women (10%-20%). In addition, about 40% of men reported mild to extremely severe depression or anxiety and 50% of women reported those negative psychological symptoms. Because of the specialty of armed forces, all these confounders should

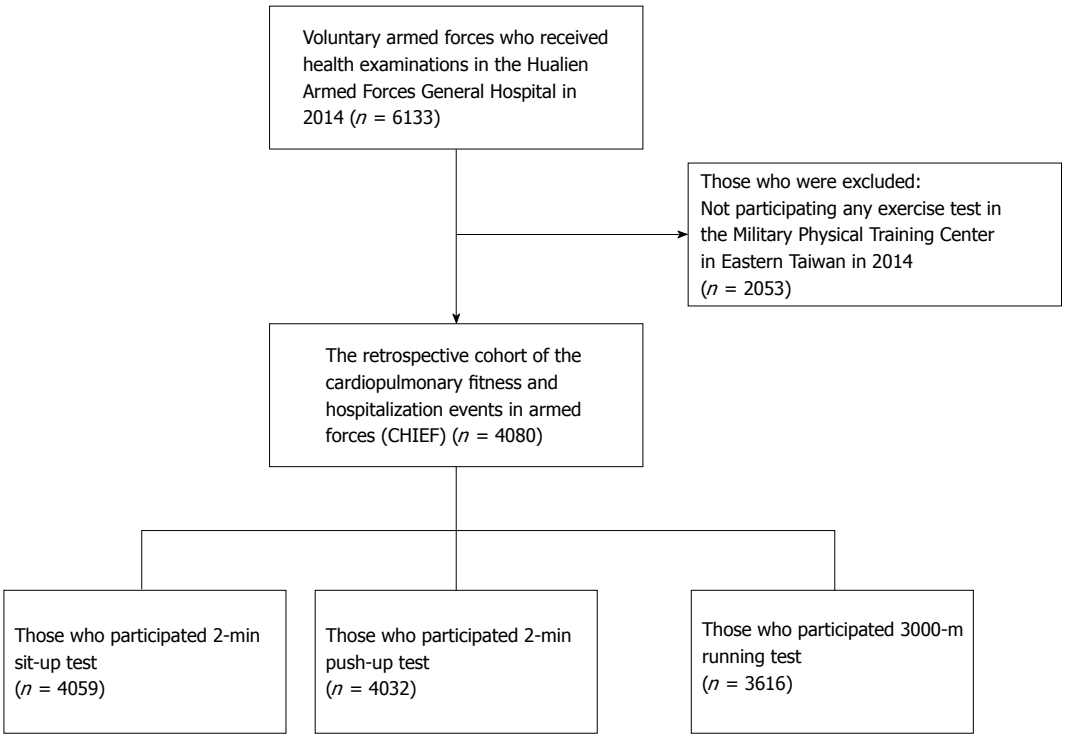

Figure 3 Flow diagram to select the eligible cardiorespiratory fitness and hospitalization events in armed forces cohort during 2014.

Table 1 Baseline demographics, hemodynamics, medical and family history, and habit of exercise of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (*n* = 3669)	Women (*n* = 411)
Age (yr)	29.3 ± 5.9	28.1 ± 6.5
Specialty (%)		
Air force	28	23.6
Army	50.5	61.6
Navy	21.5	14.8
Height (cm)	171.8 ± 5.8	160.5 ± 4.4
Weight (kg)	73.5 ± 10.2	58.1 ± 8.1
Body mass index (kg/m^2)	24.9 ± 3.1	22.5 ± 2.9
Waist circumference (cm)	83.4 ± 8.0	73.3 ± 7.4
Pulse rate (times/min)	72.2 ± 10.8	75.7 ± 10.1
Systolic blood pressure (mmHg)	118.4 ± 13.1	106.5 ± 12.4
Diastolic blood pressure (mmHg)	70.6 ± 10.1	65.2 ± 9.1
Current smoking (%)	38.1	12.2
Current alcohol intake (%)	44.7	17.1
Current betel chewing (%)	12	1.2
Medical history (%)		
Hypertension	1.5	0.2
Symptomatic arrhythmia	1.1	1.7
Chronic hepatitis B	3.4	1.7
Family history of cardiovascular disease within 3rd relatives (%)	3.4	4.6
Frequency of exercise (%)		
Never or occasionally	19.7	30.5
1-2 times/wk	38.2	42.9
Over 3-5 times/wk	42.2	26.6
Cardiopulmonary distress symptoms related to exercise (%)	8.9	15.4

Data were presented as the mean ± SD and percentage (%).

be taken into account the association between physical fitness and severe illness events.

Push-up and sit-up performance were used to assess musculoskeletal fitness. Push-up exercise is a strengthening exercise for building up strength and endurance in the muscles of the upper arm and shoulders, and sit-up exercise is performed to enhance abdominal muscular endurance. Mota *et al*[21] showed that low push-up and sit-up test performance is associated with increased risk for obesity and metabolic risk in adolescent girls. Furthermore, Katzmarzyk *et al*[22] found that sit-up but not push-up performance is predictive of mortality in the Canadian population. Performance in 3000-m (middle distance) running mainly depends on maximal aerobic power (VO_2max)[23], which are related to several physiological parameters including maximal oxygen uptake, running economy, velocity at 4 mmol/L blood lactate concentration, and the minimal velocity at which VO_2max occurs[24-28]. Accordingly, the performance of 3000-m none weight-bearing running test in armed forces could be regarded as a good surrogate for their cardiorespiratory fitness. As is known, adolescent cardiorespiratory fitness has been associated with adult fatness[29]. Several previous studies in the Western countries demonstrated that superior cardiorespiratory fitness may be associated with lower risk of hospitalization events for incident hypertension, diabetes mellitus, coronary heart disease, stroke, cataract, and diverticular complications[30-35]. Moreover, a relationship between cardiorespiratory fitness and all-cause and cardiovascular mortality has been well

Table 2 Baseline laboratory and electrocardiographic findings of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (n = 3669)	Women (n = 411)
Blood routine		
Hemoglobin (g/dL)	15.2 ± 1.0	13.0 ± 1.0
Mean corpuscular volume (fl)	85.1 ± 6.3	85.2 ± 6.8
RBC count (10^6/μL)	5.3 ± 0.5	4.7 ± 0.4
WBC count (10^3/μL)	6.8 ± 1.7	6.6 ± 1.7
Platelet count (10^3/μL)	252.9 ± 50.5	274.5 ± 53.1
Blood biochemistry		
Fasting glucose (mg/dL)	93.6 ± 13.4	89.1 ± 7.5
Total cholesterol (mg/dL)	174.4 ± 34.0	167.4 ± 29.1
LDL-cholesterol (mg/dL)	106.0 ± 29.7	93.5 ± 25.3
HDL-cholesterol (mg/dL)	47.9 ± 9.8	56.9 ± 11.0
Triglycerides (mg/dL)	115.1 ± 100.3	77.7 ± 38.9
BUN (mg/dL)	12.9 ± 2.8	10.7 ± 2.4
Creatinine (mg/dL)	1.0 ± 0.1	0.7 ± 0.1
eGFR (mL/min per 1.73 m^2)	99.8 ± 14.2	109.4 ± 18.4
Uric acid (mg/dL)	6.7 ± 1.3	4.7 ± 0.9
AST (U/L)	20.7 ± 8.9	16.2 ± 5.2
ALT (U/L)	23.1 ± 17.7	12.5 ± 7.3
Urinalysis (%)		
Protein > 1+	10.3	10.5
RBC > 1+	5.3	17.4
Occult blood > 1+	3.4	17.8
WBC > 6-10	2.1	11.2
Bacteria > 1+	2.6	22.4
12-lead electrocardiography (%)		
LVH/RVH/IVCD	17.3/1.0/0.2	2.0/0.2/0
LAE/RAE	0.2/0.2	0.2/0
ICRBBB/CRBBB	3.9/0.5	0.73/0
LAFB/LPFB	0.7/0.2	0/0
1st degree atrioventricular block	3.8	3.4
PACs/PVCs	0.4/0.6	0.2/0.2

Data were presented as the mean ± SD and percentage (%). ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood urea nitrogen; CHIEF: Cardiopulmonary fitness and hospitalization events in armed forces; CRBBB: Complete right bundle branch block; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; ICRBBB: Incomplete complete right bundle branch block; IVCD: Intraventricular conduction delay; LAE: Left atrial enlargement; LAFB: Left anterior fascicular block; LPFB: Left posterior fascicular block; LDL: Low-density lipoprotein; LVH: Left ventricular ventricular hypertrophy; PACs: Premature atrial contractures; PVCs: Premature ventricular contractures; RAE: Right atrial enlargement; RBC: Red blood cell; RVH: Right ventricular hypertrophy; WBC: White blood cell.

Table 3 Brief symptom rating score of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (n = 3669)	Women (n = 411)
Anxiety (%)		
None (0)	69.52	59.72
Mild (1)	25.1	32.2
Moderate (2)	4.7	7.6
Severe (3)	0.4	0.2
Extremely severe (4)	0.3	0.2
Depression (%)		
None (0)	72	63.2
Mild (1)	23	28.1
Moderate (2)	4.1	7.8
Severe (3)	0.7	0.7
Extremely severe (4)	0.3	0.2
Hostility (%)		
None (0)	65.7	55.1
Mild (1)	27.3	33.9
Moderate (2)	5.8	9.8
Severe (3)	0.9	0.7
Extremely severe (4)	0.3	0.5
Insomnia (%)		
None (0)	63.5	58.8
Mild (1)	28	29.5
Moderate (2)	6.7	9.5
Severe (3)	1.4	1.2
Extremely severe (4)	0.4	1
Interpersonal hypersensitivity: Inferiority (%)		
None (0)	79.3	73,2
Mild (1)	16.5	21
Moderate (2)	4	5
Severe (3)	0.5	0.2
Extremely severe (4)	0.2	1
Suicide ideation (%)		
None (0)	96.4	95
Mild (1)	2.4	3.7
Moderate (2)	0.6	1.5
Severe (3)	0.4	0
Extremely severe (4)	0.3	0

Data were presented as percentage (%).

established in the general population[1-3]. On the contrary, outstanding cardiorespiratory fitness is highly related to rigorous exercise training which may lead to hazardous cardiovascular events such as sudden death and severe cardiac arrhythmia, rhabdomyolysis, and orthopedic illness in armed forces[36]. It is important to know how to prevent exercise related lethal complications and to obtain the best physical fitness.

The strength of the study includes that: (1) the data of the historical cohort is complete since both whole body health examinations and physical exercise tests are scheduled for all professional military members annually unless those who receive these examinations elsewhere; (2) the procedures of health examinations and physical exercise tests are standardized and performed in central labs which could avoid systemic bias completely; (3) as compared with previous studies for the association of physical fitness with severe illness, the baseline data of CHIEF includes not only demographic characteristics but also a series of laboratory and imaging findings, which could be further adjusted to prevent potential bias; and (4) both health examinations and physical exercise tests will be held annually that provide the opportunity for us to follow up the interval change of the physical fitness and investigate the association with severe illness. On the contrary, we have several limitations in the study. First, there were about one third (33.5%) of the military members in armed forces who received health examinations but did not undergo any physical exercise test in Hualien during 2014. Although the baseline characteristics of drop-out individuals were similar to those enrolled in CHIEF, we could not completely exclude

Table 4 Exercise performances of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men		Women	
	n	Performance	*n*	Performance
2-min sit-up	3651	47.5 ± 8.2	408	37.7 ± 8.1
2-min push-up	3641	49.1 ± 11.7	391	33.9 ± 10.6
3000-m non-weight bearing running (s)	3296	859.9 ± 72.7	320	1007.1 ± 76.9

Data were presented as the mean ± SD.

the selection bias. Second, women account for only 10% of the CHIEF cohort and we may not have enough power to make a conclusion at last. Third, since CHIEF is a retrospective study, some potential confounders such as systemic inflammatory markers, cardiac biomarkers, nutritional support, diet, and the type of daily regular exercise trainings performed, which may affect the physical performance and hospitalization events for severe illness, will not be available without prospective collection.

In summary, physical fitness as an independent predictor of mortality and cardio-metabolic risk in the general population has not been confirmed in young military members of armed forces who have many traditional vascular risk factors. The CHIEF study is thus designed to be one of the largest military cohorts in the world and will retrospectively investigate the association of each physical fitness performance, the interval change of each physical fitness, and incident hospitalization events for severe illness. The result of CHIEF could be applied to the military members in armed forces to improve the physical trainings effectively and prevent the adverse effect related to heavy exercises in the future.

COMMENTS

Professional military members are required to take regular rigorous physical trainings to maintain their physical fitness. However, several unhealthy factors such as cigarette smoking are prevalent among arm forces, which may affect the exercise performance and increase the risk of severe illness.

Research frontiers

Frequent exercise training and well physical fitness have been associated with lower risk of cardiovascular disease and mortality in the general population. Current evidence in the Western countries showed conflicting results for the cardiovascular outcomes in those taking repetitive strenuous exercises.

Innovations and breakthroughs

There were few studies using large military cohorts, particularly of Asian young adults, with detailed data of demographics, laboratory exams, and cardiopulmonary function evaluations at baseline, to follow up the incidence of cardiovascular disease and other severe illness events such as infectious and orthopedic disease. The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of more than 4000 professional military members aged 18-50 years in Eastern Taiwan. CHIEF will be among the largest Eastern Asian armed forces cohort, in which physical status was strictly evaluated to follow up the hospitalization events for specific severe illness.

Applications

The result of CHIEF could be applied to the military members in armed forces to improve the physical trainings effectively and prevent the adverse effect related to heavy exercises in the future.

Peer-review

The authors present here the protocol of a study about cardiorespiratory fitness in a military population. It is well written and seems to me it will make a fine study when finished.

REFERENCES

1 **Wei M**, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS, Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999; **282**: 1547-1553 [PMID: 10546694 DOI: 10.1001/jama.282.16.1547]

2 **Lee DC**, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW, Blair SN. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation* 2011; **124**: 2483-2490 [PMID: 22144631 DOI: 10.1161/CIRCULATIONAHA.111.038422]

3 **Artero EG**, Jackson AS, Sui X, Lee DC, O'Connor DP, Lavie CJ, Church TS, Blair SN. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol* 2014; **63**: 2289-2296 [PMID: 24703924 DOI: 10.1016/j.jacc.2014.03.008]

4 **Schnohr P**, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. *J Am Coll Cardiol* 2015; **65**: 411-419 [PMID: 25660917 DOI: 10.1016/j.jacc.2014.11.023]

5 **Armstrong ME**, Green J, Reeves GK, Beral V, Cairns BJ. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation* 2015; **131**: 721-729 [PMID: 25688148 DOI: 10.1161/CIRCULATIONAHA.114.010296]

6 **Spirito P**, Pelliccia A, Proschan MA, Granata M, Spataro A, Bellone P, Caselli G, Biffi A, Vecchio C, Maron BJ. Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports. *Am J Cardiol* 1994; **74**: 802-806 [PMID: 7942554 DOI: 10.1016/0002-9149(94)90439-1]

7 **Pelliccia A**, Kinoshita N, Pisicchio C, Quattrini F, Dipaolo FM, Ciardo R, Di Giacinto B, Guerra E, De Blasiis E, Casasco M, Culasso F, Maron BJ. Long-term clinical consequences of intense, uninterrupted endurance training in olympic athletes. *J Am Coll Cardiol* 2010; **55**: 1619-1625 [PMID: 20378081 DOI: 10.1016/j.jacc.2009.10.068]

8 **Engel DJ**, Schwartz A, Homma S. Athletic Cardiac Remodeling in US Professional Basketball Players. *JAMA Cardiol* 2016; **1**: 80-87 [DOI: 10.1001/jamacardio.2015.0252]

9 **Pettersson K**, Saers J, Lindberg E, Janson C. Sleep disturbances among Swedish soldiers after military service abroad. *Ups J Med Sci* 2016; **121**: 65-69 [PMID: 26959327 DOI: 10.3109/03009734.2016.1144663]

10 **Toblin RL**, Anderson JA, Riviere LA, McGurk D, Sipos ML. The Impact of Unit Membership on Smoking Among Soldiers. *Mil Med* 2016; **181**: 16-20 [PMID: 26741472 DOI: 10.7205/MILMED-D-15-00063]

11 **Blackburn H**, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. *Circulation* 1960; **21**: 1160-1175 [PMID: 13849070 DOI: 10.1161/01.CIR.21.6.1160]

12 **Levey AS**, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010; **55**: 622-627 [PMID:

20338463 DOI: 10.1053/j.ajkd.2010.02.337]
13 **Lee MB**, Liao SC, Lee YJ, Wu CH, Tseng MC, Gau SF, Rau CL. Development and verification of validity and reliability of a short screening instrument to identify psychiatric morbidity. *J Formos Med Assoc* 2003; **102**: 687-694 [PMID: 14691593]
14 **Chen WJ**, Chen CC, Ho CK, Chou FH, Lee MB, Lung F, Lin GG, Teng CY, Chung YT, Wang YC, Sun FC. The relationships between quality of life, psychiatric illness, and suicidal ideation in geriatric veterans living in a veterans' home: a structural equation modeling approach. *Am J Geriatr Psychiatry* 2011; **19**: 597-601 [PMID: 21606903 DOI: 10.1097/JGP.0b013e3181faec0e]
15 **Koenig W**, Sund M, Döring A, Ernst E. Leisure-time physical activity but not work-related physical activity is associated with decreased plasma viscosity. Results from a large population sample. *Circulation* 1997; **95**: 335-341 [PMID: 9008446 DOI: 10.1161/01.CIR.95.2.335]
16 **Wagner A**, Simon C, Evans A, Ferrières J, Montaye M, Ducimetière P, Arveiler D. Physical activity and coronary event incidence in Northern Ireland and France: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *Circulation* 2002; **105**: 2247-2252 [PMID: 12010905 DOI: 10.1161/01.CIR.0000016345.58696.4F]
17 **Rothenbacher D**, Hoffmeister A, Brenner H, Koenig W. Physical activity, coronary heart disease, and inflammatory response. *Arch Intern Med* 2003; **163**: 1200-1205 [PMID: 12767957 DOI: 10.1001/archinte.163.10.1200]
18 **Sofi F**, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 247-257 [PMID: 18525378 DOI: 10.1097/HJR.0b013e3282f232ac]
19 **Lin GM**, Li YH, Lin CL, Wang JH, Han CL. Relation of body mass index to mortality among Asian patients with obstructive coronary artery disease during a 10-year follow-up: a report from the ET-CHD registry. *Int J Cardiol* 2013; **168**: 616-620 [PMID: 23465238 DOI: 10.1016/j.ijcard.2013.01.204]
20 **Guan X**, Sun G, Zheng L, Hu W, Li W, Sun Y. Associations between metabolic risk factors and body mass index, waist circumference, waist-to-height ratio and waist-to-hip ratio in a Chinese rural population. *J Diabetes Investig* 2015; Epub ahead of print [PMID: 27181937 DOI: 10.1111/jdi.12442]
21 **Mota J**, Vale S, Martins C, Gaya A, Moreira C, Santos R, Ribeiro JC. Influence of muscle fitness test performance on metabolic risk factors among adolescent girls. *Diabetol Metab Syndr* 2010; **2**: 42 [PMID: 20573222 DOI: 10.1186/1758-5996-2-42]
22 **Katzmarzyk PT**, Craig CL. Musculoskeletal fitness and risk of mortality. *Med Sci Sports Exerc* 2002; **34**: 740-744 [PMID: 11984288 DOI: 10.1097/00005768-200205000-00002]
23 **Noakes TD**. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med Sci Sports Exerc* 1988; **20**: 319-330 [PMID: 3050352 DOI: 10.1249/00005768-198808000-00001]
24 **Billat LV**. Use of blood lactate measurements for prediction of exercise performance and for control of training. Recommendations for long-distance running. *Sports Med* 1996; **22**: 157-175 [PMID: 8883213 DOI: 10.2165/00007256-199622030-00003]
25 **Houmard JA**, Craib MW, O'Brien KF, Smith LL, Israel RG, Wheeler WS. Peak running velocity, submaximal energy expenditure, VO2max, and 8 km distance running performance. *J Sports Med Phys Fitness* 1991; **31**: 345-350 [PMID: 1798303]
26 **Jones AM**. A five year physiological case study of an Olympic runner. *Br J Sports Med* 1998; **32**: 39-43 [PMID: 9562162 DOI: 10.1136/bjsm.32.1.39]
27 **Tanaka K**, Watanabe H, Konishi Y, Mitsuzono R, Sumida S, Tanaka S, Fukuda T, Nakadomo F. Longitudinal associations between anaerobic threshold and distance running performance. *Eur J Appl Physiol Occup Physiol* 1986; **55**: 248-252 [PMID: 3732252 DOI: 10.1007/BF02343795]
28 **Bragada JA**, Santos PJ, Maia JA, Colaço PJ, Lopes VP, Barbosa TM. Longitudinal Study in 3,000 m Male Runners: Relationship between Performance and Selected Physiological Parameters. *J Sports Sci Med* 2010; **9**: 439-444 [PMID: 24149638]
29 **Eisenmann JC**, Wickel EE, Welk GJ, Blair SN. Relationship between adolescent fitness and fatness and cardiovascular disease risk factors in adulthood: the Aerobics Center Longitudinal Study (ACLS). *Am Heart J* 2005; **149**: 46-53 [PMID: 15660033 DOI: 10.1016/j.ahj.2004.07.016]
30 **Strate LL**, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. *Am J Gastroenterol* 2009; **104**: 1221-1230 [PMID: 19367267 DOI: 10.1038/ajg.2009.121]
31 **Williams PT**. Prospective epidemiological cohort study of reduced risk for incident cataract with vigorous physical activity and cardiorespiratory fitness during a 7-year follow-up. *Invest Ophthalmol Vis Sci* 2009; **50**: 95-100 [PMID: 18408175 DOI: 10.1167/iovs.08-1797]
32 **Williams PT**. Reduction in incident stroke risk with vigorous physical activity: evidence from 7.7-year follow-up of the national runners' health study. *Stroke* 2009; **40**: 1921-1923 [PMID: 19299640 DOI: 10.1161/STROKEAHA.108.535427]
33 **Williams PT**. A cohort study of incident hypertension in relation to changes in vigorous physical activity in men and women. *J Hypertens* 2008; **26**: 1085-1093 [PMID: 18475145 DOI: 10.1097/HJH.0b013e3282fb81dc]
34 **Williams PT**. Changes in vigorous physical activity and incident diabetes in male runners. *Diabetes Care* 2007; **30**: 2838-2842 [PMID: 17704345 DOI: 10.2337/dc07-1189]
35 **Williams PT**. Interactive effects of exercise, alcohol, and vegetarian diet on coronary artery disease risk factors in 9242 runners: the National Runners' Health Study. *Am J Clin Nutr* 1997; **66**: 1197-1206 [PMID: 9356539]
36 **Yankelson L**, Sadeh B, Gershovitz L, Werthein J, Heller K, Halpern P, Halkin A, Adler A, Steinvil A, Viskin S. Life-threatening events during endurance sports: is heat stroke more prevalent than arrhythmic death? *J Am Coll Cardiol* 2014; **64**: 463-469 [PMID: 25082579 DOI: 10.1016/j.jacc.2014.05.025]

P- Reviewer: Amornyotin S, Nunez-Gil IJ **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.472

World J Cardiol 2016 August 26; 8(8): 472-482
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Noninvasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension

Yossra Mahran, Robert Schueler, Marcel Weber, Carmen Pizarro, Georg Nickenig, Dirk Skowasch, Christoph Hammerstingl

Yossra Mahran, Robert Schueler, Marcel Weber, Carmen Pizarro, Georg Nickenig, Dirk Skowasch, Christoph Hammerstingl, Department of Internal Medicine, Cardiology, Pneumology and Angiology, Heart Centre Bonn, University of Bonn, 53105 Bonn, Germany

Author contributions: Mahran Y was responsible for drafting the manuscript and interpreted the data; Schueler R was responsible for the study design and initiation as well as for statistical evaluation; Weber M, Pizarro C and Nickenig G were responsible for statistical interpretation and conception; Skowasch D and Hammerstingl C were responsible for statistical interpretation and conception of the analysis, furthermore they were mainly responsible for critically revising the manuscript and suggested much of its design; Mahran Y and Schueler R contributed equally to this manuscript; Skowasch D and Hammerstingl C contributed equally to this manuscript.

Supported by An unrestricted grant of Actelion Pharmaceuticals Deutschland GmbH.

Institutional review board statement: This study was approved by the ethical committee of the University of Bonn.

Informed consent statement: All involved persons (subjects or legally authorized representative) gave their written informed consent prior to study inclusion.

Conflict-of-interest statement: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Manuscript source: Invited manuscript

Correspondence to: Dr. Dirk Skowasch, Professor, MED, Department of Internal Medicine, Cardiology, Pneumology and Angiology, Heart Centre Bonn, University of Bonn, Sigmund-Freud-Str.25, 53105 Bonn, Germany. dirk.skowasch@ukb.uni-bonn.de
Telephone: +49-228-28716670
Fax: +49-228-28719010

Received: March 21, 2016
Peer-review started: March 22, 2016
First decision: April 20, 2016
Revised: April 29, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: August 26, 2016

Abstract

AIM

To find parameters from transthorathic echocardiography (TTE) including speckle-tracking (ST) analysis of the right ventricle (RV) to identify precapillary pulmonary hypertension (PH).

METHODS

Forty-four patients with suspected PH undergoing right heart catheterization (RHC) were consecutively included (mean age 63.1 ± 14 years, 61% male gender). All patients underwent standardized TTE including ST analysis of the RV. Based on the subsequent TTE-derived measurements, the presence of PH was assessed: Left ventricular ejection fraction (LVEF) was calculated by Simpsons rule from 4Ch. Systolic pulmonary artery pressure (sPAP) was assessed with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values ⩾ 30 mmHg as a surrogate parameter for RA pressure. A concomitantly elevated PCWP was considered a means to discriminate between the precapillary and postcapillary form of PH. PCWP was

considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e' ratio was measured by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. The results were then averaged with conventional measurement of mitral valve inflow. Furthermore, functional testing with six minutes walking distance (6MWD), ECG-RV stress signs, NT pro-BNP and other laboratory values were assessed.

RESULTS

PH was confirmed in 34 patients (precapillary PH, *n* = 15, postcapillary PH, *n* = 19). TTE showed significant differences in E/e' ratio (precapillary PH: 12.3 ± 4.4, postcapillary PH: 17.3 ± 10.3, no PH: 12.1 ± 4.5, *P* = 0.02), LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, *P* = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, *P* = 0.021) and systolic pulmonary arterial pressure (sPAP: 61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, *P* = 0.001). STRV analysis showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, *P* = 0.03). NT pro-BNP was higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL, precapillary PH: 1980.3 ± 3432.1 pg/mL, no PH: 367.5 ± 420.4 pg/mL, *P* = 0.03). Patients with precapillary PH presented significantly more often with ECG RV-stress signs (*P* = 0.001). Receiver operating characteristics curve analyses displayed the most significant area under the curve (AUC) for RVAS (cut-off < -6.5%, AUC 0.91, *P* < 0.001), sPAP (cut-off > 33 mmHg, AUC 0.86, *P* < 0.001) and ECG RV stress signs (AUC 0.83, *P* < 0.001). The combination of these parameters had a sensitivity of 82.8% and a specificity of 17.2% to detect precapillary PH.

CONCLUSION

The combination of non-invasive measurements allows feasible assessment of PH and seems beneficial for the differentiation between the pre- and postcapillary form of this disease.

Key words: Echocardiography; Right ventricle function; Pulmonary arterial hypertension

Core tip: We investigated the value of speckle-tracking (ST) analysis of the right ventricle (RV) in patients with suspected pulmonary hypertension. It focuses on a non-invasive model including parameters derived from standard transthorathic echocardiography (TTE) and ST, as well as electrocardiogram (ECG), six minutes walking distance and NT-pro BNP in order to distinguish the precapillary and postcapillary forms of PH. ST-derived apical RV longitudinal strain (RVAS < -6.5%), TTE-derived systolic pulmonary artery pressure (sPAP > 33 mmHg) and ECG RV stress signs were associated with precapillary PH, their combination had a sensitivity of 82.8% and a specificity of 17.2% for the detection of precapillary PH.

Mahran Y, Schueler R, Weber M, Pizarro C, Nickenig G, Skowasch D, Hammerstingl C. Noninvasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension. *World J Cardiol* 2016; 8(8): 472-482 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/472.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.472

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a precapillary form of pulmonary hypertension (PH). This severe disease is characterized by raised intrapulmonary pressures and changes in pulmonary haemodynamics that lead to high right ventricular (RV) afterload and chronic RV load[1]. The natural course of PAH is fatal within two to three years if missed and left untreated. Since heterogenous pathophysiological mechanisms[2] lead to elevated intrapulmonary pressures, it is crucial to distinguish the precapillary forms from the postcapillary forms of PH in order to initiate adequate therapy. According to current guidelines, the standard procedure for definite diagnosis is right heart catheterization (RHC)[3]. This invasive diagnostic mean is not widely available and inapplicable for routine follow-up (FU), due to its invasive nature and entails the risk of rare but serious complications. Therefore, a non-invasive diagnostic scheme that is reliable in: (1) diagnosing PAH; and (2) discriminating between the precapillary and postcapillary forms of PH would be of significant clinical benefit.

Recent research has aimed to detect different non-invasive diagnostic means that meet these requirements when combined. Thus, the design of our study was based on several considerations: A combination of electrocardiographic (ECG) criteria and N-terminal pro-Brain Natriuretic Peptide (NT pro-BNP) has been reported sufficient to rule out precapillary PH[4]. Transthorathic echocardiography (TTE) is a widespread, non-invasive and cost-effective instrument routinely used to assess left and right ventricular function. Speckle tracking (ST) analysis is a novel quantitative ultrasound technique that allows an angle-independent estimation of myocardial deformation[5] and function. We added ST analysis to our approach in order to level out the most important limitation of TTE, its angle- and observer-dependence.

The utility of echocardiography and ST analysis of the RV as an implement to assess presence and severity of PH has been the focus of current studies[6-8]. Due to its variable clinical presentation and difficult treatment, PH presents a clininal picture that needs functional assessment in its course, most commonly evaluated by six minutes walking distance (6MWD).

The aim of this study was to investigate the predictive significance of a non-invasive algorithm including parameters derived from ECG, echocardiography including RV strain analysis, functional testing with determination of 6MWD, lung function test and spirometry as well as NT pro-BNP and blood count for the diagnosis and

discrimination of pre- and postcapillary PH in a patient cohort with known RHC results, which were unknown to the assessor of the non-invasive measurements.

MATERIALS AND METHODS

Patients

Between April 2013 and April 2014 50 patients with suspected PH were prospectively included after undergoing RHC. All patients underwent informed consent and the study was approved by the Ethics Committee of the University Hospital of Bonn.

Right heart catheterization and definition of PH

Invasive hemodynamic parameters were evaluated during RHC according to current guidelines[9], defining precapillary PH as mean pulmonary arterial pressure (mPAP) $\geqslant$ 25 mmHg and pulmonary capillary wedge pressure (PCWP) of $\leqslant$ 15 mmHg and postcapillary PH as mPAP $\geqslant$ 25 mmHg and PCWP > 15 mmHg.

Non-invasive measurements

Non-invasive measurements consisting of TTE with special focus on the RV function and hemodynamics including speckle tracking analysis of the RV. Functional testing includes lung function test and 6MWD, as well as laboratory testing with the assessment of blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP.

TTE and right ventricular speckle tracking

All participants underwent a complete echocardiographic examination including two-dimensional (2D) and Doppler echocardiography performed with commercially available ultrasound scanner with a 2,5-MHz phased array transducer (Vivid 7, General Electric Medical Health, Waukesha, Wisconsin, United States; iE 33 Philips Medical Systems, Koninklijke N.V.) according to the standard echocardiography protocol used at our clinic. The echocardiographic views were obtained in 2D and color tissue Doppler imaging (TDI) modes. In addition to parasternal long- and short-axis and apical two- and four-chamber (4CV) views, RV-focused views were obtained. The following measurements derived from TTE were utilized to assess the presence of PH considering a concomitantly elevated PCWP as a means to discriminate between the pre- and postcapillary forms of PH.

Left ventricular ejection fraction (LVEF) was calculated using Simpson's formula. Systolic pulmonary artery pressure (sPAP) was measured with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values $\geqslant$ 30 mmHg. PCWP was considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e‘ ratio was measured according to recommendations of the American Society of Echocardiography by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. These measurements were then averaged with conventional measurement of mitral valve inflow[10].

The combination of sPAP > 30 mmHg and E/e‘ <12 was deemed to reflect precapillary PH, while sPAP > 30 mmHg and E/e‘ ratio >12 indicated postcapillary PH. Tricuspid annular plane systolic excursion (TAPSE) was obtained using M-Mode in the apical 4-Ch- view of the longitudinal excursion of the lateral tricuspid annulus towards the RV apex[11]. Additionally, diastolic interventricular septal thickness (IVSd), endsystolic (ESV) and enddiastolic volume (EDV) were measured. TTE derived parameters of our study population are shown in Table 1.

2DST analysis of the RV was performed using a routine grayscale apical 4-Ch view and a commercially available software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). As the region of interest, the RV endocardial border was manually delineated and was tracked by the 2D strain software. In order to ensure precise tracking of segments, visual assessment during cine loop playback was applied. The RV was divided visually in a basal, midventricular and apical segment and six corresponding time-strain curves were generated. Following the approach of Dambrauskaite[12] and Lopez-Candales[13] longitudinal lateral apical RV (RVAS) strain and global longitudinal RV strain (RVGS) entered further analysis. The longitudinal strain of the RV free wall, was calculated as the average of each of the three regional peak systolic strains along the entire right ventricle. An example for RV speckle tracking analysis is depicted in Figure 1.

Functional testing and assessment of clinical impairment

All our patients underwent a set of non-invasive testing in order to estimate the extent of their physical impairment due to PH. Shortness of breath was classified according to the World Health Organization (WHO) functional class score and gauged by 6MWD, using walking aids or portable oxygen if necessary. Standard 12-channel-ECG was screened for signs of RV strain such as RV hypertrophy, right axis deviation, right bundle block or signs of right atrial dilation[14]. Furthermore, pulmonary function was measured with spirometry and bodyplethysmography including total lung capacity, residual volume, vital capacity, forced expiratory volume and tiffeneau index. Blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP were registered one to six weeks after RHC.

Statistical analysis

Data analysis was exploratory, variables underwent no adjustments. Normal distribution of continuous variables was examined employing the Kolmogorov-Smirnov test. Continuous data was expressed as mean values ± standard deviation. Two-tailed *P*-values were computed and regarded significant if ranging below 0.05 (95%CI). Two group comparisons were done using student's-*T*

Table 1 Echocardiographic and invasive measurements

	All patients (n = 44)	No PH (n = 10)	Precapillary PH (n = 15)	Postcapillary PH (n = 19)	P
TTE					
EF, %	61.3 ± 13.8	62 ± 9.5	67 ± 10.3	56.5 ± 16.7	0.28
EDV, mL	92.8 ± 36.1	87.8 ± 33.1	73.6 ± 34	110.6 ± 31.8	0.04
ESV, mL	37.4 ± 24.6	32.2 ± 13.6	25 ± 15	49.9 ± 29.6	0.04
IVSd, cm	1.2 ± 0.4	1.1 ± 0.2	1.1 ± 0.6	1.3 ± 0.4	0.12
LAV, mL	84.0 ± 52.7	82.4 ± 55.2	79.9 ± 64.9	85.2 ± 48.7	0.6
sPAP, mmHg	51.1 ± 24.4	31.2 ± 24.6	61.2 ± 22.3	53.6 ± 20.4	0.003
RVDs, cm	2.4 ± 1.1	2.2 ± 1.0	2.4 ± 1.1	2.3 ± 1.1	0.8
RVDd, cm	3.3 ± 1.4	3.0 ± 1.2	3.4 ± 1.6	3.3 ± 1.3	0.36
TAPSE, cm	1.8 ± 0.6	2.1 ± 0.6	1.8 ± 0.5	1.8 ± 0.6	0.23
E/e' ratio	14.4 ± 7.8	12.1 ± 4.5	12.4 ± 4.4	17.3 ± 10.3	0.13
RVGS, %	-11.5 ± 5.9	-13.3 ± 7.6	-10.8 ± 4.6	-11.2 ± 6	0.82
RVAS, %	-11.6 ± 5.9	-14.3 ± 6.3	-7.5 ± 5.6	-13.3 ± 4.3	< 0.001
RHC					
mPAP, mmHg	40.1 ± 17.5	20.9 ± 3	51.8 ± 20.6	40.9 ± 8.9	< 0.001
sPAP, mmHg	55.0 ± 17.6	35.3 ± 8.5	60.3 ± 17.4	53.5 ± 17.4	0.04
PCWP	16.1 ± 7.2	11.4 ± 4.1	11.4 ± 2.1	22.3 ± 6.3	< 0.001
CO, L/min	3.6 ± 3.8	3.3 ± 3.7	3.2 ± 3.3	3.4 ± 4.2	0.46
RV systolic pressure, mmHg	63.9 ± 26.3	37.1 ± 14.3	86.7 ± 25.4	66.3 ± 17.4	< 0.001
RV diastolic pressure, mmHg	5.3 ± 5.8	4.9 ± 5.3	4.3 ± 5.8	5.6 ± 5.8	0.07
RV mean pressure, mmHg	9.4 ± 8.6	7.5 ± 6.5	11.9 ± 12.1	8.6 ± 7.1	0.04
RA mean pressure, mmHg	13.5 ± 13.1	13.2 ± 9.3	12.7 ± 5.4	13.8 ± 14.7	0.69
WHO class					0.56
Ⅰ, n (%)	2 (4.3)	2 (20)	0 (0)	0 (0)	
Ⅱ, n (%)	10 (21.7)	3 (30)	2 (13.3)	5 (26.3)	
Ⅲ, n (%)	29 (63)	5 (50)	11 (73.3)	13 (68.4)	
Ⅳ, n (%)	3 (6.5)	0 (0)	2 (13.3)	1 (5.3)	

EF: Ejection fraction; EDV/ESV: End-systolic/diastolic volume; IVSd: Diastolic interventricular septum diameter; LAV: Left atrial volume; s/mPAP: Systolic/mean pulmonary arterial pressure; RVDs/d: Systolic/diastolic right ventricular diameter; TAPSE: Tricuspid annular plane systolic excursion; RVGS/RVAS: Global/apical right ventricular longitudinal strain; PCWP: Pulmonary capillar wedge pressure; CO: Cardiac output; RV/RA: Right ventricle/atrium; WHO: World Health Organization.

test for paired samples or Wilcoxon signed rank test for paired continuous variables. Categorical data was tested with Fisher's exact test. SPSS for Windows (PASW statistic, Version 21.0.0, SPSS Inc., Chicago, Illinois, United States) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium) were utilized for statistical analysis.

Afterwards, a diagnostic model including RVAS, sPAP and E/e' ratio was generated by calculating associated ROC curves for the assumed possibilites. The corresponding AUCs along with 95%CI were calculated.

RESULTS

Six patients were excluded from the study population because of insufficient transthorathic image quality (n = 2), incomplete RHC results (n = 3) or withdrawal of consent (n = 1).

In total, 44 prospective patients [age 63.11 ± 14 years, 27 (61%), male], were consecutively included in our study. According to RHC, precapillary PH was diagnosed in 15 (34%), postcapillary PH in 19 (43%) and PH was excluded in 10 (23%) patients. Demographic baseline characteristics of the study cohort are shown in Table 2.

Echocardiography and speckle-tracking analysis

Echocardiographic measures on RV and LV functions differed significantly between patients with PH and those without PH concerning measures on LV diastolic function (E/e' ratio: Precapillary PH, 12.3 ± 4.4; postcapillary PH, 17.3 ± 10.3; no PH, 12.1 ± 4.5; P = 0.02), and LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, P = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, P = 0.021). Furthermore, sPAP showed significant differences between the patient groups (61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, P = 0.001). Concerning RV function analysis, ST analysis of the RV free wall showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, P = 0.03), but not for global longitudinal RV strain (P > 0.05). All other measures on LV and RV function did not differ relevantly between the groups Table 1.

Functional testing and non-invasive measurements

Patients with precapillary PH presented significantly more often with ECG changes indicating RV stress (precapillary PH: 87%, postcapillary PH: 58%, no PH: 20%, P = 0.001). Functional status did not differ between patients with or without PH when comparing measures on 6MWD (375.3 ± 187.8 m, 319.5 ± 132.0 m, 372.5 ± 127.5 m,

Table 2 Baseline characteristics

	All patients (*n* = 44)	No PH (*n* = 10)	Precapillary PH (*n* = 15)	Postcapillary PH (*n* = 19)	*P*
Age, yr	63.11 ± 14.2	60.3 ± 16.9	60.2 ± 13	66.9 ± 13.3	0.71
Male gender, *n* (%)	27 (61)	5 (50)	8 (53)	14 (74)	0.33
AHT, *n* (%)	30 (60)	8 (61)	7 (53)	15 (62)	0.82
Diabetes mellitus, *n* (%)	11 (22)	2 (15)	3 (23)	6 (25)	0.57
CAD, *n* (%)	26 (52)	7 (53)	7 (53)	12 (50)	0.44
HLP, *n* (%)	15 (30)	4 (31)	6 (25)	5 (38)	0.33
Nicotine, *n* (%)	10 (20)	3 (23)	5 (21)	2 (15)	
Specific PAH Therapy, *n* (%)	15 (34)	0 (0)	15 (100)	0 (0)	< 0.001
ECG RV strain, *n* (%)	26 (59)	2 (20)	13 (87)	11 (58)	0.001
NT pro-BNP (pg/mL)	2778.3 ± 5681.3	367.5 ± 420.4	1980.3 ± 3432.1	4677 ± 7764.8	0.44
Hemoglobine, mg/dL	12.8 ± 3.6	11.4 ± 0.9	12.2 ± 2.5	12.6 ± 3.4	0.09
Bilirubin, mg/dL	0.7 ± 0.5	0.5 ± 0.2	0.9 ± 0.8	0.8 ± 0.3	0.08
Uric acid, mg/dL	7.1 ± 2.6	6.0 ± 1.7	6.9 ± 2.6	7.9 ± 2.8	0.13
Serum creatinine, mg/dL	1.3 ± 0.3	1.0 ± 0.2	1.3 ± 0.4	1.2 ± 0.2	0.25
Creatinine clearance, mL/min	55.3 ± 13.4	53.2 ± 8.9	50.5 ± 11.4	57.2 ± 6.3	0.48
6MWD, m	351.9 ± 153.2	372.5 ± 127.5	375.3 ± 186.8	319.5 ± 131.9	0.55

AHT: Arterial hypertension; CAD: Coronary artery disease; HLP: Hyperlipoproteinemia; PAH: Pulmonary arterial hypertension; ECG: Electrocardiogram; RV: Right ventricular; NT pro-BNP: N-terminal pro brain-natriuretic-peptide; 6MWD: 6 min walking distance.

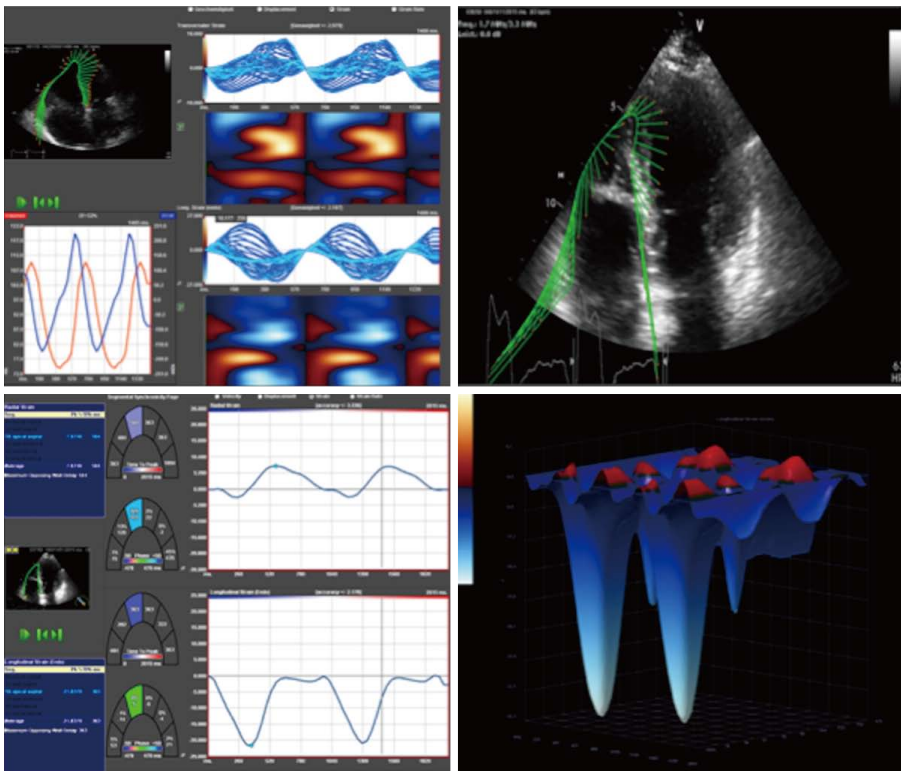

Figure 1 Example of right ventricular speckle tracking and three dimensional visualisation of longitudinal right ventricular strain values. RV: Right ventricular; 3D: Three dimensional; RVSI: Right ventricular longitudinal strain.

P > 0.05) and pulmonary function (Table 2).

Serum NT pro-BNP was significantly higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL) as compared to patients with (precapillary PH (1980.3 ± 3432.1 pg/mL), or no PH (367.5 ± 420.4 pg/mL, *P* = 0.03). All other laboratory values did not show significant differences between the subgroups (Table 1). Notably, patients with elevated pulmonary pressures had a higher WHO functional class compared to patients without PH (*P* = 0.04) (Table 1, Figure 2).

Factors predicting PAH

In order to define cut-off values for the identification of precapillary PH, ROC analyses of variables with significant differences between the patient groups were done subsequently. Only measures on regional RV function with

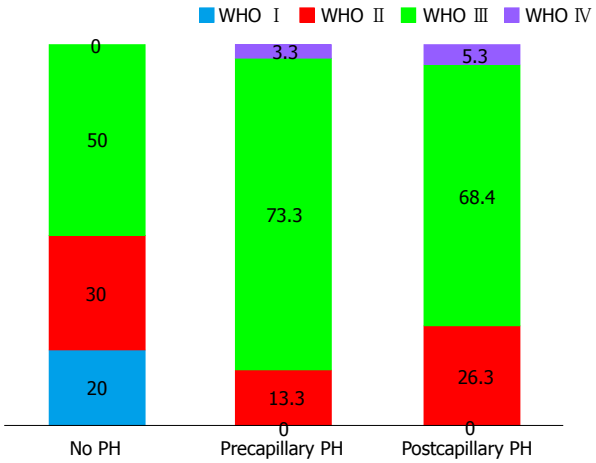

Figure 2 Distribution of World Health Organization classes in the study cohort, separated by etiology of pulmonary hypertension.

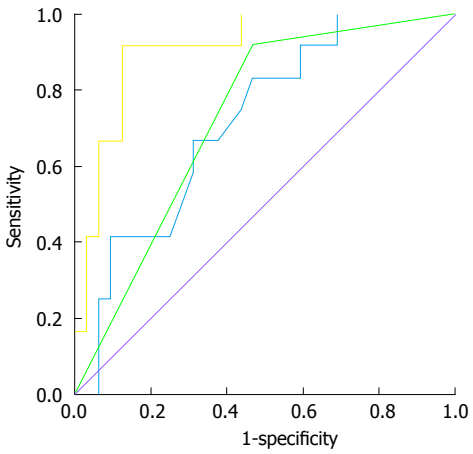

Figure 3 Incremental diagnostic value of the combination of non-invasive measures for identification of patients with precapillary pulmonary hypertension. Green curve, ECG RV stress signs alone; blue curve, apical right ventricular longitudinal strain alone; sand-colored curve, combination of non-invasive measures. RV: Right ventricle; ECG: Electrocardiograph.

strain imaging [RVAS: cut-off < -6.5%, area under the curve (AUC) 0.91, $P < 0.001$], RV hemodynamics (sPAP: cut-off > 33 mmHg, AUC 0.86, $P < 0.001$) and ECG RV stress signs (AUC 0.83, $P < 0.001$) were associated with precapillary PH.

A combination of the cut-off values showed a sensitivity of 82.8% and a specificity of 17.2% for the confirmation of precapillary PH (Figure 3).

DISCUSSION

According to current guidelines invasive testing with RHC is necessary for the diagnosis of PAH and the indication for RHC is based only on functional and clinical status in patients with persistent dyspnea of unknown cause.

Therefore, there is an unmet need for patient identification with a widespread, cost-effective and non-invasive tool[7]. Our group showed recently, that echocardiography might enable direct, easy and noninvasive diagnosis of PAH by combining non-invasive measures on RV hemodynamics utilizing sPAP, RV function RVAS and E/e' ratio as a parameter for LV diastolic function. In this study we intended to verify and extend this approach in a prospective fashion, integrating it into the newly suggested screening model for PAH in order to prove its clinical applicability.

Most importantly, the present study indicates that (1) the combined consideration of sPAP, RVAS, E/e' ratio and ECG RV stress signs seems to be a promising and easily applicable tool to discriminate between pre-, post-capillary and to some extent no PH; and (2) our data provide preliminary evidence that there does not seem to be an additional clinical benefit of functional testing with 6MWD, and/or pulmonary function tests in a preselected, severely ill patient cohort.

Need for early diagnosis of PAH

Current studies suggest the possibility of an improved long-term outcome in PAH patients when diagnosed and treated early[15,16]. Due to the unspecific symptoms of early stage PH and the limitations of routinely used screening methods, definite diagnosis is often delayed. Despite increased efforts in the early detection of PAH associated with connective tissue disease[17] and other known risk factors including bone morphogenic protein receptor 2 mutations[18], there is still a lack of general recommendations concerning screening algorithms for PAH in non-high risk populations. While 6MWD, NT pro-BNP and changes in WHO functional class have been described as significant predictors of outcome in patients with idiopathic PAH[19], Graspa *et al*[20] could demonstrate, that RV dysfunction, moderate to severe tricuspid regurgitation, a low cardiac index and elevated right atrial pressures are independent predictors in mortality in a large prospective study with patients suffering from PAH. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) detected an elevated pulmonary vascular resistance (PVR), WHO functional class Ⅲ-Ⅳ, elevated mean right atrial pressure, 6MWD and Brain Natriuretic Peptide as predictive factors in PAH[21].

Right ventricular speckle-tracking in patients with pulmonary hypertension

Although clinical trials on RV strain analysis are rare, evidence proving its feasibility and prognostic value is constantly growing[5-8,13,22,24,28]. Whilst this study failed to show a significant correlation between RVGS and PH status, Rajagopal *et al*[5] were able to detect a sufficient relation between RVGS and functional status of patients suffering from PH applying a RV-centered echocardiographic approach. However, they included 40, mainly female (85%), patients, who in contrast to our cohort had a lower WHO functional class (73% WHO FC Ⅰ and Ⅱ, 27% WHO FC Ⅲ and Ⅳ). More importantly, other studies confirmed the diagnostic value of measuring regional alterations in strains derived from the RV free wall[22], namely the averaged RV peak strain as functional measure for RV ejection fraction

in adults and children suffering from different etiologies of RV impairment. However, there is still no study to verify the correlation between RV-derived strain and WHO functional class in a large patient cohort with determined PH.

Fukuda *et al*[6] were able to show a significant correlation between ST of the RV free wall with invasively measured mPAP and PVR as well as RV ejection fraction and RV end-systolic volume determined by cardiac magnetic resonance imaging and exercise tolerance by 6MWD thus implying RV ST as a suitable method to assess patients with PH. More recently, Sano *et al*[23] established RV ST analysis to describe reverse remodeling as a marker for long-term outcome of PH and Vitarelli *et al*[24] were able to affirm the diagnostic accuracy of two- and three-dimensional ST parameters, including RVAS as a surrogate for hemodynamic assessment and thus predictor of outcome in chronic pulmonary hypertension.

Screening for PAH

Humbert *et al*[18] suggested an elaborated screening algorithm for patients at risk for developing pulmonary hypertension, clearly delineating the lack of a standardized diagnostic approach in unselected patients.

Parent *et al*[25] found evidence for a combination of echocardiographic markers, 6MWD and NT-proBNP in patients with sickle-cell anemia associated PAH, whereas Allanore *et al*[26] proposed a combination of echocardiographic assessment of sPAP, serum NT-pro BNP, erythrocyte sedimentation rate and the diffusing capacity for carbon monoxide/alveolar volume in patients with systemic sclerosis. Although annual echocardiography is recommended in high risk populations[14,27], implementation of ST based RV functional analysis has not yet found consideration in order to refine the diagnostic value of TTE. Of note, the prognostic value of RV ST has been demonstrated for patients suffering from PH irrespective of its etiology by Haeck *et al*[28].

The drawbacks of all studies are the relatively small patient numbers, which may lead to biased conclusions and thus may lack general extrapolation. Therefore, the findings of the prospective DELPHI-2 study, which follows asymptomatic carriers of the bone morphogenic protein receptor 2 mutation and will provide their hemodynamic, echocardiographic and functional characteristics, will elucidate this topic in a relevant bigger cohort of patients at high risk of developing PAH.

COMMENTS

Background

Definite diagnosis of pulmonary hypertension (PH) in general and the distinction between the precapillary and postcapillary form of this disease in is often delayed due to unspecific symptoms and the necessity of invasive testing. The authors' study results verified a useful estimation of pulmonary pressure with transthorathic echocardiography (TTE). Combined with speckle-tracking (ST) analysis of the apical right ventricle (RV) and electrocardiogram (ECG) RV stress signs it seems to be of value to strengthen the suspicion of the rare but malignantly proceeding precapillary form of PH and therefore should be considered as a diagnostic tool in patients with suspected pulmonary arterial hypertension (PAH).

Research frontiers

Although the ST assessment of our cohort was performed blinded to the results of right heart catheterization (RHC), our approach was still retrospective. Therefore, confirmation of the study result needs to be acquired in a fully prospective study. Another weakness of this trial is the relatively small number of patients included, in order to reaffirm our findings, future research should aim to comprise larger numbers of patients of the different PH subgroups. Since there are multiple differential diagnoses to pulmonary hypertension that lead to RV strain and alterations of the RV geometry and contractility that have not been considered in our analysis, a prospective study design could compare RV speckle-tracking analysis of patients with PH ideally scrutinizing the diverse etiologies of PH and disparate right heart impairments. Ultimately, as the software available to perform ST-analysis was primarily produced for the left ventricle, newly developed software specialized on the complex geometry of the RV could refine the data.

Innovations and breakthroughs

The data in this study suggests that a combination of non-invasive measurements including echocardiography and speckle-tracking analysis allows feasible estimation of PH with a sensitivity of 82.8%. Taking into consideration all our findings a model for future assessment of suspected PH could provide an incrementally invasive examination beginning with TTE and ECG on the first level, adding NT pro-BNP on a second level and only after evaluating these results, a recommendation for timely RHC should be given.

Applications

In this study, ST showed only a specificity of 17.2% for detection of precapillary PH. Therefore, it does not seem to reliably identify PAH at this point and the definite diagnosis has still to be made by invasive RHC. However, ST has become more applicable in echocardiographic examination and it should be considered as an additional diagnostic tool for patients before invasive RHC. Our study results indicate a necessity for timely RHC assessing PAH if a patient shows RVAS < -6.5%, sPAP > 33 mmHg and electrocardiographic RV stress signs. In a second step, NT pro-BNP could help to determine the necessity of RHC in patients with RVAS > -6.5%. Since sPAP < 33 mmHg, no signs of RV stress in ECG and NT pro-BNP < 1000 pg/mL seemed not to correlate with PH, suggestion for RHC should be made reluctantly and other causes of dyspnea should be considered. However, given our small sample size, this model has yet to be tested in a larger patient cohort.

Terminology

The clinical classification of PAH comprises a heterogenous group of disease patterns that show unspecific clinical presentation due to elevated pulmonary pressures and right ventricular stress. ST is a relatively novel ultrasound technique that allows estimation of myocardial deformation as thus assessment of right ventricular function which is compromised in both pre- and post-capillary forms of pulmonary hypertension.

Peer-review

Recent studies focus on the value of ST-analysis in patients with suspected pulmonary hypertension, especially as to its potential to discriminate between pre- and postcapillary forms of PH. This work provides a comprehensive literature review on this topic. PAH is caused by heterogenous etiologies and often associated with rare diseases, therefore, the majority of papers available on ST in patients with PAH are centered on a specific etiology. The study included patients with suspected PAH regardless its etiology. The results are interesting and provide evidence of the utility of right ventricular ST in patients with suspected PAH.

REFERENCES

1 **Galiè N**, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori

M, Hoeper M. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *Rev Esp Cardiol* (Engl Ed) 2016; **69**: 177 [PMID: 26837729 DOI: 10.1183/09031936.00139009]
2 **McLaughlin VV**, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006; **114**: 1417-1431 [PMID: 17000921 DOI: 10.1161/CIRCULATIONAHA.104.503540]
3 **McGoon M**, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; **126**: 14S-34S [PMID: 15249493 DOI: 10.1378/chest.126.1_suppl.14S]
4 **Bonderman D**, Wexberg P, Martischnig AM, Heinzl H, Lang MB, Sadushi R, Skoro-Sajer N, Lang IM. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. *Eur Respir J* 2011; **37**: 1096-1103 [PMID: 20693249 DOI: 10.1183/09031936.00089610]
5 **Rajagopal S**, Forsha DE, Risum N, Hornik CP, Poms AD, Fortin TA, Tapson VF, Velazquez EJ, Kisslo J, Samad Z. Comprehensive assessment of right ventricular function in patients with pulmonary hypertension with global longitudinal peak systolic strain derived from multiple right ventricular views. *J Am Soc Echocardiogr* 2014; **27**: 657-665.e3 [PMID: 24656881 DOI: 10.1016/j.echo.2014.02.001]
6 **Fukuda Y**, Tanaka H, Sugiyama D, et al. Utility of Right Ventricular Free Wall Speckle-Tracking Strain for Evaluation of Right Ventricular Performance in Patients with Pulmonary Hypertension. *J Am Soc Echocardiogr* 2011; **24**: 1101-1108 [PMID: 24879080 DOI: 10.1007/s10554-014-0460-6]
7 **Hammerstingl C**, Schueler R, Bors L, Momcilovic D, Pabst S, Nickenig G, Skowasch D. Diagnostic value of echocardiography in the diagnosis of pulmonary hypertension. *PLoS One* 2012; **7**: e38519 [PMID: 22685577 DOI: 10.1371/journal.pone.0038519]
8 **Mondillo S**, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zacà V, Ballo P, D'Andrea A, Muraru D, Losi M, Agricola E, D' Errico A, Buralli S, Sciomer S, Nistri S, Badano L. Speckle-tracking echocardiography: a new technique for assessing myocardial function. *J Ultrasound Med* 2011; **30**: 71-83 [PMID: 21193707]
9 Proceedings of the 4th World Symposium on Pulmonary Hypertension, February 2008, Dana Point, California, USA. *J Am Coll Cardiol* 2009; **54**: S1-117 [PMID: 19630151]
10 **Nagueh SF**, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009; **10**: 165-193 [PMID: 19270053 DOI: 10.1016/j.echo.2008.11.023]
11 **Rudski LG**, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685-713; quiz 786-788 [PMID: 20620859 DOI: 10.1016/j.echo.2010.05.010]
12 **Dambrauskaite V**, Delcroix M, Claus P, Herbots L, D'hooge J, Bijnens B, Rademakers F, Sutherland GR. Regional right ventricular dysfunction in chronic pulmonary hypertension. *J Am Soc Echocardiogr* 2007; **20**: 1172-1180 [PMID: 17570637 DOI: 10.1016/j.echo.2007.02.005]
13 **López-Candales A**, Rajagopalan N, Gulyasy B, Edelman K, Bazaz R. Differential strain and velocity generation along the right ventricular free wall in pulmonary hypertension. *Can J Cardiol* 2009; **25**: e73-e77 [PMID: 19279990]
14 **Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC)**; European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; **34**: 1219-1263 [PMID: 19749199 DOI: 10.1183/09031936.00139009]
15 **Humbert M**, Sitbon O, Yaïci A, Montani D, O'Callaghan DS, Jaïs X, Parent F, Savale L, Natali D, Günther S, Chaouat A, Chabot F, Cordier JF, Habib G, Gressin V, Jing ZC, Souza R, Simonneau G. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; **36**: 549-555 [PMID: 20562126 DOI: 10.1183/09031936.00057010]
16 **O'Callaghan DS**, Humbert M. A critical analysis of survival in pulmonary arterial hypertension. *Eur Respir Rev* 2012; **21**: 218-222 [PMID: 22941886 DOI: 10.1183/09059180.00003512]
17 **Khanna D**, Gladue H, Channick R, Chung L, Distler O, Furst DE, Hachulla E, Humbert M, Langleben D, Mathai SC, Saggar R, Visovatti S, Altorok N, Townsend W, FitzGerald J, McLaughlin VV. Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum* 2013; **65**: 3194-3201 [PMID: 24022584 DOI: 10.1002/art.38172]
18 **Humbert M**, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary arterial hypertension. *Eur Respir Rev* 2012; **21**: 306-312 [PMID: 23204118 DOI: 10.1183/09059180.00005112]
19 **Nickel N**, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; **39**: 589-596 [PMID: 21885392 DOI: 10.1183/09031936.00092311]
20 **Grapsa J**, Pereira Nunes MC, Tan TC, Cabrita IZ, Coulter T, Smith BC, Dawson D, Gibbs JS, Nihoyannopoulos P. Echocardiographic and Hemodynamic Predictors of Survival in Precapillary Pulmonary Hypertension: Seven-Year Follow-Up. *Circ Cardiovasc Imaging* 2015; **8**: e002107 [PMID: 26063743 DOI: 10.1161/CIRCIMAGING.114.002107]
21 **Benza RL**, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; **122**: 164-172 [PMID: 20585012 DOI: 10.1161/CIRCULATIONAHA.109.898122]
22 **Forsha D**, Risum N, Kropf PA, Rajagopal S, Smith PB, Kanter RJ, Samad Z, Sogaard P, Barker P, Kisslo J. Right ventricular mechanics using a novel comprehensive three-view echocardiographic strain analysis in a normal population. *J Am Soc Echocardiogr* 2014; **27**: 413-422 [PMID: 24508364 DOI: 10.1016/j.echo.2013.12.018]
23 **Sano H**, Tanaka H, Motoji Y, Fukuda Y, Sawa T, Mochizuki Y, Ryo K, Matsumoto K, Emoto N, Hirata K. Right ventricular function and right-heart echocardiographic response to therapy predict long-term outcome in patients with pulmonary hypertension. *Can J Cardiol* 2015; **31**: 529-536 [PMID: 25840102 DOI: 10.1016/j.cjca.2015.01.027]
24 **Vitarelli A**, Mangieri E, Terzano C, Gaudio C, Salsano F, Rosato E, Capotosto L, D'Orazio S, Azzano A, Truscelli G, Cocco N, Ashurov R. Three-dimensional echocardiography and 2D-3D speckle-tracking imaging in chronic pulmonary hypertension: diagnostic accuracy in detecting hemodynamic signs of right ventricular (RV) failure. *J Am Heart Assoc* 2015; **4**: e001584 [PMID: 25792128 DOI: 10.1161/JAHA.114.001584]
25 **Parent F**, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, Habibi A, Bennani S, Savale L, Adnot S, Maitre B, Yaïci A, Hajji L, O' Callaghan DS, Clerson P, Girot R, Galacteros F, Simonneau G. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med* 2011; **365**: 44-53 [PMID: 21732836 DOI: 10.1056/NEJMoa1005565]
26 **Allanore Y**, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, Mouthon L, Guillevin L, Meyer O, Ekindjian OG, Weber S, Kahan A. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum* 2008; **58**: 284-291 [PMID: 18163505 DOI: 10.1002/art.23187]
27 **McLaughlin VV**, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus

document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009; **53**: 1573-1619 [PMID: 19389575 DOI: 10.1016/j.jacc.2009.01.004]

28 **Haeck ML**, Scherptong RW, Marsan NA, Holman ER, Schalij MJ, Bax JJ, Vliegen HW, Delgado V. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; **5**: 628-636 [PMID: 22875884 DOI: 10.1161/CIRCIMAGING.111.971465]

29 **Montani D**, Günther S, Dorfmüller P, Perros F, Girerd B, Garcia G, Jaïs X, Savale L, Artaud-Macari E, Price LC, Humbert M, Simonneau G, Sitbon O. Pulmonary arterial hypertension. *Orphanet J Rare Dis* 2013; **8**: 97 [PMID: 23829793 DOI: 10.1186/1750-1172-8-97]

P- Reviewer: Cebi N, Feher G, Kettering K, Najafi M
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.481

World J Cardiol 2016 August 26; 8(8): 481-487
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Relationship between coronary calcium score and high-risk plaque/significant stenosis

Kohichiro Iwasaki, Takeshi Matsumoto

Kohichiro Iwasaki, Takeshi Matsumoto, Department of Cardiology, Okayama Kyokuto Hospital, Okayama 703-8265, Japan

Author contributions: All the authors contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Okayama Kyokuto Hospital.

Informed consent statement: All study participants provided informed consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Kohichiro Iwasaki, MD, Department of Cardiology, Okayama Kyokuto Hospital, 567-1, Kurata, Naka-ku, Okayama 703-8265, Japan. kiwasaki@kyokuto.or.jp
Telephone: +81-86-2763231
Fax: +81-86-2741028

Received: April 13, 2016
Peer-review started: May 26, 2016
First decision: June 16, 2016
Revised: June 29, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: August 26, 2016

Abstract

AIM

To investigate the relationship between coronary calcium score (CCS) and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

METHODS

CCTA was performed in 651 patients and these patients were divided into the four groups (CCS 0, 1-100, 101-400 and > 400). We studied the incidence of high-risk plaque, including positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign, and significant stenosis in each group.

RESULTS

High-risk plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400, respectively ($P < 0.001$). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% for each patient group, respectively ($P < 0.001$), which represented a significant stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively ($P < 0.001$), again representing a significant stepwise increase with CCS. The rate of major coronary event was 0%, 4.0%, 7.9% and 17.2% in each patient group, respectively ($P < 0.001$), another significant stepwise increase as CCS increased.

CONCLUSION

Stepwise increased risk of coronary events associated with increasing CCS is caused by increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

Key words: Coronary calcium score; Coronary stenosis; High-risk plaque; Low attenuation plaque; Napkin-ring

sign; Positive remodeling; Spotty calcification

Core tip: Coronary computed tomographic angiography was performed in 651 patients and these patients were divided into the four groups according to coronary calcium score (CCS): 0, 1-100, 101-400 and > 400. The incidence of high-risk plaque was not significantly different among the three groups, except patients with zero CCS. The incidence of significant stenosis increased stepwise as CCS increased, as did the rate of major coronary event. Therefore, the stepwise increased risk of coronary events associated with increasing CCS is caused by an increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

Iwasaki K, Matsumoto T. Relationship between coronary calcium score and high-risk plaque/significant stenosis. *World J Cardiol* 2016; 8(8): 481-487 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/481.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.481

INTRODUCTION

Coronary artery calcification represents the presence of coronary atherosclerosis and there is a strong relationship between the extent of coronary artery calcification and the total coronary plaque burden[1-3]. Many studies demonstrate that coronary calcium score (CCS) is the powerful predictor of coronary events and provide incremental risk stratification beyond traditional risk scores[4,5]. In contrast, patients with no calcium show a very low risk of coronary events[6]. However the precise mechanism of this increased risk associated with increased CCS has not been fully elucidated. Generally, most coronary events are caused by significant stenosis or vulnerable plaque. Many studies have demonstrated that significant stenosis increases the risk of coronary events[7,8]. In addition, recent studies demonstrate that 70%-80% of cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis[9,10].

Thus, we hypothesized that both significant stenosis and vulnerable plaque were associated with increased coronary events as CCS increased. We investigated the relationship between CCS and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

MATERIALS AND METHODS

Patients

From September 2010 through September 2014, 981 patients underwent CCTA. We excluded: (1) patients who underwent coronary revascularization before CCTA; (2) patients who developed acute coronary syndrome before CCTA; (3) patients who have coronary artery disease (CAD); and (4) patients with inadequate image quality because of motion artifacts, blooming artifacts, or severe calcification. Finally, we studied 651 patients. Most patients underwent CCTA for the evaluation of CAD because of multiple risk factors and/or symptom of chest pain.

CCTA

For CCTA, we used a sixty-four multi-detector computed tomography (MDCT) scanner (SOMATOM Sensation 64 Cardiac, Siemens Medical Solutions, Erlangen, Germany). Before the scan, we administered 20 mg metoprolol if patients had a heart rate more than 70 beats/min. We administered sublingual nitroglycerin 0.8 mg for all patients.

We performed a scan without contrast dye to measure the coronary calcium burden. The detail of the CCTA procedure was reported in the previous study[11].

CCTA image interpretation

For image analysis, we transferred CT data sets to a workstation (Aquarius NetStation, Terarecon Inc, San Mateo, CA, United States). We calculated total calcium score and expressed as Agatston score[12]. We divided our patients into the four groups according to the usual CCS risk classification definitions: CCS 0, 1-100, 101-400 and > 400. We defined high-risk CCS as CCS > 400.

Two reviewers, who were blinded to the patients' clinical characteristics, evaluated the CCTA data, with maximum intensity and curved multiplanar reconstruction (CMPR) techniques. We regarded positive remodeling as the ratio of plaque site diameter divided by reference segment diameter more than 1.1[13]. We regarded spotty calcification as its size less than 3 mm on CMPR images and one side occupied on cross-sectional images[13]. We regarded low attenuation plaque as the lowest CT number less than 30 HU on axial images[13]. We regarded napkin-ring sign as a ring of high attenuation around coronary artery plaque and CT attenuation of a ring higher than that of the adjacent plaque but no greater than 130 HU[14]. We regarded high-risk plaque as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin ring sign. Percent aggregate plaque volume was measured according to Nakazato's method[15]. Two reviewers identified coronary segments and these segments were classified into normal, non-significant stenosis, or significant stenosis. Normal segment was defined as smooth parallel or tapering borders. Non-significant stenosis was defined as luminal irregularities or % diameter stenosis less than 50%. Significant stenosis was defined as % diameter stenosis more than 50%.

Major coronary event

The duration of follow-up was 2.1 ± 1.3 years (median 1.9 years). Major coronary event was defined as cor-

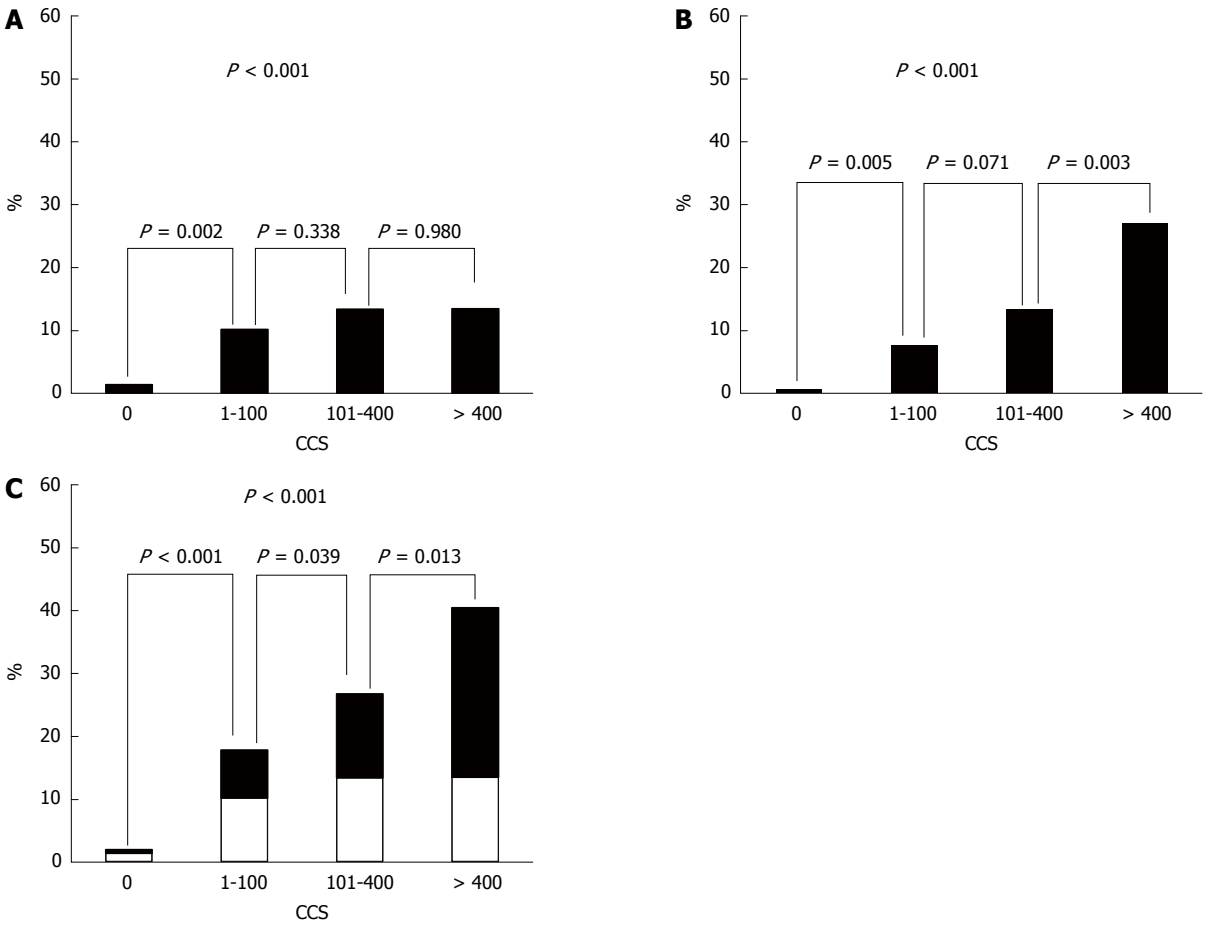

Figure 1 Prevalence of high-risk plaque and significant stenosis among the four groups. A: Prevalence of high-risk plaque; B: Prevalence of significant stenosis; C: Prevalence of combined high-risk plaque and significant stenosis. CCS: Coronary calcium score.

onary death, myocardial infarction, and coronary revascularization.

The Institutional Review Board of Okayama Kyokuto Hospital reviewed and approved this study. All patients provided informed consent.

Statistical analysis

We described continuous variables as mean ± SD. We compared continuous variables by two group *t*-test between the two groups and by one-factor ANOVA among the four groups. We described discrete variables as counts or percentage. We compared discrete variables by the χ^2 or Fisher's exact test between the two groups and by the χ^2 test for independence among the four groups. We investigated predictors of high-risk plaque, significant stenosis, and high-risk CCS by a multiple logistic regression analysis, including age, sex, and all risk factors. A *P*-value < 0.05 was regarded as statistically significant. The biomedical statistician performed statistical review of this study.

RESULTS

The patients' clinical characteristics are shown in Table 1. Figure 1 shows the incidence of high-risk plaque and significant stenosis among the four groups. The high-risk plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400, respectively (Figure 1A). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% in each patient group, respectively (Figure 1B), which represented a stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively (Figure 1C), again representing a significant stepwise increase as CCS increased.

Table 2 shows the incidence of high-risk plaque among the four groups. Apart from patients with zero CCS, there were no significant differences in the incidence of high-risk plaque, positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring appearance among the three groups. In addition, the incidence of multiple high-risk plaques was not significantly different among the four groups. The percent aggregate plaque volume was not significantly different among the four groups. Table 3 shows the predictors of high-risk plaque, significant stenosis, and high-risk CCS by stepwise increased rate of major coronary event was observed. The rate of coronary revascularization also increased stepwise. The rate of coronary death and myocardial infarction was not significantly different among the four

Table 1 Clinical characteristics of studied patients *n* (%)

CCS	0	1-100	101-400	> 400	*P*
n	154	198	165	134	
Age	63.1 ± 11.7	68.2 ± 8.5	69.6 ± 9.8	71.5 ± 8.1	< 0.0001
Male sex	76 (49.4)	137 (69.2)	121 (73.3)	98 (73.1)	< 0.0001
Risk factor					
Hypertension	85 (55.2)	125 (63.1)	115 (69.7)	99 (73.9)	0.0045
Dyslipidemia	88 (57.1)	124 (62.6)	105 (63.4)	82 (61.2)	0.6484
Diabetes	53 (34.4)	76 (38.4)	65 (39.4)	76 (56.7)	0.0007
Stroke	36 (23.4)	58 (29.3)	58 (35.2)	58 (43.3)	0.0024
CKD	30 (19.5)	47 (23.7)	47 (28.5)	43 (32.1)	0.07
BMI (kg/m^2)	25.7 ± 3.7	24.4 ± 2.6	24.2 ± 3.7	23.8 ± 4.8	0.2514
Laboratory data					
HbA1c (mmol/mol)	46.1 ± 13.4	47.4 ± 14.5	48.5 ± 13.0	48.9 ± 12.0	0.3286
BS (mmol/L)	7.43 ± 2.37	7.73 ± 2.44	7.94 ± 2.39	8.52 ± 2.99	0.0333
TC (mmol/L)	5.24 ± 0.99	5.13 ± 0.99	4.95 ± 0.98	4.72 ± 0.87	0.0054
TG (mmol/L)	1.69 ± 1.12	1.63 ± 1.01	1.73 ± 0.94	1.72 ± 0.90	0.8925
HDL-C (mmol/L)	1.50 ± 0.51	1.47 ± 0.43	1.29 ± 0.30	1.41 ± 0.39	0.0084
LDL-C (mmol/L)	3.18 ± 0.86	2.93 ± 0.91	2.96 ± 0.85	2.68 ± 0.72	0.0023
Cr (μmol/L)	69.0 ± 28.3	73.4 ± 19.4	75.1 ± 17.7	78.7 ± 21.2	0.0481
Medication					
ARB/ACE-I	70 (45.5)	101 (51.0)	98 (59.4)	97 (72.4)	< 0.0001
CCB	53 (34.4)	98 (49.5)	96 (58.2)	95 (70.9)	< 0.0001
Diuretics	5 (3.2)	10 (5.1)	9 (5.5)	7 (5.2)	0.7883
Beta-blocker	3 (1.9)	5 (2.5)	3 (1.8)	4 (3.0)	0.9096
Aspirin	37 (24.0)	60 (30.3)	61 (37.0)	60 (44.8)	0.0013
Statin	85 (55.2)	119 (60.1)	100 (60.6)	79 (59.0)	0.7559
Oral diabetics	51 (33.1)	76 (38.4)	65 (39.4)	76 (56.7)	0.0004
Insulin	10 (6.5)	15 (7.6)	16 (9.7)	19 (14.2)	0.112

CCS: Coronary calcium score; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; BS: Blood sugar; CCB: Calcium channel blocker; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

Table 2 Incidence of high-risk plaque among the four groups *n* (%)

CCS	0	1-100	101-400	> 400	*P*
n	154	198	165	134	
High-risk plaque	2 (1.3)[b]	20 (10.1)	22 (13.3)	18 (13.4)	0.0171
Positive remodeling	2 (1.3)[d]	20 (10.1)	21 (12.7)	18 (12.7)	< 0.001
Low attenuation plaque	0 (0)[e]	7 (3.5)	4 (2.4)	1 (0.7)	0.0217
Spotty calcification	0 (0)[h]	13 (6.6)	11 (6.7)	8 (6.0)	< 0.001
Napkin-ring sign	0 (0)[i]	7 (3.5)	2 (1.2)	1 (0.7)	0.0474
Multiple plaques	0 (0)	4 (2.0)	3 (1.8)	3 (2.2)	0.166
%APV	30.5 ± 24.3	42.5 ± 9.0	44.8 ± 9.2	42.2 ± 7.8	0.2537

[b]*P* = 0.0016 compared with group with CCS 1-100; [d]*P* = 0.0016 compared with group with CCS 1-100; [e]*P* = 0.0486 compared with group with CCS 1-100; [h]*P* = 0.0031 compared with group with CCS 1-100; [i]*P* = 0.0486 compared with group with CCS 1-100. CCS: Coronary calcium score; %APV: Percent aggregate plaque volume.

groups (Table 4).

DISCUSSION

Our results showed that the incidence of high-risk plaque was not significantly different among the three groups with CCS of 1-100, 101-400 and > 400. However, the incidence of significant stenosis increased stepwise as CCS increased. Thus, the combined incidence of high-risk plaque and significant stenosis increased significantly as CCS increased. These results suggest that the stepwise increased risk of coronary events associated with increasing CCS would be due to an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same except in patients who have zero CCS.

High-risk plaque

Recently, CCTA characteristics of vulnerable plaque are reported to be positive remodeling, low attenuation

Table 3 Predictors of high-risk plaque, significant stenosis, and high-risk coronary calcium score by multivariate analysis

	OR	95%CI	*P*
High-risk plaque factor			
Male	4.93	2.07-11.7	0.0003
Hypertension	2.2	1.13-4.28	0.0204
Significant stenosis factor			
Hypertension	2.66	1.44-4.89	0.0017
Dyslipidemia	2	1.15-3.47	0.0137
Diabetes	2.32	1.42-3.79	0.0008
High-risk CCS factor			
Age	1.06	1.03-1.08	0.00001
Male	1.54	1.02-2.34	0.0414
Diabetes	2.46	1.68-3.59	0.0001

CCS: Coronary calcium score.

plaque, and spotty calcification[13]. In addition, the napkin-ring sign is regarded as another sign of vulnerable plaque[14]. Thus, we regarded high-risk as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin-ring sign.

The incidence of high-risk plaque was 9.5% in our patients. Motoyama *et al*[16] detected positive remodeling and/or low attenuation plaque in 6.8%. Fujimoto *et al*[17] detected positive remodeling and low attenuation plaque in 6.3%. Their incidence is similar to our results.

In our study, the incidence of high-risk plaque was not significantly different among the three groups with CCS $\geqslant$ 1. No previous studies demonstrated this association. Fujimoto *et al*[17] studied the incidence of positive remodeling and low attenuation plaque in 1139 patients without symptoms or with atypical symptoms. High-risk plaque was detected in 0%, 4.3% and 15.5% in the low-, intermediate- and high-risk Framingham scores groups, respectively. For patients of the intermediate-risk group, the incidence of high-risk plaque was 3.3%, 4.9%, 9.8% and 6.5% in patients who have CCS of 0, 1-250, 251-500 and > 500, respectively. For patients of the high-risk group, it was 7.0%, 20.0%, 17.1% and 12.5% in the respective CCS groups. They found that the incidence of high-risk plaque was lower for CCS > 500 and > 250 in the intermediate- and high-risk groups, respectively. However, when we recalculated their results, we found that the incidence of high-risk plaque was 3.7%, 9.1%, 13.2% and 9.5% in the respective CCS categories. There were no significant differences apart from patients with zero CCS. These results are very similar to ours. Because extensive calcification appears at a later stage of atherosclerotic progression, the incidence of high-risk plaque may not increase in extensively calcified lesions.

Patients who have a high CCS may have multiple plaques compared to those with a modest CCS. Thus, we investigated the incidence of multiple plaques in each group, but there were no significant differences among the four groups. The percent aggregate plaque volume was also not significantly different among the 4 groups.

Significant stenosis

Our results also showed that the incidence of significant stenosis increased stepwise as CCS increased. Rosen *et al*[18] performed CCS measurement and coronary angiography and found a close association between baseline calcium mass score and stenosis severity in each coronary artery. Ho *et al*[19] performed CCS measurement and CCTA in 664 patients and found that the frequency of significant stenosis increased as CCS increased, being 7.9%, 8.3%, 14.5% and 27.2% in those with CCS of 1-100, 101-400, 401-1000 and > 1000, respectively. These results are consistent with ours.

Zero CCS

Our study showed that, in patients who have zero CCS, the incidence of non-calcified plaque, high-risk plaque, and significant stenosis was 13.6%, 1.3% and 0.6%, respectively. Previously, we found non-calcified plaque in 11.1% of 224 asymptomatic low-risk patients with zero CCS[20]. Hausleiter *et al*[21] detected non-calcified plaque in 15.9% of intermediate risk patients. The CONFIRM registry reported that the incidence of significant stenosis was 1.4% in patients with zero CCS[22]. Their results are consistent with ours.

Predictors of high-risk plaque, significant stenosis, and high-risk CCS

In our study, multivariate analysis demonstrated that the predictors of high-risk plaque were male sex and hypertension, while those of significant stenosis were hypertension, dyslipidemia, and diabetes. Furthermore, the predictors of high-risk CCS were age, male sex, and diabetes. These predictors are conventional coronary risk factors.

Limitations

There are several limitations to our study. The number of patients was not large enough. We need a larger patient population to confirm our results. Although the rate of major coronary event differed significantly among the four groups, this difference was caused by the difference in coronary revascularization. We selected coronary revascularization only for patients with either moderate or severe ischemia by myocardial perfusion imaging or fractional flow reserve less than 0.75. Many studies demonstrate that these patients are at increased risk of coronary events, and benefit from coronary revascularization[23,24]. We think that it is difficult to demonstrate differences in hard cardiac events among the 4 groups, because the number of patients and follow-up period were not sufficient. In addition, our patients are basically at low to intermediate risk for coronary events, because these patients have no known CAD, which means subclinical CAD. Moreover, we prescribed high-intensity statin therapy for patients with high-risk plaque. Therefore, we think that these are the reasons why there are too few events in our study.

Table 4 Major coronary event among the four groups *n* (%)

CCS	0	0-100	101-400	> 400	*P*
n	154	198	165	134	
MCE	0 (0)	8 (4.0)[a]	13 (7.9)[c]	23 (17.2)[f]	< 0.001
Coronary death	0 (0)	0 (0)	0 (0)	1(0.8)	0.6345
Myocardial infarction	0 (0)	1 (0.5)	1 (0.6)	3 (2.2)	0.4584
Revascularization	0 (0)	7 (3.5)[g]	12 (7.3)[i]	19 (14.2)[k]	< 0.001

[a]P = 0.0306 compared with group with CCS 0; [c]P= 0.1188 compared with group with CCS 1-100; [f]P = 0.0141 compared with group with CCS 101-400; [g]P = 0.0486 compared with group with CCS 0; [i]P = 0.1114 compared with group with CCS 1-100; [k]P = 0.0333 compared with group with CCS 101-400. CCS: Coronary calcium score; MCE: Major coronary event.

Our results demonstrate that the stepwise increased risk of coronary events in association with an increased CCS would be caused by an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same, except patients with zero CCS. Thus, the combined incidence of high-risk plaque and significant stenosis increased stepwise as CCS increased.

COMMENTS

Background

Coronary calcium score (CCS) is the most powerful predictor of cardiac events beyond conventional risk factors. However, the precise mechanism of increased risk of coronary events associated with increasing CCS is not fully elucidated.

Research frontiers

Many studies have demonstrated that most cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis. Recent studies demonstrate that the characteristics of vulnerable plaque by coronary computed tomographic angiography, which is called high-risk plaque, are positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign.

Innovation and breakthroughs

The authors showed that stepwise increased risk of coronary events associated with increasing CCS is caused by increasing prevalence of significant stenosis, while that of high-risk plaque remains the same. There was each study which investigated the relationship between CCS and significant stenosis, and CCS and high-risk plaque, respectively. However, the authors comprehensively showed the relationship between CCS and high-risk plaque/significant stenosis.

Applications

The higher the CCS, the more the authors have a chance to find significant stenosis in these patients. For patients with significant stenosis, non-invasive stress test to detect myocardial ischemia is needed. The authors also must pay attention to high-risk plaque even for patients with low CCS.

Terminology

Napkin-ring sign is defined as the presence of a ring of high attenuation around certain coronary artery plaque and the CT attenuation of a ring presenting higher than those of the adjacent plaque and no greater than 130 HU.

Peer-review

Very nice and interesting study, well performed.

REFERENCES

1 **Rumberger JA**, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995; **92**: 2157-2162 [PMID: 7554196 DOI: 10.1161/01.CIR.92.8.2157]

2 **Sangiorgi G**, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998; **31**: 126-133 [PMID: 9426030]

3 **Youssef G**, Budoff MJ. Coronary artery calcium scoring, what is answered and what questions remain. *Cardiovasc Diagn Ther* 2012; **2**: 94-105 [PMID: 24282703 DOI: 10.3978/j.issn.2223-3652.2012.06.04]

4 **Budoff MJ**, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, Kondos G, Kronmal RA. Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2009; **53**: 345-352 [PMID: 19161884 DOI: 10.1016/j.jacc.2008.07.072]

5 **Yeboah J**, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012; **308**: 788-795 [PMID: 22910756 DOI: 10.1001/jama.2012.9624]

6 **Erbel R**, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel KH. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol* 2010; **56**: 1397-1406 [PMID: 20946997 DOI: 10.1016/j.jacc.2010.06.030]

7 **Min JK**, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011; **58**: 849-860 [PMID: 21835321 DOI: 10.1016/j.jacc.2011.02.074]

8 **Hou ZH**, Lu B, Gao Y, Jiang SL, Wang Y, Li W, Budoff MJ. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc Imaging* 2012; **5**: 990-999 [PMID: 23058065 DOI: 10.1016/j.jcmg.2012.06.006]

9 **Arbab-Zadeh A**, Nakano M, Virmani R, Fuster V. Acute coronary events. *Circulation* 2012; **125**: 1147-1156 [PMID: 22392862 DOI: 10.1161/CIRCULATIONAHA.111.047431]

10 **Libby P**. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 2013; **368**: 2004-2013 [PMID: 23697515 DOI: 10.1056/NEJMra1216063]

11 **Iwasaki K**, Matsumoto T, Aono H, Furukawa H, Samukawa M.

Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. *Clin Cardiol* 2011; **34**: 166-171 [PMID: 21337349]

12 **Agatston AS**, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15**: 827-832 [PMID: 2407762]

13 **Motoyama S**, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007; **50**: 319-326 [PMID: 17659199]

14 **Otsuka K**, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, Shimada K, Yoshiyama M. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging* 2013; **6**: 448-457 [PMID: 23498679 DOI: 10.1016/j.jcmg.2012.09.016]

15 **Nakazato R**, Shalev A, Doh JH, Koo BK, Gransar H, Gomez MJ, Leipsic J, Park HB, Berman DS, Min JK. Aggregate plaque volume by coronary computed tomography angiography is superior and incremental to luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. *J Am Coll Cardiol* 2013; **62**: 460-467 [PMID: 23727206 DOI: 10.1016/j.jacc.2013.04.062]

16 **Motoyama S**, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009; **54**: 49-57 [PMID: 19555840 DOI: 10.1016/j.jacc.2009.02.068]

17 **Fujimoto S**, Kondo T, Kodama T, Orihara T, Sugiyama J, Kondo M, Endo A, Fukazawa H, Nagaoka H, Oida A, Ikeda T, Yamazaki J, Takase S, Narula J. Coronary computed tomography angiography-based coronary risk stratification in subjects presenting with no or atypical symptoms. *Circ J* 2012; **76**: 2419-2425 [PMID: 22864230]

18 **Rosen BD**, Fernandes V, McClelland RL, Carr JJ, Detrano R, Bluemke DA, Lima JA. Relationship between baseline coronary calcium score and demonstration of coronary artery stenoses during follow-up MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Cardiovasc Imaging* 2009; **2**: 1175-1183 [PMID: 19833306 DOI: 10.1016/j.jcmg.2009.06.014]

19 **Ho JS**, Fitzgerald SJ, Stolfus LL, Wade WA, Reinhardt DB, Barlow CE, Cannaday JJ. Relation of a coronary artery calcium score higher than 400 to coronary stenoses detected using multidetector computed tomography and to traditional cardiovascular risk factors. *Am J Cardiol* 2008; **101**: 1444-1447 [PMID: 18471456 DOI: 10.1016/j.amjcard.2008.01.022]

20 **Iwasaki K**, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of non-calcified coronary plaque on 64-slice computed tomography in asymptomatic patients with zero and low coronary artery calcium. *Can J Cardiol* 2010; **26**: 377-380 [PMID: 20847965]

21 **Hausleiter J**, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schömig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006; **48**: 312-318 [PMID: 16843181]

22 **Villines TC**, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Lin FY, Maffei E, Raff GL, Min JK. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. *J Am Coll Cardiol* 2011; **58**: 2533-2540 [PMID: 22079127 DOI: 10.1016/j.jacc.2011.10.851]

23 **Hachamovitch R**, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; **32**: 1012-1024 [PMID: 21258084 DOI: 10.1093/eurheartj/ehq500]

24 **Johnson NP**, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Domínguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jiménez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, López-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014; **64**: 1641-1654 [PMID: 25323250 DOI: 10.1016/j.jacc.2014.07.973]

P- Reviewer: Kolettis TM, Said SAM, Schoenhagen P, Tomkin GH, Vermeersch P **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i8.488

World J Cardiol 2016 August 26; 8(8): 488-495
ISSN 1949-8462 (online)

SYSTEMATIC REVIEW

Acquired aortocameral fistula occurring late after infective endocarditis: An emblematic case and review of 38 reported cases

Salah AM Said, Massimo A Mariani

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

Massimo A Mariani, Thorax Centre, Department of Cardiac Surgery, University Medical Center Groningen, 9713 GZ Groningen, The Netherlands

Author contributions: Said SAM and Mariani MA contributed equally to the manuscript.

Conflict-of-interest statement: Authors have no conflict of interest in connection with the submitted manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at salah.said@gmail.com. Informed consent, verbal, was obtained for data sharing but the presented data are anonymized and risk of identification is negligible.

Manuscript source: Invited manuscript

Correspondence to: Salah AM Said, MD, PhD, FESC, Department of Cardiology, Hospital Group Twente, Geerdinksweg 141, 7555 DL Hengelo,
The Netherlands. salah.said@gmail.com
Telephone: +31-88-7085286
Fax: +31-88-7085289

Received: February 13, 2016
Peer-review started: February 16, 2016
First decision: April 15, 2016
Revised: May 5, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: August 26, 2016

Abstract

AIM

To delineate the features and current therapeutic option of congenital and acquired aortocameral fistulas (ACF) secondary to iatrogenic or infectious disorders.

METHODS

From a PubMed search using the term "aortocameral fistula", 30 suitable papers for the current review were retrieved. Reviews, case series and case reports published in English were considered. Abstracts and reports from scientific meetings were not included. A total of 38 reviewed subjects were collected and analyzed. In addition, another case - an adult male who presented with ACF between commissures of the right and non-coronary sinuses and right atrium as a late complication of Staphylococcus aureus infective endocarditis of the AV - is added, the world literature is briefly reviewed.

RESULTS

A total of thirty-eight subjects producing 39 fistulas were reviewed, analyzed and stratified into either congenital (47%) or acquired (53%) according to their etiology. Of all subjects, 11% were asymptomatic and 89% were symptomatic with dyspnea (21 ×) as the most common presentation. Diagnosis was established by a multidiagnostic approach in 23 (60%), single method in 14 (37%) (echocardiography in 12 and catheterization in 2), and at autopsy in 2 (3%) of the subjects. Treatment options included percutaneous transcatheter closure in 12 (30%) with the deployment of the Amplatzer duct or septal occluder and Gianturco coil and surgical correction in 24 (63%).

CONCLUSION

Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV. The management of ACF is generally by surgical correction but non-surgical device intervention has recently been introduced as a safe alternative.

Key words: Aortic-atrial shunt; Aortic-atrial fistulas; Infective endocarditis; Late complication; Surgical correction

Core tip: Aortocameral fistula is an uncommon complication of native aortic valve (AV) endocarditis, which is associated with high morbidity and mortality. Acquired aortocameral fistulas (ACF) may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF. Congenital fistulas are less commonly reported than the acquired types. Acquired ACF may occur late after an episode of endocarditis of the native AV. The management of ACF is generally by surgical correction but non-surgical device intervention has recently been introduced as a safe alternative. Another case is added and the world literature is briefly reviewed.

Said SAM, Mariani MA. Acquired aortocameral fistula occurring late after infective endocarditis: An emblematic case and review of 38 reported cases. *World J Cardiol* 2016; 8(8): 488-495 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/488.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.488

INTRODUCTION

Aortocameral fistulas (ACF) may be congenital[1] or acquired complicating acute aortic dissection[2] following an intimal tear in the vicinity and proximity of the aortic root or after aortic valve (AV) replacement[3]. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality. ACF may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF[4]. The clinical manifestations of ACF may include exertional dyspnea[2,5], chest pain[6,7], palpitation[6,8], congestive heart failure[9,10] and recurrent respiratory tract infection[11,12]. ACF may incidentally be found during routine preoperative examination[13]. Untreated ACF may cause significant morbidity and early mortality. The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF[5,6,8,9]. Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV. Another case of our own is added and the world literature is briefly reviewed.

MATERIALS AND METHODS

Literature search

From the PubMed search using the term "aortocameral fistula", 30 suitable papers for the current review were retrieved (Table 1). Reviews, case series and case reports published in English were considered. Abstracts and reports from scientific meetings were not included. From 30 publications, 38 reviewed subjects were collected and analyzed. Data were analyzed using descriptive statistics.

Statistical analysis

In contrast to classic meta-analysis, the outcome is defined here as the percentages of an event (without comparison) in observed patients.

Additional clinical case

An adult male presented with ACF between the junction of RCS-NCS and RA as a late complication of Staphylococcus aureus infective endocarditis (IE) of the native AV, is added.

A 44-year-old male survivor of a prior episode of *Staphylococcus aureus* IE of the native AV (1998) presented with a recent history of rapid fatigability (2008) during sporting activities. He was afebrile and a continuous murmur was heard. Laboratory results and chest X-ray were normal. Resting ECG depicted sinus rhythm with signs of left ventricular hypertrophy (LVH). Two-dimensional transthoracic Doppler echocardiography revealed mild LVH, the right ventricle (RV) was dilated and normokinetic, and the tricuspid AV had no vegetation. Color flow mapping revealed evidence of a high velocity shunt between the commissures of the right coronary sinus (RCS) and non-coronary sinuses (NCS) terminating into the right atrium (RA) (Figure 1, Supplementary material online, Video 1). Cardiac catheterization demonstrated a shunt between the aorta and the RA and normal left ventricular kinetics (Figure 2, Supplementary material online, Video 2). Hemodynamic evaluation revealed a significant left-to-right shunt (Qp: Qs = 2.0:1.0) with normal pulmonary vascular resistance, normal intracardiac pressures and high resting cardiac output of 10 L/min. Computed tomography and cardiovascular magnetic resonance were not available at that time. The fistula was surgically closed (2008). The fistula was surgically closed (2008). After establishing median sternotomy, extracorporeal circulation was performed through standard cannulation of the aorta and right atrium. The heart was arrested with antegrade and selective blood cardioplegia. On inspection, no infectious masses or evidence of abscess or vegetations were visible. Further inspection revealed that the ascending aorta was not dilated or calcified and the LV showed moderate hypertrophy. After aortotomy, the AV could be inspected, which was tricuspid with mild thickening and the fistula was clearly visible between the RCS and NCS terminating into RA. The fistula was closed with 4.0 prolene suture and pledgets. The patient could easily be weaned off after an uneventful procedure. Postoperative transesophageal echocardiography revealed no rest shunt flow. The patient had an uneventful postoperative course. The patient had uneventful postoperative course and regained his non-professional sporting activities without any limitations. After 8 years of follow-up, he remains free of symptoms. The fistula was closed by 4.0

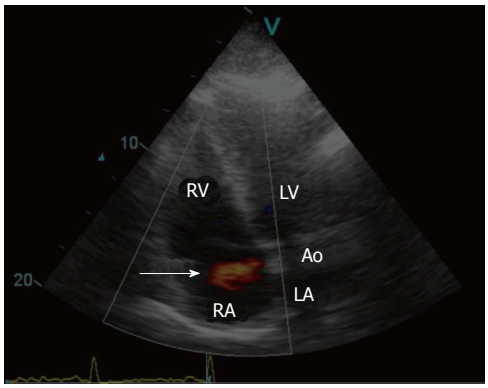

Figure 1 A frame of colored Doppler trans-thoracic echocardiography, five-chamber view illustrating the aortic-atrial fistula (arrow). Ao: Aorta; RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

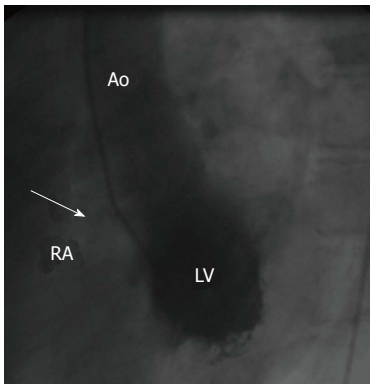

Figure 2 Levo-ventriculogram in the left anterior oblique view demonstrating the fistula (arrow) between the right and non-coronary sinuses communicating with the right atrium. RCS/NCS: Right and non-coronary sinuses; LV: Levo-ventriculogram; RA: Right atrium.

prolene suture and pledgets. The patient had uneventful postoperative course and regained his non-professional sporting activities without any limitations. After 7 years of follow-up, he remains free of symptoms.

RESULTS

A total of 38 subjects were reviewed [21 males (55%) and 17 females (45%)], with a mean age of 36.8 years (range 3-70 years). The etiology was congenital in 18 (47%) and acquired in 20 (53%). They all had 39 fistulas. Of those, 37 had a single and 1 had dual origin, with a similar outflow distribution of 37 single and one dual termination. Their origin was NCS in 21 (54%), RCS in 10 (26%), left coronary sinus (LCS) in 4 (10%) and the thoracic aorta in 4 (10%) of the subjects. The termination was into RA in 29 (74%), left atrium (LA) in 6 (15%), RV in 2 (5%), pulmonary artery in 1 (3%) and right ventricular outflow tract in 1 (3%). Four subjects (11%) were asymptomatic. In the symptomatic subjects (89%), the most common presentations were dyspnea (21 ×), followed by congestive heart failure (6 ×), chest pain (7 ×), palpitations (7 ×), IE (6 ×) with *Streptococcus mitis*[14] and *Staphylococcus epidermidis*[15]. Although syncope, hematuria, hemoptysis and recurrent respiratory tract infection are rarely reported, sudden death has also been observed[16].

Diagnosis was established by multidiagnostic approach in 23 (60%), a single method in 14 (37%) (echocardiography in 12 and catheterization in 2), and at autopsy in 2 (3%)[17] of the subjects. IE was found in 6 (16%) subjects, all originating from the NCS and communicating with the RA in 5 and the LA in one. Treatment included percutaneous transcatheter closure in 12 (30%) and surgical correction in 24 (63%) and there were 3 mortalities (7%) (Table 1).

DISCUSSION

An aortic-atrial fistula is an aortocameral fistula presenting as an extracardiac vascular communication that may be congenital[1] or acquired[2]. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality. In 1963, Kuipers *et al*[18] reported spontaneous ruptured aortic dissection into the right atrium. Congenital fistulas are less commonly reported than the acquired types. ACF may originate from any of the 3 sinuses of Valsalva. Acquired ACF may occur following bacterial endocarditis[19], acute aortic dissection[2], ruptured sinus of Valsalva aneurysm (RSVA)[19], and post-cardiovascular surgical procedures associated with[5] or without infective endocarditis (IE)[20-22]. Furthermore, ACF may occur after coronary artery bypass grafting[23], after mitral valve replacement[23], following repeat AV replacement[24] or secondary to iatrogenic endovascular injury during an invasive diagnostic procedure[4].

ACF may incidentally be found during routine preoperative examination[13] or presented with severe heart failure[2]. The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF[5,6,8,9].

In 1831, Hope[25] described a ruptured aneurysm of a sinus of Valsalva into the right atrium. Congenital or acquired aortic-atrial fistulas are rare anomalies. In 1924, a large autopsy series (n = 4000) revealed aorta to atrium fistula as an incidental finding; rupture was found in 1197, of which 13 were into the RA due to infectious, traumatic and atherosclerotic causes[26]. ACF may be congenital[1] or acquired complicating acute aortic dissection[2] following an intimal tear in the vicinity and proximity of the aortic root or after AV replacement[3] (Table 2). ACF may occur in patients with infective endocarditis[19], as was the case in the current patient and in 16% of the reviewed subjects.

Clinical presentation

Audible continuous murmur may raise suspicion for the presence of ACF[4]. The clinical manifestations of ACF may include exertional dyspnea[2,5], chest pain[6,7], palpitation[6,8], congestive heart failure[9,10] and recurrent respiratory tract infection[11,12]. Our patient presented with reduced physical fitness as the only symptom, occurring

Table 1 Clinical presentations and management of 39 subjects

Ref.	Age gender	ACF	Diagnostic modality	Clinical presentation/etiology	Management
Jung *et al*[19], 2011	49 M	NCS-right atrium	TTE	Dyspnea and high fever Ruptured sinus of Valsalva Infective endocarditis (Enterococcus gallinarum)	Patch repair AVR/TVR
Raufi *et al*[21], 2002	50 M	RCS-right atrium	TEE aortography cardiac cath	Dyspnea and chest pain Post-repair of aneurysm of right sinus of Valsalva	Repair of the ruptured sinus of Valsalva Closure of the fistula
Hsu *et al*[2], 2000	67 M	False lumen-Right atrium	TTE cardiac cath ioTEE	Dyspnea Acute aortic dissection	Fistula repair Bentall procedure
Chung *et al*[20], 2000	52 M	AAR-right atrium	TTE cardiac cath angiography MRI	Dyspnea and hemoptysis Post-repair (ARR) of acute aortic dissection	Closure of the fistula New composite aortic root graft
Ananthasubramaniam *et al*[24], 2005	66 M	LCS-left atrium	TTE TEE ioTEE	Dyspnea post-AVR	Surgical closure of the fistula/repair
Haddad *et al*[22], 2008	66 M	NCS-right atrium	TTE	Dyspnea post-repair of acute aortic dissection	Fistula repair Bentall procedure
Estévez-Loureiro *et al*[5], 2012	44 M	NCS-left atrium	TTE TEE MDCT CAG 3-D TEE	Dyspnea Infective endocarditis post-AVR (Streptococcus viridans)	Percutaneous Amplatzer vascular plug III occluder
Bouchez *et al*[13], 2012	61 M	LCS-left atrium	io TEE 3-D TEE	Asymptomatic	Conservative
Mundo-Sagardía *et al*[14], 2006	22 M	NCS-right atrium	TTE TEE	Infective endocarditis (Streptococcus mitis). Complex congenital heart disease. Perforation of sinus Valsalva aneurysm (NCS)	Closure/repair
Ladowski *et al*[4], 1984	56 F	NCS-right atrium	angiography	Iatrogenic dissection	Surgical closure/repair
Vydt *et al*[36], 2002	43 M	NCS-right atrium	TTE TEE cardiac cath angiography aortography	Chest pain, DOE, ruptured sinus Valsalva aneurysm	Surgical closure
Moiduddin *et al*[12], 2009	5 F	NCS-left atrium	TEE angiography cardiac cath	Amplatzer atrial septal occluder ASD PDA	Surgical closure/repair
Chandra *et al*[1], 2011	12 F	RCS-right atrium	TTE CTA aortography angiography cardiac cath	Dyspnea, palpitation	Percutaneous Amplatzer duct occluder
Noureddine *et al*[16], 2001	21 F	NCS-right atrium	TTE TEE	Dyspnea	Sudden death
Przybojewski *et al*[39], 1983	27 M	RCS/right atrium and right ventricle	Phonocardiography TTE cardiac cath angiography aortography	Dyspnea; biventricular heart failure, ruptured sinus Valsalva aneurysm (RCS)	Surgical closure/repair
Mujanovic *et al*[35], 2010	41 F	NCS-right atrium	TTE angiography	Heart failure; ruptured sinus Valsalva aneurysm (NCS)	Surgical closure/repair
Mello *et al*[33], 2005	16 F	NCS-left atrium	TTE TEE aortography	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASDII	Surgical closure/repair
Grayburn *et al*[7], 2005	41 F	Aorta-right atrium	TTE TEE	Chest pain, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Chun *et al*[30], 2003	10 M	NCS-right atrium	TTE TEE	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Knirsch *et al*[32], 2005	3 M	NCS-left atrium	TTE	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Jang *et al*[31], 2005	54 F	NCS-right atrium	TTE	Dyspnea, palpitation, hematuria, post-placement of Amplatzer atrial septal occluder (ASO) for ASDII	Surgical closure/repair
Ozay *et al*[45], 2007	22 F	NCS-right atrium	TTE TEE aortography cardiac catheter	Palpitation post-surgical repair of VSD and ASDII	Surgical closure/repair/correction
Elwatidy *et al*[46], 2003	3 F	Aortic isthmus-RA	TTE cardiac catheter	Presented as a case of PDA	Surgical closure/repair/correction
Akowuah *et al*[10], 2002	52 F	NCS-right atrium	TTE cardiac catheter	CHF, IE, TV, Staphylococcus aureus MRSA	Surgical TVR correction
Darwzah *et al*[15], 2006	23 M	NCS/LCS-right atrium	TTE	PVE of AVR Staphylococcus epidermidis	Surgical Re-re AVR correction
Russo *et al*[47], 2001	70 F	NCS-right atrium	TTE TEE	Chest pain, dyspnea, CHF complication of AAD type 1	Surgical closure/repair/correction
Onorato *et al*[9], 2005	48 F	NCS-right atrium	TTE TEE ICE aortography cardiac catheter	Dyspnea, CHF, ruptured sinus Valsalva aneurysm	ADO catheter closure

Chang *et al*[8], 2006	47, 22 F (2 ×) and 22,18M (2 ×)	NCS-RA (1 ×) RCS-RA (1 ×) and RCS-RV (2 ×)	4 × TEE 4 × aortography	Closure of VSD and AVR, IE (1 ×) Dyspnea and palpitation (3 ×)	ADO catheter closure (3 ×) and Gianturco coil (1 ×)
Szkutnik *et al*[6], 2009 congenital (4 ×) and acquired (1 ×)	51, 23, 41 M (3 ×) and 18, 28 F (2 ×)	RCS-RVOT (3 ×), RCS-RA (1 ×) LCS-PA (1 ×) and NCS-RA (1 ×)	TTE TEE MDCT	Dyspnea, chest pain, palpitation and syncope	ADO (5 ×) and ASO (1 ×) catheter closure
Oram *et al*[17], 1955	36, 67 M (2 ×)	NCS-RA RCS-RA, RV	Catheterization, autopsy	Chest pain, palpitation, dyspnea Chest pain, dyspnea	Post-mortem
Said and Mariani 2016	44 M	NCS-RCS-RA	TTE, aortography cardiac cath, angiography	Easy fatigability	Surgical closure

AAD: Acute aortic dissection; ACF: Aortocameral fistula; AAR: Aneurysm of the aortic root; ADO: Amplatzer duct occlude; ARR: Aortic root replacement; ASD: Atrial septal defect; ASO: Amplatzer atrial septal occlude; AVR: Aortic valve replacement; CHF: Congestive heart failure; CP: Chest pain; CTA: Computed tomography angiography; D: Dyspnea; DOE: Dyspnea on exertion; F: Female; ICE: Intra-cardiac echocardiography; IE: Infective endocarditis; io: Intra-operative; LCS: Left coronary sinus; M: Male; MDCT: Multi-detector computed tomography; MRI: Magnetic resonance imaging; NCS: Non-coronary sinus; PA: Pulmonary artery; PDA: Patent ductus arteriosus; PVE: Prosthetic valve endocarditis; RA: Right atrium; RCS: Right coronary sinus; RV: Right ventricle; RVOT: Right ventricular outflow tract; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; TV: Tricuspid valve; TVR: Tricuspid valve replacement; VSD: Ventricular septal defect.

Table 2 Etiology of aortocameral fistulas

Etiology	Condition/references
Congenital	Congenital RCS-RA fistula[1] and aortic isthmus-RA fistula[46]
Acquired-iatrogenic (post-surgical and non-surgical intervention/infectious/diagnostic procedures)	Iatrogenic aorta-right atrial fistula: late (14 years) post-surgical repair of VSD and ASD[45]
	Post-corrective surgery of sinus of Valsalva aneurysm[21]
	Post-CABG[23,48]
	Post-AVR[3,8]
	Post-MVR[23]
	Post-ARR, after operating on a type A dissection[20,47]
	Following ASO closure of the secundum ASD II [30]
	NVE[10], RCS/NCS-right atrial fistula (current case) secondary to NVE
	PVE[5,15]
	ACF associated with diagnostic cardiac catheterization (NCS-RAA)[4]
Acquired-accidental/traumatic	ACF post-non-penetrating thoracic injury[49] has been reported
Spontaneous	RSVA[27]
	Rupture of ascending aorta aneurysm[18]

ACF: Aortocameral fistula; ARR: Aortic root replacement; ASD: Atrial septal defect; ASO: Amplatzer atrial septal occlude; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement; NCS: Non-coronary sinus; NVE: Native valve endocarditis; PVE: Prosthetic valve endocarditis; RA: Right atrium; RAA: Right atrial appendage; RCS: Right coronary sinus; RSVA: Ruptured sinus Valsalva aneurysm; VSD: Ventricular septal defect.

late after the index native valve endocarditis. Among the 38 reviewed subjects, four (11%) were asymptomatic and the majority (89%) were symptomatic.

ACF may originate from any of the three sinuses of Valsalva, but origin from the NCS was infrequently reported[27]. Congenital aneurysms (origin RCS 65%-85%, NCS 10%-30% and LCS < 5%) of the sinus of Valsalva have a tendency to rupture, mainly into the right cardiac chambers (termination RV 63%, RA 32%), resulting in an ACF[28,29]. Congenital aneurysms of the sinus of Valsalva may be associated with other defects including bicuspid AV, ventricular septal defect and coarctation of the aorta[21].

ACF may occur between the aorta and right atrium[2], as was the case in our current patient, or left atrium[24]. Congenital ACF may be incidentally found in asymptomatic adult subjects[13]. There have been a few reports of iatrogenic acquired fistula formation associated with the percutaneous device closure of atrial septal defects with an Amplatzer septal occluder[30-33].

Congenital aortic-atrial fistulas are extremely rare. Acquired ACF are related to prosthetic valve disorders after aortic root repair associated with[5,15] or without infective endocarditis[22]. The current patient had a prior IE of the native AV. ACF may appear as an early[34], immediate[22] (10 d) or late (4 years)[5] postoperative complication.

Diagnostic modalities

Echocardiography [transthoracic (TTE), transesophageal (TEE) and 3-D TEE][7,32,35] is the first diagnostic modality of choice to precisely delineate the fistula components. With complete right and left cardiac catheterization and aortography of the aortic root, the fistula can be appropriately evaluated and the exact location indi-

cated[21,36]. TTE, TEE and 3-D TEE comprise a useful non-invasive diagnostic modality with which to delineate the fistula characteristics. With 2-D echocardiography, TEE, the clinical diagnosis of ACF may be established but ascending aortography is essential for confirmation and to differentiate from other disorders such as ruptured sinus of Valsalva aneurysm[36], aorta-right atrial tunnel[11] and acquired[37] or congenital[38] coronary cameral fistulas.

A multimodality imaging strategy confirms the diagnosis of ACF. Echocardiography (TTE and TEE), selective coronary angiography and retrograde aortography are used for visualization of the coronary ostia and demonstration of the course of the fistula[12,36]. This was the chosen approach in two-third (60%) of the reviewed subjects and in the presented case.

Computed tomography (CT) scan and cardiovascular magnetic resonance imaging (MRI): These diagnostic modalities were not widely applied among the reviewed subjects. In only few cases, CT scan[1,5,6] was performed and MRI technique was found in the case reported by Chung[20]. In our current case, CT and cardiovascular magnetic resonance were not available at that time and moreover, echocardiography and aortography provided adequate imaging quality of the ACF making further investigations unnecessary.

The most common termination sites of "spontaneously" ruptured aneurysms of coronary sinus of Valsalva are into the RA or RV[27,39]; more rarely, the left ventricle[27] may be involved, ensuing acute volume overload of the involved cardiac chamber. Our patient had an acquired aortic-right atrial connection.

The origin of congenital aneurysm is generally related to the right coronary sinus (65%-85%)[1,28,29,39] and those associated with infective endocarditis ensue from the left coronary sinus[40], RCS[41] or NCS[42].

Management

The first successful surgical correction of ruptured sinus Valsalva aneurysm (RSVA) was reported in 1957[43]. In 1966, Temple *et al*[44] described the successful surgical repair of aortic-right atrial fistula in an adult symptomatic male. ACF may be closed by surgical intervention[2] or by transcatheter device[5]. The treatment of choice is early surgical repair, which is necessary to prevent the development of severe symptoms and complications. Untreated ACF may cause significant morbidity and early mortality. Recently, percutaneous transcatheter treatment of ACF has been reported which is considered a novel method for selected cases[5]. Percutaneous transcatheter closure of ACF, using the Amplatzer duct occluder, Gianturco coil or Amplatzer septal occluder, has proven to be a safe technique which is gaining territory in the non-surgical management of ACF[5,6,8,9]. Our patient had a successful surgical repair with uneventful postoperative recovery.

Our current patient survived infective endocarditis of the AV occurring years prior to presentation. He remains well 7 years following the surgical correction.

ACKNOWLEDGMENTS

The assistance of the librarian of the medical library of Hospital Group Twente, Mrs. A. Geerdink during the preparation of the manuscript, catheterization laboratory personnel Almelo-Hengelo and personnel of Thorax Center Twente, Enschede are greatly acknowledged.

COMMENTS

Background

Aortocameral fistulas (ACF) may be congenital or acquired complicating acute aortic dissection following an intimal tear in the vicinity and proximity of the aortic root or after aortic valve (AV) replacement. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality.

Research frontiers

ACF may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF. The clinical manifestations of ACF may include exertional dyspnea, chest pain, palpitation, congestive heart failure and recurrent respiratory tract infection. ACF may incidentally be found during routine preoperative examination. Untreated ACF may cause significant morbidity and early mortality.

Innovations and breakthroughs

The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF. Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV.

Applications

This paper presents a case of acquired aortic-atrial fistulas occurring late after infective endocarditis of the aortic valve, the author reviewed 30 suitable papers and summarized the clinical feature, diagnostic modalities and management of such a disease.

Peer-review

The authors reviewed the published literature on the aortic-atrial fistulae, but also included several cases of similar connections that occurred between the aorta and other chambers including the ventricles, the left atrium and the pulmonary artery. The interesting side of the manuscript is the review rather than the clinical case. The review is well written and reports a total of 38 cases, presented in different clinical scenario.

REFERENCES

1 **Chandra S**, Vijay S, Kaur D, Dwivedi S. Congenital aorta right atrial fistula: successful transcatheter closure with the Amplatzer occluder. *Pediatr Cardiol* 2011; **32**: 1057-1059 [PMID: 21681644 DOI: 10.1007/s00246-011-0026-5]

2 **Hsu RB**, Chien CY, Wang SS, Chu SH. Aorto-right artrial fistula: a rare complication of aortic dissection. *Tex Heart Inst J* 2000; **27**: 64-66 [PMID: 10830634]

3 **Berman AD**, Come PC, Riley MF, Weintraub RM, Johnson RG, Aroesty JM. Two-dimensional and Doppler echocardiographic diagnosis of an aortic to right atrial fistula complicating aortic dissection. *J Am Coll Cardiol* 1987; **9**: 228-230 [PMID: 3794101 DOI: 10.1016/S0735-1097(87)80106-7]

4 **Ladowski JS**, Hardesty RL. Repair of an iatrogenic aortoatrial fistula. *Cathet Cardiovasc Diagn* 1984; **10**: 43-46 [PMID: 6713533 DOI: 10.1002/ccd.1810100110]

5 **Estévez-Loureiro R**, Salgado Fernández J, Vázquez-González N, Piñeiro-Portela M, López-Sainz Á, Bouzas-Mosquera A, Pombo F, Castro-Beiras A. Percutaneous closure of an aorto-atrial fistula after surgery for infective endocarditis. *JACC Cardiovasc Interv* 2012; **5**: e15-e17 [PMID: 22721671 DOI: 10.1016/j.jcin.2011.11.015]

6 **Szkutnik M**, Kusa J, Glowacki J, Fiszer R, Bialkowski J. Transcatheter closure of ruptured sinus of valsalva aneurysms with an Amplatzer occluder. *Rev Esp Cardiol* 2009; **62**: 1317-1321 [PMID: 19889343 DOI: 10.1016/S0300-8932(09)73084-2]

7 **Grayburn PA**, Schwartz B, Anwar A, Hebeler RF. Migration of an amplatzer septal occluder device for closure of atrial septal defect into the ascending aorta with formation of an aorta-to-right atrial fistula. *Am J Cardiol* 2005; **96**: 1607-1609 [PMID: 16310449 DOI: 10.1016/j.amjcard.2005.08.013]

8 **Chang CW**, Chiu SN, Wu ET, Tsai SK, Wu MH, Wang JK. Transcatheter closure of a ruptured sinus of valsalva aneurysm. *Circ J* 2006; **70**: 1043-1047 [PMID: 16864939 DOI: 10.1253/circj.70.1043]

9 **Onorato E**, Casilli F, Mbala-Mukendi M, Perlasca E, Santoro F, Bortone F, Arena V. Sudden heart failure due to a ruptured posterior Valsalva sinus aneurysm into the right atrium: feasibility of catheter closure using the Amplatzer duct occluder. *Ital Heart J* 2005; **6**: 603-607 [PMID: 16274025]

10 **Akowuah EF**, Casula R, Thanos A, Cooper GJ. Aorto-right atrial fistula associated with native tricuspid valve endocarditis. *J Cardiovasc Surg* (Torino) 2002; **43**: 841-842 [PMID: 12483176]

11 **Gajjar T**, Voleti C, Matta R, Iyer R, Dash PK, Desai N. Aorta-right atrial tunnel: clinical presentation, diagnostic criteria, and surgical options. *J Thorac Cardiovasc Surg* 2005; **130**: 1287-1292 [PMID: 16256780 DOI: 10.1016/j.jtcvs.2005.07.021]

12 **Moiduddin N**, Cheatham JP, Hoffman TM, Phillips AB, Kovalchin JP. Amplatzer septal occluder associated with late pulmonary venous obstruction requiring surgical removal with acquired aorta to left atrial fistula. *Am J Cardiol* 2009; **103**: 1039-1040 [PMID: 19327438 DOI: 10.1016/j.amjcard.2008.11.057]

13 **Bouchez S**, Wouters PF, Vandenplas G. Asymptomatic aorto-atrial fistula identified with intraoperative transesophageal echocardiography. *J Cardiothorac Vasc Anesth* 2012; **26**: e76-e77 [PMID: 22885119 DOI: 10.1053/j.jvca.2012.06.028]

14 **Mundo-Sagardía JA**, Johnson C, Calderón R, Quintana C. Coexistent congenital aortic defects, aneurysm of sinus of valsalva, atrial septal defect and infective endocarditis: a case report. *P R Health Sci J* 2006; **25**: 273-278 [PMID: 17203799]

15 **Darwazah A**, Kiswani M, Ismail H, Hawari M, Awad S. Aorto-right atrial fistula: a complication of prosthetic aortic valve endocarditis. A case report. *J Heart Valve Dis* 2006; **15**: 142-145 [PMID: 16480028]

16 **Noureddine M**, Raquim S, Elhattaoui M, Tahiri A, Chraibi N. [Aneurysm of the posterior sinus of Valsalva ruptured into right atrium]. *Ann Cardiol Angeiol* (Paris) 2001; **50**: 211-216 [PMID: 12555595 DOI: 10.1016/S0003-3928(01)00024-5]

17 **Oram S**, East T. Rupture of aneurysm of aortic sinus (of Valsalva) into the right side of the heart. *Br Heart J* 1955; **17**: 541-551 [PMID: 13269614 DOI: 10.1136/hrt.17.4.541]

18 **Kuipers FM**, Schatz IJ. Prognosis in dissecting aneurysm of the aorta. *Circulation* 1963; **27**: 658-661 [DOI: 10.1161/01.CIR.27.4.658]

19 **Jung TE**, Kim JH, Do HD, Lee DH. Simultaneous Aortic and Tricuspid Valve Endocarditis due to Complication of Sinus of Valsalva Rupture. *Korean J Thorac Cardiovasc Surg* 2011; **44**: 240-242 [PMID: 22263159 DOI: 10.5090/kjtcs.2011.44.3.240]

20 **Chung DA**, Page AJ, Coulden RA, Nashef SA. Aorto-atrial fistula after operated type A dissection. *Eur J Cardiothorac Surg* 2000; **17**: 617-619 [PMID: 10814930 DOI: 10.1016/S1010-7940(00)00406-1]

21 **Raufi A**, Khan IA, Nair VM, Rahmatullah SI, Rodriguez C, Sacchi TJ, Sahni G, Vasavada BC. Rupture of a surgically repaired sinus of Valsalva aneurysm. *J Clin Basic Cardiol* 2002; **5**: 199-200

22 **Haddad FG**, El-Nemnoum R, Haddad F, Maalouly G, El-Rassi I. Giant cell arteritis of the aorta: catastrophic complications without a preexisting aneurysm. *Eur J Intern Med* 2008; **19**: e59-e60 [PMID: 19013367 DOI: 10.1016/j.ejim.2008.03.011]

23 **Scalia D**, Rizzoli G, Scomparin MA, Testolin L, Isabella GB, Casarotto D. Aorto-right atrial fistula: a rare complication of aortic dissection type A. A report of two cases. *J Cardiovasc Surg* (Torino) 1997; **38**: 619-622 [PMID: 9461269]

24 **Ananthasubramaniam K**. Clinical and echocardiographic features of aorto-atrial fistulas. *Cardiovasc Ultrasound* 2005; **3**: 1 [PMID: 15655075 DOI: 10.1186/1476-7120-3-1]

25 **Hope J**. A treatise on the diseases of the heart and great vessels. 3rd ed. Germany: Nabu Press, 1839: 466-471

26 **Boyd LJ**. A study of four thousand reported cases of aneurysm of the thoracic aorta. *Am J Med Sci* 1924; **168**: 654-668 [DOI: 10.1097/00000441-192411000-00006]

27 **Babacan KM**, Tasdemir O, Zengin M, Karagöz HY, Zorlutuna YI, Ozer C, Sagban M, Yakut C, Bayazit K. Fistulous communication of aortic sinuses into the cardiac chambers. Fifteen years surgical experience and a report of 23 patients. *Jpn Heart J* 1986; **27**: 865-870 [PMID: 3573301 DOI: 10.1536/ihj.27.865]

28 **Katz ES**, Cziner DG, Rosenzweig BP, Attubato M, Feit F, Kronzon I. Multifaceted echocardiographic approach to the diagnosis of a ruptured sinus of Valsalva aneurysm. *J Am Soc Echocardiogr* 1991; **4**: 494-498 [PMID: 1742038 DOI: 10.1016/S0894-7317(14)80384-2]

29 **Chow LC**, Dittrich HC, Dembitsky WP, Nicod PH. Accurate localization of ruptured sinus of Valsalva aneurysm by real-time two-dimensional Doppler flow imaging. *Chest* 1988; **94**: 462-465 [PMID: 3044698 DOI: 10.1378/chest.94.3.462]

30 **Chun DS**, Turrentine MW, Moustapha A, Hoyer MH. Development of aorta-to-right atrial fistula following closure of secundum atrial septal defect using the Amplatzer septal occluder. *Catheter Cardiovasc Interv* 2003; **58**: 246-251 [PMID: 12552551 DOI: 10.1002/ccd.10434]

31 **Jang GY**, Lee JY, Kim SJ, Shim WS, Lee CH. Aorta to right atrial fistula following transcatheter closure of an atrial septal defect. *Am J Cardiol* 2005; **96**: 1605-1606 [PMID: 16310448 DOI: 10.1016/j.amjcard.2005.08.012]

32 **Knirsch W**, Dodge-Khatami A, Balmer C, Peuster M, Kadner A, Weiss M, Prêtre R, Berger F. Aortic sinus-left atrial fistula after interventional closure of atrial septal defect. *Catheter Cardiovasc Interv* 2005; **66**: 10-13 [PMID: 15977262 DOI: 10.1002/ccd.20436]

33 **Mello DM**, Fahey J, Kopf GS. Repair of aortic-left atrial fistula following the transcatheter closure of an atrial septal defect. *Ann Thorac Surg* 2005; **80**: 1495-1498 [PMID: 16181899 DOI: 10.1016/j.athoracsur.2004.03.098]

34 **Patsouras D**, Argyri O, Siminilakis S, Michalis L, Sideris D. Aortic dissection with aorto-left atrial fistula formation soon after aortic valve replacement: A lethal complication diagnosed by transthoracic and transesophageal echocardiography. *J Am Soc Echocardiogr* 2002; **15**: 1409-1411 [PMID: 12415238 DOI: 10.1067/mje.2002.121609]

35 **Mujanovic E**, Kabil E, Bergsland J, Stanimirovic-Mujanovic S, Caluk J. Ruptured aneurysm of the noncoronary sinus of valsalva into the right atrium. *Med Arh* 2010; **64**: 307-308 [PMID: 21287960]

36 **Vydt T**, Smolders W, Rademakers F. A massive left-to-right shunt due to a ruptured giant aneurysm of the sinus of Valsalva. *Acta Cardiol* 2002; **57**: 449-451 [PMID: 12542126 DOI: 10.2143/AC.57.6.2005472]

37 **Said SA**, Schiphorst RH, Derksen R, Wagenaar LJ. Coronary-cameral fistulas in adults: Acquired types (second of two parts). *World J Cardiol* 2013; **5**: 484-494 [PMID: 24432186 DOI: 10.4330/wjc.v5.i12.484]

38 **Said SA**, Nijhuis RL, Akker JW, Takechi M, Slart RH, Bos JS, Hoorntje CR, Houwelingen KG, Bakker-de Boo M, Braam RL, Vet TM. Unilateral and multilateral congenital coronary-pulmonary fistulas in adults: clinical presentation, diagnostic modalities, and management with a brief review of the literature. *Clin Cardiol* 2014; **37**: 536-545 [PMID: 25196980 DOI: 10.1002/clc.22297]

39 **Przybojewski JZ**, Blake RS, de Wet Lubbe JJ, Rossouw J, van der Walt JJ. Rupture of sinus of Valsalva aneurysm into both right atrium and right ventricle. A case report. *S Afr Med J* 1983; **63**: 616-625 [PMID: 6845062]

40 **Ebringer A**, Goldstein G, Sloman G. Fistula between aorta and left atrium due to bacterial endocarditis. *Br Heart J* 1969; **31**: 133-135 [PMID: 5764960 DOI: 10.1136/hrt.31.1.133]

41 **Farouque HM**, Worthley SG, Yeend RA. Aortico-atrial fistula secondary to bacterial endocarditis. *Heart* 2001; **86**: 498 [PMID: 11602538 DOI: 10.1136/heart.86.5.498]

42 **Chen MY**, Zhong DD, Ying ZQ. Aorta-to-right atrium fistula, an unusual complication of endocarditis. *J Zhejiang Univ Sci B* 2009; **10**: 230-232 [PMID: 19283878 DOI: 10.1631/jzus.B0820229]

43 **Lillehei CW**, Stanley P, Varco RL. Surgical treatment of ruptured aneurysms of the sinus of Valsalva. *Ann Surg* 1957; **146**: 459-472 [PMID: 13459295 DOI: 10.1097/00000658-195709000-00014]

44 **Temple TE**, Rainey RL, Anabtawi IN. Aortico-atrial shunt due to rupture of a dissecting aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg* 1966; **52**: 249-254 [PMID: 4225905]

45 **Ozay B**, Okmen AS, Idiz M, Okmen E, Ketenci B, Yekeler I. Aorta-right atrial fistula after VSD operation. *Thorac Cardiovasc Surg* 2007;

55: 122-123 [PMID: 17377867 DOI: 10.1055/s-2006-924411]
46 **Elwatidy AF**, Galal AN, Rhydderch D, Ashmeg AK. Aorto-right atrial fistula. *Ann Thorac Surg* 2003; **76**: 929-931 [PMID: 12963235 DOI: 10.1016/S0003-4975(03)00448-X]
47 **Russo C**, De Chiara F, Bruschi G, Ciliberto GR, Vitali E. Aorto-atrial fistula through the septum in recurrent aortic dissection. *Ann Thorac Surg* 2001; **72**: 921-922 [PMID: 11565686 DOI: 10.1016/S0003-4975(00)02478-4]
48 **Hurley DV**, Nishimura RA, Schaff HV, Edwards WD. Aortic dissection with fistula to right atrium. Noninvasive diagnosis by two-dimensional and Doppler echocardiography with successful repair. Case report and review of the literature. *J Thorac Cardiovasc Surg* 1986; **92**: 953-957 [PMID: 3773552]
49 **Chang H**, Chu SH, Lee YT. Traumatic aorto-right atrial fistula after blunt chest injury. *Ann Thorac Surg* 1989; **47**: 778-779 [PMID: 2730200 DOI: 10.1016/0003-4975(89)90146-X]

P- Reviewer: Al-Mohammad A, Formica F, Hua P
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com