ISSN 2222-0682 (online)

World Journal of *Methodology*

World J Methodol 2017 June 26; 7(2): 33-72

Published by Baishideng Publishing Group Inc

World Journal of Methodology

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

Editorial Board

2016-2019

The *World Journal of Methodology* Editorial Board consists of 618 members, representing a team of worldwide experts in methodology. They are from 59 countries, including Argentina (6), Australia (17), Austria (5), Belgium (3), Brazil (7), Bulgaria (2), Canada (14), Chile (2), China (66), Colombia (1), Croatia (2), Cuba (1), Cyprus (2), Czech Repoublic (6), Denmark (4), Egypt (11), Finland (3), France (10), Germany (16), Greece (10), Hungary (5), India (24), Iran (7), Ireland (1), Israel (5), Italy (68), Japan (29), Jordan (1), Lithuania (2), Malaysia (5), Martinique (1), Mexico (5), Netherlands (6), New Zealand (1), Norway (3), Oman (1), Pakistan (2), Poland (7), Portugal (8), Romania (8), Russia (4), Saudi Arabia (2), Senegal (1), Serbia (1), Singapore (3), Slovenia (1), South Africa (1), South Korea (13), Spain (21), Sweden (4), Switzerland (1), Thailand (7), Trinidad and Tobago (1), Turkey (15), Uganda (1), United Arab Emirates (1), United Kingdom (26), United States (137), and Uruguay (1).

EDITOR-IN-CHIEF

Yicheng Ni, *Leuven*

ASSOCIATE EDITORS

Guido Gainotti, *Rome*
António Vaz Carneiro, *Lisboa*
Val Gebski, *Sydney*
Bo Hang, *Berkeley*
George A Kelley, *Morgantown*
Sang-Soo Lee, *Chuncheon*
Gerhard Litscher, *Graz*

GUEST EDITORIAL BOARD MEMBERS

Wen-Hsiung Chan, *Chung Li*
John WC Chang, *Taoyuan*
Long-Sen Chang, *Kaohsiung*
Gwo-Shing Chen, *Kaohsiung*
Tsung-Chi Cheng, *Taipei*
Yuh-Shan Ho, *Taichung*
Shuchen Hsieh, *Kaohsiung*
Chien-Han Lai, *Taipei*
Ping-Shan Lai, *Taichung*
Shih-Chang Lin, *Taipei*
Hung-Jen Liu, *Taichung*
Ko-Huang Lue, *Taichung*
Rong-Jong Wai, *Chung Li*
Chin-Tsan Wang, *I-Lan*
Yau-Huei Wei, *New Taipei City*
Ching-Feng Weng, *Hualien*
Cheuk-Kwan Sun, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD

Argentina

Paula Abate, *Córdoba*
José Miguel Belizán, *Buenos Aires*
Rodolfo Rey, *Buenos Aires*
Enrique Roberto Soriano, *Buenos Aires*
Alejandro Sosnik, *Buenos Aires*
Rodolfo G Wuilloud, *Mendoza*

Australia

Felix Acker, *Melbourne*
Seetal Dodd, *Geelong*
Guy D Eslick, *Sydney*
Gaoqian Feng, *Melbourne*
Daniel A Galvao, *Joondalup*
Adrian J Gibbs, *Canberra*
Phillipa J Hay, *Sydney*
Moyez Jiwa, *Bentley*
Pupalan Iyngkaran, *Northcote*
Michael HJ Maes, *Geelong*
Sanjay Patole, *Perth*
Clive JC Phillips, *Gatton*
Janine Stevenson, *Wentworthville*
Zhonghua Sun, *Perth*
Shuhong Wang, *Adelaide*
Ming Wei, *Gold Coast*
Jiake Xu, *Crawley*

Austria

Gerwin A Bernhardt, *Graz*
Siegfried Trattnig, *Vienna*
Martin Voracek, *Vienna*
Andreas Weinhausel, *Vienna*

Belgium

Zeger Debyser, *Leuven*
Piet K Vanhoenacker, *Aalst*

Brazil

Monica L Andersen, *São Paulo*
Mariana de Andrea Hacker, *Rio de Janeiro*
Fábio S Lira, *Sao Paulo*
Delfim Soares Júnior, *Juiz de Fora*
Moacyr A Rebello, *Rio de Janeiro*
Flavio A Sekeff-Sallem, *Sao Paulo*
Luci F Teixeira-Salmela, *Belo Horizonte*

Bulgaria

Todor Dudev, *Sofia*
Yavor Enchev, *Varna*

Canada

Ahmed M Abou-Setta, *Edmonton*

Amir Azarpazhooh, *Toronto*
Tarik Zine Belhocine, *Toronto*
Kenneth R Chapman, *Toronto*
Issam El Naqa, *Montreal*
Martin A Katzman, *Toronto*
Alejandro Lazo-Langner, *London*
Richard WJ Neufeld, *London*
Prakesh S Shah, *Toronto*
Bhagirath Singh, *London*
Léon C van Kempen, *Montreal*
Yuzhuo Wang, *Vancouver*
Man Yu, *Toronto*
Haishan Zeng, *Vancouver*

Chile

Emilio A Herrera, *Santiago*
Mauricio Venegas, *Santiago*

China

Deng-Feng Cao, *Beijing*
Gilbert Y S Chan, *Hong Kong*
George G Chen, *Hong Kong*
William CS Cho, *Hong Kong*
Raymond Chuen-Chung, *Hong Kong*
Meng-Jie Dong, *Hangzhou*
Jun-Bao Du, *Beijing*
Zhi-Sheng Duan, *Beijing*
Hani El-Nezami, *Hong Kong*
Shen Gao, *Shanghai*
Wei-Qiang Gao, *Shanghai*
Rajiv Kumar Jha, *Xi'an*
Lin Jia, *Guangzhou*
Chun-Ping Jiang, *Nanjing*
Gang Jin, *Beijing*
Vincent Lai, *Hong Kong*
Huang-Xian Ju, *Nanjing*
Fan-Sheng Kong, *Jinan*
Joey Sum-Wing Kwong, *Hong Kong*
Hui Li, *Zhejiang*
Yun-Feng Lin, *Chengdu*
Hong Liu, *Nantong*
Wing-Yee Lui, *Hong Kong*
Feng-Ming Luo, *Chengdu*
Jing-Yun Ma, *Beijing*
Zheng Ma, *Beijing*
Ling-Jie Meng, *Xi'an*
Hong-Xiang Sun, *Hangzhou*
Nian-Sheng Tang, *Kunming*
Bo-Chu Wang, *Chongqing*
Ji-Bo Wang, *Shenyang*
Zhi-Ming Wang, *Chengdu*
Chuan-Lai Xu, *Wuxi*
Hui-Xiong Xu, *Shanghai*
Tong-Wen Xu, *Hefei*
Shi-Ying Xuan, *Qingdao*
Xi-Lin Yang, *Hong Kong*
Dengfu Yao, *Nantong*
He-Rui Yao, *Guangzhou*
Bang-Ce Ye, *Shanghai*
Yi-Cong Ye, *Beijing*
Fu-Zai Yin, *Qinhuangdao*
Jin-Hua Yu, *Nanjing*
Jin-Tai Yu, *Qingdao*
Wen-Wu Yu, *Nanjing*
Zhong-Heng Zhang, *Jinhua*
Zhong-Ying Zhao, *Hong Kong*
Chun-Fu Zheng, *Wuhan*
Shao-Bing Zhou, *Chengdu*
Jun-Jie Zhu, *Nanjing*

Colombia

Angela Dominguez, *Cali*

Croatia

Marijeta Kralj, *Zagreb*
Ivana Maric, *Rijeka*

Cuba

Mariano R Ricard, *Habana*

Cyprus

George J Kontoghiorghes, *Limassol*
Dimitrios Stasinopoulos, *Nicosia*

Czech Republic

Kamil Kuca, *Hradec Kralove*
Bozena Novotna, *Prague*
Jan Plzak, *Prague*
Jiri Sedy, *Prague*
David Skoloudik, *Ostrava*
Miroslav Sip, *Ceske Budejovice*

Denmark

Jorgen R Jepsen, *Esbjerg*
Hans E Johnsen, *Aalborg*
Lars J Petersen, *Aalborg*
Hans Sanderson, *Roskilde*

Egypt

Asmaa G Abdou, *Shebein Elkom*
Mohammed F Amin, *Elminya*
ASM Arafa, *Dokki*
Hussein M Atta, *El- Minia*
Hala Salah Elwakil, *Cairo*
Maysaa El Sayed Zaki, *Mansoura*
Mustafa Abdel Hafiz El Sherbini, *Cairo*
Kamal K Gadalla, *Tanta*
Ashraf A Khalil, *Alexandria*
Ahmad Nofal, *Zagazig*
Nervana SH Bayoumi, *Cairo*

Finland

Ilmo H Kellokumpu, *Jyvaskyla*
Terho Lehtimaki, *Tampere*
Simo Saarakkala, *Oulu*

France

Marc Y Bardou, *Dijon*
Mohammed M Bettahar, *Nancy*
Niko Hildebrandt, *Orsay*
Guido Kroemer, *Villejuif*
Florian Lesage, *Valbonne*
Patrick Maison, *Creteil*
Sandrine Marquet, *Marseille*
Yolanda Prezado, *Grenoble*
JM Regimbeau, *Amiens*
Jean Y Rotge, *Bordeaux*

Germany

Hojjat Ahmadzadehfar, *Bonn*
Henryk Barthel, *Leipzig*
Harald Hampel, *Frankfurt*
Stefan Holdenrieder, *Bonn*
Joachim Jankowski, *Berlin*
Dmitrij Kollins, *Regensburg*
Philipp le Coutre, *Berlin*
Zoltan Lukacs, *Hamburg*
Jan-Christoffer Luers, *Cologne*
Margarete Odenthal, *Cologne*
Frank Peinemann, *Cologne*
Nikolai G Rainov, *Augsburg*
Stefan Reuter, *Münster*
M Lienhard Schmitz, *Giessen*
Alfons Schnitzler, *Duesseldorf*
Frank Werner, *Magdeburg*

Greece

Konstantinos P Economopoulos, *Athens*
Don M Estes, *Athens*
Georgios A Koumantakis, *Patra*
Michael Koutsilieris, *Athens*
Giannis Mountzios, *Athens*
Demosthenes Panagiotakos, *Athens*
Issidora Papassideri, *Athens*
Falaras Polycarpos, *Pallini Attikis*
Paschalis Steiropoulos, *Alexandroupolis*
George Vaos, *Alexandroupolis*

Hungary

László Czakó, *Szeged*
Jozsef G Joo, *Budapest*
Péter Halász, *Budapest*
András Komócsi, *Pécs*
László Vécsei, *Szeged*

India

Chandrasekhar Bal, *New Delhi*
Pranjal Chandra, *Guwahati*
Dipshikha Chakravortty, *Bangalore*
Mukul Das, *Lucknow*
Pankaj K Garg, *Delhi*
Ravindra K Garg, *Lucknow*
Neeta D Grover, *Sangli*
KP Haresh, *New Delhi*
Devinder K Dhawan, *Chandigarh*
R Jayakumar, *Cochin*
Rudagi Kavita, *Wardha*
Abdul V Khan, *Aligarh*
Geetha Manivasagam, *Vellore*
Bijoy P Mathew, *Delhi*

MS Muthu, *Varanasi*
T Padma, *Salem*
Jacob Peedicayil, *Vellore*
Yenamandra S Prabhakar, *Lucknow*
Kaushal K Prasad, *Chandigarh*
Debasish Sarkar, *Rourkela*
Prashant Sharma, *Chandigarh*
Baljinder Singh, *Chandigarh*
Rakesh K Sinha, *Jharkhand*
Divya Vohora, *New Delhi*

Iran

Mohammad HK Ansari, *Urmia*
Azam Bolhassani, *Tehran*
Hafez T Fakheri, *Sari*
Mehran Javanbakht, *Tehran*
Enayat Kalantar, *Sanandaj*
Shekoufeh Nikfar, *Tehran*
Babak Saedi, *Tehran*

Ireland

Arpad Palfi, *Dublin*

Israel

Rami M Abu Fanne, *Jerusalem*
Itay Ben-Zion, *Tel Hashomer*
Dan Frenkel, *Tel Aviv*
Tamar Tadmor, *Hifa*
Eliezer Shalev, *Haifa*

Italy

Michele Anzidei, *Rome*
Emira Ayroldi, *Perugia*
Zora Baretta, *Padova*
Silvio Bellino, *Turin*
Guido Bocci, *Pisa*
Carlo Bonanno, *Vicenza*
Paolo Borrione, *Rome*
Francesco Boscia, *Bari*
Francesco Brigo, *Verona*
Filippo Cademartiri, *Giovanni XXIII*
Marco Casaccia, *Genova*
Sergio Casciaro, *Lecce*
Alberto Chiesa, *Romer*
Claudio Chiesa, *Rome*
Marco M Ciccone, *Bari*
Annamaria Cimini, *L'Aquila*
Antonio Crovace, *Bari*
Claudio Dazzi, *Ravenna*
Giovanni Di Leo, *San Donato Milanese*
Gabriele Di Lorenzo, *Palermo*
Francesco Doglietto, *Rome*
Rosario Donato, *Perugia*
Pasquale Esposito, *Pavia*
Maria F Faienza, *Bari*
Umberto Falcone, *Naples*
Alfio Ferlito, *Udine*
Giovanna Ferraioli, *Pavia*
Patrizia Ferroni, *Rome*
Maurizio Fiasché, *Milan*
Irene Floriani, *Milan*
Stefano Girotti, *Bologna*
Stefania Gonfloni, *Rome*
Roberto Grassi, *Napoli*
Paola Irato, *Padua*
Michelangelo Mancuso, *Pisa*
Giovanni Mantovani, *Cagliari*
Santino Marchi, *Pisa*
Giovanni Martinotti, *Rome*
Mario Mascalchi, *Florence*
Patrizia Mecocci, *Perugia*
Vincenzo G Mirone, *Naples*
Simone Mocellin, *Padua*
Giuseppe Murdaca, *Genova*
Vincenzo Neri, *Foggia*
Robert Nistico, *Rome*
Germano Orrù, *Cagliari*
Paola Perego, *Milan*
Raffaele Pezzilli, *Bologna*
Giusepe Piccione, *Messina*
Umberto Romeo, *Rome*
Maurizio Pompili, *Rome*
Stefano Pontone, *Rome*
Roberto Ria, *Bari*
Carlo Riccardi, *Perugia*
AC Rossi, *Bari*
Domenico Rubello, *Rovigo*
Ferdinando C Sasso, *Naples*
Antonio Sommariva, *Padova*
Francesco Soldovieri, *Napoli*
Gianfranco Spalletta, *Rome*
Alberto Spalice, *Roma*
Gambardella Stefano, *Rome*
Giovanni Storto, *Rionero*
Achille Tarsitano, *Bologna*
Carlo Torti, *Catanzaro*
Giovanni L Tripepi, *Reggio Calabria*
Mauro Valtieri, *Rome*

Japan

Kohei Akazawa, *Niigata*
Minoru Fukuda, *Nagasaki*
Masafumi Goto, *Miyagi*
Koichi Hattori, *Tokyo*
Satoshi Hirohata, *Okayama*
Yukihiro Ikeda, *Osaka-sayama*
Hiroo Imazu, *Tokyo*
Yasuhiro Ito, *Kobe*
Tatehiro Kagawa, *Isehara*
Kazuhiro Kasai, *Morioka*
Hitoshi Kawamata, *Shimotsuga*
Tomoyuki Kawase, *Niigata*
Mitsuhiro Kawata, *Tsukuba*
Kazushi Kishi, *Wakayama*
Masahiro Kohzuki, *Sendai*
Yoshinori Marunaka, *Kyoto*
Kenji Miura, *Saitama*
Ryuichi Morishita, *Suita*
Koichi Nagata, *Shimotsuke-shi*
Akinori Nakamura, *Matsumoto*
Atsushi Nanashima, *Nagasaki*
Mitsuhiko Noda, *Tokyo*
Kenoki Ohuchida, *Fukuoka*
Naoki Oiso, *Osaka-Sayama*
Yurai Okaji, *Tokyo*
Hirosato Seki, *Osaka*
Minoru Tomizawa, *Yotsukaido City*
Yutaka Tonomura, *Toyonaka*
Hisanori Umehara, *Ishikawa*

Jordan

Mohammad Y Khassawneh, *Irbid*

Lithuania

Giedrius Barauskas, *Kaunas*
A Bunevicius, *Palanga*

Malaysia

Subash CB Gopinath, *Perlis*
Yeong Y Lee, *Kota Bahru*
Veeranoot Nissapatorn, *Kuala Lumpur*
Subhada P Pani, *Ipoh*
Iis Sopyan, *Kuala Lumpur*

Martinique

Vincent Vinh-Hung, *Fort-de-France*

Mexico

Javier Camacho, *Mexico City*
Elvira G Gonzalez, *Monterrey*
Juan M Mejia-Arangure, *Mexico*
Martha Rodríguez-Moran, *Durango*
Julio Sotelo, *Mexico City*

Netherlands

Rienk E Jeeninga, *Amsterdam*
Bart J Polder, *Nijmegen*
Wiep Scheper, *Amsterdam*
Frank NM Twisk, *Limmen*
Paulus J van Diest, *Utrecht*
Arjan Vissink, *Groningen*

New Zealand

Valery Feigin, *Auckland*

Norway

Sara Germans, *Nord-Trondelag*
Cato Gronnerod, *Oslo*
David F Mota, *Oslo*

Oman

Mohamed Mabruk, *Muscat*

Pakistan

Muhammad A Noor, *Islamabad*
Yasir Waheed, *Islamabad*

Poland

Andrzej M Bugaj, *Poznań*
Piotr Dziegiel, *Wroclaw*
Dominik Golicki, *Warszawa*
Barbara M Jarzab, *Gliwice*
Tadeusz Robak, *Lodz*
Dorota I Wasko-Czopnik, *Wroclaw*
Cezary W Watala, *Lodz*

Portugal

Sofia Braga, *Lisbon*
Ilídio J Correia, *Covilha*
Paula Freitas, *Porto*
Nuno Lunet, *Porto*
Fernando Ribeiro, *Aveiro*
Hugo Sousa, *Porto*
Fernando SRR Teles, *Lisboa*

Romania

Radu Albulescu, *Bucharest*
Bogdan N Manolescu, *Bucharest*
Elena Moldoveanu, *Bucharest*
Monica Neagu, *Bucharest*
Florin-Dan Popescu, *Bucharest*
Eugen Rusu, *Galati*
Aurora Szentagotai, *Cluj-Napoca*
Cristiana P Tanase, Bucharest

Russia

Zhanna E Belaya, Moscow
Galina B Bolshakova, *Moscow*
Nikolay V Klassen, *Chernogolovka*
Sergey V Dorozhkin, *Moscow*

Saudi Arabia

Fawad Javed, *Riyadh*
Abdulhamit Subasi, *Jeddah*

Senegal

Badara Cissé, *Dakar*

Serbia

Branka S Radojcic, *Novi Sad*

Singapore

Desmond Heng, *Singapore*
Thomas WaiThong Ho, *Singapore*
Yong Zhang, *Singapore*

Slovenia

Tomaz Velnar, *Ljubljana*

South Africa

Robin A Emsley, *Cape Town*

South Korea

Byeong-Cheol Ahn, *Daegu*
Yongdoo Choi, *Goyang*
Sang Soo Hah, *Seoul*
Tae-Ho Hwang, *Busan*
Soung Won Jeong, *Seoul*
Beom Joon Kim, *Seoul*
Young-Jin Kim, *Hwasun*
Chang-Yong Lee, *Kongju*
Kwan Sik Lee, *Seoul*
Jong-Lyel Roh, *Seoul*
Yun Kyoung Yim, *Daejeon*
Myonggeun Yoon, *Seoul*

Spain

Salvador F Alino PelliIcer, *Valencia*
Mohamed F Allam, *Córdoba*
Alejandro Cifuentes, *Madrid*
Miren Lopez de Alda, *Barcelona*
Joaquin de Haro, *Madrid*
Carlos Gonzalez-Juanatey, *Lugo*
Emma Garcia-Meca, *Murcia*
Mónica H Giménez, *Zaragoza*
Josep M Guerrero, *Barcelona*
Antonio J Jara, *Murcia*
David Lobo, *Santander*
Fernando Marin, *Madrid*
José A Roldán Nofuentes, *Granada*
José A Orosa, *A Coruña*
Jesús Osada, *Zaragoza*
Bernardino Roca, *Castellón de la Plana*
Soledad Rubio, *Córdoba*
Helmut Schröder, *Barcelona*
Jesus Simal-Gandara, *Ourense*
Gabriela Topa, *Madrid*
Miguel A Vallejo, *Madrid*

Sweden

Stefan Karlsson, *Lund*
Maria Koltowska-Haggstrom, *Stockholm*
Ludmilla Morozova-Roche, *Umea*
Jenny Selander, *Stockholm*

Switzerland

Giorgio Treglia, *Bellinzona*

Thailand

Amporn Jariyapongskul, *Bangkok*
Rungroj Krittayaphong, *Bangkok*
Sombat Muengtaweepongsa, *Pathum Thani*
Apiwat Mutirangura, *Bangkok*
Kittisak Sawanyawisuth, *Khon Kaen*
Bungorn Sripanidkulchai, *Khon Kaen*
Chonlaphat Sukasem, *Bangkok*

Trinidad and Tobago

Rao R Suresh, *Mt.Hope*

Turkey

Kemal Behzatoglu, *Istanbul*
Mehmet Dogan, *Balikesir*
Cevdet Duran, *Konya*
Ilknur I Gumus, *Ankara*
Serkan Kahyaoglu, *Ankara*
Oner Mentes, *Ankara*
Tomris Ozben, *Antalya*
Emin Ozkaya, *Istanbul*
Ferda E Percin, *Ankara*
Kemal Polat, *Bolu*
Funda Saglam, *Aydin*
Seckin Tuncer, *Konya*
Nurver S Turfaner, *Istanbul*
Ahmet Yildirim, *Bornova-Izmir*
Aysegul Yildiz, *Izmir*

Uganda

Vincent Batwala, *Mbarara*

United Arab Emirates

Hassib Narchi, *Al Ain*

United Kingdom

Nadeem A Afzal, *Southampton*
Suhail Anwar, *Huddersfield*
Richard H Barton, *London*
Simon Bramhall, *Hereford*
Paolo De Coppi, *London*
Paul C Evans, *Sheffield*
Giuseppe Garcea, *Leicester*
Marta I Garrido, *London*
David E Gilham, *Manchester*
Richard O Jenkins, *Leicester*
Sinead Keeney, *Northern Ireland*
Ji-Liang Li, *Plymouth*
Tracey A Martin, *Cardiff*
Maurice J O'Kane, *Northern Ireland*
Abdullah Pandor, *Sheffield*
Susan Pang, *Middlesex*
Dmitry Pchejetski, *London*
Robert Perneczky, *London*
Shahzad G Raja, *London*
Pankaj Sharma, *London*
Sami M Shimi, *Dundee*
Andrew H Sims, *Edinburgh*
David E Whitworth, *Aberystwyth*
Jenny Worthington, *Coleraine*
Feng Wu, *Oxford*
Shangming Zhou, *Singleton Park*

United States

Nasar U Ahmed, Miami
Mike Allen, Milwaukee

Faisal M I Al-Mufarrej, Seattle
Wilbert S Aronow, Valhalla
Srinivas Ayyadevara, Little Rock
Charles F Babbs, West Lafayette
Janet Barletta, Hyattsville
Steven Benish, Platteville
Lawrence T Bish, Philadelphia
Richard W Bohannon, Storrs
Mark Bounthavong, San Diego
Rohit Budhiraja, Tucson
Alejandro Cárabe-Fernández, Philadelphia
Zheng Chang, Durham
M Ahmad Chaudhry, Burlington
Sant P Chawla, Santa Monica
Yong Q Chen, Winston-Salem
Tao Chen, Jefferson
Pei Chen, Beltsville
Lili Chen, Philadelphia
Undurti N Das, Federal Way
Lisandra de Castro Brás, Jackson
Thilo Deckersbach, Boston
Stephanie C Deluca, Roanoke
Kavit A Desouza, New York
Feng Ding, Chapel Hill
Elijah Dixon, Houston
Mary E Edgerton, Houston
Sherif A El-Nashar, Cleveland
Ronnie Fass, Tucson
Robert J Fletcher, Kingston
Naveen Gara, Washington
Vesna D Garovic, Rochester
Alexandros G Georgakilas, Greenville
Ronald Gillam, Logan
Shannon S Glaser, Temple
GA Nagana Gowda, Lafayette
Anton B Guliaev, San-Francisco
Zongsheng Guo, Pittsburgh
James P Hardwick, Rootstown
Diane M Harper, Louisville
Odette A Harris, Stanford
Rod Havriluk, Tallahassee
Kremer Heidemarie, Miami
Moonseong Heo, Bronx
Narayan S Hosmane, DeKalb
Guoyuan Huang, Evansville
Michael Huncharek, Columbia
Reinhold J Hutz, Milwaukee
Joseph Irudayaraj, West Lafayette
Bankole A Johnson, Charlottesville
Joseph M Kaminski, Silver Spring
Yong S Kim, Bethesda
Mark S Kindy, Charleston
Georgios D Kitsios, Boston
Ronald L Klein, Shreveport
Erna M Kojic, Providence
Wen-Shuo Kuo, Boston
S Lakshmivarahan, Norman
Benedict Law, Fargo
Chi H Lee, Kansas City
Renat Letfullin, Terre Haute
Da-Wei Li, New Haven
Qingdi Q Li, Bethesda
Guozheng Liu, Worcester
Yiyan Liu, Newark
Wei Liu, Houston
Huaguang Lu, State College
Christian Machado, Southfield
Kenneth Maiese, Newark
Sameer Malhotra, New York
Zdravka Medarova, Charlestown
Jawahar L Mehta, Little Rock
Ray M Merrill, Provo
Grover P Miller, Little Rock
Murielle Mimeault, Omaha
Ron B Mitchell, St Louis
Bing-Liang Mitchell, Houston
Anirban P Mitra, Los Angeles
Pavlos Msaouel, New York
Marcus O Muench, San Francisco
Walter P Murphy, Evanston
Najmunnisa Nasreen, Gainesville
Marja T Nevalainen, Philadelphia
Tianye Niu, Atlanta
Ify Osunkwo, Atlanta
Yan Peng, Dallas
George Perry, San Antonio
Ilona Petrikovics, Huntsville
Krishna C Poudel, Amherst
Shengping Qin, Davis
Peter J Quesenberry, Providence
Swapan K Ray, Columbia
P Hemachandra Reddy, Bethesda
Brian Rodgers, New Olreans
James V Rogers, Columbus
Troy T Rohn, Boise
L Ross, Research Triangle Park
Juan C Salazar, Farmington
Paul R Sanberg, Tampa
Tor C Savidge, Galveston
Dong-Chul Seo, Bloomington
Igor Sevostianov, Las Cruces
John D Sheppard, Norfolk
Qizhen Shi, Milwaukee
Yanggu Shi, Omaha
Michael J Silverman, Minneapolis
Kenji Suzuki, Chicago
Weihong Tan, Gainesville
Judy Y Tan, Storrs
Guangwen Tang, Boston
Paul D Terry, Knoxville
Guochuan E Tsai, Torrance
Yusuke Tsugawa, Boston
Catherine EU Ulbricht, Somerville
John Varlotto, Hershey
Alexander Vlassov, Austin
Moritz C Wyler von Ballmoos, Milwaukee
Thomas TH Wan, Orlando
Huamin Wang, Houston
Xiao-Jing Wang, Aurora
Jang-Yen Wu, Boca Raton
Qing Wu, Scottsdale
Eleftherios S Xenos, Lexington
Lijun Xia, Oklahoma City
Xiong Xu, New Orleans
Lijun Yang, Gainesville
Wan-Cai Yang, Chicago
Xinan Yang, Chicago
Fahd A Zarrouf, Anderson
Henry C Zeringue, Pittsburgh
Jingbo Zhang, New York
Zhongyun Zhao, Thosand Oaks
Li Zhong, Worcester
Hongming Zhuang, Philadelphia

Uruguay

Matías Victoria, *Salto*

World Journal of Methodology

Contents

Quarterly Volume 7 Number 2 June 26, 2017

World Journal of Methodology
Volume 7 Number 2 June 26, 2017

Contents

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Science Editor: *Fang-Fang Ji*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editorial Office Director: *Ze-Mao Gong*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

NAME OF JOURNAL
World Journal of Methodology

ISSN
ISSN 2222-0682 (online)

LAUNCH DATE
September 26, 2011

FREQUENCY
Quarterly

EDITOR-IN-CHIEF
Yicheng Ni, MD, PhD, Professor, Department of Radiology, University Hospitals, KU, Leuven, Herestraat 49, B-3000, Leuven, Belgium

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2222-0682/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Methodology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
June 26, 2017

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

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

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Methodology

Submit a Manuscript: http://www.f6publishing.com

World J Methodol 2017 June 26; 7(2): 33-36

DOI: 10.5662/wjm.v7.i2.33

ISSN 2222-0682 (online)

FIELD OF VISION

Synergetic role of integrating the departments of cancer registry and clinical research at an academic comprehensive cancer center

McKenzie Bedra, Tammy Vyskocil, Jennifer Emel, Crystal Edwards, Cherif Boutros

McKenzie Bedra, Tammy Vyskocil, Jennifer Emel, Crystal Edwards, Cherif Boutros, Tate Cancer Center, University of Maryland Baltimore Washington Medical Center, Glen Burnie, MD 21061, United States

Cherif Boutros, Department of Surgery, University of Maryland School of Medicine, Baltimore, MD 21201, United States

Author contributions: Bedra M and Boutros C wrote the manuscript; Vyskocil T and Emel J abstracted the data that contributed to the findings; Edwards C and Boutros C designed and oversaw the project.

Conflict-of-interest statement: There is no conflict of interest to disclose for any of the authors.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Cherif Boutros, MD, MSc, FACS, Tate Cancer Center, University of Maryland Baltimore Washington Medical Center, 305 Hospital Drive Ste. 304, Glen Burnie, MD 21061, United States. cboutros@smail.umaryland.edu
Telephone: +1-410-5538146
Fax: +1-410-5538181

Received: January 28, 2017
Peer-review started: February 10, 2017
First decision: March 28, 2017
Revised: April 10, 2017
Accepted: May 3, 2017
Article in press: May 5, 2017
Published online: June 26, 2017

Abstract

Integration of the cancer registry and clinical research departments can have a significant impact on the accreditation process of a Commission on Cancer (CoC) Program. Here in we demonstrate that the integration of both departments will benefit as there is increased knowledge, manpower and crossover in job responsibilities in our CoC-accredited Academic Comprehensive Cancer Center. In our model this integration has led to a more successful cooperative interaction among departments, which has in turn created an enhanced combined effect on overall output and productivity. More manpower for the cancer registry has led to increased caseloads, decreased time from date of first contact to abstraction, quality of data submissions, and timely follow-up of all patients from our reference date for accurate survival analysis along with completeness of data. In 2016, our Annual Facility report showed an additional 163 cases over prediction by the state of Maryland Cancer Registry and a 39% increase in case completeness. As proof of the synergetic effectiveness of our model within one year of its implementation, the cancer center was able to apply for, and was awarded membership from Alliance for Clinical Trials in Oncology, Central IRB, and in turn led to increased clinical trial accrual from 2.8% in 2014 compared to 13.2% currently. Our cancer registry in year one submitted over 150 more cases than predicted, improved quality outcome measures displayed by our Cancer Program Practice Profile reports and had more timely and complete data submissions to national and state registries. This synergetic integration has led to a better understanding, utilization and analysis of data by an integrated team with Clinical Research expertise.

Key words: Cancer registry; Clinical research; Commission on Cancer; Synergetic integration; American College of Surgeons

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In the current era, the evolution of healthcare management has focused on limiting resources while increasing the value of healthcare delivery. As hospitals and health care organizations operate under tighter budgets year after year, the executive teams must prioritize and utilize the resources available in the optimal way to produce the best patient care with limited funding. Integrating the cancer registry and clinical research departments can have a significant impact on outcomes. Both departments benefit as there is increased knowledge, manpower and crossover in job responsibilities. This leads to increased caseloads, decreased time from date of first contact to abstraction, and quality and completeness of data.

Bedra M, Vyskocil T, Emel J, Edwards C, Boutros C. Synergetic role of integrating the departments of cancer registry and clinical research at an academic comprehensive cancer center. *World J Methodol* 2017; 7(2): 33-36 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i2/33.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i2.33

MAIN TEXT

Health organizations all over the world are required to set priorities and allocate resources within the constraint of limited funding[1]. The Commission on Cancer (CoC) is a program of the American College of Surgeons (ACoS) that was established in 1922. CoC membership is composed of 110 individuals who are either surgeons representing the ACoS or who are representatives from one of the 56 national professional organizations or member organizations affiliated with the CoC[2]. Patients who obtain care at a CoC-accredited cancer program receive many benefits and they are directly related to the quality of their cancer care. They have the opportunity to receive surgical treatment in innovative ways including equipment such as robotic, laparoscopic and other minimally invasive approaches to cancer treatment. Accredited programs participate in multidisciplinary cancer conferences for each specialty where all key physicians are present to decide the best patient-centered care for each individual. In addition to cancer treatment, CoC-accredited programs also offer a vast range of support services for patients who receive treatment at their facilities. Some examples of support services include social work, dietitians, genetics counselors, nurse navigators, nurse practitioners specializing in survivorship which includes life after cancer treatment is complete, clinical research opportunities and a cancer registry that collects data on cancer type, stage, treatment result, and offers lifelong patient follow-up. Being part of a CoC-accredited program raises the bar by ensuring all programs adhere to the ACoS CoC program standards on an annual basis.

Clinical Research and Cancer Registry departments play an integral role in achieving the standards set forth by the CoC for accredited programs. There is currently one standard for clinical research. CoC Standard 1.9 states, "as appropriate to the cancer program category, the required percentages of patients are accrued to cancer-related clinical research studies each calendar year. The Clinical Research Coordinator documents and reports clinical research study enrollment information to the cancer committee annually[3]". It is required that each accredited cancer program accrue the minimum percentage of patients based on the program's CoC designated category, and the number of reportable cancer cases on an annual basis. For the cancer registry there are two standards that outline the minimum percentage of follow-up of cancer patient's year around. CoC Standard 5.3 states, "for all eligible analytic cases, an 80% follow-up rate is maintained from the cancer registry reference date". CoC Standard 5.4 states, "a 90 percent follow-up rate is maintained for all eligible analytic cases diagnosed within the last five years or from the cancer registry reference date, whichever is shorter[3]". These two standards are applicable to both departments as ensuring a high percentage of patients in the cancer registry are followed from the registries reference date forward in turn leads to accurate survival analysis and opportunities for retrospective research.

Each CoC-accredited program is required to report data to the National Cancer Data Base (NCDB) during the annual Call for Data which falls during the beginning of each calendar year. Reporting of data falls under two standards. CoC standard 5.5 states, "each year, complete data for all requested analytic cases are submitted to the NCBD in accordance with the annual Call for Data[3]". CoC Standard 5.6 states, "annually, cases submitted to the NCDB that were diagnose on January 1, 2003, or later meet the established quality criteria and resubmission deadline specified in the annual Call for Data[3]". Reporting of this data is mandatory for every CoC-accredited program regardless of the program category on an annual basis. By reporting based on the standards above, it helps measure performance of the program and its cancer care quality. The data is used to monitor treatment patterns and outcomes and to also enhance cancer control and clinical surveillance activities. Utilization of this data helps in the development of effective educational interventions and clinical research to improve cancer prevention, early detection, cancer care delivery and outcomes in health care settings[3].

Synergetic integration of the cancer registry and clinical research departments can have a significant impact on outcomes of a CoC accredited Academic Comprehensive Cancer Program (ACAD). As the standards of the CoC continue to develop and set the bar higher for accredited programs, individual cancer programs need to meet or exceed these standards. In

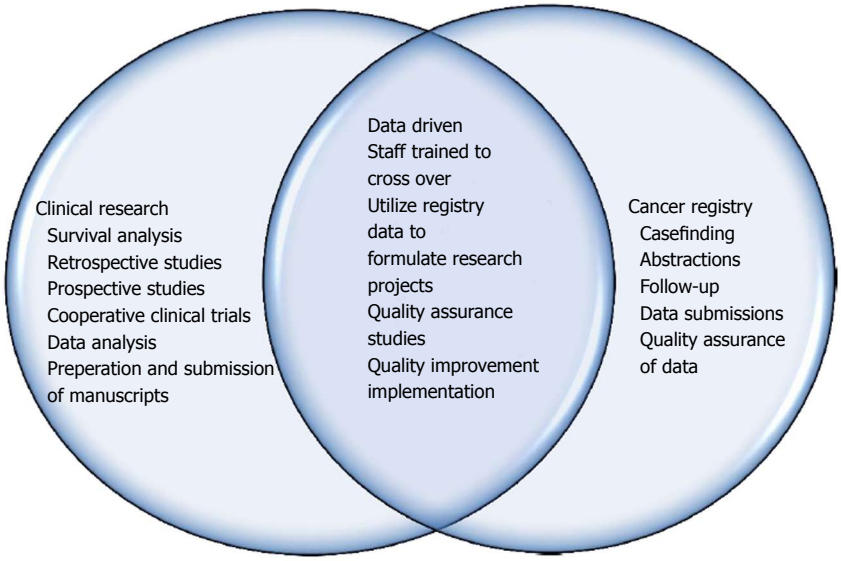

Figure 1 Roles and responsibilities of departments.

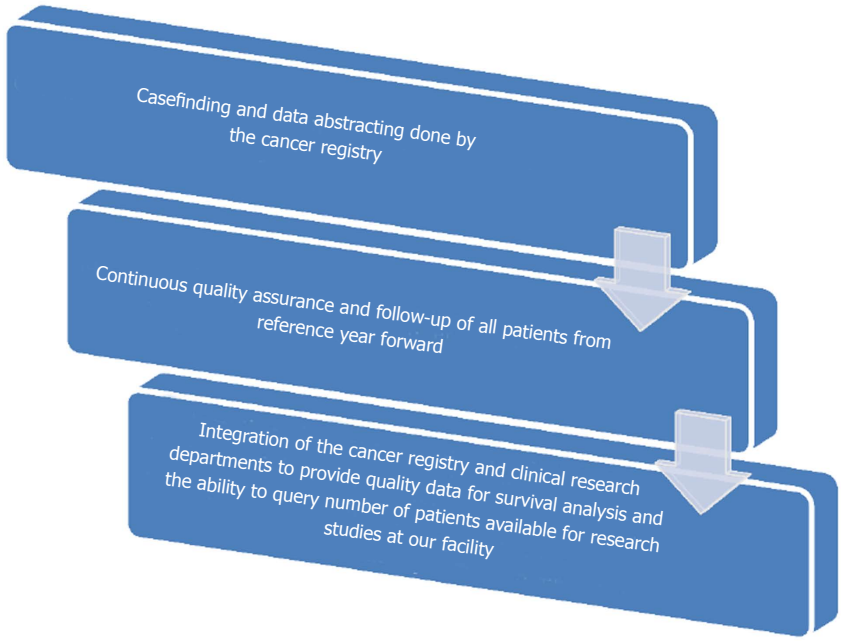

Figure 2 Synergistic integration effects on productivity and output.

the current state of healthcare, there is a major question about the priority setting and the dilemma of resource scarcity. This process should be evidenced based and encompass a wide range of challenges[1]. Today, there is a significant increase in the workload which is needed to comply with CoC accreditation and deliver quality care to patients. As health organizations all over the world are required to set priorities and allocate resources within the constraint of limited funding, this has led to an increase in workload within the cancer registry and clinical research departments[1]. These departments already have limited resources which has led us to the development of our model to still deliver quality care with the current scarce resources. This project was started as a vision by our facility to combine two departments which have one common theme, data. The idea was put into place in August of 2015 as there was a need to utilize the vast amount of data available in the cancer registry for research. The two teams were merged and the data was utilized for both departments in many ways.

Results have shown that both departments have benefited as there is increased knowledge, manpower and crossover in job responsibilities. This integration has led to a more successful cooperative interaction among departments, which has in turn created an enhanced combined effect on overall output and productivity. More manpower for the Cancer Registry has led to

increased caseloads, decreased time from date of first contact to abstraction, quality of data submissions, and timely follow-up of all patients from our reference date for accurate survival analysis along with completeness of data. In 2016, our Annual Facility report showed an additional 163 cases over prediction by the state of Maryland Cancer Registry and a 39% increase in case completeness. Figure 1 below shows the roles and responsibilities of the two departments along with how the integration has led to a combined effort and crossover within the departments. Figure 2 below represents the synergistic integration and the flow of effects it has had on our success as an ACAD with less resources and more productivity.

Since becoming a part of Alliance for Clinical Trials in Oncology and Central IRB, our model has led to increased clinical trial accrual from 2.8% in 2014 compared to 13.2% currently. This synergetic integration has led to a better understanding, utilization and analysis of data by an integrated team with Clinical Research expertise.

Based on our experience, we advocate for synergetic integration and implementation of our model in a CoC-accredited program. Our model will assure the ability to continuously meet standards of accreditation and add value to healthcare delivery while limiting cancer program resources.

REFERENCES

1 **Mitton C**, Donaldson C. Health care priority setting: principles, practice and challenges. *Cost Eff Resour Alloc* 2004; **2**: 3 [PMID: 15104792 DOI: 10.1186/1478-7547-2-3]

2 **Commission on Cancer**. American College of Surgeons Website. 1996. [updated 2016 Jan 1, accessed 2017 Jan]. Available from: URL: https://www.facs.org/quality-programs/cancer/coc

3 **American College of Surgeons**. Cancer program standards: ensuring patient-centered care. 2016 ed. Chicago, IL: American College of Surgeons, 2015: 1-82

P- Reviewer: Sonoda K, Neri V **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Wu HL

World Journal of Methodology

Submit a Manuscript: http://www.f6publishing.com

World J Methodol 2017 June 26; 7(2): 37-45

DOI: 10.5662/wjm.v7.i2.37

ISSN 2222-0682 (online)

REVIEW

Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards?

George Vaos, Nick Zavras

George Vaos, Nick Zavras, Department of Paediatric Surgery, "ATTIKON" University General Hospital, National and Kapodistrian University of Athens, School of Medicine, 12462 Haidari, Athens, Greece

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: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: George Vaos, MD, PhD, FEBPS, Professor, Department of Paediatric Surgery, "ATTIKON" University General Hospital, National and Kapodistrian University of Athens, School of Medicine, 1 Rimini Street, 12462 Haidari, Athens, Greece. gvaos@med.uoa.gr
Telephone: +30-210-5831299
Fax: +30-210-5326411

Received: January 28, 2017
Peer-review started: February 8, 2017
First decision: March 28, 2017
Revised: April 21, 2017
Accepted: May 12, 2017
Article in press: May 15, 2017
Published online: June 26, 2017

Abstract

Testicular torsion (TT) is a medical emergency that primary affects newborns and young adolescents. It causes testicular injury due to the torsion of the spermatic cord and its components, initially in the venous blood flow and finally in the arterial blood flow. Prompt diagnosis and early surgical management are necessary in managing this urgent situation. The process of the pathophysiological events in ischemia-reperfusion is multifactorial and deals with the perception of the oxidative stress responsible for the consequences of ischemia/reperfusion (I/R) stress following TT. Duration and severity of torsion also play a significant role in the oxidative stress. A detrimental result of the defense system of the testes takes place resulting finally in testicular atrophy and impaired function. Antioxidant factors have been experimentally studied in an effort to front this state. They have been classified as endogenous or exogenous antioxidants. Endogenous antioxidants comprise a structure of enzymic enzymatic and non-enzymic enzymatic particles presented within cytoplasm and numerous other subunits in the cells. Exogenous antioxidants include a variety of natural and pharmaceutical agents that may prevent or ameliorate the harmful effects of I/R injury. In this study we review those factors and their ability to enhance the oxidative status of the testis. A feature insight into where we are heading is attempted.

Key words: Testis; Torsion; Experimental; Ischemia-reperfusion injury; Antioxidants

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Testicular torsion is an emergency condition, most commonly seen in newborns and adolescents, which can be considered as an ischemia-reperfusion injury. We provide an overview of the molecular pathogenesis of the disease, and the current evidence of antioxidants use in the experimental torsion-detorsion situation. Possible adaptation of the experimental factors in the clinical practice is discussed.

Vaos G, Zavras N. Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards? *World J Methodol* 2017; 7(2): 37-45 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i2/37.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i2.37

INTRODUCTION

Testicular torsion (TT) is one of the most serious surgical emergencies, deriving from the twisting of the spermatic cord and its contents, and causing decreased blood flow to the affected testis and finally testicular atrophy[1,2]. The testis is exclusively prone to ischemic insults due to anatomical reasons (terminal arteries without anastomoses) and the inflexible properties of the tunica albuginea which restricts satisfactory expansion of the testis[3]. Although, TT can be detected at any age, it is usually seen during perinatal period and puberty[4-6]. Two main types of TT exist: Extravaginal and intravaginal[3]. Extravaginal TT is usually seen during perinatal period, and is ought to the absence of normal fixation between testicular coverings and tunica vaginalis resulting in abnormal motility of the testis within scrotum. Intravaginal TT is most commonly seen in adolescent boys and results from a long mesorchium which allows a greater mobility of the testis within the tunica albuginea[4].

TT has an annual incidence of about 3.8 per 100000 males less than 18 years[7], and in cases of bilateral torsion, there is evidence that may be inherited[8]. If left untreated within 4 to 6 h, loss of spermatogenic cells will occur[9] leading to harmful results such as infertility and subfertility[10]. The degree of twisting of the spermatic cord may also play an important role. In animal studies, 720° torsion caused significant reduction blood flow when compared with a twisted spermatic cord of 360° or less[11].

There are two kinds of injuries responsible for testicular necrosis after TT: The first is related to ischemia (I) injury during torsion, and the second to reperfusion (R) injury during detorsion[12]. I/R injury can cause cell damage from generation of reactive oxygen species (ROS), proinflammatory cytokines and adhesion molecules, lipid peroxidation, apoptosis, anoxia and alteration in microvascular blood flow, which finally lead to testicular atrophy[13]. Although the testicular environment is characterized by low oxygen tensions, testes are susceptible to oxidative stress due to the plethora of highly unsaturated fatty acids and the presence of ROS[14].

Antioxidants represent the first line defense of the organism in order to prevent the harmful consequences of I/R injury occurring in the environment of the testicular cell[15]. Antioxidants may be classified as endogenous and exogenous[15]. Endogenous antioxidants include a variety of enzymatic molecules that are presented within the cytoplasm. Common existing endogenous antioxidant enzymes include superoxide dismutase (SOD), catalase, and peroxidases[15,16]. Exogenous antioxidants include natural derived components such herb productions[17-25], vitamins[26-31], selenium[32], hormones[33-36], hormones receptors[37,38], vascular agents[39-41], phosphodiesterase inhibitors[42,43], anesthetic and non-steroid anti-inflammatory drugs[44-47], mucolytic agents[48], and hyperbaric oxygen[49]. All have been used in an effort to prevent the consequences of the oxidative stress in I/R injury.

The aim of this review is to present the pathophysiological changes that take place during I/R injury and to summarize the current literature regarding the role of antioxidants in the prevention of experimental I/R injury. Possible translation from the experimental laboratory studies to clinical practice is discussed.

SEARCH

Literature search

We conducted a search focusing on TT and experimental I/R injury in PubMed publishing over the last five years, between 2012 and 2016. The following search terms were used: "testicular torsion", "experimental ischemia-reperfusion injury", "protective agents". A total number of 22 full papers were extracted.

Pathophysiologic alterations during I/R injury

The pathophysiological alterations during I/R injury are multifactorial and difficult to understand. A cascade of events take place during the course of ischemia and further perturbations of biomolecules in cells are seeing during the blood re-establishment after reperfusion. The basic mechanisms of I/R are described below.

Ischemia injury: The role of Ca^{2+}: During ischemia a decrease of cell pH is observed due to accumulation of lactic acid, protons and NAD^+. To balance these alterations, the cell forces out H^+ *via* the Na^+/H^+ exchanger system[50]. Thereafter, Na^+ ions are swapped for Ca^{2+} by the plasmalemmal Na^+/Ca^{2+} exchanger, which results in increase of Ca^{2+}, exacerbated furthermore during reperfusion. These huge alterations in Ca^{2+} stimulate an array of systems, which finally contribute to cell death[50-52]. For instance, Ca^{2+} entry into the mitochondria *via* a mitochondrial protein further increases the lethal concentration of Ca^{2+}[53-55]. In addition, the Ca^{2+} cytosolic elevation during I/R can trigger the Ca^{2+}/calmodulin-dependent protein kinases, which further added to cell death and tissue dysfunction[53]. Additionally, the activation of calpains, a family of cysteine proteases by Ca^{2+} elevation, further degrades a group of intracellular proteins, including cytoskeletal, endoplasmic reticulum, and mitochondrial proteins[56]. Furthermore, Ca^{2+} forces the creation of calcium pyrophosphate structures and uric acid, a pair that binds to a protein complex called inflammasomes which in turn increase the production

of cytokines IL-1β, and TNF, which lead to a cytokine cyclone that irritate further the I/R injury[53].

Reperfusion injury: Studies have shown that during reperfusion, the returned oxygenated blood restores the ATP production but also results in production of ROS, which in turn may modify every biomolecule found in cells, producing further cell dysfunction (oxygen paradox)[57,58]. Redox molecules derived from nitric oxide (NO), the so called reactive nitrogen species (RNS) interact with ROS and lead to the production of reactive nitric oxide species (RNOS), such as peroxynitrite, responsible for harmful damage of macromolecules, initiation of death of endothelial and parenchymal cells, stimulation and release of pro-inflammatory mediators by various cell groups, and induction of adhesion molecules supporting leukocyte/lymphocyte-endothelial cells interactions, and reduction of protective NO[57-59].

Oxidative stress: The classic theory of oxidative stress was that it arises from an imbalance between pro-oxidants *vs* antioxidants intracellular compounds[39]. Currently, it is believed that oxidative stress is involved in three mechanisms in I/R injury: (1) indirect, through non-radical oxidants such as hydrogen peroxide (H_2O_2); (2) modulator, *via* molecular bond, oxidative or nitrosative modification of principle regulatory proteins; and (3) direct damage by oxidant radicals of DNA, proteins, lipids and carbohydrates[53,60].

Superoxide anion radical (O_2^-) is the first product of ROS during I/R injury, and subsequently all the other reactive species are derived from interactions or dismutation with other reactive species[39]. This is supported by experimental studies showing that I/R were considerably attenuated by treatment with SOD or SOD analogues[53,61,62]. O_2^- oxidizes various biomolecules and inactivates enzymes such as NADH, creatine kinase, and calcineurin[58]. Sources of O_2^- are xanthine oxidoreductase, NADPH oxidase, cytochrome P450, and uncoupled nitric oxide species (NOS)[53].

Nitric oxide stress: Nitric oxide (NO^-) is elicited during oxidation of arginine to citrulline, through nitrite or nitrate through the action of xanthine oxidoreductase, or by mitochondrial cytochrome c[63,64]. NO^- plays a protective role in the vascular system by producing dilation of blood vessels, modulating platelets aggregation and adhesions, and inhibiting leukocyte-endothelial adhesive interactions and angiogenesis[53]. Interactions of NO with O_2 or O_2^- forming N_2O_3 or peroxynitrite, are associated with overproduction of NO and O_2^- resulting in pathophysiological nitrosative and oxidative stress[53].

In summary, the oxidative/nitric oxide stress may have negative impact on the cell function in I/R stress through three ways: (1) destruction of cellular macromolecules such as membrane lipids, proteins, and DNA; (2) production of possibly toxic peroxynitrite and other RNOS; and (3) side effects on distinct cellular systems and functions[53].

Current antioxidant treatment of I/R injury in experimental TT

Comparable to other tissue-cells which live under aerobic conditions, spermatozoa produce ROS which is a physiological process activity[65]. Moreover, spermatozoa contain an array of ROS scavengers such as SOD, catalase, and substances such as ascorbic acid, taurine, hypotaurine, albumin, and carnitine to balance any ROS high concentration. However, any increased concentration of toxic metabolic products over the ROS scavenging ability, may cause loss of sperm motility and viability[66-68].

A substantial number of experimental studies by using different agents have studied experimental TT focusing on the effect of I/R injury on ipsilateral and contralateral testis, on treatment and prevention of this injury[53]. However, conflicting results are raised due to different animal species, such as rats or pigs, model of I/R injury, age, and technique that has been performed to evaluate the I/R damage[69]. Furthermore, several experimental studies proposed that the contralateral testis is not affected by unilateral torsion[70-72]. Nevertheless, there is evidence that both testes are affected, and contralateral testis is not disturbed by initial removal of the torsed testis and pretreatment with antioxidants[73-75].

There are two therapeutic opportunities to counteract oxidative stress. In the first, the superoxide radical and hydrogen peroxide are eliminated by using specific enzymes such as SOD, catalase, and glutathione peroxidase (GPX) either by administration of these enzymes or by increasing them *in vivo* actions. In the second, radical production is prevented by antioxidant scavenging systems[66].

Some authors showed that apigenin may prevent lipid peroxidation and protect the antioxidant system[76,77]. We also found a decrease in immunoreactivity of TNF and IL-10, suggesting a synergistic action of apigenin with endogenous IL-10. This antioxidant effect may be due to the H^+ donation of the OH^- aromatic group[6]. Among others, we demonstrated[42] that intraperitoneal injection of erythropoietin and sildenafil protects against I/R injury.

Amlodipine is a calcium channel blocker with antioxidants properties, effectively decreasing experimental vascular ischemia-induced damage in the liver and other tissues[78]. Dogan *et al*[79] examined the effect of amlodipine in a rat model of TT injury. They found a significant decrease of TNF and transforming growth factor-beta in the treatment group, decreases in free radicals and increases in antioxidants such as SOD and GSH.

Goji berry (GB) is a traditional Chinese plant product, from the Solanaceae family with antioxidant effects. In experimental studies, GB has been shown to reduce blood sugar and lipid levels, and exhibits male fertility-enhancing effects, immunomodulating,

antitumor, and anti-fatigue properties. GB is composed from six monosaccharides and influences its effects *via* ion exchange chromatography. In a rat experimental study of TT, administration of GB reduced I/R injury by the antioxidant effects of GB[9].

Mannitol is usually administered before partial nephrectomy to reduce renal damage due to intravascular volume expansion and its free-radical scavenging[80]. Kurt *et al*[81] in a rat model of TT, demonstrated that the treatment with mannitol group had less seminiferous tubules disruptions when compared to the TT group without mannitol treatment.

Hesperidin, is another antioxidant compound belonging to flavones with significant antioxidant effects in many tissues[82,83]. Hesperidin was given intraperitoneally by Celik *et al*[12] in an experimental group of rats underwent TT and the sample was compared to control group. They found a reduced effect on histological examinations of the hesperidin group when compared to control, while MDA levels were increased, and SOD, catalase and GSH levels were decreased as compared to the control group, concluding that hesperidin has positive results in cases of TT.

Polyphenolic catechins are components of green tea and comprise (-)- epicatechin, (-)- epigallocatechin, (-)- epicatechin gallate, and (-)- epigallocatechin gallate (EGCG)[84]. Sugiyama *et al*[85] studied an experimental rat model by producing 4 hours' ischemia and giving orally a single dose of (-)- EGCG 1 h before reperfusion. Histologic examination 4 wk after reperfusion found that EGCG protected against testicular damage from I/R injury and inhibited a further decrease in the activity of SOD.

Dexketoprofen, is a racemic mixture from the arylpropionic acid family of NSAIDS. Yildirim *et al*[86] studied the intraperitoneal effect of dexketoprofen in a rat model of I/R injury. Malondialdehyde (MDA) levels were investigated in tissue and serum of torsioned testicles in the dexketoprofen group and control group. They found a statistically lower serum MDA levels in the dexketoprofen group compared to control group, and decreased, but not statistically significant, pathological changes in the spermatogenic cells of the control group.

Tyrphostin AG 556 is a tyrosine kinase inhibitor and belongs to the tyrphostin group which has been assessed in animal models of spinal cord and coronary I/R injury[87,88]. Karaguzel *et al*[89] investigated the effect of Tyrphostin AG 556 by giving it intraperitoneally and measured the following biochemical parameters: MDA, ischemia modified albumin, signal peptide-CUB (complement C1r/C1s, Uegf, and Bmp1), epidermal growth factor like domain-containing protein1, oxidative stress index, total oxidant status, and total antioxidant status. They concluded that tyrphostin AG 556 has a protective effect on I/R injury

The protective effect of udenafil citrate, piracetam and dexmedetomidine in different doses was evaluated by Tuglu *et al*[90] and found that all these agents have antioxidant effects on I/R injury.

Grape seed proanthocyanidin extract has been reported to display better antioxidant activity than other antioxidants such as vitamin C, vitamin E, and gallic acid[91]. Bayatli *et al*[92] examined the protective effect of grape seed proanthocyanidin after TT performed for 2 h and administered it daily for a week prior to torsion/detorsion. They reported that grape seed proanthocyanidine prohibited the rise of MDA, apoptosis and endothelial nitric oxide synthase expression and enhanced testicular morphology.

Carnosine, is a dipeptide found in high amounts in mammalian tissues[93]. Abbasoğlu *et al*[94] demonstrated that carnosine treatment has a protective effect on prooxidant and antioxidant status in rat testes with I/R injury.

Ozone has been studied as a potential therapeutic agent for the treatment of various physio-pathologic conditions expressing high levels of ROS[95,96]. Ekici *et al*[97] assessed the potential effects of ozone in testicular function and morphology in a rat experimental study, in a mixture of ozone/oxygen and compared the results with those of melatonin. They found similar results in the amelioration of I/R injury between melatonin and ozone, but in different pathways.

Ethyl pyruvate, a ROS scavenger, has been found to ameliorate in different conditions such as sepsis, acute pancreatitis, burn, radiation injury and hemorrhagic shock[98,99]. Turkmen *et al*[100] reported that ethyl pyruvate has a positive effect on torsion-detorsion associated I/R injury in an experimental rat model.

Carvedilol is a third generation vasodilator agent which has been used in the treatment of hypertension, congestive heart failure and ischemic heart disease[101,102]. Parlaktas *et al*[103] investigated the antioxidant effects of carvedilol against I/R injury, and found a decrease in MDA and protein carbonyl and an increase in the level of antioxidant enzymes SOD, and GPX, but not histopathological changes against the control group. They concluded, that carvedilol may have a potential therapeutic value and improve fertility in the clinical practice in patients with TT.

Jiang *et al*[104] investigated the effect of intraperitoneally injected hydrogen rich saline solution on the protection against testicular damage induced by I/R injury in rats. They found a significant decrease of MDA and a significant improvement of SOD activity in the group of rats which received hydrogen rich saline solution. Therefore, hydrogen rich saline solution may have a protective and therapeutic action against testicular damage.

Inhaled hydrogen gas has been shown to produce a therapeutic activity in a middle cerebral artery occlusion in a rat model and reduce infarct volumes of brain, liver, and myocardium[105,106]. Lee *et al*[107] studied the possible therapeutic properties of inhaled 2% hydrogen in pubertal rat model underwent testicular I/R injury. The results of histopathological and biochemical studies suggested that inhalation of hydrogen gas has anti-apoptotic and anti-oxidant properties in cases of TT.

Alpha-lipoic acid is an eight-carbon endogenous cofactor which works against oxygen radicals[108]. It is established that α-lipoic acid catches hydroxyl and nitric oxide radicals, peroxynitrite anions and hydrogen peroxide. Moreover, α-lipoic acid may act indirectly by enhancing the level of other natural antioxidants such as glutathione, ascorbic acid and tocopherol[31,109-111]. Ozbal *et al*[108] investigated the role of α-lipoic acid in testicular I/R injury in rats and concluded that it is a potential beneficial agent in preserving testicular function.

Genistein is an isoflavone extracted by soy[112] which displays anti-oxidant and anti-inflammatory properties[113]. Furthermore, genistein promotes steroidogenesis by restriction progesterone synthesis and decreases secretion of cortisol and corticosterone in mature female pigs[114] In addition, it has a protective role against gamma irradiation-induced testicular dysfunction[115]. Recently, Al-Maghrebi *et al*[116] reported that genistein protects the extracellular matrix of the testis which is responsible for the structural integrity of the testicular components, and prevents spermatogenesis's suppression, mitigating oxidative stress and apoptosis in experimental testicular I/R injury.

Nuclear factor kappa B plays a crucial role in immune response, cellular proliferation, inflammatory, and apoptosis[117]. Pyrrolidine dithiocarbamate (PDTC) is a stable low-molecular thiol compound which acts by neutralizing ROS[118]. Kemahli *et al*[118] studied the antioxidant effect of PDTC in a TT model and found that administration of PDTC exaggerates the antioxidant system by lowering MDA levels, increasing SOD activity and improving Johnson scores of biopsy specimen.

Urocortin, is a 40-amino acid peptide found in different organs, such as digestive tract, cardiovascular and reproductive system[119]. For instance, urocortin has been shown that protect cardiovascular system against I/R injury[120]. Sumii *et al*[121] investigated the role of urocortin in testicular apoptosis in an experimetnal I/R rat model and found a cytoprotective role in germ cells through the activation of anti-apoptotic proteins.

Melatonin is an endogenous compound secreted by the pineal gland and influences reproduction *via* its activity on the hypothalamus[122]. Kurcer *et al*[123] reported that melatonin protects testicular tissue against oxidation and alleviates histopathologic changes after experimental testicular I/R injury. Metformin belongs to the biguanide family and has the capacity to reduce ROS[124]. Asghari *et al*[125] investigated a combined use of melatonin and metformin in a rat model and found that may protect the testes from I/R injury by restoring SOD activity, and MDA and myeloperoxidase levels.

Very recently Erol *et al*[126] investigated the effect of a antioxidant factors combination, constituting either by l-carnitine, fructose, citric acid, ascorbic acid, cyanocobalamin, selenium, coenzyme Q10, zinc and folic acid or fructose, cellulose microcrystalline, pygeum shell, L-arginine, L-carnitine, zinc, vitamin E, folic acid, vitamin B6, sodium selenite, and hydroxypropyl methyl cellulose. They found that combined antioxidants were more effective than one protective antioxidant by reducing apoptosis and preventing I/R injury.

Antioxidants and I/R injury in clinical practice

The large body of experimental studies demonstrated undoubtedly that oxidative stress is a dominant factor in the creation of testis impairment after I/R injury. Furthermore, all these antioxidative compounds have been sought to be clearly capable to protect testicular function from oxidative stress. However the relationship between experimental results and clinical practice has not come together until now. A feature mandatory pursuit is to advance understanding of the basic mechanism of oxidative stress in the male reproductive tract and to develop optimizing antioxidant factors in order to treat the pathological consequences from imbalance in the oxidation state of testicular tissue. These mandatory demands are beyond laboratory ways that outline the present approach to counterbalance the deleterious effects of TT.

CONCLUSION

Currently, a large number of studies investigate the role of I/R injury in experimental animal models and many antioxidants and free radical scavengers have been studied to indicate their possible application in human beings. However, the molecular mechanism by which these agents may control the harmful effect of TT has to be clarified. Moreover, experimentally checked drugs or compounds still anticipate clinical utilization. Additional experimental and future clinical studies have to be performed to further assess the effects on antioxidant therapy.

REFERENCES

1 **Moslemi MK**, Kamalimotlagh S. Evaluation of acute scrotum in our consecutive operated cases: a one-center study. *Int J Gen Med* 2014; **7**: 75-78 [PMID: 24470769 DOI: 10.2147/IJGM.S52413]

2 **Sharp VJ**, Kieran K, Arlen AM. Testicular torsion: diagnosis, evaluation, and management. *Am Fam Physician* 2013; **88**: 835-840 [PMID: 24364548]

3 **Karaguzel E**, Kadihasanoglu M, Kutlu O. Mechanisms of testicular torsion and potential protective agents. *Nat Rev Urol* 2014; **11**: 391-399 [PMID: 24934447 DOI: 10.1038/nrurol.2014.135]

4 **Bowlin PR**, Gatti JM, Murphy JP. Pediatric Testicular Torsion. *Surg Clin North Am* 2017; **97**: 161-172 [PMID: 27894425 DOI: 10.1016/j.suc.2016.08.012]

5 **Drlík M**, Kočvara R. Torsion of spermatic cord in children: a review. *J Pediatr Urol* 2013; **9**: 259-266 [PMID: 22763105 DOI: 10.1016/j.jpurol.2012.05.016]

6 **Skondras I**, Lambropoulou M, Tsaroucha A, Gardikis S, Tripsianis G, Simopoulos C, Vaos G. The role of Apigenin in testicular damage in experimental ischemia-reperfusion injury in rats. *Hippokratia* 2015; **19**: 225-230 [PMID: 27418781]

7 **Zhao LC**, Lautz TB, Meeks JJ, Maizels M. Pediatric testicular torsion epidemiology using a national database: incidence, risk of orchiectomy and possible measures toward improving the quality of care. *J Urol* 2011; **186**: 2009-2013 [PMID: 21944120 DOI: 10.1016/j.juro.2011.07.024]

8 **Shteynshlyuger A**, Yu J. Familial testicular torsion: a meta analysis suggests inheritance. *J Pediatr Urol* 2013; **9**: 683-690 [PMID:

23017841 DOI: 10.1016/j.jpurol.2012.08.002]
9 **Dursun R**, Zengin Y, Gündüz E, İçer M, Durgun HM, Dağgulli M, Kaplan İ, Alabalık U, Güloğlu C. The protective effect of goji berry extract in ischemic reperfusion in testis torsion. *Int J Clin Exp Med* 2015; **8**: 2727-2733 [PMID: 25932226]
10 **Parlaktas BS**, Atilgan D, Ozyurt H, Gencten Y, Akbas A, Erdemir F, Uluocak N. The biochemical effects of ischemia-reperfusion injury in the ipsilateral and contralateral testes of rats and the protective role of melatonin. *Asian J Androl* 2014; **16**: 314-318 [PMID: 24407181 DOI: 10.4103/1008-682X.122202]
11 **Lievano G**, Nguyen L, Radhakrishnan J, Fornell L, John E. New animal model to evaluate testicular blood flow during testicular torsion. *J Pediatr Surg* 1999; **34**: 1004-1006 [PMID: 10392923 DOI: 10.1016/S0022-3468(99)90778-9]
12 **Celik E**, Oguzturk H, Sahin N, Turtay MG, Oguz F, Ciftci O. Protective effects of hesperidin in experimental testicular ischemia/reperfusion injury in rats. *Arch Med Sci* 2016; **12**: 928-934 [PMID: 27695481 DOI: 10.5114/aoms.2015.47697]
13 **Cuzzocrea S**, Riley DP, Caputi AP, Salvemini D. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. *Pharmacol Rev* 2001; **53**: 135-159 [PMID: 11171943]
14 **Aitken RJ**, Roman SD. Antioxidant systems and oxidative stress in the testes. *Adv Exp Med Biol* 2008; **636**: 154-171 [PMID: 19856167 DOI: 10.1007/978-0-387-09597-4_9]
15 **Rahal A**, Kumar A, Singh V, Yadav B, Tiwari R, Chakraborty S, Dhama K. Oxidative stress, prooxidants, and antioxidants: the interplay. *Biomed Res Int* 2014; **2014**: 761264 [PMID: 24587990 DOI: 10.1155/2014/761264]
16 **Turner TT**, Lysiak JJ. Oxidative stress: a common factor in testicular dysfunction. *J Androl* 2008; **29**: 488-498 [PMID: 18567643 DOI: 10.2164/jandrol.108.005132]
17 **Lin Y**, Shi R, Wang X, Shen HM. Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr Cancer Drug Targets* 2008; **8**: 634-646 [PMID: 18991571 DOI: 10.2174/156800908786241050]
18 **Diplock AT**, Charleux JL, Crozier-Willi G, Kok FJ, Rice-Evans C, Roberfroid M, Stahl W, Viña-Ribes J. Functional food science and defence against reactive oxidative species. *Br J Nutr* 1998; **80** Suppl 1: S77-112 [PMID: 9849355 DOI: 10.1079/BJN19980106]
19 **Jaganathan SK**, Mandal M. Antiproliferative effects of honey and of its polyphenols: a review. *J Biomed Biotechnol* 2009; **2009**: 830616 [PMID: 19636435 DOI: 10.1155/2009/830616]
20 **Korkmaz A**, Kolankaya D. Protective effect of rutin on the ischemia/reperfusion induced damage in rat kidney. *J Surg Res* 2010; **164**: 309-315 [PMID: 19592016 DOI: 10.1016/j.jss.2009.03.022]
21 **Guimarães SB**, Santos JM, Aragão AA, Kimura OS, Silveira ER, Vasconcelos PR. Ternatin pretreatment attenuates testicular injury induced by torsion/detorsion in Wistar rats. *Acta Cir Bras* 2011; **26**: 325-328 [PMID: 21808848 DOI: 10.1590/S0102-86502011000400014]
22 **Aktoz T**, Kanter M, Aktas C. Protective effects of quercetin on testicular torsion/detorsion-induced ischaemia-reperfusion injury in rats. *Andrologia* 2010; **42**: 376-383 [PMID: 21105888 DOI: 10.1111/j.1439-0272.2010.01044.x]
23 **Hekimoglu A**, Kurcer Z, Aral F, Baba F, Sahna E, Atessahin A. Lycopene, an antioxidant carotenoid, attenuates testicular injury caused by ischemia/reperfusion in rats. *Tohoku J Exp Med* 2009; **218**: 141-147 [PMID: 19478470 DOI: 10.1620/tjem.218.141]
24 **Kim YH**, Kim GH, Shin JH, Kim KS, Lim JS. Effect of korean red ginseng on testicular tissue injury after torsion and detorsion. *Korean J Urol* 2010; **51**: 794-799 [PMID: 21165202 DOI: 10.4111/kju.2010.51.11.794]
25 **Maffei Facino R**, Carini M, Aldini G, Berti F, Rossoni G. Panax ginseng administration in the rat prevents myocardial ischemia-reperfusion damage induced by hyperbaric oxygen: evidence for an antioxidant intervention. *Planta Med* 1999; **65**: 614-619 [PMID: 10575376 DOI: 10.1055/s-1999-14034]
26 **Azizollahi S**, Babaei H, Derakhshanfar A, Oloumi MM. Effects of co-administration of dopamine and vitamin C on ischaemia-reperfusion injury after experimental testicular torsion-detorsion in rats. *Andrologia* 2011; **43**: 100-105 [PMID: 21382063 DOI: 10.1111/j.1439-0272.2009.01028.x]
27 **Romeo C**, Antonuccio P, Esposito M, Marini H, Impellizzeri P, Turiaco N, Altavilla D, Bitto A, Zuccarello B, Squadrito F. Raxofelast, a hydrophilic vitamin E-like antioxidant, reduces testicular ischemia-reperfusion injury. *Urol Res* 2004; **32**: 367-371 [PMID: 15316698 DOI: 10.1007/s00240-004-0436-4]
28 **Antonuccio P**, Minutoli L, Romeo C, Nicòtina PA, Bitto A, Arena S, Altavilla D, Zuccarello B, Polito F, Squadrito F. Lipid peroxidation activates mitogen-activated protein kinases in testicular ischemia-reperfusion injury. *J Urol* 2006; **176**: 1666-1672 [PMID: 16952711 DOI: 10.1016/j.juro.2006.06.086]
29 **Slyshenkov VS**, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. *FEBS Lett* 2004; **569**: 169-172 [PMID: 15225628 DOI: 10.1016/j.febslet.2004.05.044]
30 **Etensel B**, Ozkisacik S, Ozkara E, Serbest YA, Oztan O, Yazici M, Gürsoy H. The protective effect of dexpanthenol on testicular atrophy at 60th day following experimental testicular torsion. *Pediatr Surg Int* 2007; **23**: 271-275 [PMID: 17205291 DOI: 10.1007/s00383-006-1871-9]
31 **Petersen Shay K**, Moreau RF, Smith EJ, Hagen TM. Is alpha-lipoic acid a scavenger of reactive oxygen species in vivo? Evidence for its initiation of stress signaling pathways that promote endogenous antioxidant capacity. *IUBMB Life* 2008; **60**: 362-367 [PMID: 18409172 DOI: 10.1002/iub.40]
32 **Ursini F**, Bindoli A. The role of selenium peroxidases in the protection against oxidative damage of membranes. *Chem Phys Lipids* 1987; **44**: 255-276 [PMID: 3311419 DOI: 10.1016/0009-3084(87)90053-3]
33 **Katavetin P**, Tungsanga K, Eiam-Ong S, Nangaku M. Antioxidative effects of erythropoietin. *Kidney Int Suppl* 2007; **(107)**: S10-S15 [PMID: 17943138 DOI: 10.1038/sj.ki.5002482]
34 **Yazihan N**, Ataoglu H, Koku N, Erdemli E, Sargin AK. Protective role of erythropoietin during testicular torsion of the rats. *World J Urol* 2007; **25**: 531-536 [PMID: 17690891 DOI: 10.1007/s00345-007-0200-9]
35 **Chikuma M**, Masuda S, Kobayashi T, Nagao M, Sasaki R. Tissue-specific regulation of erythropoietin production in the murine kidney, brain, and uterus. *Am J Physiol Endocrinol Metab* 2000; **279**: E1242-E1248 [PMID: 11093910]
36 **Koksal M**, Oğuz E, Baba F, Eren MA, Ciftci H, Demir ME, Kurcer Z, Take G, Aral F, Ocak AR, Aksoy N, Ulas T. Effects of melatonin on testis histology, oxidative stress and spermatogenesis after experimental testis ischemia-reperfusion in rats. *Eur Rev Med Pharmacol Sci* 2012; **16**: 582-588 [PMID: 22774397]
37 **Yapanoglu T**, Aksoy Y, Gursan N, Ozbey I, Ziypak T, Calik M. Antiapoptotic effects of dehydroepiandrosterone on testicular torsion/detorsion in rats. *Andrologia* 2008; **40**: 38-43 [PMID: 18211300 DOI: 10.1111/j.1439-0272.2008.00806.x]
38 **Minutoli L**, Bitto A, Squadrito F, Irrera N, Rinaldi M, Nicotina PA, Arena S, Magno C, Marini H, Spaccapelo L, Ottani A, Giuliani D, Romeo C, Guarini S, Antonuccio P, Altavilla D. Melanocortin 4 receptor activation protects against testicular ischemia-reperfusion injury by triggering the cholinergic antiinflammatory pathway. *Endocrinology* 2011; **152**: 3852-3861 [PMID: 21828180 DOI: 10.1210/en.2011-1016]
39 **Mak IT**, Freedman AM, Dickens BF, Weglicki WB. Protective effects of sulfhydryl-containing angiotensin converting enzyme inhibitors against free radical injury in endothelial cells. *Biochem Pharmacol* 1990; **40**: 2169-2175 [PMID: 2173602 DOI: 10.1016/0006-2952(90)90250-O]
40 **Yancopoulos GD**, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature* 2000; **407**: 242-248 [PMID: 11001067 DOI: 10.1038/35025215]
41 **Shirazi M**, Noorafshan A, Karbalay-Doust S, Ardeshiri M, Afrasiabi MA, Monabati A. Comparison of the protective effects of papaverine, lidocaine and verapamil on the sperm quality of the

testis after induced torsion-detorsion in rats. *Scand J Urol Nephrol* 2010; **44**: 133-137 [PMID: 20166843 DOI: 10.3109/00365591003636588]
42 **Zavras N**, Kostakis ID, Sakellariou S, Damaskos C, Roupakas E, Tsagkari E, Spartalis E, Velaoras K, Dontas IA, Karatzas T. Comparison of erythropoietin and sildenafil protective role against ischemia/reperfusion injury of the testis in adult rats. *Int Urol Nephrol* 2014; **46**: 731-736 [PMID: 24097275 DOI: 10.1007/s11255-013-0569-x]
43 **Istanbulluoglu MO**, Zor M, Celik A, Cicek T, Basal S, Ozgok A, Ustun H, Ozgok Y. Effects of vardenafil on testicular torsion/detorsion damage: an experimental study in pigs. *Urol Int* 2011; **86**: 228-232 [PMID: 21124003 DOI: 10.1159/000321492]
44 **Kidambi S**, Yarmush J, Fong W, Kamath S, Schianodicola J, Nahmias Y. Propofol induces ERK-dependant expression of c-Fos and Egr-1 in neuronal cells. *Neuroreport* 2009; **20**: 657-662 [PMID: 19349923 DOI: 10.1097/WNR.0b013e328329a449]
45 **Yagmurdur H**, Ayyildiz A, Karaguzel E, Ogus E, Surer H, Caydere M, Nuhoglu B, Germiyanoglu C. The preventive effects of thiopental and propofol on testicular ischemia-reperfusion injury. *Acta Anaesthesiol Scand* 2006; **50**: 1238-1243 [PMID: 17067323 DOI: 10.1111/j.1399-6576.2006.01145.x]
46 **Hanci V**, Erol B, Bektaş S, Mungan G, Yurtlu S, Tokgöz H, Can M, Ozkoçak Turan I. Effect of dexmedetomidine on testicular torsion/detorsion damage in rats. *Urol Int* 2010; **84**: 105-111 [PMID: 20173379 DOI: 10.1159/000273476]
47 **Dokmeci D**, Kanter M, Inan M, Aydogdu N, Basaran UN, Yalcin O, Turan FN. Protective effects of ibuprofen on testicular torsion/detorsion-induced ischemia/reperfusion injury in rats. *Arch Toxicol* 2007; **81**: 655-663 [PMID: 17345063 DOI: 10.1007/s00204-007-0189-2]
48 **Aktaş BK**, Bulut S, Bulut S, Baykam MM, Ozden C, Senes M, Yücel D, Memiş A. The effects of N-acetylcysteine on testicular damage in experimental testicular ischemia/reperfusion injury. *Pediatr Surg Int* 2010; **26**: 293-298 [PMID: 19911182 DOI: 10.1007/s00383-009-2538-0]
49 **Zhang Y**, Lv Y, Liu YJ, Yang C, Hu HJ, Meng XE, Li MX, Pan SY. Hyperbaric oxygen therapy in rats attenuates ischemia-reperfusion testicular injury through blockade of oxidative stress, suppression of inflammation, and reduction of nitric oxide formation. *Urology* 2013; **82**: 489.e9-489.e15 [PMID: 23769121 DOI: 10.1016/j.urology.2013.04.016]
50 **Sanada S**, Komuro I, Kitakaze M. Pathophysiology of myocardial reperfusion injury: preconditioning, postconditioning, and translational aspects of protective measures. *Am J Physiol Heart Circ Physiol* 2011; **301**: H1723-H1741 [PMID: 21856909 DOI: 10.1152/ajpheart.00553.2011]
51 **Baines CP**. The mitochondrial permeability transition pore and ischemia-reperfusion injury. *Basic Res Cardiol* 2009; **104**: 181-188 [PMID: 19242640 DOI: 10.1007/s00395-009-0004-8]
52 **Baines CP**. The molecular composition of the mitochondrial permeability transition pore. *J Mol Cell Cardiol* 2009; **46**: 850-857 [PMID: 19233198 DOI: 10.1016/j.yjmcc.2009.02.007]
53 **Kalogeris T**, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. *Int Rev Cell Mol Biol* 2012; **298**: 229-317 [PMID: 22878108 DOI: 10.1016/B978-0-12-394309-5.00006-7]
54 **Contreras L**, Drago I, Zampese E, Pozzan T. Mitochondria: the calcium connection. *Biochim Biophys Acta* 2010; **1797**: 607-618 [PMID: 20470749 DOI: 10.1016/j.bbabio.2010.05.005]
55 **Szydlowska K**, Tymianski M. Calcium, ischemia and excitotoxicity. *Cell Calcium* 2010; **47**: 122-129 [PMID: 20167368 DOI: 10.1016/j.ceca.2010.01.003]
56 **Croall DE**, Ersfeld K. The calpains: modular designs and functional diversity. *Genome Biol* 2007; **8**: 218 [PMID: 17608959 DOI: 10.1186/gb-2007-8-6-218]
57 **Kvietys PR**, Granger DN. Role of reactive oxygen and nitrogen species in the vascular responses to inflammation. *Free Radic Biol Med* 2012; **52**: 556-592 [PMID: 22154653 DOI: 10.1016/j.freeradbiomed.2011.11.002]
58 **Raedschelders K**, Ansley DM, Chen DD. The cellular and molecular origin of reactive oxygen species generation during myocardial ischemia and reperfusion. *Pharmacol Ther* 2012; **133**: 230-255 [PMID: 22138603 DOI: 10.1016/j.pharmthera.2011.11.004]
59 **Granger DN**. Ischemia-reperfusion: mechanisms of microvascular dysfunction and the influence of risk factors for cardiovascular disease. *Microcirculation* 1999; **6**: 167-178 [PMID: 10501090 DOI: 10.1111/j.1549-8719.1999.tb00099.x]
60 **Granger DN**, Korthuis RJ. Physiologic mechanisms of postischemic tissue injury. *Annu Rev Physiol* 1995; **57**: 311-332 [PMID: 7778871 DOI: 10.1146/annurev.ph.57.030195.001523]
61 **Lima B**, Forrester MT, Hess DT, Stamler JS. S-nitrosylation in cardiovascular signaling. *Circ Res* 2010; **106**: 633-646 [PMID: 20203313 DOI: 10.1161/CIRCRESAHA.109.207381]
62 **Granger DN**. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *Am J Physiol* 1988; **255**: H1269-H1275 [PMID: 3059826]
63 **Horie Y**, Ishii H. Liver dysfunction elicited by gut ischemia-reperfusion. *Pathophysiology* 2001; **8**: 11-20 [PMID: 11476968 DOI: 10.1016/S0928-4680(01)00063-3]
64 **Golwala NH**, Hodenette C, Murthy SN, Nossaman BD, Kadowitz PJ. Vascular responses to nitrite are mediated by xanthine oxidoreductase and mitochondrial aldehyde dehydrogenase in the rat. *Can J Physiol Pharmacol* 2009; **87**: 1095-1101 [PMID: 20029546 DOI: 10.1139/Y09-101]
65 **Bansal AK**, Bilaspuri GS. Impacts of oxidative stress and antioxidants on semen functions. *Vet Med Int* 2010; **2010**: pii: 686137 [PMID: 20871827 DOI: 10.4061/2011/686137]
66 **Dockmeci D**. Oxidative stress and testicular torsion. In: Agarwal A, et al (eds). Studies on Men's Health and Fertility. Oxidative stress in Applied Basic Research and Clinical Practice. Springer Science and Business Media, LLC, 2012: 355-398 [DOI: 10.1007/978-1-61779-776-7_17]
67 **Said TM**, Agarwal A, Sharma RK, Mascha E, Sikka SC, Thomas AJ. Human sperm superoxide anion generation and correlation with semen quality in patients with male infertility. *Fertil Steril* 2004; **82**: 871-877 [PMID: 15482762 DOI: 10.1016/j.fertnstert.2004.02.132]
68 **Saleh RA**, Agarwal A. Oxidative stress and male infertility: from research bench to clinical practice. *J Androl* 2002; **23**: 737-752 [PMID: 12399514 DOI: 10.1007/978-3-642-02062-9_7]
69 **Romero FR**, Gomes RP, Lorenzini F, Erdmann TR, Tambara Filho R. Ipsilateral testicular necrosis and atrophy after 1,080-degree torsion of the spermatic cord in rats. *Acta Cir Bras* 2009; **24**: 118-123 [PMID: 19377780 DOI: 10.1590/S0102-86502009000200008]
70 **Akgür FM**, Kilinç K, Aktuğ T. Is ipsilateral testis mandatory for the occurrence of contralateral intratesticular biochemical changes indicative of hypoxia after unilateral spermatic cord torsion? *Eur Urol* 1995; **28**: 143-146 [PMID: 8529740]
71 **Becker EJ**, Turner TT. Endocrine and exocrine effects of testicular torsion in the prepubertal and adult rat. *J Androl* 1995; **16**: 342-351 [PMID: 8537252]
72 **Turner TT**. Acute experimental testicular torsion. No effect on the contralateral testis. *J Androl* 1985; **6**: 65-72 [PMID: 3972720 DOI: 10.1002/j.1939-4640.1985.tb00817.x]
73 **Cosentino MJ**, Rabinowitz R, Valvo JR, Cockett AT. The effect of prepubertal spermatic cord torsion on subsequent fertility in rats. *J Androl* 1984; **5**: 93-98 [PMID: 6715258 DOI: 10.1002/j.1939-4640.1984.tb00781.x]
74 **Tanyel FC**, Büyükpamukçu N, Hiçsönmez A. Contralateral testicular blood flow during unilateral testicular torsion. *Br J Urol* 1989; **63**: 522-524 [PMID: 2731010 DOI: 10.1111/j.1464-410X.1989.tb05949.x]
75 **Thomas WE**, Cooper MJ, Crane GA, Lee G, Williamson RC. Testicular exocrine malfunction after torsion. *Lancet* 1984; **2**: 1357-1360 [PMID: 6150364 DOI: 10.1016/S0140-6736(84)92056-7]
76 **Singh JP**, Selvendiran K, Banu SM, Padmavathi R, Sakthisekaran D. Protective role of Apigenin on the status of lipid peroxidation and antioxidant defense against hepatocarcinogenesis in Wistar albino rats. *Phytomedicine* 2004; **11**: 309-314 [PMID: 15185843

DOI: 10.1078/0944711041495254]
77 **Nagaraja HS**, Anupama BK. Apigenin reduces cyclosporine-A induced changes in lipid hydroperoxides and total antioxidants in Sprague-Dawley rats. *J Chin Clin Med* 2009; **4**: 26-31
78 **Halici Z**, Karaca M, Keles ON, Borekci B, Odabasoglu F, Suleyman H, Cadirci E, Bayir Y, Unal B. Protective effects of amlodipine on ischemia-reperfusion injury of rat ovary: biochemical and histopathologic evaluation. *Fertil Steril* 2008; **90**: 2408-2415 [PMID: 18178199 DOI: 10.1016/j.fertnstert.2007.10.007]
79 **Dogan C**, Halici Z, Topcu A, Cadirci E, Karakus E, Bayir Y, Selli J. Effects of amlodipine on ischaemia/reperfusion injury in the rat testis. *Andrologia* 2016; **48**: 441-452 [PMID: 26259852 DOI: 10.1111/and.12464]
80 **Zager RA**, Mahan J, Merola AJ. Effects of mannitol on the postischemic kidney. Biochemical, functional, and morphologic assessments. *Lab Invest* 1985; **53**: 433-442 [PMID: 3930877]
81 **Kurt O**, Yazici CM, Erboga M, Turan C, Bozdemir Y, Akbas A, Turker P, Aktas C, Aydin M, Yesildag E. Mannitol has a protective effect on testicular torsion: An experimental rat model. *J Pediatr Urol* 2016; **12**: 167.e1-167.e8 [PMID: 26879410 DOI: 10.1016/j.jpurol.2016.01.004]
82 **Shagirtha K**, Pari L. Hesperetin, a citrus flavonone, protects potentially cadmium induced oxidative testicular dysfunction in rats. *Ecotoxicol Environ Saf* 2011; **74**: 2105-2111 [PMID: 21719105 DOI: 10.1016/j.ecoenv.2011.06.002]
83 **Gaur V**, Kumar A. Hesperidin pre-treatment attenuates NO-mediated cerebral ischemic reperfusion injury and memory dysfunction. *Pharmacol Rep* 2010; **62**: 635-648 [PMID: 20885004 DOI: 10.1016/S1734-1140(10)70321-2]
84 **Nagle DG**, Ferreira D, Zhou YD. Epigallocatechin-3-gallate (EGCG): chemical and biomedical perspectives. *Phytochemistry* 2006; **67**: 1849-1855 [PMID: 16876833 DOI: 10.1016/j.phytochem.2006.06.020]
85 **Sugiyama A**, Chiba M, Nakagami T, Kawano S, Sanada Y, Tajiri T, Toki A. Beneficial effects of (-)-epigallocatechin gallate on ischemia-reperfusion testicular injury in rats. *J Pediatr Surg* 2012; **47**: 1427-1432 [PMID: 22813808 DOI: 10.1016/j.jpedsurg.2012.01.069]
86 **Yildirim Y**, Karakaya D, Kelsaka E, Aksoy A, Gülbahar MY, Bedir A. The effect of dexketoprofen on ischemia reperfusion injury. *Bratisl Lek Listy* 2014; **115**: 256-259 [PMID: 25174054 DOI: 10.4149/bll_2014_053]
87 **Usul H**, Cakir E, Cobanoglu U, Alver A, Peksoylu B, Topbas M, Baykal S. The effects of tyrphostine Ag 556 on experimental spinal cord ischemia reperfusion injury. *Surg Neurol* 2004; **61**: 45-54; discussion 54 [PMID: 14706378 DOI: 10.1016/S0090-3019(03)00539-1]
88 **Altavilla D**, Squadrito F, Campo GM, Saitta A, Squadrito G, Quartarone C, Deodato B, Arlotta M, Ferlito M, Minutoli L, Tringali M, Urna G, Sardella A, Caputi AP. The reduction of myocardial damage and leukocyte polymorphonuclear accumulation following coronary artery occlusion by the tyrosine kinase inhibitor tyrphostin AG 556. *Life Sci* 2000; **67**: 2615-2629 [PMID: 11104363 DOI: 10.1016/S0024-3205(00)00845-6]
89 **Karaguzel E**, Sivrikaya A, Mentese A, Yulug E, Turkmen S, Kutlu O, Guler Y, Us D, Turedi S, Alver A, Kazaz IO. Investigation of tyrphostin AG 556 for testicular torsion-induced ischemia reperfusion injury in rat. *J Pediatr Urol* 2014; **10**: 223-229 [PMID: 24070787 DOI: 10.1016/j.jpurol.2013.08.007]
90 **Tuglu D**, Yuvanc E, Ozan T, Bal F, Yilmaz E, Atasoy P, Kisa U, Batislam E. Protective effects of udenafil citrate, piracetam and dexmedetomidine treatment on testicular torsion/detorsion-induced ischaemia/reperfusion injury in rats. *Andrologia* 2016; **48**: 676-682 [PMID: 26589469 DOI: 10.1111/and.12499]
91 **Ariga T**. The antioxidative function, preventive action on disease and utilization of proanthocyanidins. *Biofactors* 2004; **21**: 197-201 [PMID: 15630197 DOI: 10.1002/biof.552210140]
92 **Bayatli F**, Akkuş D, Kilic E, Saraymen R, Sönmez MF. The protective effects of grape seed extract on MDA, AOPP, apoptosis and eNOS expression in testicular torsion: an experimental study. *World J Urol* 2013; **31**: 615-622 [PMID: 23475212 DOI: 10.1007/s00345-013-1049-8]
93 **Aldini G**, Facino RM, Beretta G, Carini M. Carnosine and related dipeptides as quenchers of reactive carbonyl species: from structural studies to therapeutic perspectives. *Biofactors* 2005; **24**: 77-87 [PMID: 16403966 DOI: 10.1002/biof.5520240109]
94 **Abbasoğlu L**, Kalaz EB, Soluk-Tekkeşin M, Olgaç V, Doğru-Abbasoğlu S, Uysal M. Beneficial effects of taurine and carnosine in experimental ischemia/reperfusion injury in testis. *Pediatr Surg Int* 2012; **28**: 1125-1131 [PMID: 22961384 DOI: 10.1007/s00383-012-3168-5]
95 **Peralta C**, Xaus C, Bartrons R, Leon OS, Gelpi E, Roselló-Catafau J. Effect of ozone treatment on reactive oxygen species and adenosine production during hepatic ischemia-reperfusion. *Free Radic Res* 2000; **33**: 595-605 [PMID: 11200091 DOI: 10.1080/10715760000301121]
96 **Yu G**, Liu X, Chen Z, Chen H, Wang L, Wang Z, Qiu T, Weng X. Ozone therapy could attenuate tubulointerstitial injury in adenine-induced CKD rats by mediating Nrf2 and NF-κB. *Iran J Basic Med Sci* 2016; **19**: 1136-1143 [PMID: 27872711]
97 **Ekici S**, Doğan Ekici AI, Öztürk G, Benli Aksungar F, Sinanoğlu O, Turan G, Lüleci N. Comparison of melatonin and ozone in the prevention of reperfusion injury following unilateral testicular torsion in rats. *Urology* 2012; **80**: 899-906 [PMID: 22950989 DOI: 10.1016/j.urology.2012.06.049]
98 **Park SY**, Yi EY, Jung M, Lee YM, Kim YJ. Ethyl pyruvate, an anti-inflammatory agent, inhibits tumor angiogenesis through inhibition of the NF-κB signaling pathway. *Cancer Lett* 2011; **303**: 150-154 [PMID: 21333439 DOI: 10.1016/j.canlet.2010.12.024]
99 **Turkmen S**, Cekic Gonenc O, Karaca Y, Mentese A, Demir S, Beyhun E, Sahin A, Gunduz A, Yulug E, Turedi S. The effect of ethyl pyruvate and N-acetylcysteine on ischemia-reperfusion injury in an experimental model of ischemic stroke. *Am J Emerg Med* 2016; **34**: 1804-1807 [PMID: 27324856 DOI: 10.1016/j.ajem.2016.06.003]
100 **Turkmen S**, Mentese A, Karaguzel E, Karaca Y, Kucuk A, Uzun A, Yulug E, Turedi S. A comparison of the effects of N-acetylcysteine and ethyl pyruvate on experimental testicular ischemia-reperfusion injury. *Fertil Steril* 2012; **98**: 626-631 [PMID: 22717346 DOI: 10.1016/j.fertnstert.2012.05.034]
101 **Singh D**, Chander V, Chopra K. Carvedilol attenuates ischemia-reperfusion-induced oxidative renal injury in rats. *Fundam Clin Pharmacol* 2004; **18**: 627-634 [PMID: 15548233 DOI: 10.1111/j.1472-8206.2004.00279.x]
102 **Hayashi T**, De Velasco MA, Saitou Y, Nose K, Nishioka T, Ishii T, Uemura H. Carvedilol protects tubular epithelial cells from ischemia-reperfusion injury by inhibiting oxidative stress. *Int J Urol* 2010; **17**: 989-995 [PMID: 20946473 DOI: 10.1111/j.1442-2042.2010.02644.x]
103 **Parlaktas BS**, Atilgan D, Gencten Y, Akbas A, Markoc F, Erdemir F, Ozyurt H, Uluocak N. The effects of carvedilol on ischemia-reperfusion injury in the rat testis. *Int Braz J Urol* 2014; **40**: 109-117 [PMID: 24642157 DOI: 10.1590/S1677-5538.IBJU.2014.01.16]
104 **Jiang D**, Wu D, Zhang Y, Xu B, Sun X, Li Z. Protective effects of hydrogen rich saline solution on experimental testicular ischemia-reperfusion injury in rats. *J Urol* 2012; **187**: 2249-2253 [PMID: 22503049 DOI: 10.1016/j.juro.2012.01.029]
105 **Fukuda K**, Asoh S, Ishikawa M, Yamamoto Y, Ohsawa I, Ohta S. Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. *Biochem Biophys Res Commun* 2007; **361**: 670-674 [PMID: 17673169 DOI: 10.1016/j.bbrc.2007.07.088]
106 **Hayashida K**, Sano M, Ohsawa I, Shinmura K, Tamaki K, Kimura K, Endo J, Katayama T, Kawamura A, Kohsaka S, Makino S, Ohta S, Ogawa S, Fukuda K. Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia-reperfusion injury. *Biochem Biophys Res Commun* 2008; **373**: 30-35 [PMID: 18541148 DOI: 10.1016/j.bbrc.2008.05.165]
107 **Lee JW**, Kim JI, Lee YA, Lee DH, Song CS, Cho YJ, Han JS. Inhaled hydrogen gas therapy for prevention of testicular ischemia/reperfusion injury in rats. *J Pediatr Surg* 2012; **47**: 736-742 [PMID: 22498389 DOI: 10.1016/j.jpedsurg.2011.09.035]
108 **Ozbal S**, Ergur BU, Erbil G, Tekmen I, Bagrıyanık A, Cavdar Z.

The effects of α-lipoic acid against testicular ischemia-reperfusion injury in Rats. *ScientificWorldJournal* 2012; **2012**: 489248 [PMID: 23193380 DOI: 10.1100/2012/489248]

109 **Shay KP**, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. *Biochim Biophys Acta* 2009; **1790**: 1149-1160 [PMID: 19664690 DOI: 10.1016/j.bbagen.2009.07.026]

110 **Biewenga GP**, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. *Gen Pharmacol* 1997; **29**: 315-331 [PMID: 9378235 DOI: 10.1016/S0306-3623(96)00474-0]

111 **Gorąca A**, Huk-Kolega H, Piechota A, Kleniewska P, Ciejka E, Skibska B. Lipoic acid - biological activity and therapeutic potential. *Pharmacol Rep* 2011; **63**: 849-858 [PMID: 22001972 DOI: 10.1016/S1734-1140(11)70600-4]

112 **Nagaraju GP**, Zafar SF, El-Rayes BF. Pleiotropic effects of genistein in metabolic, inflammatory, and malignant diseases. *Nutr Rev* 2013; **71**: 562-572 [PMID: 23865800 DOI: 10.1111/nure.12044]

113 **Kim SH**, Kim SH, Kim YB, Jeon YT, Lee SC, Song YS. Genistein inhibits cell growth by modulating various mitogen-activated protein kinases and AKT in cervical cancer cells. *Ann N Y Acad Sci* 2009; **1171**: 495-500 [PMID: 19723095 DOI: 10.1111/j.1749-6632.2009.04899.x]

114 **Kaminska B**, Ciereszko R, Kiezun M, Dusza L. In vitro effects of genistein and daidzein on the activity of adrenocortical steroidogenic enzymes in mature female pigs. *J Physiol Pharmacol* 2013; **64**: 103-108 [PMID: 23568977]

115 **Kim JS**, Heo K, Yi JM, Gong EJ, Yang K, Moon C, Kim SH. Genistein mitigates radiation-induced testicular injury. *Phytother Res* 2012; **26**: 1119-1125 [PMID: 22162311 DOI: 10.1002/ptr.3689]

116 **Al-Maghrebi M**, Renno WM. Genistein alleviates testicular ischemia and reperfusion injury-induced spermatogenic damage and oxidative stress by suppressing abnormal testicular matrix metalloproteinase system via the Notch 2/Jagged 1/Hes-1 and caspase-8 pathways. *J Physiol Pharmacol* 2016; **67**: 129-137 [PMID: 27010902]

117 **Ahn KS**, Sethi G, Aggarwal BB. Nuclear factor-kappa B: from clone to clinic. *Curr Mol Med* 2007; **7**: 619-637 [PMID: 18045141 DOI: 10.2174/156652407782564363]

118 **Kemahli E**, Yildiz M, Firat T, Özyalvaçli ME, Üyetürk U, Yilmaz B, Gücük A. An experimental study on effects of pyrrolidine dithiocarbamate on ischemia-reperfusion injury in testis. *Can Urol Assoc J* 2016; **10**: E104-E109 [PMID: 27330576 DOI: 10.5489/cuaj.3160]

119 **Scarabelli T**, Knight R. Urocortins: take them to heart. *Curr Med Chem Cardiovasc Hematol Agents* 2004; **2**: 335-342 [PMID: 15320777 DOI: 10.2174/1568016043356174]

120 **Takahashi K**. Distribution of urocortins and corticotropin-releasing factor receptors in the cardiovascular system. *Int J Endocrinol* 2012; **2012**: 395284 [PMID: 22675352 DOI: 10.1155/2012/395284]

121 **Sumii K**, Miyake H, Enatsu N, Chiba K, Fujisawa M. Characterization of urocortin as an anti-apoptotic protein in experimental ischemia-reperfusion model of the rat testis. *Biochem Biophys Res Commun* 2016; **479**: 387-392 [PMID: 27659706 DOI: 10.1016/j.bbrc.2016.09.091]

122 **Take G**, Erdogan D, Helvacioglu F, Göktas G, Ozbey G, Uluoglu C, Yücel B, Guney Y, Hicsonmez A, Ozkan S. Effect of melatonin and time of administration on irradiation-induced damage to rat testes. *Braz J Med Biol Res* 2009; **42**: 621-628 [PMID: 19578641 DOI: 10.1590/S0100-879X2009000700006]

123 **Kurcer Z**, Oguz E, Ozbilge H, Baba F, Aksoy N, Celik N. Effect of melatonin on testicular ischemia/reperfusion injury in rats: is this effect related to the proinflammatory cytokines? *Fertil Steril* 2008; **89**: 1468-1473 [PMID: 17681337 DOI: 10.1016/j.fertnstert.2007.04.065]

124 **Esteghamati A**, Eskandari D, Mirmiranpour H, Noshad S, Mousavizadeh M, Hedayati M, Nakhjavani M. Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: a randomized clinical trial. *Clin Nutr* 2013; **32**: 179-185 [PMID: 22963881 DOI: 10.1016/j.clnu.2012.08.006]

125 **Asghari A**, Akbari G, Meghdadi A, Mortazavi P. Effects of melatonin and metformin co-administration on testicular ischemia/reperfusion injury in rats. *J Pediatr Urol* 2016; **12**: 410.e1-410.e7 [PMID: 27595505 DOI: 10.1016/j.jpurol.2016.06.017]

126 **Erol B**, Sari U, Amasyali AS, Ozkanli S, Sogut S, Hanci V, Efiloglu O, Danacioglu YO, Engin P, Yencilek F, Atis G, Yildirim A, Alkoc OA, Caskurlu T. Comparison of combined antioxidants and thymoquinone in the prevention of testis ischemia - reperfusion injury. *Andrology* 2017; **5**: 119-124 [PMID: 27748062 DOI: 10.1111/andr.12268]

P- Reviewer: Chan WH, Weng CF **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Wu HL

World Journal of Methodology

Submit a Manuscript: http://www.f6publishing.com

World J Methodol 2017 June 26; 7(2): 46-54

DOI: 10.5662/wjm.v7.i2.46

ISSN 2222-0682 (online)

REVIEW

Role of metabolic stress for enhancing muscle adaptations: Practical applications

Marcelo Conrado de Freitas, Jose Gerosa-Neto, Nelo Eidy Zanchi, Fabio Santos Lira, Fabrício Eduardo Rossi

Marcelo Conrado de Freitas, Jose Gerosa-Neto, Fabio Santos Lira, Fabrício Eduardo Rossi, Exercise and Immunometabolism Research Group, Department of Physical Education, São Paulo State University (UNESP), Presidente Prudente, SP 19060-900, Brazil

Nelo Eidy Zanchi, Laboratory of Cellular and Molecular Biology of Skeletal Muscle (LABCEMME), Department of Physical Education, Federal University of Maranhão (UFMA), São Luís, MA 65085-580, Brazil

Author contributions: de Freitas MC, Gerosa-Neto J, Zanchi NE and Rossi FE carried out the study design, field work, and drafted the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Dr. Fabio Santos Lira, Exercise and Immunometabolism Research Group, Department of Physical Education, São Paulo State University (UNESP), Roberto Simonsen Street, nº 305 - Educacional center, Presidente Prudente, SP 19060-900, Brazil. fabiolira@fct.unesp.br
Telephone: +55-18-32295826
Fax: +55-18-32295388

Received: August 31, 2016
Peer-review started: September 5, 2016
First decision: November 10, 2016
Revised: March 10, 2017
Accepted: March 16, 2017
Article in press: March 17, 2017
Published online: June 26, 2017

Abstract

Metabolic stress is a physiological process that occurs during exercise in response to low energy that leads to metabolite accumulation [lactate, phosphate inorganic (Pi) and ions of hydrogen (H^+)] in muscle cells. Traditional exercise protocol (*i.e.*, Resistance training) has an important impact on the increase of metabolite accumulation, which influences hormonal release, hypoxia, reactive oxygen species (ROS) production and cell swelling. Changes in acute exercise routines, such as intensity, volume and rest between sets, are determinants for the magnitude of metabolic stress, furthermore, different types of training, such as low-intensity resistance training plus blood flow restriction and high intensity interval training, could be used to maximize metabolic stress during exercise. Thus, the objective of this review is to describe practical applications that induce metabolic stress and the potential effects of metabolic stress to increase systemic hormonal release, hypoxia, ROS production, cell swelling and muscle adaptations.

Key words: Metabolic stress; Muscle mass; Exercise

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This review aimed to describe practical applications for inducing metabolic stress and the potential effects on the increase of systemic hormonal release, hypoxia, reactive oxygen species production, and cell swelling. These effects are responsible for enhancing muscle adaptations through changes in exercise routines (intensity, volume, rest between sets) and training modes (resistance training, low-intensity resistance training plus blood flow restriction, and high intensity interval training).

de Freitas MC, Gerosa-Neto J, Zanchi NE, Lira FS, Rossi FE. Role

of metabolic stress for enhancing muscle adaptations: Practical applications. *World J Methodol* 2017; 7(2): 46-54 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i2/46.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i2.46

INTRODUCTION

It has been reported that chronic exercise can promote changes in many organs because of cellular adaptations. Skeletal muscle is extremely adjustable in response to contractile activity[1,2], therefore, repeated muscle contractions during exercise can lead to numerous metabolic modifications[3,4]. Overtime, these adaptive responses have shown beneficial effects on health, body composition and performance[5-7].

During acute exercise, the energy used by skeletal muscle contractions are essential in transforming organelles, enzymatic activity, intracellular signaling and transcriptional responses[8-10]. Metabolic stress is a physiological process that occurs during exercise in response to low energy which leads to metabolite accumulation [lactate, phosphate inorganic (Pi) and ions of hydrogen (H^+)] in muscle cells[11,12]. Researchers have suggested that metabolic stress has an important impact on hormonal release, hypoxia, cell swelling and production of reactive oxygen species (ROS)[13-15]. All of these components can initiate anabolic signaling for muscle growth and adaptations on energy metabolism[16].

In situations with elevated ATP hydrolysis and glycolytic flux in muscle cells, there is a great accumulation of adenosine monophosphate (AMP) and metabolites[12,17,18]. Furthermore, the reduction of intracellular oxygen levels can also lead to hypoxia[19]. All these metabolic parameters are a powerful stimulus to activate AMP-activated protein kinase (AMPK) and hypoxia-inducible factor (HIF-1α) pathway, the main regulators of mitochondrial biogenesis and angiogenesis[20,21].

Moreover, metabolite accumulation and hypoxia that is produced during exercise may increase ROS production through mitochondrial electron transport chain[22,23]. It is well established that ROS production by endurance exercise has positive effects on mitochondrial adaptations because it stimulates peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) and p38 mitogen-activated protein kinase (p38-MAPK) pathways[24]. Scientific evidence shows that suppression of ROS production through the use of the antioxidants impairs some adaptive responses to endurance exercise[25,26], and these results suggest that ROS production has positive effects on mitochondrial adaptations.

Nevertheless, besides stimulating mitochondrial biogenesis and angiogenesis, the metabolic stress also has positive effects on muscle hypertrophy. Resistance training (RT) has great impact on increasing metabolite accumulation, which influences hormonal release, hypoxia, ROS production and cell swelling. All these processes can mediate anabolic signaling that stimulates muscle protein synthesis and activation of satellite cells[13-15].

In this context, changes in acute exercise routines (intensity, volume and rest between sets) are the main factors in determining the magnitude of metabolic stress[27-29]. Furthermore, blood flow restriction training has been considered a tool to maximize metabolic stress[30,31]. Studies have reported great effects of this training method on aerobic adaptations and muscle hypertrophy[32,33].

Therefore, the purpose of this paper is to describe practical applications that cause metabolic stress. In addition, we will discuss the potential effects of metabolic stress on the increase of systemic hormonal release, hypoxia, ROS production, and cell swelling for enhancing muscle adaptations.

RESISTANCE TRAINING

Skeletal muscle hypertrophy depends on positive muscle protein balance (protein synthesis exceeds breakdown)[34]. Thus, RT is excellent for the stimulation of anabolic signaling and the promotion of muscle hypertrophy[35]. Metabolic stress is one of the primary mechanisms that makes RT increase muscle mass, mainly due to the rise of anabolic hormonal release, hypoxia, ROS production and cell swelling[13]. However, studies have shown that the magnitude of metabolic stress depends on the changes of acute RT program variables[14,15].

Scientific evidence shows that load, number of repetitions, and reset between intervals are important factors to induce metabolite accumulation. Gonzalez *et al*[29] found that acute RT with moderate repetitions combined with short rest intervals (70% 1RM, 10-12 repetitions and one minute rest interval) shows an increase in blood lactate, serum concentration of lactate dehydrogenase, growth hormone (GH) and cortisol when compared to higher loads, low repetitions combined with longer rest intervals (90% 1RM, 3-5 repetitions and three minute rest intervals). Concerning these findings, duration of rest intervals may reflect directly on the magnitude of metabolic stress. In a review study, researchers demonstrated that short interval sets (less than one minute) are essential in increasing blood lactate and GH production, mainly because of insufficient recovery of phosphocreatine and H^+ accumulation[36].

Additionally, Nishimura *et al*[37] demonstrated higher effects of muscle hypertrophy when RT is performed during hypoxia, possibly because of the strong influence of hormonal release, the recruitment of fast-twitch muscle fibers, ROS production and cell swelling[38]. During RT, muscle contractions compress blood vessels in active muscles, and this occlusion can lead to a reduction of oxygen levels and, consequently, resulting

in a hypoxic environment[39]. Intramuscular hypoxia during exercise can increase the necessity of anaerobic latic metabolism by activation of HIF-1α that regulates the expression of glycolytic enzymes[40]. Thus, exercise that produces high levels of lactate can be associated with hypoxia. One study showed that performing hypertrophy-type RT (70% 1RM, 10 repetitions and 90 s rest intervals) induces higher production of lactate and reduction in pH than performing a strength-type RT (85% 1RM, 4-6 repetitions with five minute rest intervals)[41]. In this context, it can be hypothesized that RT can generate hypoxia when performed at moderate/high repetitions combined with short rest intervals, possibly due to a high demand on anaerobic metabolism.

Furthermore, another study found that knee extension RT at low intensity (50% 1RM) generates a significant decrease in muscle oxygenation when compared to high-intensity (80% 1RM) exercise performed with one-second rest between repetitions[42]. These findings suggest, keeping continuous tension on muscles without relaxation can be essential to reducing oxygen levels and maximizing the levels of hypoxia in the skeletal muscle.

Research suggests that ROS production also has important implications on muscle hypertrophy[43,44]. In addition, studies have shown that utilization of antioxidants can modify protein signaling after a RT session and impairs muscle mass gains[45,46]. Muscle contractions during exercise produces ROS at low physiological levels and plays an important role in cell signaling to promote beneficial adaptations[47]. Researchers have found that the production of ROS has an influence in stimulating anabolic signaling, because ROS can act with a signaling molecule to activate the mammalian target of rapamycin (mTOR) through IGF-1 and MAPK pathways[48,49].

Although it is becoming clear that ROS has a profound impact on muscle hypertrophy, the limits of these adaptations are not clear. Hornberger *et al*[50] observed that selenium-deficient transgenic mice (animals with decreased protein expression of antioxidant enzymes containing selenium) exhibited an increased muscle hypertrophy when stimulated by synergist ablation (a muscle overload model), compared to other animals. In this study, rapamycin treatment (a pharmacological inhibitor of mTOR) completely abolished the hypertrophy effect, thus proving that mTOR is necessary for hypertrophy. It is interesting to note that, contrary to this study (where muscle antioxidant defense was decreased and muscle hypertrophy was optimized), other studies evaluating the impact of antioxidants in humans (through vitamin E and C supplementation) were shown to impair muscle hypertrophy response and cell signaling leading to muscle hypertrophy[45,46]. Several studies have observed that RT increases hypoxia, metabolite accumulation and ROS production, which seems to be strictly related[22,23,51,52]. In this context, we can hypothesize that RT with moderate/high repetitions and short rest intervals can be a stimulus to produce ROS.

Another potent anabolic signaling event produced by RT is cell swelling. Studies have demonstrated that cell swelling mediated by hydration can lead to an increase in protein synthesis and a decrease in proteolysis mainly through the activation of MAPK pathway[53-55]. During intense muscle contractions, veins are obstructed but the arterial system keeps the delivery of blood active[13]. This process can increase intracellular swelling, which leads to an increased pressure against the cytoskeleton. Thus, the cell perceives a threat and initiates an anabolic signaling response to promote reinforcement of its ultrastructure[56]. Studies indicate that cell swelling occurs during metabolite accumulation (lactate, H^+ and Pi) which leads to additional intracellular fluid[57,58]. Therefore, it seems reasonable to conclude that RT during hypertrophy causes high metabolite accumulation and can promote more cell swelling than strength RT.

Finally, another aspect that we should consider, especially among well-trained subjects, is RT with moderate/high repetitions until failure. Recent studies show that, when RT is executed with low load (30%-50% 1RM and 25-35 repetitions) until failure, hypertrophy is similar when compared to high load (70%-90% 1RM and 8-12 repetitions)[59-61]. Although no studies have confirmed this hypothesis, we believe that muscular failure can exert additional metabolic stress and then induce anabolic signaling. These findings suggest that the greater time under tension with moderate/high repetitions without relaxation combined with short rest interval and muscular failure can generate a strong hypertrophic response similar to RT with high loads. However, caution should be taken, because restricting rest periods would cause a reduction in the volume performed during a RT session, thus affecting hypertrophy process negatively[62].

This effect can be caused by high metabolic stress, leading to anabolic signaling through hypoxia, hormonal release, ROS production and cell swelling (Figure 1).

LOW-INTENSITY RESISTANCE TRAINING PLUS BLOOD FLOW RESTRICTION

During the last decade, blood flow restriction training (BFRT), also known as KAATSU or occlusion[63], combined with low-intensity strength training (20%-30% 1RM), has been shown to increase strength and muscle size among trained/untrained athletes[64-66] injured[67] and the elderly[68]. This training model requires the use of cuffs that are placed at the proximal ends of the upper arms or thighs reducing blood flow from the muscle (approximately 100-200 mmHg). Thus, the external pressure applied maintains arterial inflow while blocking venous outflow of blood[69], resulting in an ischemic/hypoxic environment that enhances the training effect[70].

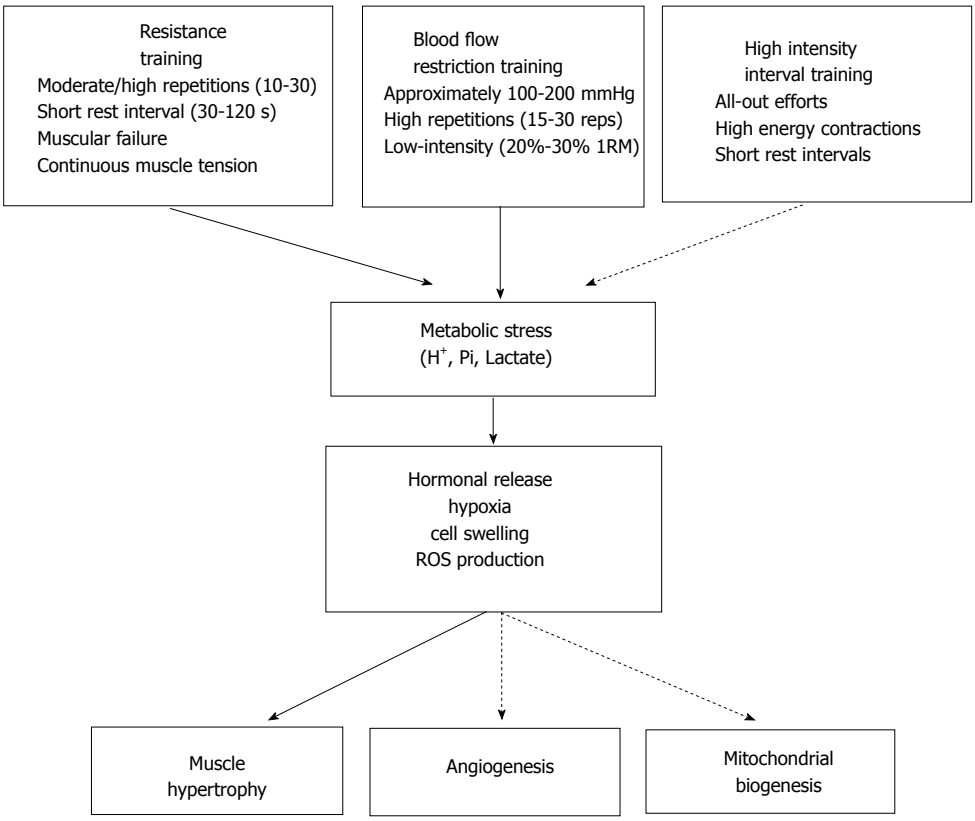

Figure 1 Role of metabolic stress induced by different kinds of training (resistance, blood flow restriction and high intensity interval intraining) for enhancing muscle adaptations. ROS: Reactive oxygen species.

Several studies have compared low-intensity strength training with BFRT and high-intensity without BFRT and demonstrated a significant increase in muscle cross-section area in both exercise protocols[64,69,71,72]. However, RT performed with moderate/high intensities seems to lead to similar degrees of muscle hypertrophy when combined with BFRT. It is not clear if the maximal degree of muscle hypertrophy can be optimized by increasing external loads or if the ceiling for maximal hypertrophy is achieved with low-moderate loads[73].

Cumming *et al*[74] performed a study with nine healthy volunteers performing five sets of unilateral knee extension at 30% of 1RM until failure combined with BFRT and the same workout without BFRT. Analysis of muscle biopsies revealed a rapid translocation of heat-shock proteins (HSP27 and aB-crystallin) from cytosol to cytoskeletal structures, both of which have been identified as important HSPs for repair and stabilization of stressed and damaged proteins[75]. This indicates that cytoskeletal proteins are stressed during BFRT even without myofibrillar disruptions. Thus, muscle hypertrophy induced by BFRT seems to be mediated by metabolic stress and mechanical tension, and sarcolemmal-bound mechanosensors (*i.e.*, integrins) stimulate intracellular anabolic and catabolic pathways, which convert mechanical energy into chemical signals, promoting protein synthesis instead of degradation[76].

Suga *et al*[77] investigated metabolic stress (intramuscular phosphocreatine (PCr), Pi, Diprotonated phosphate-H_2PO_4 and Intramuscular pH) in subjects that performed four unilateral plantar flexion (two min of 30 repetitions/min) using three different intensities (20%, 30% and 40% 1RM) with two resistance exercises (20% 1 RM and 65% 1RM) without BFRT. They concluded that 30% of 1RM induced a similar intramuscular metabolites and pH response than high-intensity RT without BFRT. In addition, Suga *et al*[31] also showed that multiple low-intensity BFRT sets increase fast-twitch fiber recruitment that could assist the slow twitch fiber to keep the strength during training, however, the authors did not observe statistical significance between multiple sets of high intensity exercise without BFRT. Therefore, these results suggest that multiple-set exercise are more effective than single-set RT.

Previous studies have shown that metabolic stress induced by low-intensity plus BFRT increases GH secretion and muscle hypertrophy[64,65,78], furthermore, this could stimulate metabolic stress markers, such as IL-6[79,80]. The recovery process is initiated by IL-6 by modulating muscle regulatory genes (*i.e.*, MyoD)[81-83] and activating muscle satellite cells[80], and therefore may play a role in regulating muscle growth/hypertrophy[80].

An acute increase in anabolic hormones (*e.g.*, testosterone, GH) has been found during short rest periods (30 to 60 s)[84], however, regarding cytokine production,

a recent study compared 30 s *vs* 90 s of rest after four sets of squat and four sets of bench press with 70% of 1RM until failure without BFRT in healthy adults and observed higher IL-6 levels when 90 s rest was used[85]. In addition, Phillips *et al*[86] reported greater post-exercise IL-6 concentrations with 65% of 1RM compared to 85% of 1RM with two minutes of recovery. Thus, short rest period induce an acute increase in anabolic hormones, however, it seems that longer recovery intervals combined with higher loads contribute to an increase in IL-6 concentration during RT.

Therefore, changes in variables, such as recovery intervals, volume, intensity, and repetition speed, could be used to optimize the specific adaptation during low-intensity RT plus BFRT.

HIGH-INTENSITY INTERVAL TRAINING

Studies have investigated the benefits of metabolic stress on skeletal muscle remodeling, angiogenesis, mitochondrial biogenesis, performance, and high-intensity interval training (HIIT) has shown to be a promising training routine. This exercise/training routine is based on high-intensity exercise sets with passive or low-intensity intervals between them. Endurance training adaptations have been found with HIIT[87,88].

The HIIT configuration allows intervals of effort and pause, and the various forms of stimuli can cause adaptations, such as: (1) mechanical stretching and muscle tension; (2) increase of ROS; (3) increase of intramuscular calcium concentrations and (4) changes of energy "status" in the cell.

Two HIIT routines that are commonly used are: four sets of 30 s at 100%[88] and four sets of four minutes[89] at 90%-95% of the maximum power (Pmax), velocity (Vmax) or maximum heart rate (HR max). Wahl *et al*[90] compared the acute responses of these two routine with another routine done continuously (two hours at 55% Pmax) in triathlon athletes and found that the most intense stimulus (four sets of 30 s at 100%) generated higher metabolic acidosis (pH) and higher concentrations of anabolic hormones (testosterone and GH) after the session. Supporting these results, Wahl *et al*[91] compared the use of buffer solution (sodium bicarbonate) and placebo with HIIT (four sets of 30 s at 100%), and showed a significant decrease in pH in the placebo group with increases in GH compared to the buffer group. The elevation of these hormones mean hypertrophic adaptations and also important stimuli expression of oxidative enzymes and erythropoiesis, promoting improvements in aerobic performance. This can be explained by the direct stimulation of bone marrow by testosterone, supporting the synthesis of erythropoietin in kidney cells[92].

Mitochondrial biogenesis is another adaptation of great importance in this process and one of the most studied. A key molecule for this adaptation is PGC-1α, a coactivator of several transcription factors related to metabolic and mitochondrial adaptations[93]. Burgomaster *et al*[87] found that six weeks of HIIT (three times per week, four to six sets of 30 at 100%) and continuous training (five times per week, 40 to 60 min at 55% VO_{2max}) showed significant improvements in mitochondrial functions with optimization lipid oxidation, increased activity of oxidative enzymes (citrate synthase and 3-hydroxyacyl CoA dehydrogenase) and contents of PGC-1α. The important finding of this study was the difference in the duration of training sessions, ranging from approximately 1.5 h to 4.5 h per week for HIIT and continuous training, respectively.

Due to the importance of PGC-1α, the expression and activation of proteins that stimulate it has great relevance. Two proteins, which are unquestionably stimulated by metabolic stress, are p38MAPK and AMPK[94-96]. Gibala *et al*[97] showed a significant increase in phosphorylation of AMPK and p38MAPK after acute sessions of HIIT (four sets of 30 s at 100%), and despite a great increase in mRNA of PGC-1α, its protein content did not change. Additionally, Little *et al*[98], using the same protocol of exercises, showed significantly higher values of p38MAPK after exercise, as well as an increase of 750% of mRNA PGC-1α and 66% of protein already in the nucleus of muscle cells, confirming the potential of these training routine.

Mitochondrial biogenesis and angiogenesis are essential for aerobic adaptations and improvement of performance. Considering the efficiency of HIIT (short training repetitions and metabolic stress), with BFRT seems to be beneficial to increase vascular adaptations. Consequently, Taylor *et al*[32] compared acute HIIT (four sets of 30 s at 100%), with HIIT + BFR (cuff in the thigh, two minutes, 130 mmHg). The results of these biopsies (vastus lateralis) showed a significant increase in p38MAPK after HIIT and HIIT+BFRT, with no differences between them. After three hours of exercise, a significant increase in mRNA PGC-1α was observed, vascular endothelial growth factor (VEGF) and its receptor (VEGFR-2), however mRNA of HIF-1α only increased in HIIT + BFRT. These results indicate that HIIT by itself is capable of stimulating angiogenesis, but the fact that only HIIT + BFRT increased HIF-1α cannot be overlooked, because it is a key factor for hypoxia and metabolic stress. Low PO_2 increases concentrations, favoring translocation to the nucleus and subsequent activation of VEGF in the human skeletal muscle[99].

CONCLUSION

Changes in acute exercise routine variables, such as intensity, volume, recovery interval and type of training are determinants that influence the magnitude of metabolic stress. Despite, traditional training protocol, such as RT, increase metabolite accumulation and influence hormonal release, hypoxia, ROS production and cell swelling. In this review, we discussed that low-intensity RT plus BFRT and HIIT are alternative exercise

routines that increase metabolic stress and muscle adaptation among different populations. However, the difference between exercise protocols used in literature and different levels of physical fitness should be considered when interpreting the results.

REFERENCES

1 **Coffey VG**, Shield A, Canny BJ, Carey KA, Cameron-Smith D, Hawley JA. Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. *Am J Physiol Endocrinol Metab* 2006; **290**: E849-E855 [PMID: 16338907 DOI: 10.1152/ajpendo.00299.2005]

2 **Ferraro E**, Giammarioli AM, Chiandotto S, Spoletini I, Rosano G. Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy. *Antioxid Redox Signal* 2014; **21**: 154-176 [PMID: 24450966 DOI: 10.1089/ars.2013.5773]

3 **Egan B**, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab* 2013; **17**: 162-184 [PMID: 23395166 DOI: 10.1016/j.cmet.2012.12.012]

4 **Hood DA**, Irrcher I, Ljubicic V, Joseph AM. Coordination of metabolic plasticity in skeletal muscle. *J Exp Biol* 2006; **209**: 2265-2275 [PMID: 16731803 DOI: 10.1242/jeb.02182]

5 **Camera DM**, Smiles WJ, Hawley JA. Exercise-induced skeletal muscle signaling pathways and human athletic performance. *Free Radic Biol Med* 2016; **98**: 131-143 [PMID: 26876650 DOI: 10.1016/j.freeradbiomed.2016.02.007]

6 **Carter CS**, Hofer T, Seo AY, Leeuwenburgh C. Molecular mechanisms of life- and health-span extension: role of calorie restriction and exercise intervention. *Appl Physiol Nutr Metab* 2007; **32**: 954-966 [PMID: 18059622 DOI: 10.1139/H07-085]

7 **Kraemer WJ**, Deschenes MR, Fleck SJ. Physiological adaptations to resistance exercise. Implications for athletic conditioning. *Sports Med* 1988; **6**: 246-256 [PMID: 3067312]

8 **Adhihetty PJ**, Irrcher I, Joseph AM, Ljubicic V, Hood DA. Plasticity of skeletal muscle mitochondria in response to contractile activity. *Exp Physiol* 2003; **88**: 99-107 [PMID: 12525859]

9 **Flück M**, Hoppeler H. Molecular basis of skeletal muscle plasticity--from gene to form and function. *Rev Physiol Biochem Pharmacol* 2003; **146**: 159-216 [PMID: 12605307 DOI: 10.1007/s10254-002-0004-7]

10 **Coffey VG**, Hawley JA. The molecular bases of training adaptation. *Sports Med* 2007; **37**: 737-763 [PMID: 17722947]

11 **Tesch PA**, Colliander EB, Kaiser P. Muscle metabolism during intense, heavy-resistance exercise. *Eur J Appl Physiol Occup Physiol* 1986; **55**: 362-366 [PMID: 3758035]

12 **Volianitis S**, Secher NH, Quistorff B. The intracellular to extracellular proton gradient following maximal whole body exercise and its implication for anaerobic energy production. *Eur J Appl Physiol* 2010; **109**: 1171-1177 [PMID: 20379830 DOI: 10.1007/s00421-010-1451-5]

13 **Schoenfeld BJ**. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res* 2010; **24**: 2857-2872 [PMID: 20847704 DOI: 10.1519/JSC.0b013e3181e840f3]

14 **Schoenfeld BJ**. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med* 2013; **43**: 179-194 [PMID: 23338987 DOI: 10.1007/s40279-013-0017-1]

15 **Pearson SJ**, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med* 2015; **45**: 187-200 [PMID: 25249278 DOI: 10.1007/s40279-014-0264-9]

16 **Ozaki H**, Loenneke JP, Buckner SL, Abe T. Muscle growth across a variety of exercise modalities and intensities: Contributions of mechanical and metabolic stimuli. *Med Hypotheses* 2016; **88**: 22-26 [PMID: 26880629 DOI: 10.1016/j.mehy.2015.12.026]

17 **Robergs RA**, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R502-R516 [PMID: 15308499 DOI: 10.1152/ajpregu.00114.2004]

18 **Wojtaszewski JF**, Nielsen P, Hansen BF, Richter EA, Kiens B. Isoform-specific and exercise intensity-dependent activation of 5'-AMP-activated protein kinase in human skeletal muscle. *J Physiol* 2000; **528 Pt 1**: 221-226 [PMID: 11018120]

19 **Casey DP**, Joyner MJ. Local control of skeletal muscle blood flow during exercise: influence of available oxygen. *J Appl Physiol* (1985) 2011; **111**: 1527-1538 [PMID: 21885800 DOI: 10.1152/japplphysiol.00895.2011]

20 **Niemi H**, Honkonen K, Korpisalo P, Huusko J, Kansanen E, Merentie M, Rissanen TT, André H, Pereira T, Poellinger L, Alitalo K, Ylä-Herttuala S. HIF-1α and HIF-2α induce angiogenesis and improve muscle energy recovery. *Eur J Clin Invest* 2014; **44**: 989-999 [PMID: 25208310 DOI: 10.1111/eci.12333]

21 **Marcinko K**, Steinberg GR. The role of AMPK in controlling metabolism and mitochondrial biogenesis during exercise. *Exp Physiol* 2014; **99**: 1581-1585 [PMID: 25261498 DOI: 10.1113/expphysiol.2014.082255]

22 **Clanton TL**. Hypoxia-induced reactive oxygen species formation in skeletal muscle. *J Appl Physiol* (1985) 2007; **102**: 2379-2388 [PMID: 17289907 DOI: 10.1152/japplphysiol.01298.2006]

23 **Morales-Alamo D**, Calbet JA. Free radicals and sprint exercise in humans. *Free Radic Res* 2014; **48**: 30-42 [PMID: 23879691 DOI: 10.3109/10715762.2013.825043]

24 **Ji LL**, Kang C, Zhang Y. Exercise-induced hormesis and skeletal muscle health. *Free Radic Biol Med* 2016; **98**: 113-122 [PMID: 26916558 DOI: 10.1016/j.freeradbiomed.2016.02.025]

25 **Strobel NA**, Peake JM, Matsumoto A, Marsh SA, Coombes JS, Wadley GD. Antioxidant supplementation reduces skeletal muscle mitochondrial biogenesis. *Med Sci Sports Exerc* 2011; **43**: 1017-1024 [PMID: 21085043 DOI: 10.1249/MSS.0b013e318203afa3]

26 **Merry TL**, Ristow M. Do antioxidant supplements interfere with skeletal muscle adaptation to exercise training? *J Physiol* 2016; **594**: 5135-5147 [PMID: 26638792 DOI: 10.1113/JP270654]

27 **Spiering BA**, Kraemer WJ, Anderson JM, Armstrong LE, Nindl BC, Volek JS, Maresh CM. Resistance exercise biology: manipulation of resistance exercise programme variables determines the responses of cellular and molecular signalling pathways. *Sports Med* 2008; **38**: 527-540 [PMID: 18557656]

28 **Goto K**, Ishii N, Kizuka T, Takamatsu K. The impact of metabolic stress on hormonal responses and muscular adaptations. *Med Sci Sports Exerc* 2005; **37**: 955-963 [PMID: 15947720]

29 **Gonzalez AM**, Hoffman JR, Townsend JR, Jajtner AR, Boone CH, Beyer KS, Baker KM, Wells AJ, Mangine GT, Robinson EH, Church DD, Oliveira LP, Willoughby DS, Fukuda DH, Stout JR. Intramuscular anabolic signaling and endocrine response following high volume and high intensity resistance exercise protocols in trained men. *Physiol Rep* 2015; **3**: pii: e12466 [PMID: 26197935 DOI: 10.14814/phy2.12466]

30 **Sugaya M**, Yasuda T, Suga T, Okita K, Abe T. Change in intramuscular inorganic phosphate during multiple sets of blood flow-restricted low-intensity exercise. *Clin Physiol Funct Imaging* 2011; **31**: 411-413 [PMID: 21771263 DOI: 10.1111/j.1475-097X.2011.01033.x]

31 **Suga T**, Okita K, Takada S, Omokawa M, Kadoguchi T, Yokota T, Hirabayashi K, Takahashi M, Morita N, Horiuchi M, Kinugawa S, Tsutsui H. Effect of multiple set on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *Eur J Appl Physiol* 2012; **112**: 3915-3920 [PMID: 22415101 DOI: 10.1007/s00421-012-2377-x]

32 **Taylor CW**, Ingham SA, Ferguson RA. Acute and chronic effect of sprint interval training combined with postexercise blood-flow restriction in trained individuals. *Exp Physiol* 2016; **101**: 143-154 [PMID: 26391312 DOI: 10.1113/EP085293]

33 **Slysz J**, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & amp; meta-analysis. *J Sci Med Sport* 2016; **19**: 669-675 [PMID: 26463594 DOI: 10.1016/j.jsams.2015.09.005]

34 **Phillips SM**. Physiologic and molecular bases of muscle hypertrophy and atrophy: impact of resistance exercise on human skeletal muscle

(protein and exercise dose effects). *Appl Physiol Nutr Metab* 2009; **34**: 403-410 [PMID: 19448706 DOI: 10.1139/H09-042]
35 **Damas F**, Phillips S, Vechin FC, Ugrinowitsch C. A review of resistance training-induced changes in skeletal muscle protein synthesis and their contribution to hypertrophy. *Sports Med* 2015; **45**: 801-807 [PMID: 25739559 DOI: 10.1007/s40279-015-0320-0]
36 **Henselmans M**, Schoenfeld BJ. The effect of inter-set rest intervals on resistance exercise-induced muscle hypertrophy. *Sports Med* 2014; **44**: 1635-1643 [PMID: 25047853 DOI: 10.1007/s40279-014-0228-0]
37 **Nishimura A**, Sugita M, Kato K, Fukuda A, Sudo A, Uchida A. Hypoxia increases muscle hypertrophy induced by resistance training. *Int J Sports Physiol Perform* 2010; **5**: 497-508 [PMID: 21266734]
38 **Scott BR**, Slattery KM, Sculley DV, Dascombe BJ. Hypoxia and resistance exercise: a comparison of localized and systemic methods. *Sports Med* 2014; **44**: 1037-1054 [PMID: 24715613 DOI: 10.1007/s40279-014-0177-7]
39 **Tamaki T**, Uchiyama S, Tamura T, Nakano S. Changes in muscle oxygenation during weight-lifting exercise. *Eur J Appl Physiol Occup Physiol* 1994; **68**: 465-469 [PMID: 7957136]
40 **Favier FB**, Britto FA, Freyssenet DG, Bigard XA, Benoit H. HIF-1-driven skeletal muscle adaptations to chronic hypoxia: molecular insights into muscle physiology. *Cell Mol Life Sci* 2015; **72**: 4681-4696 [PMID: 26298291 DOI: 10.1007/s00018-015-2025-9]
41 **Nicholson G**, Mcloughlin G, Bissas A, Ispoglou T. Do the acute biochemical and neuromuscular responses justify the classification of strength- and hypertrophy-type resistance exercise? *J Strength Cond Res* 2014; **28**: 3188-3199 [PMID: 24832969 DOI: 10.1519/JSC.0000000000000519]
42 **Tanimoto M**, Ishii N. Effects of low-intensity resistance exercise with slow movement and tonic force generation on muscular function in young men. *J Appl Physiol* (1985) 2006; **100**: 1150-1157 [PMID: 16339347 DOI: 10.1152/japplphysiol.00741.2005]
43 **Wadley GD**. A role for reactive oxygen species in the regulation of skeletal muscle hypertrophy. *Acta Physiol* (Oxf) 2013; **208**: 9-10 [PMID: 23383683 DOI: 10.1111/apha.12078]
44 **Ito N**, Ruegg UT, Kudo A, Miyagoe-Suzuki Y, Takeda S. Activation of calcium signaling through Trpv1 by nNOS and peroxynitrite as a key trigger of skeletal muscle hypertrophy. *Nat Med* 2013; **19**: 101-106 [PMID: 23202294 DOI: 10.1038/nm.3019]
45 **Bjørnsen T**, Salvesen S, Berntsen S, Hetlelid KJ, Stea TH, Lohne-Seiler H, Rohde G, Haraldstad K, Raastad T, Køpp U, Haugeberg G, Mansoor MA, Bastani NE, Blomhoff R, Stølevik SB, Seynnes OR, Paulsen G. Vitamin C and E supplementation blunts increases in total lean body mass in elderly men after strength training. *Scand J Med Sci Sports* 2016; **26**: 755-763 [PMID: 26129928 DOI: 10.1111/sms.12506]
46 **Paulsen G**, Hamarsland H, Cumming KT, Johansen RE, Hulmi JJ, Børsheim E, Wiig H, Garthe I, Raastad T. Vitamin C and E supplementation alters protein signalling after a strength training session, but not muscle growth during 10 weeks of training. *J Physiol* 2014; **592**: 5391-5408 [PMID: 25384788 DOI: 10.1113/jphysiol.2014.279950]
47 **Thannickal VJ**, Fanburg BL. Reactive oxygen species in cell signaling. *Am J Physiol Lung Cell Mol Physiol* 2000; **279**: L1005-L1028 [PMID: 11076791]
48 **Handayaningsih AE**, Iguchi G, Fukuoka H, Nishizawa H, Takahashi M, Yamamoto M, Herningtyas EH, Okimura Y, Kaji H, Chihara K, Seino S, Takahashi Y. Reactive oxygen species play an essential role in IGF-I signaling and IGF-I-induced myocyte hypertrophy in C2C12 myocytes. *Endocrinology* 2011; **152**: 912-921 [PMID: 21239445 DOI: 10.1210/en.2010-0981]
49 **Kefaloyianni E**, Gaitanaki C, Beis I. ERK1/2 and p38-MAPK signalling pathways, through MSK1, are involved in NF-kappaB transactivation during oxidative stress in skeletal myoblasts. *Cell Signal* 2006; **18**: 2238-2251 [PMID: 16806820 DOI: 10.1016/j.cellsig.2006.05.004]
50 **Hornberger TA**, McLoughlin TJ, Leszczynski JK, Armstrong DD, Jameson RR, Bowen PE, Hwang ES, Hou H, Moustafa ME, Carlson BA, Hatfield DL, Diamond AM, Esser KA. Selenoprotein-deficient transgenic mice exhibit enhanced exercise-induced muscle growth. *J Nutr* 2003; **133**: 3091-3097 [PMID: 14519790]
51 **Morales-Alamo D**, Ponce-González JG, Guadalupe-Grau A, Rodríguez-García L, Santana A, Cusso MR, Guerrero M, Guerra B, Dorado C, Calbet JA. Increased oxidative stress and anaerobic energy release, but blunted Thr172-AMPKα phosphorylation, in response to sprint exercise in severe acute hypoxia in humans. *J Appl Physiol* (1985) 2012; **113**: 917-928 [PMID: 22858621 DOI: 10.1152/japplphysiol.00415.2012]
52 **Korthuis RJ**, Granger DN, Townsley MI, Taylor AE. The role of oxygen-derived free radicals in ischemia-induced increases in canine skeletal muscle vascular permeability. *Circ Res* 1985; **57**: 599-609 [PMID: 4042285]
53 **Lang F**, Busch GL, Ritter M, Völkl H, Waldegger S, Gulbins E, Häussinger D. Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 1998; **78**: 247-306 [PMID: 9457175]
54 **Grant AC**, Gow IF, Zammit VA, Shennan DB. Regulation of protein synthesis in lactating rat mammary tissue by cell volume. *Biochim Biophys Acta* 2000; **1475**: 39-46 [PMID: 10806336]
55 **Zhou X**, Naguro I, Ichijo H, Watanabe K. Mitogen-activated protein kinases as key players in osmotic stress signaling. *Biochim Biophys Acta* 2016; **1860**: 2037-2052 [PMID: 27261090 DOI: 10.1016/j.bbagen.2016.05.032]
56 **Lang F**. Mechanisms and significance of cell volume regulation. *J Am Coll Nutr* 2007; **26**: 613S-623S [PMID: 17921474]
57 **Sjøgaard G**, Adams RP, Saltin B. Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. *Am J Physiol* 1985; **248**: R190-R196 [PMID: 3970234]
58 **Sjøgaard G**. Water and electrolyte fluxes during exercise and their relation to muscle fatigue. *Acta Physiol Scand Suppl* 1986; **556**: 129-136 [PMID: 3471050]
59 **Mitchell CJ**, Churchward-Venne TA, West DW, Burd NA, Breen L, Baker SK, Phillips SM. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *J Appl Physiol* (1985) 2012; **113**: 71-77 [PMID: 22518835 DOI: 10.1152/japplphysiol.00307.2012]
60 **Morton RW**, Oikawa SY, Wavell CG, Mazara N, McGlory C, Quadrilatero J, Baechler BL, Baker SK, Phillips SM. Neither load nor systemic hormones determine resistance training-mediated hypertrophy or strength gains in resistance-trained young men. *J Appl Physiol* (1985) 2016; **121**: 129-138 [PMID: 27174923 DOI: 10.1152/japplphysiol.00154.2016]
61 **Schoenfeld BJ**, Peterson MD, Ogborn D, Contreras B, Sonmez GT. Effects of Low- vs. High-Load Resistance Training on Muscle Strength and Hypertrophy in Well-Trained Men. *J Strength Cond Res* 2015; **29**: 2954-2963 [PMID: 25853914 DOI: 10.1519/JSC.0000000000000958]
62 **Helms ER**, Cronin J, Storey A, Zourdos MC. Application of the Repetitions in Reserve-Based Rating of Perceived Exertion Scale for Resistance Training. *Strength Cond J* 2016; **38**: 42-49 [PMID: 27531969 DOI: 10.1519/SSC.0000000000000218]
63 **Abe T**, Beekley MD, Hinata S, Koizumi K, Sato Y. Day-today change in muscle strength and MRI-measured skeletal muscle size during 7 days KAATSU resistance training: A case study. *Int J KAATSU Train Res* 2005; **1**: 71-76
64 **Takarada Y**, Sato Y, Ishii N. Effects of resistance exercise combined with vascular occlusion on muscle function in athletes. *Eur J Appl Physiol* 2002; **86**: 308-314 [PMID: 11990743]
65 **Wilson JM**, Lowery RP, Joy JM, Loenneke JP, Naimo MA. Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. *J Strength Cond Res* 2013; **27**: 3068-3075 [PMID: 23446173 DOI: 10.1519/JSC.0b013e31828a1ffa]
66 **Clark BC**, Manini TM, Hoffman RL, Williams PS, Guiler MK, Knutson MJ, McGlynn ML, Kushnick MR. Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand J Med Sci Sports* 2011; **21**: 653-662 [PMID: 21917016 DOI: 10.1111/j.1600-0838.2010.01100.x]
67 **Loenneke JP**, Young KC, Wilson JM, Andersen JC. Rehabilitation of an osteochondral fracture using blood flow restricted exercise: a

case review. *J Bodyw Mov Ther* 2013; **17**: 42-45 [PMID: 23294682 DOI: 10.1016/j.jbmt.2012.04.006]
68 **Libardi CA**, Chacon-Mikahil MP, Cavaglieri CR, Tricoli V, Roschel H, Vechin FC, Conceição MS, Ugrinowitsch C. Effect of concurrent training with blood flow restriction in the elderly. *Int J Sports Med* 2015; **36**: 395-399 [PMID: 25700103 DOI: 10.1055/s-0034-1390496]
69 **Kaijser L**, Sundberg CJ, Eiken O, Nygren A, Esbjörnsson M, Sylvén C, Jansson E. Muscle oxidative capacity and work performance after training under local leg ischemia. *J Appl Physiol* (1985) 1990; **69**: 785-787 [PMID: 2146245]
70 **Takada S**, Okita K, Suga T, Omokawa M, Kadoguchi T, Sato T, Takahashi M, Yokota T, Hirabayashi K, Morita N, Horiuchi M, Kinugawa S, Tsutsui H. Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. *J Appl Physiol* (1985) 2012; **113**: 199-205 [PMID: 22628373 DOI: 10.1152/japplphysiol.00149.2012]
71 **Farup J**, de Paoli F, Bjerg K, Riis S, Ringgard S, Vissing K. Blood flow restricted and traditional resistance training performed to fatigue produce equal muscle hypertrophy. *Scand J Med Sci Sports* 2015; **25**: 754-763 [PMID: 25603897 DOI: 10.1111/sms.12396]
72 **Ellefsen S**, Hammarström D, Strand TA, Zacharoff E, Whist JE, Rauk I, Nygaard H, Vegge G, Hanestadhaugen M, Wernbom M, Cumming KT, Rønning R, Raastad T, Rønnestad BR. Blood flow-restricted strength training displays high functional and biological efficacy in women: a within-subject comparison with high-load strength training. *Am J Physiol Regul Integr Comp Physiol* 2015; **309**: R767-R779 [PMID: 26202071 DOI: 10.1152/ajpregu.00497.2014]
73 **Laurentino G**, Ugrinowitsch C, Aihara AY, Fernandes AR, Parcell AC, Ricard M, Tricoli V. Effects of strength training and vascular occlusion. *Int J Sports Med* 2008; **29**: 664-667 [PMID: 18213536 DOI: 10.1055/s-2007-989405]
74 **Cumming KT**, Paulsen G, Wernbom M, Ugelstad I, Raastad T. Acute response and subcellular movement of HSP27, αB-crystallin and HSP70 in human skeletal muscle after blood-flow-restricted low-load resistance exercise. *Acta Physiol* (Oxf) 2014; **211**: 634-646 [PMID: 24762334 DOI: 10.1111/apha.12305]
75 **Noble EG**, Milne KJ, Melling CW. Heat shock proteins and exercise: a primer. *Appl Physiol Nutr Metab* 2008; **33**: 1050-1065 [PMID: 18923583 DOI: 10.1139/H08-069]
76 **Zou K**, Meador BM, Johnson B, Huntsman HD, Mahmassani Z, Valero MC, Huey KA, Boppart MD. The $\alpha_7\beta_1$-integrin increases muscle hypertrophy following multiple bouts of eccentric exercise. *J Appl Physiol* (1985) 2011; **111**: 1134-1141 [PMID: 21817112 DOI: 10.1152/japplphysiol.00081.2011]
77 **Suga T**, Okita K, Morita N, Yokota T, Hirabayashi K, Horiuchi M, Takada S, Omokawa M, Kinugawa S, Tsutsui H. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* (1985) 2010; **108**: 1563-1567 [PMID: 20360434 DOI: 10.1152/japplphysiol.00504.2009]
78 **Fujita S**, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, Sato Y, Volpi E, Rasmussen BB. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* (1985) 2007; **103**: 903-910 [PMID: 17569770 DOI: 10.1152/japplphysiol.00195.2007]
79 **Patterson SD**, Leggate M, Nimmo MA, Ferguson RA. Circulating hormone and cytokine response to low-load resistance training with blood flow restriction in older men. *Eur J Appl Physiol* 2013; **113**: 713-719 [PMID: 22922803 DOI: 10.1007/s00421-012-2479-5]
80 **Serrano AL**, Baeza-Raja B, Perdiguero E, Jardí M, Muñoz-Cánoves P. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab* 2008; **7**: 33-44 [PMID: 18177723 DOI: 10.1016/j.cmet.2007.11.011]
81 **Warren GL**, Hulderman T, Jensen N, McKinstry M, Mishra M, Luster MI, Simeonova PP. Physiological role of tumor necrosis factor alpha in traumatic muscle injury. *FASEB J* 2002; **16**: 1630-1632 [PMID: 12207010 DOI: 10.1096/fj.02-0187fje]
82 **Gleeson M**, Bishop NC. The T cell and NK cell immune response to exercise. *Ann Transplant* 2005; **10**: 43-48 [PMID: 17037088]
83 **Tidball JG**. Inflammatory processes in muscle injury and repair. *Am J Physiol Regul Integr Comp Physiol* 2005; **288**: R345-R353 [PMID: 15637171 DOI: 10.1152/ajpregu.00454.2004]
84 **Kraemer WJ**, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med* 2005; **35**: 339-361 [PMID: 15831061]
85 **Rossi FE**, Gerosa-Neto J, Zanchi NE, Cholewa JM, Lira FS. Impact of Short and Moderate Rest Intervals on the Acute Immunometabolic Response to Exhaustive Strength Exercise: Part I. *J Strength Cond Res* 2016; **30**: 1563-1569 [PMID: 26978328 DOI: 10.1519/JSC.0000000000001189]
86 **Phillips MD**, Mitchell JB, Currie-Elolf LM, Yellott RC, Hubing KA. Influence of commonly employed resistance exercise protocols on circulating IL-6 and indices of insulin sensitivity. *J Strength Cond Res* 2010; **24**: 1091-1101 [PMID: 20168253 DOI: 10.1519/JSC.0b013e3181cc2212]
87 **Burgomaster KA**, Howarth KR, Phillips SM, Rakobowchuk M, Macdonald MJ, McGee SL, Gibala MJ. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J Physiol* 2008; **586**: 151-160 [PMID: 17991697 DOI: 10.1113/jphysiol.2007.142109]
88 **Gibala MJ**, Little JP, van Essen M, Wilkin GP, Burgomaster KA, Safdar A, Raha S, Tarnopolsky MA. Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol* 2006; **575**: 901-911 [PMID: 16825308 DOI: 10.1113/jphysiol.2006.112094]
89 **Helgerud J**, Høydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, Simonsen T, Helgesen C, Hjorth N, Bach R, Hoff J. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc* 2007; **39**: 665-671 [PMID: 17414804 DOI: 10.1249/mss.0b013e3180304570]
90 **Wahl P**, Mathes S, Köhler K, Achtzehn S, Bloch W, Mester J. Acute metabolic, hormonal, and psychological responses to different endurance training protocols. *Horm Metab Res* 2013; **45**: 827-833 [PMID: 23794400 DOI: 10.1055/s-0033-1347242]
91 **Wahl P**, Zinner C, Achtzehn S, Bloch W, Mester J. Effect of high- and low-intensity exercise and metabolic acidosis on levels of GH, IGF-I, IGFBP-3 and cortisol. *Growth Horm IGF Res* 2010; **20**: 380-385 [PMID: 20801067 DOI: 10.1016/j.ghir.2010.08.001]
92 **Shahidi NT**. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. *Clin Ther* 2001; **23**: 1355-1390 [PMID: 11589254]
93 **Hood DA**. Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle. *Appl Physiol Nutr Metab* 2009; **34**: 465-472 [PMID: 19448716 DOI: 10.1139/H09-045]
94 **Jäger S**, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. *Proc Natl Acad Sci USA* 2007; **104**: 12017-12022 [PMID: 17609368 DOI: 10.1073/pnas.0705070104]
95 **Knutti D**, Kressler D, Kralli A. Regulation of the transcriptional coactivator PGC-1 via MAPK-sensitive interaction with a repressor. *Proc Natl Acad Sci USA* 2001; **98**: 9713-9718 [PMID: 11481440 DOI: 10.1073/pnas.171184698]
96 **Fan M**, Rhee J, St-Pierre J, Handschin C, Puigserver P, Lin J, Jäeger S, Erdjument-Bromage H, Tempst P, Spiegelman BM. Suppression of mitochondrial respiration through recruitment of p160 myb binding protein to PGC-1alpha: modulation by p38 MAPK. *Genes Dev* 2004; **18**: 278-289 [PMID: 14744933 DOI: 10.1101/gad.1152204]
97 **Gibala MJ**, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle. *J Appl Physiol* (1985) 2009; **106**: 929-934 [PMID: 19112161 DOI: 10.1152/japplphysiol.90880.2008]
98 **Little JP**, Safdar A, Bishop D, Tarnopolsky MA, Gibala MJ. An acute bout of high-intensity interval training increases the nuclear abundance of PGC-1α and activates mitochondrial biogenesis in human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol* 2011; **300**: R1303-R1310 [PMID: 21451146 DOI: 10.1152/ajpregu.00538.2010]

99 **Ameln H**, Gustafsson T, Sundberg CJ, Okamoto K, Jansson E, Poellinger L, Makino Y. Physiological activation of hypoxia inducible factor-1 in human skeletal muscle. *FASEB J* 2005; **19**: 1009-1011 [PMID: 15811877 DOI: 10.1096/fj.04-2304fje]

P- Reviewer: Dobrian AD, Elner VM, Kimchi A, Li W
S- Editor: Song XX **L- Editor**: A **E- Editor**: Wu HL

World Journal of Methodology

Submit a Manuscript: http://www.f6publishing.com

World J Methodol 2017 June 26; 7(2): 55-67

DOI: 10.5662/wjm.v7.i2.55

ISSN 2222-0682 (online)

REVIEW

Targeted temperature management in neurological intensive care unit

Sombat Muengtaweepongsa, Winchana Srivilaithon

Sombat Muengtaweepongsa, Division of Neurology, Department of Medicine, Faculty of Medicine, Thammasat University, Pathum Thani 12120, Thailand

Winchana Srivilaithon, Department of Emergency Medicine, Thammasat University Hospital, Pathum Thani 12120, Thailand

Author contributions: Muengtaweepongsa S contributed to conception and design of the work, data collection, drafing the article, critical revision of the article, final approval; Srivilaithon W contributed to data collection, drafing the article.

Conflict-of-interest statement: No conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Sombat Muengtaweepongsa, MD, Division of Neurology, Department of Medicine, Faculty of Medicine, Thammasat University, Rangsit Campus, Patholyothin Rd., Pathum Thani 12120, Thailand. musombat@tu.ac.th
Telephone: +66-29-269794
Fax: +66-29-269793

Received: January 30, 2017
Peer-review started: February 12, 2017
First decision: March 28, 2017
Revised: April 12, 2017
Accepted: May 18, 2017
Article in press: May 19, 2017
Published online: June 26, 2017

Abstract

Targeted temperature management (TTM) shows the most promising neuroprotective therapy against hypoxic/ischemic encephalopathy (HIE). In addition, TTM is also useful for treatment of elevated intracranial pressure (ICP). HIE and elevated ICP are common catastrophic conditions in patients admitted in Neurologic intensive care unit (ICU). The most common cause of HIE is cardiac arrest. Randomized control trials demonstrate clinical benefits of TTM in patients with post-cardiac arrest. Although clinical benefit of ICP control by TTM in some specific critical condition, for an example in traumatic brain injury, is still controversial, efficacy of ICP control by TTM is confirmed by both *in vivo* and *in vitro* studies. Several methods of TTM have been reported in the literature. TTM can apply to various clinical conditions associated with hypoxic/ischemic brain injury and elevated ICP in Neurologic ICU.

Key words: Targeted temperature management; Neuroprotective therapy; Ischemic/hypoxic encephalopathy; Intracranial pressure; Surface cooling; Endovascular cooling

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Two main purposes of targeted temperature management (TTM) in patients admitted in neurological intensive care unit are neuroprotective therapy and intracranial pressure (ICP) control. TTM is the most potent neuroprotective treatment due to its numerous methods of protection against ischemic/hypoxic injury. TTM provides capable ICP reductive action. Two most popular methods using in clinical practice and clinical trials are invasive endovascular technique and non-invasive surface cooling. Fast induction, smooth maintenance and slow rewarming are the important steps to achieve ideal TTM.

Muengtaweepongsa S, Srivilaithon W. Targeted temperature management in neurological intensive care unit. *World J*

Methodol 2017; 7(2): 55-67 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i2/55.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i2.55

INTRODUCTION

Clinical benefit of therapeutic hypothermia in patients with post-cardiac arrest syndrome (PCAS) has been demonstrated by two randomized control trials since 2002[1,2]. However, the term "therapeutic hypothermia" has been replaced with "targeted temperature management (TTM)" since 2011 after the meeting of five major professional physician societies[3]. TTM defines as a type of treatment that reduces a subject's core temperature until a specific target with the purpose in salvage or alleviate the tissue injury from deficiency of blood perfusion[4]. TTM is recognized as a only established neuroprotective therapy for hypoxic/ischemic brain injury, particularly in patients after cardiac arrest[5]. The clinical practice guidelines state that TTM should apply as a major treatment for patients following successful resuscitation from cardiac arrest[6-10].

Elevated intracranial pressure (ICP) is one of the common conditions found in patients admitted in neurologic intensive care unit (ICU)[11]. Many clinical and animal trials demonstrate that TTM effectively lowers ICP[12]. However, the application of TTM as ICP control in each particular disease, for examples in primary intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI) and cerebral infarct, needs to be proved by large randomized controlled trial[13].

HYPOXIC/ISCHEMIC CASCADE

Hypoxic/ischemic brain damage is associated with the abruption of cerebral blood flow (CBF)[14]. Cessation of brain circulation leads to compound neurologic damages, the so-called hypoxic/ischemic cascade[15]. After the deficiency of oxygen and circulation supplying occur, adenosine triphosphate (ATP) manufacturing malfunction develops[16]. Neurons and glials change from aerobic to anaerobic process, resulting in accumulation of lactic acids[17]. Cells become depolarized due to the sodium-potassium ATPase pumps failure, letting ions, particularly calcium (Ca^{2+}), to invade themselves[18]. Elevated intracellular Ca^{2+} stimulates the release of the well-known excitatory amino acid neurotransmitter such as glutamate[19]. Glutamate permits further Ca^{2+} influx the cells by activate the opening of Calcium-permeable NMDA receptors and AMPA receptors[20]. After excessive calcium Ca^{2+} influx, the production of deleterious substances including various free radicals, reactive oxygen species, phospholipases, ATPases, and endonucleases, the so-called excitotoxicity materials, initiates[21]. Membrane and mitochondria break down and lead to development of necrotic cells and apoptosis. Glutamate and other harmful materials are then released from these necrotic cells into the environment[22]. These materials cause further damage to adjacent cells. This continuous injury, the so-called reperfusion damage, usually starts when the cerebral tissue gets reperfused[23]. Inflammatory scavengers get accumulated to eat up the debris tissue and then generate many cytokines[24]. These toxic materials disrupt the blood-brain barrier (BBB). Destroyed BBB conducts to leakage of huge protein molecules particularly albumins into the environment causing brain edema[25]. Brain edema produces pressure effect of and further harm to adjacent brain tissue[26]. The hypoxic/ischemic cascade are shown in Figure 1.

ICP

The theory of ICP, the so-called Monro-Kellie doctrine, was first postulated by Alexander Monro in 1783 before George Kellie published the article support Monro's idea in 1824[27,28]. This theory states that since the skull is a permanent volume and the brain is enclosed by rigid meninges, therefore, alterations in the volume of the intracranial components will affect ICP[29]. The intracranial components include blood, cerebrospinal fluid (CSF), and brain tissue, all of which are relatively constant. An enlargement in one component or development of a mass lesion will elevate ICP and require a diminishing in another component in order to preserve the permanent intracranial volume[30]. An expanding lesion can initially shift CSF and blood out of the cranium without much change in ICP. However, this capacity to compensate for changes in volume has limitation. If the lesion continues expansion, ICP will get elevated[31]. Elevated ICP leads to cerebral herniation[32]. Moreover, increased ICP harms CBF by depressed cerebral perfusion pressure (CPP), where CPP is calculated by subtraction of ICP from mean arterial pressure[33].

MECHANISMS OF TTM

The multiple sites of actions are thought to be the protective effects of TTM on ischemic cascade[34]. These multiple sites of actions include prevention of BBB disruption, reduction of oxygen derivative free radical release, reduction of excitotoxic neurotransmitter production, anti-inflammatory action and delayed apoptosis[35]. The major neuroprotective effect of TTM in patients after cardiac arrest with restored of systemic circulation (ROSC) is apparently the protective effect on reperfusion damage[36]. Numerous effects resulted from reperfusion damage, including oxygen free radical production, excitotoxic neurotransmitter release, and calcium influx, are all diminished by TTM[5,6,34]. Moreover, TTM also reduces cerebral metabolic rate, protects mitochondrial break down and prevents cell membrane leakage[37,38]. The neurons and glials are finally prevented to turn apoptosis[38]. Protection of BBB damage is an important action of TTM[39]. Diminution of BBB disruption helps to

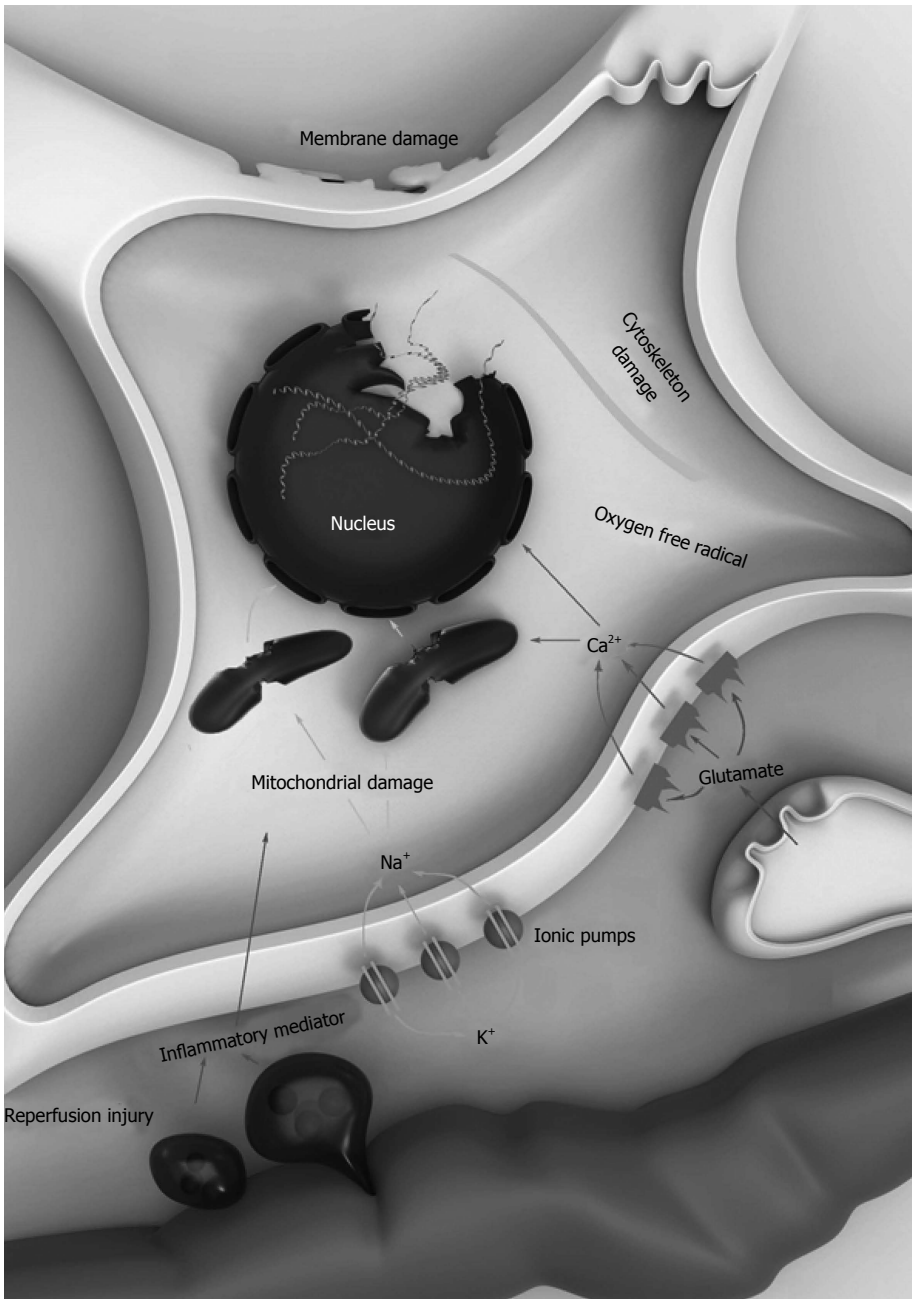

Figure 1 Hypoxic/ischemic cascade[44] (modified from ref. [44], use with permission).

reduce brain edema then lower ICP[38]. Effectiveness of ICP reduction by TTM in various brain disorders has been demonstrated in many clinical and experimental studies[12,40-43]. However, absolute profit of ICP control by TTM in diverse clinical features needs to be confirmed with large scale RCTs[3,13].

THE IDEAL TTM

The course of TTM is divided into three phases[44]. The beginning of TTM is known as induction phase. The main idea of induction phase is to lower the current core temperature to the target as fast as possible[45,46]. Subsequently, that target temperature is smoothly maintained for certain duration (usually for 24 h), the so-called maintenance or sustainment phase[45,46]. The last part, the so-called rewarming phase, the core temperature is slowly raised to the ordinary point with actively control rate, usually at 0.2-0.5 ℃/h[45,46]. Most of the important complications, particularly infection, usually happen during this last phase when the temperature is passively rewarmed with too rapid and out-of-control rate[4]. The ideal temperature curve of a patient with cardiac arrest treated with TTM is showed in Figure 2.

METHODS TO ACHIEVE IDEAL TTM

Many methods of TTM have been reported in the literature. Some methods are no longer utilized in

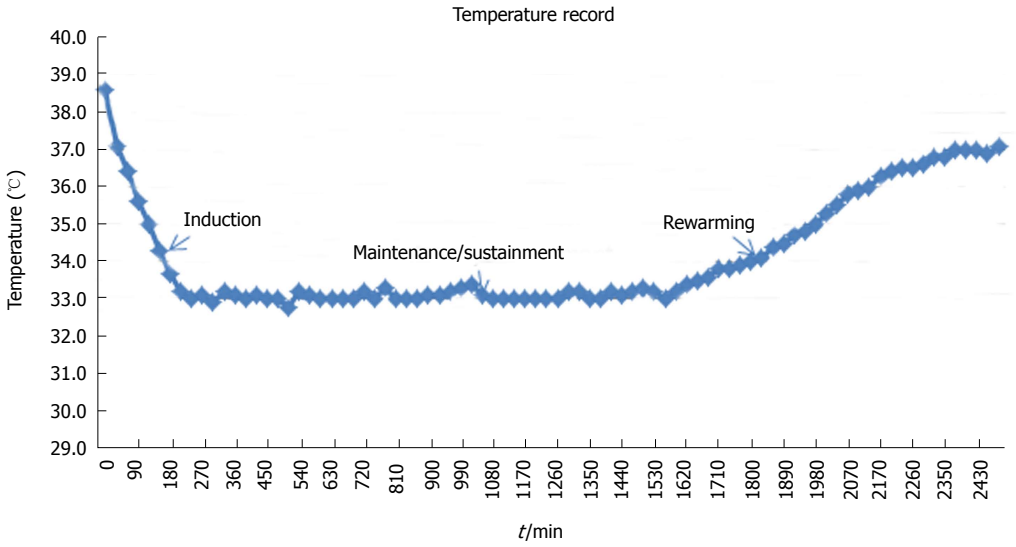

Figure 2 Temperature record of a patient with post-cardiac arrest with targeted temperature management.

clinical practice any more due to their unfeasibility or their ineffectiveness. The method with antipyretic drugs alone are, of course, not sufficient to achieve ideal TTM[47]. Under lack of electricity source circumstance, intravenous cold crystalloid solution may be helpful for initiation of TTM during pre-hospital period[48,49]. However, large volume is needed for induction phase. It is still not possible to achieve ideal TTM with intravenous cool fluid alone. Cooling helmets or hoods is effective to achieve selective cerebral TTM in infants however it seems to be ineffective in adults[6,50]. The two most accepted methods in clinical practice and major clinical trials are non-invasive surface technique and invasive endovascular technique[51,52].

Invasive endovascular methods

The hallmark of invasive endovascular techniques is central venous catheter with extracorporeal cooling machine[4]. The central venous catheter can be sticked *via* femoral, jugular or subclavian vein. Of course, the auto-feedback temperature regulated system is integrated with the machine. Two commercial brands are obtainable in universal market: CoolGard 3000® and Celcius Control System®. The advantage of endovascular system is effective performance including rapid temperature reduction to the target, smoothly sustainment of target temperature and rewarm with actively controlled rate[53,54]. Application of non-pharmacologic shivering control with skin counter-warming is much convenient and more effective during endovascular cooling[55]. Without sedative effect from pharmacologic shivering control, intubation for airway protection can be avoided under skin counter-warming[56]. That's why endovascular method is the recommend technique in several studies of TTM in subjects with acute ischemic stroke[57-59]. However, catheter-related complications and limitation of central venous access are disadvantage issues for endovascular method[51,60].

Non-invasive surface methods

Compression of ice packs to neck, axilla and groin is the simplest way for surface cooling. Two landmark randomized-controlled-trials (RCT) for TTM in patients with PCAS demonstrated effectiveness of this ice packs application[1,2]. However, disadvantage of this technique is awkward, required strenuous staff effort, unreliable temperature control and high risk for complications[61]. The auto-feedback temperature regulated machine provides reliable temperature management and is favorable to perform in clinical practice[47]. The machine comes with circulatory cold water blankets/pads or cold air-flow blankets. Several trademarks of machine are commercially distributed in the worldwide market, including ArcticSun®, CritiCool® andBlanketrol®. The effective automatic cooling system with temperature feedback of the machine helps rapidly lower the temperature to the target and supports slowly rewarm back to the normal baseline temperature. Core temperature monitoring straight connected to the machine is the key for auto-feedback temperature regulated system. The temperature of water within the blankets or pads is automatically regulated by the machine upon target temperature setting and feedback data from core temperature measurement[52]. The surface method with cold water pads is showed in Figure 3.

EMCOOL® pads consist of graphite elements, the high heat conductivity, for cooling media which apply right to the superficial skin. This pads have to get frozen up in ordinary freezer to become 9 ℃ before application however do not require power supply while using[62]. Consequently, this system is extremely practical in pre-hospital situation for TTM induction[63].

The novel esophageal cooling device, the most recent non-invasive method, shows preliminary benefit

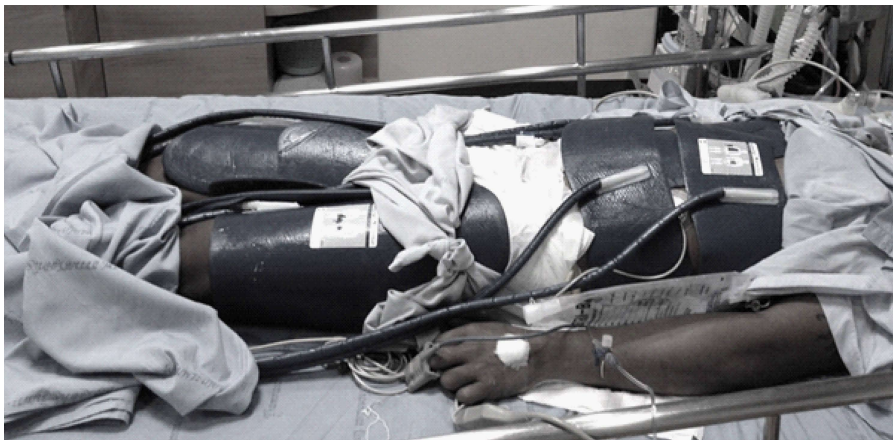

Figure 3 A patient is undergoing targeted temperature management with cold water pads.

of its use in PCAS patients[64]. The United States Food and Drug Administration has already approved this device[65].

SHIVERING AND COMMON PHYSIOLOGIC RESPONSE

Peripheral vasoconstriction is the initial physiologic response when temperature begins to go down[66]. When temperature declines to the certain point, shivering usually occurs[4]. Occurrence of shivering may represent intact physiologic response and indicate good neurologic outcomes[67]. Wonderful shivering control is a key of success to achieve ideal TTM and should be included in the treatment protocol[55,68]. Shivering is usually monitored with the Bedside Shivering Assessment Score during TTM (Table 1)[69]. Elevated peripheral vascular resistance during induction phase of TTM is usually transient and takes no effect to systemic blood pressure[70]. Sinus bradycardia with heart rate less than 50 beats per minute occurs in almost 50% of patients with PCAS during maintenance phase[71]. Nevertheless, this bradycardia should also indicate an intact physiologic response, does not require any treatment due to no hemodynamic effect and may predict good prognosis[72]. Platelets dysfunction and coagulation defect are hematologic abnormalities associated with hypothermia found in non-human experimental models[4,66]. However, abnormal bleeding associated with TTM is infrequently found in real world clinical practice[3,73]. Hypothermia also obliges kidneys to excrete water leading to volume reduction[74]. Serum potassium becomes lower during maintenance phase due to intracellular shift and renal loss however it is expected to be elevated once temperature goes up in rewarming period[4]. Serum amylase becomes elevated when temperature declines, nonetheless, this high serum amylase does not cause pathologic pancreatitis at all[75]. Although elevated blood sugar due to lower insulin level usually occurs during maintenance phase, supplementary insulin may worsen the pre-existing hypokalemia[76]. Infection, particularly pneumonia and sepsis, is a well-known adverse event in patients treated with TTM, however it is usually not associated with unfavorable outcomes[47,77].

APPLICATION OF TTM IN VARIOUS CLINICAL ENTITIES

TTM in PCAS

Combination of complex pathophysiologic process after resuscitated from cardiac arrest, known as PCAS, attribute to multiple organs damage[78]. Global ischemic cascade occurs in the brain due to generalized and severe ischemia during cardiac arrest along with reperfusion process after return of spontaneous circulation (ROSC) leading to hypoxic/ischemic brain injury[79-81]. This global brain damage is responsible for a major cause of mortality in patients with PCAS pertaining to 68% of out-of hospital cardiac arrest (OHCA) and 23% of in-hospital cardiac arrest (IHCA)[82]. TTM is a well-known neuroprotective therapy for ischemic/hypoxic brain injury[83-85].

Two landmark (RCT show that induced mild hypothermia can reduce mortality rate and improve neurologic outcome in adult patients who remained comatose after resuscitated from out-of hospital cardiac arrest and had ventricular fibrillation (VF) or ventricular tachycardia (VT) as initial cardiac rhythm[1,2]. The benefit from these two RCTs is excellent with number-needed-to-treat (NNT) 7 for avoidance of mortality and NNT 6 for favorable neurological/clinical outcomes[86]. The summary of the two landmark RCTs is revealed in Table 2. Base on the results from these two RCTs, International Liaison Committee on Resuscitation and American Heart Association declared, in 2003 and 2010 respectively, that unconscious adults who become ROSC following OHCA with VT/VF or shockable rhythm should be treated with TTM under target temperature between 32 ℃ and 34 ℃ for 12 to 24 h[6,7].

The appropriate target temperature for TTM in

Table 1 Bedside Shivering Assessment Score[69]

0	No shivering
1	Mild: Shivering confines to cervical and/or thorax only
2	Moderate: Shivering extends to whole movement of upper limbs
3	Severe: Shivering spreads to overall movement of trunk, upper limbs and lower limbs

adult patients with PCAS then becomes an important dilemma. TTM Trial is a landmark RCT for comparing benefit of TTM in adult patients after OHCA with any initial rhythm at 33 ℃ *vs* 36 ℃[87]. In November 2013, TTM Trial concludes the same benefit of neurologic outcomes and survival at six months in adult patients with OHCA treated with TTM at 33 ℃ *vs* which of 36 ℃[88]. Furthermore, at six months after discharge from the hospital, survivals in 33 ℃ and 36 ℃ group have similarly good quality of life and same level of cognitive function[89].

Clinical profit of TTM in patients with PCAS from other etiologies except OHCA with shockable rhythm remains not well-established[90]. Some small clinical trials report evidence of marginal outcomes benefit in OHCA subgroup with asystole/pulseless electrical activity, the so-called non-shockable rhythm, and also in IHCA subgroup[6,7,90]. For patients after OHCA with non-shockable rhythm, few observational studies show no difference in neurologic outcomes with TTM but possible reduction of mortality at six months[2,91,92]. A recent observational study included more than 90% of adult patients with non-shockable rhythm show improvement of neurologic outcomes and better survival to hospital discharge with TTM[73]. For patients with IHCA, few observational studies show marginal benefit of TTM in both neurologic outcomes and survival[73,93]. The most update recommendation declared by International Liaison Committee on Resuscitation, American Heart Association and European Resuscitation Council similarly state in 2015 that unconscious adult patients with ROSC after either OHCA or IHCA with either shockable or non-shockable rhythm should be treated with TTM at 32 ℃ to 36 ℃ for at least 24 h[8-10]. From the recent meta-analysis, TTM confers to better neurological outcomes than no temperature management in adult patients with PCAS, however, TTM in specific subgroup including initial non-shockable rhythm, IHCA and non-cardiac causes of arrest does not have sufficient data to make any conclusion[94]. The inclusion and exclusion criteria for TTM in adult patients with PCAS at Thammasat University Hospital are showed in Table 3.

Therapeutic Hypothermia after Paediatric Cardiac Arrest (THAPCA) Trial is a landmark study for TTM in all aspects of pediatric patients with PCAS[95]. The results from THAPCA trial demonstrated that TTM with target temperature of 33 ℃ in pediatric patients with PCAS due to either OHCA or IHCA did not show any outcomes benefit as compared with which of target temperature of 36.8 ℃[96,97].

Table 2 Summary of the landmark randomized control trials for targeted temperature management in post-cardiac arrest syndrome

	Australian trial	European trial
Sample size	*n* = 77	*n* = 275
TTM *vs* untreated	43 TTM *vs* 34 untreated	137 TTM *vs* 138 untreated
Initial rhythm	VT/VF	VT/VF
Method of TTM	Surface with ice packs	Surface with cooling blankets/pads and ice packs
Place of initiation	Emergency department	Prehospital setting
Target temperature	33 ℃	32 ℃-34 ℃
Duration of TTM	12 h	24 h
Time of Follow up	30 d	6 mo
Outcomes	NNT of 7 to avoid death	NNT of 6 to improve neurological outcomes

TTM: Targeted temperature management; VF: Ventricular fibrillation; VT: Ventricular tachycardia; NNT: Number-needed-to-treat.

TTM in ischemic stroke

In non-human experimental models with on focal brain ischemia, TTM demonstrates a very capable neuroprotective outcomes[98]. However, application of TTM in patients with ischemic stroke still has a lot of limitations[99]. Invasive endovascular method is preferred to apply in patients with acute ischemic stroke due to its feasibility and safety as reported by most clinical studies[56,100]. Under endovascular method, shivering control is convenient with non-pharmacologic skin counter-warming technique[55]. For this reason, pharmacologic anti-shivering technique which usually associated with sedative effect can be avoided[54,100]. Endovascular method is apparently not associated with bleeding complications even in post-thrombolytic condition[100]. Unfortunately, the RCT of TTM with endovascular method at 33 ℃ following intravenous recombinant plasminogen activator (rtPA) in patients with ischemic stroke (ICTuS 2 Trial) is early stopped due to the approval of interventional thrombectomy and lack of funding[101]. The sample size of ICTus 2 Trial is too small to make any conclusion on efficacy or clinical outcomes of the treatment[101].

With its reperfusion protective action, TTM should be useful to decrease symptomatic intracerebral hemorrhage (sICH) after intravenous rtPA as well as after endovascular treatment[102,103]. The landmark RCT of TTM as neuroprotective treatment with target temperature at 34 ℃ to 35 ℃ in patients with acute ischemic stroke (EuroHYP-1) is still ongoing[104]. At this moment, routine application of TTM in patients with acute ischemic stroke is not recommended[105].

Fever control with TTM technique, to keep target temperature less than 37.5 ℃, is helpful for patients with acute ischemic stroke[106]. Reduction of ICP with TTM in malignant brain infarct is demonstrated in both experimental and clinical studies[40,42,107]. TTM is helpful

Table 3 Inclusion and exclusion criteria for targeted temperature management after cardiac arrest at Thammasat University Hospital

Inclusion criteria
Witnessed arrest
Any initial rhythm, However initial rhythm VF or pulseless VT is the first priority
Time to ACLS was less than 15 min and total of ACLS time less than 60 min
GCS of 8 or below
SBP of > 90 with or without vasopressors
Less than 8 h have elapsed since ROSC
Exclusion criteria
Pregnancy
Known functional dependence
Down time of > 30 min
ACLS preformed for > 60 min
Known terminal illness
Comatose state prior to cardiac arrest
Prolonged hypotension (*i.e.*, MAP < 60 for > 30 min)
Evidence of hypoxemia for > 15 min following ROSC
Known coagulopathy that cannot be reversed

VF: Ventricular fibrillation; VT: Ventricular tachycardia; ROSC: Restored of systemic circulation.

for ICP reduction in patients with large middle cerebral artery (MCA) infarct[40]. However, routine application of TTM as ICP reduction in any type of malignant brain infarct is controversial due to insufficient support clinical data of its benefit[3,106].

TTM in TBI

Pertaining to experimental animal models for TBI, TTM provides excellent mechanism of action in both Neuroprotection and ICP reduction[108-110]. Two clinical trials in patients with severe TBI from China demonstrated good effect of TTM on ICP control with favorable outcomes after six months to one year[111,112]. Unfortunately, the following meta-analysis, which includes small to medium scale RCTs before 2003, did not demonstrate any benefit to apply TTM as neuroprotective therapy in patients with TBI[113-115]. Finally, two landmark RCTs of TTM as neuroprotective therapy in either adults or children with TBI fail to demonstrate any beneficial outcomes[70,116,117]. Elevated ICP in patients with TBI is common and associated with poor outcomes[118,119]. The previous TTM trials begin rewarming when the peak of elevated ICP occurs at around 48 h after onset of TBI leading to clinical deterioration[120]. This rebound elevated ICP found during rewarming phase is assumed to be one of the key reasons of failure in previous landmark RCT[121]. Specific group of elevated ICP in patients with TBI may get clinical profit from ICP reduction with TTM[12]. Clinical trial of TTM according to high ICP in patients with TBI was proposed[122]. Unfortunately, large scale RCT of TTM in specific TBI patients with high ICP more than 20 mmHg (Eurotherm3235 Trial) does not demonstrate any clinical benefit[123]. Recent meta-analysis of TTM *vs* normothermia in adult patients with TBI does not demonstrate any clinical benefit of TTM but reveal risk of developing pneumonia and cardiovascular complications associated with TTM[124]. Large scale RCT of TTM in particular aspects of patients with TBI is still ongoing[125]. At this moment, ordinary application of TTM in patients with TBI without clinical study is not recommended[126].

Fever controls in neurological ICU with TTM machine

Fever is commonly found in patients admitted in Neurological ICU, increases risk of complications, and is usually associated with unfavorable clinical outcomes[127,128]. For example, in patients with ischemic stroke, chance to develop poor outcomes increases 2.2 times in each one degree exceeding 37 ℃ when compared with patients who have normal temperature[129]. Most common cause of fever in Neurological ICU is infection[130]. Similar method of TTM can be applied for fever control in Neurological ICU[131,132]. The commonly use techniques such as surface and endovascular are convenient and save to employ for fever control[131,132]. Fever control in patients with septic shock with external TTM machine reduces early mortality[133]. However, overall benefit of antipyretic therapy with external TTM in patients with sepsis is still not approved[134,135]. Fever control in patients with acute ischemic stroke is recommended per standard guidelines[105].

TTM in other clinical entities

TTM can apply as organ protective therapy from ischemic effect during cardiovascular surgery with circulatory arrest[136,137]. The landmark RCT of TTM for the period of operation in patients with benign grade SAH from ruptured intracranial aneurysm (World Federation of Neurological Surgeons scale between one and three) did not show any clinical benefit with more frequent associated infection[138]. TTM can reduce perilesional edema with favorable outcomes in animal models with intracerebral hemorrhage (ICH)[139]. The TTM after intracerebral hemorrhage (TTM-ICH) trial is ongoing[140]. At this moment, routine use of TTM in patients with ICH is not recommended[141]. The prospective protocol-selected trial demonstrated potential clinical benefit of local TTM in patients with neurologically complete spinal cord injury[142]. Experts recommend that TTM can be the option for ICP control in patients with fulminant hepatic encephalopathy particularly while waiting for liver transplantation[143].

Application of TTM in donors demonstrates organ protective effect on kidney in recipients[144]. This RCT is the first ever for clinical trial which demonstrates organ defensive action of TTM from hypoxic/ischemic cascade outside the brain. The process of TTM at 34 ℃-35 ℃ in kidney donors in this study is convenient and the cost of treatment is economic[145]. TTM in kidney donors can be its second class Ⅰ recommendation per standard guidelines following post-cardiac arrest in the near future.

CONCLUSION

Two main purposes of TTM in patients admitted in Neurological ICU are neuroprotective therapy and ICP control. TTM is the most potent neuroprotective treatment due to its numerous effects against ischemic/hypoxic injury. TTM provides reliable ICP reductive action. Two most popular methods of TTM using in clinical practice and clinical trials are invasive endovascular technique and non-invasive surface cooling. Fast induction, smooth maintenance and slow rewarming are the important steps to achieve ideal TTM. The strongest clinical benefit of TTM is the excellent outcomes with neuroprotective effect in patients with PCAS. TTM has been recommended as the essential treatment for OHCA with shockable rhythm for more than 10 years. Even with marginal benefit, TTM is still recommended for non-shockable rhythm and IHCA subgroup. TTM may give benefit in patients with acute ischemic stroke however its role needs to be proved with large scale RCT. TTM should be clinically useful for ICP reduction in patients with malignant MCA infarct. Routine use of TTM in patients with TBI as neuroprotective therapy or ICP control is still not recommended due to lacking of any benefit from many RCTs. TTM machine can be applied as fever control in patients with various conditions in Neurological ICU. Fever control should help to improve clinical outcomes in patients admitted in Neurological ICU.

ACKNOWLEDGMENTS

The authors acknowledgement the National Research University Project of Thailand from Office of Higher Education Commission and Center of Excellence in Integrated Sciences for Holistic Stroke Research from Thammasat University.

REFERENCES

1 **Hypothermia after Cardiac Arrest Study Group.** Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346**: 549-556 [PMID: 11856793 DOI: 10.1056/NEJMoa012689]

2 **Bernard SA**, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557-563 [PMID: 11856794 DOI: 10.1056/NEJMoa003289]

3 **Nunnally ME**, Jaeschke R, Bellingan GJ, Lacroix J, Mourvillier B, Rodriguez-Vega GM, Rubertsson S, Vassilakopoulos T, Weinert C, Zanotti-Cavazzoni S, Buchman TG. Targeted temperature management in critical care: a report and recommendations from five professional societies. *Crit Care Med* 2011; **39**: 1113-1125 [PMID: 21187745 DOI: 10.1097/CCM.0b013e318206bab2]

4 **Mayer SA**, Sessler DI. Therapeutic hypothermia. In: Mayer SA, Claassen J, editors. Prevention and Treatment of Fever in Neurocritical Care. New York, 2005: 629

5 **Polderman KH**. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. *Intensive Care Med* 2004; **30**: 556-575 [PMID: 14767591 DOI: 10.1007/s00134-003-2152-x]

6 **Nolan JP**, Morley PT, Vanden Hoek TL, Hickey RW, Kloeck WG, Billi J, Böttiger BW, Morley PT, Nolan JP, Okada K, Reyes C, Shuster M, Steen PA, Weil MH, Wenzel V, Hickey RW, Carli P, Vanden Hoek TL, Atkins D. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003; **108**: 118-121 [PMID: 12847056 DOI: 10.1161/01.CIR.0000079019.02601.90]

7 **Peberdy MA**, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; **122**: S768-S786 [PMID: 20956225]

8 **Callaway CW**, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, Zimmerman JL. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015; **132**: S465-S482 [PMID: 26472996 DOI: 10.1161/CIR.0000000000000262]

9 **Nolan JP**, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive Care Med* 2015; **41**: 2039-2056 [PMID: 26464394 DOI: 10.1007/s00134-015-4051-3]

10 **Hazinski MF**, Nolan JP, Aickin R, Bhanji F, Billi JE, Callaway CW, Castren M, de Caen AR, Ferrer JM, Finn JC, Gent LM, Griffin RE, Iverson S, Lang E, Lim SH, Maconochie IK, Montgomery WH, Morley PT, Nadkarni VM, Neumar RW, Nikolaou NI, Perkins GD, Perlman JM, Singletary EM, Soar J, Travers AH, Welsford M, Wyllie J, Zideman DA. Part 1: Executive Summary: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2015; **132**: S2-S39 [PMID: 26472854 DOI: 10.1161/CIR.0000000000000270]

11 **Kurtz P**, Fitts V, Sumer Z, Jalon H, Cooke J, Kvetan V, Mayer SA. How does care differ for neurological patients admitted to a neurocritical care unit versus a general ICU? *Neurocrit Care* 2011; **15**: 477-480 [PMID: 21519958 DOI: 10.1007/s12028-011-9539-2]

12 **Sadaka F**, Veremakis C. Therapeutic hypothermia for the management of intracranial hypertension in severe traumatic brain injury: a systematic review. *Brain Inj* 2012; **26**: 899-908 [PMID: 22448655 DOI: 10.3109/02699052.2012.661120]

13 **Corry JJ**. The use of targeted temperature management for elevated intracranial pressure. *Curr Neurol Neurosci Rep* 2014; **14**: 453 [PMID: 24740807 DOI: 10.1007/s11910-014-0453-9]

14 **Muengtaweepongsa S**. Methods and clinical applications of targeted temperature management. *Neurology Asia* 2015; **20**: 325-333

15 **Gusev EISVI**. Brain ischemia. New York: Kluwer Academic/Plenum Publishers, 2003

16 **Zhao H**, Kilgas S, Alam A, Eguchi S, Ma D. The Role of Extracellular Adenosine Triphosphate in Ischemic Organ Injury. *Crit Care Med* 2016; **44**: 1000-1012 [PMID: 26825859 DOI: 10.1097/CCM.0000000000001603]

17 **Xing C**, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. *Int J Stroke* 2012; **7**: 378-385 [PMID: 22712739 DOI: 10.1111/j.1747-4949.2012.00839.x]

18 **Stead SM**, Daube JR. Basics of Neurophysiology. *Clinical Neurophysiology* 2016: 3

19 **Hinkle JL**, Bowman L. Neuroprotection for ischemic stroke. *J Neurosci Nurs* 2003; **35**: 114-118 [PMID: 12795039]

20 **Bennett MV**, Pellegrini-Giampietro D, Gorter J, Aronica E, Connor J, Zukin RS. The GluR2 hypothesis: Ca -permeable AMPA receptors in delayed neurodegeneration. Proceedings of the Cold Spring Harbor symposia on quantitative biology. New York: Cold Spring Harbor Laboratory Press, 1996: 373-384

21 **Labiche LA**, Grotta JC. Clinical trials for cytoprotection in stroke. *NeuroRx* 2004; **1**: 46-70 [PMID: 15717007 DOI: 10.1602/

neurorx.1.1.46]
22 **Hazell AS**. Excitotoxic mechanisms in stroke: an update of concepts and treatment strategies. *Neurochem Int* 2007; **50**: 941-953 [PMID: 17576023 DOI: 10.1016/j.neuint.2007.04.026]
23 **Aronowski J**, Strong R, Grotta JC. Reperfusion injury: demonstration of brain damage produced by reperfusion after transient focal ischemia in rats. *J Cereb Blood Flow Metab* 1997; **17**: 1048-1056 [PMID: 9346429 DOI: 10.1097/00004647-199710000-00006]
24 **Iadecola C**, Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med* 2011; **17**: 796-808 [PMID: 21738161 DOI: 10.1038/nm.2399]
25 **Xi G**, Keep RF, Hoff JT. Pathophysiology of brain edema formation. *Neurosurg Clin N Am* 2002; **13**: 371-383 [PMID: 12486926]
26 **Strbian D**, Durukan A, Pitkonen M, Marinkovic I, Tatlisumak E, Pedrono E, Abo-Ramadan U, Tatlisumak T. The blood-brain barrier is continuously open for several weeks following transient focal cerebral ischemia. *Neuroscience* 2008; **153**: 175-181 [PMID: 18367342 DOI: 10.1016/j.neuroscience.2008.02.012]
27 **Monro A**. Observations on the structure and function of the nervous system. Edinburgh: Creech & Johnson, 1783
28 **Kelly G**. Appearances observed in the dissection of two individuals; death from cold and congestion of the brain. *Trans Med Chir Sci Edinb* 1824: 84-169
29 **Neff S**, Subramaniam RP. Monro-Kellie doctrine. *J Neurosurg* 1996; **85**: 1195 [PMID: 8929522]
30 **Mokri B**. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology* 2001; **56**: 1746-1748 [PMID: 11425944]
31 **Kincaid MS**, Lam AM. Monitoring and managing intracranial pressure. *Continuum* 2006; **12**: 16 [DOI: 10.1212/01.con.0000290439.87946.ed]
32 **Sheth K**, McCullough M, Kazmi S, Lazaridis C, O'Phelan K, Shepherd SA, DeJesus-Alvelo I, Marshall SA, Willis AM, Durrant JC. Cerebral Herniation Syndromes and Intracranial Hypertension: Rutgers University Press, 2016
33 **Villa F**, Citerio G. Intracranial pressure monitoring. Oxford: Oxford Textbook of Neurocritical Care, 2016: 107 [DOI: 10.1093/med/9780198739555.003.0009]
34 **Polderman KH**. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 2009; **37**: S186-S202 [PMID: 19535947 DOI: 10.1097/CCM.0b013e3181aa5241]
35 **Talma N**, Kok WF, de Veij Mestdagh CF, Shanbhag NC, Bouma HR, Henning RH. Neuroprotective hypothermia - Why keep your head cool during ischemia and reperfusion. *Biochim Biophys Acta* 2016; **1860**: 2521-2528 [PMID: 27475000 DOI: 10.1016/j.bbagen.2016.07.024]
36 **Madathil RJ**, Hira RS, Stoeckl M, Sterz F, Elrod JB, Nichol G. Ischemia reperfusion injury as a modifiable therapeutic target for cardioprotection or neuroprotection in patients undergoing cardiopulmonary resuscitation. *Resuscitation* 2016; **105**: 85-91 [PMID: 27131843 DOI: 10.1016/j.resuscitation.2016.04.009]
37 **Erecinska M**, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in Mammalian central nervous system. *J Cereb Blood Flow Metab* 2003; **23**: 513-530 [PMID: 12771566 DOI: 10.1097/01.WCB.0000066287.21705.21]
38 **González-Ibarra FP**, Varon J, López-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. *Front Neurol* 2011; **2**: 4 [PMID: 21331282 DOI: 10.3389/fneur.2011.00004]
39 **Chi OZ**, Liu X, Weiss HR. Effects of mild hypothermia on blood-brain barrier disruption during isoflurane or pentobarbital anesthesia. *Anesthesiology* 2001; **95**: 933-938 [PMID: 11605935 DOI: 10.1097/00000542-200110000-00023]
40 **Schwab S**, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 2001; **32**: 2033-2035 [PMID: 11546893]
41 **Seule MA**, Muroi C, Mink S, Yonekawa Y, Keller E. Therapeutic hypothermia in patients with aneurysmal subarachnoid hemorrhage, refractory intracranial hypertension, or cerebral vasospasm. *Neurosurgery* 2009; **64**: 86-93
42 **Park CK**, Jun SS, Kim MC, Kang JK. Effects of systemic hypothermia and selective brain cooling on ischemic brain damage and swelling. *Acta Neurochir Suppl* 1998; **71**: 225-228 [PMID: 9779191]
43 **Kawai N**, Nakamura T, Okauchi M, Nagao S. Effects of hypothermia on intracranial pressure and brain edema formation: studies in a rat acute subdural hematoma model. *J Neurotrauma* 2000; **17**: 193-202 [PMID: 10757325]
44 **Brott T**, Bogousslavsky J. Treatment of acute ischemic stroke. *N Engl J Med* 2000; **343**: 710-722 [PMID: 10974136 DOI: 10.1056/NEJM200009073431007]
45 **Suwannakin A**, Muengtaweepongsa S. Initial experience of therapeutic hypothermia after cardiac arrest with surface cooling method in Thammasat Chalerm Prakiat Hospital: two cases report. *J Med Assoc Thai* 2011; **94** Suppl 7: S190-S193 [PMID: 22619928]
46 **Pinichjindasup A**, Homvises B, Muengtaweepongsa S. Therapeutic hypothermia with extracorporeal membrane oxygenation (ECMO) and surface cooling in post-cardiac arrest patients: 4 case reports. *J Med Assoc Thai* 2014; **97** Suppl 8: S223-S227 [PMID: 25518319]
47 **Polderman KH**. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality--Part 2: Practical aspects and side effects. *Intensive Care Med* 2004; **30**: 757-769 [PMID: 14767590 DOI: 10.1007/s00134-003-2151-y]
48 **Polderman KH**, Rijnsburger ER, Peerdeman SM, Girbes AR. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. *Crit Care Med* 2005; **33**: 2744-2751 [PMID: 16352954 DOI: 10.1097/2701.CCM.0000190427.0000188735.0000190419]
49 **Bernard S**, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003; **56**: 9-13 [PMID: 12505732]
50 **Wang H**, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, Rodde M, Burnham J, Wang D. Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg* 2004; **100**: 272-277 [PMID: 15086235]
51 **Oh SH**, Oh JS, Kim YM, Park KN, Choi SP, Kim GW, Jeung KW, Jang TC, Park YS, Kyong YY. An observational study of surface versus endovascular cooling techniques in cardiac arrest patients: a propensity-matched analysis. *Crit Care* 2015; **19**: 85 [PMID: 25880667 DOI: 10.1186/s13054-015-0819-7]
52 **Glover GW**, Thomas RM, Vamvakas G, Al-Subaie N, Cranshaw J, Walden A, Wise MP, Ostermann M, Thomas-Jones E, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wetterslev J, Friberg H, Nielsen N. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest - an analysis of the TTM trial data. *Crit Care* 2016; **20**: 381 [PMID: 27887653 DOI: 10.1186/s13054-016-1552-6]
53 **Al-Senani FM**, Graffagnino C, Grotta JC, Saiki R, Wood D, Chung W, Palmer G, Collins KA. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation* 2004; **62**: 143-150 [PMID: 15294399 DOI: 10.1016/j.resuscitation.2004.02.016]
54 **Lyden PD**, Allgren RL, Ng K, Akins P, Meyer B, Al-Sanani F, Lutsep H, Dobak J, Matsubara BS, Zivin J. Intravascular Cooling in the Treatment of Stroke (ICTuS): early clinical experience. *J Stroke Cerebrovasc Dis* 2005; **14**: 107-114 [PMID: 17904009 DOI: 10.1016/j.jstrokecerebrovasdis.2005.01.001]
55 **Choi HA**, Ko SB, Presciutti M, Fernandez L, Carpenter AM, Lesch C, Gilmore E, Malhotra R, Mayer SA, Lee K, Claassen J, Schmidt JM, Badjatia N. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. *Neurocrit Care* 2011; **14**: 389-394 [PMID: 21210305 DOI: 10.1007/s12028-010-9474-7]
56 **De Georgia MA**, Krieger DW, Abou-Chebl A, Devlin TG, Jauss M, Davis SM, Koroshetz WJ, Rordorf G, Warach S. Cooling for

Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. *Neurology* 2004; **63**: 312-317 [PMID: 15277626]
57 **Lyden PD**, Hemmen TM, Grotta J, Rapp K, Raman R. Endovascular therapeutic hypothermia for acute ischemic stroke: ICTuS 2/3 protocol. *Int J Stroke* 2014; **9**: 117-125 [PMID: 24206528 DOI: 10.1111/ijs.12151]
58 **Wolfe MM**, Boylan MO. Obesity and the gastrointestinal tract: you are what you eat. *J Clin Gastroenterol* 2014; **48**: 817-822 [PMID: 24828362]
59 **Krieger DW**, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, Mayberg MR, Furlan AJ. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke* 2001; **32**: 1847-1854 [PMID: 11486115]
60 **Fischer M**, Lackner P, Beer R, Helbok R, Pfausler B, Schneider D, Schmutzhard E, Broessner G. Cooling Activity is Associated with Neurological Outcome in Patients with Severe Cerebrovascular Disease Undergoing Endovascular Temperature Control. *Neurocrit Care* 2015; **23**: 205-209 [PMID: 25693893 DOI: 10.1007/s12028-015-0122-0]
61 **Seder DB**, Van der Kloot TE. Methods of cooling: practical aspects of therapeutic temperature management. *Crit Care Med* 2009; **37**: S211-S222 [PMID: 19535949 DOI: 10.1097/CCM.0b013e3181aa5bad]
62 **Uray T**, Sterz F, Janata A, Wandaller C, Holzer M, Laggner AN, Behringer W. Surface cooling with a new cooling-blanket for rapid induction of mild hypothermia in humans after cardiac arrest: A feasibility trial. *Circulation* 2006; **114**: 1190-1190
63 **Dhaese HL**, Martens PR, Müller NH, Casier IM, Mulier JP, Heytens L. The use of emergency medical cooling system pads in the treatment of malignant hyperthermia. *Eur J Anaesthesiol* 2010; **27**: 83-85 [PMID: 19851114 DOI: 10.1097/EJA.0b013e328330404a]
64 **Hegazy A**, Lapierre D, Althenayan E. Targeted temperature management after cardiac arrest and fever control with an esophageal cooling device. *Critical Care* 2015; **19** (Suppl 1): P424 [DOI: 10.1186/cc14504]
65 CritiCool Specification M (Rehovot, Israel). 510K for CritiCool system. Available from: URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN140018
66 **Arrica M**, Bissonnette B. Therapeutic hypothermia. *Semin Cardiothorac Vasc Anesth* 2007; **11**: 6-15 [PMID: 17484169 DOI: 10.1177/1089253206297409]
67 **Nair SU**, Lundbye JB. The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome. *Resuscitation* 2013; **84**: 626-629 [PMID: 23201502 DOI: 10.1016/j.resuscitation.2012.11.018]
68 **Presciutti M**, Bader MK, Hepburn M. Shivering management during therapeutic temperature modulation: nurses' perspective. *Crit Care Nurse* 2012; **32**: 33-42 [PMID: 22298716 DOI: 10.4037/ccn2012189]
69 **Logan A**, Sangkachand P, Funk M. Optimal management of shivering during therapeutic hypothermia after cardiac arrest. *Crit Care Nurse* 2011; **31**: e18-e30 [PMID: 22135340 DOI: 10.4037/ccn2011618]
70 **Clifton GL**, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerssen TG, Chesnut RM, Schwartz M. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001; **344**: 556-563 [PMID: 11207351]
71 **Thomsen JH**, Hassager C, Bro-Jeppesen J, Søholm H, Nielsen N, Wanscher M, Køber L, Pehrson S, Kjaergaard J. Sinus bradycardia during hypothermia in comatose survivors of out-of-hospital cardiac arrest - a new early marker of favorable outcome? *Resuscitation* 2015; **89**: 36-42 [PMID: 25619443 DOI: 10.1016/j.resuscitation.2014.12.031]
72 **Muengtaweepongsa S**, Jantanukul A, Suwanprasert K. Should the heart rate including the heart rate variability be important prognostigators in cardiac arrest? *Resuscitation* 2016; **98**: e15 [PMID: 26597105 DOI: 10.1016/j.resuscitation.2015.08.026]
73 **Srivilaithon W**, Muengtaweepongsa S. The Outcomes of Targeted Temperature Management After Cardiac Arrest at Emergency Department: A Real-World Experience in a Developing Country. *Ther Hypothermia Temp Manag* 2017; **7**: 24-29 [PMID: 27835072 DOI: 10.1089/ther.2016.0014]
74 **Varon J**, Acosta P. Therapeutic hypothermia: past, present, and future. *Chest* 2008; **133**: 1267-1274 [PMID: 18460529 DOI: 10.1378/chest.07-2190]
75 **Bernard SA**, Buist M. Induced hypothermia in critical care medicine: a review. *Crit Care Med* 2003; **31**: 2041-2051 [PMID: 12847402 DOI: 10.1097/01.CCM.0000069731.18472.61]
76 **Lehot JJ**, Piriz H, Villard J, Cohen R, Guidollet J. Glucose homeostasis. Comparison between hypothermic and normothermic cardiopulmonary bypass. *Chest* 1992; **102**: 106-111 [PMID: 1623737]
77 **Gagnon DJ**, Nielsen N, Fraser GL, Riker RR, Dziodzio J, Sunde K, Hovdenes J, Stammet P, Friberg H, Rubertsson S, Wanscher M, Seder DB. Prophylactic antibiotics are associated with a lower incidence of pneumonia in cardiac arrest survivors treated with targeted temperature management. *Resuscitation* 2015; **92**: 154-159 [PMID: 25680823 DOI: 10.1016/j.resuscitation.2015.01.035]
78 **Nolan JP**, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Hoek TV. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation* 2008; **79**: 350-379 [PMID: 18963350 DOI: 10.1016/j.resuscitation.2008.09.017]
79 **Bro-Jeppesen J**, Kjaergaard J, Stammet P, Wise MP, Hovdenes J, Åneman A, Horn J, Devaux Y, Erlinge D, Gasche Y, Wanscher M, Cronberg T, Friberg H, Wetterslev J, Pellis T, Kuiper M, Nielsen N, Hassager C. Predictive value of interleukin-6 in post-cardiac arrest patients treated with targeted temperature management at 33 °C or 36 °C. *Resuscitation* 2016; **98**: 1-8 [PMID: 26525271 DOI: 10.1016/j.resuscitation.2015.10.009]
80 **Adrie C**, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care* 2004; **10**: 208-212 [PMID: 15166838]
81 **Adrie C**, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002; **106**: 562-568 [PMID: 12147537]
82 **Laver S**, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. *Intensive Care Med* 2004; **30**: 2126-2128 [PMID: 15365608 DOI: 10.1007/s00134-004-2425-z]
83 **Gunn AJ**, Thoresen M. Hypothermic neuroprotection. *NeuroRx* 2006; **3**: 154-169 [PMID: 16554254 DOI: 10.1016/j.nurx.2006.01.007]
84 **Holzer M**, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Müllner M. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005; **33**: 414-418 [PMID: 15699847]
85 **Froehler MT**, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. *J Neurol Sci* 2007; **261**: 118-126 [PMID: 17559883 DOI: 10.1016/j.jns.2007.04.042]
86 **Arrich J**, Holzer M, Herkner H, Müllner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2009; **(4)**: CD004128 [PMID: 19821320 DOI: 10.1002/14651858.CD004128.pub2]
87 **Nielsen N**, Wetterslev J, al-Subaie N, Andersson B, Bro-Jeppesen J, Bishop G, Brunetti I, Cranshaw J, Cronberg T, Edqvist K, Erlinge

D, Gasche Y, Glover G, Hassager C, Horn J, Hovdenes J, Johnsson J, Kjaergaard J, Kuiper M, Langørgen J, Macken L, Martinell L, Martner P, Pellis T, Pelosi P, Petersen P, Persson S, Rundgren M, Saxena M, Svensson R, Stammet P, Thorén A, Undén J, Walden A, Wallskog J, Wanscher M, Wise MP, Wyon N, Aneman A, Friberg H. Target Temperature Management after out-of-hospital cardiac arrest--a randomized, parallel-group, assessor-blinded clinical trial--rationale and design. *Am Heart J* 2012; **163**: 541-548 [PMID: 22520518 DOI: 10.1016/j.ahj.2012.01.013]

88 **Nielsen N**, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013; **369**: 2197-2206 [PMID: 24237006 DOI: 10.1056/NEJMoa1310519]

89 **Cronberg T**, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Åneman A, Stammet P, Erlinge D, Friberg H, Hassager C, Kuiper M, Wanscher M, Bosch F, Cranshaw J, Kleger GR, Persson S, Undén J, Walden A, Winkel P, Wetterslev J, Nielsen N. Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33°C vs 36°C After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. *JAMA Neurol* 2015; **72**: 634-641 [PMID: 25844993 DOI: 10.1001/jamaneurol.2015.0169]

90 **Dumas F**, Grimaldi D, Zuber B, Fichet J, Charpentier J, Pène F, Vivien B, Varenne O, Carli P, Jouven X, Empana JP, Cariou A. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. *Circulation* 2011; **123**: 877-886 [PMID: 21321156 DOI: 10.1161/CIRCULATIONAHA.110.987347]

91 **Hessel EA**. Therapeutic hypothermia after in-hospital cardiac arrest: a critique. *J Cardiothorac Vasc Anesth* 2014; **28**: 789-799 [PMID: 24751488 DOI: 10.1053/j.jvca.2014.01.015]

92 **Oddo M**, Ribordy V, Feihl F, Rossetti AO, Schaller MD, Chioléro R, Liaudet L. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Crit Care Med* 2008; **36**: 2296-2301 [PMID: 18664785 DOI: 10.1097/CCM.0b013e3181802599]

93 **Chan PS**, Berg RA, Tang Y, Curtis LH, Spertus JA. Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest. *JAMA* 2016; **316**: 1375-1382 [PMID: 27701659 DOI: 10.1001/jama.2016.14380]

94 **Arrich J**, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2016; **2**: CD004128 [PMID: 26878327 DOI: 10.1002/14651858.CD004128.pub4]

95 **Moler FW**, Silverstein FS, Meert KL, Clark AE, Holubkov R, Browning B, Slomine BS, Christensen JR, Dean JM. Rationale, timeline, study design, and protocol overview of the therapeutic hypothermia after pediatric cardiac arrest trials. *Pediatr Crit Care Med* 2013; **14**: e304-e315 [PMID: 23842585 DOI: 10.1097/PCC.0b013e31828a863a]

96 **Moler FW**, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Clark AE, Browning B, Pemberton VL, Page K, Shankaran S, Hutchison JS, Newth CJ, Bennett KS, Berger JT, Topjian A, Pineda JA, Koch JD, Schleien CL, Dalton HJ, Ofori-Amanfo G, Goodman DM, Fink EL, McQuillen P, Zimmerman JJ, Thomas NJ, van der Jagt EW, Porter MB, Meyer MT, Harrison R, Pham N, Schwarz AJ, Nowak JE, Alten J, Wheeler DS, Bhalala US, Lidsky K, Lloyd E, Mathur M, Shah S, Wu T, Theodorou AA, Sanders RC, Dean JM. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med* 2015; **372**: 1898-1908 [PMID: 25913022 DOI: 10.1056/NEJMoa1411480]

97 **Moler FW**, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Browning B, Pemberton VL, Page K, Gildea MR, Scholefield BR, Shankaran S, Hutchison JS, Berger JT, Ofori-Amanfo G, Newth CJ, Topjian A, Bennett KS, Koch JD, Pham N, Chanani NK, Pineda JA, Harrison R, Dalton HJ, Alten J, Schleien CL, Goodman DM, Zimmerman JJ, Bhalala US, Schwarz AJ, Porter MB, Shah S, Fink EL, McQuillen P, Wu T, Skellett S, Thomas NJ, Nowak JE, Baines PB, Pappachan J, Mathur M, Lloyd E, van der Jagt EW, Dobyns EL, Meyer MT, Sanders RC, Clark AE, Dean JM. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. *N Engl J Med* 2017; **376**: 318-329 [PMID: 28118559 DOI: 10.1056/NEJMoa1610493]

98 **van der Worp HB**, Sena ES, Donnan GA, Howells DW, Macleod MR. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain* 2007; **130**: 3063-3074 [PMID: 17478443]

99 **van der Worp HB**, Macleod MR, Kollmar R. Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? *J Cereb Blood Flow Metab* 2010; **30**: 1079-1093 [PMID: 20354545 DOI: 10.1038/jcbfm.2010.44]

100 **Hemmen TM**, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S, Wijman CA, Rapp KS, Grotta JC, Lyden PD. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. *Stroke* 2010; **41**: 2265-2270 [PMID: 20724711 DOI: 10.1161/strokeaha.110.592295]

101 **Lyden P**, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz T, Parker S, Concha M, Hussain S, Agarwal S, Meyer B, Jurf J, Altafullah I, Raman R. Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). *Stroke* 2016; **47**: 2888-2895 [PMID: 27834742 DOI: 10.1161/STROKEAHA.116.014200]

102 **Tang XN**, Liu L, Koike MA, Yenari MA. Mild hypothermia reduces tissue plasminogen activator-related hemorrhage and blood brain barrier disruption after experimental stroke. *Ther Hypothermia Temp Manag* 2013; **3**: 74-83 [PMID: 23781399]

103 **Hong JM**, Lee JS, Song HJ, Jeong HS, Choi HA, Lee K. Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. *Stroke* 2014; **45**: 134-140 [PMID: 24203846 DOI: 10.1161/STROKEAHA.113.003143]

104 **van der Worp HB**, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, Gluud C, Kollmar R, Krieger DW, Lees KR, Molina C, Montaner J, Roine RO, Petersson J, Staykov D, Szabo I, Wardlaw JM, Schwab S. EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. *Int J Stroke* 2014; **9**: 642-645 [PMID: 24828363 DOI: 10.1111/ijs.12294]

105 **Jauch EC**, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870-947 [PMID: 23370205]

106 **Wijdicks EF**, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, Schwab S, Smith EE, Tamargo RJ, Wintermark M. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 1222-1238 [PMID: 24481970 DOI: 10.1161/01.str.0000441965.15164.d6]

107 **Murtha LA**, McLeod DD, Pepperall D, McCann SK, Beard DJ, Tomkins AJ, Holmes WM, McCabe C, Macrae IM, Spratt NJ. Intracranial pressure elevation after ischemic stroke in rats: cerebral edema is not the only cause, and short-duration mild hypothermia is a highly effective preventive therapy. *J Cereb Blood Flow Metab* 2015; **35**: 592-600 [PMID: 25515213 DOI: 10.1038/jcbfm.2014.230]

108 **Dietrich WD**, Alonso O, Busto R, Globus MY, Ginsberg MD. Post-traumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat. *Acta Neuropathol* 1994; **87**: 250-258 [PMID: 8009957]

109 **Jiang JY**, Lyeth BG, Kapasi MZ, Jenkins LW, Povlishock JT. Moderate hypothermia reduces blood-brain barrier disruption

following traumatic brain injury in the rat. *Acta Neuropathol* 1992; **84**: 495-500 [PMID: 1462764]
110 **Gu X**, Wei ZZ, Espinera A, Lee JH, Ji X, Wei L, Dix TA, Yu SP. Pharmacologically induced hypothermia attenuates traumatic brain injury in neonatal rats. *Exp Neurol* 2015; **267**: 135-142 [PMID: 25725354 DOI: 10.1016/j.expneurol.2015.02.029]
111 **Zhi D**, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003; **59**: 381-385 [PMID: 12765810]
112 **Jiang J**, Yu M, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg* 2000; **93**: 546-549 [PMID: 11014530 DOI: 10.3171/jns.2000.93.4.0546]
113 **Henderson WR**, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ. Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis. *Intensive Care Med* 2003; **29**: 1637-1644 [PMID: 12915937 DOI: 10.1007/s00134-003-1848-2]
114 **Peterson K**, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *J Neurotrauma* 2008; **25**: 62-71 [PMID: 18355159 DOI: 10.1089/neu.2007.0424]
115 **McIntyre LA**, Fergusson DA, Hébert PC, Moher D, Hutchison JS. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA* 2003; **289**: 2992-2999 [PMID: 12799408 DOI: 10.1001/jama.289.22.2992]
116 **Hutchison JS**, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008; **358**: 2447-2456 [PMID: 18525042]
117 **Clifton GL**, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, Janis LS, Wilde E, Taylor P, Harshman K, Conley A, Puccio A, Levin HS, McCauley SR, Bucholz RD, Smith KR, Schmidt JH, Scott JN, Yonas H, Okonkwo DO. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol* 2011; **10**: 131-139 [PMID: 21169065]
118 **Ghajar J**. Traumatic brain injury. *Lancet* 2000; **356**: 923-929 [PMID: 11036909]
119 **Ducrocq SC**, Meyer PG, Orliaguet GA, Blanot S, Laurent-Vannier A, Renier D, Carli PA. Epidemiology and early predictive factors of mortality and outcome in children with traumatic severe brain injury: experience of a French pediatric trauma center. *Pediatr Crit Care Med* 2006; **7**: 461-467 [PMID: 16885795 DOI: 10.1097/01.PCC.0000235245.49129.27]
120 **Wijayatilake DS**, Shepherd SJ, Sherren PB. Updates in the management of intracranial pressure in traumatic brain injury. *Curr Opin Anaesthesiol* 2012; **25**: 540-547 [PMID: 22914351 DOI: 10.1097/ACO.0b013e328357960a]
121 **Sinclair HL**, Andrews PJ. Bench-to-bedside review: Hypothermia in traumatic brain injury. *Crit Care* 2010; **14**: 204 [PMID: 20236503 DOI: 10.1186/cc8220]
122 **Lei J**, Gao G, Mao Q, Feng J, Wang L, You W, Jiang J. Rationale, methodology, and implementation of a nationwide multicenter randomized controlled trial of long-term mild hypothermia for severe traumatic brain injury (the LTH-1 trial). *Contemp Clin Trials* 2015; **40**: 9-14 [PMID: 25460339 DOI: 10.1016/j.cct.2014.11.008]
123 **Andrews PJ**, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, Murray GD. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. *N Engl J Med* 2015; **373**: 2403-2412 [PMID: 26444221 DOI: 10.1056/NEJMoa1507581]
124 **Zhu Y**, Yin H, Zhang R, Ye X, Wei J. Therapeutic hypothermia versus normothermia in adult patients with traumatic brain injury: a meta-analysis. *Springerplus* 2016; **5**: 801 [PMID: 27390642 DOI: 10.1186/s40064-016-2391-2]
125 **Ahmad FU**, Starke RM, Komotar RJ, Connolly ES. A Randomized Clinical Trial of Hypothermia as a Preferred Second-Line Treatment for Elevated Intracranial Pressure After Traumatic Brain Injury. *Neurosurgery* 2016; **78**: N10-N11 [PMID: 26779789 DOI: 10.1227/NEU.0000000000001171]
126 **Yokobori S**, Yokota H. Targeted temperature management in traumatic brain injury. *J Intensive Care* 2016; **4**: 28 [PMID: 27123304 DOI: 10.1186/s40560-016-0137-4]
127 **Rehman T**, Deboisblanc BP. Persistent fever in the ICU. *Chest* 2014; **145**: 158-165 [PMID: 24394828 DOI: 10.1378/chest.12-2843]
128 **Diringer MN**, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med* 2004; **32**: 1489-1495 [PMID: 15241093 DOI: 10.1097/01.ccm.000-0129484.61912.84]
129 **Olsen TS**, Weber UJ, Kammersgaard LP. Therapeutic hypothermia for acute stroke. *Lancet Neurol* 2003; **2**: 410-416 [PMID: 12849119]
130 **Niven DJ**, Laupland KB. Pyrexia: aetiology in the ICU. *Crit Care* 2016; **20**: 247 [PMID: 27581757 DOI: 10.1186/s13054-016-1406-2]
131 **Diringer MN**. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. *Crit Care Med* 2004; **32**: 559-564 [PMID: 14758179 DOI: 10.1097/01.ccm.0000108868.97433.3f]
132 **Mayer SA**, Kowalski RG, Presciutti M, Ostapkovich ND, McGann E, Fitzsimmons BF, Yavagal DR, Du YE, Naidech AM, Janjua NA, Claassen J, Kreiter KT, Parra A, Commichau C. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. *Crit Care Med* 2004; **32**: 2508-2515 [PMID: 15599159]
133 **Schortgen F**, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, Dellamonica J, Bouadma L, Cook F, Beji O, Brun-Buisson C, Lemaire F, Brochard L. Fever control using external cooling in septic shock: a randomized controlled trial. *Am J Respir Crit Care Med* 2012; **185**: 1088-1095 [PMID: 22366046 DOI: 10.1164/rccm.201110-1820OC]
134 **Zhang Z**. Antipyretic therapy in critically ill patients with established sepsis: a trial sequential analysis. *PLoS One* 2015; **10**: e0117279 [PMID: 25710375 DOI: 10.1371/journal.pone.0117279]
135 **Zhang Z**, Chen L, Ni H. Antipyretic therapy in critically ill patients with sepsis: an interaction with body temperature. *PLoS One* 2015; **10**: e0121919 [PMID: 25822614 DOI: 10.1371/journal.pone.0121919]
136 **Bigelow WG**, Callaghan JC, Hopps JA. General hypothermia for experimental intracardiac surgery; the use of electrophrenic respirations, an artificial pacemaker for cardiac standstill, and radio-frequency rewarming in general hypothermia. *Trans Meet Am Surg Assoc Am Surg Assoc* 1950; **68**: 211-219 [PMID: 14788154]
137 **Bigelow WC**. Methods for inducing hypothermia and rewarming. *Ann N Y Acad Sci* 1959; **80**: 522-532 [PMID: 13800633]
138 **Todd MM**, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med* 2005; **352**: 135-145 [PMID: 15647576 DOI: 10.1056/NEJMoa040975]
139 **MacLellan CL**, Girgis J, Colbourne F. Delayed onset of prolonged hypothermia improves outcome after intracerebral hemorrhage in rats. *J Cereb Blood Flow Metab* 2004; **24**: 432-440 [PMID: 15087712 DOI: 10.1097/00004647-200404000-00008]
140 **Rincon F**, Friedman DP, Bell R, Mayer SA, Bray PF. Targeted temperature management after intracerebral hemorrhage (TTM-ICH): methodology of a prospective randomized clinical trial. *Int J Stroke* 2014; **9**: 646-651 [PMID: 24450819 DOI: 10.1111/ijs.12220]
141 **Lopez GA**. Temperature Management in the Neurointensive Care Unit. *Curr Treat Options Neurol* 2016; **18**: 12 [PMID: 26920417 DOI: 10.1007/s11940-016-0393-6]
142 **Hansebout RR**, Hansebout CR. Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature. *J Neurosurg Spine* 2014; **20**: 550-561 [PMID: 24628130 DOI: 10.3171/2014.2.SPINE13318]
143 **Neuberger J**. Management of the Patient with Fulminant Hepatic Failure Awaiting Liver Transplantation. Liver Transplantation: John Wiley & Sons, Ltd, 2013: 93-100
144 **Niemann CU**, Feiner J, Swain S, Bunting S, Friedman M, Crutchfield M, Broglio K, Hirose R, Roberts JP, Malinoski D. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. *N Engl J Med* 2015; **373**: 405-414 [PMID: 26222557 DOI: 10.1056/

NEJMoa1501969]
145 **Jochmans I**, Watson CJ. Taking the Heat Out of Organ Donation. *N Engl J Med* 2015; **373**: 477-478 [PMID: 26222564 DOI: 10.1056/NEJMe1507573]

P- Reviewer: Bugaj AM, Maric I, Sip M, Zhang Z **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Methodology

Submit a Manuscript: http://www.f6publishing.com

World J Methodol 2017 June 26; 7(2): 68-72

DOI: 10.5662/wjm.v7.i2.68

ISSN 2222-0682 (online)

ORIGINAL ARTICLE

Basic Study

Nutech functional score: A novel scoring system to assess spinal cord injury patients

Geeta Shroff, Jitendra Kumar Barthakur

Geeta Shroff, Nutech Mediworld, New Delhi 110016, India

Jitendra Kumar Barthakur, Department of Statistics, Nutech Mediworld, New Delhi 110016, India

Author contributions: Shroff G conceptualized the study, and participated in its design and coordination, helped to draft the manuscript, and contributed to study design and data analysis of the manuscript; Shroff G and Barthakur JK read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Nutech Mediworld, New Delhi, India.

Conflict-of-interest statement: The authors declare no conflict of interest regarding the publication of this paper.

Data sharing statement: Our all publications are PubMed indexed and are available online (open access).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Geeta Shroff, MBBS, Founder, Medical Director, Nutech Mediworld, H-8, Green Park Extension, New Delhi 110016, India. geetashroff@hotmail.com
Telephone: +91-11-26565548
Fax: +91-11-46067841

Received: June 14, 2016
Peer-review started: June 17, 2016
First decision: September 2, 2016
Revised: March 8, 2017
Accepted: March 16, 2017

Article in press: March 17, 2017
Published online: June 26, 2017

Abstract

AIM

To develop a new scoring system, nutech functional scores (NFS) for assessing the patients with spinal cord injury (SCI).

METHODS

The conventional scale, American Spinal Injury Association's (ASIA) impairment scale is a measure which precisely describes the severity of the SCI. However, it has various limitations which lead to incomplete assessment of SCI patients. We have developed a 63 point scoring system, *i.e.*, NFS for patients suffering with SCI. A list of symptoms either common or rare that were found to be associated with SCI was recorded for each patient. On the basis of these lists, we have developed NFS.

RESULTS

These lists served as a base to prepare NFS, a 63 point positional (each symptom is sub-graded and get points based on position) and directional (moves in direction BAD → GOOD) scoring system. For non-progressive diseases, 1, 2, 3, 4, 5 denote worst, bad, moderate, good and best (normal), respectively. NFS for SCI has been divided into different groups based on the affected part of the body being assessed, *i.e.*, motor assessment (shoulders, elbow, wrist, fingers-grasp, fingers-release, hip, knee, ankle and toe), sensory assessment, autonomic assessment, bed sore assessment and general assessment. As probability based studies required a range of (-1, 1) or at least the range of (0, 1) to be useful for real world analysis, the grades were converted to respective numeric values.

CONCLUSION

NFS can be considered as a unique tool to assess the

improvement in patients with SCI as it overcomes the limitations of ASIA impairment scale.

Key words: Spinal cord injury; American Spinal Injury Association's Impairment Scale; Nutech functional score; Comparison of assessment; Positional scoring system

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Spinal cord injury (SCI) is a devastating disease which impacts the patient physically, psychologically and financially. American Spinal Injury Association's (ASIA) Impairment Scale is a universally accepted scale to assess the SCI, but this scale does not cover all parameters of SCI. The present study focuses on the development of a new scoring system called nutech functional score for patients with SCI and compare it with internationally used scoring system ASIA.

Shroff G, Barthakur JK. Nutech functional score: A novel scoring system to assess spinal cord injury patients. *World J Methodol* 2017; 7(2): 68-72 Available from: URL: http://www.wjgnet.com/2222-0682/full/v7/i2/68.htm DOI: http://dx.doi.org/10.5662/wjm.v7.i2.68

INTRODUCTION

Spinal cord injury (SCI) is a neurological injury that affects conduction of sensory and motor signals across the site(s) of lesion(s) and the autonomous nervous system leading to long-lasting degeneration of locomotor and sensory neurons below the point of injury[1]. Spinal cord is generally injured during work or recreation related mishaps, motor vehicle accidents as well as violence[2]. According to factsheet of the World Health organization (November 2013), around 250000 and 500000 persons are estimated to suffer from SCI each year[3]. Though survival over SCI has improved, yet it is of paramount importance to focus on the issue of assessment of SCI patients as perfectly as possible[2].

There are many international standards available for examination of the neurological damage. "American Spinal Injury Association's (ASIA) Impairment Scale" is a universally accepted scale which consolidates "scores" and assesses the extent of injury, and the overall condition in its own way. These conventional scoring scales examine sensory and motor levels on right and left sides, sensory scores using pin prick and light touch, motor scores for upper and lower limb, *etc*. They precisely determine neurological levels, the extent of incomplete injury and achieve more consistent and reliable data[1,4-6].

The ASIA impairment scale is a categorical scale which classifies the extent of SCI injury as motor complete and motor incomplete using grades A, B, C, D and E. "A" refers to complete injury where no function, neither sensory nor motor, has been preserved in the sacral segments S4-S5. "B" is assigned to SCI patients where no motor function is preserved below the neurological level and sacral segments S4-S5, whereas, sensory function is preserved. The SCI patients who are diagnosed with motor incomplete condition, *i.e*., motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade < 3, are assigned with grade "C". "D" refers to the motor incomplete condition where motor function is preserved below the neurological level, and at least half or more of key muscle functions below the neurological level have a muscle grade > 3. "E" refers to the normal condition of the patient, where sensory as well as motor functions are normal[1]. There is a direction of BAD → GOOD from A to E, where → stands for "to" or "moves towards". The routes are distinctly two and they are A → B → E and A → C → D → E[7]. These routes only allow counting of ASIA impairment scale which are neither numeric nor ordinal. They disconnect the ability of the sensory symptoms from the motility of the motor symptoms, as both run along two different routes. This confines the analysis with clinical research to count and rank in two streams of the scores. It was refined/improved on various basis from 1989 to 2013 which led to addition of some more parameters, such as T3 sensory examination, motor examination, testing position, wrist extension, hip flexors, ankle dorsiflexors, long toe extension, anorectal examination, *etc*[4,5,8]. However, there are many parameters such as bed sore assessment, improvement assessment, breathing pattern, *etc*. that are important to assess in case of SCI patients but are not covered under ASIA impairment scale yet.

The present study focuses on the development of a new scoring system called nutech functional scores (NFS) for patients with SCI and compare it with the internationally used scoring system ASIA. All the improtant parameters that are missed out in ASIA scale have been included in NFS that makes it more valuable in assessing the complications and improvement after treatment in patients with SCI.

MATERIALS AND METHODS

The symptoms, either common or rare, with which the patients were evaluated, were recorded in the diagnostic history. We started preparing a list of all the possible symptoms from the diagnostic history of the patients. These lists are revised time and again to maintain accuracy and precision and are used to assess patients with SCI.

Each symptom had five ordinal grades in BAD → GOOD direction. We assessed the SCI patients simultaneously with ASIA impairment scale and our new scoring system. The study was approved by Institutional Review Board of Nutech Mediworld.

Table 1 Conversion table from categorical grades to numeric range for nutech functional score

No. of scores	Numeric (Y_n)	Categorical scores (Y_c)				
		1	2	3	4	5
5	Score (Y_n)	0.122	0.310	0.500	0.690	0.890
	Range (Y_n)	0-0.241	0.241-0.379	0.379-0.621	0.621-0.759	0.759-1.00
3	Score (Y_n)	0.167	0.5	0.833	-	-
	Range (Y_n)	0-0.333	0.333-0.667	0.667-1.00	-	-

RESULTS

We developed a 63 point grading system which consisted of five grades in number for each parameter. For non-progressive diseases, 1, 2, 3, 4, 5 denote worst, bad, moderate, good and best (normal), respectively. The symptoms that are found not to be associated with SCI are scored as not afflicted in SCI (NA). Supplementary table presents the parameters assessed with NFS along with their grades. NFS for SCI has been divided into different groups based on the affected part of the body being assessed, *i.e*., motor assessment (shoulders, elbow, wrist, fingers-grasp, fingers-release, hip, knee, ankle and toe), sensory assessment, autonomic assessment, bed sore assessment and general assessment.

The hypothetical spread of five symptoms ranging in (0.5, 5.5) were treated as equidistant to each other and were continuous. As probability based studies required a range of (-1, 1) or at least the range of (0, 1) to be useful for real world analysis, the grades were converted to respective numeric values. The "0.5" and "5.5" in the range of (0.5, 5.5) was treated as "0" and "1" of the (0, 1) in numeric scale, respectively. The configuration used to convert the range (0.5, 5.5) to the range (0, 1) demonstrated the internal consistency of the two methods of grading. It is now universal and usable for one symptom. An equation has been derived using the polynomial smoothing and graphical methods for converting categorical scores into numeric scores. The equation is as follows:

$$Y_n = 0.096 \times (Y_c + 0.5) - 0.166$$

where, Y_n = numeric score and Y_c = categorical score.

Table 1 explains the layout of the conversions. Depending upon the symptoms of parameters assessed by NFS, the five/three categorical grades in the range (0.5-5.5) can be converted to five/three numeric grades in the range (0, 1), respectively.

DISCUSSION

The spinal cord is the major conduit through which motor and sensory information travels between the brain and body. It can get injured which leads to SCI affecting the smooth functioning of the body[1]. Though, last decade reveals various reports emphasizing the medical management of SCI, still, there is no effective treatment to completely cure SCI. The pathophysiology, either primary injury phase or secondary, involved in SCI is essential to determine the type of possible therapeutic application that can be used after SCI.

Preceding clinical management, it is essential to determine the extent of injury. There are various scales to determine the cord segments affected by SCI[1]. ASIA impairment scale is such a tool where its grades relate directly to a case and form categorical distributions of frequencies.

Though, many revisions have taken place in ASIA impairment scale scoring system, few limitations have been observed during assessment of SCI which restrict/limit its use. It doesn't specify the classification score for SCI patients who have patchy motor and sensory functions intact, irrespective of the level. It does not specify if motor or sensory function is non-contiguous or on one side of the body. It gives the classification of function affected below the level of injury, but doesn't describe the gross condition of the patients, such as if breathing is affected; if the patient can sit without support or even maintain the sitting posture. A study by Gündoğdu *et al*[9] reported that the ASIA impairment scale to assess the recovery in SCI patient, it can lead to incorrect diagnosis as it may show the worsening of the condition despite of the neurological improvement of the patient. Thus, we may retrieve at an incorrect conclusion when AIS grade is considered alone without observing any motor or sensory changes during recovery[9]. Determination of motor levels and differentiation between AIS B and AIS C/D is one of the most difficult classification tasks in AIS scoring system[10].

The major addition made in NFS is the improvement assessment parameter. It documents even the slightest improvement by using parameters which redefined the motor and sensory functions, thereby overcoming one of the important existing limitations of ASIA impairment scale.

In our previous study, we reported several signs of improvement in our study patients who did not show any improvement when assessed with ASIA scale. Their score remained "A", both before and after the therapy. But, these patients showed improvement in sensation of fullness of bowel and bladder and control over bowel and bladder[11]. Thus, ASIA scale lacks in assessing these parameters. Other parameters such as bed sore number and size, breathing and swallowing pattern, deformity, sweating below the level of injury, spasticity, deformity, sitting balance, standing balance, flaccidity, bulk/limb atrophy, walking distance and other general assessments including requirement of gait with calipers, calipers for standing and mobility aid, *etc*. are also not assessed by ASIA, but are included in our

Table 2 A hypothetical example showing nutech functional scores of a spinal cord injury patient before and after therapy

Parameters	NFS score before therapy	NFS score after therapy
Motor assessment (shoulder)		
Flexion	1	4
Extension	1	3
Adduction	2	5
Abduction	NA	NA
Internal rotation	2	5
External rotation	1	5
Motor assessment (elbow)		
Flexion	NA	NA
Extension	NA	NA
Supination	2	5
Pronation	2	5
Motor assessment (wrist)		
Flexion	1	3
Extension	1	4
Radial deviation	2	5
Ulnar deviation	NA	NA
Motor assessment (fingers - grasp)		
Use full palmar grasp	NA	NA
Use radial-digital grasp	NA	NA
Use standard pincer grasp	2	5
Use spherical grasp	3	5
Use intrinsic-plus grasp	3	5
Use power grasp on tool	2	5
Motor assessment (fingers - release)		
Release object freely	1	5
Release 1-inch object in container	1	5
Stack 1-inch blocks	1	5
Release tiny objects	1	3
Throw small ball at least 3 feet	1	4
Motor assessment (hip)		
Flexion	NA	NA
Extension	NA	NA
Adduction	1	3
Abduction	1	5
Internal rotation	1	5
External rotation	2	5
Motor assessment (knee)		
Flexion	1	3
Extension	1	3
Motor assessment (ankle)		
Plantar flexion	NA	NA
Dorsi flexion	NA	NA
Inversion	NA	NA
Eversion	NA	NA
Motor assessment (toe)		
Flexion	1	4
Extension	1	5
Sensory assessment		
Superficial sensation	2	5
Deep sensation	2	5
Autonomic assessment		
Bladder sensation	NA	NA
Bladder control	1	4
Bowel sensation	1	5
Bowel control	2	5
Blood pressure assessment	3	5
Bed sore assessment		
Bed sore number	1	5
Bed sore size	1	5
General assessment		
Breathing	NA	NA
Sweating	NA	NA
Swallowing	2	5
Gait with calipers	NA	NA
Calipers	1	5
Spasticity	1	5
Clonus	NE	NE
Deformity	1	5
Contracture	NA	NA
Flaccidity	3	5
Bulk/limb atrophy	1	4
Sitting balance	2	5
Standing balance	NA	NA
Walking aid	1	5
Walking distance	NA	NA
Total	67	197

NFS: Nutech functional scores; NA: Not afflicting; NE: Not existing.

newly developed NFS scoring system. This has led to a complete assessment of the patient's condition which is lacking in ASIA impairment scale.

All the parameters in NFS scoring system are graded on a scale of 1 to 5 in the range of 0.5 to 5.5, *i.e.*, NFS is ordinal, which provides complete information regarding the condition of the patients before and after the therapy. It is important to note that NFS does not include "0" as a grade. Analytical work based on "count" stays unaffected.

Let's take a hypothetical example to explain how the affected parameters are graded with NFS and ASIA. Table 2 presents a detailed manner of grading a SCI patient with NFS. Addition of scores for each parameter gives us the total score. The total NFS score of the patient before therapy is 67 and increases to 197 after the therapy. This shows a remarkable improvement in the patient after undergoing therapy. When assessed with ASIA, the grade of the patient before therapy is "A" (complete) and moves to "B" (Sensory incomplete) after the therapy. ASIA score "B" is defined as "sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5, AND no motor function is preserved more than three levels below the motor level on either side of the body". Thus, it means that patients had no improvement in motor function following the therapy which is contrary to the assessment with NFS. With NFS, we have observed improvement in motor functions of shoulder, elbow, wrist, finger-grasp, finger-release, wrist, ankle, hip and toe (Table 2). In NFS, scores can be added or subtracted; therefore even slightest improvement/deterioration in the patient's condition can be assessed.

At our facility, we have evaluated the effectiveness of NFS in assessing the patients treated with human embryonic stem cell (hESC) therapy. Thus, NFS can be considered as a unique tool to assess the improvement in patients with SCI receiving the hESC therapy. However, the universal use of the NFS will help in determining its usability in assessing the improvement in patients being treated with other therapies.

In conclusion, the NFS scoring system for SCI in numeric form is an adequate instrument to examine and score the patients with SCI. The ASIA impairment scale is based on categorical descriptions which are not

comparable with a numeric based system.

ACKNOWLEDGMENTS

The authors acknowledge all the doctors, staff and patients of the Nutech Mediworld. The authors also acknowledge Knowledge Isotopes Pvt. Ltd. (http://www.knowledgeisotopes.com) for the medical writing support.

COMMENTS

Background

Spinal cord injury (SCI) is a neurological injury that affects conduction of sensory and motor signals across the site(s) of lesion(s) and the autonomous nervous system leading to long-lasting degeneration of locomotor and sensory neurons below the point of injury. There are many international standards available for examination of the neurological damage.

Research frontiers

In the current study, the authors have introduced a new scoring system called nutech functional score (NFS) for assessment of patients with SCI and compare it with the internationally used scoring system American Spinal Injury Association's (ASIA) Impairment Scale. All the improtant parameters that are missed out in ASIA scale has been included in NFS that makes it more valuable in assessing the complications and improvement after treatment in patients with SCI.

Innovations and breakthroughs

The authors have developed a 63 point scoring system, *i.e*., NFS for patients suffering with SCI. A list of symptoms either common or rare that were found to be associated with SCI was recorded for each patient. This list is the basis to develop NFS.

Applications

NFS for SCI patients is a 63 point, positional (each symptom is sub-graded and get points based on position) and directional (moves in direction BAD → GOOD) scoring system that can be used to assess patients with SCI and compare it with the internationally used scoring system ASIA. All the important parameters that are missed out in ASIA scale have been included in NFS.

Terminology

NFS is a 63 point, positional (each symptom is sub-graded and get points based on position) and directional (moves in direction BAD → GOOD) scoring system.

Peer-review

The manuscript proposes a new scoring system, for assessing the patients with SCI. It is well written.

REFERENCES

1 **Kirshblum SC**, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, Johansen M, Jones L, Krassioukov A, Mulcahey MJ, Schmidt-Read M, Waring W. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med* 2011; **34**: 535-546 [PMID: 22330108 DOI: 10.1179/204577211X13207446293695]

2 **Sekhon LH**, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* (Phila Pa 1976) 2001; **26**: S2-12 [PMID: 11805601]

3 **Shroff G**, Barthakur JK. Safety of human embryonic stem cells in patients with terminal/incurable conditions- a retrospective analysis. *Ann Neurosci* 2015; **22**: 132-138 [PMID: 26130921 DOI: 10.5214/ans.0972.7531.220303]

4 **Waring WP**, Biering-Sorensen F, Burns S, Donovan W, Graves D, Jha A, Jones L, Kirshblum S, Marino R, Mulcahey MJ, Reeves R, Scelza WM, Schmidt-Read M, Stein A. _ 2009 review and revisions of the international standards for the neurological classification of spinal cord injury. *J Spinal Cord Med* 2010; **33**: 346-352 [PMID: 21061894]

5 **Buehner JJ**, Forrest GF, Schmidt-Read M, White S, Tansey K, Basso DM. Relationship between ASIA examination and functional outcomes in the NeuroRecovery Network Locomotor Training Program. *Arch Phys Med Rehabil* 2012; **93**: 1530-1540 [PMID: 22920450 DOI: 10.1016/j.apmr.2012.02.035]

6 **Shavelle RM**, Paculdo DR, Tran LM, Strauss DJ, Brooks JC, DeVivo MJ. Mobility, continence, and life expectancy in persons with Asia Impairment Scale Grade D spinal cord injuries. *Am J Phys Med Rehabil* 2015; **94**: 180-191 [PMID: 24919073 DOI: 10.1097/PHM.0000000000000140]

7 **Barthakur JK**. Human embryonic stem cell: Cerebrovascular accident clinical study report. New Delhi: Nutech Photolithographers, 2012

8 **Parashari UC**, Khanduri S, Bhadury S, Kohli N, Parihar A, Singh R, Srivastava RN, Upadhyay D. Diagnostic and prognostic role of MRI in spinal trauma, its comparison and correlation with clinical profile and neurological outcome, according to ASIA impairment scale. *J Craniovertebr Junction Spine* 2011; **2**: 17-26 [PMID: 22013371 DOI: 10.4103/0974-8237.85309]

9 **Gündoğdu İ**, Akyüz M, Öztürk EA, Cakcı FA. Can spinal cord injury patients show a worsening in ASIA impairment scale classification despite actually having neurological improvement? The limitation of ASIA Impairment Scale Classification. *Spinal Cord* 2014; **52**: 667-670 [PMID: 24891005 DOI: 10.1038/sc.2014.89]

10 **Schuld C**, Franz S, van Hedel HJ, Moosburger J, Maier D, Abel R, van de Meent H, Curt A, Weidner N, Rupp R. International standards for neurological classification of spinal cord injury: classification skills of clinicians versus computational algorithms. *Spinal Cord* 2015; **53**: 324-331 [PMID: 25487243 DOI: 10.1038/sc.2014.221]

11 **Shroff G**, Gupta R. Human embryonic stem cells in the treatment of patients with spinal cord injury. *Ann Neurosci* 2015; **22**: 208-216 [PMID: 26526627 DOI: 10.5214/ans.0972.7531.220404]

P- Reviewer: Anand A, Papachristou GC **S- Editor**: Song XX
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

© 2017 Baishideng Publishing Group Inc. All rights reserved.