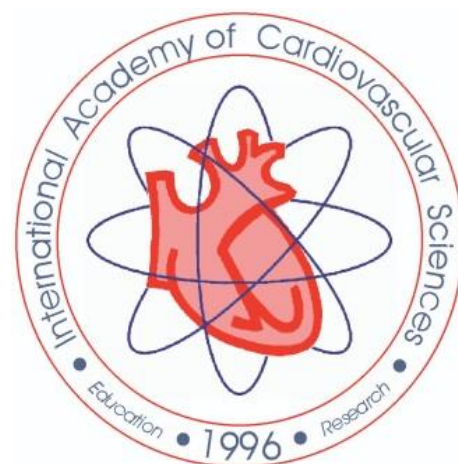


Promoting Cardiovascular Education, Research and Prevention

CV Network

THE OFFICIAL BULLETIN OF THE INTERNATIONAL ACADEMY OF CARDIOVASCULAR SCIENCES

PUBLISHED WITH THE ASSISTANCE OF THE ST. BONIFACE
HOSPITAL ALBRECHTSEN RESEARCH CENTRE



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Grant Pierce Elected as IACS-President-Elect

At the recent election by the Fellows of the Academy from all over the world, Dr. Grant Pierce, Winnipeg, Canada, was chosen as President-Elect for a term of 3 years effective, July 1, 2018. He is replacing Dr. Roberto Bolli, Louisville, USA, who is assuming the position of President of the Academy. Drs. Lorrie A. Kirshenbaum (Canada), Gary Lopaschuk (Canada), Tatiana Ravingerova (Slovak Republic) and Dobromir Dobrev (Germany) were elected as new Members of the Council of the Academy. The Council of the Academy for 2018-2021 is as follows:

Officers and Member of the IACS-Council

(Hon. Life President: Dr. Naranjan S. Dhalla)

President: Dr. Roberto Bolli, Louisville, USA

President-Elect: Dr. Grant Pierce, Winnipeg, Canada

Past President: Dr. Bohuslav Ostadal, Prague, Czech Republic

Executive Director: Dr. Naranjan S. Dhalla, Winnipeg Canada

Council Members:

Dr. Michael Czubyrt, Winnipeg Canada

Dr. Dragan Djuric, Belgrade, Serbia

Dr. Dobromir Dobrev, Essen, Germany

Dr. Ricardo J. Gelpi, Buenos Aires, Argentina

Dr. Otoni M. Gomes, Belo Horizonte, Brazil

Dr. Ramesh K. Goyal, New Delhi, India

Dr. Chandrasekharan Kartha, Trivandrum, India

Dr. Lorrie Kirshenbaum, Winnipeg, Canada

Dr. Gary Lopaschuk, Edmonton, Canada

Dr. Naoki Makino, Beppu, Japan

Dr. Jawahar L. Mehta, Little Rock, USA

Dr. Tatiana Ravingerova, Bratislava, Slovakia

Dr. Pawan K. Singal, Winnipeg, Canada

Dr. Jan Slezak, Bratislava, Slovak Republic

Dr. Andras Varro, Szeged, Hungary

Significant Achievements and Professional Career of Dr. Grant Pierce



Dr. Grant N. Pierce

Dr. Grant Pierce received his MSc degree from Dalhousie University and his PhD degree in the Department of Physiology at the University of Manitoba in 1983 before returning after postdoctoral training at UCLA as an Assistant Professor in the same Department in 1986.

His entire academic career

has been spent here at the University of Manitoba. He is currently a Distinguished Professor in the University of Manitoba. Dr. Pierce's contributions in research, service and teaching to Winnipeg, to Manitoba, and to Canada

have been exceptional as described in the following passages.

1) Research

Dr. Pierce's research accomplishments are varied and exceptional in three different aspects: research advancements through knowledge creation, research administration and research leadership. Each is distinctly different and within each category Dr. Pierce's contributions have been exceptional and world class. Each is described separately:

Research advancements through knowledge creation:

Dr. Pierce has had uninterrupted research grant support from MRC/CIHR since 1987. He currently holds a CIHR Foundation grant, one of precious few in the University of Manitoba. He has published over 225 peer reviewed

papers in some of the top cardiovascular, nutritional, biochemistry & cell biology journals in addition to authoring or editing 8 textbooks. According to Google Scholar he has over 10,300 citations, a Google Scholar H-index of 57 and an i10-index of 181. His major findings are i) defining the subcellular basis of the diabetic cardiomyopathy at a time when the existence of a cardiomyopathy in diabetes was strongly denied (it is now a well accepted pathology), ii) an identification of a primary pathway (the Na^+/H^+ and $\text{Na}^+/\text{Ca}^{2+}$ exchanger cascade) for ischemic/reperfusion injury to the heart (one of the major causes of death today), iii) he is a world leader in dietary flaxseed and its effects on heart disease (specifically hypertension where it may have major effects on the incidence of heart attacks and stroke), iv) the first to show a cause and effect relationship for Chlamydia Pneumonia infection and heart disease, which has led to v) his most impressive recent discovery of a breakthrough in antibiotic targeting and drug design. This development of a novel platform of antibiotics received national and international attention for their potential to avoid multi-drug resistance in pathogenic bacteria. For his research accomplishments, Dr. Pierce has received the Queen Elizabeth II Diamond Jubilee Medal from the Government of Canada and was elected Fellowship in the Royal Society of Canada. Induction into the Royal Society of Canada “represents Canadian scholars, artists, and scientists, peer-elected as the best in their field... from all branches of learning who have made remarkable contributions in the arts, the humanities and the sciences, as well as in Canadian public life.” He has also received awards in recognition of research excellence from the Governments of Canada, Cuba, Serbia, India, Slovakia, Hungary, the American Heart Association, the International Society for Heart Research, and the International Academy of Cardiovascular Sciences. Over his career, Dr. Pierce has been invited to present his data in nearly 300 invited lectures in 31 different countries.

Research service/administration:

Dr. Pierce has served as a member of peer review research Committees for the Medical Research Council of Canada, Alberta Innovates Health Solutions, Alberta Heritage Foundation for Medical Research, Manitoba Health Research Council, Winnipeg Rh Institute, the University of Manitoba, St Boniface Hospital, Manitoba Medical Service Foundation, Canada Research Chairs Program, and the Michael Smith Foundation for Health Research. He was responsible for all peer review conducted by the Heart and Stroke Foundation of Canada (HSFC) in his capacity as Chair of the Scientific Review Executive Committee from 2005-08. He was the first and remains the only Manitoban to ever be appointed to this position and his three year term is the longest of any previous or current HSFC Chair. He has served on Research Advisory Panels for the HSFC and HSF of Manitoba, CIHR, the

Centre for Substance Use in Sport and Health, the University of Saskatchewan, University of Prince Edward Island, Queen's University, Lakehead University, Canadian Foundation for Innovation, the Canadian Agri-food Policy Institute, CentreStone Ventures Fund, Medicare, the Ranjiv Gandhi Biotechnology Centre in India and the Scientific Advisory Board for the CIHR Institute of Circulatory and Respiratory Health (in many cases as Chair or Vice Chair of these committees). He has been a member of the Board of Directors for 6 different provincial and national health boards. He speaks to the media (print, radio and television) regularly on a number of health topics, most recently to the Parliamentary Health Caucus in Ottawa on behalf of Research Canada. Dr. Pierce has been the longest serving Editor of the Canadian Journal of Physiology and Pharmacology in its distinguished history (2003-2016). He has also served on Editorial Boards of some of the best scientific journals in the world.

Research leadership:

As Executive Director of Research for St Boniface Hospital, a teaching hospital for the University of Manitoba for the last 13 years, Dr. Pierce has been directly responsible for all research that occurs on the St Boniface Hospital campus, both basic and clinical. This research enterprise consists of about 40 Principal Investigators (most of whom hold University of Manitoba faculty positions), 250 research staff and trainees with an annual budget of about \$14M. Last year Research InfoSource Inc., an independent organization out of Toronto, ranked St Boniface Hospital as the #1 Research Intensive Hospital in Western Canada and in the top 10 of all Canada for the 5th consecutive year. Dr. Pierce is also currently in the position of Assistant Executive Director of the Manitoba Medical Service Foundation (MMSF). The primary role of MMSF is to review grant applications and adjudicate research funds to deserving young faculty in Winnipeg. As a leader of MMSF, Dr. Pierce forms a key component of the function of MMSF and he is always available to media and staff to guide their research process. Dr. Pierce created the Canadian Centre for Agri-food Research in Health and Medicine at St Boniface Hospital. This was instituted in its original form in 1999 and was the first organized functional food research group in Western Canada and one of the first in Canada. This remains highly successful and a template model for the union of three distinct groups: Universities (University of Manitoba and University of Winnipeg), a teaching Hospital (St. Boniface Hospital) and a federal organization (Agriculture and Agri-food Canada) into one fully functional research organization. His efforts have not gone unrecognized. He has won many awards for his research leadership (26 national and 29 international). To name just a few, he has won the inaugural Ron Duhamel Innovation Award for innovation and leadership in the

advancement of health care for Manitobans in 2004, the Outstanding Leadership in Health Research Award from the Life Sciences Association of Manitoba in 2009, and this capacity for leadership in research was formally recognized nationally with the 2016 Research Canada Leadership Award at a gala event held in Toronto. In 2018 he was inducted into the Order of Manitoba, the highest honour the province can award. This award recognizes those who demonstrate excellence and achievement.

2) Teaching

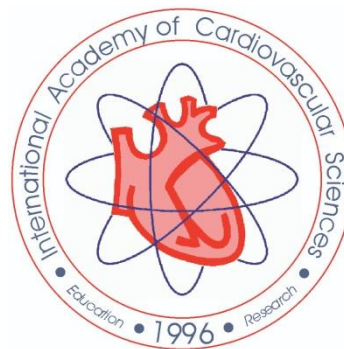
Dr. Pierce's accomplishments in teaching at the University of Manitoba are no less impressive. Dr. Pierce has had an impressive impact as a supervisor and mentor at the University of Manitoba. Dr. Pierce has supervised undergraduate students every year at the University of Manitoba for the last 25+ years. These students have moved into graduate school (6), medical schools (16), and become health professionals (4). Dr. Pierce also has a strong history of training graduate students at the University of Manitoba. In peer reviewed publications originating from the Pierce lab, his trainees have been the 1st author of 90% of the publications (135 of 150). His graduate students have won 46 Studentships/Scholarships, 23 poster awards and 61 competitive awards for research excellence. His latest student, Dr. Stephanie Caligiuri, was awarded a Distinguished Dissertation Award from the University of Manitoba for her PhD work. Dr. Pierce has been the Primary Supervisor for 23 PhD & MSc students, 17 postdocs and visiting scientists who have gone on to successful careers and leadership roles as University Professors, Clinicians and Surgeons, Clinical Directors, Research Directors, Clinical Research Scientists, Senior Managers in the pharmaceutical industry, Project Managers, Technology Transfer Managers, Physician Assistants, Clinical Physiotherapists, Directors of Regulatory Affairs, Health Canada Senior Compliance Officers, Research Facilitators, Medical Students and Postdoctoral Fellows in Canada, France, Germany, Japan, Cuba, Argentina and USA. His postdoctoral fellows have gone on to successful faculty positions (5) in Canada, Japan, France, Lebanon and the Czech Republic, positions in industry (2) and become physicians (2). His postdoctoral fellows have co-authored 31 peer reviewed papers, 15 as 1st author. Advancing the careers of technicians at the University of Manitoba is often forgotten. Dr. Pierce has moved technicians into faculty positions (2), physicians (3), health industry (4), graduate school and as postdoctoral fellows (3). His technicians have co-authored 64 peer reviewed papers, 9 as first author.

3) Community Service

Dr. Pierce created the RBC Youth BioLab at St Boniface Hospital, to allow children (primarily Grades 5-8) to be

involved in hands-on experiments about science, research and health. The teaching program has been incorporated into the Manitoban educational curriculum. Children dissect brains & hearts, culture bacteria, learn about organ function in a real hospital laboratory. All Provincial children (rich or poor) have access to this laboratory opportunity. It is the only one of its kind in the world. This was a partnership between the Louis Riel School District, the Government of Manitoba, RBC Bank and St Boniface Hospital. It is now funded on an annual basis by these partners in addition to a competitive grant obtained from NSERC to operate this one-of-a-kind facility. Last year, over 5,000 Manitoban children came to the RBC Youth BioLab to learn and become excited by the experience of scientific discovery. This program over its 12 years of existence has interacted with over 50,000 Manitoban children. His teaching efforts have been recognized locally and internationally with the University of Manitoba Merit Award for Outstanding Achievement in Research, Teaching and Service twice (1991 and 2001), as well as the Makato Nagano Award for Distinguished Achievements in Cardiovascular Education in an international meeting in Marseille France.

Dr. Pierce has also led the creation and annual organization of the "Hoops From The Heart" event. Every year, the best male and female basketball players in Manitoba play basketball in an exciting evening event held just for underprivileged inner city kids. In this annual event, about 150 inner city kids are welcomed to the University of Winnipeg where they receive a meal, a Hoops From The Heart T shirt and a basketball signed by one of the players to keep and take home. The event is now in its 10th year and has entertained over 1000 inner city children. In addition, through their fundraising activities, two endowed Scholarships have been created, one at the University of Winnipeg and one at the University of Manitoba, to support an inner city boy or girl to go to University and play on one of their basketball teams. It is the hope of Dr. Pierce and his team that this provides an opportunity through both the annual event and the Scholarship to encourage a child to obtain a University education when most inner city kids would not have thought of this opportunity otherwise.



Gary Lopaschuk Assumes the Position of IACS-North America Section President



Dr. Gary D. Lopaschuk

Dr. Gary Lopaschuk received his BSc (Pharmacy, 1978), MSc (1980), and PhD (1983) from the University of British Columbia in Vancouver, Canada. This was followed by a post-doctoral training at the Hershey Medical School of Penn State University. He is currently a Distinguished University Professor of Pediatrics at the University of Alberta, Edmonton.

Dr. Lopaschuk is a Fellow of the Royal Society of Canada. He has served as Scientific Director of the Mazankowski Alberta Heart Institute, and has previously served in a number of capacities with the Heart Stroke Foundation of Canada, including as Chair of the Scientific Review Committee and the Vice-Chair of the Research Planning and Priorities Committee. He has also served as President of the International Society for Heart Research, North American Section. He serves on a number of journal editorial boards, including *Circulation Research*, *Journal of Clinical Investigation*, *American Journal of Physiology*, *Cardiovascular Research*, *Journal of Molecular and Cellular Cardiology*, *Canadian Journal of*

Physiology and Pharmacology, *Heart and Metabolism*, and *Cardiovascular Drugs and Therapy*. He is also the President and CEO of a biotechnology company (Metabolic Modulators Research Ltd.), that is developing novel drugs to treat heart disease that optimize energy metabolism in the heart. His research has resulted in the publication of over 400 research articles, and he has been recognized by awards such as the Canadian Cardiovascular Research Achievement Award and the International Academy of Cardiovascular Sciences Naranjan Dhalla Research Achievement Award and the Norman Alpert Research Achievement Award.

Dr. Lopaschuk's research focuses on the regulation of fatty acid oxidation in the heart, and the mechanism by which high rates of fatty acid oxidation contribute to heart disease and heart failure. This involves the use of isolated working hearts in which cardiac energy metabolism can be directly measured. He is also examining how alterations in fatty acid metabolism contribute to cardiovascular disease in the diabetic. At a molecular level he has characterized a number of key enzymes important in the regulation of cardiac fatty acid oxidation. He is also developing a number of therapeutic strategies that involve optimizing energy metabolism in the heart that can be used to prevent the development of heart disease, and that can also be used to treat heart failure.

Manitoba Cardiovascular Leader Named to Canadian Medical Hall of Fame

Karen Hiebert

***Manager, Communications & Media Services
St. Boniface Hospital Research, Winnipeg, Canada
Email: khiebert@sbrc.ca***

St. Boniface Hospital Research is extremely proud to share the news that Dr. Naranjan S. Dhalla will be inducted into the Canadian Medical Hall of Fame next spring in recognition of his 50 year career advancing knowledge, resources and collaboration in the realm of cardiovascular sciences.

Dr. Dhalla is Distinguished Professor and Director of Cardiovascular Developments, St. Boniface Hospital

Albrechtsen Research Centre, Max Rady College of Medicine at the University of Manitoba, and a founding leader of two worldwide organizations of cardiovascular science: the International Society of Heart Research (ISHR) devoted to basic cardiovascular science research, and the International Academy of Cardiovascular Sciences (IACS) promoting cardiovascular health education and community involvement. He served as Editor-in-Chief of the journal *Molecular and Cellular*



Dr. Naranjan S. Dhalla

Biochemistry, was Director of the Institute of Cardiovascular Science at St. Boniface Hospital in Winnipeg for 19 years, edited/authored more than 50 books, trained more than 150 graduate students and postdoctoral fellows and presented at more than 500 conferences worldwide.

“Dr. Dhalla is an innovative leader who created and grew

a number of institutions and organizations that have world class status in cardiovascular research. To have him as a long-standing member of our faculty here at St. Boniface Hospital Research and now as a Laureate in the Canadian Medical Hall of Fame is an honour of the highest degree,” said Dr. Grant Pierce, Executive Director of Research, St. Boniface Hospital, “We send our heartiest congratulations to him.”

“Our research facility here at St. Boniface Hospital is internationally recognized as one of the premier institutes in biomedical cardiovascular sciences, and it wouldn’t have existed at all without Dr. Dhalla’s role as the founding Director of the Institute of Cardiovascular Sciences. He is extremely deserving of this award and we are thrilled to celebrate this honour,” said Martine Bouchard, President & CEO, St. Boniface Hospital. Canadian Medical Hall of Fame Laureates are individuals whose contributions to medicine and the health sciences have led to extraordinary improvements in human health.

Their work may be a single meritorious contribution or a lifetime of superior accomplishments. Pioneers in their field, they are role models for Canadians and an inspiration to our youth to pursue careers in the health sciences. “Dr. Dhalla is known for his commitment to developing and advancing the careers of Canadian research trainees and scientists and elevating their profile internationally. His founding of the International Academy of Cardiovascular Sciences and the International Society for Heart Research, with strong Canadian representation at the leadership level, truly established our country’s scientists as internationally influential,” said Dr. Henry Friesen, Distinguished Professor Emeritus University of Manitoba.

“Dr. Dhalla’s career of teaching and research is to be commended,” said Dr. Digvir Jayas, vice-president (research and international) and Distinguished Professor, University of Manitoba. “His influence on the field of cardiovascular science has been transformative globally as a result of his numerous contributions. He is a true visionary leader and most deserving of this prestigious recognition.”

Dhalla will be formally inducted with five other Canadians at a ceremony held in association with McGill University Faculty of Medicine on May 2, 2019 in Montreal, Quebec. This designation makes him the seventh Manitoban in history to be recognized as a Hall of Fame Laureate, joining Dr. Bruce Chown, Dr. Henry Friesen, Dr. Arnold Naimark, Dr. Cheryl Rockman-Greenberg, Dr. Allan Ronald, and Dr. F. Estelle R. Simons.



Dr. Naranjan S. Dhalla (right) with pioneers of medical research at St Boniface Research Centre, L to R: Drs. Henry Friesen, John Foerster and Arnold Naimark



Statue of Dr. Naranjan S. Dhalla in the Citizens Hall of Fame in Winnipeg

Dr. Pawan Singal Receives Honorary Doctorate

Karen Hiebert

*Manager, Communications & Media Services
St. Boniface Hospital Research, Winnipeg, Canada
Email: khiebert@sbrc.ca*



Dr. Pawan K Singal

Dr. Pawan Singal's pioneering studies in cardiovascular research, his community leadership and reputation as a superb educator, were recognized with a Doctor of Laws honorary degree at the 114th Convocation of The University of Winnipeg on October 12, 2018. He was recognized not only for his medical research, but also for his outstanding teaching skills and his leadership in facilitating cross-cultural awareness through his work with the India Centre for Academic, Business and Community Excellence - a partnership between The University of Winnipeg and the India Association of Manitoba.

Dr. Singal acknowledged in his Convocation Address to the University Graduands that "in honouring me, you have honoured all those I have had the privilege of working with and in the process learning much." Dr. Singal shared how a few acts of mentorship and guidance led him to a distinguished career in cardiovascular research; a deep engagement in the building of professional international societies; and helping to establish a cultural centre in Winnipeg, an India Centre in the University of Winnipeg, just to name a few.

Indeed, it is abundantly clear that Dr. Singal has a particular talent for leading cross-cultural projects that

bring together great scientific minds and ambitions, as well as the unique social traditions and experiences of different countries. In 2013-2016, he led a research project under the Canada-Brazil Awards - Joint Research Projects. Not only were lasting fruitful collaborations the result of this initiative, but lifelong friendships as well. In his convocation address to the Class of Fall 2018, Dr. Singal touched on the importance of relationships, emphasizing the benefits of listening, learning and helping others in our academic and personal journeys in order to build productive and mutually respectful bonds with every person we meet in our lives.

"Dr. Singal is an exceptionally committed individual who embodies the qualities of leadership and excellence. We are proud to have him as a colleague and mentor, and congratulate him on this very deserving award," said Dr. Grant Pierce, Executive Director of Research, St. Boniface Hospital.

Dr. Singal served as the Director of the Institute of Cardiovascular Sciences at St. Boniface Hospital Research, and is currently a Principal Investigator of the Cell Pathophysiology laboratory. He is a Professor in the Department of Physiology and Pathophysiology and has served as Associate Dean (Academic) Graduate Studies at the University of Manitoba. He is also holder of the Naranjan S. Dhalla Chair established by the St. Boniface Hospital Foundation. Dr. Singal has published 285 papers, has co-edited 31 books, trained more than 100 students, fellows and visiting scientists and has received more than 100 national and international recognitions.



Dr. Singal being congratulated by Dr. James Currie, Provost and Vice-President, Academic, University of Winnipeg

Report of the 4th Congress of Physiological Sciences of Serbia, Nis, Serbia, September 19-22, 2018

Dragan Djuric, MD, PhD¹ and Vladimir Jakovljevic, MD, PhD²,

¹Institute of Physiology “Richard Burian”, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

²Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Email: dr_djuric@yahoo.com; drvladakgbg@yahoo.com

The 4th congress of physiological sciences of Serbia with international participation was held from 19-22 September 2018 at the Faculty of Medicine, University of Nis, city of Nis, in south part of Serbia. The Congress was organized by the Serbian Physiological Society and the Faculty of Nis, University of Nis, and supported by the Faculty of Medical Sciences, University of Kragujevac, by the Ministry of Education, Science and Technological Development of Republic of Serbia as well as by a few commercial sponsors. The Congress was announced and held under the auspices of Federation of European Physiological Societies, International Union of Physiological Sciences, International Society for Pathophysiology, IACS, and accredited to satisfy the needs of continuous medical education by the Health Council of Serbia as the highest-ranked international meeting.

Co-chairs of the Program and Organizing Committee of the Congress were Dr. Dragan Djuric, Institute of Medical Physiology “Richard Burian”, Faculty of Medicine, University of Belgrade, and Dr. Vladimir Jakovljević, Department of Physiology, Faculty of Medical Sciences, University of Kragujevac. Dr. Nenad Stojiljkovic, Department of Physiology, Faculty of Medicine, University of Nis, served as a Chair of the Local Organizing Committee.

The participants were welcomed by Dr. Jakovljević, on behalf of the Serbian Physiological Society and Organizing Committee; Dr. Djuric, on behalf of the Program Committee; Dr. Naranjan Dhalla, Founder and CEO of the IACS, on behalf of the International Physiological Community, and Dr. Grant Pierce, President on behalf of the IACS, both from the Institute of Cardiovascular Sciences, St. Boniface General Hospital Albrechtsen Research Centre, and Department of Physiology and Pathophysiology, Rady College of Medicine, University of Manitoba, Winnipeg, Canada; Dr. Stojiljkovic, on behalf of the Local Organizing Committee, and Dr. Gordana Kocic, Vice-Dean, on behalf of the Faculty of Medicine, University of Nis.

This was followed by the presentations of biographies, lectures and awards of the Serbian Physiological Society to the distinguished researchers in the domain of physiological sciences: worldly recognized researchers, Dr. Mihajlo Spasic, PhD, Institute of Biological Research “Sinisa Stankovic”, University of Belgrade, Belgrade, Serbia, and Prof. Suresh Tyagi, PhD, Department of Physiology, School of Medicine, University of Louisville, Louisville, USA, for their contributions to the development of physiological sciences.



Dr. Mihajlo Spasic (middle) recipient of the Serbian Physiological Society Life time Achievement Award with Dr. Dragan Djuric (left) and Dr. Vladimir Jakovljević (right)



Dr. Suresh Tyagi (middle) recipient of the Serbian Physiological Society Life time Achievement Award with Dr. Dragan Djuric (left) and Dr. Vladimir Jakovljević (right)

The abstract book (cataloged at Serbian National Library, eds. Djuric DM, Jakovljevic V, Zivkovic V) was published as well as final program, both in English. The abstract book consisted of 130 accepted abstracts (selected by the Program Committee) from 19 countries (Bosnia and Herzegovina, Bulgaria, Canada, Czech Republic, Croatia, France, FYR Macedonia, Germany, Greece, Hungary, Montenegro, Romania, Russian Federation, Slovak Republic, Slovenia, Sweden, Switzerland, USA and Serbia). Out of total number of abstracts, 62 were planned to be presented orally while 68 abstracts were planned to be presented in two different poster sessions, and with educational and teaching issues of medical physiology in USA and Serbia.

The Congress included the following 12 sessions: opening ceremony and welcome addresses, presentation of Serbian Physiological Society awards for contribution in physiology and lifetime achievement, cardiac physiology and cardioprotection, advances in vascular biology and atherosclerosis research, sudden cardiac death and novel regulators of cardiac activity, genomics and genetic epidemiology, redox homeostasis and gasotransmitters, redox regulation between health and disease, endocrinology, adipobiology and aging, advances in nutrition and exercise research, advances in neurophysiology and neurobiology research, neurophysiology and neuropharmacology of pain: basic and translational aspects, varia, and concluding remarks.

More than two hundred researchers from the country and abroad participated in the congress. In addition to participants, executive director and regional directors for Europe and North America of the International Academy of Cardiovascular Sciences, the members of academies of

sciences from Canada, Slovak- and Czech Republic, immediate past president of the German Atherosclerosis Society, officials of neighboring physiological societies, editors of prestigious international scientific journals Canadian Journal of Physiology and Pharmacology, and Molecular and Cellular Biochemistry were present at the Congress.

It should be noted that social program was also very interesting, and that the participants had warm memories from the city of Nis, located in south part of Serbia, which is not only the place where someone will find typical Serbian spirit of life, but also the place which is known for the worldwide recognized sacral and historical objects, monuments, museums, galleries, monasteries, ethnic music etc.



Conference Organizers, from L to R: Drs. Dragan Djuric, Grant Pierce, Nenad Stojiljkovic, Naranjan Dhalla, Vladimir Jakovljević and Bohuslav Ostadal

Regenerative Landscape for Cardiovascular Disorders

Glen Lester Sequiera, MSc and Sanjiv Dhingra, PhD
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre
Regenerative Medicine Program, Department of Physiology and Pathophysiology
University of Manitoba, Winnipeg, Canada
Email: sdhingra@sbr.ca

Cardiovascular disorders (CVD) are currently the leading cause of death globally, accounting for ~18 million deaths in 2015 (1). Underlying mechanisms for the CVD can vary widely depending on the type of complications. The end result is usually the loss of cardiomyocytes that leads to permanent damage (2). Currently, pharmacological treatments include anticoagulants, antiplatelet agents and dual antiplatelet therapy, ace inhibitors, angiotensin ii receptor blockers, angiotensin-receptor neprilysin

inhibitors, beta blockers, calcium channel blockers, cholesterol-lowering medications and vasodilators among others. Invasive treatments involve percutaneous transluminal coronary angioplasty, stent implantation, coronary artery bypass grafting, and implantation of electrical devices. These options are more directed towards symptom alleviation and slowing down the progression of the disease (3). Curative modalities are usually highly risky and fraught with failures- heart valve

repair or replacement, aneurysm repair, cardiomyoplasty, and heart transplantation. These approaches have not been proven to be fully effective as a permanent solution. One of the biggest hurdles is the heart's non-specific attempt to repair itself – by forming fibrotic scar. None of the before mentioned treatment options, except for physical replacement and whole heart transplant can remedy the issue of fibrosis. This akinetic tissue results in taxing of the remaining cardiomyocytes, leading to progressively deteriorating cardiac output. Lately stem cell therapy has shown promise in terms of regenerating and repairing the damaged heart (4). The stem cells mediated restoration can be effected through cellular replacement (cardiomyocytes and/or progenitors), neovascularisation, paracrine mechanisms, immunodulation and stimulation of endogenous progenitors. Over time, these different avenues of exploration have found their application in numerous pre-clinical and clinical trials. The cells being used for cardiac regenerative therapies can be largely categorized into pluripotent or multipotent stem cells and adult cells. Here we highlight the advances in cardiac stem cell therapy.

Embryonic Stem Cells

Embryonic stem cells (ESCs) are established from the inner cell mass of the blastocyst. They are known for their unlimited self-renewal by symmetric cell division. Their capabilities also include differentiation into all the three germ layers ectoderm, mesoderm and endoderm. Doetschman (1985) demonstrated that the removal of mice embryonic stem cells from conditions supporting pluripotency will induce three dimensional “embryoid bodies (EBs)” that will include foci of functioning cardiomyocytes (CMs) (5). Presently robust protocols exist to derive CMs directly and in xeno-free conditions from embryonic stem cells, which has thrown up the possibilities of adapting these cells in a GMP setup. Further, embryonic stem cells derived cardiomyocytes display appropriate morphology, sarcomeric organization, electrophysiological properties and expected responses to pharmacological responses. The human ESC-CMs derived through embryoid bodies were shown to decrease scar tissue following an infarct and form conducting tissues after transplantation into animal models of cardiac injury. The injection of small amounts of human ESC-cardiomyocytes electrically coupled with the host tissue have found success in the suppression of arrhythmias (6). Ethical conundrum of using an embryo, genetic instability, possible immune reaction and limitation of cell line generation make it difficult for embryonic stem cells to be brought to the bedside in the near future.

Induced Pluripotent Stem Cells

An alternate approach of ESCs is the use of induced pluripotent stem cells (iPSCs), which are derived from human somatic cells. They are for all intent and purposes

similar to ESCs, but without the ethical baggage of destroying an embryo. The processes of reprogramming the somatic cells to iPSCs involve introducing transcription factors (e.g. Oct4, Sox2, c-Myc, Klf4 and Lin28) through viral or non-viral means. Induced pluripotent stem cells share the karyotype, phenotype, and telomerase activity that allows them to have the ability to indefinitely divide and differentiate into multiple functional cells types (7). Induced pluripotent stem cells derived cardiomyocytes have found themselves applied to numerous pre-clinical studies. The transplantation of iPSCs derived CMs into small animal models has shown successful engraftments, improved cardiac function with a proper syncytium formation with the host tissue. Some of the studies have also reported increased wall thickness and reduction in scar tissue after it had been formed. Swine studies have shown that iPSC-CMs can form beating patches, enhance vessel formation, better cardiac output and even attenuate LV remodelling. In monkeys, both ESCs and iPSCs after transplantation differentiated into cardiomyocytes and showed no tumour formation. The year “2018” has turned out to be a big year for iPSCs based therapies, as iPSCs derived cardiomyocyte sheets have been approved for the world's first clinical study in Japan.

The pluripotent stem cells in general suffer from a lot of hurdles. The nature of derived cells either from ESCs or iPSCs is more immature (foetal) in nature. Therefore, a scare of improper integration leading to (and not limiting to) arrhythmia (demonstrated in monkeys) after transplantation is always a possibility. There is also a likelihood that non-differentiated stem cell might be retained, leading to probable teratoma or tumour formation. Despite a lot of pre-clinical work having been conducted, there is still not a general consensus about the clinical translation of pluripotent stem cells. Also, the belief that syngeneic iPSC-CMs might be immune-evasive or immunoprivileged is now being challenged.

Adult Stem cells

Adult stem cells, also known as somatic stem cells, could be sourced from multiple adult tissues of an organism or the human body. They are undifferentiated in nature and have the capability of self-renewal. The number of cells which could be differentiated from adult stem cells is not anywhere as high or diverse as pluripotent stem cells. Their presence has been known for a much longer time than pluripotent stem cells and consequentially adult cells benefit from a lot of literature and are presently being used in numerous clinical trials.

Skeletal Myoblasts (SkMs)

The source of SkMs is satellite cells. These progenitor populations reside under the basal lamina of skeletal muscle fibres. SkMs have very limited potential of

differentiation, with the ability to differentiate into muscle fibres. They are easy to extract and grow in cultures. Thus, these cells were one of the first cell types employed to test the concept of cell therapy. Numerous animal models did show encouraging results for ischemic and non-ischemic cardiomyopathies. Small non-randomized clinical trials showed improvement in left ventricular ejection fraction (LVEF), with enhanced regional wall motion, but a good number of patients displayed arrhythmia too (8). Large trials, like MAGIC, however did not show improvement in cardiovascular function (9). The absence of benefits and the arrhythmia was chalked to the fact that SkMs can only form myotubes and would not have the ability to differentiate into cardiac cells.

Mesenchymal Stem Cells (MSCs)

Discovered in 1970, Friedstein et al extracted stromal cells from bone marrow that readily expanded in culture and were found to be highly plastic adherent (10). These cells have demonstrated a considerable ability of self-renewal and multi-lineage differentiation, thereby making them a prime candidate for adult stem cell therapy. They differentiate into osteogenic, chondrogenic and adipogenic lineages. They have been demonstrated to differentiate into cardiomyocyte-like cell types, replete with expression of few cardiac markers and responses to electric stimuli. These discoveries led to presumption that MSCs, once transplanted, might be able to engraft into the heart tissue, differentiate and become a part of myocardium. As more studies were conducted, the school of thought shifted. The CM differentiation of MSCs was eventually called into question. With better evaluations, it was found out that MSCs seem to secrete certain factors that might help damaged tissues to repair themselves. These paracrine functions were later proven to also be the domain of the different types of adult stem cells (11). Their culture presently has been upgraded to clinical GMP grade facilities. They possess immunoprivilege, which makes them highly ideal for allogeneic setup. This also benefits the findings that MSCs from younger donors worked the best in older hosts (the demographic where cardiac diseases usually present). Initially established through bone-marrow, they have also been found in adipose tissue, umbilical cord, dental pulp, intestinal and mammary tissue.

As mentioned before, the MSCs (especially bone marrow derived ones) are the interest of numerous completed and ongoing trials (12). REPAIR-AMI findings reported better functional improvements. BOOST trial reported a net increase in ejection fraction compared to baseline. FINCELL trial maintained the safety of the MSCs and also attested to better left ventricular ejection fraction in the group treated with MSCs. Larger studies like REGENT and HEBE though have not been able to demonstrate the benefits to the degree observed in the

smaller trials. But HEBE did report prevention of further remodelling in patients with dilated ventricles. Despite providing early benefits, long term follow-up of the transplanted cells has shown that they are lost over a period of time. This loss leads to complete abrogation of benefits and demands re-transplantation (13). A general consensus on routes of administration and possible contraindications still don't exist. The isolation, expansion, preservation and delivery of MSCs have been debated to be the primary causes of variations observed in a lot of pre-clinical and clinical trials. These processes can spell trouble in the immunogenic response that the MSCs could elicit after having transplanted, once their early benefits are lost.

Cardiac Stem Cells (CSCs)

Formerly, the adult heart was believed to be post-mitotic. In the later years, it has been increasingly proven that there is possibility of cardiomyocyte turnover. This turnover unfortunately suffers from low progenitor cells number within the niche and is quite limited in nature. However, the opportunity to recruit CPCs seems highly lucrative and has the promise of best candidate cell type for heart repair (14). The field of CPCs is highly underdeveloped and without proper categorization. Different research groups have attempted to characterize the CPCs using different markers: cardiosphere-derived, cardiac side population, stem cell antigen (Sca)-1 positive cells, c-kit positive cells, and insulin gene enhancer protein (Isl)-1 positive cells. Despite these markers being identified, they have generated controversies, because even cardiac fibroblasts express most, if not all, of the abovementioned markers. Their inclusion in various clinical trials – SCIPIO, CADUCEUS and PERSEUS trials showed better cardiac function, improved regional contractility and regional systolic wall thickening and absolute changes in LV function compared to baseline.

Where Are We Going From Here

Pluripotent stem cells seem to be the likely option of future, and organic solution for heart tissue generation made in a dish to a patient's specification. The biggest issue in the use of PSCs is the absence of literature and complete understanding of their mechanisms. As these voids are filled, we would be better prepared in considering and applying the potential of PSCs. A lot of issues are being investigated in several ongoing projects. The risk of tumorigenicity is being minimized by selecting only cardiac committed progenitors and by stringent selection of cardiac markers. The improved culture conditions to avoid chromosomal aberrations and induced maturity of CMs, while maintaining their adaptability, are being developed.

In terms of adult cells, MSCs are almost on the cusps of wide clinical application. The biggest contributor as a

hindrance here is the loss of cells and as a result the benefits following transplantation. One of the main underlying factors is understood to be the post-transplantation shift in the immunological landscape of MSCs. These are being tackled through genetic changes and employment of soluble factors like prostaglandin E2 (PGE2) to help maintain the immunoprivilege of the MSCs (15).

Functional microenvironment generation using biomaterials is growing in quantum leaps in the last 2 decades. Many of the products have already commercialized in the field of joint repair, valve replacement and other afflictions where physical moving parts were involved. The realisation that heart is not just made up of cells but requires a lot of support in terms of its physical makeup, electrophysiological capabilities, structure fidelity and elasticity, has helped propel interests in developing materials to meet these specifications. These materials are being engineered from organic or a combination of organic-inorganic components. They are being developed as scaffolds, gels and liquid phase, each with their sets of benefits and disadvantages. Their goal is primarily to help prime the stem cells akin to the microenvironment of heart tissue and deliver them to a highly dynamic and kinetic system. Functionalization of biomaterials has been carried out to better and prolonging of the immune-suppression of the stem cells, to help them mature and retain them at the site of injury for an extended period of time.

All these avenues being actively studied will provide better knowledge to help overcome the limitations in the success of stem cell therapy. That they are being pursued provides a promising future where cure of cardiovascular disorders looks achievable through reversal of different conditions that caused them in the first place.

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Gut Microbes and Heart Diseases

Madhu Khullar, PhD and Satish K Raut, PhD

Post Graduate Institute of Medical Education and Research, Chandigarh, India

Email: madhu.khullar@gmail.com

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We have known for decades that there is a strong link between the foods we eat and our risk of developing heart diseases. Still we do not know why certain foods reduce the risk of heart disease and others do not. Recent studies suggest that there may be a link among our diet, bacteria present in our gut (gut microbiota) and heart diseases.

The human body is inhabited by a large number of bacteria, viruses, and unicellular organisms. The human gut harbours nearly 100 trillion microbial cells, which live in harmony with their hosts. Gut bacteria have been shown to help us digest our food, strengthen our immune system against various infections and help us fight many diseases including cancer and heart diseases. An imbalance between good and harmful gut microbes, called dysbiosis, can result in a diseased condition. For example, changes in prevalence of different types of gut bacteria have been found to be linked with diseases such as cancer, obesity, asthma, type 2 diabetes, arthritis and heart disease.

Recent research suggests that when certain bacteria are present in excess numbers, they produce harmful compounds which can cause 'clogging of the arteries' result in heart disease. For example, a comparison of bacteria present in stool samples from patients with heart disease and healthy subjects showed that stool samples from patients had increased number of bacteria such as Enterobacteriaceae and Streptococcus spp which cause inflammation and a fewer number of bacteria (fermentative) which help in reducing inflammation. It has been suggested that some of the harmful bacteria produce metabolites which promote hardening of arteries. The reasons for and mechanisms, which increase these bacteria are not well understood. A change in blood supply to intestinal wall due to a variety of reasons such as infection or injury can cause a leaky gut. This 'leaky gut' allows translocation of endotoxins, microbial components, and microbial metabolites produced by gram positive bacteria to systemic circulation. This process can further activate cytokines and generate systemic inflammation and contribute to progression of heart failure.

It has been observed that gut bacteria may interact with certain foods, producing metabolites that have harmful effects on the heart. For example, some bacteria such as Acinetobacter may convert foods rich in lecithin, phosphatidylcholine, and L-carnitine into harmful compounds such as trimethylamine N-oxide (TMAO). TMAO alters cholesterol metabolism in various organs such as intestines, liver, and in arterial wall. In presence of TMAO, there is increased deposition of cholesterol in the cells of the arterial wall. TMAO has been found to cause hardening of arteries by increasing deposition of cholesterol in the arterial wall. High TMAO levels, therefore, increase risk of heart disease. High concentration of L-carnitine is found in red meat, some of the energy drinks, and some dietary supplements; whereas lecithin is found in soy and eggs in processed foods. It is also sold as a dietary supplement. Consumption of such foods can increase the risk for heart diseases. Increased TMAO levels also can increase the risk for kidney diseases and heart failure.

The type of food that we eat also influences the type of bacteria in the gut. For example, the guts of people eating diet rich in meat have more of bacteria which make TMAO in comparison to those who have a vegetarian diet, suggesting that vegetarian diet is better for heart health.

Can changing gut bacteria composition prevent heart disease?

Lower consumption of foods such as red meat, egg yolks and high-fat dairy products may be beneficial to the heart as this can result in a gut bacterial population which reduces TMAO generation. Further, consumption of foods such as olive oil and grape seed oil which contain a natural substance DMB (3,3-dimethyl-1-butanol) reduces TMAO levels and is considered to decrease atherosclerosis (fat deposition in arterial wall). Search is also on for drugs which can inhibit TMAO production by bacteria and thus decrease risk for heart disease. Prebiotics and probiotics are also being suggested as a therapy to reduce atherosclerosis. For example, consumption of non-fat

foods fermented with Lactobacilli may be effectively used for prevention of heart disease. Probiotic bacteria reduce blood cholesterol by increasing metabolism and excretion of cholesterol, thereby inhibiting intestinal cholesterol absorption and reducing blood levels of bad cholesterol.

Although scientific evidence linking heart health to gut bacteria is yet scanty, available preclinical and clinical evidences support the theory that gut microbes and their metabolites have the potential to be novel therapeutic and preventive targets for heart diseases.

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Peripheral Arterial Disease, Amputation and Rehabilitation: A Regional Canadian Perspective

Amarjit S. Arneja, MD, FRCPC

*Director Day Hospital Program, Director CPD, Section of Rehabilitation Medicine, University of Manitoba
RR139 – 800 Sherbrook Street, Winnipeg, Manitoba, Canada*

Email: AArneja@hsc.mb.ca

Editor's Note: The purpose of this invited article is to describe the influence of peripheral arterial disease (PAD) and diabetes in the development of lower limb amputations. It also discusses the epidemiology of amputations in Manitoba, Canada and globally as well as best practice strategies for lower limb amputations and rehabilitation.

Peripheral Arterial Disease and Diabetes Mellitus

The most common cause of lower limb amputations in developed countries is peripheral arterial disease (PAD) which is often associated with diabetes. More than 90% of amputations are associated with peripheral arterial disease. Other causes of lower limb amputations include trauma, tumor, severe infections and frostbite in colder climates. PAD is a general term used to describe progressive atherosclerosis narrowing of the peripheral arteries most often used in reference to the arteries of the lower extremities. This disease affects 12 to 20% of Americans over 65 years of age (1). PAD is considered a coronary disease equivalent as it confers equal risk of morbidity and mortality from cardiovascular disease regardless of whether coronary disease is known to be present or not. PAD is a stronger predictor of myocardial

infarction (MI), stroke and death from vascular causes. Coronary artery disease (CAD) and PAD share their common risk factors that is, cigarette smoking, diabetes mellitus, hypertension, and hyperlipidemia (2). Aggressive medical treatment of atherosclerotic risk factors has been shown to significantly decrease morbidity and mortality associated with PAD (3). There has been increase in the prevalence of diabetes globally and evidence of diabetes has doubled from 1980 to 2017 from 4.7 to 8.8%. In 2015, 9.3% of Canadians had diabetes. It is now estimated that diabetes accounts for 70% of lower limb amputations as a result of vascular complications. Rates of limb amputations are also affected by an increasing number of comorbidities where individuals with 3 or more are more likely to undergo limb amputation as a result of diabetes. These co-

morbidities compromise of peripheral neuropathy, hypertension, cerebrovascular disease, hyperlipidemia and end stage renal disease. Risk factors such as male gender, advancing age and smoking can also affect rates of amputation. Furthermore, race is strongly co-related with the need for limb amputation.

Epidemiology of Amputations in Manitoba, Canada and globally

The incidence of lower limb amputation (LLA) varies widely throughout the world ranging from 8.8 per 100,000 in the Netherlands in 2004 to 92.5 per 100,000 individual in Ireland in 2009. Unlike earlier studies that have shown an increase in the incidents of LLA in western countries, the most recent studies have reported decline or no change in the rates. Hospital episode statistics (HES) for 2009-2010 showed a total number of 5,498 recorded episodes for lower limb amputations in England. These rates have remained relatively constant over the last decade. Lower limb amputations accounted for 91% of total amputations (4). In the US, the rates have been reported to decline from 2000 to 2010. The overall age adjusted rate in Canada has reduced from 2011, 24.1 per 100,000 to 22.4 in 2016. The number of diabetes related LLA's increased by 13% (5).

In Manitoba, the incidence of major lower limb amputations (transtibial (BK), transfemoral (AK)) has declined from 381 in 1985 to 253 in 2016. In Canada Indigenous population represents nearly 5% of the total population. According to Canadian and Manitoba Health statistics, Manitoba has the largest Indigenous population in Canada representing over 10% of the population and make up approximately 25.6% of all lower extremity amputation in 2016-2017 fiscal year. In 1985 in Manitoba Indigenous people major amputations were 21 which has increased steadily to 87 in 2016. First Nations individuals therefore have rates of lower limb amputation 3 to 4 times than of non-First Nations. Aboriginals consistently face numerous socio-economic challenges including low income, low level of education, poor employment rates, social exclusion and substance abuse. Diabetes prevalence among First Nations communities in Manitoba has been associated with low income and westernized lifestyle, while amputation rates were significantly higher in remote communities with decreased health care access. Thus, barrier to health care access must be addressed in addition to coordination of care through Amputee Rehabilitation Programs (6).

Manitoba Rehabilitation Program

A formal Amputee Rehabilitation Program was organized by the Section of Rehabilitation Medicine's Amputee Program Director, Dr. Amarjit Arneja, for Manitoba for in-patient and early care of amputees, prosthetic rehabilitation and for follow up in the Amputee Clinic.

The management and rehabilitation of people who have had or will be having lower limb amputation is multi-disciplinary and inter-disciplinary and is considered in the following phases.

1. Pre-amputation.
2. Post-amputation.
3. Amputee Rehabilitation.
 - a. In-patient.
 - b. Day Hospital.
4. Amputee Clinic follow up.

All amputees are referred to the Amputee Rehabilitation Program and are seen by the Physical Medicine and Rehabilitation Specialist. The care of the amputees coordinated by the Rehabilitation team. In our Amputee Rehabilitation Program, 98% of transtibial (BK) amputees and 95% of transfemoral (AK) amputees achieved successful prosthetic rehabilitation (1980-1987 reviews). Life expectancy of vascular amputees is short and in the elderly is associated with a considerable morbidity and deterioration of functional and residual limb status. Amputees have multiple Challenging comorbidities and that includes end stage renal disease (ESRD) (7), rheumatoid arthritis (8), chronic obstructive lung disease (COPD) (9) and musculoskeletal impairment with the dedicated and experienced team, the majority of the patients have been able to achieve useful function with a prosthesis. LLA is a disabling and costly condition, cost estimates are not available for Canada, however, in the United States, the cost associated with acute and post-acute care for LLA exceeds \$4 billion annually. The costs to society are especially high in cases of amputations and ulcers that fail to heal and subsequently require additional amputation or become infected. These costs are primarily driven by prolonged hospitalization, rehabilitation, the need for home nursing care and lost work reduction for the disabled patient and his/her family. The currently adjusted direct cost of treating a diabetic foot wound exceeds \$30,000.00 over its life cycle with the direct cost of performing a single amputation approaching \$34,000.00. These costs do not account for increased utilization of in-patient services, prosthetic/rehabilitation or Home Care/Social Services (10).

Innovation: Day Hospital

In June 2002 Manitoba transitioned from an in-patient rehabilitation model to the incorporation of Rehabilitation Day Hospital (RDH) in order permit earlier discharge from in-patient care and prevent unnecessary admission for patients. The purpose of this program was to promote easier transition from in-patient to out-patient rehabilitation, to improve coordination and continuity of care and to respond to the changing needs of patients. The review of our program from 2002 to 2015 has shown that we were able to provide rehabilitation care to the

Indigenous people in the Day Hospital, increase the coordination of care and improved health care delivery, increase the efficiency and service delivery as well as improved patient, staff and stake holders satisfaction. In 2007 based on a national survey of amputee in-patient and out-patient rehabilitation program, the RDP at Winnipeg's Health Sciences Centre appeared to have the most comprehensive Amputee Rehabilitation Program offered in Canada. The development of the RDP which allowed coordination of care in such a way that patients could be seen as out-patient rather than in-patients allowing a cost saving of approximately \$973,500.00 yearly. This was largely due to the development of an In-take Coordinator for the program and making use of an efficient multi-disciplinary and inter-disciplinary care model (11).

The majority of centers in western countries are following evidence-based global standards for amputee rehabilitation. These were produced and published in 2017 in collaboration between WHO, ISPO and US Aid.

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The Use of Prehabilitation to Enhance Recovery and Improve Health-Related Quality of Life after Cardiac Surgery

Rohan M. Sanjanwala, MD, MPH¹ and Rakesh C. Arora, MD, PhD, FRCSC, FACS^{1,2}

¹Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada

²Cardiac Sciences Program, St. Boniface Hospital, Winnipeg, Manitoba, Canada

Email: rakeshcarora@gmail.com

Introduction

With advances in health care practices and delivery, the overall life expectancy of the Western population has increased. There has been a resultant higher prevalence of increasingly older and frail patients undergoing complex cardiac procedures. The combination of advanced cardiac disease and high rates of comorbid-disease exacerbates the decline in physiological reserve in older, vulnerable patients (1). Following cardiac surgery, such patients experience worse postoperative outcomes and a complicated recovery process (2). Further, these vulnerable patients experience a disproportionate decline in functional capacity (physical, cognitive), translating into worse longer-term health-related quality of life (HRQoL) (2–4). Furthermore, during the preoperative waiting period, the cardiac symptoms and anxiety induced inactivity compounds the physical and mental deconditioning (5–7). Prehabilitation (a.k.a “Prehab”), a component of an Enhanced Recovery Protocol (ERPs) provides a proactive framework to optimize health status of older, frail patients prior to surgery. The intention of this short review is to increase awareness and provide a helpful approach on the potential methods to optimize older, vulnerable patients prior to a cardiac surgery procedure.

What is Prehabilitation?

Prehabilitation, a preoperative rehabilitative intervention, is a combination of exercise training, dietary modifications and social support. The goals of this intervention is to improve a patients’ readiness for cardiac surgery with the overarching goal to reduce postoperative complications as well as improving the transition from the hospital to community (5,8). The fundamental premise of prehab is that improving functional reserve before surgery will enhance postoperative recovery, improve postoperative outcomes including HRQoL (5,8).

What are the components of “NEW” Prehab in Cardiac Patients?

At present, there is no formal consensus defining the framework and necessary duration for Prehab intervention, current evidence points towards (3) important aspects including the Nutrition (N), Exercise

(E) and mindfulness/ Worry reduction (W). The “NEW”, approach seeks to optimize the functional capacity and alleviate psychological distress prior to undergoing cardiac surgery (Figure 1) (9,10). Previous studies among the non-cardiac surgery (i.e. colorectal, thoracic and orthopedic surgeries) patients have demonstrated a

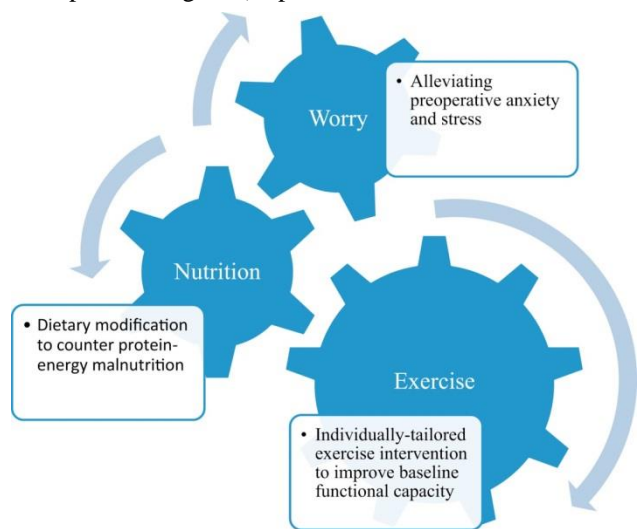


Figure 1: The components of ‘NEW’ Prehabilitation in cardiac surgery patients

decrease in the rates of postoperative complication, shorter length of hospital stay as well as enhanced recovery, translating into improved HRQoL compared to patients not receiving such intervention.

Nutrition Optimization- The “N”

The surgery-induced inflammatory and regenerative responses stipulate a higher nutritional demand inducing metabolic stress. Preoperative protein-energy malnutrition (not necessarily accompanied by lower body weight) was found associated with postoperative complication and mortality (11,12). Pre-procedure nutritional supplementation in the form of protein-energy substitution not only improves the homeostatic state but also supplements the strength surges following surgical trauma. Nonetheless, benefits of such intervention among cardiac surgery patients require further research validation.

Exercise therapy – the “E”

Physical activity and exercise therapy have been shown to effectively decrease morbidity and mortality in patients waiting for coronary artery bypass graft (CABG) surgery (6,13–15). The seminal study of 269 patients awaiting elective CABG patients, randomized to either eight-week preoperative exercise program or usual care, experienced shorter intensive care unit (ICU) and hospital length of stay and an improved quality of life⁸. However, the feasibility of such exercise intervention among higher risk, frail cardiac disease patients with varying degrees of exercise tolerance remains to be investigated.

Alleviating psychological distress — the “W”

The higher level of preoperative anxiety and depression among patients awaiting cardiac surgery was associated with poor improvement in the postoperative functional capacity (16,17). In addition, a positive psychological intervention targeted towards reducing anxiety has been found to be associated with patients experiencing less pain and reported a higher postoperative functional capacity (18).

Who should undergo “Prehab”?

Previous randomized controlled trial by Cameron et. al demonstrated that frailty progression can be reduced, or potentially reversed, among community dwelling older adults through implementing multi-dimensional prehab approach (such as ‘NEW’) for 12 months (19). The ‘NEW’ prehabilitation approach (or one of its components) has been applied in different non-cardiac settings including colorectal and orthopedic surgery. The study by Gillis et al. demonstrated enhanced postoperative functional recovery among colorectal patients receiving prehab intervention (20). These results were consistent among orthopedic surgical patients. The use ‘NEW’ prehab model has been piloted in cardiac surgery setting, demonstrating shorter hospital stay and better postoperative quality of life (5,21,22). Further validation, however, is imperative that to delineate important aspects of such intervention in an older, frail population. whether such approach would be feasible and effective for frail cardiac surgery patients during the waiting period prior to their procedure requires further investigation. Specifically, exercise program tolerance, and feasibility (including) patients-related logistics needs to be determined the effectiveness and sustainability of such as program in routine clinical practice.

For how long does a patient typically engage in prehab?

The American College of Sports Medicine Guidelines for Exercise Testing and Prescription (7th edition) recommends two sessions of supervised, structured exercise sessions per week for eight weeks, with progression to a moderated to high-intensity interval program along with an ongoing assessment of the

patient’s capabilities. In studies directed towards reversing frailty among the community dwellers and among the non-cardiac surgery patients, a total of 8-12 weeks of prehab intervention likely provides necessary enhancement in the postoperative recovery (19). Such intervention has been shown to be safe and effective. The prehab components, such as exercise therapy, has been tested among heart failure patients, however the evidence base regarding the duration and the components of prehab in patients prior to a cardiac surgery procedure is currently being studied. The cardiac surgery patients differ in frailty severity and requires an individually-tailored approach adapt to patients’ abilities and needs. For the frail patient with mobility difficulties, existing research data evaluating a prehab intervention is lacking. There are preliminary studies such as by Waite et. al suggesting benefits of a home-based exercise program in alleviating frailty. Such programs may be beneficial, but the feasibility and effectiveness for severely frail patients remains to be investigated.

What are some important barriers that preclude the use of prehab?

Although preoperative optimization of older adults would seem to be a natural fit for ERPs in cardiac surgery, at present prehab is seldom incorporated in to clinical practice. The evidence base for the effectiveness and widespread implementation, at present, is limited. A fundamental limitation surrounding the prehab approach is the use of elective surgery waitlist times. As current cardiac surgery waitlist times are variable (i.e. often shorter than the typical 6-8 weeks required for a prehab program), it is not clear if the benefits of prehab would outweigh the risk of delaying surgery for patients with advanced cardiac disease. In addition, the specific characteristics of a prehab program in the frail older adult have not been well defined and the patient-related barriers surrounding the implementation of prehab components still remain. Further integration of prehab program, as a practice norm into an ongoing surgical practice system, requires a strategic framework and implementation models. This expansive change will require guidance and strategic management by key stakeholders involved with the patient journey.

The target populations who might derive the most benefit from prehab have not been well defined. Although it is clear that frail patients have worse outcomes after surgery, some have argued that pre-frail patients may actually derive the most benefit. It has been speculated the targeting pre-frail (a transitional physiological state between robustness and frailty, characterized by intermediate accumulation of physiological dysfunction, resulting in a minimal decline in physiological reserve and functional capacity (23–25) older adults with such health optimization approach would delay or possibly

prevent frailty development from the outset. The existing literature investigating exercise intervention alone among the pre-frail, have shown improvement in the functional capacity. The Pre-Frail Intervention Trial (PRE-FIT) is underway, that would help validate whether such multi-dimensional approach would have demonstrable effect delaying frailty progression and enhancing post cardiac surgery recovery (26).

What is coming in the future?

The PREHAB Study

The Pre-Operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery (PREHAB study; NCT02219815) endeavors to provide safety information on the utility of prehab in this vulnerable patient population. The study will provide further understanding surrounding the feasibility of exercise intervention before elective cardiac surgery and its efficacy in improving postoperative recovery as well as impact on patients-related outcomes such as health-related quality of life.

The PERFORM TAVR

This is another multicenter trial that is underway, seeking to evaluate the impact on patient-centered outcomes and transitions of care in frail older adults undergoing transcatheter aortic valve replacement (TAVR; NCT03522454). The trial will use a combination of home-based physical activity program including walking and strength-building exercises under supervision of a trained physiotherapist, and nutritional supplementation with a goal to empower patients adopting self-care that would enhance recovery and diminish frailty progression.

Conclusion

It is increasingly understood that patients with heart disease are getting older and sicker. In Canada, over 5.7 million people are estimate to be aged over 65 years, out of which 1.4 million are aged more than 80 years. The increasing number of older adults with a heart disease and subsequent increase in demand for heart procedure represents a veritable “silver tsunami”. These patients are more vulnerable to the stress of a heart procedure leading to long recovery time afterwards. In some cases, they experience a worse quality of life despite a successful heart treatment or procedure. There is, therefore, an urgent need for the heart team to focus on ensuring that patients don’t just survive but thrive after provide care in the hospital.

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Theme of the conference

The SJICR has great pleasure to announce hosting of the International Conference of the Academy of Cardiovascular Sciences (International Academy of Cardiovascular Sciences - India Section) titled "Translational research in cardiovascular sciences" that would be held at the NIMHANS Convention Centre, Bangalore, from 15th – 17th February, 2019. The focus of the conference is translational research in cardiovascular and allied sciences - taking bench side research to bed side. The conference would provide a platform for both the basic scientists and clinicians to meet, discuss and interact with each other and deliberate upon the recent developments in the field of cardiovascular and allied sciences. Participants would get an insight into the clinical perspectives, the scientific advancements and current trends from elite clinicians and scientists in the field.

Symposia

- Jayadeva Institute Symposium on **Translational cardiovascular research**
- Riya and Paul Ganguly Symposium on **Diabetes**
- Torrent Pharmaceuticals Symposium on **Heart failure**
- **Cardiology for the Masses**
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- **Other advancements in cardiovascular sciences**

Orations

- **SK Gupta Oration:**
Jawahar Mehta, University of Arkansas for Medical Sciences, USA
- **RK Goyal Oration:**
Paul Ganguly, Alfaisal University, Kingdom of Saudi Arabia
- **Rakesh Kukreja Oration:**
K Shivakumar, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum
- **Harpal Buttar Oration:**
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