Myocardial Preservation

Translational Research and Clinical Application

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Dedicated to the Memory of
Professor-Academician
Gregory D. Skalkeas
Man of Unequalled Vision
and Unsurpassed Achievement

Foreword

The idea for this book came from the realization, over many years, that the main and determining factor of cardiovascular morbidity and mortality is loss of myocardium. The cardiac muscle, the prime engine of our body, is at a constant danger: before and just after birth from genetically transmitted disease and cardiac defects and at childhood and adolescence from rheumatic fever in developing countries; nonfamilial cardiomyopathy can manifest itself at any time; myocarditis may fell its victim at any age.

Hypertension and valve disease nowadays are not left to progress to myocardial loss; however, at the onset of middle age, coronary heart disease begins to take its toll. An initial or recurrent myocardial ischemic insult or infarct sets the stage for cardiac remodeling and its sequelae, heart failure, and death. In old age together with experience and arguable wisdom comes "presbycardia." Thus, the toil toward cardiac protection is constant and persists throughout a person's lifetime. "Myocardial preservation" is an all-inclusive term, since it encompasses all forms of conditioning, pharmacological therapy, revascularization, both interventional and surgical, and device therapy. Moreover, it entails efforts at preserving cardiac structure and function after initial protective mechanisms have been overwhelmed and cardiac integrity has been compromised. Another important feature to be appreciated is that cardiomyocyte loss from any initial cause eventually follows common pathways and that cardiorestorative efforts are based on similar and parallel mechanisms.

Having complemented my clinical duties with efforts at research with cardiopreservation as its main goal, I felt tempted to write a book with a common unifying thread and concept.

Mr. Grant Weston, who helped me with my previous Springer book *Introduction to Cardiovascular Translational Research*, encouraged me from the start.

It proved a heavy responsibility. Soon I realized that in some subjects I had to enlist the aid of two expert colleagues: Professor Dimitris Tousoulis and Doctor Konstantinos Malliaras and their co-workers. Their efforts have produced excellent fruits. I am deeply indebted to their friendship and help.

The completion of this book on the very tight limits set to me would have been impossible without the expert, extremely efficacious, and friendly secretarial aid of Ms. Athinais Danou.

During the last 52 years, my every effort has been supported through the tolerance afforded to me by my wife Vana who provides me the inspiration for all my undertakings. As an eminent physician herself, she has lent me her criticism and suggestions.

The book was conceived and completed in the friendly and warm academic environment of the Biomedical Research Foundation of the Academy of Athens.

Constant interchange of ideas with my peers, colleagues and young collaborators, has been an invigorating breath of fresh ideas. A continuing collaboration with my former hospital, the Onassis Cardiac Surgery Center, has been fortunate and complementary and has helped advance the collaboration between these two outstanding institutions.

The man who conceived, created, and directed the Biomedical Research Foundation of the Academy of Athens, a giant of our times, a man of unlimited vision and inspired leadership, was Professor-Academician Gregory D. Skalkeas. He encouraged me wholeheartedly to undertake this endeavor. He had been my mentor for more than half a century. I dedicate this book to his memory with respect, admiration, and deep gratitude.

Athens, Greece Dennis V. Cokkinos

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Chapter 1
Introduction

Dennis V. Cokkinos

The great German poet Johann Wolfgang von Goethe had anatomical knowledge. He discovered the intermaxillary bone or Goethe's Bone in 1784 [1]. In his masterpiece "Faust" he wrote that "Blut ist ein ganz besonderer Saft" which can be translated that "blood is a totally particular humour" or "fluid" in contemporary expression [2].

The author of this book, admitting to being biased as a cardiologist by specialty, can claim that the same holds true for the heart. The heart is one of the single organs of the body, thus it cannot be relieved by a partner at moments of dysfunction, nor can it be removed without the subject's unavoidable immediate demise. It does not rule motionless and supreme, as the brain does, but it must toil incessantly during the 80plus years of the medium life duration of the contemporary human. It is an old pastime to calculate how many times the heart must go into diastole, stasis and systole during a lifetime.

It would be commonplace but true to say that the heart caters to all the organs of the body by sending the "exceptional humour", blood, faithfully to them.

However, this irreplaceable organ is constantly threatened and imperiled during its existence.

A child can be blessed to come to life but burdened by a heart defect which may render its "in utero" or at newborn age correction a necessity.

After birth, rheumatic fever was formerly a world epidemic. I remember as a medical intern honing my skills in auscultation in the Cardiology wards of the "Evangelismos Hospital" in Athens; more than 70% of the patients had mitral or aortic valve disease, a dire legacy of rheumatic fever; the tricuspid at that time, before the advent of echocardiography, was less appreciated. Rheumatic fever may

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have been eradicated in Western societies, but together with famine various and illnesses threatens young lives all over the developing world countries [3].

Although most of the congenital heart defects can be corrected with little danger and low mortality, cardiomyopathies, the Long QT syndrome and the Brugada syndrome and other rhythm disorders can cut the thread of a young sportive life.

In a recent prospective study, in 5255 middle-school (13 years old) children [4] screened with ECG and cardiac magnetic resonance, the following high-risk conditions were found: Long QT Interval (0.69%, QTc > 0.470 s) anomalous origin of a coronary artery from the opposite sinus (0.44%), dilated cardiomyopathy (0.23%) hypertrophic cardiomyopathy (0.06%), Brugada pattern (0.02%).Apart from dilated cardiomyopathy, in which some forms could be ameliorated as regards their course, if representing the evolution of acute myocarditis, all the others could be protected with early antiarrhythmic prevention.

Although these percentages are low from the statistical viewpoint, they represent a total loss for the young victims' parents.

Some more data in mortality of young people should be given.

In persons 1- 35 years old studied in North Spain, the incidence of sudden unexplained death (SUD) was 0.43/100.000 persons per year, a total of 107. Of these 19 were due to atheromatous coronary disease, 13 to cardiomyopathies, 6 to the abnormalities of the cardiac conduction system; 19 were thought to be due to sudden unexpected death (SUD) [5].

In the 25 year-review of autopsies in 6.3 million military recruits, aged 18-35 years, sudden non traumatic death occurred at a rate of 13.0 per100.000 recruit years [6, 7]. Of these 126 autopsied deaths, over half had an identifiable cardiac abnormality. One-third had an anomalous coronary artery. Importantly, more than one-third of deaths had no explanation.

Here an important diagnostic improvement has occurred. Additionally to the classic autopsy the molecular autopsy is attaining importance in SUD. This technique gives a diagnosis in nearly 30% causes of SUD and 10% in the sudden infant death syndrome. Long QT syndrome, channelopathies and catecholaminergic polymorphic ventricular tachycardia are the most important findings. It can save future lives in family members of victims of SUD [8–13].

However, it does not only concern arrhythmic deaths: It was employed in 17 aortic dissection sudden cardiac death cases [14].

At the young adult life, atherosclerotic cardiovascular disease raises its ugly head.

In autopsy studies in soldiers killed in the Korea war up to 25% [15] and in young male accident victims 20% [16] were found to have severe atherosclerotic heart disease.

Again, the efforts of Public Health experts, nutritionists but also clinicians and lay people with vision have appreciably lowered the incidence of atherosclerotic cardiovascular disease in modern societies. However, with the expected adoption of the "western" type of diet, this epidemic is predicted to replace as a threat malnutrition and infections in the developing world according to the prevalent contemporary statistics. In fact, in China, mortality from ischemic heart disease has risen from

2004 to 2010, mostly in rural males (19.2%/yr) and females (7.0%/yr) and in the age group over 80 years [17].

In a 2010 study of the global burden of disease [3] the following 20-year differences from 1990 where found:

In both 1990 and 2010 ischemic heart disease and stroke were the first two causes of mortality.

Lower respiratory infections and COPD reversed their status as third and fourth respectively.

Lung cancer (5th) and HIV/AIDS (6th) in 2010 replaced diarrhea which now ranks 7th, followed by road injuries (8th), diabetes (9th), and tuberculosis (10th). Interestingly, diabetes ranked only 15th in 1990; with diabetes, cardiovascular disease, especially myocardial infarct prevalence and mortality, heart failure and stroke are affected.

A 2015 update from the same group [18] showed that globally, life expectancy increased from 61.7 years in 1922 to 71.8 years in 2015. However, many geographical differences were seen.

According to the WHO media center fact sheet, updated in January 2017 [18], in 2015, of the 56.4 million deaths worldwide, more than half (54%) of deaths were due to the top 10 causes. Ischemic heart disease and stroke are the world's biggest killers, accounting for a combined 15 million deaths in 2015.

Chronic obstructive pulmonary disease claimed 3.2 million lives in 2015, while lung cancer (along with trachea and bronchus cancers) caused 1.7 million deaths. Diabetes killed 1.6 million people in 2015, up from less than one million in 2000. Deaths due to dementia more than doubled between 2000 and 2015, making it the seventh leading cause of global deaths in 2015.

Lower respiratory infections remained the most deadly communicable disease, causing 3.2 million deaths worldwide in 2015. The death rate from diarrhea diseases almost halved between 2000 and 2015, but still caused 1.4 million deaths in 2015. Similarly, tuberculosis killed fewer people during the same period, but is still among the top 10 causes with a death toll of 1.4 million. HIV/AIDS is no longer among the world's top 10 causes of death, having killed 1.1 million people in 2015 compared to 1.5 million in 2000.

Thus, 10 leading causes of death in 2015 were, in rank order [19].

Ischemic heart disease, stroke, lower respiratory infections, chronic obstructive pulmonary lung disease, trachea, bronchus lung cancers, diabetes mellitus, Alzheimer's disease and other dementias, diarrheal disease, tuberculosis, road injuries.

Heron et al. [20] give a slightly different picture for the 10 leading causes of death in the USA in 2014, as classified by ICD-10.

The 10 leading causes of death in 2014 were, in rank order: Diseases of heart; malignant neoplasms; chronic lower respiratory diseases, accidents (unintentional injuries); cerebrovascular diseases; Alzheimer's disease; diabetes mellitus; influenza and pneumonia; nephritis, nephrotic syndrome and nephrosis; and intentional self-harm (suicide). They accounted for 74% of all deaths occurring in the United States.

Here a word of caution is warranted. In 2015, life expectancy of Americans dipped slightly as compared to the previous year, according to data from the Center for Disease Control and Prevention National Center for Health statistics. For males, life expectancy at birth changed from 76.5 years in 2014 to 76.3 years in 2015, a decrease of 0.2 year, and for females, it decreased 0.1 year from 81.3 years in 2014 to 81.2 in 2015.

Infant mortality did not change [21].

If a person reaches old age with either a completely unblemished or even repaired or convalescing heart, presbycardia is the reward of his or her persistence. Atrial fibrillation, conduction defects, aortic stenosis, beleaguer the strife for survival in the last remaining years.

During the onslaught of all these foes to its integrity, the heart can be maimed or totally destroyed.

Thus, its protection becomes of paramount importance. This protection needs to be constantly applied throughout all these phases, thus it becomes a lifelong effort. It entails and includes prevention against cardiovascular risk factors, protection against myocardial loss during an acute myocardial infarction, protection during cardiac intervention or surgery, in the post-operative period, detection and prevention of a life-threatening arrhythmia, and monitoring of cardiac function during anti-neoplastic therapy which also can damage the heart.

I believe that this incessant strife overreaches the term "cardioprotection" and can be better expressed by the term "myocardial preservation". This term formerly was employed to denote protection of the heart during cardiac surgery. However surgery is declining in favor of interventional techniques, in which "preservation" is not so important due to their short duration and absence of imposed cardiac arrest and restart. However, in the rapidly exploding approach of the TAVR technique, an increase of troponins is routinely found [22, 23] and has prognostic significance. Thus, I believe that the term "myocardial preservation" should rightly attain the wider significance that it deserves, and should render us more aware of its constant importance. I first employed this term in a symposium in Sept. 2009.

In this book I tried to combine basic and clinical knowledge; in fact it is a book with translational approach. This term is overemployed in recent years since its inception in the early 1990's but still remains a sound perception.

The many aspects of myocardial preservation arise in everyday life. Consider a patient with severe coronary artery disease. If he has a chronic decrease of coronary flow reserve he may develop myocardial hibernation with cardiac dysfunction. The discerning clinician will guide him to the appropriate tests and to eventual revascularization.

Our patient may instead develop prodromal angina [24]. Under the right circumstances his myocardium may become preconditioned [25], diminishing the size of an infarction which may occur during the early (1 h) or late phase (24–48 h) protection zone. This protection may diminish the infarct size. Whether this occurs or not, reperfusion will have be carried out in a contemporary medical system. His attending physician and the one performing primary angioplasty is not sure if any drug will be used to it to administer while the patient is "en route" in the ambu-

lance or from “door to needle”. Should he benefit from the application of remote preconditioning? After the artery is opened should he undergo local or remote postconditioning? Should he be given cyclosporine in anticipation of more multicenter trials [25–27]? What if he develops ischemia reperfusion injury related no reflow? Will the interventionist trust his level C “expert” experience and give IC Verapamil [28]? If the patient comes to the CCU alive but with a large infarct by ECG and routine echocardiograpy what are the next steps? Shall contrast echocardiography or MRI be used to predict the inexorable road to remodeling? What drugs apart from the “big 4” (beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aldosterone inhibitors, statins) should be used, from one from more than 20 reported in recent reviews to choose from [29]. Should he receive IC stem cells? Should stem cells be repeated? For how many times if the findings of Bolli’s group [30] are verified? Should gene therapy be tried despite the findings of CUPID-2, which showed no benefit with SERCA-2 viral delivery [31]?

If an LBBB is found, should resynchronization be applied? If cardiac dysfunction persists when should LVAD be placed? If it is successful should a donor heart be hoped for or could the heart be expected to be successfully weaned, or should it be left as destination therapy?

One can understand that these are difficult and costly questions. The attending physician cannot rest complacently just offering tender loving care and sympathy but seek and consult all new developments. These are the result of painstaking work by many collaborating centers at sometimes exorbitant cost. This “places the monkey” not only on the shoulder of the clinician but also on that of laboratory researchers.

My hope is that this book will be useful to basic researchers orienting them to the practical/clinical utility of their toil at the bench, and to practicing cardiologists alerting them to the possibility that during the frightful moments of opening an artery in a dying heart they could spare some thought and effort to try a new promising technique of cardiopreservation invented by their “alchemist” peers on the sacrificed laboratory animal or in the “dry lab”. Of course, such an intermediating effort may leave both sides dissatisfied, but this is a peril which other authors have faced successfully.

I hope to emulate them.

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