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Interview with Dr. George Dangas
Chairman of the WHBA advisory board

Q: Dr. Dangas, could you please brief us about your professional background?
R: I completed medical and doctorate studies at the National Kapodistrian University of Athens, and after my duty in the Hellenic Navy, I completed specialization in Medicine and Cardiology at Brown University in RI and Mount Sinai in NY. Since then, I have been in academic medicine, as Associate Professor at NYU and then Columbia University, and since 2010 Professor and Director of Cardiovascular Innovation at Mount Sinai Medical Center in New York. I practice cardiology and cardiovascular interventions (minimally invasive surgery) at Mount Sinai Hospital. I also had the great opportunity to be the Chairman of Cardiology at the Onassis Heart Center in Athens.

I have been President of the Hellenic Medical Society of NY (2005-2008), founding president (2007-2009, and currently Emeritus) of the Global Hellenic Medical & Bioscientific Network and I am very pleased to have taken part in the present form of WHBA.

Q: Dr. Dangas, could you please tell us how you view the current dynamics of the World Hellenic Biomedical Association and where you see it evolving within the next years?
R: The role of WHBA can be quite important these years. First of all, it comes with a rich history of over 20 years, and spanning more than 2 continents in activity and participation. On top of this robust foundation, one should add the enthusiasm of the new beginning of the headquarters in the USA and recent conferences in London, Chicago and in other places outside the traditional locations of Greece and Cyprus. This broad involvement in both medicine and biosciences is anticipated to increase with an efflux of postdoctoral fellows from Greece and Cyprus to the various centers associated with WHBA. It is not a secret that this increased trend of academic quest outside the traditional areas of Hellenism boosts the responsibilities as well as the opportunities for WHBA to play a significant role.

Q: Dr. Dangas, as the Chairman of the Advisory Board of the WHBA, how do you plan to capitalize on the outstanding quality of the advisory board members with respect to the WHBA activities and aims?
R: The difference between the current WHBA status and other organizations (even including WHBA itself in earlier times), is the fact that we have a very notable history behind us and the recognition that comes with it, due to the fact that we have honored they pioneers of WHBA for their achievements and they have honored the current Executive Board with their trust!
The WHBA Advisory Board represents a forum for distinguished individuals in medicine and biosciences to participate and contribute despite their otherwise very limited time. However, these people can communicate very fast, to the point, and have very useful things to say due to their very broad experience and perspective. It would be a pity if we did not have the opportunity to capitalize on what ideas they have to offer just because
they very limited in time commitment, in accordance to their very busy schedules.

My simple (to say, but not do) role is to interface with them periodically and offer summary messages to the Executive Board regarding their opinions and views on the general area of medical and bioscientific research and education, the role of WHBA and the prospects of international collaborations, essentially along the lines of the present interview.

**Q: Dr. Dangas, what activities should the World Hellenic Biomedical Association develop so that it achieves its major aim, which is to create a communication and scientific interaction platform among prominent Hellenes physicians and researchers from around the world?**

**R:** In the past, WHBA had been very successful in organizing all-inclusive medical meetings and related forum-type sessions, but I think more specialized and focused meetings are required from now on. This is simply due to the different trends of medical and bioscientific endeavors overtime.

For example, I do not think many people will be interested to sit around and talk about diverse topics that pose little challenge or interest to them (aside from their own contribution); 21st century scientists rather discuss within their specialties and secondarily find ways to bring in academic collaborations and affiliations with fellows and institutions from Greece and Cyprus or among others of Hellenic heritage.

The topic of discussion and research has inevitably become more important than the ancestry and if we are to involve high level clinicians and academicians in WHBA, we have to recognize that they take little pride in self-promoting and speaking and mostly value listening to great ideas and avoid wasting their time.

**Q: How can the WHBA contribute in the development and scientific advancement of the individual physicians and bioscientists that constitute the membership of its’ participant societies, so that they follow the current trends of the medical and biosciences fields?**

**R:** WHBA should explore focused sessions at the most prominent meetings and in association with the most prominent professional and research societies where all these people take professional pride in attending, gain recognition through such achievements and ultimately foster collaborations. For example, we held for the first time a WHBA research symposium in association with the University of Chicago in parallel with the American Heart Association conference in November 2010 and another one in association with the American College of Cardiology in April 2011, that included a major award to a legendary Professor of Pediatric Cardiology from Los Angeles who was in fact an immigrant from Greece many years ago.

The level of faculty participants was outstanding and I attribute it not only to their Hellenic heritage or to the fact that they might be intrigued by what WHBA would look like, but to the astute way of organizing a focused
academic program in a convenient way that required very little extra travel and down-time for them. If these components do not coexist, nothing can be accomplished nowadays with the ever increasing number of organizations, conferences and academic initiatives.

I would certainly like these repeated and expanded to many other specialty areas. It is unrealistic to expect that cardiovascular disease can lift the entire activity of WHBA. All the specialties need to be represented and the respective physicians, surgeons and bioscientists are encouraged to organize accordingly within their own areas of interest.

Q: What activities should the WHBA engage with in order to facilitate the interaction and cooperation of the Hellenic Biomedical society of the “Omogeneia” with medical and research institutes in Greece and Cyprus?

R: First of all, we need to understand who is going to be the credible and durable collaborators from Greece and Cyprus. This is more difficult than we think. There are too many professional societies, educational colleges, government organizations and initiatives. At the same time, WHBA should also appear as a credible and durable association to their eyes. We are responsible for the latter.

Based on my experience, I find that these collaborations are too complex to try deciphering them ad hoc. The best way is to create a momentum of little dynamic initial collaboration between active (or new) WHBA members/societies and their respective (already existing) collaborators in the Universities or other institutions in Greece and Cyprus. Then we can look how to transition them to true long-lasting institutional collaborations and broaden the activities beyond these initial ones.

Of course every person initially developing these activities has a natural sense of ownership over them and it is a critical point how to seamlessly enhance the institutional role and de-emphasize the individualized personal roles; at the same time, we should pay appropriate respect and recognition to the pioneers.

Q: Dr Dangas, you have long experience with both Hellenic and American medical and scientific networks. What is your advice for the boards of such societies in order to succeed in their endeavors?

R: I am a firm believer that all the Societies, Networks and Associations should (1) respect their related history and try to build on it (rather than reject the past and reinvent the wheel from the beginning), (2) try to unify around fewer of them (rather than subdivide or keep creating new ones), and (3) create an environment of expected succession and continuous involvement at all levels (rather than appear as personally driven/focused and eventually aging along with their stationary leadership).

In fact, the third one is the critical one that sparks a light of hope to the first 2 items and differentiates an organization (with continuous activity) from the solo activities of a gifted person (typically creating the hype of great achievement but are ultimately winding down and disappearing).

The keys to achieve this are the generation of interest and some time commitment from new members through new events and activities, as well as the “restraint” of the active leadership from overextending their tenure, and overshadowing newer members.

Q: Thank you for your time.

R: Thank you for your opportunity to discuss these topics and congratulations on your efforts to WHBNews!
Calcium Cycling Circuits in Cardiac Physiology and Pathophysiology

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ABSTRACT
Heart disease results from a diverse range of multifaceted factors that impair cardiac function. Several signaling pathways have been shown to be involved in the induction of cardiac disease and heart failure. Many of these pathways are linked to cardiac sarcoplasmic reticulum (SR) calcium (Ca)-cycling. Abnormal Ca-handling by the SR proteins, Ca-ATPase (SERCA2a) and phospholamban (PLN), has been shown to have a vital role in cardiac pathophysiology. PLN is an endogenous inhibitor of SERCA2a and as such is a primary player in cardiac function by regulating Ca-uptake. Moreover, we have recently identified other regulatory proteins in the SR Ca-cycling protein complex, namely inhibitor-1 of protein phosphatase 1 (PP1), the small heat shock protein 20 (Hsp20), histidine-rich calcium binding protein (HRC), and the HS-1 associated protein X-1 (HAX1). We have shown that these new players could influence the PLN/SERCA activity and consequently, SR Ca-transport, cardiomyocytes Ca-handling, cardiac remodeling, cell apoptosis and survival. This review concentrates on the crucial role of these Ca-handling proteins in the regulation of cardiac function in physiological and pathophysiological conditions as well as the role of naturally occurring variants in these genes, which impact cardiomyocyte Ca-handling and may serve as modifiers of heart failure development.

INTRODUCTION
Cardiovascular disease is the leading cause of morbidity and mortality worldwide, with heart failure representing the fastest growing subcategory over the past ten years. Aberrant Ca handling is a hallmark of heart failure, which is partially attributed to alterations in the function of the SR. Coordinated regulation of cytosolic Ca by the SR of myocytes is required during each cycle of cardiac contraction and relaxation. Cytosolic Ca is sequestered into the SR lumen by SERCA2a, permitting muscle relaxation; subsequently, the stored Ca is released through ryanodine receptor channels to activate myofilament contraction (1) (Fig. 1A). The activity of SERCA2a is reversibly regulated by PLN, a 52 amino acid phosphoprotein (2). Dephosphorylated PLN interacts with SERCA2a and inhibits Ca-pump activity, whereas protein kinase A mediated phosphorylation of PLN through the β-adrenergic pathway relieves its inhibitory effects and augments relaxation (3). In turn, the restoration of contractility to basal levels is modulated by protein phosphatase 1 (PP1), which dephosphorylates PLN. Interestingly, PP1 is also regulated by an inhibitory phosphoprotein, inhibitor-1 (I-1), which can enhance β-adrenergic mediated phosphorylation of PLN, thereby improving SERCA2a activity. Recently, we identified the 35-kD anti-apoptotic HAX1, a ubiquitously expressed protein that protects cardiomyocytes from programmed cell death, as a binding partner of PLN and SERCA2a (4). Therefore, the PLN/SERCA2a/HAX1 interaction was postulated to regulate contractility and Ca cycling in the heart. In addition, of particular interest is a small heat shock protein (~20 kDa) named Hsp20. Our studies have shown that Hsp20 overexpression protected the heart from isoproterenol-induced maladaptive remodeling, contractile dysfunction and apoptosis (5, 6) as well as myocardial infarction (7). We have also investigated the role of Hsp20 phosphorylation in cardiac remodeling, induced by various signaling pathways.

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In addition, we have demonstrated that the histidine-rich calcium binding protein, HRC, interacts with the ryanodine receptor Ca release complex as well as SERCA2a. Importantly, upon overexpression of HRC in a cardiac specific manner in mice, the SR Ca uptake was impaired (8). Thus, HRC is a key regulator of SR Ca-uptake, storage and release.

Collectively, studies on the SR calcium cycling proteins at the intact animal, organ, cellular, and molecular levels (Fig. 2) demonstrated that these proteins are important not only in the physiological cardiac function but also in pathological conditions, and may represent promising therapeutic targets for heart failure.

Role of SR Calcium Cycling Proteins and Cardiac Function

Sarcoplasmic Reticulum Ca-ATPase and Phospholamban - The sarcoplasmic reticulum Ca-ATPase pump (SERCA), a 110 kD transmembrane protein, is the major regulator of Ca homeostasis and contractility in cardiac and skeletal muscle. SERCA belongs to a family of highly conserved proteins and SERCA2a is primarily expressed in the heart (9). As mentioned above, the excitation-contraction coupling in the heart is dependent on the Ca reuptake function of the SR, which is mainly regulated by the SERCA2a pump. Decreases in SERCA2a gene expression levels and activity have been correlated with defects in SR Ca-uptake function in animal heart failure models and in human failing cardiomyocytes (10). We have extensively examined the role of SERCA2a in cardiomyocyte function and the modulation of SERCA2a activity by PLN, utilizing transgenic approaches (11). These studies suggest that there is a direct correlation between SERCA2a activity by PLN and modulation of cardiac contractility, which further support the notion that SERCA2a function is one of the fundamental determinants of cardiac contractility (12, 13).

To elucidate the role of PLN in the regulation of basal contractility, we have developed genetically engineered mouse models. PLN ablation resulted in significant increases in cardiac contractile parameters, while PLN overexpression was associated with depressed cardiac function (14, 15). An inverse relationship between the ratio of PLN/SERCA2a and myocardial contractility was
demonstrated, indicating that any process, which alters the relative levels of these proteins and/or the interaction between them, may result in altered myocardial contractility. These studies demonstrate the importance of PLN’s interaction with SERCA2a and suggest that interfering with this interaction may provide a novel therapeutic approach for combating dilated cardiomyopathy.

Since the SERCA2a and PLN interaction regulates Ca levels, the most crucial ion for regulation of both cardiac excitation-contraction coupling and remodeling, we postulated that any naturally occurring genetic variations in the human SERCA2a gene, may modify this interaction and predispose to the development of heart failure. Screening of two large dilated cardiomyopathy patient cohorts from the U.S.A and Greece, for mutations in the coding region of the SERCA2a gene, revealed only four single nucleotide substitutions that did not result in any amino acid alterations (16). This suggests that SERCA2a is a tightly regulated and highly conserved gene, which may be essential for controlling intracellular Ca homeostasis and excitation-contraction coupling. However, we identified two naturally occurring mutations in the coding region of the human PLN gene in two Greek families with hereditary heart failure (17, 18). The T116G point mutation resulted in a stop codon (L39stop) and the second mutation deleted the arginine 14 amino acid in PLN. We proceeded to examine the functional consequences of these mutations in transgenic mouse models, and observed similar phenotypes as in human dilated cardiomyopathy patients, indicating that these PLN mutations may be associated with predisposition to dilated cardiomyopathy (17, 18).

The role of Hax-1 in cardiac function

Given the major role of PLN in calcium homeostasis and the limited information available on its binding partners, an extensive yeast-two-hybrid screening approach was used and the HS-1 associated protein X-1 (HAX1) emerged as a promising new PLN binding protein (19). Although
HAX1 had not been previously studied in the context of cardiomyocyte function, its established antiapoptotic role as a ubiquitously expressed mitochondrial protein could be of importance in cardiomyocyte survival under physiological and pathological conditions. Extensive protein studies led to the identification of the minimal binding domains of HAX1 (residues 203–245) and PLN (residues 16–22), indicating a direct physical interaction (Fig. 1B). Phosphorylation of PLN or elevation of the concentration of Ca led to dissociation of HAX1 from PLN, similar to findings on the PLN/SERCA2a interaction, thus indicating a physiological/pathophysiological significance of this association in cardiac muscle. Although HAX1 localizes to mitochondria, we demonstrated that in the presence of PLN it is redistributed and colocalizes with PLN at the endoplasmic reticulum (ER). Analysis of the anti-apoptotic function of HAX1 revealed that the presence of PLN enhanced the HAX1 protective effects from hypoxia/reoxygenation induced cell death. These findings suggest a possible link between the Ca handling by the SR and cell survival mediated by the PLN/HAX1 interaction. Importantly, the PLN/HAX1 complex may regulate SR/ER Ca homeostasis and, consequently, mitochondrial Ca redistribution.

To elucidate whether these regulatory effects are mediated through SERCA2a activity, the potential interaction of SERCA2a and HAX1 was assessed and found to be positive (4). The minimal interacting domains involved the SERCA2a residues 575–594 and the HAX1 residues 203–245. The interaction between PLN and SERCA2a occurs independently of PLN, and it is diminished by increasing Ca concentration, similar to the PLN/SERCA2a and PLN/HAX1 interactions (19). Furthermore, overexpression of HAX1 in HEK cells appeared to regulate the SERCA2a protein levels and ER Ca stores, which may play an important role in the antiapoptotic function of HAX1.

The Role of Inhibitor-I in Cardiac Function

Inhibitor-1, an endogenous inhibitor of type-1 protein phosphatase (PP1), is a critical regulator of cardiac contractility. Inhibitor-1 is activated by PKA-phosphorylation and this results in potent inhibition of PP1, a known regulator of PLN signaling, leading to regulation of PLN activity, Ca-cycling and cardiac remodeling. To elucidate the role of I-1 in the heart, we generated various transgenic models. Chronic overexpression of a truncated (AA: 1–65) and constitutively active (T35D) form of I-1 (I-1c) demonstrated that I-1c could attenuate the hypertrophic response and delay the onset of heart failure (20). In addition, cardiac-specific and inducible expression I-1c in the adult heart revealed that I-1c enhances cardiac function, which is associated with increases in PLN phosphorylation levels (21). Furthermore, under stress conditions (transverse aortic constriction or in vivo ischemia/reperfusion), either conventional or inducible expression of I-1c was associated with increased PLN phosphorylation, resulting in increased SR Ca-cycling. This enhanced SR calcium cycling improved the heart’s ability to accommodate the hypertrophic stimulus, delay the progression from hyper trophy to failure and impact cell survival under stress conditions. Thus, targeting I-1 may be beneficial in alleviating the detrimental effects of heart failure, through specific modulation of the SR-coupled PP1 activity.

Interestingly, we have identified a naturally occurring genetic variant in I-1 (G147D), which diminishes the cardiomyocyte response to β-adrenergic stimulation (22). Thus, I-1 genetic variants may act as modifiers of heart failure development.

Role of Hsp20 in SR Ca-Cycling

Heat shock proteins (Hsps) are known to enhance cell survival under various stress conditions. In the context of cardiac function, the small heat shock protein Hsp20 has emerged as a key mediator of protection against apoptosis, remodeling and ischemia/reperfusion injury. To determine the role of Hsp20 in the heart and the mechanisms underlying its regulatory effects in Ca-cycling, we have utilized a variety of in vitro and in vivo approaches. Interestingly, acute increases of Hsp20 levels or activity in isolated cardiomyocytes were associated with enhanced contractile parameters (23), which were further supported by cardiac specific Hsp20 overexpression in transgenic mouse hearts. Hsp20 overexpression resulted in significant enhancement of cardiac function in intact animals, and in augmented Ca-cycling and SR Ca-load in isolated cardiomyocytes (5). This was associated with specific increases in the phosphorylation of PLN, relieving its inhibitory effect on the apparent Ca-affinity of SERCA2a. In addition, Hsp20
The Role of HRC in the Heart

The histidine-rich calcium binding protein is a novel regulator of SR Ca-uptake, storage and release. Transgenic mice with cardiac overexpression of HRC, generated by our team, presented with impaired SR Ca uptake rates (35%) and attenuated cardiomyocyte Ca transient decay (38%), without alterations in peak Ca transients or SR Ca load (8). This impaired SR Ca uptake led to the development of cardiac hypertrophy and remodeling and ultimately the presentation of congestive heart failure.

In humans, DNA analysis of 123 Greek patients with DCM led to the identification of an HRC variant, Ser96Ala, which was associated with life-threatening ventricular arrhythmias in these patients. This finding represents the first genetic variant of an SR Ca-cycling gene associated with malignant arrhythmias in DCM and could serve as an independent predictor of susceptibility to arrhythmogenesis in the setting of DCM (26).

These studies raise the question as to the full spectrum of molecular mechanisms through which HRC regulates Ca homeostasis. Although HRC had been shown to bind triadin, affect the RyR affinity for ryanodine and thus participate in Ca release from the SR, this function alone did not suffice to interpret the aforementioned phenotypes in transgenic mice and DCM patients. Through a series of in vitro studies, we demonstrated that HRC can also bind directly SERCA2a, and this binding is sensitive to Ca concentration (27). While increases in Ca concentration were associated with significant reduction of the HRC binding to SERCA2a, they had opposite effects on the interaction between HRC and triadin. These findings suggest that HRC may play a key role in the regulation of SR Ca-cycling through its direct interactions with SERCA2 and triadin, mediating a fine cross-talk between SR Ca uptake and release in the heart.

In view of the role of SR Ca-cycling in myocardial ischemia/reperfusion injury, we studied the role of HRC during ischemia/reperfusion (28). Our results demonstrated that increased cardiac HRC expression protected against ischemia/reperfusion injury in the heart, resulting in improved recovery of function and reduced infarction. Thus, HRC appears to be important under pathological conditions and a potential therapeutic target.

CONCLUSION

In summary, several lines of experimental evidence indicate that proper cardiac function is maintained, in part, through the complex regulation of SR calcium cycling. Indeed, the cross-talk between SR Ca-cycling proteins mediates signaling pathways, which coordinately regulate cardiac performance. Our studies demonstrate that there appears to be “a regulatory SR Ca-transport ensemble” composed of SERCA2a, PLN, Hax-1, PP1, I-1, Hsp20 and HRC, and disturbances in the fine regulation of these proteins are implicated as important contributors to depressed cardiac function and remodeling in the failing heart.
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SUMMARY
Congenital heart disease, the most common, global inborn defect has come of age. Advances over the past half-century have transformed the outlook for these patients; while at the same time present us with new challenges. Our first priority is to raise the level of understanding of CHD beyond the tight boundaries of tertiary specialist care. These patients, most of them in their adulthood now, often require non-cardiac health care; we need to better educate the profession, the patients themselves and the public. There is clearly precious need for clinical and basic research in the adult CHD field. Some of the natural experiments and multiple adaptive mechanisms operational here merit closer observation and improved understanding. Cyanosis for example, briefly discussed herewith with regards to secondary erythrocytosis, is probably the most potent driver to neo-vascularization. Chronic adaptation of the right ventricle to pressure and load overload—a very common CHD scenario—may inform us and assist management of acquired heart disease.

The spectrum of CHD disease, the richness of clinical material, the dynamic nature of physiology and early and late intervention and the potential to form a life-long relationship with the CHD patient is perhaps unparalleled in modern medicine. It naturally invites young physicians and scientists to join in. Yes, we are at crossroads in this field right now, but we can move forward with greater participation and more education, so that we can truly extend the outstanding results of pediatric cardiology and cardiac surgery into adulthood and enable every patient with CHD to reach and enjoy their full life potential.

INTRODUCTION
Advances in diagnosis and surgical care of patients born with congenital heart disease (CHD) have resulted in an ever-increasing number of these patients reaching adulthood (85–90% of them including patients with complex disease). To put this in the context of numbers, CHD affects approximately 1% of newborn infants globally, it is indeed the most common inborn defect; there are currently approximately 250,000 adults with CHD in the UK, 1,000,000 in the US with similar numbers around the developed world. Despite the improved outlook of CHD patients, however, long-term follow-up and treatment remain challenging. The complexity of anatomy and physiology often persist in these patients following early intervention/s. Residual and progressive haemodynamic lesions are the norm, as surgical “cure” in a true sense is not feasible for the majority of lesions and patients. It is estimated that approximately 50% of adult CHD patients face the prospect of further surgery and other intervention/s. Furthermore, the impact of chronic exposure to volume or pressure overload and of previous surgical procedures (often multiple) create a molecular and anatomical substrate for heart failure, malignant arrhythmia and sudden cardiac death. As patients move into adulthood, acquired medical conditions including obesity, hypertension, diabetes, chronic lung conditions and coronary artery disease, further complicate management and reinforce the mandate for life-long multi-disciplinary care. Unfortunately, such planning and infrastructure are lacking in most parts of the world. To complicate matters further, the majority of adults with CHD have been lost to specialist follow-up, on the assumption that they received curative surgery in childhood. This fact obviously compromises their longer-term outlook.

While major advances have been seen in anatomy, physiology and early intervention over the past 5 decades, the late pathophysiology and associated morbidity and mortality in this population remain uncertain. There are potential
late medical, surgical and or percutaneous therapeutic interventions but their safety and efficacy profile remain largely unknown. Contrary to evidence-based medicine through large, randomised prospective trials being the cornerstone of modern cardiology practice, treatment of paediatric and adult CHD remains largely empirical. Extrapolations from pharmacological and interventional studies from patients with acquired heart disease to patients with CHD are clearly inappropriate. This is because of the specific characteristics of CHD anatomy and physiology and of the multiple adaptive mechanisms that operate in these patients (most not fully understood). It is fair to say, that the mainstay of treatment for adult CHD remains at present to target haemodynamic lesions, when present with haemodynamic interventions (surgical or catheter).

Despite all this uncertainty, there has been progress in the field over the past decade or two. With this progress, some of the old dogmas, such as of fixed pulmonary vascular disease in patients with Eisenmenger physiology or of the need of venesections in patients with chronic cyanosis to alleviate symptoms and reduce the risk of stroke have been appropriately challenged.

The scope of this review is to highlight briefly such advances, which had an impact on clinical practice, with a particular reference to work that has been generated from the Royal Brompton Hospital.

Tetralogy of Fallot, pulmonary regurgitation and risk stratification for arrhythmia and sudden cardiac death

Tetralogy of Fallot is the most common cyanotic CHD, affecting approximately 1/1000 infants around the world. Intracardiac repair has provided excellent short and long-term results over the past fifty years or so. Peri-operative mortality has fallen dramatically (currently in lower single figures for most large centres) and patients live long-years after repair. Tetralogy is perhaps the best-studied model following reparative surgery. Yet, this success story has been hampered by the increasing burden of arrhythmia and sudden cardiac death (SCD). Furthermore, pulmonary regurgitation (PR), secondary to aggressive relief of right ventricular outflow tract obstruction has a detrimental long-term effect on right ventricular function and, in turn, on propensity to arrhythmia.

An early serendipitous observation of a link between haemodynamics and arrhythmogenesis in our institution on this population, expressed in a simple, readily available and reproducible marker (QRS duration on the EKG) -provided us with novel mechanistic and prognostic information on sustained ventricular arrhythmia and sudden cardiac death. This data was subsequently validated in a larger multi-centre cohort of adults with repaired tetralogy of Fallot. This study confirmed severe pulmonary regurgitation and secondary right ventricular dilatation/dysfunction to be the culprit haemodynamic substrate to ventricular tachycardia and sudden cardiac death. Older age at repair and QRS duration/ QRS interval change were strong and independent predictors of clinical events (sudden cardiac death and sustained ventricular tachycardia respectively). This data were subsequently validated by other groups and have since influenced practice for a) early repair of tetralogy; b) preservation of the pulmonary valve function during repair and c) for timely pulmonary valve implantation in patients with severe PR to preserve right ventricular function and reduce the risk of malignant arrhythmia. This work on risk stratification was refined further with invasive electrophysiological studies for high-risk patients and with advanced imaging, such as cardiac MRI (novel work on detrimental role of ventricular fibrosis). Last but not least, echocardiographic and histologic data from Toronto and the Royal Brompton hospital established the late morbidity associated with aortic disease in tetralogy, a lesion that has been traditionally thought to be confined to the right heart. This new evidence suggested that both intrinsic abnormalities of the aorta and early haemodynamics before repair were responsible for this late aortopathy, and again it informed
practice for early repair and for life-long monitoring of the aorta.

**Common heart failure pathways**
Successful surgical and catheter interventions, as mentioned above, have led to improved quality of life and survival amongst CHD patients. Residual cardiac defects, causing progressive volume and/or pressure overload, coupled with acquired heart and other disease impact on late morbidity and mortality. Chronic heart failure with progressive exercise intolerance and neurohormonal activation was recently reported in this relatively young population with structural heart disease. Simple markers such as BNP seem to convey prognostic information. Ventricular diastolic and systolic dysfunction—the latter often with ventricular fibrosis—abnormal ventriculo-arterial coupling and, in many patients multi-organ involvement seem to be common and recurrent themes. Renal dysfunction, for example is far more common amongst CHD patients compared to general population. A multi-factorial aetiology is likely here, including chronic low-cardiac output status, the presence of cyanosis and or the impact of early intervention on myocardial and other organ perfusion. Renal dysfunction, itself, carries prognostic information in CHD. Furthermore, it may promote cardiac remodeling and progression of cardiac dysfunction through loss of sodium balance and volume overload. It may also lead to deterioration of cardiac function by aggravating hypertension and anemia. Finally, patients with renal dysfunction may be less likely to receive aggressive therapy and to be offered cardiac or other intervention as renal impairment increases perioperative risks.

Neurohormonal antagonism may convey mid to long-term benefits in CHD patients. Our group has recently failed to demonstrate improved right ventricular systolic function or improved exercise capacity in patients with dilated right ventricles after repair of tetralogy of Fallot (with severe pulmonary regurgitation) receiving ramipril for 6 months in a randomized, placebo control study, utilizing cardiac MRI and cardiopulmonary exercise testing. There were however, some positive changes on ventricular long axis function on the ramipril arm; it maybe that the length of observation and patient numbers were in part responsible for the negative nature of this study. This is clearly an area that further investment is required; this is to examine the potential benefit/s of established heart failure therapies in stable CHD patients, allowing for the heterogeneity of this population.

**Prognostic value of exercise testing in morbidity and mortality**
The identification of high-risk CHD patients is clearly important, as it may facilitate refinements in treatment, ultimately improving individual patient quality of life and outlook. As suggested by work on ischemic heart disease/dilated cardiomyopathy, exercise testing may be of value in evaluating symptoms and prognosis in patients with CHD. Diller et al from our group provided one of the first reports on the common prevalence of exercise intolerance amongst clinically stable adults with CHD, even among “asymptomatic” patients. Chronotropic incompetence, pulmonary arterial hypertension (PAH), and impaired pulmonary function were all predictive of exercise intolerance, as was underlying cardiac anatomy. Impaired exercise capacity was associated with an increased risk of hospitalization or death (independent of symptom status), suggesting that measurement of peak oxygen consumption should be incorporated in the periodic assessment of these patients. More parameters have emerged since; ventilation efficiency, expressed as ventilation per unit of carbon dioxide production (VE/VCO2 slope), has been shown to be a strong predictor of survival. While other groups have validated these early reports, and we and others have looked at the prognostic value of cardiopulmonary exercise testing in individual CHD groups (as in Fontan patients with complex CHD), there is little data on the effect of regular exercise on exercise capacity and cardiovascular function. “Nous ygis en somati ygii” our predecessors used to say, this applies to healthy individuals and to patients with acquired heart disease; there is no reason to believe that CHD patients are an exemption.
This is clearly an area that warrants further studying and the potential impact of exercise on functional capacity, quality of life and overall outcome - including arrhythmia - should not be underestimated.

**Pulmonary arterial hypertension associated with CHD and the Eisenmenger Syndrome: pathophysiology and therapy**

PAH is relatively common amongst adults with CHD (5-10%), impacting on quality of life and outcome. The extreme end of the spectrum is represented by the Eisenmenger syndrome; this starts as a large intracardiac or extracardiac left to right shunt, which was not repaired in early childhood and has led to progressive pulmonary vascular disease, with ultimate reversal of shunt flow and ensuing cyanosis. Sadly, there are many misconceptions haunting this field; it is believed that Eisenmenger patients are relatively well, with a stable disease and with a fixed/irreversible pulmonary vascular bed. Recent data from our group suggest that these patients are severely limited with progressive disease and significant morbidity and mortality, particularly given their young age. Furthermore, BREATHE-5 a randomized placebo control study, examined the potential role of dual endothelin receptor antagonist bosentan in Class III Eisenmenger patients; it showed a drop in pulmonary vascular resistance index (i.e. a labile and not fixed pulmonary vascular bed), coupled with improved walking distance and improved functional class. Patients on placebo, in contrast, had further progression of pulmonary vascular disease within the 16-week study period. Furthermore, Dimopoulos et al from our group recently showed improved survival on 229 adults with Eisenmenger syndrome treated with oral advanced therapy (more than 2/3 treated with Bosentan, less than 1/3 with sildenafil, the remainder on combination therapy), compared to patients on conventional therapy only. During the 4-year of follow-up period, there was significant morbidity and mortality even for patients who were functional class II, reinforcing the fact that Eisenmenger syndrome is a progressive condition, albeit mortality was half in Class II compared to Class III patients. The evidence, therefore, suggests that patients with Eisenmenger syndrome respond well to advanced PAH therapy and should, thus, be considered for it. One of the many remaining challenges is that the majority of patients are lost to specialist cardiac follow-up. In fact, a number of these patients not attending cardiac clinics seem to be seen in haematology clinics (because of cyanosis), where they are subjected to potentially harmful venesections. Which brings up another dogma or myth that haunts cyanotic patients, including those with Eisenmenger syndrome. This is the myth of hyperviscosity syndrome, where routine venesections to lower Hb and haematocrit levels are believed to ameliorate symptoms and reduce the risk of stroke. In fact the evidence suggests otherwise; the risk of stroke is higher amongst patients on periodic venesections and the so-called symptoms of hyperviscosity mimic symptoms of iron deficiency. The latter is typically exaggerated or induced by venesections. While the multiple chronic adaptive mechanisms for chronic cyanosis, including that of secondary erythrocytosis are poorly understood, it seems that routine venesections compromise the patient’s oxygen transport capacity, increase the risk of stroke, reduce exercise capacity, and thus should be abandoned. Clearly, more work needs to be done in this area.

Last but not least, we need to agree on surrogate markers of PAH severity, progression and response to therapy. The 6-minute walk test seems to be appropriate for this patient population. Our group has unpublished data on the distance walked and on BNP levels carrying prognostic information (personal communication Dr Diller, Royal Brompton). Endothelial progenitor cells (EPC), bone marrow derivatives with pulmonary vascular bed repair properties, were recently reported by Diller et al to be diminished in PAH patients. Patients with Eisenmenger syndrome and associated Down syndrome had the lowest levels. In contrast EPC levels were higher amongst patients on sildenafil, where a dose related response was observed. While there are currently trials examining the potential role of exogenous
administration of EPCs in patients with PAH, this is not immediate priority for PAH and CHD. We are in need of more epidemiologic data, what happens to patients with left to right shunts with mild PAH over a lifetime? There has been a lot of discussion for a treat (with advanced PAH therapy) and repair (close defects) approach; there is however, little evidence to suggest that this is beneficial long-term. Surely, one cannot judge success by merely reporting peri-operative survival. We should seriously examine the long-term impact of haemodynamic intervention – against what we know for example for Eisenmenger syndrome- and the real risk of converting patients with PAH associated with CHD into “idiopathic” PAH (by aborting the patients ability to shunt right to left and, thus, compromising their longer term outlook). In general, when PAH is established, it usually progresses and the current range of advanced therapy is not aetiologic, but conveys symptomatic benefits to patients with PAH, including those with Eisenmenger syndrome.

REFERENCES


The World Hellenic Biomedical Association

Founded in 1990

By Unanimous Movement of the Board

We hereby recognize

George Emmanouilides, MD

Distinguished Career Achievement Award

For his lifetime achievements in Pediatric Cardiology

New Orleans – Louisiana

April 2011
- **Winter Social and Vasilopita:** On a wintery January evening, over 80 professionals attended the winter social and networking event at Estia. Lawyers, Business people and medical professionals mingled and networked, followed by traditional Vasilopita cutting by Father Nektarios from St George Cathedral.

- **"State of the Debate: Perspectives and Possibilities of Healthcare Reform"** at Drexel LeBow School of Business. Co-organized by the Greek American Chamber of Commerce and American Hellenic Lawyers Association, over 50 attended the symposium discussing the impact of the current healthcare reform legislation. Speakers included Congressman Rob Andrews, Mr. John DiAngelo CFO South Jersey HealthCare, Mr Vishal Petigara ESQ from Obermeyer and Mr. Debjit Ghosh from Analysis group. The lively and informative event illustrates the intellectual prowess of the Hellenic Professional community and our relationship with the American Community.

- **Medical section in the Hellenic News of America:** With the support of the HNA, HMS Philadelphia board and members will contribute medical articles and information to develop a medical section. This section will serve to highlight the talented professionals of the HMS and also as a reference for patients and medical professionals alike.

- **Greek Independence Day Parade** in Philadelphia, on March 20, 2011. Over 30 members of the Hellenic medical society of Philadelphia and New York as well as North Jersey Hellenic Health Professionals participated in the Parade in Philadelphia on a beautiful Sunday in March. The HMS of Philadelphia was also invited to participate in the Greek Independence Parade in New York City on March 27th with the sister society, Hellenic Medical Society of New York. This was an exciting opportunity to showcase the medical societies together.

- **Community Service Initiative** of HMS Philadelphia:
  a) Blood Pressure (BP) screening and glucose/cholesterol event at Coffee hour at St George, Trenton NJ in March or April 2011.
  b) Cretan House Heart Healthy Event, Highland Park NJ, April 12th 2011 BP screening and Cholesterol testing, co-sponsored with North Jersey Health Professional Associations.
  c) BP screening and Cholesterol event at St George, Media PA, May 1, 2011.
- **2nd annual Continuing Medical Education Event** at the Hermes Expo on April 2, 2011. The CME was entitled “Hippocrates Seminars: The Future of Medicine, New Paradigms of Care”. Speakers from HMS NY, North Jersey and Philadelphia did outstanding lectures. The HMS Philadelphia presented the 2011 Distinguished Physician Award to Dr. James Argires of Lancaster PA. The Keynote speaker was Congressman John Sarbanes from Maryland.

HMS Philadelphia wish to thank the speakers including Sandy Tzaferos, PharmD; Anamea Adamidis, MD, Elleni Pippis, PharmD, Nicholas H.E. Mezitis, MD, Constantine Kosmas, MD, and Spiro Spireas, PhD. Also they wish to thank the moderators: Fran Zappalla, DO, Martina Harris MA, Tara Morrison MD, and Alex Poulathas, DO, for their time and preparation. Lastly, HMS NY and Philadelphia acknowledge the efforts of the administrators Evangelia Tsavaris and Sophia Pappas.

- HMS Philadelphia participated at the cultural event “Cretan Night” organized by the Hellenic University Club at Wilmington, and held at the Wilmington Delaware Holy Trinity Community center church on April 9th, 2011. Dr. Maria Hnaraki, Director of Greek Studies of Drexel University gave a talk on "Performing in the Labyrinth -Unraveling the Cretan Music Thread". Also, the Cretan Dancers of Greater Philadelphia-Knossos performed Cretan dances, and Lenten pot luck was served.

**Upcoming Events**

- **General Assembly** of the HMS Philadelphia **May 17th, 2011**. Please save the date as a Dinner meeting is being organized to discuss the projects and objectives of the Society. Location: being confirmed and dinner provided. Please join various members of your society socially while learning more about the programs and events of the society.

- **HMS Philadelphia Spring Social** on **June 15th, 2011**, at 6:30pm at Riverwinds Restaurant, West Deptford, NJ. Co-sponsored by Hellenic University Club, Hellenic Medical Society, American Hellenic Lawyers Association and Greek American Chamber of Commerce, a spring social has been organized and we look forward to socializing with our Hellenic professional community. More details to follow.

- **Educational Event** of the Hellenic Medical Society of Philadelphia **May 25th, 2011** 630pm at Adelphia Restaurant, Deptford, New Jersey. Through our relationship with the American Hellenic Lawyers Association, HMS Philadelphia has arranged an educational lecture entitled, “How to Avoid Litigation for the Medical Professional.” Light dinner fare will be provided and all are welcome to attend.

- Hellenic Medical Society of Philadelphia **Student scholarship program**: The HMS supports a medical student (MD, DO, DMD, DDS) and allied health student scholarship (RN, PharmD, RT, PT) each year and awarded our first scholarship to Ms. Natalie Saffos of Drexel nursing. As of May 1, applications are being sent to local (NJ, PA, DE) colleges and universities with a submission deadline of Oct 15th. The Award will be presented at the Society’s November Dinner meeting. Please contact our administrator Sophia Pappas to receive an application at HMSPHL@gmail.com or spappas@aol.com.
Past Events
Archdiocesan Memorial Service for Members Deceased of The HMS NY on February 6, 2011, at the Holy Trinity Cathedral, NYC. This service was in memory of past presidents and members of the Hellenic Medical Society of New York, and coincided with the 75th anniversary of the founding of the society.

- The HMSNY participated in a Tsiknopempti Celebration with Cosmos FM 91.5 on February 24, 2011
- The Hellenic Medical Society of New York participated in the Greek Independence Day Parade on Sunday, March 27, 2011

Upcoming Events
(1) Hypoglycemia - Dinner Symposium on May 3, 2011 at Stamatis Restaurant, Astoria
(2) Papanicolaou Symposium and Awards on May 11, 2011 at Cornell Medical College

Ongoing Project
HMS NY Scholarships and Awards: Dr. Theo Diktaban and Dr. Michael Michelis reviewing applications for 2011 Specialty Area Scholarships and Awards. Please refer deserving students for consideration. To review the various awards and qualifications visit our website: http://www.hmsny.org/scholarship.html
The 13th Annual Hygeia Awards & Scholarships Dinner Dance of the New England Hellenic medical and dental society took place on Saturday, May 7, at The Annunciation Greek Orthodox Cathedral Center of Brookline, MA.

The event was attended by a surprisingly high number of members and friends of the society. His Eminence Metropolitan Methodios attended the dance and offered the prayer and a short address to the crowd. The General Consul of Greece in Boston, Mr. Ilias Fotopoulos with his wife Yioula Salesiotou was present and offered a short greeting.

The NEHMDS president Ioannis P Glavas, M.D. FACS initiated the awards ceremony. During his introductory speech he mentioned the passing of Dr Harilaos Sakellarides a prominent orthopedic surgeon of Boston who was also a founding member of the NEHMDS. NEHMDS Board Member Dr. Kosta Steliou was invited to the podium to speak about Dr Sakellarides’ achievements and personality as well as anecdotes from his personal and professional life.

The event was a tremendous success. The 13th annual Hygeia award was presented to Stella Kourembanas, MD, Clement A. Smith Professor of Pediatrics at Harvard Medical School, Chief of the Division of Newborn Medicine at Children’s Hospital Boston & Academic Chair of the Harvard Program in Neonatology of the three Longwood Medical Area Teaching Hospitals (Children’s Hospital Boston, Brigham and Women’s Hospital, and Beth Israel Deaconess Medical Center).

The Hygeia Award was presented by Dr. Theoharis C. Theoharides, Professor of Pharmacology, Internal Medicine and Biochemistry, Tufts University School of Medicine.

Dr Theoharis C. Theoharides and Dr Nikos Madias were congratulated for recently being awarded the highest honorary academic title by the National Kapodistrian University of Athens in Greece.

The Ceremony continued with presentation of scholarship awards by the Treasurer of NEHMDS Dr. Alex Georgakis. The 15th Annual Dr. Nicholas C. & Anna F. Marcopoulos Charitable Foundation Scholarship awards were also presented by Mrs. Nancy Rallis representing the Macopoulos Family to:

- **Steven Kyriakos Constantino Jr - TUFTS University School of Medicine 2012**
- **Sophia Paraschos - University of Massachusetts Medical School 2013**
- **Vanessa Mitsialis - Harvard Medical School 2013**
- **Nicholas Theodosakis - Yale University School of Medicine 2016**
The Hellenic Bioscientific Association in USA (HBA-USA) in cooperation with the Columbia University Hellenic Association would like to invite you to the 2nd Pan-American Meeting:

"Moving from basic to translational research via novel technologies"

October 15-16, 2011

Meeting sessions
- Cancer & Immunology
- Metabolism & Cardiovascular biology
- Novel technologies and applications
- Collaborations in Life Sciences Education and Research in the United States and Greece

Columbia University
Schermerhorn Building,
116th Street and Broadway,
New York

2011 "Aristoteles Award"
for outstanding achievements in Biosciences:
Professor Haralambos Gavras
The HMS-UK 2011 Annual Dinner Dance

On Saturday, 18th June 2011 at the Great Hall, Hellenic Centre

16-18 Paddington Street, Marylebone, London, W1U 5AS

Guest of Honor: Prof Elias Mossialos
Member of the Greek Parliament
Professor of Health Policy, London School of Economics

Hellenic Medical Association of Quebec, Canada

Past events

Osteoarthritis of the knee and MRI in day to day family physician practice
February 16th, 2011
Dr. Michel Pagé MD specialised in musculo-skeletal
Centre médecine sportive de Laval
Dr. Étienne Cardinal,
Radiologist (MD, FRCPC, Université de Montréal)
Sponsored by Genzyme, Synviscon

Medicine and orthodoxy: two journeys (March 29th 2011)
Dr. Emanuel Kolyvas, M.D., Microbiologist and infectious disease specialist
Associate professor of microbiology and Adjunct professor of pediatrics, McGill (retired)
Fr. Cyprian Hutcheon, M.D., PhD (Theology)
Associate professor of pediatrics, McGill (Retired)

Financial Strategies and Incorporation (April 27th 2011)
Mr. Lewis Rosen and Mr. Morris Jacobson of Spiegel Sohmer Inc.

Future events

May 31st, 2011
“Atrial Fibrillation: New Approaches to Prevention of Thrombo-embolic Complications”
George Honos, MD - Head of Cardiology, CHUM
Sponsored by: Canadian Cardiovascular Society