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Preface to heart failure

Towards modern genetics, diagnostics and therapeutics of heart failure in a new era

Heart failure is a complex combination of symptoms based on malfunction of either the left or right ventricle due to diminished contraction or relaxation [1]. The number of causes is numerous, but predominant are ischemic heart disease and hypertension [2]. The struggle to improve the very poor prognosis in patients with symptoms is ongoing and steps towards the benefit of patients are being made. Not only is survival improving gradually, more important is improvement of the quality of life. What is the value of a prolonged life without improvement of quality of life in highly symptomatic patients? Although big pharma appears to be stepping away from heart disease in general and heart failure more specifically, there are always new insights and potential targets that are worthwhile to pursue [3]. In this special issue of BBA various groups have contributed their insights in the current state-of-the-art and where the new diagnostic and therapeutic targets can be found. The review papers go from early development and cardiogenesis through molecular mechanisms of hypertrophy and failure. Here several important breakthroughs have been listed with even the first modest steps to interventions where especially the field of the antagomirs seems to be an area where the time gap between target recognition and therapeutic intervention in man could be reduced considerably. Finally, there are contributions to discuss the value of molecular tools to improve our diagnostic capabilities to recognize the disease and predict outcome.

Sergeeva and Christoffels focus on the molecular regulation of expression of atrial (ANF) and brain natriuretic peptide (BNP) during the early steps of heart formation and in cardiac disease [4]. The mammalian heart is known to express both natriuretic peptide (NP) hormones. The physiological role of NPs is to act to increase natriuresis and decrease vascular resistance, thereby decreasing blood volume, systemic blood pressure and afterload. In addition, plasma levels of BNP are used as specific markers for the differentiating working myocardium in the developing heart and their gene structures serve as a platform to investigate gene regulatory mechanisms in heart development and disease. NPs are also widely used in biomedical research to assess the hypertrophic response in cell culture or the development of HF in animal models. Finally, NPs are clinically widely used as diagnostic and prognostic markers for hypertrophy and heart failure. However, despite decades of research, the mechanisms regulating the NP genes during development and disease are not well understood and in their review Sergeeva and Christoffels update the field on the regulation of expression of the genes for ANF and BNP and their role as biomarkers, and give future directions to identify the in vivo regulatory mechanisms.

Dirkx and De Windt zoom in on the gene regulatory mechanisms underlying the so-called fetal gene program [5]. Cardiomyocytes will react to biomechanical stress by activating pathways that induce either apoptosis [6] or pathological hypertrophy [7], where hypertrophy forms an independent risk factor for the development of heart failure [8]. Accompanied with hypertrophy are gene expression patterns and molecular changes that bear resemblance to those observed during fetal cardiac development as previously discussed by Sergeeva and Christoffels [4]. The reactivation of fetal genes in the adult failing heart is a complex biological process that involves transcriptional, posttranscriptional and epigenetic regulators of the cardiac genome. In this overview, the mechanistic actions of transcription factors, microRNAs [9] and chromatin remodeling processes in regulating fetal gene expression in heart failure is discussed in more depth.

Ather and colleagues focus on alterations in Ca^{2+} release and reuptake during excitation–contraction coupling [10]. These processes start within the dyadic region, where the adjacent transverse (T)-tubules and SR membranes allow RyR2 clusters to release SR Ca^{2+} following Ca^{2+} influx through adjacent LTCCs. SR Ca^{2+} released during systole binds to troponin-C and initiates actin–myosin cross-bridging, leading to muscle contraction. During diastole, the cytosolic Ca^{2+} concentration is restored by the resequestration of Ca^{2+} into the SR by SR/ER Ca^{2+}-ATPase (SERCA2a) and by the extrusion of Ca^{2+} via the Na^{+}/Ca^{2+}-exchanger (NCX1). This process is highly coordinated and determines the force of contraction, providing a link between the electrical and mechanical activities of cardiac muscle. In heart failure, the heart undergoes maladaptive changes that result in depressed intracellular Ca^{2+} cycling and decreased SR Ca^{2+} concentrations. As a result, the amplitude of CICR is reduced resulting in less force production during EC coupling. In this review, the specific proteins that alter the regulation of Ca^{2+} during HF are discussed, with a particular focus on defects in RyR2-mediated SR Ca^{2+} release. Heart failure is also associated with ventricular arrhythmias, at times leading to sudden cardiac death. The electrophysiological remodeling is reviewed by Coronel and changes in intracellular calcium handling are discussed. Intercellular uncoupling and fibrosis are identified as major arrhythmogenic factors. Both factors contribute to the origin of the arrhythmic substrate. Modulating factors like diet and ventricular wall stress are discussed. A special section is focusing on. Finally, emphasis is placed on right ventricular failure.

Gaggin and Januzzi comprehensively introduce the rapidly changing field of clinical heart failure diagnostics and prognostics [11]. Heart failure biomarkers have impacted the way HF patients are evaluated and managed with B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) serving as the gold standard biomarkers in determining the diagnosis and prognosis of the disease, and natriuretic peptide-guided heart failure management looking promising. New and exciting biomarkers are also emerging, each reflecting different pathophysiological processes in the development and progression of heart failure, more closely reflecting myocardial insult, inflammation and remodeling. Novel biomarkers such as mid-regional pro atrial natriuretic peptide (MR-proANP), mid-regional pro adrenomedullin (MRproADM), highly sensitive troponins, soluble ST2 (sST2), growth differentiation factor (GDF)-15 and Galectin-3, show potential in determining prognosis

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beyond the established natriuretic peptides, likely serving a role as additional biomarkers in multiplexed biomarker platforms.

Finally, Lopes and Elliot present the evidence that the risk of heart failure in the general population depends on genetic predisposition [12]. In a small, but probably underestimated proportion of the population, heart failure is caused by Mendelian inherited forms of myocardial disease. The genetic background of these genetic conditions is a matter of intensive research and the results of these efforts are also shedding light onto the genetics and mechanisms of common forms of heart failure. In this review, the insights provided by candidate gene and genome-wide association approaches in common heart failure are described and the authors go on to update the main genetic causes of inherited heart muscle disease and give the current challenges and future research needs for both forms of heart failure.

Composing the special section was very rewarding. We hope that reading the papers is even more stimulating, and will help to revive interest in the fascinating field of cardiac pathophysiology.

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Leon J. De Windt obtained his PhD in Cardiovascular Physiology at Maastricht University in 1999. Subsequently, He received an *American Heart Association Fellowship* for a postdoctoral residence at the *Howard Hughes Medical Institute* of Prof. Dr. Jeffery D. Molkentin in Cincinnati OH, USA. In the early phase of his career as group leader at the Hubrecht Institute in Utrecht (*director: Prof.dr. Hans Clevers*), his research interests shifted to the pro-hypertrophic mechanisms of calcineurin-responsive transcription factors. Mid 2010, he was appointed as full professor of Molecular Cardiology at CARIM School for Cardiovascular Diseases (*director: Prof. Mat Daemen*) at Maastricht University. More recently, his laboratory has gained interest in microRNAs (miRNAs), a class of endogenous, small, noncoding RNAs, which suppress protein expression by either messenger RNA degradation or translational inhibition. Each miRNA potentially targets multiple transcripts, suggesting that miRNAs, not unlike transcription factors, have a fundamental role in regulating gene expression. Leon De Windt is the recipient of several Awards, including the Louis N. and Arnold M. Katz Basic Science Research Award for Young Investigators from the American Heart Association; recipient of a 2003 Innovational Research Incentives Scheme VENI and VIDI awards from the Netherlands Organization of Scientific Research (NWO); in 2008 he was selected as core member of a Fondation Leducq Transatlantic Network of Excellence; he is the recipient of the 2012 Outstanding Achievement Award of the ESC Council for Basic Cardiovascular Science as well as the 2012 Galenus Research Prize. In 2012, he received an ERC Starting Grant from the European Research Council to support his work.

Pieter A. Doevendans became a cardiologist in Maastricht (H. Wellens) after his medical training at the Leiden University. In 1993–1994 he had the opportunity to work with Ken Chien at UCSD San Diego where the work on mouse embryonic stem cells started. The work was completed in Maastricht and provided the basis for a thesis on the function of the promoter of the atrial Myosin Light Chain gene. Upon return to the Netherlands he worked with Christine Mummery and Hans Clevers (Hubrecht Laboratory) on both human Embryonic as well as human Cardiac stem cells. In the meantime he remained active as an interventional cardiologist initially in Maastricht, but from 2002 on in Utrecht at the University Medical Center. Here he was appointed full professor in Translational Cardiology in 2004 and head of the department in 2005. The focus of the department of cardiology is on Cardiac Failure, stem cells and genetics. Thus far (2013) he has published more than 450 peer reviewed papers and 10 books.

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