Biophysical Reviews (2018) 10:943–947
https://doi.org/10.1007/s12551-018-0444-1

EDITORIAL

Non-sarcomeric causes of heart failure

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Received: 29 June 2018 / Accepted: 5 July 2018 / Published online: 14 July 2018

The heart is the first organ to become functional during mammalian development and by rhythmic contractions serves to pump blood through the entire body to supply peripheral tissues with oxygen and nutrients. Impairment of cardiac function has a profound effect on the organism, and cardiovascular disease is the major cause of morbidity and mortality in the world (WHO 2011). Cardiac disease can be downstream of adverse cardiovascular events, such as heart tissue damage following a myocardial infarction or hypertension-induced pathological hypertrophy. Cardiomyopathies are a subset of cardiovascular diseases and are defined as mainly affecting the heart itself. There are life-style induced and viral causes of cardiac disease, but there is also a significant genetic contribution to cardiomyopathy (Wilcox and Hershberger 2018). Aim of this Special Issue is to have a closer look at the molecular and cellular mechanisms and signalling pathways that underlie a cardiomyopathy phenotype, but that are not necessarily directly associated with the contractile units, the myofibrils.

The contractile tissue of the heart is made up of mono- to binucleated cells, the cardiomyocytes. They contribute to the bulk of heart mass (90%; Reiss et al. 1996), despite their nuclei only accounting for 15% of the cells that are in the heart (Soonpaa et al. 1996). Cardiomyocytes display a rod-like shape and make up heart tissue similar to bricks making up a wall (Fig. 1a). In the healthy adult heart, they are characterised by an extremely fine-tuned cytoarchitecture, with cell-cell contacts (called the intercalated discs) only being present at the bipolar ends and the cells being ensheathed laterally by extracellular matrix (Fig. 1b). This effectively creates a kind of insulated cable made up of strands of end-to-end connected cardiomyocytes and is crucial for co-ordinated contraction. Any interference with this organisation will contribute to arrhythmias, which are for example often observed in conditions of fibrotic remodelling of the myocardium or when stem cells are used to try to replace damaged heart tissue following a myocardial infarction (Chong et al. 2014). The cardiomyocytes themselves are filled with the contractile proteins actin and myosin, which are arranged in a paracrystalline fashion to the myofibrils. The basic unit of a myofibril is called a sarcomere (Fig. 1c), which is defined as the region between two neighbouring Z-discs, into which the thin filaments (composed of actin and its regulatory proteins tropomyosin and the troponins) are inserted (for review, see Pluess and Ehler 2015). The thick filaments, composed of bipolar arrangements of myosin (heavy and light chains) and myosin binding protein-C are situated in the A-band and anchored to the elastic filament system, which is composed of titin, in a structure in the middle of the sarcomere, which is called the M-band (for review, see Agarkova and Ehler 2015).

Based on morphological and histological criteria, five major types of cardiomyopathy can be defined, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic (right ventricular) cardiomyopathy (ARVC/ACM) and left ventricular noncompaction (LVNC) cardiomyopathy (for schematic illustration see Fig. 2). DCM is usually characterised as a ballooning heart, i.e. the diametre of the left ventricle is increased and the ventricular walls tend to be thinner. Systolic function is normally compromised. At the level of the electron microscope, the tissue of dilated cardiomyopathy patients does not look much different to healthy controls apart from regions of necrosis and fibrosis, and the majority of alterations are seen at

This article is part of a Special Issue on 'Heart Failure Due to Non-Myofibrillar Defects' edited by Elisabeth Ehler and Katja Gehmlich.

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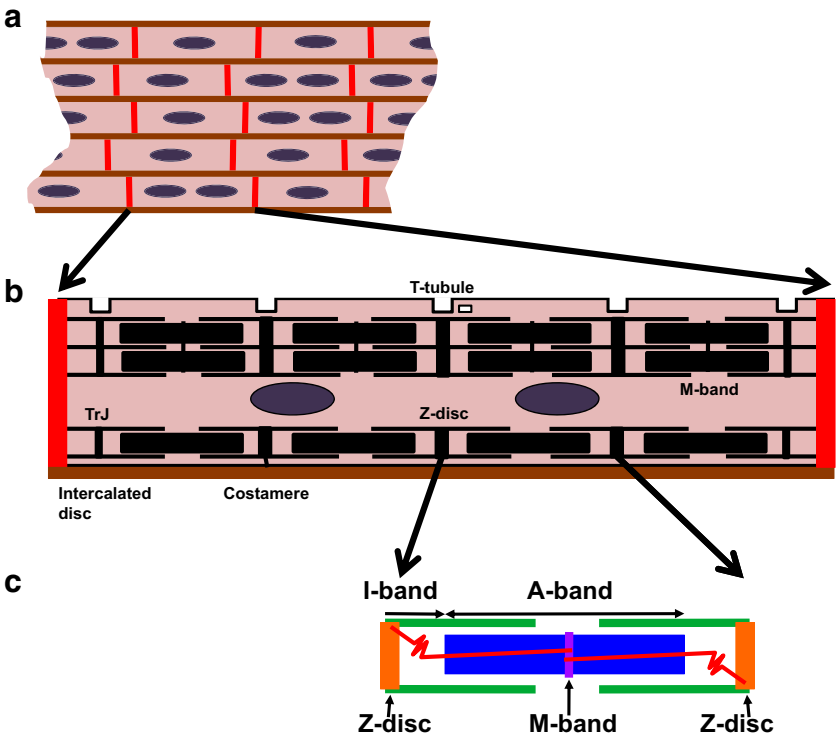

Fig. 1 Schematic illustration of heart tissue, a single cardiomyocyte and the sarcomere, the basic unit of a myofibril. **a** Schematic view of longitudinally sectioned heart tissue (non-muscle cells, such as fibroblasts and endothelial and smooth muscle cells making up blood vessels are not shown). In the murine and human heart the tissue is made up of mono- and binucleated cardiomyocytes; cells are depicted in pink, nuclei in purple, the specialised cell-cell contacts, the intercalated discs are shown in red and the lateral extracellular matrix between the strands of cardiomyocytes is coloured brown. **b** A simplified scheme of a rod-shaped cardiomyocyte. Myofibrils (not at real scale) are shown in black, intercalated disc in red, nuclei in purple, extracellular matrix in brown. Mitochondria (30% of cell volume) are not depicted. TrJ stands for transitional junction, a kind of "Z-disc light" that links the last sarcomere to the intercalated disc. **c** A scheme of a sarcomere, the basic unit of a myofibril. It stretches between two Z-discs (shown in orange; marker protein is sarcomeric alpha-actinin), which mark the tranverse borders, in the middle is another transverse structure, the M-band (shown in purple, marker protein is myomesin). The elastic filaments, composed of titin (in red), link the two transverse structures, with titin's N-terminus being anchored at the Z-discs, while its C-terminus sits in the M-band. The thin filaments (green; main components are actin, tropomyosin, troponin T, I and C) and thick filaments (blue; made up of myosin heavy chain, myosin light chain, myosin binding protein-C) interdigitate and are responsible for sarcomere shortening during contraction

the cellular level at the intercalated disc, the special type of cell-cell contact between cardiomyocytes (Perriard et al. 2003; Pluess et al. 2015). DCM can be caused by truncating mutations in *TTN*, the gene that encodes the elastic filament protein titin (Herman et al. 2012), but also by mutations in cytoskeletal and contractile proteins (Hershberger et al. 2013). HCM displays usually a thickening of the ventricular and septal walls and a reduced chamber volume. This can include obstruction of the outflow tract and diastolic dysfunction is often prominent. At the histological level, HCM is characterised by myocyte disarray (for review, see Seidman and Seidman 2001). For a long time, genetic forms of HCM were attributed solely to mutations in genes that encode for proteins of the sarcomere and, while it is still the case that missense mutations in *MYH7* (beta-myosin heavy chain) and mainly truncating mutations in *MYBPC3* (cardiac myosin binding protein-C) account for the majority of hereditary HCM, a mutation on *CSRP3* (encoding Muscle LIM Protein, MLP) was among the first of an expanding list of non-sarcomeric proteins to become associated with HCM (Geier et al. 2003). RCM is a heterogeneous disorder that can have similarities to HCM (also by affecting mainly proteins involved in contraction), but usually shows an increased stiffness of the left ventricular wall accompanied by impaired diastolic function (Kushwaha et al. 1997). ARVC classically predominantly affects the right ventricle and leads to thinner walls and replacement of cardiomyocytes by fibrous-fatty tissue, but can also only involve the left ventricle (Marcus et al. 2010). It is often characterised by systolic dysfunction, especially of the right ventricle, and arrhythmias are common. ARVC/ACM has been christened the "disease of the desmosome", since the majority of mutations are found in genes that encode for desmosomal proteins that make up a type of cell-cell contact that is crucial for structural integrity of cardiac tissue (see article by Vimalanathan et al. in this issue). Together, HCM and ARVC/ACM are the leading cause of sudden cardiac death in young

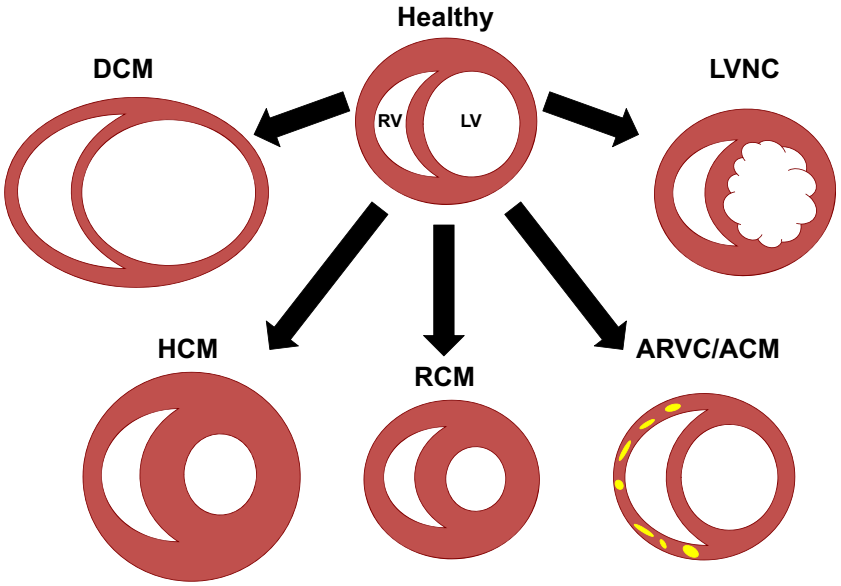

Fig. 2 Schematic illustration of different types of cardiomyopathy. A cross-section through the ventricles is shown. Dilated cardiomyopathy (DCM) is characterised by increased ventricular diameter and thinning of the wall, while hypertrophic cardiomyopathy (HCM) shows thickened ventricular and septal walls and reduced left ventricular chamber volume, a feature it shares with restrictive cardiomyopathy (RCM). Arrhythmogenic (right ventricular) cardiomyopathy (ARVC/ACM) can have fibrofatty areas in the RV (shown in yellow), while left ventricular noncompaction cardiomyopathy (LVNC) is characterised by persisting trabeculation and a failure to form compact myocardium. LV left ventricle

athletes, which makes the identification of carriers of a disease-causing mutation a priority (Basso et al. 1999). LVNC is characterised by a failure to form compact myocardium during development, and thus, persistent trabeculation, with or without impairment of cardiac (systolic) function. Recently, it was shown that LVNC can also be caused by a mutation in titin (A178D; Hastings et al. 2016), which will not be discussed in this issue, since the giant muscle proteins titin and obscurin were the theme of a previous Special Issue of Biophysical Reviews (Titin and its binding proteins in striated muscles. Biophys Rev. Volume 9, Issue 3; Pages 177–267; 2017).

Unsurprisingly, with myofibrils making up the bulk of a cardiomyocyte, this Special Issue is not going to be as strictly non-myofibrillar as its title would suggest and sarcomeric proteins will feature in some of the articles as well (Fig. 3). In addition to the myofibrils, which perform the contractile function per se, the "toolkit" that allows a cardiomyocyte to function are molecules involved in excitation-contraction coupling, such as L-type calcium channels and the ryanodine receptor, RyR (the latter reviewed by Laver in this issue), which are crucial to transfer the contractile stimulus from the plasma membrane into the cell to lead to calcium release from the sarcoplasmic reticulum. Calcium is not the only ion that is relevant to the cardiac contraction cycle, and the article by Rahm and colleagues in this issue will cover other ion channels, such as the sodium and potassium channels. Intercellular communication between cardiomyocytes happens at the intercalated disc via gap junctions that serve for ion and small molecule exchange. Structural aspects of the intercalated disc will be discussed by Bennett, while the article by Manring et al. will focus more on signalling that emanates from the intercalated disc. Signalling also originates from the sarcomeres and the proteins FHL1 and FHL2, which are the focus of the article by Liang et al., are sarcomere-associated molecules (I-band and M-band) that were shown to play distinct roles in cardiomyopathy. In a terminally differentiated cell, protein turnover mechanisms are obviously crucial and Anderson-Fabry disease, which is characterised by lysosomal dysfunction, is discussed in the article by Akhtar and Elliot. The intercalated disc is the anchorage point for the intermediate filament protein desmin, which when mutated can lead to ARVC/ACM (as described by Brodehl et al.). In addition to desmin there is another type of intermediate filament proteins, the lamins, which make up the nuclear lamina, and their contribution to cardiomyopathy are reviewed by Tsikitis et al. Other proteins that are situated in the nuclear envelope and provide a mechanical link from the nucleo- to the cytoskeleton are covered by Stroud in his article. The advancement of next-generation sequencing has been a blessing and a curse; while it is now much faster to sequence a genome, it can be extremely challenging to identify disease-causing mutations in the haystack of abundant but benign genetic variation. These pitfalls and online strategies to deal with them are reviewed by Adriaens and Bezzina in this issue. Cardiomyopathies are often accompanied by changes in gene expression, with a switch back to a more embryonic phenotype, and Beqqali discusses how this is achieved at the level of alternative splicing. Finally, the contribution of the actin cytoskeleton that is not directly involved in contraction will be reviewed by Ehler.

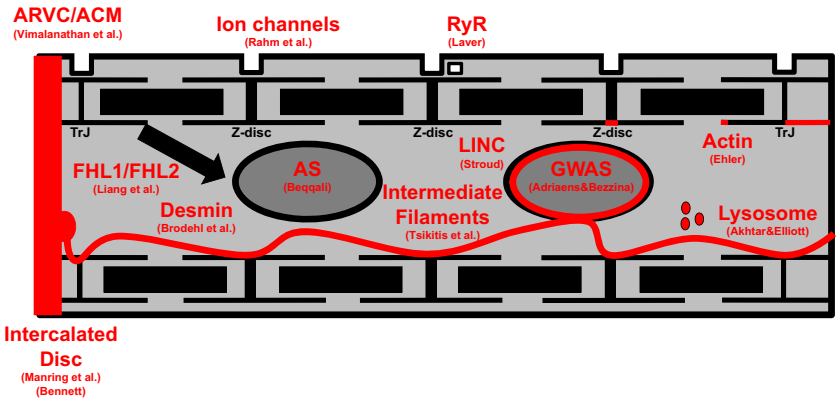

Fig. 3 Schematic illustration of a single cardiomyocyte. At the bipolar ends are the intercalated discs, the specialised types of cell-cell contacts in the heart. Two myofibrils and two nuclei are shown as well. The approximate subcellular localisation of proteins, cellular structures and mechanistic concepts discussed in the articles that are published in this Special Issue are depicted in red in the cell together with information on the authors. ARVC, arrhythmogenetic right ventricular cardiomyopathy; TrJ, transitional junction; FHL, four and a half LIM domain protein; AS, alternative splicing; RyR, ryanodine receptor; LINC, linker of nucleoskeleton and cytoskeleton; GWAS, genome-wide association studies

The Sydney Heart Bank (SHB) has been a major provider of human heart tissue, particularly from the left ventricle. The Executive of the SHB has compiled a summary of the publications arising from experiments using human failing and non-failing tissue (see Letter to the Editor by dos Remedios et al. in this Special Issue). Of the 60 laboratories that have published data using tissue from the SHB, about a quarter of them employed tissue from the same failing and non-failing hearts. Their "perspective" is largely consistent with the comments in this editorial.

While we have attempted to cover a wide range of topics in this Special Issue, there are glaringly obvious gaps, such as mitochondria function that were not at all covered and that may become the focus of a future Special Issue. We are grateful to all the authors of this special issue for committing their valuable time to the writing of these enlightening reviews and hope they will provide a helpful link between cardiology and biophysics in understanding the complexity of cardiac pathogenic networks.

Compliance with ethical standards

Conflict of interest Katja Gehmlich declares that she has no conflicts of interest. Elisabeth Ehler declares that she has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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