Myocardial remodeling, an overview

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Myocardial remodeling (REM) is a deleterious process characterized by gradual cardiac enlargement, cardiac dysfunction and typical molecular changes. It is a universal phenomenon, being caused by many pathological conditions [1, 2].

Of these, myocardial infarction is the more common. It has been estimated that even with the timely use of primary angioplasty, and with the subsequent use of all the currently recommended drug therapies, which will be discussed later, the emergence of REM is around 30%, eventually leading to heart failure and death [3, 4]. It has been stressed that if 20% of the “myocardium at risk” is salvaged, the course toward heart failure can be avoided [5].

Moreover, uncontrolled hypertension is still a major cause of heart failure, evolving to REM. It must not be forgotten that valvular heart disease, even with the progress of cardiac surgery, can still lead to cardiac dilatation, effectively REM.

Only very recently it was stated that in mitral regurgitation, operation before the left ventricular end-systolic diameter exceeds 40 mm, survival is higher [6]. REM is also an end result of cardiomyopathy, either post-myocarditis or genetically produced, and cancer chemotherapy [7].

The term was first introduced by Janice Pfeffer’s group in 1985 [8].

A comprehensive review was given 4 years ago by Opie et al. [9]. One part of the 1990 definition which they re-iterate is very important, i.e. it represents an important therapeutic target. REM must be viewed as a process that is initially “adaptive”; aiming at offsetting an unfavorable situation. Thus, in aortic stenosis and hypertension, the ensuing left ventricular concentric hypertrophy results in reduced myocardial wall stress; conversely, in the course, in mitral and aortic regurgitation, left ventricular eccentric hypertrophy concerns stroke volume conservation. Thus, hypertrophy finally leads to ventricular dilatation and becomes “maladaptive” and detrimental [10].

However, it is not only the myocardium that undergoes pathological changes. It is currently widely recognized that two more elements contribute to REM and cardiac malfunction:

- The development of myocardial fibrosis, resulting from increased abnormal collagen production. Fibrosis results in systolic but also diastolic dysfunction through increased cardiac stiffness [11].
- The inadequate increase in capillary density of the hypertrophying and remodeling myocardium that results in inadequate oxygenation [12]. Indeed, even after an acute myocardial infarction, capillary density is decreased as REM ensues [13]

As already mentioned, a main characteristic of the remodeling myocardium is the return to the “fetal” phenotype, which is characterized by decreased contractility but also lower energy consumption [14]. Also, the ratio HMC α/β is decreased, ANP and BNP and α -actin over-expressed, and the SERCA/phospholamban activity decreased.

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The eminent research group of Taegtmeyer et al. stresses the increase point that the fetal myocardium is more resistant against necrosis [15]. A parallel paradigm is myocardial hibernation, in which diminished performance is offset by persistence of viability [16].

However, the fetal myocardium as an evolutionary model is dysfunctional.

Baker et al. have shown that immature hearts cannot be preconditioned [17].

Moreover, Krenz and Robbins, in a model to transgenic mice overexpressing β -MHC, have shown a more unfavorable post-infarct course [18]. Proteomic [19] and genomic [20] analyses have been recently carried out. Very recently, MiR423-5p has been described as involved in heart failure [21], while MiR 133 α is protective against cardiac fibrosis [22]. The number of serum markers that also reflect myocardial concentrations is rapidly increasing. Galectin-3 is acquiring prominence as a marker of fibrosis and heart failure progression [23].

ST-2 has recently been considered as a specific marker of REM [24]. Myostatin is also a marker of hypertrophy [25] and heart failure [26].

As already stated, continuous efforts are aimed at the prevention and regression of REM. These efforts are either invasive or pharmacological [27, 28].

However, the main thrust is the combination of the two approaches of which Table 1 gives only an approximation.

It is not surprising that many journals are devoting whole issues to REM [1].

In this issue of “Heart Failure Reviews”, we attempt a necessarily incomplete account of molecular aspects of REM, with frequent references to therapeutic approaches. Nabeebaccus, Zhang and Shah from King’s College in London provide an account of the NADPH oxidases in REM. These oxidases are significant sources of ROS and particularly important in redox signaling. The two main isoforms in the expressed in the heart are NOX2 and NOX4. The authors point that some of the main families in the treatment of heart failure such as ACE inhibitors are ARBs and statins, which act through NOX2 inhibition. Additionally, they reply that the modulation of NOX activity may lead to new therapeutic targets.

Gajarsa and Kloner from the Harbor-UCLA Medical Center in Torrance and the University of Southern California, Los Angeles, California examine the neuro-hormonal activity of the renin-angiotensin-aldosterone axis and its molecular effects on the myocardium.

They point out the importance of the extracellular matrix and the matrix metalloproteinases (MMPs) and their tissue inhibitor counterparts. The many transcription factors regulating MMP activity are discussed. Trials involving selective and broad MMP inhibitors or TIMP activators are discussed.

Table 1 Approaches to prevention and regression of remodeling

(A) Pharmacological

(1) During ischemia reperfusion

Adenosine, nicorandil, ANP, statins, cyclosporin
Post-conditioning opioids

(2) Long term

(a) Proposed through animal data

Valproic acid (HDAC inhibitor)

(b) Metabolic modulators

Exenatide, insulin

Mimetic

Tropic

Etomoxir, trimetazidine, ranolazine

MAPK activators- AICAR (exercise mimetic?)

PPAR activators

Metformin

Clenbuterol (β 2 receptor agonist)

Tetracyclines ($\uparrow$ SERCA)

(c) Hormones—peptides

Thyroid hormones

Growth hormone

Estradiol

Testosterone

(d) Antioxidants—quercetin, resveratrol, curcumin

Erythropoietin

Atrial and brain natriuretic peptide Neseritide

(e) Miscellaneous

Sildenafil

Rapamycin (mTor inhibitor)

Interleukin receptor antagonists (anakinra)

(f) Clinically used

β -blockers, ACE inhibitors-angiotensin receptor blockers, aliskiren, statins, aldosterone inhibitors

(B) Interventional—surgical—electrophysiological

Exercise

Progenitor cell infusion

Cardiac shock wave therapy

Biventricular pacing (cardiac resynchronization)

Early reperfusion (thrombolysis, primary angioplasty)

Left ventricular reconstruction surgery

Left ventricular assist devices

Cell-based therapy and mechanical assist devices and their molecular effects are described.

The aspects of myocardial necrosis and replacement fibrosis are discussed by Gandhi et al. from Weber’s team from the University of Tennessee in Memphis. The authors stress that replacement fibrosis appears at areas of previous necrosis. It initially plays the role of preserving the structural integrity of the myocardium, but it subsequently has adverse

functional consequences contributing to progressive heart failure. Intracellular Ca^{2+} overloading and induction of oxidative—predominantly mitochondrial—stress are involved in cardiomyocyte necrosis.

Pro-oxidant Ca^{2+} overloading is counterbalanced by a intrinsically coupled Zn^{2+} entry, which acts as an antioxidant. A simple cardioprotective strategy might involve adjuvant nutraceuticals. Hyposelenemia and its association with dilated cardiomyopathy is also discussed.

The role of STAT3 that is involved in cardiomyocyte protection and hypertrophy are discussed by Haghighi, Stapel, Hoch and Hilfiker-Kleiner from the Medical School of Hannover. This protein also impacts on the vasculature and extracellular matrix through paracrine pathways.

Additionally, it is also a mitochondrial protein involved in energy protection. STAT3 is activated by many factors, i.e. cytokine growth factors, neurohormones, mechanical load and ischemia. They point out possible therapeutic targets and the need of satisfactory control, since persistent activation of STAT3 in other organs may produce malignant de-differentiation and tumor growth, but can also be involved in vascular remodeling and arterial neointimal hyperplasia—another aspect of the yin and yang concept [29].

The role of the innate immune system is amply covered in two articles.

Petra Kleinbongard, Schulz and Heusch from the University Clinic of Essen discuss the role of TNF α in myocardial ischemia/reperfusion, remodeling and heart failure. This cachexin is part of the response to different forms of stress. Myocardial TNF α and its receptor activation have an ambivalent role:

Excessive TNF α expression and receptor type 1 activation induce contractile dysfunction, hypertrophy, fibrosis and cell death, while lower concentration and stimulation are protective.

The conflicting results of TNF α antagonist trials with etanercept and infliximab are discussed. Potential explanations are given. They stress that a selective suppression of TNFR 1 activation or a selective activation of TNFR2 may give better results.

Another aspect of innate immunity and its effect on REM is provided by Guro Valen from the University of Oslo. She points out that innate immunity is expressed in the injured heart as cytokine release from the heart, activation of toll-like receptors and the transcription factor nuclear factor Kappa B. However, although activation immunity is actually detrimental in acute inflammation, the long-term outcomes in *in vivo* models of hypertrophy and REM are less clear. Activation of innate immunity may provide a beneficial process counteracting the vicious cycle of heart failure development. Thus, TLR signaling may reduce hypertrophic response and cardiac fibrosis, while

TLR2-deficient mice had less REM after an experimental myocardial infarction.

Finally Pantos, Mourouzis and Cokkinos from the University and Biomedical Research Foundation of the Academy of Athens describe the role of thyroid hormones (TH) in REM. They point out that an experimental myocardial infarction or pressure overload decrease TH signaling and activate the fetal gene program in the heart. TH administration limits reperfusion injury and prevents or induces regression of REM by favorably affecting cardiac chamber geometry in a time-dependent manner and may convert pathological to physiological hypertrophy. They re-iterate the fact that although earlier and small clinical studies have provided favorable results, the efficiency of TH in large clinical trials in the treatment of REM and heart failure still await evaluation.

The above cited articles do not pretend to cover the whole range of REM. A larger publication in the form of a book might be logically perspective. However, all the contributions in this issue of “Heart Failure Reviews” are provided by groups long immersed in their respective fields of expertise. They provide an up to date and hopefully detailed view of this fascinating and clinically very important aspect.

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