Update review

Recent advances in cardiac hypertrophy

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1. Introduction

In 1977 Sen, Tarazi and Bumpus in a brief article in *Cardiovascular Research* discussed the variable effects obtained with anti-hypertensive therapy on cardiac hypertrophy and its regression [1]. Having the aim of intervening with medical treatment on cardiac hypertrophy the authors attained results quite different from the expected one. Although this event is very common in research the authors were able to take advantage from the discrepancy suggesting new hypotheses, possible explanations and innovating conclusions. They found that in spontaneous hypertensive rats (SHR), an animal model that mimics essential hypertension in humans, the vasodilator \( \alpha \)-methyldopa was able to reduce blood pressure, renin activity and reverse cardiac hypertrophy, whereas minoxidil another vasodilator reduced blood pressure, increased heart weight and renin activity. Finally, beta blockade not affecting blood pressure, reduced cardiac mass and renin activity. These results highlighted the uncertainty in the relation between cardiac hypertrophy, arterial blood pressure levels and renin, implying that blood pressure 'may not be the sole factor for the development and reversal of cardiac hypertrophy'. Today, more than 20 years after the publication of this article there is evidence that these ideas are of relevance and extremely important to understanding the mechanisms involved in the development and progression of cardiac hypertrophy. This is also demonstrated by the large number of quotations of this article in the following years.

In this review the results obtained in human and some animal models of cardiac hypertrophy will be summarized in the attempt to illustrate the complexity of the phenomena implicated in the hypertrophy of the heart and the evolution of the process toward dysfunction and failure. Furthermore, some new attempts to modify the consequence of myocardial hypertrophy or to prevent myocyte cell loss will be also examined to document the difficulties that we are still facing more than 20 years after the pioneer study of Sen et al. [1]. A complete review of the argument, however, is beyond the aim of this article.

2. Definition

Since cardiac hypertrophy is a condition in which myocardial mass is increased beyond the normal range, the establishment of normal and abnormal limits is needed in order to define the presence and the degree of this disease. Anatomical studies (Figs. 1 and 2) have demonstrated that the upper limit of a normal heart is 450 g in men and 400 g in women [2]. These values, however, must be corrected for epicardial fat, body mass and age [2]. In both genders, left ventricular myocardial weight to body height ratio

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normally does not exceed 36 g/m². These values are in agreement with a cut-off limit of 50 g/m² used to separate normal from hypertrophied hearts by echocardiography [3].

Different causes may produce cardiac hypertrophy but in general, it occurs in response to an overload. When the working load increases, myocytes enlarge (Fig. 3) until the stress per cell returns to normal. However, myocyte lengthening with addition of new sarcomeres in series is the prevailing mechanism following volume overloads, i.e. eccentric hypertrophy, in which ventricular chamber dilatation is accompanied by a proportional increase in wall thickness. Lateral expansion of myocytes with the addition of new sarcomeres in parallel represents the typical pattern of myocyte growth following pressure overload, i.e. concentric hypertrophy, in which wall thickness increases with minor chamber enlargement [4]. Reactive compensatory hypertrophy after myocyte cell loss, i.e. in non-infarcted portion of the heart following an acute myocardial infarction [5], is characterized by different degrees of myocyte lengthening and widening [6]. Early on, after the imposition of the stimulus, a well balanced response occurs and the hypertrophied heart is characterized by a constant wall thickness-to-chamber radius or myocardial mass-to-chamber volume ratio. These patterns of growth may vary with type, magnitude and duration of the inciting stimulus, sex, age, diet, hormonal and environmental influences and concomitant diseases. Furthermore, in patients with genetic cardiomyopathies, myocardial hypertrophy develops without external stimuli [7].

The hypertrophic growth of the heart, when challenged by increased work demand, has commonly considered a useful mechanism to preserve myocardial function. However, epidemiological studies have demonstrated that cardiac hypertrophy and left ventricular hypertrophy in particular, represents a powerful blood pressure-independent risk factor for cardiovascular morbidity and mortality [8], is associated with an increased frequency of ventricular arrhythmias in the absence of coronary artery disease [9] and has a negative impact on survival more in females than in males [10]. These results are consistent with anatomical studies demonstrating that chamber enlargement and ventricular thinning are present in concomitance with impairment in ventricular function in decompensated ventricular hypertrophy [11,12]. The terminal phase of this process is the end-stage cardiac failure which still represents nowadays, a very common cardiac disorder with an unfavorable outcome [13,14]. Thus, cardiac hypertrophy per se cannot be considered a physiological process and seems to contain maladaptive changes which affect the short and long-term prognosis. Irrespective of mechanisms and loading conditions, the evolution of cardiac hypertrophy to ventricular dysfunction is an irreversible on-going process dependent upon several factors, among them the duration of the overload appears to be one of the more significant parameters. Additionally, several studies have suggested that loss of contractile cells, the consequent amount of reparative tissue, and the extent of growth of the remaining cardiomyocytes are major components for the remodeling of the hypertrophied heart and for the transition from a well compensated myocardial growth to a decompensated heart. Thus, any attempt to attenuate myocyte growth is justified and should be performed before the occurrence of myocyte cell loss with the hope to maintain heart dimensions within a normal range.

3. Cardiac hypertrophy and aging

Quantitative studies have demonstrated that the aging process of the heart in animals and humans is characterized by a significant loss of myocytes and reactive hypertrophy
of the remaining viable cells [2,15]. Furthermore, gender differences exist in the remodeling of the heart with age. Myocardial weight remained essentially constant in women and decreased with time in men [2]. In women, the number of mononucleated and binucleated myocytes in the left and right ventricles is constant from 20 to 95 years of age. In contrast, the heart of a 20-year-old man contains approximately $5.8 \times 10^9$ myocytes in the left ventricle and $2 \times 10^9$ in the right ventricle and the same man at 70 years is expected to have $3.6 \times 10^9$ and $1 \times 10^9$ myocytes in the left and right ventricle, respectively. These changes are the consequence of a 38% and 50% drop out of myocytes in the left and right ventricles during a 50-year interval. Myocyte cell loss is coupled with a progressive increase in volume of the remaining still viable cells but this reactive growth is unable to maintain a constant heart weight with aging [2]. The different response of the heart with aging in men and women is difficult to understand, but seems to be independent from hormonal changes. In any case, women are less frequently affected by cardiovascular events and have a greater capacity to sustain an hemodynamic overload with age [16–18]. Interestingly, gender-dependent differences in left ventricular mass and function with aging have been found in rat hearts [19] and early and late responses of the heart to a pressure overload are distinctively better in female than in male rats [20].

Although the mechanism responsible for myocyte cell death with aging has not been identified yet, defects in coronary vasculature may lead to ischemic myocytolytic necrosis [21]. Recently, programmed cell death has been detected in adult myocytes of humans and animals and this condition may be considered to be part of the aging process of the heart [22,23]. Apoptosis, a term often used as a synonymous for programmed cell death, is characterized by the activation of an endogenous endonuclease that results in a regular pattern of DNA degradation in oligonucleosomes. This characteristic type of DNA cleavage can be demonstrated morphologically by the terminal deoxynucleotidyl transferase (TdT) assay (Fig. 4) and biochemically by agarose gel electrophoresis. Monoclonal antibody to cardiac myosin injected in vivo, was also used to detect and measure necrotic myocyte cell death in the myocardium [24]. The antibody can reach the intracellular antigen only in the presence of irreversible damage of the sarcomembran in necrotic myocytes.

These methods have been used to measure the different contribution of necrotic and apoptotic myocyte cell death with aging in Fischer 344 rats [23]. Myocyte necrosis involved 1300 myocytes in the left ventricle and septum combined at 3 months of age reaching a value of 23 000 at 24 months. In the right ventricle there were 270 necrotic myocytes at 3 months and 9000 at 24 months. Apoptotic myocyte cell death was restricted to the left ventricle and included 140 cells at 3 months and 874 myocytes at 24 months. These morphological changes were associated with a progressive decrease in ventricular function, resulting in overt left ventricular failure and right ventricular dysfunction at the latest interval examined [25]. It should be noted that in the Fischer 344 animal model, myocardial injury, in the form of multiple foci of replacement fibrosis, increases in the ventricle as a function of age and myocyte hypertrophy and proliferation occur in response to myocyte cell death [15,25]. These alterations, together with mural thinning, chamber dilatation and elevated transmural circumferential stress, contribute substantially to the development of decompensated ventricular hypertrophy seen in the senescent rat heart.

In summary, the aging heart is characterized by progressive loss of myocytes by apoptosis and necrosis, hypertrophy of the remaining myocytes and extensive reparative processes. All these structural changes can contribute to limit the capacity of the aged heart to sustain an increased workload. The female heart, however, seems to be protected from these events. These observations confirm the original statement of Sen et al. [1] that the hypertrophy of the heart may be independent from the load and underscore the possibility that the hypertrophic growth may be present exclusively at the cellular level independently from the changes visible at the organ level.

### 4. Induced cardiac hypertrophy

In the early stages of pressure overload induced cardiac hypertrophy or in SHR, no significant structural changes or myocardial damage were detectable, despite significant growth of the contractile component [26,27]. However, shortly after an abrupt increase in afterload by ascending aortic banding, myocyte cell loss by apoptosis was detected [28]. A long-term (5–6 months) slowly developing pressure overload imposed on the right ventricle disclosed myocyte hypertrophy and hyperplasia, capillary prolifer-
ation and an increased number of mastcells within the tissue [29–31]. In contrast, long-term one-kidney-one-clip renal hypertension is characterized by elevation in left ventricular end-diastolic pressure, ventricular chamber dilatation, thinning of the wall, extensive myocardial damage in the form of scattered areas of replacement fibrosis and myocyte hypertrophy and hyperplasia [32,33]. Similarly, myocardial structure in old SHR is modified by the presence of large areas of replacement fibrosis across the left ventricular wall [34]. In old SHR these anatomical and structural findings are associated with several indexes of congestive heart failure [35] and an increased propensity to arrhythmogenesis [34]. The alterations described above may be carefully considered in the interpretation of the effects of the pharmacological treatment of animals and humans with hypertrophied hearts [1]. In fact, lack of changes in the entire heart may differ from the alterations found at tissue and cellular level.

The risk to develop congestive heart failure in humans with hypertension and cardiac hypertrophy is elevated [36]. However, there is no definite answer to explain this ominous outcome. It is well known that coronary vascular growth is limited in animals and humans with pressure-induced cardiac hypertrophy [37,38] and severe ischemia resulting in myocardial infarction is present in half the patients with hypertension [36]. These observations appear to support the concept that hypertrophied myocytes are more prone to ischemia than normal cells. However, other factors may be operative. Myocardial remodeling in severe cardiac hypertrophy in humans differs in relations to cardiac failure and age [39,40]. Myocyte cellular hypertrophy is responsible for ventricular hypertrophy in hypertensive cardiomyopathy of middle age individuals in its compensated stage despite a significant loss of myocytes [39]. In contrast, cardiac hypertrophy of the aged and senescent human heart in failure is characterized by an increased number of myocytes, dilatation of the ventricular cavity and thinning of the wall [40].

Hearts from patients in end-stage cardiac failure undergoing cardiac transplantation, demonstrated extreme degrees of cardiac hypertrophy [41–43]. In ischemic [42] and dilated cardiomyopathies [43] a 2-fold increase in myocardial mass is associated with more than 4-fold increase in ventricular chamber volume, resulting in a significant reduction of muscle mass-to-chamber volume ratio. According to the law of Laplace, the circumferential diastolic stress per myocyte may be increased to unaffordable levels inducing myocyte cell death and explaining the irreversibility of this pathology. Recently, in these end-stage failing hearts, myocyte apoptosis was documented and found in an average of 2318 myocyte nuclei per million, a value 232-fold higher than controls [22]. These results were coupled with alterations in the expression of members of the Bcl-2 family of proteins: specifically, the level of Bcl-2, that promotes cell survival, increased in cardiomyopathies, whereas Bax, which induces apoptosis, remained unchanged. Additionally, in ischemic cardiomyopathies an average 28% and 13% collagen accumulation (Fig. 5) was found in the left and right ventricular myocardium, respectively [44] and in dilated cardiomyopathies myocardial scarring represented almost 20% of ventricular myocardium [43]. This degree of fibrotic tissue, indicative of a large amount of myocyte cell loss, may explain the limited possibility to improve cardiac function in these hearts.

However, compelling evidence from the results obtained with the use of left ventricular mechanical supporting devices in patients with end-stage cardiac failure reinforced the concept that prolonged left ventricular unloading may improve ventricular and myocyte function and reverse ventricular dilatation [44]. Although the recovery after the implantation of these devices is low, these data together with those obtained with partial left ventriculotomy recently used to treat patients with intractable dilated cardiomyopathy in failure [45] confirm the early mechanistic hypothesis that the stress per se is deleterious for myocytes.

In experimental models a measurement of the amount of stress generated by ventricular dysfunction has been obtained. In rats, acute and healed myocardial infarction affecting 60% or more of the left ventricular free wall, by combining functional and anatomical data the amount of diastolic circumferential stress per myocyte layer within the wall has been determined [46,47]. In these conditions wall stress increased more than 7-fold acutely and, after 1 month, was almost 8-fold higher than in sham-operated animals. Furthermore, ventricular dilatation was associated with thinning of the wall brought about through lengthening of myocytes and transmural side-to-side slippage of myofibers. Single or multiple myocyte cell death has been postulated to occur in order to permit the translocation of myocyte bundles from the inner to the outer layer of the myocardium. Thrichrome staining. Bar indicates 1.4 mm in length.
This hypothesis has been verified in the papillary muscle in vitro in which overstretching is associated with mechanical and oxidant stress, impairment in force development, programmed myocyte cell death with architectural rearrangement and overexpression of Fas protein within the myocytes [48]. Experiments in dogs with tachycardia induced cardiac failure [49], in rats with aortic banding [28] and several observations in humans [50–53] provided supportive evidences that apoptosis may be induced in the myocardium exposed to abnormal stress. Finally, apoptotic myocyte cell death has been found to be increased in aged SHR and its amount is decreased by ACE treatment. These results demonstrated again that myocyte cell loss is an important determinant in the transition from compensated to decompensated cardiac hypertrophy [54].

Although the signals that transduce the stimulus generated by the physical forces from the sarcolemma to the nucleus and activate the genes responsible for apoptosis are still unclear, recent observations suggest that myocyte cell death may be induced by substances that are activated in animal models of cardiac hypertrophy [55] and in humans with heart failure [56]. Angiotensin II (Ang II) was found to be able to increase the amount of apoptotic cell death when added to enzymatically dissociated ventricular myocytes from neonatal and adult rat hearts [57,58]. The mechanism by which the Ang II binding to AT receptor induces DNA strand breaks appears to be related to the increase of intracellular calcium, which in turn activates a calcium-dependent endogenous endonuclease. This apoptotic effect was drastically reduced by the addition of AT, receptor antagonist or chelating intracellular calcium [57]. In addition, in adult myocytes Ang II increases intracellular calcium through a protein kinase C mediated pathway [58]. Similarly, stimulation of beta adrenergic receptor with norepinephrine or isoproterenol induces apoptotic myocyte cell death in adult myocytes in vitro [59]. This result is blocked by agents that inhibit beta-adrenergic receptors, protein kinase A and L-type calcium channels [59]. Furthermore, 24-h infusion of isoproterenol in rats resulted in a significant number of apoptotic cardiomyocytes [60]. Atrial natriuretic peptide, cytokines such as interleukin 1β, TNF-α and interferon γ and nitric oxide are additional inducers of myocyte apoptosis [61,62].

It should be noted that some of the apoptotic agents described above act as growth factors for neonatal and adult cardiomyocytes. In an attempt to explain these contrasting data it has been suggested that in response to beta-adrenergic stimulation apoptotic signals prevail in adult cells and an anti-apoptotic/growing effect is apparent in neonatal myocytes [59]. Several studies have demonstrated that Ang II is a growth factor for myocytes via AT, receptor, despite the apoptotic action [63–65]. In addition, growth hormone is able to stimulate myocyte cell growth [66], but acromegalic cardiomyopathic hearts manifest quite a large number of apoptotic myocyte cell death [67].

The assumption that a variety of mechanisms, other than hemodynamic, are responsible for myocardial growth [1] is corroborated by numerous animal transgenic models of cardiac hypertrophy, overexpressing factors like calmodulin [68], beta 1 adrenergic receptor [69], p21ras [70], alpha cardiac myosin heavy chain [71], CREB [72] and many others [73] that may influence myocardial growth without changes in load. At the same time in animals overexpressing a variety of factors such as MLP [74], Galfaq [75], tumor necrosis factor-α [76] or deprived of different molecules such as Myo D [77] or ANP receptors [78], cardiac hypertrophy is associated with the development of cardiac failure. The extent at which a single gene defect may simulate human cardiac hypertrophy, however, remains to be determined.

It is of interest to note that the human heart may increase 2- to 3-fold in size under pathologic conditions (Figs. 1 and 2) and myocytes hyperplasia must occur since myocyte hypertrophy alone cannot account for such ventricular enlargement [11]. Other studies have reached similar conclusions [79–81]. In this regard, in dilated cardiomyopathic human hearts, despite the significant amount of connective tissue accumulation, the average myocyte number was not reduced [43], implying that myocyte hyperplasia must have occurred. Furthermore, mitotic figures have been found in cardiac myocytes of humans with end-stage cardiac failure [82], in pacing induced cardiac failure in dogs [49] and in rat hearts after myocardial infarction [83]. More recently, in hypertrophied hearts above 500 g in weight, an increased number of mononucleated myocytes have been measured [84]. Additional examples of myocyte hyperplasia have been found in hearts with an increased number of mononucleated myocytes have been measured [84]. Additional examples of myocyte hyperplasia have been found in humans and animals and different growth factors appear to be able to stimulate myocyte hyperplasia in vivo and in vitro [85–91]. In this regard, the overexpression of IGF-1R in the heart of transgenic mice during the maturational growth resulted in myocardial hypertrophy associated with an increased number of myocytes [92]. Finally, the overexpression of cyclin D1, a key regulatory factor for DNA synthesis, in cardiomyocytes of transgenic mice [93,94] and in aortic constricted rats [95], during the development of left ventricular hypertrophy, revealed sustained myocytes DNA synthesis.

In conclusion, myocardial growth in response to moderate or stressful conditions may not be dependent on increased afterload [1] and is associated with myocyte cell death by apoptosis, necrosis or both. Myocyte cell loss may represent the cause of the progressive evolution of myocardial hypertrophy to ventricular failure. The reparative process, the increased stress produced by the dilatation of the ventricular chamber and the thinning of the wall are additional important factors limiting myocyte survival and compensatory growth by hypertrophy and/or hyperplasia.

Finally, it should be remembered that, although the efficacy demonstrated by different therapeutical treatments, only a few attempts were made to intervene directly on cardiac dysfunction. The addition of new myocytes to the
failing heart is now possible and may give new avenues to substitute myocyte cell lost [96,97]. The use of spontaneously and synchronously beating cells similar to fetal ventricular myocytes, derived from bone marrow stromal cells may be a more futuristic approach [98]. Increasing oxygen delivery to the stressed myocardium with vascular growth factor [99], or blocking hormonal and neurotransmitter receptors coupled to a common receptor interface [100], are additional ways to decrease myocyte stress and damage.

In summary, at the end of this century, comparing the pioneer study of Sen et al. in 1977 [1] with some of the results obtained in more recent years, it is apparent that we have accumulated information on basic physiology, mechanisms, genetic, pathologic and molecular events that characterize the hypertrophy of the heart in the early stages, during compensated and decompensated states and in the evolution to dysfunction and failure. At the same time, we now know that the role suggested for neurohumoral factors in cardiac hypertrophy [1] is a reality and we discovered molecules that may exert protective or damaging consequences on myocytes. However, we have only scratched the surface of the problem and patients with cardiovascular diseases are still exposed to severe prognosis. This is because we do not have complete answers to the fundamental question: why the hypertrophied heart fails? Nevertheless, at the beginning of the third millennium, we have new tools to address our research on how we can prevent, avoid or, at least, delay the progression of the hypertrophied overstressed heart to failure.

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References


[85] Rumyantsev PP, Kassem AM. Cumulative indices of DNA syn-
theses in different compartments of the working myocardium and conductive system of the rat heart muscle following extensive left ventricular infarction. Virchows Arch (B) 1976;20:329–342.


