

## MINIREVIEW

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# Pathophysiological Principles of the Relation Between Myocardial Hypertrophy of the Left Ventricle and Its Regression

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### Summary

Hypertrophy of the left heart ventricle as a consequence of a haemodynamic overload is a process of ambiguous biological value. Although hypertrophy allows to increase the performance of the ventricle without substantial elevation in wall tension, it represents a risk factor of cardiac morbidity and mortality. The regression of hypertrophy seems to be a rational outcome of this ambivalent situation. Not every reversal of hypertrophied muscle mass, however, can be unambiguously considered therapeutic success. The biological value of hypertrophy regression depends on the type of hypertrophy, on the level of deterioration of the heart by a long-lasting haemodynamic overload, as well as on the way in which the reversal of hypertrophy is achieved. Even in the case when functional characteristics are preserved or even improved compared to the hypertrophied heart, hypertrophy regression need not automatically mean a decrease of the cardiovascular risk induced by ventricular hypertrophy. Regression of hypertrophy may be even disadvantageous in those situations when reduction of hypertrophy and reduction of the haemodynamic overload proceed in a disproportional manner. Spontaneously developing regression of the hypertrophied left ventricle as demonstrated on the model of aortic insufficiency, is an explicitly pathological state, resulting in heart failure. Regression of myocardial hypertrophy should not be considered the primary therapeutic aim but rather a part of the management of haemodynamic overload of the heart. The main aim is to achieve optimal perfusion of the periphery, yet at the same time to provide such conditions which would prevent the working load of the heart to become a limiting factor of survival.

### Key words

Myocardial hypertrophy – Induced and spontaneous regression of hypertrophy

### Introduction

Hypertrophy of the left heart ventricle represents structural adaptation to a longlasting haemodynamic overload. The increased haemodynamic load is thus distributed over a greater number of myocardial mass units, which helps to maintain adequate perfusion of the peripheral tissues without a substantial increase in wall tension (Grossman 1980).

The nature of the hypertrophied tissue is usually altered as far as its biochemical, functional and ultrastructural characteristics are concerned when compared to the normal myocardium (Grossman *et al.*

1980). The increase of the muscle mass of the left ventricle resulting from hypertrophic growth is linked to an increased incidence of heart failure, myocardial infarction, sudden death and stroke (Messerli and Soria 1992, Devereux *et al.* 1993, Messerli and Ketelhut 1993). Despite its adaptive nature, myocardial hypertrophy may represent a limiting factor of adequate heart function and is thus considered as a risk factor of cardiac morbidity and mortality (Tarazi and Frohlich 1987, Weber *et al.* 1993, Devereux *et al.* 1993, Messerli and Ketelhut 1993, Phillips 1993). Reversal of

excessive myocardial mass seems to be the approach of choice in this ambivalent situation.

In order to put the therapeutic induction of hypertrophy regression on a rational theoretical basis, the nature of the special type of hypertrophy must be known. This justified demand is, however, not easy to match as there is no reliable parameter for assessing the nature of the hypertrophied myocardium. The causal relationship with a deficiency of cardiac mechanics fails to be unambiguously defined even for such a convenient and frequently emphasized indicator of myocardial function as contractility (Wikman-Coffelt *et al.* 1979). The decisive criterion of the biologically beneficial effect of hypertrophy and of potential regression of hypertrophy is the prolongation of survival and improvement of the quality of life in patients with changed myocardial mass in comparison to patients in whom hypertrophy or regression of hypertrophy did not occur under the same haemodynamic conditions.

It is primarily the variable nature of the hypertrophied myocardium itself that accounts for the uncertainty in interpreting the biological consequences of hypertrophied myocardial mass reversion. The interpretation is even more difficult because of the different ways by which regression of hypertrophy is achieved and because of the complexity of the relationships between the altered structure, function and metabolism of the heart which may arise during the regression.

## Problems connected with induction of hypertrophy regression

### *Induction of hypertensive hypertrophy regression*

As the hypertrophic growth is in most cases induced by a haemodynamic overload, it seems logical to suppose that a reduction of increased haemodynamic demands would lead to a reduction of hypertrophied myocardial mass (Frohlich 1987). The results achieved by removal of the haemodynamic overload are not unequivocally positive and warn against mechanistic simplification (Strauer 1985, Motz *et al.* 1991, Aronow 1992). When left ventricular hypertrophy results from hypertensive disease, regression of hypertrophy may be achieved by administration of ACE (angiotensin converting enzyme) inhibitors (Julien *et al.* 1990), alpha-methyldopa (Fouad *et al.* 1982), prazosin (Ram *et al.* 1989), clonidine (Strauer 1985), calcium antagonists (Gerstenblith and Schulman 1990, Schulman *et al.* 1990) and in some cases by administration of beta-blockers (Hansson 1991). Vasodilators and diuretics, however, did not significantly reduce the weight of the hypertrophied heart despite pronounced reduction of

arterial blood pressure (Strauer 1985, Julien *et al.* 1990).

It follows from the above given facts that induction of hypertrophy regression does not depend exclusively on the extent to which hypertension is reduced (Tarazi and Fouad 1985, Cody 1990). Diminution of the hypertrophied myocardial mass is also modulated by the stability of the reduced arterial pressure, by the cause and severity of hypertension, by the intensity of cardioadrenergic stimulation, by individual variability due to diverse genotypes, by different species-specific reactivity, by concomitant diseases of the heart, by age (Klaus 1985, Tarazi and Fouad 1985), and by the rate of end-systolic stress before onset of therapy (Sugishita *et al.* 1990). Regression is probably achieved only when sympathetic activity is reduced or when at least reflex sympathetic activity is not increased with afterload reduction, as the sympathetic system is considered to be one of the crucial factors participating in hypertrophy development (Klaus 1985, Zähringer 1985, Fujita *et al.* 1989).

The renin-angiotensin-aldosterone system, which is activated through hypoperfusion of the kidneys as a consequence of arterial pressure reduction, seems also to participate in the maintenance of left ventricular hypertrophy despite successful antihypertensive treatment (Smith *et al.* 1991). Hypertrophy which is originally concentric might also be preserved through the secondarily increased volume overload (Smith *et al.* 1991) or by the proteosynthetic influence of angiotensin II (Zähringer 1985).

### *Induction of hypertrophy regression during volume overload*

The fact that the reduction of increased working demands does not regularly result in reversal of hypertrophied mass is valid also in the case of volume overload (Frenzel 1985, Roman *et al.* 1989). Complete regression of hypertrophy is achieved reliably only by reduction of increased physical activity in the case of physiological hypertrophy of the "athletic heart" (Dickhuth *et al.* 1985). As a consequence of surgical correction of aortal insufficiency (Krayenbuehl *et al.* 1985, Roman *et al.* 1989) or of correction of the septal defect in children (Jarmakani *et al.* 1971), hypertrophy regression is achieved only in some patients who have been operated and even in these patients the regression is incomplete. Residual persistent hypertrophy could be the result of irreversible deterioration of cardiomyocytes by a long-lasting intensive haemodynamic overload. On the other hand, persistent hypertrophy may represent a certain compensatory mechanism for the maintenance of the normal pumping function of the heart in the presence of increased interstitial fibrosis (Hess *et al.* 1984).

## Biological characteristics of hypertrophy and regression of hypertrophy

### *The ambivalent nature of hypertrophic growth*

Hypertrophy of the left ventricle is an ambivalent phenomenon (Krayenbuehl 1977, Frohlich 1987, Jacob 1991). The enlargement of the contractile mass increases the general performance of the heart, but the thickened myocardial wall, increased concentration of fibrotic tissue and calcium overload of the cardiomyocytes increase the stiffness of the ventricle. The diastolic filling is decreased despite normal or increased ventricular pressure. Moreover, the sarcomeres are less stretched and thus the role of the Frank-Starling mechanism is decreased, which in turn limits the pumping ability of the ventricle (Jacob 1991). From the point of view of energy metabolism, the lower consumption of energy due to decreased tension in hypertrophy (Grossman *et al.* 1980) is counteracted by the relative deficit of energy production determined by the increased diffusion pathway of oxygen (Anversa *et al.* 1986), by deterioration of transcappillary exchange caused by perivascular fibrosis (Tomanek *et al.* 1979, Weber *et al.* 1993, Weber and Brilla 1993), by the restricted vasodilatory capacity of coronary vessels (Karam *et al.* 1990) and by the energetically inconvenient mitochondria: myofibrils relation (Tomanek *et al.* 1979). Moreover, a change in isoenzyme composition of myosine ATPase was observed in small animals. Although the increased genetic expression of isoenzyme V3 (in comparison with the originally predominant V1 isoenzyme) results in slowing-down the contraction speed, the energy is utilized more effectively (Swynghedauw *et al.* 1984).

In the light of the above mentioned counteracting and mutually interfering factors involved in hypertrophy, regression of hypertrophy should be assessed in a complex way and in relation to the given haemodynamic situation.

### *Hypertrophy regression and heart function*

The diastolic properties of the heart usually improve when the regression of hypertrophy is achieved by ACE inhibitors (Schulman *et al.* 1990, Marmor and Schneeweiss 1993) or calcium antagonists (Granier *et al.* 1990, Schulman *et al.* 1990, Phillips 1993). This effect may be caused not only by the regression but also by the ability of the above mentioned antihypertensives to reduce the concentration of collagen (Zähringer *et al.* 1985, Weber and Brilla, 1993) or by the direct effect of these drugs on diastolic properties of the left ventricle (Phillips 1993). On the other hand, the fibrotic tissue concentration was relatively increased when regression was achieved by alpha-methyldopa or hydralazine

treatment (Zähringer 1985), by operative removal of aortal stenosis or insufficiency (Krayenbuehl *et al.* 1985), or by withdrawal of isoprenaline in left ventricular hypertrophy of the rat heart induced by this drug (Čihák *et al.* 1992). The stiffness of the heart was increased in the case of aortal stenosis, yet in aortal insufficiency it was unchanged (Hess *et al.* 1984). Alteration of the diastolic properties during regression of hypertrophy does probably not depend only on changes in fibrotic tissue concentration but also on the initial supracellular architecture of the ventricle (Hess *et al.* 1984), or potentially on changes in the relative representation of collagen type I and III (Weber *et al.* 1990, Weber and Brilla 1993).

The evaluation of the systolic parameters of the heart with regression of hypertrophy is difficult because the effect of reduction of the haemodynamic overload cannot practically be distinguished from the consequences of the myocardial changes determined by reversal of the hypertrophied mass. Neither regression of volume- (Roman *et al.* 1989) nor of pressure-induced hypertrophy (Strauer 1985, Julien *et al.* 1990, Sugishita *et al.* 1990, Ketelhut *et al.* 1992) and regression of hormonally induced experimental hypertrophy (Čihák *et al.* 1992) did not affect systolic function or even improved it compared to the hypertrophied heart.

### *Potential risks linked with regression of hypertrophy*

Neither maintenance nor improvement of heart function in hypertrophy regression answers the question whether regression of myocardial hypertrophy is linked to the decrease of cardiovascular risks induced by hypertrophy (Tarazi and Frohlich 1987, Frohlich 1989, Messerli *et al.* 1993). These risks may even increase under certain conditions (Frohlich 1987). Sudden death, for example, has been presumed to be related to electrical instability of the hypertrophied myocardium. Besides other factors, this instability may be determined by areas of fibrosis which could conceivably limit the smooth propagation of the electrical signal and give rise to re-entry mechanism (Messerli and Soria 1992). As the concentration of fibrotic tissue increases in some types of hypertrophy regression (Hess *et al.* 1984, Krayenbuehl *et al.* 1985, Čihák *et al.* 1992), it might result in an increased risk of re-entry mechanism, dysrhythmias and sudden death.

If the regression of hypertrophy is proportional to the extent to which the haemodynamic overload is reduced, the wall tension does not change and coronary flow through the mass unit may even improve as a consequence of normalization of capillary density. Problems may, however, arise when reduction of blood pressure and concomitant hypertrophy develop in a disproportional manner. Thus, for example, alpha-methyldopa administered in small doses did not affect the blood pressure, yet it was found

to induce regression of hypertrophy in some individuals. Although no changes in the functional characteristics were observed (Fouad *et al.* 1982), such an intervention is potentially dangerous from the pathophysiological point of view. Even when capillary network density and the ratio of mitochondria: myofibrils are normalized as a consequence of hypertrophy regression, the persistence of overload with simultaneous reduction of hypertrophy may deteriorate the energetic situation in the heart due to inadequately increased wall tension.

On the other hand, normalization of increased afterload without achievement of hypertrophy reversal may be equally inadequate. Coronary flow and coronary reserve are determined, besides other factors, by the mutual relation between the left ventricular mass and arterial blood pressure (Wicker *et al.* 1983). Therapeutic depression of blood pressure without adequate reduction of the hypertrophied myocardial mass may, especially by concomitant atherosclerosis of coronary arteries and hypertrophy of the arterioles, manifest itself as ischaemia of subendocardial layers.

Good results were achieved by the administration of such antihypertensive drugs, which proportionally reduce both hypertrophy of the left ventricle and blood pressure (Tarazi and Frohlich 1987, Wicker *et al.* 1983) and simultaneously diminish smooth muscle hypertrophy in the small arterioles (Motz and Strauer 1992). However, even when regression of hypertrophy meets these demands, there is still a potential danger that a sudden surge in blood pressure which may be induced by a hypertensive crisis or by noncompliance of drug intake, will find the left ventricle unprepared and heart failure may develop (Strauer 1985).

### Regression of remodelling by chronic myocardial infarction?

The term "remodelling" in its broadest sense represents the combination of changes of ventricular geometry, myocardial mass and structure (Smith *et al.* 1991) and overlaps with the traditionally established term "adaptation to haemodynamic overload". In myocardial infarction, however, remodelling has a specific meaning involving mainly chronically progressive dilatation of the affected ventricle, which may be linked to hypertrophy of the surviving musculature resulting from a volume overload (Pfeffer and Braunwald 1990). The impulse triggering these changes is the elimination of function of the infarcted area and its consequent expansion, which may gradually lead to progressive dilatation of the whole ventricle with a concomitant increase in wall tension (McKay *et al.* 1986, Weisman *et al.* 1985).

Reduction of hypertrophy induced by myocardial infarction appears to be questionable. Despite the fact that infarction-induced hypertrophy

presents a similar risk as hypertrophy occurring in other types of haemodynamic overload, its positive adaptive nature is evident (Bumberger *et al.* 1993). Hypertrophy compensates the loss of musculature caused by necrosis thus helping to maintain a sufficient performance of the infarcted ventricle. Moreover, by decreasing wall tension in the surviving tissue, hypertrophy reduces the tendency of progressive dilatation (McKay *et al.* 1986). Stimulation of mitotic activity of the surviving cardiomyocytes resulting in an increase of the contractile mass is even considered as a potential future alternative therapeutic approach improving contraction ability of the infarcted ventricle (Williams 1993). It is conceivable that even a relative increase of ventricular stiffness, as a result of increased interstitial fibrosis in hypertrophy resulting from infarction, may act as a factor protecting the chamber from progressive dilatation (Smith *et al.* 1991). On the other hand, prevention of postinfarctional hypertrophy development of the rat left ventricle by beta-blockers (Fishbein *et al.* 1988) caused prognostically unfavourable volume enlargement of the infarcted ventricle.

The term "regression of remodelling" is not used for genuine reversal of the hypertrophied mass but for such an intervention, which slows down the expansion of the infarcted focus and limits the progression of dilatation of the affected ventricle (Smith *et al.* 1991). Besides recanalization with restoration of coronary flow (Nidorf *et al.* 1993) beneficial effects can be achieved by pharmacological substances which act positively by reducing considerably the haemodynamic load at the level of pre- and/or afterload (e.g. ACE inhibitors, prazosin, nitrates) (Pfeffer and Braunwald 1990).

### Spontaneous regression of hypertrophy

In their attempt to characterize the sequence of adaptational changes in haemodynamic overload, Fízel' and Fízel'ová (1969, 1971) differentiated four periods of left ventricular hypertrophic growth on the experimental model of aortal insufficiency in rabbits. Compared to the findings of Zak (1984) and Meerson (1965) who described the period of haemodynamic overload development, the period of developed hypertrophy and the period of heart failure, Fízel' and Fízel'ová (1969, 1971) supplemented the sequence of periods of hypertrophic growth by a period of regression of hypertrophy, which precedes the period of heart failure. Within the period of developed hypertrophy, a steady state between the actual haemodynamic situation, enlarged myocardial mass and function of the left ventricle is achieved. The transition into the period of hypertrophy regression is characterized by a relative diminution of left ventricular weight (Fízel' and Fízel'ová 1969, 1971, Fízel' *et al.* 1984), of cardiomyocyte volume (Šimko *et al.*

1986, Šimko and Fízel 1988) and by a list of unfavourable ultrastructural, biochemical and functional changes. This period is followed by the period of heart failure in which the weight of the heart again increases slightly (as a result of right ventricle enlargement), but biochemical, ultrastructural and functional parameters continue to deteriorate and congestive heart failure develops (Fízel and Fízelová 1969, 1971, Fízel *et al.* 1984).

The above mentioned model, however, raises the question: Why does spontaneous regression of hypertrophy develop when the haemodynamic situation which induced hypertrophy still persists? This is probably related to the fact that the hypertrophied heart as a whole develops a greater pressure than does the control heart. However, the pressure exerted by a unit of contractile protein mass is significantly lower. The authors suppose that the heart adapts to a chronic haemodynamic overload with a certain redundant capacity of subcellular structures which should apparently enable the heart to respond adequately to acute additional haemodynamic stress (e.g. muscular activity). When this excessive myocardial mass is not functionally used for a longer period, gradual diminution of the redundant myocardium sets in (Fízel *et al.* 1984). However, it is not clear at present why the process of regression overshoots and a new equilibrium does not develop between the wall stress and the actual haemodynamic situation.

It seems reasonable to suppose that spontaneous regression of hypertrophy also develops in the human heart with serious aortal insufficiency in the long course. Such a type of regression of hypertrophy would, however, signalize prognosis deterioration and danger of cardiac insufficiency. On the other hand, potential detection of the period of spontaneous regression in clinical conditions may help to specify the optimal period for surgical correction of aortal valve insufficiency.

## Conclusions

The term regression of hypertrophy involves a list of substantially distinct biological phenomena. The nature of regression is, to a considerable extent,

determined by the type of hypertrophic growth. Nevertheless, even within a given type of hypertrophy, regression may have different manifestations depending on the inducing stimulus. The stimulus responsible for hypertrophy reversal is complex and involves more than just modification of the haemodynamic load.

The phenotypic alteration manifested as myocardial hypertrophy is determined by preferential expression of a certain part of the genotype in dependence on the nature of the given type of haemodynamic overload. Since reversal of excessive myocardial mass may also be achieved through other mechanisms besides those inducing hypertrophy, it does not seem unreasonable to suppose that reduction of myocardial mass to its original level and even restoration of the original function need not be associated with a return to the original expression of the genotype. Does hypertrophy regression represent a return to the initial state or is it a new specific state of the heart? This crucial question remains to be answered.

The therapy of haemodynamic overload of the circulation cannot be focused only on excessive myocardial mass reduction. The primary aim should be to achieve optimal perfusion of peripheral tissues so that the working load of the heart would not become a limiting factor of survival. Teleologically expressed, hypertrophy of the heart means a compromise which the body accepts in its effort to prevent or postpone disaster. In this respect, regression of hypertrophy cannot be conceived as the final aim but as a necessary compromise which is rarely the ideal.

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