Controversies in Cardiology 4

Controversies in ventricular remodelling

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Ventricular remodelling describes structural changes in the left ventricle in response to chronic alterations in loading conditions, with three major patterns: concentric remodelling, when a pressure load leads to growth in cardiomyocyte thickness; eccentric hypertrophy, when a volume load produces myocyte lengthening; and myocardial infarction, an amalgam of patterns in which stretched and dilated infarcted tissue increases left-ventricular volume with a combined volume and pressure load on non-infarcted areas. Whether left-ventricular hypertrophy is adaptive or maladaptive is controversial, as suggested by patterns of signalling pathways, transgenic models, and clinical findings in aortic stenosis. The transition from apparently compensated hypertrophy to the failing heart indicates a changing balance between metalloproteinases and their inhibitors, effects of reactive oxygen species, and death-promoting and profibrotic neurohumoral responses. These processes are evasive therapeutic targets. Here, we discuss potential novel therapies for these disorders, including: sildenafil, an unexpected option for anti-transition therapy; surgery for increased sphericity caused by chronic volume overload of mitral regurgitation; an antifibrotic peptide to inhibit the fibrogenic effects of transforming growth factor β; mechanical intervention in advanced heart failure; and stem-cell therapy.

The concept of ventricular remodelling was focused in 1985, from fundamental work that has come to have immense clinical application. Janice Pfeffer and colleagues[1] studied the causes and patterns of increased left-ventricular dilation and impaired ventricular function after coronary artery ligation in rats (figure 1).[2] They referred to such changes in the ventricular architecture as remodelling. Post-infarct remodelling was further defined in 1990 as the changes in ventricular topography, occurring both acutely and chronically after infarction and identified as an important therapeutic target.[3]

Since then, the concept has been applied to various ventricular patterns occurring in response to the mechanical stresses of other heart diseases. Here, we first contrast the changes induced by pressure and volume loads (figure 2)[2] and describe the molecular mechanisms implicated. Corresponding clinical patterns include aortic stenosis (pressure overload) and mitral regurgitation (volume overload). We then focus on the more complex changes in the infarcted heart, in which left-ventricular remodelling is a combination of infarct expansion, pressure overload, and volume overload. Finally, we look at the controversies regarding the best methods to reverse such remodelling towards normality. Although progressive left-ventricular remodelling is a key feature of heart failure and affects the clinical outcome,[4] this paper is not about overt heart failure, but rather is an analysis of the basic and clinical data relating to the remodelling patterns that are relevant to heart failure.

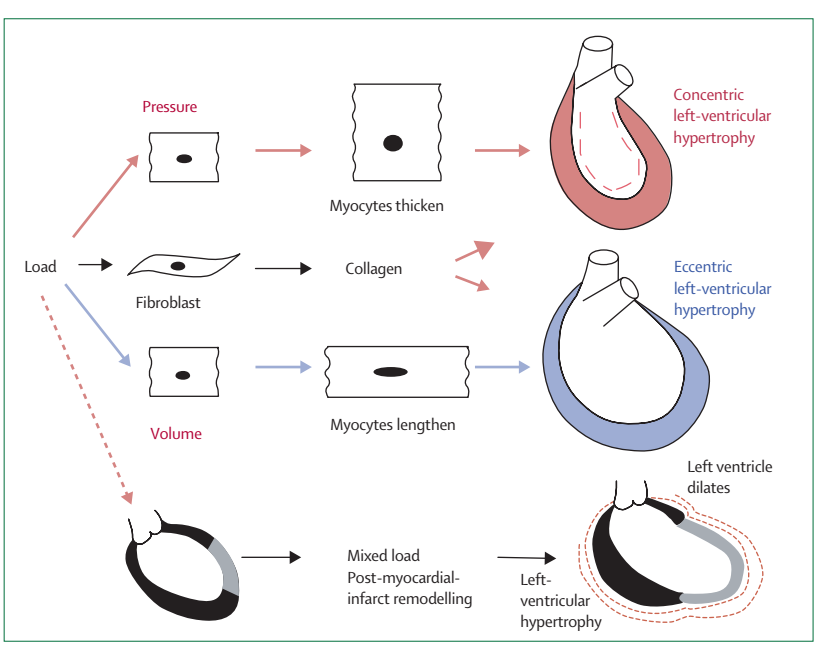

Figure 1: **Three major patterns of ventricular remodelling**
Patterns are: concentric left-ventricular hypertrophy, when a pressure load leads to growth in cardiomyocyte thickness (dotted lines represent left ventricle growing inwards); eccentric hypertrophy, when a volume load produces myocyte lengthening; and post-infarct, when the stretched and dilated infarcted tissue increases the left-ventricular volume with a combined volume and pressure load on the non-infarcted zones (dotted lines represent combined effects of concentric and eccentric hypertrophy). Fibrosis contributes to all three patterns (fibrosis in post-infarct model not shown in figure). Figure adapted from reference 2, with permission.

Search strategy and selection criteria

We searched MEDLINE using "remodelling" as the key word in combination with "myocardial infarction", "heart failure", "aortic stenosis", "mitral regurgitation", "pressure overload", and "volume overload". We searched all major cardiovascular journals: *The Lancet*, *British Medical Journal*, *New England Journal of Medicine*, and the *Journal of the American Medical Association* for similar and related articles. Reference lists in key articles were searched to identify older publications. More than 300 articles were analysed.

Does left-ventricular hypertrophy constitute an adaptive or maladaptive response to the increased pressure load?

Wall-stress hypothesis

This controversy first needs exploration of the classic wall-stress hypothesis, and then analysis of the molecular pathways that can be transgenically altered to modify the wall-stress response. According to Grossman's systolic-stress-correction hypothesis,[5] pressure overload causes myocytes to grow in width to increase wall thickness (figure 1),[2] thereby regulating the pressure-induced increase in wall stress. This concept relies on the Laplace law, whereby increased wall thickness reduces wall stress. If the hypertrophy is adequate, the systolic wall-stress normalises and the heart is mechanically compensated. This effect corresponds to Meerson's compensatory hyperfunction of the heart produced by experimental constriction of the aorta.[6] Thereafter, the left ventricle undergoes transition to failure and dilation.[6] With respect to a sustained volume load, Grossman proposed that increased diastolic wall stress gave rise to myocyte elongation with eccentric hypertrophy, with an increased ventricular diameter. Extensive studies of hypertrophic signalling pathways have questioned the wall-stress hypothesis.

Pressure-induced adaptive and maladaptive signals

A fundamental hypothesis is that, according to the nature of signalling stimulus, the myocyte can either survive, leading to beneficial hypertrophy,[7] or undergo apoptosis (programmed cell death), which promotes left-ventricular failure and dilation.[8] These molecular pathways therefore result in either adaptive or maladaptive patterns of hypertrophy.

One such pathway takes place when angiotensin II is released from the myocardium in response to an abrupt mechanical load[9] or to increased systolic wall stress.[10,11] After angiotensin II binds to its receptor, it activates the G protein Gq, and then the ϵ isoform of protein kinase C,[12] to initiate signalling to the enzyme complex of mitogen-activated protein (MAP) kinase (figure 2).[2] Some of the MAP-kinase components promote pro-survival signalling, whereas others stimulate apoptosis and decrease cell survival.[8] Increased apoptosis might also directly cause contractile protein dysfunction.[13] Other maladaptive pathways include those that promote fibrosis in response to angiotensin II, aldosterone,[14] and transforming growth factor (TGF) β.[15,16] Cytokines such as tumour necrosis factor (TNF) α seem to have bidirectional effects, with low concentrations being protective and high concentrations being maladaptive.[17]

Thus, if pressure-induced stimulation of angiotensin II leads to maladaptive growth rather than adaptive growth and apoptosis rather than survival, then genetic interruption of this pathway would lessen hypertrophy yet protect the myocardium. In a mouse model with transgenic inactivation of Gq, hypertrophy from pressure loading was less than predicted with decreased correction of wall stress.[18] However, contractility in the transgenic model was better than that in the wild type with more left-ventricular hypertrophy (figure 3).[2,18,19] This finding argues against the wall-stress model, but does not imply that all hypertrophy is deleterious. For example, in another transgenic model when only extracellular-signal-regulated kinase (ERK) was activated,[19] the end result was an adaptive hypertrophy with normalised wall-stress and full compensation for an increased load (figure 3).[2]

Another adaptive pressure-induced process begins with insulin-like growth factor (IGF) I,[11] which has a signal system involving the potent growth-promoting enzyme protein kinase B (PKB or AKT). Such stimulation has prosurvival effects, both promoting growth and inhibiting apoptosis via many downstream regulators.[13] Another protective path, not shown in figure 2,[2] is the formation of cyclic guanosine monophosphate (GMP) in response to atrial natriuretic peptide, thereby restricting hypertrophy.[20]

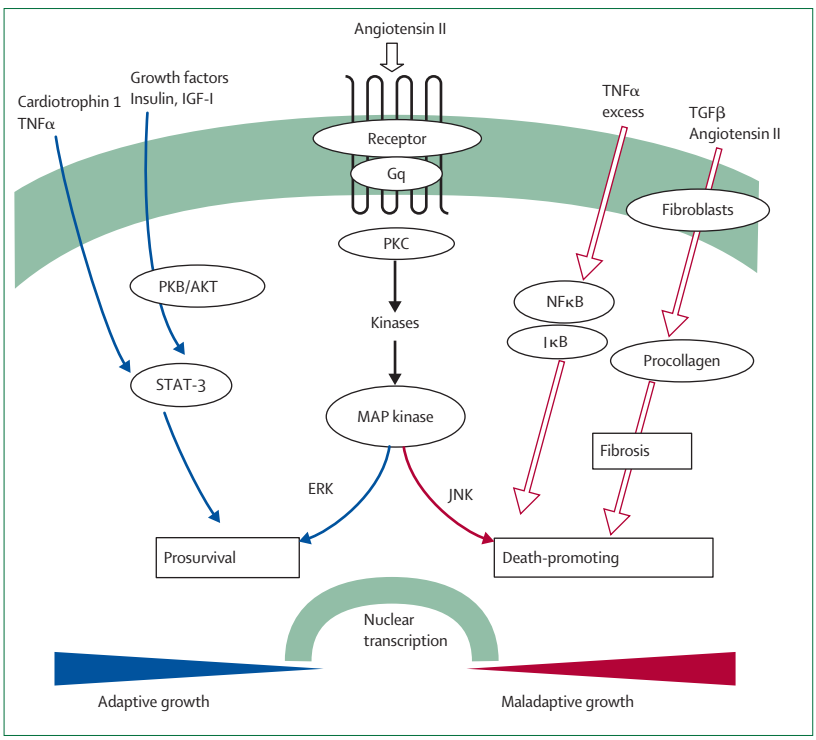

Figure 2: **Hypertrophic signalling pathways**
Pathways on the left lead predominantly to myocyte survival (adaptive hypertrophy), with those on the right leading to death by apoptosis and fibrosis (maladaptive hypertrophy). A major pathway leads from angiotensin II to mitogen-activated-protein (MAP) kinase that, depending on which member of the kinase family mediates the stimulus, diverges either to prosurvival effects via extracellular-regulated kinase (ERK) or to proapoptosis via Jun N-terminal kinase (JNK). Angiotensin II also leads to fibrosis. Cytokines such as cardiotrophin 1 and tumour necrosis factor (TNF) α could have prosurvival effects at low-level stimulation, or proapoptotic effects at high pathological levels in the case of TNFα. Signalling pathways are not necessarily clear-cut in their sequences, although the patterns shown here indicate the overall pathways presently proposed. PKC=protein kinase C. PKB=protein kinase B. IGF-I=insulin-like growth factor. TGFβ=transforming growth factor β. NFκB=nuclear factor κB. IκB=inhibitor of NFκB. Figure adapted from reference 2, with permission.

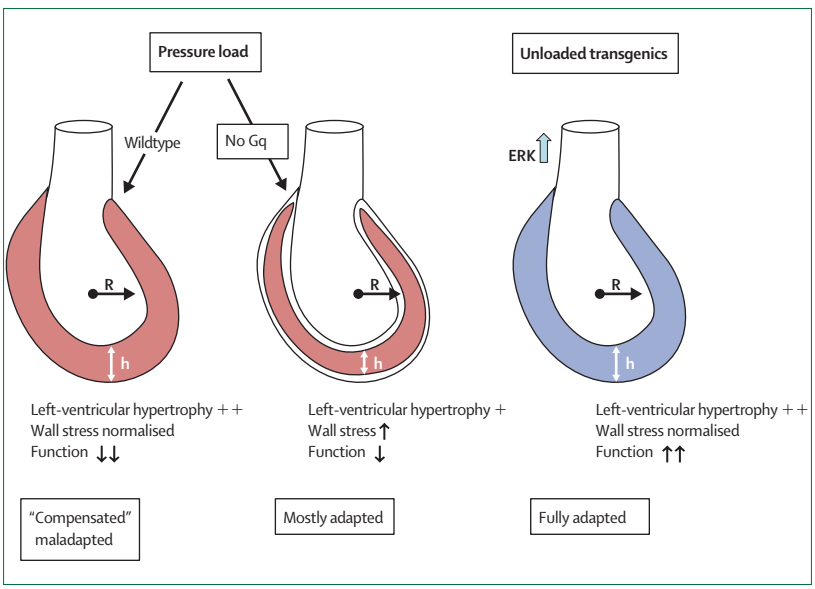

Figure 3: **When compensated hypertrophy is not necessarily compensated**
Left panel: left-ventricular hypertrophy in which wall stress, the relation between the radius of the ventricular chamber (R) and the thickness of the ventricular wall (h), is normalised in response to sustained pressure load. Contrary to the wall-stress correction hypothesis, left-ventricular mechanical function is reduced and not maintained. Middle panel: reduced hypertrophic response to pressure load in transgenic mice with inhibited Gq signalling,[18] which means that the agonists of angiotensin II and related receptors such as endothelin that lead to maladaptive signalling (figure 2) cannot operate. The reduced hypertrophy is shown by comparison of the ventricular-wall thickness (red) with the ventricular pattern in the wildtype as shown by the two outlines, which match the extent of left-ventricular hypertrophy in the wildtype. Although transgenic wall stress has increased as shown by the lower ratio of wall thickness (h) to the radius (R), mechanical function is less reduced than in the so-called compensated heart of the wild type (left panel). Right panel: in a different transgenic model with chronic activation of extracellular regulated kinase (ERK), a truly compensated well-adapted state is reached.[19] Figure adapted from reference 2, with permission.

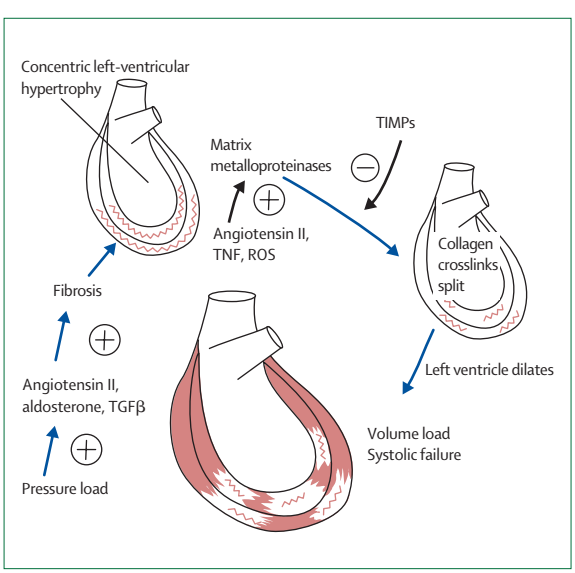

Figure 4: **Proposed transition from concentric hypertrophy to dilated failing left ventricle**
Note the role of matrix metalloproteinases that break down collagen compared with the opposing role of TIMPs. Primary stimulus to the increased collagen is shown as stretch-induced formation of angiotensin II. Metalloproteinases disrupt collagen crosslinks (red lines) with cell restructuring and left-ventricular dilation. ROS=reactive oxygen species. Figure adapted from reference 2, with permission.

Can these experimental studies be applied to human beings?

Although there have been several studies in the failing heart with tissue obtained during the implantation of a left-ventricular assist device, there are few studies on the hypertrophic heart. In aortic stenosis, strong evidence indicates that growth signals such as angiotensin II and TGFβ are associated not only with myocyte growth, but also with maladaptive fibrosis, myocyte degeneration, and eventual myocyte loss.[16] Epidemiologically, left-ventricular hypertrophy is a major risk factor for cardiovascular morbidity and mortality, independent of blood pressure level.[21]

Opinion

With respect to extensive animal and scarce human data, good evidence supports the proposal that a sustained pressure load is often due to a mixed stimulus that produces both beneficial adaptive and adverse maladaptive remodelling. The occurrence of maladaptive remodelling could explain why the wall-stress correction hypothesis does not always apply.

Can cellular mechanisms account for the transition from apparently compensated hypertrophy to the failing heart? Could these findings lead to new therapy?

Meerson[6] contrasted the anatomical changes in concentric left-ventricular hypertrophy with the pathological changes (such as ventricular dilation) in failure. What causes this transition? Currently, one hypothesis states that maladaptive biological forces overwhelm adaptive forces, but how does this event occur? Three major hypotheses have been proposed.

(1) Role of metalloproteinases and their inhibitors

The extracellular matrix, synthesised by cardiac fibroblasts (figure 1),[2] usually maintains the myocardial architecture. Increased collagen synthesis causes fibrosis when induced by angiotensin II, TGFβ,[17] and aldosterone.[22] Metalloproteinases are enzymes that break down collagen, with their actions restricted by TIMPs (tissue inhibitors of matrix metalloproteinases; figure 4).[2] Of the many isoforms, the roles of metalloproteinase 9[23] and TIMPs 1 and 2[24] are important in human beings. Once the metalloproteinase-TIMP balance is upset in favour of increased metalloproteinase activity, collagen crosslinks degenerate so that the hypertrophied left ventricle begins to dilate,[25] which has also been recorded in patients.[26] Ventricular dilation could precipitate further degeneration through many mechanisms, including neurohumoral activation, stretch-induced apoptosis, and oxidative stress.[27]

(2) Role of oxidative stress and nitric oxide synthase

Growth initiators including angiotensin II, α agonists, TNFα, and mechanical strain also promote the

formation of reactive oxygen species (ROS).[28] ROS stimulation potentially has both adaptive and maladaptive signalling consequences, from a hypertrophic response at low rates of ROS production to fibrosis[29] and myocyte death at high rates.[30] ROS formation is also stimulated by endothelial nitric oxide synthase (eNOS). In a transgenic eNOS knockout model with low ROS production, severely pressure-loaded hearts developed only modest concentric hypertrophy with little fibrosis and without left-ventricular cavity dilation.[28] Consonant with overall knowledge,[30] high rates of ROS production can thus contribute to the transition from left-ventricular hypertrophy to heart failure. Although these findings may be controversial,[31] there has been recent confirmation of the concept.[32] Notably, plasma and pericardial markers of oxidative stress are increased in patients with chronic systolic failure of the left ventricle, with these increases related to the clinical severity of heart failure.[33,34]

(3) Neurohumoral activation

Adrenergic and renin-angiotensin-aldosterone activation is induced by ventricular dilation and can be expected to quicken the transition to overt clinical failure. Once adrenergic signalling and cellular hyperadrenergic signalling are initiated, the former probably exaggerates the activation of metalloproteinases,[35] whereas the latter lead to myocardial β-receptor downregulation and hyperphosphorylation, with inhibition of the sarcolemmal calcium-release channels,[36] thereby causing further mechanical dysfunction of the left ventricle. Hyperadrenergic signalling also leads to cellular calcium overload with a threat of apoptotic cardiomyocyte death.[37] Additionally, increased myocardial angiotensin II augments apoptosis via increased cytosolic calcium,[37] and also by ROS formation. Furthermore, angiotensin II promotes the expression of the profibrotic mediator, TGFβ.[38] Conversely, angiotensin-converting-enzyme (ACE) inhibition blocks TGFβ and lessens myocardial and perivascular fibrosis.[38] Raised concentrations of circulating angiotensin II lead to increased renal reabsorption of sodium with water retention and an increased volume load on the heart with more stretch-induced abnormalities. Increased angiotensin-II-mediated release of aldosterone promotes both sodium retention and cardiac fibrosis. The combination of fibrosis and increased cell death leads to a disorganised, poorly contracting myocardium.[16]

Protective role of cyclic GMP—sildenafil as potential treatment option

The inhibitory cardiovascular signals mediated by cyclic GMP combat harmful adrenergic effects.[39] Furthermore, genetically increased synthesis of cyclic GMP inhibits pressure-induced pathological remodelling.[40] Sildenafil inhibits the breakdown of cyclic GMP to deactivate many growth pathways and to prevent and reverse hypertrophy and failure induced by aortic constriction.[40] Via cyclic-GMP-induced formation of nitric oxide, sildenafil could also be a systemic vasodilator in patients with heart failure to reduce vascular stiffness.[41] In lungs congested by heart failure, sildenafil lowers pulmonary vascular resistance and increases alveolar gas exchange.[42] Taken together, these data strongly suggest the desirability of large trials with sildenafil in both developing and established heart failure.

Opinion

To prevent hypertrophic hearts from overt failure, the activity of metalloproteinases could be reduced by the stimulation or use of TIMPs or by the restriction of ROS production. The problem is that there are many isoforms of both metalloproteinases and TIMPs, as well as multiple sources of ROS. Therefore, despite theoretical promise, human application will be difficult. Sildenafil is more promising and is already in the early phases of testing. ACE inhibitors and β-adrenergic blockers should, theoretically, be started very early to reduce the progression of heart failure.

Aortic stenosis: do clinical findings match basic science concepts?

Aortic stenosis is a classic cause of pressure-induced concentric remodelling.[16,26,43] To what extent do clinical observations fit the animal data and support the Meerson[6] progression from concentric left-ventricular hypertrophy to failure? This particular issue will never be solved by prospective studies, in view of the ethical concerns about the non-treatment of patients with symptomatic aortic stenosis. However, for aortic stenosis, postoperative regression of left-ventricular hypertrophy provides reverse longitudinal evidence,[44] from which the presumed pattern of pre-operative progression can be inferred but not proven.

A fundamental observation in aortic stenosis is that the increase in intraventricular pressure stimulates the ratio of left-ventricular wall thickness to chamber volume.[45] In unoperated aortic stenosis, so-called typical concentric hypertrophy takes place with impaired diastolic filling, a healthy ejection fraction, and often normal cardiac output.[46] After valve replacement, these changes all revert towards normal.[46,47] In severe and probably sustained aortic stenosis, the cardiac output falls, the end-diastolic pressure rises, and the left-ventricular cavity dilates, while still with striking diastolic dysfunction.[44]

In a study of symptomatic aortic stenosis, about half the affected individuals had clinical heart failure, and about a third had eccentric hypertrophy.[48] Post-operatively, reductions have been recorded in left-ventricular mass and end-diastolic cavity size,[49] which return to a healthy state in the late postoperative phase (when indexed to left-ventricular mass), as does diastolic

function.[44] Reduced left-ventricular ejection fraction and increased left-ventricular cavity size before surgery are associated with poor postoperative recovery,[50] which has resulted in surgery now being undertaken earlier. In individuals with aortic stenosis and symptoms of heart failure, eccentric hypertrophy and depressed systolic function are often both present, but absent in those without clinical heart failure.[51]

An important finding from clinical studies is that pressure-induced concentric hypertrophy can coexist with both left-ventricular diastolic dysfunction and cavity dilation.[44,49] The cellular pattern of left-ventricular hypertrophy includes thickened myocytes, cell death, and increased fibrous tissue.[44,49] These findings are consistent with the basic science concepts of both adaptive and maladaptive cell signalling in pressure-induced left-ventricular hypertrophy. We propose that these clinical studies show that the pressure-induced starting point in aortic stenosis is concentric hypertrophy with early impairment of diastolic filling,[50] followed by increased left-ventricular filling pressures with reverse changes taking place after aortic-valve surgery.[44,49] At a cellular and signalling level, early activation of maladaptive growth signals could occur, leading to deleterious remodelling[16,52] with myocyte degeneration and loss.[16] Increasing fibrosis is associated with complex changes in metalloproteinase activity.[26,53] This cellular progression is matched by increasing left-ventricular failure (figure 4),[2,16] which suggests that early concentric hypertrophy deteriorates into a dilated eccentric pattern. No clinical longitudinal data directly proves this sequence of events, although increased left-ventricular mass does coincide with increased left-ventricular systolic dysfunction and heart failure.[54]

Opinion

In clinical aortic stenosis, Meerson's stage of compensatory hypertrophy[6] is not truly compensated but already contains maladaptive seeds of future failure, hence progressively blending into eccentric dilation with systolic heart failure. This conclusion is important, challenging some conventional concepts.

Do different pathways exist for pressure-induced and volume-induced hypertrophy?

Graded mechanical stress with large left-ventricular volumes results in increasing amounts of TNFα being released from the healthy myocardium.[55] Passive stretching of ventricular muscle promotes the synthesis of TNFα mRNA.[56] The low rate of TNFα stimulation interlinks with other cytokines such as cardiotrophin 1[17] acting on the gp130 receptor to promote prosurvival pathways (figure 2),[2] so that sarcomere units form in series to result in eccentric hypertrophy.[57,58] Cardiotrophin 1 also participates in the response to pressure loading to protect from apoptotic death.[59] Increased expression of myocardial mRNA TNFα recorded in patients with mitral regurgitation is reversed when the volume overload is corrected by mitral-valve surgery.[60] However, TNFα excess leads to maladaptive responses.[17,61] To support this concept, circulating concentrations of TNFα in patients are increased with respect to the severity of heart failure in both aortic stenosis and mitral regurgitation.[62] Other maladaptive stimuli include: (1) overstretching-induced release of ROS with increased apoptosis and myocyte restructuring;[27] and (2) increased metalloproteinase activity, which is associated with the breakdown of interstitial collagen and foci of reactive fibrosis.[63] These patterns are similar to the end-stages of pressure-induced hypertrophy (figure 4).[2]

Volume overload releases cardiac atrial natriuretic peptide. In a knockout mouse without the peptide, exaggerated cardiac hypertrophy was recorded,[64] hypothetically because the peptide stimulates the formation of myocardial cyclic-GMP, which in turn inhibits hypertrophy.[20] However, the use of human recombinant natriuretic peptide, nesiritide, is very controversial in clinical practice. In trained athletes with eccentric hypertrophy, the growth pathways involve adaptive IGF-I (figure 2)[2] rather than angiotensin II or endothelin, which are both maladaptive in nature.[65]

Opinion

Much less is known about signal systems for volume overload than those for pressure loads. Additionally, fewer transgenic models exist for volume overload. Remodelling in early volume overload could be related to stretch-induced signalling via adaptive signals such as cardiotropin 1, low-level TNFα, cyclic-GMP, and IGF-I, with excess TNFα and stretch-induced ROS exerting later maladaptive effects.

Is remodelling in mitral regurgitation volume-induced?

The clinical picture for volume overload differs greatly from that for chronic pressure loading (figure 5). When severe left-ventricular volume overload is caused by primary chronic mitral regurgitation, it may lead to irreversible mechanical dysfunction.[66] In the chronic compensated phase of mitral regurgitation, eccentric hypertrophy and left-ventricular dilation increases total stroke volume and maintains forward flow despite the regurgitation. The chronic decompensated phase is marked by increased end-diastolic and end-systolic volumes. Here, ventricular dilation could increase the degree of regurgitation and promote progression.[67] The second pathway for ejection of blood into the left atrium tends to reduce afterload whereas the volume load increases preload.[68] Intrinsic myocardial dysfunction in this phase could be masked by these favourable loading conditions, allowing measures of ventricular systolic shortening (ejection fraction, shortening fraction) to remain within a supposedly healthy range.

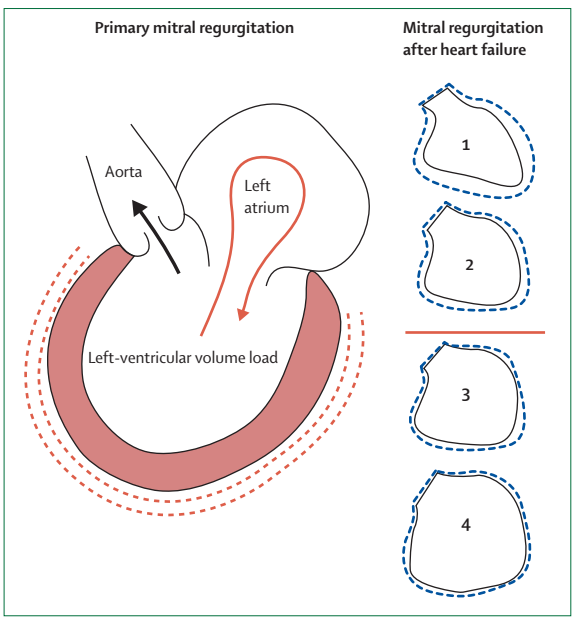

Figure 5: **Mitral regurgitation as an example of chronic volume overload**
Left panel: Development of eccentric hypertrophy in primary mitral regurgitation. Right panel: Increasing sphericity of left-ventricular shape in functional mitral regurgitation after experimental microembolisation causing cardiomyopathy. Onset of functional mitral regurgitation (red horizontal line) induces further remodelling that aggravates the process to increase remodelling. Stages are at (1) baseline, (2) 2 weeks, (3) 3 months, and (4) end-stage dilated spherical thin-walled hypodynamic heart. Figure adapted from references 2 and 77, with permission.

The pathophysiology of the transition from the compensated phase to decompensation and clinical heart failure in chronic mitral regurgitation is poorly understood. Loss of myofibrils,[69] altered calcium handling[70] and activation of the sympathetic nervous system[71] have all been implicated. Increased ventricular volume and mitral regurgitation might be linked in a vicious cycle whereby regurgitation causes ventricular dilation that in turn changes ventricular shape (remodelling), thereby promoting progression of regurgitation (as in other forms of secondary or functional mitral regurgitation). The improvement in left-ventricular contractile function in some patients after successful valve surgery for longstanding mitral regurgitation[72] and the relation between severity of regurgitation and outcome[73] suggests that the volume overload itself contributes to myocardial dysfunction.

Secondary or functional mitral regurgitation refers to regurgitation caused by ventricular remodelling that changes the functional anatomy of the mitral complex[74,75] when the papillary muscles, leaflets, and chordae are all healthy. Such remodelling could occur in dilated cardiomyopathy or post-infarct. Experimentally, left-ventricular dysfunction without dilation does not result in functional regurgitation.[76] Global left-ventricular remodelling transforms the usual ellipsoid shape of the left ventricule to a sphere (known as increased sphericity) to promote functional mitral regurgitation (figure 5).[2,77,78]

Post-infarct, a change of global or local left-ventricular shape could change mitral functional anatomy. Experimentally, volume overload worsens post-infarction remodelling, causing left-ventricular enlargement and adverse molecular and cellular effects that are reversible on removal of the overload.[79] Functional mitral regurgitation, a consequence of remodelling, could contribute to progressive remodelling. Surgical repair of functional mitral regurgitation may benefit some patients[80] without affecting mortality;[81] thus randomised studies are needed.[82]

The importance of ventricular shape in the development of functional mitral regurgitation is further illustrated by passive epicardial containment that reduces sphericity and experimentally abolishes regurgitation completely.[83] This effect is coupled with beneficial cellular and extracellular mechanisms modifying left-ventricular and myocyte remodelling[84] and offers clinical promise.[85]

Is the Grossman hypothesis supported?

Do the cellular anatomical changes in severe mitral regurgitation correspond to Grossman's proposal[5] of longitudinal fibre growth in chronic volume overload? Grossman studied patients with chronic mitral or aortic regurgitation who did not clinically have congestive heart failure. Measurement of cardiomyocyte length and width on human hearts is difficult and data are scarce. In advanced idiopathic dilated cardiomyopathy, increased metalloproteinase activity is linked to loss of collagen and left-ventricular sphericity.[63] Experimentally, after only 3 months of severe mitral regurgitation in dogs, left-ventricular mass increased while end-diastolic volume and wall-stress rose substantially.[86] Cardiomyocyte length increased and end-diastolic wall thickness decreased. All these features are compatible with the Grossman hypothesis. However, by contrast with the unchanged peak systolic stress in patients, this variable doubled in the dogs, because of an increased systemic vascular resistance. In another similar model, the striking feature was the increased length of the cardiomyocytes but with increasing loss of myofibrils correlating with decreased contractile function.[69] Overall, the changes in cell length fit the Grossman hypothesis, whereas further changes could be related to the vascular resistance.

Opinion

The Grossman concept of volume-related cell lengthening holds in experimental mitral regurgitation, allowing for an increased afterload while systemic vascular resistance rises. We propose that volume-induced effects are self-perpetrating. Clinically, clear guidelines exist that are based on the response of the left ventricle to volume overload[87] and on the timing of surgical repair.[72] Secondary or functional mitral regurgitation is best prevented by strategies that control left-ventricular function and shape, with surgical correction in reserve.

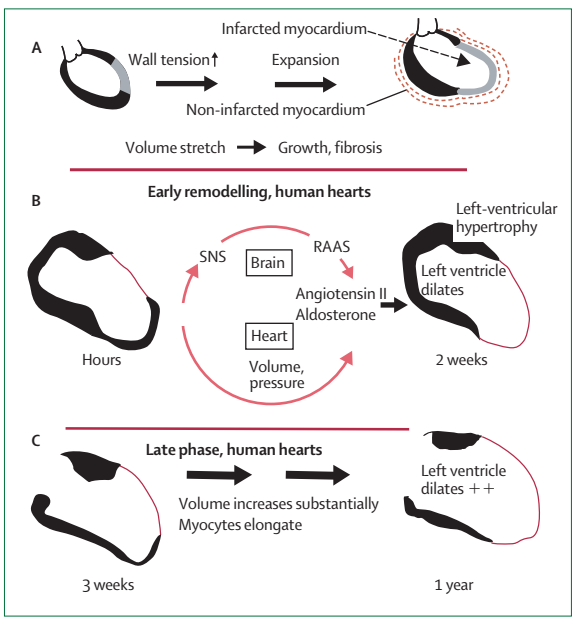

Figure 6: **Post-infarct left-ventricular remodelling patterns**
(A) Simplified overall pattern based on animal models. There is potential for substantial remodelling of infarct zone and increased volume of non-infarcted zone. Endocardial wall motion of two different human hearts in (B) early post-infarct phase and (C) late post-infarct phase derived from contrast ventriculography. Black=extent of preserved movement of endocardial surface in non-infarcted zone. Note substantial remodelling in accordance with the animal models, with emphasis on progressively increased volume of left ventricle. SNS=sympathetic nervous system. Figure adapted from references 89 and 90. (McKay RG, Pfeffer MA, Pasternak RC, et al. *Circulation* 1986; **74:** 693–702), with permission.

Post-infarct remodelling: combined volume and pressure loads

Here, a complex series of progressive adverse effects takes place, including: (1) non-contractile and potentially expanding scar tissue forming in the infarcted zone; (2) the volume load induced by such expansion; and (3) the pressure load induced by the increased volume load. Additional ischaemic insults could contribute to remodelling. Thus, a mixed pressure and especially volume load exists,[88,89] with remodelling of the entire left ventricle in proportion to infarct size,[90] with a fall in ejection fraction in direct relation to the size of the infarct.[3] However, the increase in the left-ventricular volume augments the stroke volume by the Starling mechanism so that cardiac output is relatively normal.[90] Figure 6 summarises the three patterns of remodelling.[89,90]

Therefore, early post-infarct remodelling could be beneficial and promote survival, but with deleterious long-term haemodynamic consequences. In anteroseptal infarcts, the crucial issue enlarging the left-ventricular volume is the early increase in apical regional wall stress.[91] Late ventricular enlargement is not the result of progressive infarct expansion, but rather is caused by an increase in the length of the remaining contractile tissue,[89] which is the pattern of volume overload. Long-term progressive remodelling of the left ventricle with increases in the ventricular cavity size can occur up to 2 years post-infarct with increased cardiovascular death even in patients treated with ACE inhibitors.[92] Conversely, seemingly minor reductions in remodelling can be associated with decreased heart failure and cardiovascular death.[92]

With respect to therapy, once the infarct has occurred, load reduction should aim to lessen the distending or deforming forces. ACE-inhibitor therapy helps to attenuate the increase in apical wall stress and to reduce dilation of the left-ventricle.[91,93] This treatment acts in part by reducing the preload and thus the left-ventricular operating volume.[94] If left-ventricular dilation is avoided, then the pure hypertrophic response of surviving myocytes gives haemodynamic benefit.[95] Remarkably, in predominantly reperfused patients with anteroseptal infarcts receiving an ACE inhibitor, only about half had an increase in left-ventricular volume at 90 days,[91] and 22% of those with abnormal ejection fractions on day 1 had fully recovered by 90 days.[96] Such early recovery could be explained by postreperfusion stunning or intrinsic repair of the surviving left-ventricular myocytes, as recorded in animals,[88] with perhaps intrinsic myocardial self-repair.[97] ACE-inhibitor therapy at high doses attenuates left-ventricular dilation more than at low doses.[91] β blockade also reduces the afterload, and hence the intracavity systolic pressure. In patients with heart failure who have already been treated with an ACE inhibitor, carvedilol increased the ejection fraction while reducing end-diastolic left-ventricular volumes (both systolic and diastolic) at 12 months.[98] Load-independent effects of the blockade of the renin-angiotensin-aldosterone system (RAAS) on the progression of atherosclerosis could also have a role by lessening reinfarction.

Will our current understanding of the molecular biology of post-infarct remodelling lead to new therapies or merely provide more sophisticated explanations for existing therapy?

Relation between fibrosis and post-infarct function

In the post-infarct period, enhanced activity of metalloproteinases breaks down the existing collagen while promoting the formation of new collagen that is poorly crosslinked,[3,99,100] which in turn could explain the side-to-side slippage of myocytes that hypothetically contributes to ischaemic ventricular remodelling.[101–104] The standard argument for slippage is elongation of myocytes with thinning of the left-ventricular wall. Other explanations include altered myocyte transverse shape, from round to ellipsoid.[102] Slippage in human hearts remains a controversial concept that has not been examined with the same rigour as in animal hearts. However, whenever metalloproteinase activity increases,[26,63] impaired collagen crosslinks could promote slippage. With respect to late remodelling, the

balance between TIMPs and metalloproteinases changes with time in mice infarcts. Late activation of TIMPs occurs, hence inhibiting metalloproteinases and increasing fibrosis in the already dilated hearts.[105] This late fibrosis is associated with increasing activity of TGFβ1, the fibrogenic cytokine.[16,105,106]

How can post-infarct fibrosis be contained?

Two interlinked signalling systems could be modified; the TGFβ system[107,108] and RAAS. TGFβ is implicated in left-ventricular remodelling[107] and activates fibroblasts to promote fibrosis.[38,109] ACE inhibitors restrict the breakdown of a novel peptide that lessens TGFβ expression.[39] Atorvastatin inhibits TGFβ-mediated collagen production by cardiac fibroblasts.[110]

In overall RAAS, the unconventional aspect is that remodelling after myocardial infarction increases the sympathetic drive, thereby activating brain angiotensinogen, which experimentally promotes myocyte hypertrophy, tissue aldosterone, interstitial fibrosis, and left-ventricular dilation.[111] Apart from systemic activation of RAAS, there is probably local cardiac activation.[59,112] Some remodelling after myocardial infarction is independent of angiotensin-II blockade, probably because of persistent cardiac aldosterone synthesis.[22] Spironolactone can improve experimental remodelling after myocardial infarction, even if infused centrally.[111] Experimentally, eplerenone slows the transition from hypertrophy to failure while reducing fibrosis, oxidative stress, and inflammation.[14] These data on RAAS blockade by ACE inhibitors and aldosterone blockers correlate with many clinical studies. For example, spironolactone added to ACE-inhibitor therapy lessened remodelling, improved the ejection fraction, and reduced markers of myocardial fibrosis.[113] The new data showing that adrenergic activation promotes central activation of angiotensinogen, suggests an additional mode of action of β blockade. Furthermore, β blockade should inhibit the activation of metalloproteinase 2 associated with increased circulating norepinephrine in human studies.[35]

Endothelin is major vasoconstrictor and growth-promoting peptide with increased circulating concentrations in heart failure. Disappointingly, endothelin-A antagonism has added little to previous RAAS blockade, which inhibits endothelin synthesis. Other measures include stimulation of adaptive pro-survival pathways (figure 2).[2] Overexpression of IGF-I in mice restricts apoptotic and necrotic cell death in viable myocardium, decreasing left-ventricular dilation and cardiac hypertrophy.[114] Prosurvival signalling is probably via the AKT pathway,[115] which is stimulated by IGF-I, insulin, and statins to lessen experimental reperfusion-induced apoptosis.[116]

Opinion

Laboratory and clinical patterns accord with each other. ACE inhibition for heart failure after myocardial infarction, evolved from rat experiments, remains the mainstay of clinical therapy, with new impressive data for the addition of aldosterone blockade and β blockade. We have gained a better understanding of how these therapies work rather than finding new therapies. Further modulation of fibrosis beyond the effects of angiotensin II and aldosterone blockade is desirable but not simple to achieve. TGFβ has become a potential therapeutic target of ACE inhibition and statins.

Will mechanical-induced intervention with remodelling lead to new non-mechanical therapies?

Restoration of function in advanced heart failure can occur in response to various experimental interventions such as a new left-ventricular external pocket constraining device that improves left-ventricular dimensions and peri-infarct collagen,[84] biventricular pacing,[117,118] and left-ventricular assist devices.[119,120] Tissue sampling before and after implantation of such an assist device shows a host of favourable changes called reverse remodelling. Anatomically, there is regression of cell thickening and elongation.[121] Improved myocyte contractile activity can be related to the recovery of function of the sarcoplasmic reticulum[120] and increased L-calcium-channel density[122] including reverse molecular remodelling of the genes controlling calcium cycling.[123] Calcium content of the myocytes then rises,[124] after which matrix metalloproteinases are downregulated with reduced collagen damage.[125] There is then increased β-adrenergic-receptor density and response to stimulation,[119] with reduced hyperphosphorylation of the sarcoplasmic reticulum,[126] which is thought to promote calcium leakage from the sarcoplasmic reticulum. Similar reverse remodelling of the sarcoplasmic reticulum can result from β blockade.[36]

Opinion

Although some reverse remodelling can be obtained by pharmacological substances, the concept that mechanical intervention induces reverse remodelling is important and will strengthen the views of interventionalists.

Stem-cell therapy: pipe dream or practicality?

Innovative animal experiments have shown that progenitor cells from various sources can populate acutely damaged regions of the myocardium, refurbishing functional units and reversing remodelling.[127] Whether bone-marrow-derived stem cells can acquire sufficient cardiomyocyte-like properties to reconstitute myocardium lost by infarction is uncertain. By contrast, both myocytes and coronary vessels can be regenerated from a cardiac stem-cell compartment that can regenerate in vitro.[97,128] Injection of cardiac stem cells with a bioengineered scaffolding and selective growth

factors such as insulin-like growth factor could provide enough myocardial regeneration and mechanical support to rescue severely damaged hearts. Clinical evidence does not directly support this theory, but is proceeding briskly. Studies are under way in which skeletal myoblasts harvested from peripheral tissue and grown in culture are injected directly into scarred regions of the myocardium with improved ejection fraction.[129] Other ongoing approaches are using prompt extraction of autologous mesenchymal stem cells harvested from bone marrow, with intracoronary delivery to the necrotic region during the acute phase of myocardial infarction. In a well-designed study of 67 patients, this approach decreased myocardial infarct size and improved recovery of regional systolic function; long-term follow-up is still awaited.[130]

The interest and excitement that has been generated is understandable but we still do not know whether stem-cell regeneration is clinically meaningful. The harsh scrutiny of clinical trials is needed, proceeding in tandem with basic science investigations. Premature trials could doom a promising line of work.[131]

Opinion

The pipe dream can only become reality if the concept holds under the rigours of well-designed and correctly implemented clinical trials.

Conflict of interest statement

L H Opie has given lectures on behalf of Abbott, Aventis, Bayer, Cardiovascular Therapeutics, and Servier and received travel funds. These lectures have been approved for continuing medical programmes in South Africa or by the American Heart Association for satellite events. He has no conflicts of interest with respect to this article. P J Commerford has been an investigator in several pharmaceutical trials in heart disease; any financial support from those trials were accrued to the University of Cape Town Cardiac Clinic Research Fund. He has received honoraria from Bristol-Myers Squibb and Aventis. B J Gersh serves on the Scientific Advisory Board of Cardiovascular Therapeutics. He has received honoraria and educational grants from Genentec and Astra Zeneca. He has served on the data monitoring committee of trials funded by Abbott Laboratories, The Medicines Company, Boston Scientific, and Guidant Corporation. None of these activities was related to the contents of this paper. M A Pfeffer has received honoraria and education or research grants, and serves as consultant for: Amgen, Astra Zeneca, Atherogenics, Bristol-Myers Squibb, Genzyme, Guidant, Mitsubishi Pharma Corp, Novartis, and Pfizer. He is named as a co-inventor on a patent awarded to the Brigham and Women's Hospital regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis and the Brigham and Women's Hospital, which is not linked to sales.

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