Cardiovascular remodelling in coronary artery disease and heart failure

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Remodelling is a response of the myocardium and vasculature to a range of potentially noxious haemodynamic, metabolic, and inflammatory stimuli. Remodelling is initially functional, compensatory, and adaptive but, when sustained, progresses to structural changes that become self-perpetuating and pathogenic. Remodelling involves responses not only of the cardiomyocytes, endothelium, and vascular smooth muscle cells, but also of interstitial cells and matrix. In this Review we characterise the remodelling processes in atherosclerosis, vascular and myocardial ischaemia–reperfusion injury, and heart failure, and we draw attention to potential avenues for innovative therapeutic approaches, including conditioning and metabolic strategies.

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Introduction

"The heart is the beginning of life, for it is by the heart the blood is moved…the source of all action", wrote William Harvey in 1673. The concept that such action could vary and the heart undergo remodelling in disease stretches back to the classic writings of Corvisart in 1806, when he described "two types of dilatation, active with thick walls and increased force of contraction, and passive with thinning of the walls and a decreased force of contraction". These notions correspond to current concepts of left ventricular hypertrophy and dilatation as two contrasting types of cardiac remodelling. Yet we have to wait till 1984 before the then novel term remodelling more precisely described the early and later structural changes that occurred in infarcted and non-infarcted ventricular myocardium after coronary artery ligation.[1] The next conceptual advance was that disproportionate thinning and dilatation occurred in the infarct region, accompanied by remote remodelling of non-infarcted myocardium, correlated with the extent of expansion. By 2000 the topic was sufficiently prominent to merit a consensus review document from the International Forum on Cardiac Remodelling. Patients with major remodelling underwent progressive worsening of cardiac function, and slowing or reversal of remodelling became a new goal of heart failure therapy.[2]

Originally, the term remodelling was proposed to characterise the response of remote myocardium to regional infarction and the progression from acute myocardial infarction to chronic heart failure.[1,3] Independently and at about the same time, the term remodelling was also used to characterise the progression of atherosclerotic vascular lesions.[4,5] In our Review, we advocate the concept of remodelling in a broader and more general sense to characterise the responses of myocardium and vasculature to potentially noxious haemodynamic, metabolic, and inflammatory stimuli, a process that is initially functional, compensatory, and adaptive in nature but, when sustained, progresses to structural changes that become self-perpetuating and pathogenic. Remodelling involves not only responses of the specific cardiovascular cells—cardiomyocytes, endothelium, smooth muscle cells—but also the interstitial cells and matrix.

Endothelial remodelling

The endothelial cell, positioned at the interface between the blood vessels and tissues, stands poised to sense the environment and signal modulations of vascular function to maintain homoeostasis and host defences against microbial invaders and injury.[6] Inappropriate signalling from vascular endothelial cells can also contribute to common diseases characterised by arterial remodelling, notably atherosclerosis and hypertension. Endothelial cells sense the environment in two major ways: local hydrodynamics, and responses to circulating chemical signals. Mediators released by endothelial cells in turn modulate the function of the subjacent vascular smooth muscle cells in a manner that decisively affects vascular remodelling.

Many risk factors for atherosclerosis impinge on endothelial cells uniformly throughout the circulation (eg, LDL), yet lesions of atherosclerosis tend to occur segmentally, particularly at branch points of arteries. The laminar shear stress in normal portions of arteries produces a programme from endothelial cells that mitigates the effects of risk factors such as LDL and tonically combats vasoconstriction by releasing nitric oxide, the endothelial-derived relaxing factor. These effects include suppression of vasoconstrictor, inflammatory, and prothrombotic gene expression through increasingly well understood molecular mechanisms. At flow dividers, disturbed flow impedes such atheroprotective functions, with activation of the proinflammatory transcription factor nuclear factor κB to provoke recruitment of inflammatory cells, and impaired vasodilator activity. The consequent accumulation of leucocytes, mainly mononuclear phagocytes, in the arterial intima sets the stage for foam-cell formation due to engulfing of modified lipoproteins that build up in the intima exposed to excess LDL (figure 1).[7]

Search strategy and selection criteria

For this Review, each contributing author selected references that he viewed as most relevant for his particular topic.

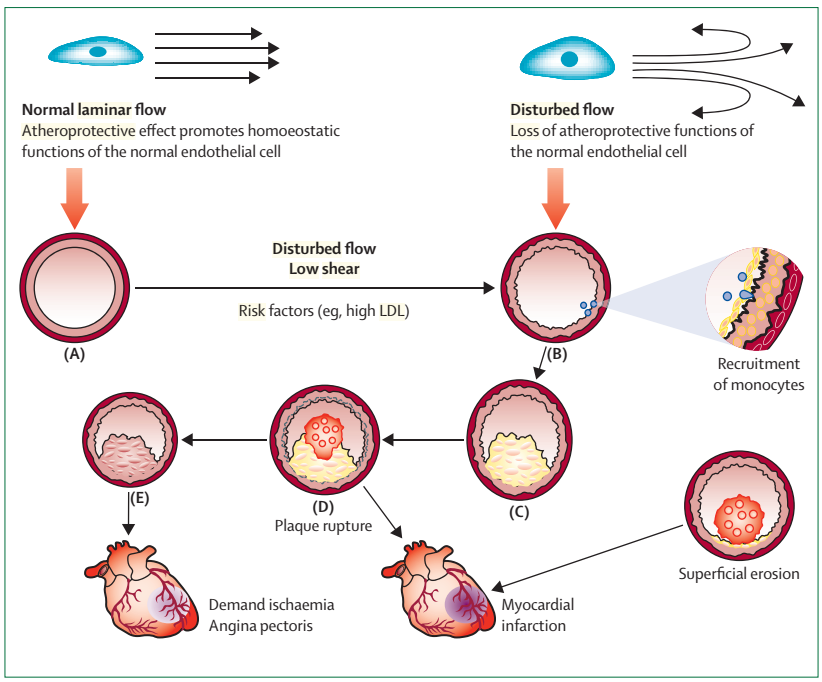

Figure 1: **Positive and negative arterial remodelling influences the clinical consequences of atherosclerosis**
Normal laminar shear stress (upper left) elicits the atheroprotective and homoeostatic functions of endothelial cells. These functions maintain normal arterial calibre and properties (A). The reversed arrows in the upper right represent disturbed blood flow as encountered in regions of lesion predilection. In (B) the red circle portrays the tunica media, and the inner circle indicates the intima of the artery. Disturbed flow promotes the recruitment of monocytes, as depicted to the right in the enlarged nascent plaque (B). Monocyte/macrophage accumulation yields a thin-capped, lipid-rich inflamed plaque (C), which can rupture and cause a thrombus (D), leading to myocardial infarction (central bottom). Alternatively the plaque in (E) can undergo constrictive remodelling to promote flow-limiting stenosis that can cause demand ischaemia and angina pectoris. Less commonly, superficial erosion (bottom right) can cause myocardial infarction.

Macrophage foam cells produce many mediators that amplify and sustain the local inflammatory response that promotes progression and the eventual thrombotic complications of atherosclerosis. Moreover, these messages from macrophages signal smooth muscle cells to enter the arterial intima from the tunica media, where they elaborate extracellular matrix macromolecules that lead to fibrous lesions. These lesions can cause arterial stenoses and impede blood flow, leading to ischaemic conditions such as angina pectoris, intermittent claudication, and cerebrovascular disease. Loss of arterial elasticity increases pulse pressure, a finding associated with ageing and heightened risk of cardiovascular events. The arterioles resist the plaque formation that is characteristic of larger arteries, but develop medial hypertrophy and intimal thickening, a form of remodelling associated with high blood pressure and implicated in sustaining and aggravating hypertension.[8]

Matrix metalloproteinases promote arterial remodelling. Among the extracellular matrix molecules manufactured by intimal smooth muscle cells, proteoglycans bind lipoprotein particles, increasing LDL residence time in the intima and favouring oxidative modification in this environment that is sequestered from plasma antioxidants.[9] Smooth muscle cells, unlike endothelial cells, do not sense luminal shear stress but experience cyclic circumferential deformation due to arterial pulsations. This force augments the synthesis of proteoglycans by smooth muscle cells thereby increasing LDL retention in the intima.[10] Smooth muscle cells in the intima, activated by proinflammatory cytokines produced by macrophages (eg, interleukin 1), can also produce more collagen, leading to arterial fibrosis characteristic of ageing and hypertension, thereby boosting the release of matrix-degrading proteinases (eg, matrix metalloproteinases). These enzymes can remodel the arterial extracellular matrix structure, including the elastin in the external elastic membrane that forms the artery's outer perimeter. This matrix remodelling paves the way for abluminal expansion—or outward growth—of the growing atheroma (positive remodelling) that preserves the lumen of the artery and maintains flow.[11] Ultimately, plaque growth can outstrip this compensatory enlargement of the artery wall, allowing the atheroma to encroach on the lumen and cause stenosis (figure 1).

The plaque macrophages themselves secrete many matrix-degrading proteinases when they encounter inflammatory signals. These enzymes can attack on a different front—the plaque's fibrous cap, a structure that typically overlies the lesion's macrophage-rich lipid core at the inner perimeter of the artery.[12] Collagenolysis due to enzymes overproduced by macrophages can weaken and thin the fibrous cap, rendering it susceptible to disruption.[13] Fibrous cap fracture allows coagulation proteins in blood to contact the procoagulant tissue factor generated by macrophages in response to proinflammatory cytokines, unleashing the thrombotic cascade and promoting local clot formation. This scenario causes most fatal myocardial infarctions.

There are many more macrophage-packed and proteinase-packed plaques than there are those that rupture. The mechanisms that trigger a susceptible plaque to rupture and provoke thrombosis at a particular instant remain poorly understood. Thus, despite all of the newer insights into plaque biology and remodelling, we still have a fragmentary understanding of the precipitants of clinical events and the process might hinge not only on the vulnerable plaque, but also on the vulnerable patient. Moreover, superficial erosion of the endothelial monolayer—another type of plaque disruption—causes a substantial minority of lethal myocardial infarctions. The mechanisms of formation and of triggering thrombotic events due to superficial erosions remain even less well defined than the mechanisms for episodes of acute plaque rupture.[12–14]

Most episodes of plaque disruption probably pass below the clinical threshold and do not cause a sustained total arterial occlusion such as the type of thrombi that lead to ST-segment elevation myocardial infarctions. Rather, they cause mural thrombi rooted in the intimal lesion that form a provisional matrix that evokes a local

wound healing response. Platelet products and thrombin can signal proliferation of smooth muscle cells and extracellular matrix synthesis that remodels an initially lipid-rich lesion into a fibrous plaque. Contrary to outward remodelling, the healing process causes constrictive remodelling, restricting the lumen and favouring the formation of flow-limiting stenoses.[12] Plaque calcification, previously regarded as a passive degenerative process, we now know to involve a complex biological cascade subject to considerable regulation and associated with inflammation.[15]

Arterial remodelling, often beginning with altered endothelial function, has many faces and varies throughout the life history of an atheroma or a vessel subjected to chronic hypertension. The biological mechanisms described here not only shed light on the pathogenesis of common cardiovascular diseases, but also have therapeutic implications for daily practice. Control of blood pressure can limit the adverse remodelling of both conduit and resistance arteries, reducing the risk of stroke and aggravation of atherosclerosis. Lipid lowering, particularly with statins—a class of drugs with direct anti-inflammatory effects beyond LDL reduction—can limit plaque progression and in some cases, can regress lesions and change plaque characteristics that are associated with rupture and thrombosis.[16]

Coronary microvascular dysfunction and remodelling in ischaemic and reperfused myocardium

Remodelling of the epicardial coronary arteries has preoccupied clinical cardiologists because constrictive remodelling often yields stenotic plaques that cause chronic myocardial ischaemia, whereas expansive remodelling characterises plaques that rupture and provoke acute thromboses. The reperfusion era brought substantial changes in the management of acute myocardial infarction. The relief of symptoms in stable coronary artery disease and the prognosis of acute coronary syndromes have improved substantially with reperfusion and coronary revascularisation, but these successes should not divert attention from the coronary microcirculation, which evades direct visualisation and intervention, but ultimately determines the extent of myocardial perfusion and function and the clinical outcomes of ischaemia–reperfusion injury.[17,18]

Experimentally, multiple and interactive mechanisms mediate coronary microvascular dilation during myocardial ischaemia, including autoregulatory adjustments to reduced perfusion pressure, release of adenosine and nitric oxide, and hypoxia.[19] Yet, even during profound myocardial ischaemia, coronary vasodilation is not at a maximum and substantial residual coronary vasoconstrictor tone remains in the microcirculation.[20] The mechanisms of such persistent vasoconstriction during myocardial ischaemia are largely unclear, but include α-adrenergic coronary vasoconstriction, in particular during exercise, and cardiocardiac reflexes in coronary interventions.[21]

Under controlled experimental conditions, recruitment of the persistent dilator reserve by pharmacological agents improves flow and function in ischaemic myocardium.[20,22] Vasodilator reserve also persists distal to chronic stenosis, producing impaired resting flow and function. Experimental models of hibernating myocardium[23] have blunted myogenic vasodilatation and increased constriction in response to endothelin.[24] Chronically ischaemic hibernating myocardium also displays structural remodelling of the coronary microvasculature with mild hypertrophy of smaller and atrophy of larger microvessels[25] and reduced vascular distensibility.[24]

Reperfusion—ie, removal of the flow obstruction at the site of the epicardial culprit lesion—does not simply restore coronary microvascular perfusion, but imposes an acute stress, apart from and in addition to any pre-existing chronic remodelling. Stressors include particulate debris and soluble substances originating from the culprit lesion[26] as well as functional and structural changes originating in the coronary microvasculature itself.[27] In the most extreme but nonetheless relatively frequent cases, the stress of reperfusion to the coronary microvasculature results in no-reflow despite a patent epicardial coronary artery. Spontaneous or interventional plaque rupture at the culprit lesion releases particulate debris from the atherosclerotic lesion that mixes with platelet aggregates and coagulation material and can lodge in the coronary microcirculation (figure 2).

Experimentally, coronary microembolisation causes patchy microinfarcts with a subsequent inflammatory reaction.[28] Autopsy of patients with unstable angina who had sudden deaths can also show embolic material within the coronary microcirculation and patchy microinfarcts.[29] Moreover, remodelling with microvascular dysfunction as measured by various techniques strongly affects late mortality in patients with patent epicardial vessels after mechanical or pharmacological reperfusion.[18] Coronary microembolisation not only causes microinfarcts and increases infarct size, but also interferes with potentially protective conditioning strategies.

In pigs, coronary microembolisation several hours before sustained coronary occlusion augments myocardial tumour necrosis factor (TNF) α expression and protects through the survivor activating factor enhancement (SAFE) pathway,[30,31] possibly explaining in part the clinical association of preinfarction angina with protection from infarction.[32,33] Some interventionalists do not use ischaemic postconditioning for fear of coronary microembolisation from further manipulation of the culprit lesion. However, even if coronary micro-embolisation occurring at the time of reperfusion adds to infarct size in pigs, ischaemic postconditioning still largely reduces infarct size, and this protection is not offset by coronary microembolisation.[34] The only way to

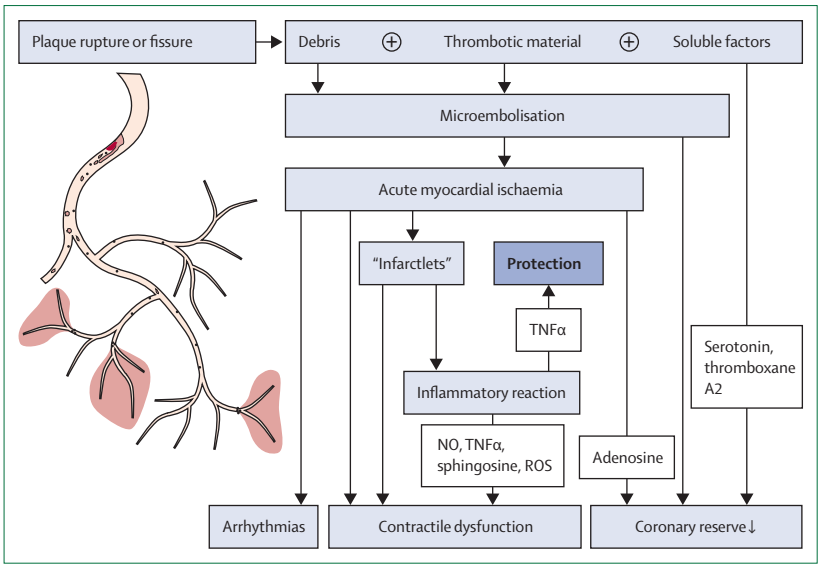

Figure 2: **Role of microembolisation in coronary vascular remodelling**
Plaque rupture or fissure without complete epicardial coronary occlusion releases particulate debris from the atherosclerotic culprit lesion, which, together with superimposed thrombotic material and soluble substances such as serotonin and thromboxane A_2, is washed into the coronary microcirculation by the residual blood flow. Coronary microembolisation causes microinfarcts with an inflammatory reaction. Inflammatory mediators such as nitric oxide (NO), tumour necrosis factor (TNF) α, and sphingosine induce contractile dysfunction through increased reactive oxygen species (ROS) formation and oxidative modification of the contractile machinery. TNFα in lower concentrations is, however, cardioprotective (upward arrow). Arrhythmias, contractile dysfunction, and impaired coronary reserve are the functional consequences of coronary microembolisation. Modified from Heusch and colleagues.[26]

prevent embolisation of particulate debris in patients might be its capture and removal with protection devices, but the results of these strategies have been mixed.[26]

In patients undergoing elective interventional revascularisation, rupture of the epicardial culprit lesion releases not only particulate debris but also soluble vasoconstrictor, thrombogenic, and inflammatory factors that all contribute to microvascular flow impairment (figure 2). The nature of these soluble factors depends partly on the underlying lesion and situation (native *vs* saphenous vein graft, acute coronary syndrome *vs* elective intervention), but serotonin, thromboxane A_2, and endothelin are important vasoconstrictors[35,36] and TNFα impairs endothelial dilator function.[35] Aspiration devices that remove thrombus and atherosclerotic debris can also remove these vasoconstrictors and other soluble factors. Their functional antagonism is another attractive target in treatment of microvascular obstruction and no-reflow phenomena after percutaneous coronary intervention (PCI). Nitroprusside and verapamil effectively relieve such microvascular obstruction, whereas protection by adenosine is less certain.[35,37]

Apart from particulate and soluble factors originating from the upstream culprit lesion, the microcirculation suffers directly from myocardial ischaemia–reperfusion, even when a virgin coronary artery experiences experimental occlusion and reperfusion.[27] Endothelial cell swelling and eventual sloughing together with platelet aggregates obstruct the capillary bed, and interstitial oedema compresses the vasculature. More advanced capillary destruction goes along with intramural bleeding.[38] These severe structural changes are localised to the area of infarcted myocardium and possibly represent a consequence rather than a cause of myocardial infarction. Interventions that protect from infarction usually also lessen microvascular obstruction and no-reflow. Lack of reflow in reperfused myocardial infarction associates with poor recovery of function and prognosis.[39] However, no-reflow phenomena are only the tip of the iceberg and reflect the most severe form of microvascular impairment. Direct and indirect measures of microvascular function such as a calculated index of coronary microvascular resistance, ST-segment resolution on electrocardiogram, or myocardial blush grade predict prognosis in patients undergoing primary PCI.[40,41]

In pigs with myocardial infarction, altered vasomotion extends beyond the infarcted myocardium to the remote remodelled myocardium where vascular growth does not keep up with myocardial hypertrophy, but the vasoconstrictor effect of angiotensin and endothelin is blunted to minimise a potential impairment of myocardial oxygen supply.[42]

Remodelling after myocardial reperfusion injury

Acute myocardial infarction is a major cause of death and disability worldwide. Much of this morbidity and mortality relates to the remodelling that occurs post infarction. Although cardiac remodelling is often associated with events that occur in the weeks and months after an acute myocardial infarction, its consequences invariably relate to the initial size of the associated infarction. Therefore optimum positive remodelling after a severe acute ischaemia–reperfusion event can improve patient outcomes.

The first treatment priority for patients presenting with an acute ST-segment elevation myocardial infarction is timely reperfusion to reduce the extent of myocardial ischaemic injury and limit the size of the evolving infarction. This aim is achieved by either primary PCI or thrombolysis. However, myocardial reperfusion not only saves the majority of the ischaemic cells, but paradoxically has a downside called myocardial reperfusion injury with further fresh myocardial injury and cardiomyocyte death, in part from microvascular injury and obstruction (see above). Although optimum reperfusion, with use of novel antiplatelet and antithrombotic drugs to maintain the patency of the infarct-related coronary artery, is standard practice, there is currently no well established therapy for protecting the heart against myocardial reperfusion injury (figure 3). Because lethal reperfusion injury accounts for up to 50% of the final infarct size,[43] prevention or limitation of such injury could improve the outcome of patients substantially, both by decreasing the size of the eventual infarct and thereby limiting the severity of consequent heart failure.[44]

Experimental studies have identified an endogenous self-protective programme that can be activated by brief cycles of myocardial ischaemia–reperfusion that precede (ischaemic preconditioning)[45] or follow the sustained myocardial ischaemia during early reperfusion (ischaemic postconditioning).[46] A cardioprotective programme can even be activated at a distance,[47] by brief cycles of ischaemia–reperfusion in organs remote from the heart—ie, remote conditioning.[48]

Reperfusion injury can be attenuated through activation of cardioprotective signalling pathways. Many signalling steps of such pathways have been identified in numerous experimental studies. Extracellular trigger molecules (neurohormones, autacoids, cytokines) activate through sarcolemmal receptors an intracellular cascade of proteins and ultimately converge on the mitochondria.[49] Yellon and colleagues introduced the reperfusion injury salvage kinase (RISK) pathway,[50,51] including a range of anti-apoptotic kinases such as Akt and the p42/p44 mitogen-activated protein kinase. Unexpectedly, this protective pathway was diminished in animals with features of the metabolic syndrome or in diabetic obese mice,[52–54] and in human muscle taken from patients with diabetes undergoing coronary artery bypass grafting (CABG).[55] Insufficient RISK activation[52–54] accounted for this impairment, illustrating how animal experiments can simulate the major comorbid pathological changes present in patients with coronary heart disease.

Strong experimental data were followed by evidence from smaller clinical trials that supported the notion of cardioprotection by other interventions, namely: (1) ciclosporin, which inhibits opening of the mitochondrial permeability transition pore;[56,57] (2) ischaemic postconditioning during primary PCI;[48,58–60] (3) remote ischaemic preconditioning by intermittent limb ischaemia–reperfusion, especially in elective CABG and in primary PCI;[61–63] (4) activation of STAT-3[64] or STAT-5,[65] which are part of the SAFE pathway;[31] and, most recently, (5) the antidiabetic incretin mimetic exenatide[66] and the β-adrenergic blocking drug metoprolol.[67] Approaches to limit adverse remodelling also include clinical benefit from glucose-insulin-potassium (GIK) given intravenously in the ambulance to patients with acute coronary syndrome[68] (an intervention that has yielded mixed outcomes when given too late).

The translation of the many encouraging experimental studies advocating cardioprotective strategies to reduce infarct size has not yet resulted in robust evidence-based medicine with improvement of patient outcome. There are many reasons for such difficulty in translation, including the reductionist nature of many experimental models on the one hand and the many comorbidities and comedications in elderly patients on the other hand.[44] Ischaemic preconditioning has been translated to patients in elective settings of interventional and surgical coronary revascularisation, but is not feasible in acute myocardial infarction because of its unpredictable onset.[32] Ischaemic postconditioning has been successfully translated in smaller studies on selected patients undergoing primary PCI for acute myocardial infarction under tightly controlled conditions;[58–60,69] however, the duration of coronary occlusion, presence of collaterals, eventual spontaneous reperfusion before the intervention, and use of direct stenting are important variables that contribute to the difficulty in general use of ischaemic postconditioning in a real-world scenario.[70]

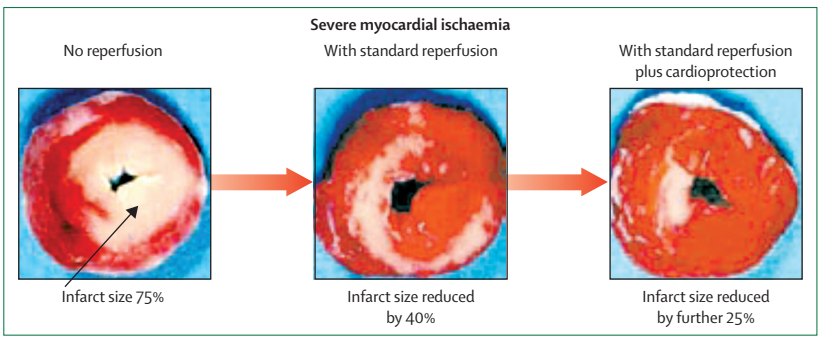

Figure 3: **Reduction of infarct size**
In acute myocardial ischaemia, rapid reperfusion decreases infarct size variably, roughly by about 40%, leaving 30% still damaged by lethal reperfusion injury. With molecular cardioprotection or pharmacological agents that inhibit reperfusion injury, the final myocardial infarct size can be rescued by a further 25%, thereby achieving a much smaller final infarct. Modified from Yellon and Hausenloy.[43]

The simplest and most successfully translated cardioprotection strategy is remote ischaemic preconditioning. Recent trials reported not only reduced infarct size, as assessed from biomarkers or imaging, but also reduced major adverse cardiovascular events and all-cause mortality in patients undergoing elective interventional[71] or surgical[72] coronary revascularisation with previous remote ischaemic preconditioning and in patients with acute myocardial infarction undergoing preconditioning during transport to the hospital for primary PCI.[73] If ongoing larger trials show benefit on clinical endpoints, guidelines might recommend its use in all ambulances transporting patients with acute chest pain and suspected acute coronary syndromes to the nearest hospital emergency room.

Myocardial remodelling in heart failure

Factors such as loading conditions, neurohormonal activation patterns, genetic background, and comorbid conditions affect the size, shape, and ultrastructure of the heart. In conditions such as pregnancy or endurance exercise terms such as physiological, adaptive, beneficial, or compensated remodelling are used, whereas during pathological stimulation by pressure or volume overload, the condition is described as maladaptive or decompensated remodelling.[74] The phenotype, including ventricular structure and mechanical function, is well characterised in patients, whereas mechanisms such as signal transduction have mainly been identified in cell and animal models.

Remodelling describes the reorganisation of myocytes, intercellular matrix components, and vessels in response

to the index stimuli. Clinical remodelling depends on internal diameters and myocardial wall thickness. Either of these can be reduced, normal, or increased, resulting in changes in the myocardium that depend on the loading conditions, neuroendocrine activation, and genetic factors (figure 4). In concentric remodelling, the ejection fraction is maintained, ventricular volumes are normal or reduced, and the left ventricular mass to volume ratio is increased. Clinically, this condition can present as heart failure with preserved ejection fraction.[76] By contrast is the pattern of heart failure with reduced ejection fraction and increased end-diastolic volume to wall thickness ratio, also giving heart failure symptoms.[77] In both conditions, remodelling involves reorganisation of myocytes, interstitial cells, and vessels leading to increased stiffness or impaired contractility, or both. Right ventricular remodelling results from increased filling pressures in response to left ventricular failure,[78] but also occurs in valve disease and primary pulmonary vascular hypertension.[79] Increased left ventricular stiffness results in left atrial remodelling that can promote atrial fibrillation, the most common arrhythmia in elderly people.[80] Therefore, remodelling not only affects the left ventricle, but also impairs the function of the right ventricle and atria.

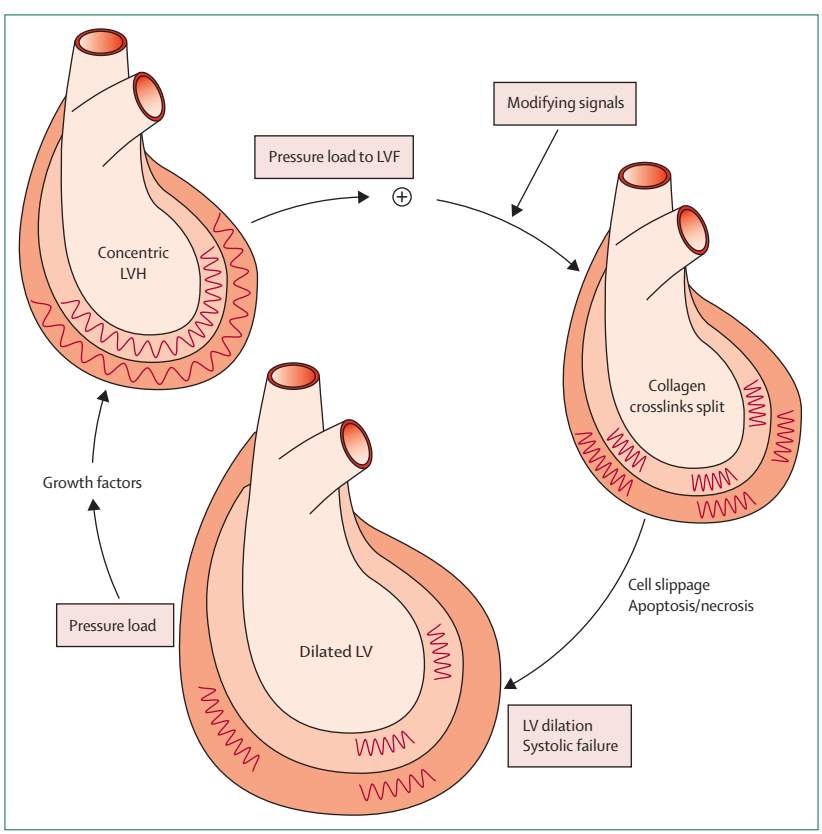

Figure 4: **Myocardial remodelling in response to pressure load**
Proposed transition from pressure load to concentric hypertrophy to dilated failing left ventricle (LV). Note the role of signals that break down collagen compared with the opposing role of tissue inhibitors of matrix metalloproteinases. The primary stimulus to the increased collagen are stretch-induced growth factors such as angiotensin II. Concentric remodelled myocardium undergoes splitting of the collagen crosslinks in response to modifying molecular signals such as metalloproteinases and other signals that disrupt collagen crosslinks to promote LV dilation and systolic heart failure. LVF=left ventricular failure. LVH=left ventricular hypertrophy. Adapted from Opie and colleagues.[75]

Myocardial remodelling is characterised by intrinsic changes of the cardiomyocyte and the interstitium. The failing myocardium, irrespective of its pathogenic origin, has typical features that relate not only to cardiomyocyte viability, neurohumoral control, and excitation–contraction coupling, but also to interstitial cells and matrix. Cardiomyocytes represent 20–30% of cells, but 70–80% of myocardial mass. Myocyte renewal can occur in the human heart[81] and is increased in experiments in response to exercise or injury.[82] Resident stem cells or bone marrow stem cells can transdifferentiate into myocytes.[81] Myocytes are capable of undergoing hypertrophy and shape changes accompanied by a myosin isoform shift.[83] Whereas pressure overload increases thickness, volume overload increases length.[84] In genetic familial hypertrophic cardiomyopathy, fibre disarray occurs.[85]

The failing human myocardium can contain many apoptotic cells.[86] A lesser amount of cell death can relate to various forms of remodelling[87] or ischaemia–reperfusion.[88] Autophagy is a physiological, often age-related, process in which myocytes digest damaged and modified proteins during chronic ischaemia,[88] hibernation,[89] and post infarct.[90] Inhibition of autophagy aggravates adverse remodelling, whereas increased autophagy improves experimental post myocardial infarction remodelling.[90]

Enhanced left ventricular wall stress activates the myocardial renin-angiotensin system resulting in myocardial hypertrophy.[91] Aldosterone[92] and angiotensin-II further promote interstitial remodelling.[93] α-Adrenergic stimulation induces myocardial hypertrophy.[94] Chronic β-adrenergic stimulation suppresses β-adrenergic receptors and augments Giα proteins in hypertensive cardiac hypertrophy[95] and in human heart failure,[96] while also inducing myocardial apoptosis.[97] These mechanisms provide a mechanistic background for evidence-based heart failure treatment with neurohumoral antagonists.[77]

Transmembrane calcium fluxes trigger calcium release from the sarcoplasmic reticulum. Released calcium re-enters the sarcoplasmic reticulum via the calcium ATPase (SERCA2a). In heart failure, excitation–contraction coupling is impaired.[98] In particular, SERCA2a is reduced in heart failure in human beings[99] leading to high cytosolic and low sarcoplasmic reticulum calcium concentrations. The resulting decrease in the calcium transient is aggravated by leaky ryanodine receptors,[100] experimentally secondary to increased activity of calcium/calmodulin-dependent protein kinase II.[98]

In the interstitial compartment, fibroblasts modify the extracellular matrix with effects on ventricular size, structure, and stiffness. Transforming growth factor β1 is involved in maladaptive remodelling,[101] and insulin-like growth factor 1 results in adaptive remodelling.[102] The maturation and stability of fibrotic scar tissue are of particular importance in infarct healing.[103] Matrix

metalloproteinases that degrade extracellular matrix proteins can increase ventricular remodelling in dilated cardiomyopathy or valve disease. Plasma biomarkers reflecting determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure in patients.[104]

The clinical effectiveness of interventions can support the relevance of such mechanisms in human beings. Unloading of the heart attenuates left ventricular hypertrophy and improves outcomes.[105] Renal sympathetic denervation reduces blood pressure[106] and myocardial hypertrophy.[107] High heart rates indicate poor outcome in patients with heart failure,[108] whereas rate reduction reduces left ventricular remodelling[109] and events.[110]

Impaired mitochondrial oxidative metabolism and adverse energetic remodelling of the failing heart

In addition to structural remodelling, remodelling of cardiac energy metabolism can contribute to the severity of heart failure.[111] In particular, both a decrease in energy production and a switch in energy substrate use that occur with remodelling can worsen heart failure.[111,112]

The progression of heart failure is associated with compromised myocardial energy production indicated by decreased concentrations of both ATP and phosphocreatine.[113,114] This depletion seems to result primarily from a decrease in mitochondrial oxidative metabolism,[111,112] which results in compromise of mitochondrial oxidation of both fatty acids and carbohydrates.[111] A compensatory increase in glucose uptake and glycolysis accompanies the reduced oxidative metabolism (figure 5).

As a result of the decrease in fatty acid oxidation and the increase in glucose uptake and glycolysis, the failing heart appears to revert toward a so-called fetal metabolic phenotype.[111,112] The decrease in oxidative metabolism and rise in glycolysis observed in the failing heart is associated with changes in expression and activity of metabolic enzymes consistent with this switch to fetal metabolism. These changes include the expression of peroxisome proliferator-activated receptor (PPAR) α and PPAR γ cofactor α, regulators of mitochondrial biogenesis and fatty acid oxidation enzyme expression, processes that are decreased in the failing heart.[116]

Although the failing heart shifts energy metabolism, the exact switch that occurs is unclear. The general consensus is that there is a switch from fatty acid to glucose use.[112,117] However, clinical studies disagree as to whether fatty acid oxidation is decreased,[118] increased,[119,120] or unchanged[121] in the failing heart. Irrespective of what occurs with fatty acid oxidation at the level of the myocardium, the hyperadrenergic state that develops in heart failure will increase blood concentrations of free fatty acid.[120] As a consequence, based on the Randle cycle, fatty acids will be preferred over carbohydrates for whatever mitochondrial oxidative capacity the heart retains.

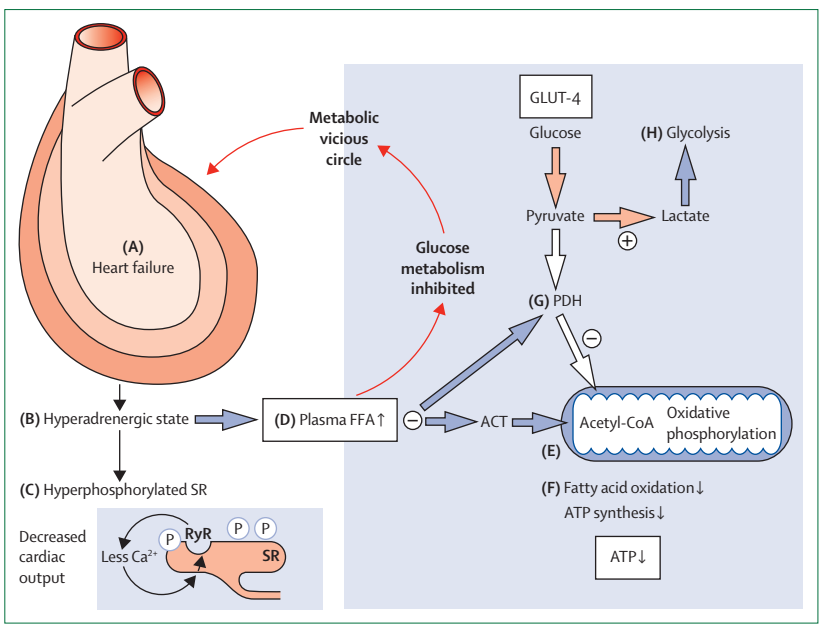

Figure 5: **The metabolic vicious circle in heart failure**
Dilation of the myocardium in heart failure (A) leads to adrenergic activation (B) that in turn hyperphosphorylates the SR (C) and increases concentrations of circulating FFA (D). FFA inhibit mitochondrial function at the level of ACT (E), thus inhibiting fatty acid oxidation and synthesis of ATP (F). Plasma FFA also inhibit PDH (G) to promote anaerobic glycolysis (H) rather than oxidative metabolism. SR=sarcoplasmic reticulum. RyR=ryanodine receptor. FFA=free fatty acids. ACT=acyl carnitine transferase. PDH=pyruvate dehydrogenase. GLUT-4=glucose uptake transporter 4. Adapted from Opie.[115]

With respect to the changes in glucose metabolism in heart failure, the heart uses two pathways for glucose metabolism: glycolysis and glucose oxidation (figure 5). Like fatty acid oxidation, glucose oxidation rates depend on mitochondrial oxidative capacity, and as such a decrease in mitochondrial function in the failing heart not only limits fatty acid oxidation, but also restricts glucose oxidation.[122] This decrease in glucose oxidation results from a decrease in the activity of pyruvate dehydrogenase, the rate-limiting enzyme of glucose oxidation. The production of protons and lactate rises because of augmented glycolysis and decreased glucose oxidation in heart failure. This increase in lactate and proton production in the failing heart can decrease cardiac efficiency and is potentially detrimental.[111]

Therapeutic strategies to attenuate adverse remodelling and worsening of heart failure include both increasing energy supply to the heart and switching energy substrate preference to increase cardiac efficiency.[111,112] Stimulating glucose oxidation is one way to improve both energy supply and cardiac efficiency, and it improves cardiac function in experimental models[123] and in human heart failure.[124] Changing of fatty acid oxidation rates offers another approach to improve cardiac function. However, there is no consensus regarding alteration of fatty acid oxidation. Increasing fatty acid oxidation might increase energy supply to the failing heart, but also could decrease glucose oxidation rates. By contrast, inhibition of fatty acid

oxidation will increase mitochondrial glucose oxidation and potentially increase cardiac efficiency in heart failure.

Clinical studies, however, suggest that inhibition of fatty acid oxidation with trimetazidine can improve cardiac function in patients with heart failure (see Gao and colleagues[125] for meta-analysis of existing clinical studies). Drugs that inhibit carnitine acyltransferase, a key enzyme involved in mitochondrial fatty acid uptake (figure 5), have beneficial effects on the function of the failing heart.[126,127] Decreasing cardiac fatty acid oxidation secondary to lowering circulating fatty acid concentrations also has potential benefit in heart failure. This process might include the use of PPAR agonists, which decrease the severity of heart failure in pigs,[128] although some drugs in this class can aggravate clinical heart failure.

Some of the benefits of β-adrenergic receptor blockers might occur secondary to lowering of circulating free fatty acid concentrations, as shown with carvedilol.[129] When given chronically to patients with systolic heart failure, carvedilol compared with atenolol, bisoprolol, metoprolol, and nebivolol in randomised direct comparison trials reduced all-cause mortality.[130] Similar metabolic principles might explain the clinical benefit in some studies of GIK given intravenously in the ambulance to patients with acute coronary syndromes[68] and the reduction of infarct size with the β-adrenergic blocker metoprolol when given intravenously before reperfusion.[67]

Summary

Remodelling of the heart and vessels characterises coronary artery disease, hypertension, and heart failure. Remodelling of the coronary arteries starts in the endothelium and progressively advances towards the atherosclerotic plaque that when causing ischaemia and infarction provokes myocardial remodelling. The arteriolar microvascular response to hypertension, luminal narrowing, smooth muscle hyperplasia, and medial thickening perpetuates raised blood pressure that predisposes to myocardial ischaemia, infarction, and failure. These biological mechanisms not only shed light on the pathogenesis of common cardiovascular diseases, but also have therapeutic implications for daily practice. Control of blood pressure can limit the adverse remodelling of both conduit and resistance arteries. Lipid lowering can modulate the remodelling of atherosclerotic lesions and change plaque characteristics associated with rupture and thrombosis.

A wealth of sound animal experimental data has identified several potential therapeutic targets for the modification of microvascular dysfunction and reperfusion injury. Nonetheless, the results of clinical trials have been disappointing, a discord that might be explained by species differences in microvascular function, the presence of comorbidities and co-medications in patients as opposed to animals, and differences between the evolving and dynamic course of clinical myocardial infarction by contrast with early rapid reperfusion experimentally. Also by contrast with experimental reperfusion studies, the typical patient with myocardial infarction presents relatively late in the clinical course by which time the ability to make a difference is limited. Thus reperfusion and treatment of reperfusion injury must be initiated as early as possible to avert damage to the myocardium and the coronary microcirculation.

Substantial remodelling of the myocardium occurs in response to reperfusion for acute myocardial infarction. A reduction in such adverse myocardial remodelling can be achieved experimentally by stimulation of molecular defences such as the RISK and SAFE pathways at the time of reperfusion. Activation of protective pathways by ciclosporin A or metoprolol at reperfusion, remote limb conditioning before surgical revascularisation or in the ambulance, and early infusion of GIK provide protection in patients. Positive results of larger clinical trials would justify greater use of such therapies to reduce adverse remodelling during reperfusion.[44]

The extent of myocardial remodelling relates to the reorganisation of cardiac function and structure in response to physiological (adaptive) or pathological (maladaptive) stimuli, involving all tissue components including myocytes, interstitial cells, and interstitial matrix. Remodelling is reflected in changes of excitation–contraction coupling, neurohormonal activation, and morphology. The index events are different, such as hypertension, overload hypertrophy, and increased wall stress secondary to myocyte loss after myocardial infarction and myocarditis or tachycardia secondary to neuroendocrine activation.

Remodelling can substantially change cardiac energy metabolism in the failing heart, manifested as decreased mitochondrial oxidative metabolism and increased glycolysis. Increasing of both overall energy metabolism and switching the source of cardiac energy used by inhibition of fatty acid oxidation are potential therapeutic approaches to treat heart failure.

Contributors

LO and GH combined sections written by each author and circulated the manuscript for general comment and changes to the text. The manuscript was a combined interactive effort, with each author making comments on each version, as well as on the final version. PL wrote the first section, submitted figure 1, read the final manuscript, checked the choice of words, and shortened the final text. GH wrote the second section with BG, submitted figure 2, read each revision from each author, and read and corrected the final proofs. BG wrote the second section with GH and read and checked the final text sent to him by LO. DY wrote and revised the third section, submitted a revision of figure 3, and read and checked the final text sent to him by LO. MB wrote and revised the fourth section, visited LO to discuss the pre-final version of the text and the figure revisions, and read and checked the final version sent to him by LO. GL wrote the fifth section, interacted with LO about details of metabolism and remodelling, helped to select the final figure and its legend, and read and checked the final text sent to him by LO. LO brought the other authors together in Cape Town in May, 2013, to present relevant data and to draw up initial details of the proposed paper, gave the title to the proposed combined paper, wrote the Introduction, revised and checked text and contents at every stage, interacted with GH in manuscript preparation from the five components, and submitted the final text.

Declaration of interests
MB has participated in advisory boards for AstraZeneca, Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi-Aventis, and Servier and in speakers' bureau for AstraZeneca, AWD Dresden, Bayer, Boehringer Ingelheim, Berlin Chemie, Daiichi-Sankyo, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier, and Medtronic. GH, PL, BG, DY, GL, and LO declare that they have no competing interests.

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