Cardiac Remodeling

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Rebuilding and remodeling following myocardial infarction: The Good, the Bad, and the Ugly of tissue repair

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Heart failure is a worldwide health problem. It appears most often in patients with ischemic cardiomyopathy. Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve survival and quality of life in patients with chronic heart failure, whether asymptomatic and without renin-angiotensin-aldosterone system (RAAS) activation or symptomatic and with RAAS activation, as well as in patients with acute myocardial infarction (MI) accompanied by left ventricular systolic dysfunction. Factors responsible for these salutory responses are under investigation. MI involves a segmental loss of cardiac myocytes followed by tissue repair, ie, scar tissue formation ("the good"). Fibrosis also appears remote to the MI ("the bad") and is considered the major component of adverse structural remodeling. De novo generation of angiotensin (Ang) II at sites of repair by myofibroblasts regulates the fibrogenic cytokine TGF-ß1, thus modulating the expression of extracellular matrix proteins. Chronic activation of the circulating RAAS and elevations in its effector hormones—Ang II and aldosterone—promote further fibrosis ("the ugly") at these sites. This overview addresses: (i) post–MI rebuilding and remodeling; (ii) the molecular and cellular events and regulatory signals involved in tissue repair; (iii) pharmacologic and molecular-based approaches as cardioprotective strategies; and (iv) the potential use of noninvasive monitoring modalities and genetic predisposition to remodeling.

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Heart failure is a worldwide health problem of major proportions. Its incidence and prevalence will only continue to escalate given the advancing age of our collective society. In the United States, at the turn of the next millennium, 1 in every 7 Americans will be over the age of 65; by 2010, one in every 5. It is estimated that several million Americans already have heart failure and each year 400 000 new cases will be diagnosed. Contributing to the increased incidence of heart failure is an improved overall management of patients with acute myocardial infarction (MI). This includes coronary care units, where monitoring and attention to electrical and mechanical complications post-MI are possible, and prompt restoration of coronary blood flow to the compromised segment of myocardium achieved through thrombolysis and/or mechanical intervention.

Particularly disturbing is the progressive nature of chronic cardiac failure and attendant poor patient prognosis. Following MI, an acute impairment in left ventricular systolic function (ie, ejection fraction, EF) may persist or even worsen as the ventricle is transformed from its normal elliptical shape to a mechanically disadvantaged, enlarged sphere. This pathophysiologic sequence led Jan and Mark Pfeffer to explore the potential for an angiotensin-converting enzyme (ACE) inhibitor to prolong survival and minimize such architectural remodeling in a rat model of MI.[1] Such salutory responses were indeed observed in this experimental setting, particularly in rats with larger MI and impaired EF. This important study became the impetus for a multicenter clinical trial that addressed the utility of an ACE inhibitor, introduced during week 1 post-MI, in reducing overall mortality and attenuating morbid events in asymptomatic patients with EF <40%. In this study, known as SAVE (Survival and Ventricular Enlargement), the ACE inhibitor (compared to placebo) was associated with a reduction in all-cause and cardiovascular-related mortalities and bouts of symptomatic heart failure that required hospitalization over the

course of 42 months.[2] Why an ACE inhibitor should achieve these favorable end points was uncertain. This circumstance is reminiscent of pellagra whose management was identified centuries before the discovery of niacin (nicotinamide) and the importance of a niacin-deficient diet was appreciated.

Many different lines of investigation have been explored to address the salutory properties of ACE inhibition post-MI, which are likely to be multifactorial. Some have focused on the aforementioned architectural remodeling,[3,4] others on an activated renin-angiotensin-aldosterone system (RAAS) and endocrine properties of its circulating effector hormones

(angiotensin [Ang] II and aldosterone) on classic target tissues, such as the vasculature and kidneys.[5] Yet other studies have addressed the potential for an ACE inhibitor to alter the structural remodeling of the heart that follows MI and which accounts for abnormal electrical and mechanical behavior of involved myocardium.[6-8] This report will address this latter topic and the recognition that Ang II, generated at the site of injury, is involved in modulating tissue repair via its regulation of the fibrogenic cytokine transforming growth factor β1 (TGF-β1).

REBUILDING AND REMODELING FOLLOWING INFARCTION

Definitions

The term remodeling is used frequently and can have different meanings. It may indicate: (i) *architectural* (or geometrical) iterations in ventricular size and shape and the thickness of its wall; (ii) *biochemical* modification of cardiac myocytes, such as myosin light chain phosphorylation, or expression of myocyte genes that favor iterations in myosin isoform composition or which induce programmed cell death (apoptosis); or (iii) *structural* alterations of infarcted tissue and viable myocardium remote to the site of MI by fibrous tissue. This review focuses exclusively on adverse structural remodeling due to fibrosis and which appears in the infarcted heart both at and remote to the site of injury and which will henceforth be referred to as rebuilding and remodeling of tissue, respectively.

Structural rebuilding and remodeling

From a morphologic perspective *(see Figure 1)*, cardiac tissue consists of a muscular compartment, composed of large cardiac myocytes, and an interstitial compartment that contains extracellular matrix and vasculature, each having their own distinctive cellular composition, and adrenergic nerves.[9] Myocytes account for but one third of all cells of cardiac tissue. Transmural MI involves a segmental loss of cardiac myocytes. Tissue repair must follow to restore structural integrity to the infarct site *(see Figure 2)*. Scar tissue, composed predominantly of type I and III fibrillar collagens, forms at this site over the course of 6 to 8 weeks.[10-12] This represents a rebuilding of injured tissue. It is a necessary response to myocyte loss and can be considered *"the good"* of tissue repair. Scar tissue is derived from type I fibrillar collagen, whose tensile strength exceeds that of steel.

SELECTED ABBREVIATIONS AND ACRONYMS	
Ang II	angiotensin II
Ao	angiotensinogen
AP-1	adaptor protein complex–1
ASO	antisense oligonucleotides
AT$_1$	angiotensin receptor subtype 1
ECM	extracellular matrix
ELAM-1	endothelial cell leukocyte adhesion molecule–1 = L-selectin
hsp	heat shock protein
HVJ-liposomes	hemagglutinating virus of Japan liposomes
ICAM-1	intercellular cell adhesion molecule–1
LVH	left ventricular hypertrophy
MMP	matrix metalloproteinases
MyoD	myogenic determination factor gene
myoFb	myofibroblast
NF-κB	nuclear factor kappa B
PDGF	platelet-derived growth factor
SPARC	secreted protein acidic and rich in cysteine
TFO	triplex-forming oligonucleotides
TGF-β1	transforming growth factor β1
TIMP	tissue inhibitor of matrix metalloproteinases
VCAM-1	vascular cell adhesion molecule–1
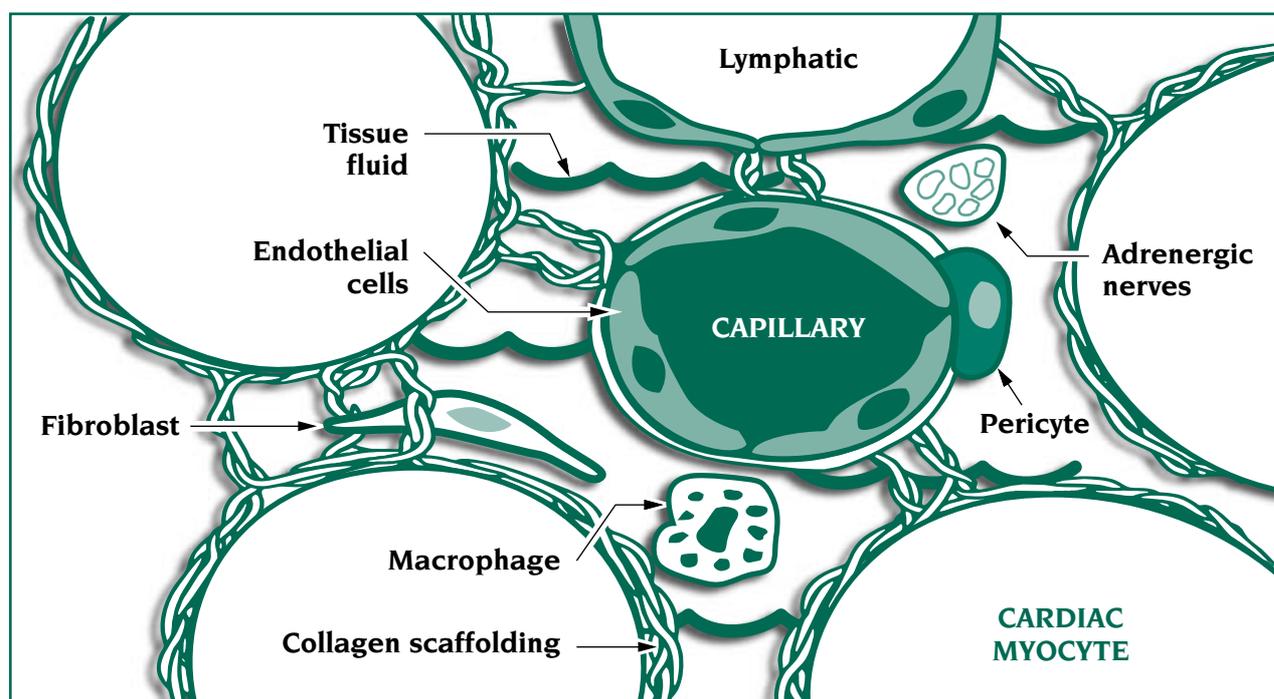
Figure 1. *The myocardium is composed of a muscular compartment, in which large cardiac myocytes are found, and an extracellular compartment with its own distinctive cell population (eg, fibroblasts, macrophages, endothelial cells, pericytes), a fibrillar collagen scaffolding, and adrenergic nerve terminals. A structural remodeling of the myocardium may include cardiac myocytes and/or constituents of the extracellular space. Modified from: Weber KT. In search of common ground. In: Weber KT, ed. Wound Healing in Cardiovascular Disease. Armonk, NY: Futura; 1995:295-305. Copyright © 1995, Futura. With permission.*

It therefore will withstand hemodynamic strains that exist in the normotensive or hypertensive ventricle. Ventricular pressure must be raised experimentally in excess of 500 mm Hg to disrupt cardiac tissue at the infarct site.[13] A ventricular aneurysm therefore suggests impaired scar tissue tensile strength.

In addition to fibrous tissue formation that appears at the infarct site, a large transmural MI is associated with fibrosis at remote sites that include viable left ventricle, interventricular septum and right ventricle.[6,7,14] In rats, the fibrous tissue response at these sites includes perivascular/interstitial fibrosis and microscopic scars that replace necrotic myocytes. In addition, endocardial fibrosis may appear in response to mural thrombus and fibrosis of the visceral pericardium. Morphologic studies of the failing explanted human heart with ischemic cardiomyopathy have shown that it is fibrosis at these remote sites that accounts for the dominant adverse structural remodeling of the myocardium and the majority (two thirds) of fibrous tissue found in these hearts; the infarct scar accounts for but one third.[15] Fibrosis at sites remote to the MI is a remodeling of tissue and can be considered *"the bad"* of tissue repair *(see Figure 2 and Table I)*.

INFARCT SITE

• Scar tissue formation

REMOTE SITES TO THE INFARCT

• Perivascular fibrosis of intramyocardial coronary arteries and contiguous interstitial fibrosis of right ventricle and interventricular septum

• Endocardial fibrosis

• Fibrosis of visceral pericardium

• Foreign-body fibrosis involving silk ligature around the coronary artery

OTHER TISSUES

• Foreign-body fibrosis involving silk ligature in skin

• Renal scarring following embolic infarction

• Subcutaneous pouch tissue

Table I. *Summary of anatomic coincidence between myofibroblasts, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and transforming growth factor β1 (TGF-β1) receptors and type I collagen gene expression at sites of fibrosis in the rat.*

LARGE TRANSMURAL MI

TISSUE REPAIR

① **REBUILDING**
- **Scar tissue**
- **Persistent myoFb and fibrogenic signals (eg, Ang II, TGF-β1)**

② **REMODELING**
- **Fibrosis at remote sites**

③ **Elevated circulating Ang II and ALDO**

Progressive LV remodeling & dysfunction

Circulating RAAS activation

Impaired renal perfusion
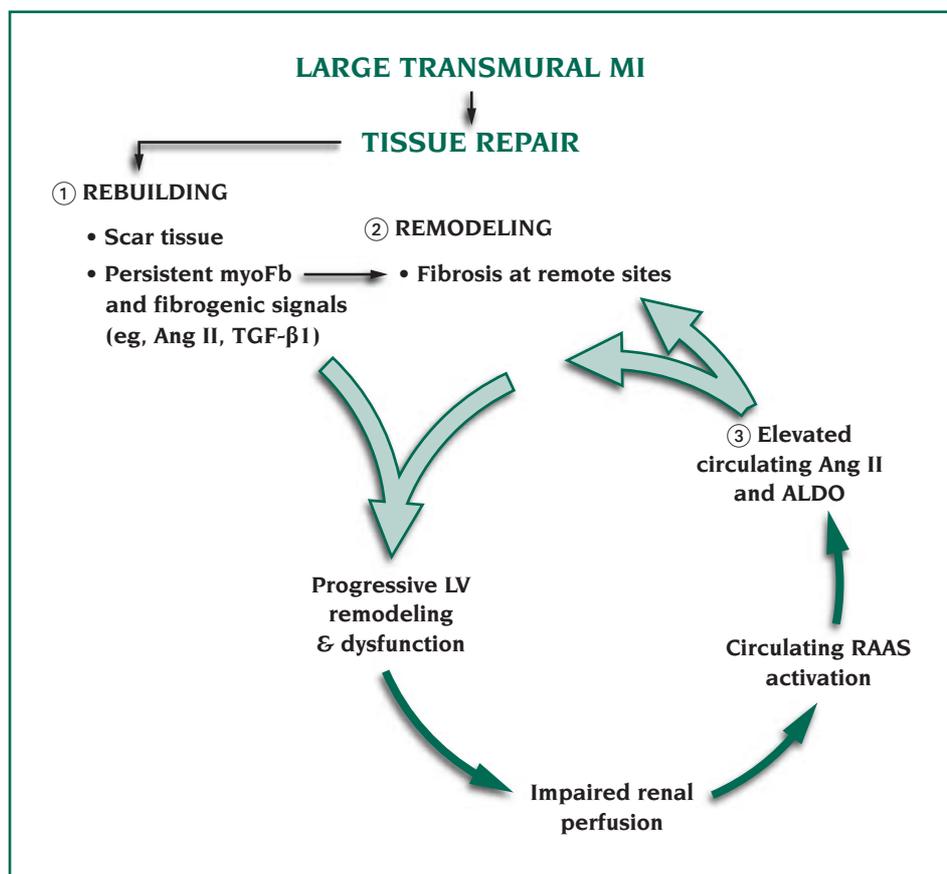
Figure 2.

Following a large transmural myocardial infarction (MI), a reparative process is initiated to rebuild necrotic tissue ①. Scar tissue formation is produced by myofibroblasts (myoFb) and their elaboration of fibrogenic signals, which include angiotensin II (Ang II) and transforming growth factor β1 (TGF-β1). These signals can traverse the interstitial space and gain access to distant sites of viable myocardium, where they invoke an unwanted fibrous tissue response, or remodeling ②. A persistence of myoFb is accompanied by a continued generation of fibrogenic signals that promote a progressive remodeling at remote sites. Together, the infarct scar and progressive fibrosis at remote sites adversely alter ventricular function, leading to impaired renal perfusion and activation of the circulating renin-angiotensin-aldosterone system (RAAS). Chronic RAAS activation and elaboration of its effector hormones, Ang II and aldosterone (ALDO) ③, promotes a progressive remodeling of cardiac tissue, and a vicious cycle ensues.

Functional consequences

Mechanical consequences of fibrous tissue formation include a reduction in tissue distensibility, which is reflected in left ventricular diastolic dysfunction.[16] For normal intravascular and, by implication, intraventricular volumes, this alone does not account for any marked increment in ventricular, atrial, and pulmonary venous pressures (>25 mm Hg) which would be necessary for the appearance of pulmonary edema. Rats with an infarct scar that occupies 40% of the ventricle's circumference 8 weeks post-MI, for example, do not die in pulmonary edema. Renal sodium excretion and intravascular volume remain normal in such rats since the circulating RAAS is not activated. In man, however, diastolic dysfunction post-MI can be associated with pulmonary edema when intravascular pressure is increased secondary to RAAS activation. Episodic pulmonary edema appears in this setting when intravascular volume is normal but pulmonary venous pressure is raised, in association with the appearance of supraventricular tachycardia (eg, atrial fibrillation) and reduced

diastolic filling period. A tonic contraction of scar tissue, based on the presence of fibroblast-like cells containing α-smooth muscle actin microfilaments (vide infra), may prove another causative factor leading to diastolic dysfunction. This merits investigation.

Scar tissue is anchored into viable myocardium by fibrillar collagen that encircles cardiac muscle.[3,4] This creates a structural heterogeneity within this normally homogenous tissue and can account for altered electrical dispersion and reduced threshold for reentrant ventricular arrhythmias. The border zone between viable myocardium and scar tissue is often the site of such arrhythmias. Endocardial resection and removal of this zone restores tissue homogeneity and reduces arrhythmogenic potential.[17]

Clinical compensation and decompensation

The presence or absence of symptoms of heart failure in patients with chronic left ventricular (LV) dysfunction

following MI is related to reduced renal sodium excretion and attendant expansion of intravascular and extravascular volumes. Activation of the circulating RAAS is responsible for renal sodium avidity in this setting. This has been clearly underscored in the now well-known SOLVD trial (Studies of Left Ventricular Dysfunction), where all patients entered had reductions in EF (<35%). Those randomized to the prevention arm of the study were asymptomatic; those in the treatment arm were symptomatic. Plasma renin activity was normal in asymptomatic patients (except those receiving diuretics, likely in excess), but was increased in symptomatic patients.[18] It should therefore be evident that EF does not predict renal perfusion and therefore the clinical severity of heart failure. The same can be said for the lack of correlation between EF and exercise tolerance or cardiac reserve.

Activation of circulating RAAS is quite important to cardiac remodeling following MI. Persistent elevations in circulating Ang II and/or aldosterone found in chronic cardiac failure are associated with an adverse structural remodeling of cardiac tissue of the right and left ventricles and atria *(see Figure 2)*. This includes perivascular fibrosis of intramural coronary arteries involving the contiguous interstitial space and microscopic scars, each of which are progressive in nature if the elevation in these circulating effector hormones of the RAAS is persistent.[19] This has been simulated experimentally in rats by implantation of a mini-pump containing either of these hormones. Progressive remodeling secondary to RAAS activation represents *"the ugly"* of tissue repair.

MOLECULAR AND CELLULAR EVENTS

Rebuilding at the site of infarction

Events contributing to tissue repair have been examined in experimental animals. Following cardiac myocyte necrosis, circulating and resident inflammatory cells are attracted to the site of injury. These include circulating cells of monocyte lineage, which elaborate various cytokines that activate macrophages, and circulating macrophages that first appear at the site of injury on day 1 and reach a peak level by day 3. Resident macrophages are also involved in repair, but appear more gradually (peak levels on day 14) and to a lesser extent than their circulating counterparts.[20] Macrophages express genes encoding for inducible forms of nitric oxide synthase and cyclooxygenase, each of which contribute to a complex scenario of repair that includes collagen degradation and ultimately apoptosis of these cells. Fibroblasts appear at the site of injury following the early entry of inflammatory cells. Macrophage-derived TGF-β1 is thought responsible for the phenotype transformation of fibroblasts into myofibroblasts (vide infra).[21,22] An activation of matrix metalloproteinases (MMP), which normally reside in the myocardium in latent form, appears early on during the reparative response. Activated MMP-1 (interstitial collagenase) degrades fibrillar collagen. Cleutjens et al[23] found increased collagenase activity at the infarct site on day 2, which peaks by day 7 and declines thereafter. Tissue inhibitors of MMP, referred to as TIMP, are expressed by fibroblasts on day 2 at the infarct site, declining thereafter over ensuing 14 days.

Cleutjens et al[11] have addressed the fibrogenic component of repair. Activated during week 1, it includes an orderly expression of fibronectin, type III, and then type I collagens. Increased expression of type III procollagen appears on day 2 and peaks by day 21, declining thereafter. Type I procollagen mRNA is increased on day 4 and remains elevated, albeit at a lower level until week 12, in keeping with ongoing collagen synthesis. Fibrillar collagen appears at the infarct site on day 7 and increases progressively to form a three-dimensional meshwork over the course of 8 weeks.[24] Hydroxyproline concentration and collagen cross-linking in the scar likewise increase during this period.[10,25] An architectural remodeling of scar tissue appears at week 6 and includes its thinning and retraction. Cells responsible for this active iteration in scar topography are phenotypically transformed fibroblast-like cells, termed myofibroblasts (myoFb), because like vascular smooth muscle they expresses α-smooth muscle actin and are contractile.[26] Their cell-cell connections and attachments to fibrillar collagen of scar tissue create a contractile assembly, whose tonic contraction appears in response to Ang II, catecholamines, and endothelin-1.[27-29]

In situ hybridization and immunohistochemistry have identified myoFb as responsible for the expression of fibrillar collagen genes at the infarct site.[11,14] They may be derived from several sources, a pool of interstitial fibroblasts that invade the site of injury and fibroblasts residing in the adventitia of intramyocardial coronary arteries. Their phenotype switch is thought to be induced by TGF-β1 elaborated by activated macrophages.[30] MyoFb are arranged in highly organized arrays that contribute to scar tissue thinning. They may furthermore prevent ventricular aneurysmal dilatation. MyoFb express a homolog of *Drosophila* tissue polarity gene frizzled *(fz2)* upon their migration into the infarct site,

which declines once their alignment has been attained.[31] The *fz2* gene may be involved in three-dimensional spatial control of tissue repair.

MyoFb persist in the infarct scar for prolonged periods of time (months in rats, years in man).[26,32] It is uncertain whether they remain active, elaborating signals that drive their turnover of collagen. If this is the case, it could have profound implications on a progressive adverse remodeling of infarcted and remote myocardium. Regulatory signals involved in promoting repair are discussed below.

Remodeling at remote sites

Soluble peptides generated at the site of MI (vide infra) reach distant sites in a concentration-dependent manner dependent on diffusion distance. Expression of procollagen I and III mRNAs by fibroblast-like cells is increased in the interventricular septum and right ventricle on days 4 and 7, respectively.[11] In the septum closest to the anterior transmural MI, where signals are generated, type I collagen mRNA remains elevated until day 28. In the right ventricle, more distant to the infarct site, message for these collagens is attenuated after day 7. Fibrillar collagen appears at each of these remote sites by day 14 and continues to accumulate for weeks. Fibroblast-like cells are involved in collagen turnover at these sites.

Collagen expressing α-smooth muscle actin–containing myoFb are seen within the endocardial fibrosis that appears in the left ventricle and the fibrosed visceral pericardium.[26]

REGULATORY SIGNALS

Local angiotensin II and TGF-β1

Normal heart valve leaflets, a site of high collagen turnover, are a site of high-density ACE- and Ang II–receptor autoradiographic binding.[33-35] Given that valve leaflets are composed primarily of fibrillar collagen, the prospect was raised for an analogous circumstance with fibrous tissue found at pathologic sites. Filip et al[36] reported that fibroblast-like cells found within leaflet matrix are myoFb with α-smooth muscle actin microfilaments. Their extensive cell-cell connections, which provide for intercytoplasmic cross-talk, and attachments to fibrillar collagen impart leaflets with dynamic and contractile behavior induced by Ang II and catecholamines. Leaflets have an extensive innervation.[37]

In vitro autoradiography has localized and quantitated ACE- and Ang II–receptor binding densities in normal and infarcted rat heart, where MI was created by permanent ligation of the left coronary artery.[14,38,39] Low-density binding is present in normal atrial and ventricular tissue. The same is true for noninfarcted tissue in the infarcted heart. By contrast, high-density binding is present at the site of MI. This is first evident on day 7, increased progressively thereafter over the course of 8 weeks, and is still evident, albeit at a reduced level, at 8 months. In serial heart sections, such high-density binding is anatomically coincident with the expression of type I collagen (in situ hybridization) and fibrillar collagen accumulation (histochemistry) *(see Figure 3)*. High-density ACE- and Ang II–receptor binding are each markers of active fibrosis. This is also the case for the endocardial and pericardial fibrosis that appeared in the infarcted rat heart, as well as the pericardial fibrosis following sham operation (without MI). It also holds true for the foreign body fibrosis that surrounds the silk ligature placed around the left coronary artery, incised and sutured skin that is part of the thoracotomy, and the infarcted kidney in rats with systemic embolization secondary to left ventricular mural thrombus. These findings strongly suggest Ang II is involved in tissue repair irrespective of the etiologic basis of injury or the tissue involved. It further sheds light on why tissue ACE activity is increased in the infarcted heart and why Ang II concentration is markedly increased at the site of MI.[40-42] Both are a result of fibrous tissue and its cellular population.

The fibrosed visceral pericardium, an external fibrous tissue surface and site of high-density ACE binding, offered a unique opportunity to address Ang I substrate conversion. An isolated, crystalloid perfused heart preparation, bathed by a superfusate of known chemical composition, was used for this purpose.[43] Ang II conversion is seen within 60 minutes and could be abrogated by the addition of ACEI to the superfusate.

To identify cells expressing ACE and Ang II receptors at these various sites, immunohistochemistry combined with emulsion autoradiography was used in serial heart sections of the infarcted rat heart studied at various time points post-MI.[26,44] α-Smooth muscle actin–positive cells are found to express ACE and Ang II receptors at all times examined over he course of 8 weeks. Macrophages present during the early inflammatory phase post-MI also express ACE as do endothelial cells, but not Ang II receptors. More recent findings[45] would indicate myoFb express
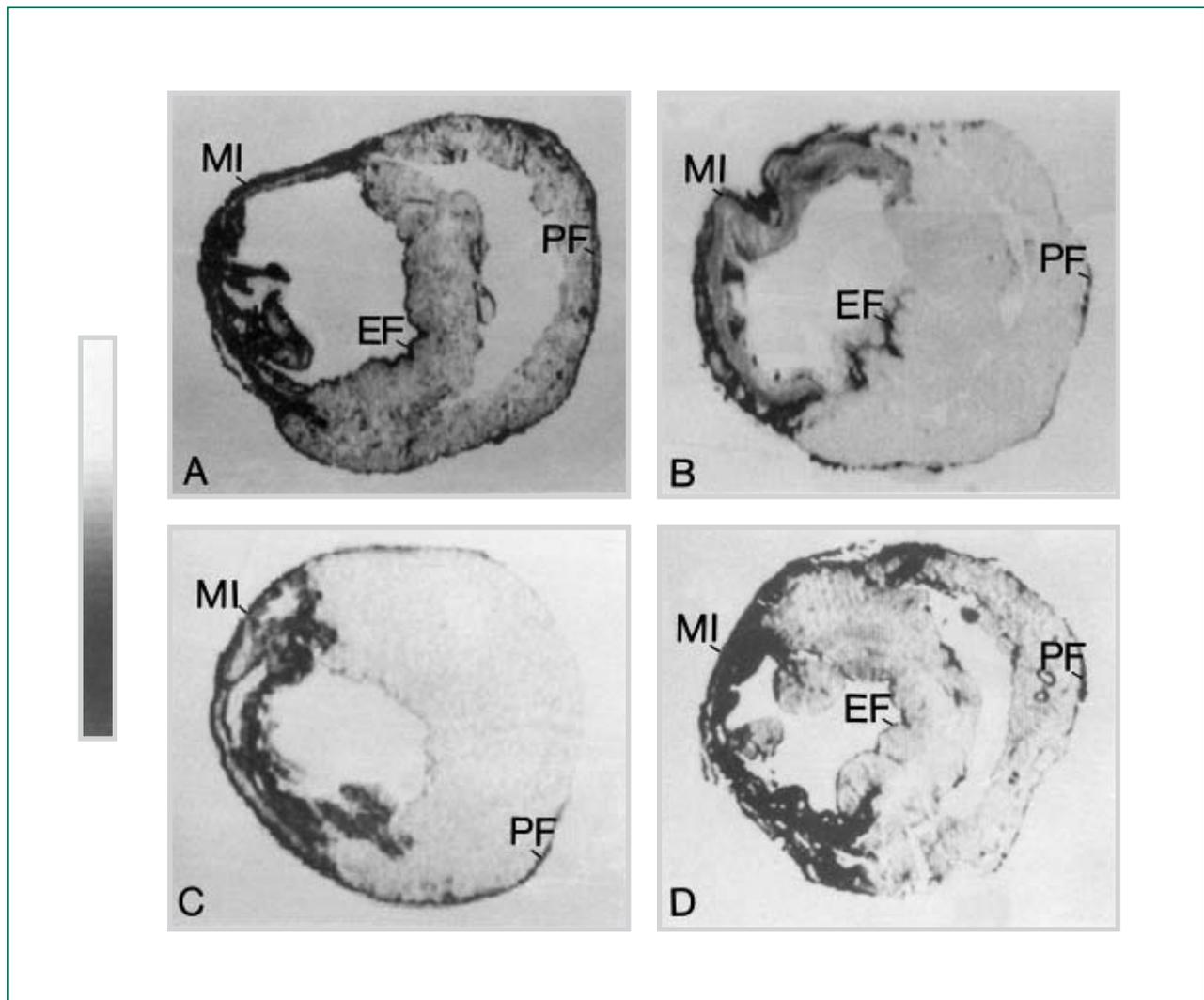
Figure 3. *Sites of tissue repair in the infarcted rat heart, 4 weeks following coronary artery ligation, were examined. In vitro autoradiography demonstrated high-density (dark gray) angiotensin-converting enzyme (panel A) and angiotensin II receptor (panel B) binding which are anatomically coincident with expression of type I collagen mRNA as detected by in situ hybridization (panel C) and fibrillar collagen accumulation evident in picrosirius red–stained tissue (panel D). Low-density binding appears light gray. MI, myocardial infarct; EF, endocardial fibrosis; PF, pericardial fibrosis.*

TGF-β1 receptors at these sites of repair and where the concentration of TGF-β1 is increased in comparison to noninjured tissue.

Katwa et al[46-48] isolated myoFb from 4-week-old scar tissue or from heart valve leaflets for cell culture studies. To qualify as an angiotensin peptide–generating unit, it was first necessary to address whether these cells express requisite components at mRNA and protein levels. This was found to be the case. Using reverse transcriptase polymerase chain reaction for amplification, myoFb express angiotensinogen (Ao), an aspartyl protease that proved to be cathepsin D, not renin, and ACE. Cytosolic generation of Ang I was evident in myoFb and could be abrogated by pepstatin A, a cathepsin inhibitor, but not a renin inhibitor. Immunofluorescein labeling and confocal microscopy identified the distribution of immunoreactive cathepsin D, plasma membrane–bound ACE, and angiotensin receptor subtype 1 (AT_1) receptors in intact, permeabilized myoFb. Displacement studies demonstrated these receptors were predominantly of the AT_1 subtype. Ang II–induced expression of type I collagen (mRNA and protein) was evident and mediated via AT_1 receptor–ligand binding. Campbell and Katwa[49] have recently reported Ang II–induced expression (mRNA and protein) of TGF-β1 by these cells mediated primarily by AT_1 receptor–binding tissue.

Pharmacologic interventions

Pharmacologic interventions with either an ACE inhibitor or an AT_1-receptor antagonist have further underscored the importance of locally generated Ang II and TGF-β1 in promoting both tissue rebuilding and remodeling.[3,4,6-8,22,45,50] Introduced at or soon after induction of MI in rats and dogs, infarct size, hydroxyproline concentration of scar tissue, and myocardium bordering on the infarct were each reduced by these agents. They likewise attenuated fibrous tissue formation at remote sites, eg, interventricular septum and right ventricle, endocardium, and visceral pericardium. In association with these interventions has been the attenuation in infarct tissue Ang II concentration and TGF-β1 expression. Similar responses have not been observed with β-adrenergic receptor antagonists.

The ability of these agents to protect an injured organ against unwanted fibrosis, mediated by the expression and elaboration of Ang II and TGF-β1, has now been demonstrated in multiple organs after diverse forms of injury, including kidney, lungs, liver, and skin. A detailed accounting of these findings can be found elsewhere.[51]

Thus, findings from multiple laboratories whose research is focused on addressing the regulation of unwanted fibrous tissue formation—a final common pathway to organ failure—have underscored the importance of de novo generation of Ang II by myoFb and autocrine induction of the fibrogenic cytokine TGF-β1 by this peptide in mediating tissue repair. This is now recognized as a common paradigm of repair. This concept draws attention to the potential adverse outcome on tissue structure associated with chronic elevations in circulating Ang II (vide infra).

A model of local tissue repair

Figure 4 depicts our working concept of tissue repair in the infarcted rat heart.[51] It features a two-part generation of Ang II and the fibrogenic cytokine TGF-β1: first, Ang II generated by activated macrophages, which stimulates expression of TGF-β1 that is integral to the phenotype conversion of fibroblasts to myoFb (①, see Figure 4) and second, a subsequent generation of Ang II by myoFb, which likewise stimulates TGF-β1 expression in an autocrine manner and regulates myoFb collagen turnover and fibrous tissue formation at the site of MI (②). Soluble Ang II and/or TGF-β1, present within tissue fluid, traverse the interstitial space to reach the interventricular septum and more remote right ventricle in a concentration-dependent pattern
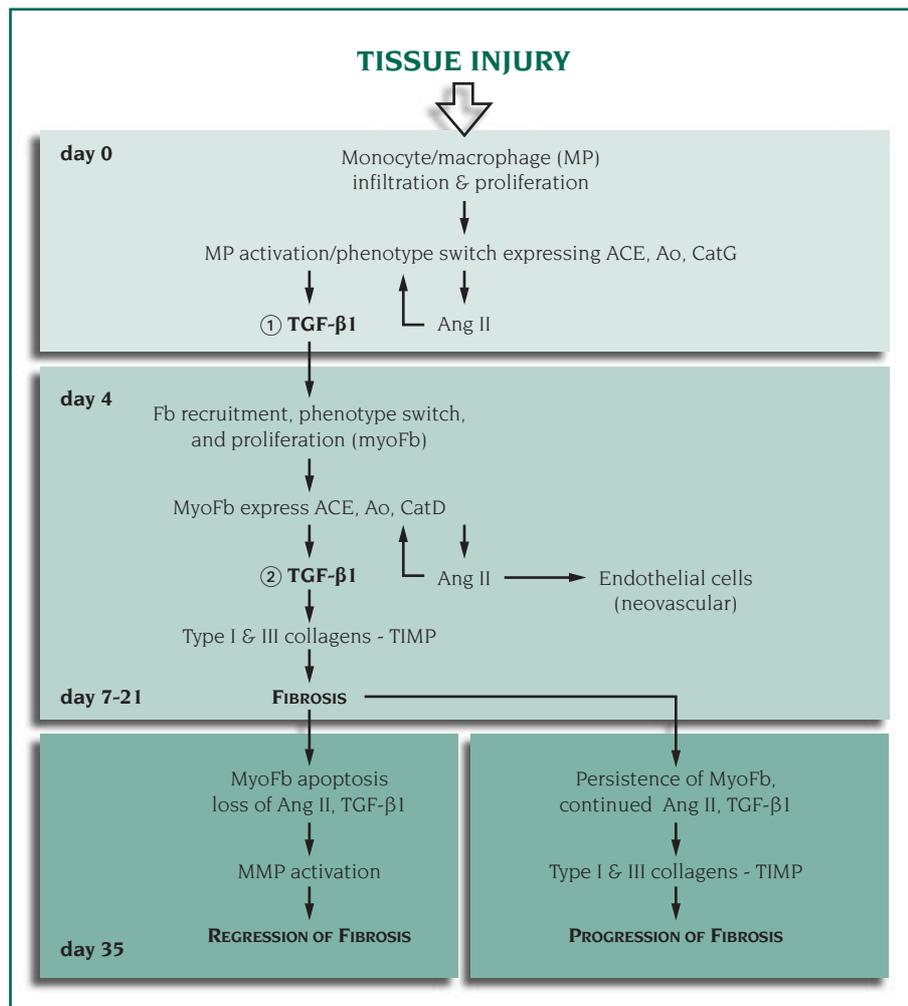
Figure 4. *A paradigm of tissue repair following acute myocardial infarction. See text for details. ACE, angiotensin-converting enzyme; Ang II, angiotensin II; Ao, angiotensinogen; CatD, cathepsin D; CatG, cathepsin G; Fb, fibroblast; MMP, matrix metalloproteinases; MP, macrophage; myoFB, myofibroblast; TGF-β1, transforming growth factor–β1; TIMP, tissue inhibitor of matrix metalloproteinases.*

of diffusion where they activate tissue repair at these remote sites. Other paracrine properties of these peptides include their interaction with other neighboring cells, such as endothelial cells of the neovasculature, involved in repair.

MyoFb persist in the infarct scar for prolonged periods of time (many months in rats, years in man), where they could continue to generate fibrogenic signals that perpetuate tissue repair and promote fibrosis at and remote to the MI *(see Figure 2)*. Why myoFb persist in the infarcted heart has not been elucidated. This contrasts to skin, where they disappear (via apoptosis) once healing is complete.[53] Their persistence in other organs is associated with a progressive fibrosis and predicts organ failure.[54] In an experimental model of toxic nephritis, progressive renal fibrosis is seen only in those kidneys in which myoFb failed to disappear. In humans with immunoglobulin A nephropathy, the extent of α-smooth muscle actin labeling on renal biopsy tissue is a predictor of poor renal function and correlates with progressive renal fibrosis.[55] The importance of persistent fibrogenic signals that perpetuate tissue repair and an unwanted fibrosis is emphasized not only within a particular organ, but takes on even broader implications for multiple tissues when such signals are chronically elevated and not neutralized in the circulation. Such a circumstance exists in chronic cardiac failure with persistent activation of the circulating RAAS.

Circulating angiotensin II and aldosterone

As noted earlier, chronic RAAS activation is associated with adverse cardiac remodeling and represents *"ugly"* remodeling, a progressive process, as reviewed previously.[56] This has been demonstrated in intact adult rats with endogenous activation of RAAS secondary to surgically induced unilateral renal ischemia or who received a mini-pump containing Ang II, and in uninephrectomized rats on a high-salt diet that received aldosterone.[19,57,58] Exogenous infusions raised circulating levels of these hormones to those found in chronic cardiac failure. These infusion models have several advantages in addressing hormone-induced remodeling: (i) they eliminate the need to create myocardial injury as a means to reduce renal perfusion; (ii) they eliminate such injury as a confounding variable from the analysis of cardiac structure, while placing a direct correlation between observed remodeling and these circulating hormones; (iii) the Ang II infusion model is more reliable than surgically induced unilateral renal

artery stenosis, where survival of the "endocrine" (or ischemic) kidney elaborating renin is not always predictable; (iv) they permit a direct assessment of Ang II vs aldosterone in promoting remodeling; and (v) they can be combined with a pharmacologic intervention.

Animals were studied at 2, 4 and 6 weeks of infusion and compared to age/gender-matched controls. The infusion of Ang II led to the gradual appearance of systemic hypertension and subsequent left ventricular hypertrophy (LVH). Remodeling, expressed as a perivascular/interstitial fibrosis, was observed in both normotensive, nonhypertrophied atria, and right ventricle, as well as the hypertensive, hypertrophied left ventricle. Great vessels were also involved. An increase in thickness of the adventitia of the pulmonary artery and aorta appeared in response to each hormone. These collective findings were evident within 2 weeks of the Ang II infusion and became progressively more advanced at 4 and 6 weeks, while they did not appear until week 4 of aldosterone administration and then became more advanced at week 6. They are further in keeping with a role for circulating Ang II in inducing cardiac remodeling and support the role of local Ang II in promoting tissue repair. At each fibrous tissue site, high-density ACE binding was found, suggesting that fibrous tissue ACE is not subject to feedback regulation. Ang II–receptor binding, on the other hand, was reduced, in keeping with receptor downregulation.[59] MyoFb were found at these fibrous tissue sites, as were α-smooth muscle actin–negative fibroblasts. Microscopic scars were also found in both atria and ventricles in this model and could be attributed to Ang II–induced release of catecholamines from the adrenal medulla, a site of high-density AT$_2$–receptor binding. Bilateral adrenalectomy or bilateral removal of each adrenal medulla prevented such scarring (and by implication myocyte necrosis).[60]

Aldosterone administration also leads to a perivascular/interstitial fibrosis of both atria and ventricles and increased adventitial thickness of the great vessels, but not until week 4 of the infusion, after which time they become progressively more advanced. Hence, and as is the case for the Ang II infusion model, hemodynamic factors could not be implicated. Instead, a direct association of the hormone with target tissue is more likely. This notion is further emphasized by coadministration of aldosterone and spironolactone, an aldosterone receptor antagonist. Brilla et al[61] administered a small dose of spironolactone, which did not prevent the gradual appearance of arterial hypertension in response to aldosterone. Fibrosis was pre-

vented in both ventricles. A larger dose of spironolactone, which achieved this end point and also prevented hypertrophy, had a similar cardioprotective effect. Captopril was used to prevent hypertension in association with aldosterone administration; nonetheless, the reactive fibrosis appeared. Robert et al[62] have found increased mRNA expression for type I and III collagens in both the right and left ventricles in this aldosterone model, while hypertrophy (addressed by the expression of atrial natriuretic peptide) was found only in the left ventricle. Administration of another mineralocorticoid, deoxycorticosterone acetate, in uninephrectomized rats on a high-salt diet, was likewise associated with this adverse structural remodeling.[63] Young et al[64,65] have advanced this field even further. They demonstrated that systemic administration of aldosterone, together with an intracerebroventricular infusion of a mineralocorticoid antagonist (RU 28318) to prevent hypertension, still led to cardiac fibrosis. Contrariwise, hypertension and LVH secondary to fluorocortisol administration were not associated with such remodeling. Brilla et al[58] found that infrarenal abdominal aortic banding likewise leads to elevated arterial pressure and LVH without fibrosis. Microscopic scarring also appears with aldosterone infusion or deoxycorticosterone acetate (DOCA) administration and could be prevented by spironolactone or amiloride, a potassium-sparing diuretic, or by dietary potassium supplements.[66-68] Amiloride, on the other hand, does not prevent the reactive fibrosis of the interstitial space associated with elevated circulating aldosterone. Thus, evidence gathered to date implicates aldosterone (and a high-salt diet) in promoting cardiac fibrosis.

RAAS activation therefore represents a double-edged sword. Its endocrine properties adversely alter sodium homeostasis in individuals in whom sodium intake and intravascular volume are normal, leading to clinical decompensation, and they promote an adverse structural remodeling of the myocardium that can be progressive in nature if not checked.

MOLECULAR-BASED APPROACHES TO REMODELING

Role of NF-κB in remodeling

MI is a result of cardiac myocyte necrosis that follows interrupted coronary blood flow to a segment of myocardium. Tissue repair follows at the site of injury. The DNA binding nuclear factor (NF-κB) plays a pivotal role in the activation of stress-inducible genes and

genes that are implicated in cell adhesion, migration, and proliferation. A variety of stimuli to gene expression include mitogens (eg, platelet-derived growth factor [PDGF], antigens), cytokines (eg, tumor necrosis factor α [TNF-α], interleukin [IL]-1, IL-2, interferon [INF]-γ), leukotrienes, prostaglandins (PGE_2), oxidative stress, and hypoxia. NF-κB , which binds to the recognition sequences 5'-GGGATTTCCC-3', stimulates expression of a number of genes, such as angiotensinogen, nitric oxide synthase, vimentin, decorin, IL-6, IL-8, and adhesion molecules endothelial cell leukocyte adhesion molecule–1 (ELAM-1), vascular cell adhesion molecule–1 (VCAM-1), and intercellular cell adhesion molecule–1 (ICAM-1),[69] which contribute to the recruitment of inflammatory cells to the site of injury. That these responses are important to repair have been underscored by inhibiting NF-κB. "Decoy" oligonucleotides containing NF-κB binding sequence were prepared in hemagglutinating virus of Japan [HVJ]-liposomes and delivered to the heart by infusion through a coronary artery.[70] An inhibitory effect on the area (or size) of infarction was observed. A significant reduction in the number of neutrophils, IL-6 and VCAM was likewise found in NF-κB "decoy" oligonucleotide-treated animals.[70] These studies open up a new avenue for control of myocyte injury and repair following MI.

Following the initial inflammatory cell response to myocyte necrosis, a healing response ensues, which results in scar tissue formation and unwanted fibrosis remote to the infarct. Progressive unabated healing due to continuous activation of Ang II results in accumulation of type I and III collagens and fibrosis. NF-κB is known to activate angiotensinogen, the precursor to all angiotensin peptides. Locally generated Ang II elicits a number of responses via AT_1 receptor binding, including mitogenic response of fibroblasts and their phenotypic conversion to myoFb. Ang II stimulates expression of a vast number of genes, including TGF-β1 and several components of extracellular matrix (ECM), the principal components being type I and III collagens and fibronectin.[71] These sustained effects lead to overexpression of α1(I) and α2(I) procollagen genes, resulting in fibrosis.

TGF-β1 and fibrosis

Fibrosis constrains heart muscle with ECM, mainly type I collagen. Ang II action through TGF-β1 augments expression of collagen genes both at transcription and translation levels (reviewed in 72 and 73). TGF-β1 regulates production of a number of collagen genetic types.[74] TGF-β1 not only can induce its own synthesis in an

autocrine regulation, but can also be regulated by a variety of other stimuli.[75] It regulates a number of ECM components that play an important role in tissue repair, and this regulation is mediated via three different receptors.[76] In fibroblasts, TGF-β1 increases the production of type I collagen, suppresses the synthesis of collagen-degrading metalloproteinases, and increases the activity of the collagenase inhibitor, TIMP.[77] In addition to these fibrogenic properties, TGF-β1 regulates fibronectin, tenacin, SPARC (secreted protein acidic and rich in cysteine), integrins, and syndecans. More pertinent to fibrosis is type I collagen accumulation. Although somewhat controversial, TGF-β1 upregulates α1(I) and α2(I) procollagen promoters through the transcription of factor Sp1. Only under conditions that preclude binding of Sp1 does TGF-β1 activate α2(I) promoter through AP-1.[78] However, these studies were conducted in cultured cells and it is unknown whether TGF-β1 acts through Sp1 in cardiac myoFb. Regardless of which signal pathways are operative in the activation of ECM components, an exciting possibility to control fibrosis is to target expression of collagen genes.

Collagen genes

Modulation of collagen synthesis in fibrotic tissues can be achieved by: (i) antisense oligonucleotides (ASO); (ii) triplex-forming oligonucleotides (TFO) specific to type I collagen mRNA; and (iii) some of the unique posttranslational enzymes involved in the biosynthesis of this structural protein.[79,80] In tissue culture these ASO effectively inhibit collagen levels. The most ideal ASO appear to be those directed against sequences that are predicted to form clustered double-stranded structures in RNA transcripts.[79] An antisense gene for human type I has been shown to be effective in transgenic mice.[81] One of the major limitations in this strategy, however, is that ASO need to be maintained at certain concentrations to inhibit abundant levels of mRNA, especially for collagen genes. An effective approach would be to downregulate transcription of the α1(I) or α2(I) procollagen genes. This is possible because of the presence of a unique polypyrimidine tract at -130 to -140 and -170 to -200, which have the ability to form triple helices when an antiparallel third strand is added.[82,83] This exciting possibility has been tested in tissue culture and shown to be effective.[83] Since one is targeting only one promoter, it would theoretically be possible to control transcription with lower concentrations of the TFO. The third possibility is to develop agents that are specific to enzymes involved in collagen biosynthesis such as prolyl-4-hydroxylase, procollagen C-proteinase. Pyridine-2,4-dicarboxylate inhibits prolyl-4-hydroxylases.[80,84] One of these derivatives has been shown to inhibit liver fibrosis in rats.[84] We think that although a variety of modulators of collagen synthesis can in theory be targeted, the collagen gene itself would be more effective, because other targets, such as Ang II and TGF-β1 signaling molecules, will have a plethora of effectors that would also be affected.

With the advent of viral vectors for transfer of genes it has become possible to introduce genes into various tissues. Direct injection of DNA into the myocardium is expressed in cardiac myocytes.[85] Increased gene expression has been demonstrated after myocardial injection of adenoviral vectors or by direct injection into the coronary arteries of HVJ-liposomes containing the vector DNA (reviewed in 86 and 87). Using adenoviral or retroviral vectors, it should be possible to introduce antisense type I collagen gene sequences into myocardium and control fibrosis by modulating their expression. Another exciting possibility is to convert collagen-overexpressing fibroblasts to myoblasts and then into myocytes by transferring the MyoD gene through a viral vector, as has been elegantly shown recently.[88]

Heat shock proteins

It is known that hypoxia, heat, and other cytotoxins induce a variety of stress proteins, or heat shock proteins, such as hsp60, hsp70, and hsp47, which can prevent cytotoxic effects. For example, tumor necrosis factor–α causes cytotoxicity of myogenic cells, and heat stress is protective.[89,90] Hsp70 is the most prominent of these proteins and is being used as a potential cardioprotective agent.[91-93] Hsp70 and its associated proteins can stabilize translating and newly synthesized polypeptides until all segments of the chain necessary for folding are available (reviewed in 94). Hsp47 has been shown to be a collagen-specific chaperone localized in the endoplasmic reticulum. It interacts with newly synthesized procollagen through the RDEL (Arg-Asp-Glu-Leu) sequence and causes its retention in the endoplasmic reticulum.[95] Under conditions of stress, hsp47 prevents secretion of procollagen with abnormal conformation. In addition to its role as a molecular chaperone of procollagen, hsp47 synthesis parallels that of collagen throughout embryonic development and in collagen-related pathologic conditions, such as fibrosis (reviewed in 96). Like procollagen genes, hsp47 can be used as a target to control fibrosis. Only recently, the cDNA encoding hsp47 has been cloned from zebrafish.[97] Another cardioprotective approach is to

enhance expression of hsp70 and other stress-inducible genes. Bimoclomol (2-hydroxy-3-[1-piperidinyl] propoxy-3-pyridinecarboxymidoil-chloride maleate) has been shown to induce expression of hsp70. It confers cytoprotective effects in a murine ischemic model and is currently investigated in clinical trials.[98]

NONINVASIVE MONITORING

Type I and III collagens are the major components of fibrous tissue, and are synthesized and secreted into the cardiac interstitial space as large precursor molecules or procollagens. They contain propeptide sequences at both the amino terminal (N) and carboxy terminal (C) ends, which are cleaved from collagen molecules before forming fibrillar collagen. If the amount of propeptide released into the interstitium and which subsequently gains entry to the circulation is proportional to fibrillar collagen formation, it follows that the propeptide would serve as a marker of collagen deposition. This is the case for the C and N propeptides for type I collagen. The N propeptide of fibrillar type III collagen is not completely cleaved. Many molecules are retained on their surface after fiber formation. Hence the release of N terminal type III collagen propeptide reflects synthesis and degradation through the release of bound propeptide. Serum concentration of each propeptide will also depend on their rate of release and access to the circulation and other factors reviewed elsewhere. Radioimmunoassays of carboxy terminal propeptide of type I procollagen (PICP) and amino terminal propeptide of type III procollagen (PIIINP) have been used to address collagen turnover in a variety of clinical disorders, such as metabolic bone disease and hepatic cirrhosis. Their application in addressing early tissue repair (or rebuilding) in the infarcted heart has recently been reviewed.[99] This approach would be complementary to monitoring the extent of myocardial injury based on the release of the heart's creatine kinase/MB isoform. Whether they will prove useful in addressing remodeling remote to the MI and the progressive remodeling of the infarcted heart during RAAS activation remains to be examined. Aside from the potential of serum markers to detect alterations in cardiac collagen turnover, other noninvasive methods are under development to identify the presence of fibrosis, eg, characterization of tissue composition using high frequency ultrasound imaging.[100-102] Other venues to consider would be to take advantage of myoFb expression of ACE and Ang II receptors, as localized and quantitated by high-density autoradiographic binding, with sites of active fibrous tissue formation.

GENETIC PREDISPOSITION

The prospects of genetic predisposition to adverse cardiovascular events based on the importance of myoFb is intriguing from several vantage points. First, these cells promote connective tissue formation in the cardiovasculature during normal growth and development. Second, they are integral to fibrous tissue formation at sites of repair in adult tissue. Thirdly, these cells regulate connective and fibrous tissue formation via their production of Ang II, which modulates expression of the fibrogenic cytokine TGF-β1. In the fetus, where this cytokine is not expressed by these cells, there is scarless healing of surgical incisions.[103] It is not known whether certain adult populations would be more susceptible to adverse remodeling and thereby have increased risk for cardiovascular events (eg, myocardial infarction, heart failure, stroke, renal failure). Candidate genes might include angiotensinogen and ACE. A T235 homozygote of the Ao gene and a homozygous deletion allele of the ACE gene are under investigation as they may relate to increased risk for these events.[104,105]

THREE KEY QUESTIONS

As stated at the beginning of our review, the incidence of cardiac remodeling and its outcome (heart failure), will inevitably increase due to the aging of the population in Western countries. Massimo Chiariello and Pasquale Perrone-Filardi take a closer look at the implications of remodeling in the over 65s in their article **"How important is cardiac remodeling in the elderly?"** These patients have increased vulnerability to the consequences of cardiac remodeling, and yet prevention is rendered more difficult by the many contraindications and the lesser effectiveness of thrombolytic therapy in this that age-group. In reply to the question **"Is ACE involved in ventricular remodeling?"** Luigi Tavazzi explains that the most compelling evidence that such is the case derives from studies showing that ACE inhibitors are able to reverse remodeling. This leads quite naturally to the question **"Should cardiac remodeling be manipulated, and how?"** to which Norman Sharpe answers with a vigorous "yes," indicating that the best results are obtained by combining an ACE inhibitor and a β-blocker.

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Cardiac Remodeling

Expert Answers to Three Key Questions

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How important is cardiac remodeling in the elderly?

M. Chiariello, P. Perrone-Filardi

—— ② ——

Is ACE involved in ventricular remodeling? The clinical experience

L. Tavazzi

—— ③ ——

Cardiac remodeling: should you manipulate it, and how?

N. Sharpe

How important is cardiac remodeling in the elderly?

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The elderly are particularly vulnerable to the consequences of cardiac remodeling as, in this population, the incidence of myocardial infarction is higher and remodeling precipitates overt heart failure more rapidly than in younger patients. Furthermore, thrombolytic therapy is less effective and has more contraindications in this age-group. Although no studies have specifically addressed remodeling in the elderly, the findings of large trials suggest that thrombolytic therapy and early initiation of angiotensin-converting enzyme (ACE) inhibition, especially following extensive anterior myocardial infarction, may prevent or reduce the dilation of the left ventricle. Recent reports show that the ß-blockers improve survival and functional capacity in patients with severe left ventricular dysfunction, but whether this beneficial effect, which is additive to that of the ACE inhibitors, is correlated with regression of remodeling remains to be determined.

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The ongoing increase in life expectancy is determining a parallel increase in the prevalence of coronary artery disease in the elderly. Indeed, it is estimated that more than one half of all deaths among persons aged 65 years or more are due to coronary artery disease, and that more than three quarters of all deaths from ischemic heart disease occur in older individuals. Thus, acute myocardial infarction and its complications, including cardiac remodeling, is a common disease in this population. It is well recognized that in-hospital and subsequent mortality, as well as reinfarction and congestive heart failure, are all increased in old patients. In addition, treatment of acute myocardial infarction in old people is more problematic and less effective than in younger patients. Although thrombolytic therapy increases survival in old people, fewer older patients are eligible to undergo thrombolysis. This is mainly due to the presence of relative or absolute contraindications, such as a history of stroke, gastrointestinal bleeding, or hypertension. As to the effectiveness of thrombolytic therapy in old patients, it has been reported in the GISSI-2 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell Infarto miocardico II) that, although the extent of the first infarction is not different compared with young patients, the degree of the ensuing left ventricular dysfunction is increased with age.[1] In old patients in whom thrombolytic therapy is contraindicated, an age-related increase in cardiovascular mortality due to congestive heart failure, recurrent infarction, or arrhythmias is observed.

CARDIAC REMODELING IN THE AGING HEART

In old people, cardiac remodeling takes place on top of a number of paraphysiologic abnormalities that are associated with the aging process of the normal heart. These changes include structural, hemodynamic, and neurohormonal modifications of the cardiovascular system. This is important to consider when interpreting the consequences of a pathological process in the aged heart where, due to the preexisting abnormalities of the aging process, a relatively mild injury may result in a substantial deterioration of the clinical status of the patient. Therefore, cardiac remodeling can be particularly detrimental in an old individual in whom cardiac (in particular diastolic) and vascular functions are already impaired compared with a younger heart.

The most important structural changes of the aging process include increased myocyte size, diminished myocyte density, and increased matrix connective tissue.[2] At the functional level, the aged heart is characterized by prolonged contraction, prolonged action potential, and diminished action potential and contraction velocity, with a diminished β-adrenergic contractile response and increased myocardial

and vascular stiffness. Thus, both systolic and diastolic function are impaired as a result of the aging process, and these changes are mainly reflected during the response to exercise. Compared with young individuals, older otherwise healthy subjects show a marked increase in end-diastolic and end-systolic volume during exercise, indicating increased venous return and recruitment of the preload reserve in the presence of reduced intrinsic contractility and augmented afterload, whereas the exercise-induced increase in heart rate is blunted. Therefore, cardiac remodeling and the subsequent ventricular dilation at rest (which limits the availability of the preload reserve during exercise) may be particularly detrimental in the elderly.

The remodeling process starts immediately after acute myocyte damage (infarction), and persists over a period of months and years, eventually leading to deterioration of global systolic function and overt congestive heart failure. The triggering event of cardiac remodeling is infarct expansion, which is defined by McKay et al[3] as an intramural myocardial rupture due to disruption of myofibrils in the infarcted area, with subsequent deposition of connective tissue, which is a source of resistance to further elongation of the infarcted segment. At the macroscopic level, these processes lead to wall thinning of the area of infarction not explained by additional necrosis.[4] The thinning of the infarcted segment is ascribed to slippage between muscle bundles and a reduction in the number of myocytes.[5] The slippage of myocytes may be the consequence of collagenase activation with dissolution of intermyofibrillar collagen bridges.[5]

It should also be emphasized that cardiac remodeling also induces alterations in the noninfarcted segments, principally hypertrophy of the normal cells.[4,5] The increase in size of the remaining viable cells is eccentric, thus leading to changes in the shape of the ventricle and dilation.[4,5] Thus, cardiac remodeling following myocardial damage may be viewed, in its early phase and when myocardial damage compromises global systolic function, as an adaptive process, which initially prevents deterioration of cardiac systolic function by recruitment of the preload reserve (Frank-Starling mechanism), and permits preservation of stroke volume and cardiac output. However, as the remodeling process evolves over time, these adaptive responses are overwhelmed, leading to frank impairment of cardiac performance both during exercise and at rest. It is obvious that the adaptive phase is of shorter duration in older patients in whom the remodeling process is aggravated by the preexisting reduction in cardiac performance.

TREATMENT OF CARDIAC REMODELING IN THE ELDERLY

The extent of cardiac remodeling following myocardial infarction is determined by a number of factors, including infarct size,[4,6] thrombolytic therapy,[7] patency of the infarct vessel,[8] residual exercise-induced ischemia,[9] and drug treatment following thrombolytic therapy.[10,11] Two recent studies have shed further light on the pathophysiology of the remodeling process. Bolognese et al reported that the presence of residual viable cells surrounding or within the infarct zone prevented cardiac dilation and remodeling in patients following acute myocardial infarction.[12] These authors postulated that the presence of residual viable myocardium in the subepicardium

of the infarct zone may contribute to prevent changes in ventricular shape and dilation. Their findings showed that, in patients with residual viability, left ventricular dilation 6 months following reperfused myocardial infarction was reduced compared with patients in whom no viable myocardium in the infarct zone was present. Similar findings on the influence of residual viable cells on remodeling were reported by Ito et al in an earlier study using contrast echocardiography.[13] In this study, adverse cardiac remodeling was evidenced in patients with reperfused myocardial infarction in whom contrast echocardiography demonstrated the so-called no-reflow phenomenon, ie, lack of myocardial perfusion despite the patency of the infarct vessel.

Since infarct size is a major determinant of subsequent ventricular enlargement, its limitation is crucial to prevent remodeling in the elderly. Data from the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico) trial demonstrated that end-systolic and end-diastolic volumes were smaller at 6 months in patients treated with thrombolytic therapy compared with untreated patients, and this reduction in left ventricular end-diastolic volume was still observed when the analysis was restricted to patients aged 65 years or over.[7] However, as mentioned above, thrombolytic therapy is less effective in preventing left ventricular dysfunction in the elderly,[1] and, although it is very effective in promoting vessel patency, data from the GUSTO trial (Global Utilization of Streptokinase and t-PA for Occluded arteries)[14] indicate that in old people it is associated with a substantial increase in complications, mainly intracranial bleeding. Data from the PAMI study (Primary Angioplasty in Myocardial Infarction), which compared primary angioplasty

and thrombolytic therapy, indicated, in a subgroup of patients aged 70 years or above, a significant advantage of primary angioplasty with respect to mortality, which decreased from 10% in the thrombolytic group to 2% in the angioplasty group.[15]

A number of large trials in the treatment of acute myocardial infarction have shown that, apart from reperfusion therapy, angiotensin-converting enzyme (ACE) inhibitors were effective in reversing cardiac remodeling, especially following extensive anterior infarctions.[10,16,17] Although the mechanisms by which these drugs act on cardiac remodeling are not entirely clear, it is well recognized that these compounds halt the progression of cardiac dilation compared with untreated patients, and may even determine a reduction in cavity dimension in selected patients.[10,16] Although regression of chamber dilation has been causally associated with a reduction in adverse cardiac events in some patients, it appears that the latter can only explain in part the favorable effect of ACE inhibition in patients with left ventricular dysfunction. There are no studies in the elderly that specifically evaluated the effect on cardiac remodeling of ACE inhibition compared with untreated patients. Thus, information can only be obtained from subgroup analysis of large trials. Among these, a subgroup analysis in patients aged 65 years or more in the GISSI-3 trial[18] demonstrated a favorable effect on combined cardiovascular events (death and congestive heart failure) in old patients treated with lisinopril or nitrates in the acute phase of myocardial infarction. An even greater effect on combined end points was observed when both lisinopril and nitrates were administered. However, in this study, no data were reported on the left

ventricular dimension before and after treatment. A favorable effect on all-cause mortality was recently observed in patients aged 70 years or above receiving losartan, an antagonist of the angiotension II AT_1 receptor.[19] In this study, the effect of losartan was significantly greater than that of captopril, but again, no data are available on cardiac dimension. Thus, these observations suggest that ACE inhibition favorably affects cardiovascular mortality and morbidity in old people.

It is interesting to speculate on the mechanisms underlying the effect of ACE inhibition on remodeling. Expression of ACE has recently been evidenced in myocytes as well as fibroblasts and vascular endothelium of myocardium of elderly patients with previous myocardial infarction and dilated left ventricle, whereas no ACE expression was found in control subjects.[20] In addition, patients with the DD genotype for ACE, in whom increased ACE activity is found, have been reported to develop a larger increase in cardiac size following myocardial infarction compared to non-DD patients.[21] Enhanced ACE expression leads to increased levels of circulating or local angiotension II, a growth factor known to be capable of inducing the myocyte hypertrophy observed in cardiac remodeling. However, the angiotensin system may also act through neurohumoral activation, with detrimental effects on cardiac survival.[21] Conceivably, the two mechanisms may coexist. Other beneficial mechanisms of the ACE inhibitors could also explain a favorable effect on survival despite the lack of regression of remodeling observed in some studies.

Recently, β-blockers have been introduced in the treatment of severe left ventricular systolic dysfunction. In particular, carvedilol, a β-blocker

with some α-blocking activity, has been reported to reduce mortality and ameliorate exercise performance in patients with left ventricular dysfunction.[22,23] A subanalysis of the SAVE population showed that use of β-blockers in addition to ACE inhibitors provides significant additional benefit in mortality in relatively old patients (mean age 60 years) with severe left ventricular dysfunction.[24] At present, however, it is not known whether any of these effects is related to modification of left ventricular geometry. Also, there is no confirmation whether the beneficial effects of carvedilol are also observed in old patients.

CONCLUSION

Cardiac remodeling can be particularly detrimental in the aged heart, resulting in accelerated left ventricular dysfunction and clinically manifest heart failure. From an epidemiological point of view, the increasing incidence of myocardial infarction with age and the problems associated with the use of thrombolytic therapy in many old patients make prevention of cardiac remodeling a clinically desirable goal in the management of elderly patients recovering from acute myocardial infarction. However, as for younger patients, cardiac remodeling is probably only one determinant in the poor prognosis of patients with left ventricular systolic dysfunction. In addition, the mechanisms that induce the structural and functional changes characterizing cardiac remodeling are not completely understood. Future research should be directed toward a thorough understanding of the pathophysiology of cardiac remodeling and of its impact on cardiac mortality with a view to selecting the most appropriate therapeutic interventions.

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Is ACE involved in ventricular remodeling? The clinical experience

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Evidence that activation of the renin-angiotensin-aldosterone system is involved in the pathophysiology of heart failure derives from a number of experimental and clinical studies. The most compelling evidence that the chronic stimulation of this system is harmful derives from experience with angiotensin-converting enzyme (ACE) inhibitors, which consistently improve both the clinical course and the ventricular dysfunction, particularly in subjects with myocardial infarction, arterial hypertension, or advanced ventricular remodeling of any etiology. The most relevant findings reported in the literature that deal with reversal of remodeling related to ACE-inhibitor therapy are discussed in this paper.

Keywords: heart failure; ventricular remodeling; ACE inhibitors; myocardial infarction; arterial hypertension

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A current view interprets the clinical syndrome of congestive heart failure (CHF) as a result of two related but largely independent processes. One is ventricular remodeling, resulting in a dilated chamber with a low ejection fraction; the other is represented by the activation of several noncardiac mechanisms mainly responsible for the symptoms of HF. This interpretation has important clinical implications, because treatment of HF should target both these processes.

Evidence that activation of the renin-angiotensin system is involved in the pathogenesis of ventricular remodeling and pathophysiology of CHF derives from a number of studies. Angiotensin II increases coronary artery permeability, allowing diffusion of growth factors into the myocardial interstitium.[1,2] It is also known to cause necrosis and fibrosis through its cytotoxic effect on cardiac myocytes.[3] Increased aldosterone production as a result of increased angiotensin II has hemodynamic consequences, and stimulates collagen synthesis by myocardial fibroblasts.[2] Increased aldosterone levels may also play a role in myocyte death through their effect on electrolyte balance.[4]

Perhaps the most compelling evidence that chronic renin-angiotensin stimulation is harmful derives from experience with angiotensin-converting enzyme inhibitors (ACEIs), which consistently improve the clinical course of a broad spectrum of patients with left ventricular (LV) dysfunction. Most studies dealing with LV remodeling and ACEIs have been performed in patients with myocardial infarction, arterial hypertension, and LV dysfunction and CHF of various etiology.

ACE INHIBITION AND REMODELING AFTER MYOCARDIAL INFARCTION

Acute myocardial infarction can initiate a dynamic process of change in LV size, shape, and myocardial architecture, which can profoundly affect LV function. This process involves acutely and chronically both infarcted and noninfarcted zones of the left ventricle, and affects wall thickness and structure, as well as chamber size, shape, and function.

Three large studies examined the effects of ACEIs on LV remodeling after an acute myocardial infarction (Survival And Ventricular Enlargement [SAVE], COoperative New Scandinavian ENalapril SUrvival Study II [CONSENSUS II], and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–3 [GISSI 3]), all of which showed a reduction in LV dilation and remodeling in groups treated with ACEIs with respect to controls.

The SAVE echocardiographic study[5] included 512 myocardial infarction patients at baseline and 420 survivors at 1-year follow-up.
The absolute difference in end-diastolic and end-systolic areas between captopril and placebo was around 3 cm[2] at 1 year. Despite this small absolute difference in LV size, attenuation of LV enlargement was associated with a reduction in adverse cardiovascular events after myocardial infarction.

In the 428 patients considered by the CONSENSUS II Multi-Echo Study Group,[6] the absolute difference in LV end-diastolic volume index between enalapril and placebo was around 3 ml•m^{-2} at 6 months after myocardial infarction.
The CONSENSUS II trial, however, showed that early administration of intravenous enelaprilat to all eligible patients with myocardial infarction followed by oral enalapril did not improve survival during the 180 days after the index event, even though LV dilatation was attenuated by enalapril.

The largest study in which the effects of ACEIs on LV remodeling was evaluated in post–myocardial infarction patients was the GISSI-3 trial.[7] GISSI-3 was a controlled, multicenter, open trial with central randomization and 2 × 2 factorial design with four treatment groups: lisinopril alone, transdermal glyceryl trinitrate alone, combined therapy, and no trial therapy.
Treatment was assigned by randomization to 19 394 eligible patients admitted to hospital within 24 h of symptom onset with a diagnosis of myocardial infarction. The trial drugs were withdrawn at 6 weeks in the absence of specific indications for continuation, and the patients were followed up to 6 months. The GISSI-3 study protocol required complete 2-D echocardiographic examination

to be performed in all randomized patients at 6 weeks and 6 months after the index myocardial infarction, in order to calculate the combined end point of mortality and severe left ventricular dysfunction. A 2-D echocardiographic examination was also recommended predischarge. Overall, the database consisted of 8619 echocardiograms at predischarge, 12 125 at 6 weeks, and 10 726 at 6 months, ie, 50.8%, 72.6%, and 73.3%, respectively, of all patients with confirmed myocardial infarction followed up at each time point and for whom asynergy and ventricular volumes were analyzable. A subpopulation of

6 405 patients, who underwent all three echocardiographic examinations, was also selected in order to evaluate the time course of the effects of lisinopril on LV remodeling in 6-month survivors.[8]

Predischarge end-diastolic and end-systolic volumes and ejection fraction predicted 6-month mortality and nonfatal clinical congestive heart failure ($P<0.01$). Patients with wall motion asynergy ≥27% showed an increase in LV volumes over time, which was significantly reduced by 6 weeks of lisinopril treatment *(Figure 1)*. The difference in end-diastolic volume between patients
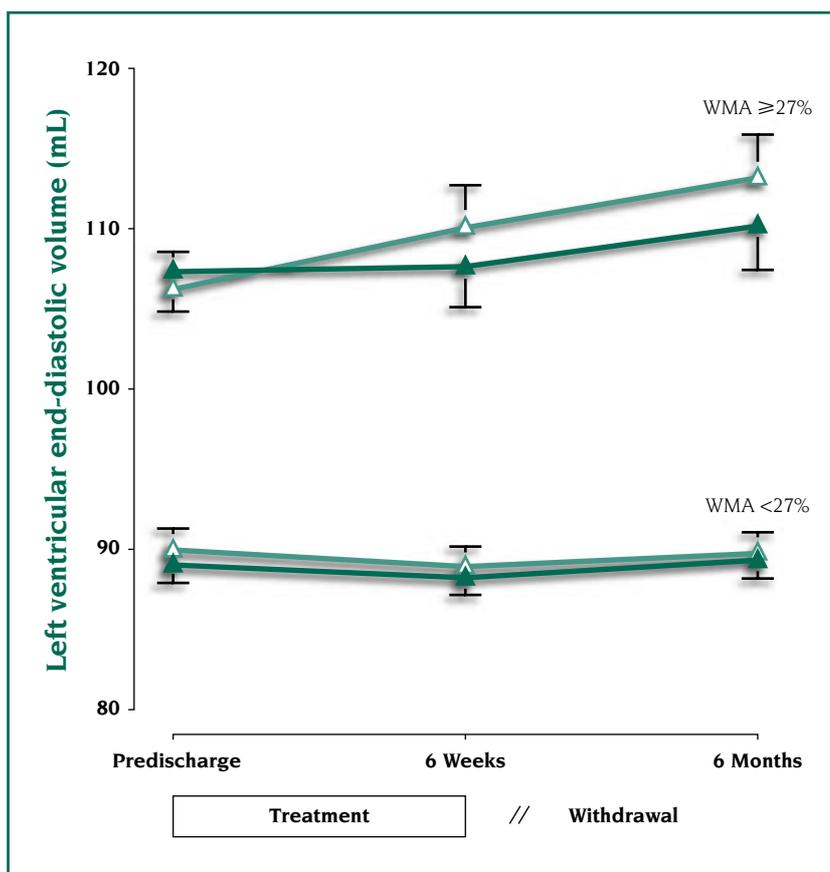
Figure 1. *Left ventricular end-diastolic volume in lisinopril (▲) and no-lisinopril (△) patients with wall motion asynergy (WMA) <27% and with WMA ≥27% (n=6405). Sample sizes were as follows: WMA ≥27%; lisinopril = 909, no lisinopril = 903. WSA <27%; lisinopril = 2277, no lisinopril = 2316.*

Reproduced from ref 8: Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Eur Heart J. *1996;17:1646-1656. Copyright © 1996, The European Society of Cardiology. With permission.*

allocated lisinopril and patients allocated no lisinopril was significant in larger infarcts (ie, wall motion asynergy ≥27%), while smaller infarcts (ie, wall motion asynergy <27%) did not show any major changes during follow-up, regardless of treatment.[8] This finding is in agreement with previous data showing that ventricular remodeling is observed mainly in infarctions of at least moderate size.

A similar trend over time was observed for end-systolic volumes, even though the difference between patients receiving lisinopril or not did not reach statistical significance.[8] At variance with other studies, ejection fraction was not modified by lisinopril. The absolute differences in LV volumes between the lisinopril

and no-lisinopril groups were very small (<5 mL), but statistically significant in patients with larger infarcts. These are probably reliable estimates of the real effects of ACE inhibition in a large population of patients with moderate-sized myocardial infarction. Given the large number of participating centers and the absence of strict selecting entry criteria of the patients, the GISSI-3 population may well be considered a representative sample of the general population of acute myocardial infarction patients in the thrombolytic era.

Interestingly, spontaneous reduction in wall motion asynergy was also observed during follow-up, independently of lisinopril treatment.[8] These results suggest late

recovery of stunned and/or hibernating myocardium and confirm, in a large population, the experimental data and clinical observations made in selected patients.[9] The reported studies demonstrated that when ACEI therapy is begun shortly after an acute myocardial infarction, progressive LV dilatation can be inhibited or attenuated. The problem of the duration of this effect is still open.

In the SAVE Echocardiographic substudy, 373 survivors up to 2 years after acute myocardial infarction, with serial echocardiograms recorded during this period, were evaluated to assess whether LV remodeling continued beyond 1 year after the infarction and, if so, whether this late LV dilatation was attenuated by continued administration of ACEI
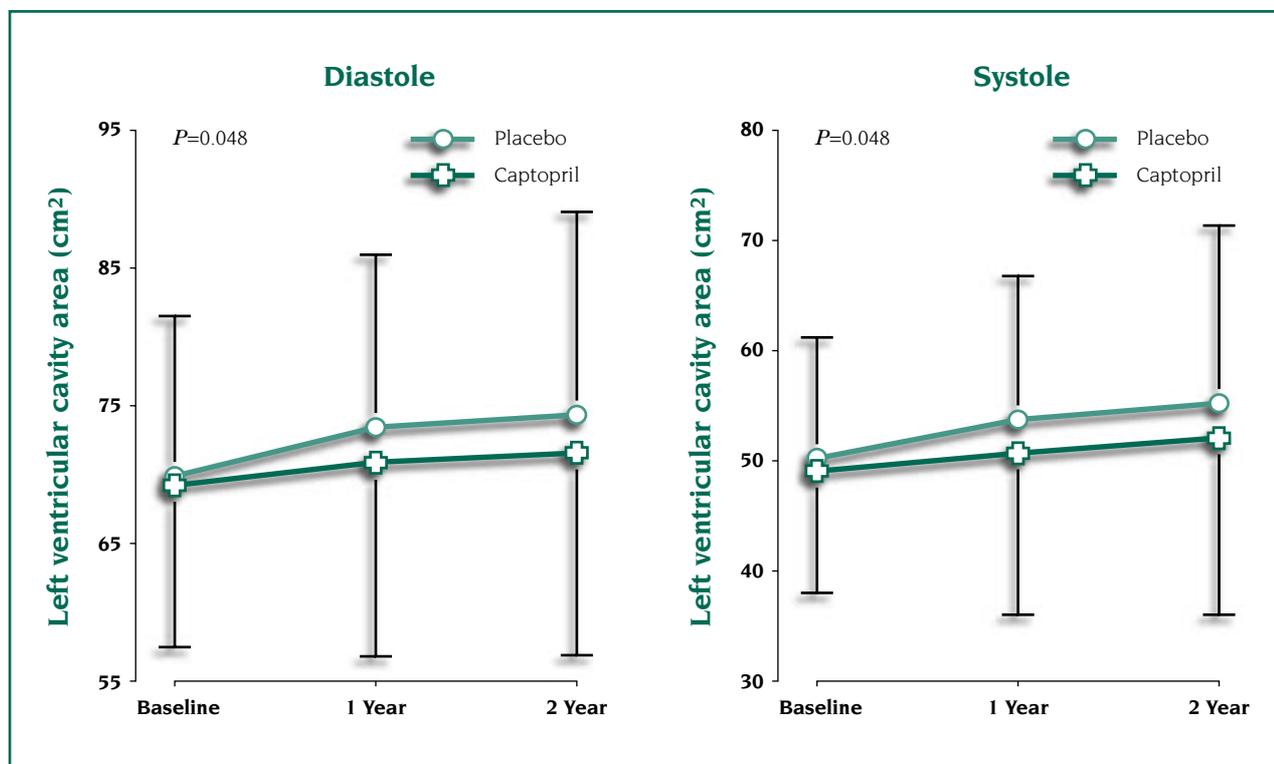
Figure 2. *Survival And Ventricular Enlargement (SAVE) trial echocardiographic substudy. Left ventricular cavity areas at end-diastole and end-systole in the captopril and placebo treatment groups at 1 and 2 years after myocardial infarction. Attenuation of left ventricular dilatation by captopril is evident at 2 years. However, after 1 year, left ventricular sizes at end-diastole and end-systole increase in parallel in both placebo and treatment groups.*

Reproduced from ref 10: St John Sutton, Peffer MA, Moye L, et al, for the SAVE Investigators. Cardiovascular death and left ventricular remodeling two years after myocardial infarction. Baseline predictors and impact of long-term use of captopril: information from the Survival And Ventricular Enlargement (SAVE) trial. Circulation. *1997;96:3294-3299. Copyright © 1997, American Heart Association. With permission.*

therapy. The main findings of this study were twofold.[10] First, more than one third of patients developed LV dilatation beyond 1 year, with significant increases in both diastolic and systolic cavity areas. In addition, increasing LV size was associated with increasing distortion of cavity shape and progressive deterioration in LV performance. Second, captopril attenuated diastolic LV dilatation at 2 years, but this effect was carried over from the first year of therapy because changes in LV size with captopril beyond 1 year were similar to those with placebo *(Figure 2)*. This finding seems to indicate that patients may escape from the attenuating effects of ACEI therapy on LV dilation. This might suggest that, in the long run, mechanisms different from ACE activation may become prominent in maintaining and aggravating LV remodeling.

ACE INHIBITION AND REMODELING IN HYPERTENSION

Recently, arterial hypertension has been reported to be the most common risk factor for CHF in a population-based setting. In the Framingham study, during an average follow-up of 14 years, 392 new cases of CHF occurred, and in 91% hypertension (defined as arterial pressure >140/95 mm Hg) antedated the development of CHF. Adjusting for age and other risk factors, the hazard for developing CHF was about 2-fold in hypertensive men and 3-fold in hypertensive women compared with normotensive subjects.[11] In other studies and in different settings, the role of hypertension as a risk factor for CHF was less prominent. In particular, the use of hypertensive drugs seems to have substantially altered the incidence of CHF, prolonging survival and allowing cardiovascular and coronary complications to rank in top position

among the causes of mortality and morbidity in hypertensive subjects.

According to the conventional paradigm of compensatory ventricular response to a chronic pressure overload, ventricular wall thickness should increase proportionally to blood pressure level to maintain normal wall stress, and the left ventricle is thought to develop concentric hypertrophy. LV dilatation is considered to represent a late transition toward myocardial failure. However, LV adaptation to human hypertension has been shown to be more complex than expected. In a study of geometric remodeling in hypertension,[12] besides many patients with mild-to-moderate hypertension exhibiting a normal left ventricle (52%), only 8% of patients showed the typical hypertensive concentric hypertrophy with an increase in both wall thickness and ventricular mass, 13% had increased relative wall thickness with normal ventricular mass (called "concentric remodeling"), and 27% had increased mass with normal relative wall thickness (eccentric hypertrophy). Systemic hemodynamics paralleled ventricular geometry, with the highest peripheral resistance in the groups with concentric remodeling and hypertrophy, whereas cardiac index was low-normal in patients with concentric remodeling and high in those with eccentric hypertrophy. The author's hypothesis is that, in concentric remodeling, normality of LV mass results from a compensation of pressure overload by low cardiac output (a sort of "volume underload"), whereas eccentric hypertrophy results from concomitant pressure and volume overload. These findings are important, because an increased ventricular mass seems to be the strongest risk factor for the development of complications (including heart failure) and death in patients with

arterial hypertension. During a 10-year follow-up period in patients with uncomplicated essential hypertension, the event rate was 21% and 31% for cardiovascular death and morbid events, respectively, in patients with concentric hypertrophy, no cardiovascular death and 11% of morbid events in those with normal LV geometry; the risk was intermediate for patients with concentric remodeling and eccentric hypertrophy.[12]

In hypertensive patients with no apparent functional decompensation, an increase in size of myocytes in the left and right ventricles is responsible for the increase in left and right ventricular mass and is associated with a decrease in the total number of cells in both ventricles. Myocyte proliferation can occur late during the course of hypertensive heart disease and may constitute the ultimate growth reserve mechanism of the overloaded adult heart before intractable ventricular dysfunction and failure supervene. Activation of the renin-angiotensin system has been proved experimentally to act as a trophic stimulus of the myocardial cell, and similar observations have been made in humans. As a consequence, blockade of angiotensin II with ACEIs may contribute, independently of blood pressure, to the reversal of myocardial hypertrophy.

A recent meta-analysis with strict qualitative criteria for study inclusion aimed to determine the ability of various antihypertensive agents to reduce LV hypertrophy in subjects with essential hypertension, and showed that pretreatment left ventricular mass index (LVMI), decrease in blood pressure, duration of therapy, and antihypertensive drug class determined the decrease in LV hypertrophy.[13] Drug therapy with ACEIs seemed to be the most effective in reducing LV hypertrophy.
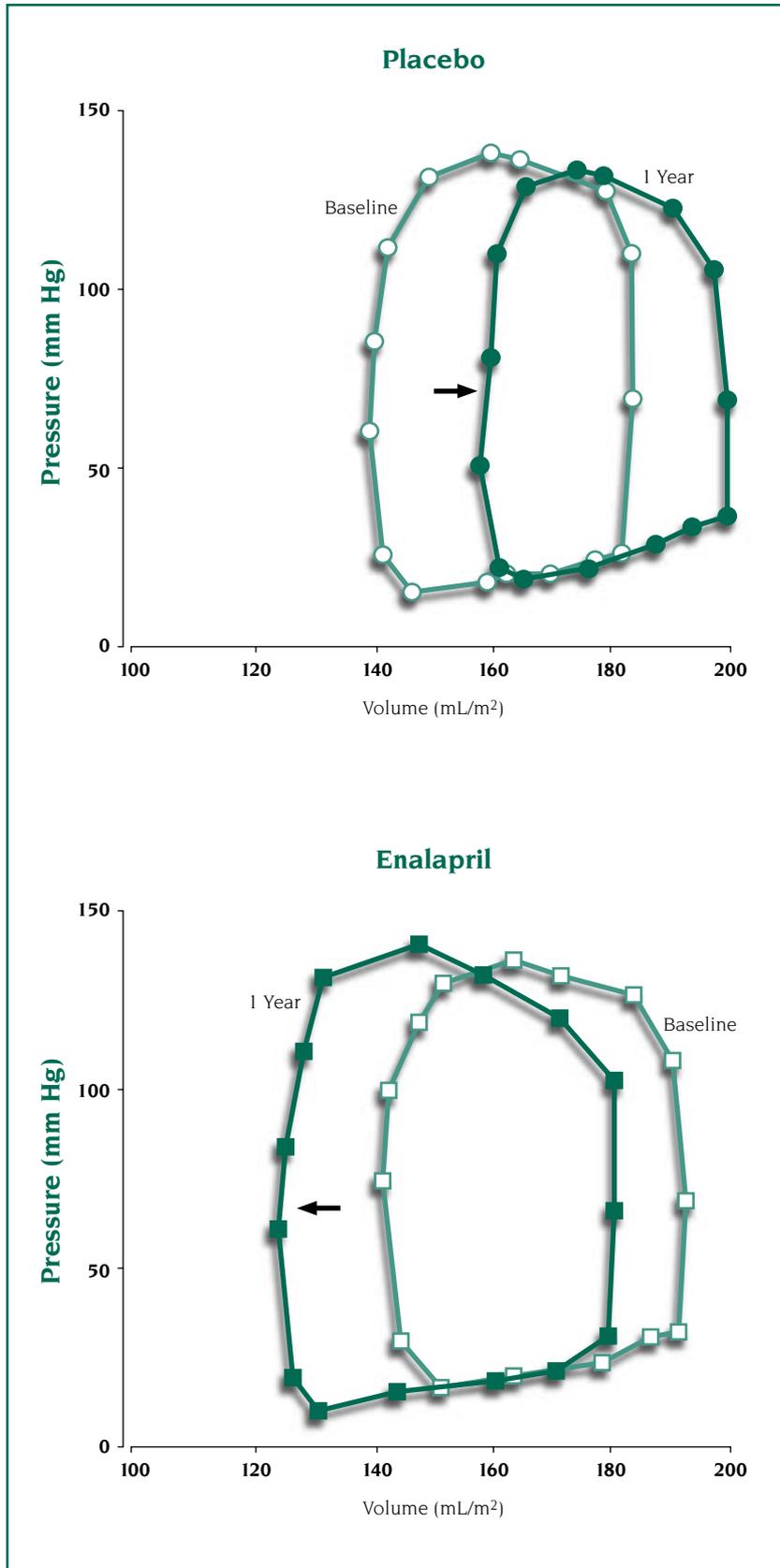
The decrease in LVMI was greater with ACEIs than with β-blockers (significant) or diuretics (tendency).

ACE INHIBITION IN LEFT VENTRICULAR DYSFUNCTION

The effects of ACEI therapy on LV structure and function in patients with long-standing LV dysfunction of whatever etiology has been carefully investigated in the Studies Of Left Ventricular Dysfunction (SOLVD).[14-18] In this trial, combined Doppler-echocardiographic evaluation and invasive LV function recordings were made longitudinally in subsets of patients recruited from both the Prevention (patients with LV ejection fraction <35% and no symptoms) and Treatment (patients with LV ejection fraction <35% and symptoms of CHF) arms of the trial.

Patients were treated in a double-blind fashion with enalapril or placebo and followed up for 3 years.[14-16] Overall, LV end-diastolic and end-systolic volumes increased in placebo-treated but not in enalapril-treated patients, and the difference in response between the treatment groups was statistically significant *(Figure 3)*.

Figure 3. *Studies Of Left Ventricular Enlargement (SOLVD) trial, treatment arm. Averaged left ventricular pressure/volume loops of 16 patients who underwent serial left heart chatheterization before and after randomization to placebo or enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.*

Reproduced from ref 15: Konstam MA, Rousseau MF, Kronenberg MW, et al, for the SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. Circulation. 1992;86:431-438. Copyright © 1992, American Heart Association. With permission.

Similarly, LV mass tended to increase in placebo patients and to be reduced in enalapril-treated patients. It is noteworthy that this happened in patients in whom considerable LV dilatation and hypertrophy were already present when the treatment was started, demonstrating both the chronic, progressive nature of the remodeling process and the opportunity for effective interventions even after considerable structural changes have developed.

Figure 4 reports the averaged LV pressure/volume loops of symptomatic patients of the Treatment arm, and asymptomatic patients of the Prevention arm of SOLVD.[14] The main difference in ventricular function parameters between the groups of symptomatic and asymptomatic patients was neither the ventricular filling pressure nor the ability of the ventricle to generate active tension (as assessed by end-systolic wall stress), which were similar in both groups, but the cardiac volumes, which were greater in symptomatic patients and affected equally end-diastolic and end-systolic volumes. Thus, an exaggerated diastolic LV distensibility characterized these patients. It is noteworthy that in the SOLVD study as well as in others,[17] the cavity enlargement was not dependent on changes in filling pressure. Indeed, the structural dilatation was accompanied by a displacement of the entire pressure-volume relation curve to the right along the volume axis, resulting in larger volumes at any distending pressure. In other words, the ventricular compliance appeared abnormally increased. These findings suggest that changes in ventricular dimension, shape, and architecture are a cause rather than a consequence of the decline of pump function, and that the ACE system is involved in the process.

The beneficial effects on LV remodeling shown in the small invasive substudy mentioned above were confirmed in a larger echocardiographic substudy of the SOLVD trial, which included 301 patients who underwent Doppler echocardiographic evaluation at baseline and after 4 and 12 months of therapy.[18] The main results were that either LV end-diastolic and end-systolic volumes or LV mass increased in placebo, but not in enalapril-treated patients, the difference in response between the treatment groups being statistically significant.

CONCLUSION

Ventricular remodeling can occur as a consequence of many cardiac diseases, it can be the expression of a compensatory response, but can become an unfavorable process generating by itself, or perpetuating, cardiac disease.

The renin-angiotensin system, mainly as trophic regulator, can play a pivotal role in such a process. Many studies have shown that modulation of ACE can modify the ventricular remodeling process, prevent or delay the occurrence of CHF, and favorably affect the natural history of several cardiovascular diseases.

PLACEBO
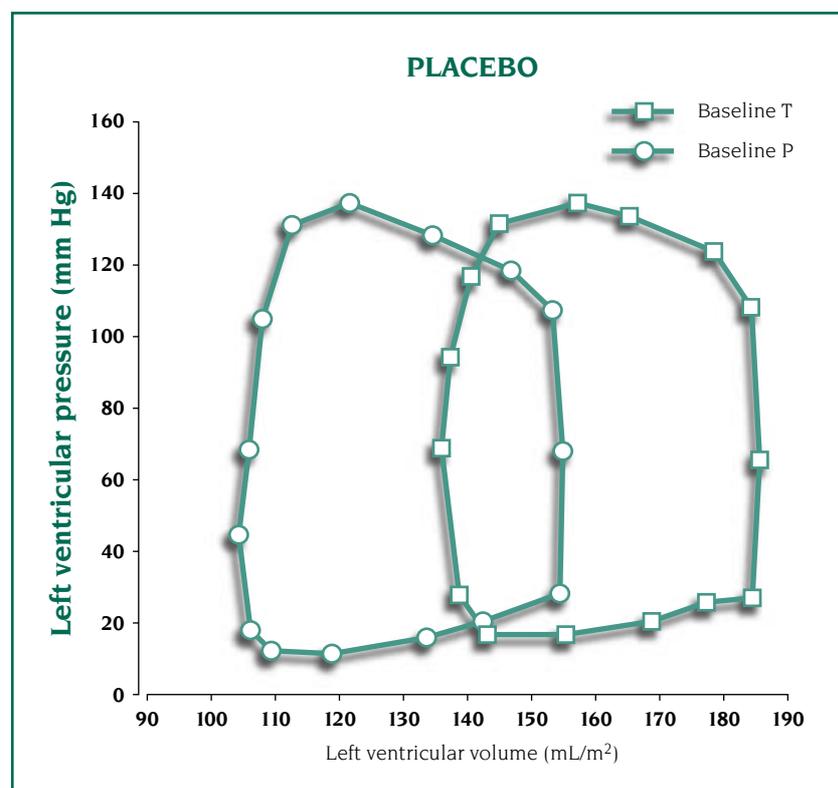
Figure 4. Studies Of Left Ventricular Enlargement (SOLVD) trial. Averaged left ventricular pressure/volume loops of 16 symptomatic patients with congestive heart failure in the treatment arm (T), and 49 asymptomatic patients of the prevention arm (P). The left ventricular pressure profiles were similar in both groups, whereas the volumes were markedly different.

Reproduced from ref 14: Pouleur H, Rousseau MF, van Eyll C, Melin Y, Youngblood, Yusuf S, for the SOLVD Investigators. *Cardiac mechanics during development of heart failure.* Circulation. 1993;87(5, suppl IV):IV14-IV20. Copyright © 1993, American Heart Association. With permission.

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Circulation. 1993;87:755-763.

Cardiac remodeling: should you manipulate it, and how?

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Ventricular remodeling in the context of hypertensive heart disease (ventricular hypertrophy) and following myocardial infarction or congestive heart failure (ventricular dilatation) is an adverse, progressive process with a poor prognosis, and should now be included as a treatment target in these conditions. Antihypertensive treatment should be more vigorous, so as to achieve true normalization of blood pressure and regression of ventricular hypertrophy. Patients with ventricular systolic dysfunction following myocardial infarction should receive angiotensin-converting enzyme (ACE)–inhibitor treatment as part of standard therapy to prevent progressive ventricular dilatation and dysfunction and improve long-term outcomes. In congestive heart failure, combination of neurohormonal blockade with ACE-inhibitor and ß-blocker therapy provides additive benefits in improving ventricular remodeling and survival.

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In addressing the question as to whether cardiac remodeling should be manipulated and if so, how, it is appropriate first to reconsider the definition of remodeling from the clinical viewpoint. Cardiac remodeling has molecular, cellular, and interstitial components. However, the clinical manifestations relate to the resultant changes in ventricular size, shape, wall thickness, and function, which occur following myocardial injury or overload. These changes, which can be detected and measured clinically, may be viewed as part of a complex response to injury or overload, initially compensatory, but eventually maladaptive, being closely linked to heart failure progression.

The now well-acknowledged adverse nature of remodeling, together with clinical trial evidence of the beneficial effects of intervention, provide the justification for "manipulation" or modification of this process at an early stage to improve long-term outcomes. Furthermore, the management of hypertension, heart failure, and related mechanisms should now be broadened to include ventricular remodeling as a target. The principal clinical settings in which modification of ventricular remodeling should indeed be considered a therapeutic target and where there is a sound basis for such intervention, are those of hypertensive heart disease with left ventricular hypertrophy, acute myocardial infarction, post–myocardial infarction left ventricular dysfunction, and chronic congestive heart failure.

HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY

Hypertension is a common risk factor for heart failure accounting for the greater part of the population-attributable risk.[1] Hypertension may result in heart failure via coronary heart disease or progressive ventricular hypertrophy or a combination of both *(Figure 1)*. Left ventricular hypertrophy is strongly predictive of the development of coronary heart disease.[2] A significant proportion of heart failure patients in the community have relatively preserved left ventricular systolic function, but are older patients with previous hypertension, left ventricular hypertrophy, and primary diastolic dysfunction.[3] Treated hypertensive patients continue to experience substantially higher risks of coronary heart disease and overall mortality than normotensive individuals.[4,5] In a large case-control study of hypertensive patients compared with matched normotensive controls in the primary care setting, persisting left ventricular hypertrophy was evident in treated hypertensives to the same degree as in untreated cases.[6] Thus, the broader aims of treatment for hypertension should
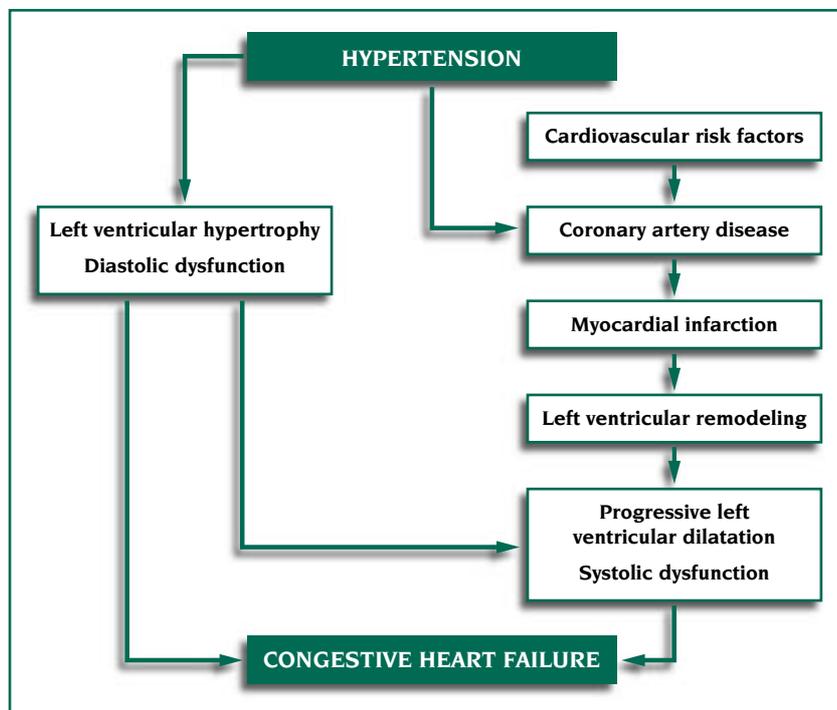
Figure 1. *Pathways from hypertension to heart failure.*

include regression of left ventricular hypertrophy (reverse remodeling) to improve long-term prognosis. Generally, a more vigorous approach to blood pressure control can be advocated, aimed at achieving normotension rather than accepting partial control with associated persisting problems.[6]

Numerous studies of the effects of antihypertensive treatments on left ventricular hypertrophy indicate that the different classes of agents can all regress hypertrophy. An overview of 109 studies[7] comparing different classes of agents showed significant regression with diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors—the first three groups to a similar extent, with a trend to greater regression with ACE inhibitors. Definitive comparative data are lacking, although the overview does suggest the possibility of greater regression of hypertrophy

with ACE inhibition, perhaps due to blood pressure reduction combined with a direct tissue effect on cardiac myocytes and interstitium. Finally, further evidence of a causal linkage between hypertension and heart failure, which emphasizes the importance of effective long-term blood pressure treatment and optimal control, is provided from trials that have shown large reductions in heart failure risk with treatment of hypertension.[8-10]

## ACUTE MYOCARDIAL INFARCTION

Various factors can influence progression to heart failure following myocardial infarction *(Figure 2)*. In the acute phase, the principal determinant is infarct size. Infarct artery patency may confer a beneficial effect on ventricular remodeling both through limitation of infarct size acutely and through preventing continuing infarct expan-

sion and subsequent left ventricular dilatation. Reperfusion may preserve endocardial tissue, and it is also possible that reperfused infarcts with contraction band necrosis may have higher tensile strength and reduced propensity to later expansion than unperfused infarcts.[11] Restoration of infarct artery patency with thrombolysis or early angioplasty following acute myocardial infarction may be effective in interrupting the progressive ventricular remodeling that might otherwise occur, thus improving long-term outcomes.[12,13]

POST–MYOCARDIAL INFARCTION LEFT VENTRICULAR DYSFUNCTION

Improved understanding of the process of ventricular remodeling and the prime prognostic importance of left ventricular volumes following myocardial infarction[14] led to experimental and clinical studies of pharmacologic intervention for treatment of left ventricular dysfunction in the postinfarct period. Thrombolysis and other measures are of proven benefit in the acute phase where the primary objective is limitation of infarct size and salvage of ischemic myocardium. Once infarct evolution is complete, however, the opportunity exists to intervene to minimize the sequelae of infarct expansion and ventricular dilatation and improve the long-term prognosis *(Figure 2)*.

Nitroglycerin may have a role in this context,[15] but clear evidence of long-term benefit from nitrate therapy is lacking.[16] In contrast, the data for ACE inhibition are compelling in all respects, making such treatment a standard requirement for patients with significant left ventricular dysfunction following myocardial infarction.

Figure 2. *From myocardial infarction to heart failure: factors influencing progression.*
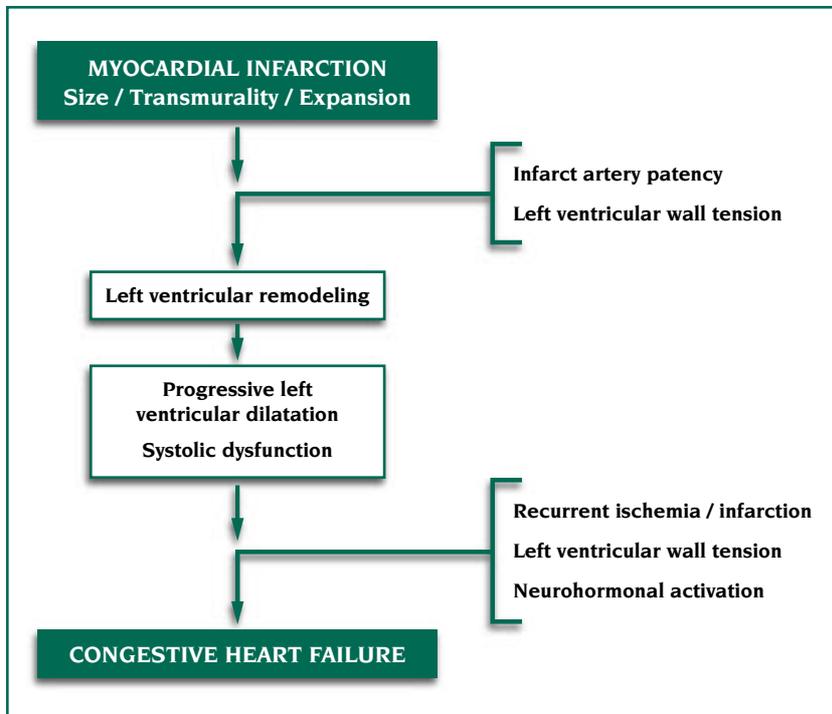
The beneficial effect of ACE inhibition on ventricular remodeling is clearly exemplified in the two studies summarized schematically in *Figure 3*.[17,18] In the first study,[17] selected patients with asymptomatic ventricular dysfunction (ejection fraction less than 45%) 1 week following Q-wave myocardial infarction showed improved left ventricular volumes and function during 1 year of treatment with captopril compared with a placebo group who showed further deterioration, the ejection fraction difference between the two groups at 1 year being about 10% (absolute). In the second study,[18] patients with Q-wave myocardial infarction treated earlier with captopril, from 24 to 48 hours following infarction for 3 months, showed a similar benefit.

Figure 3. *Left ventricular (LV) remodeling following myocardial infarction (MI). Effect of angiotensin-converting enzyme inhibition. Quantitative 2-D echocardiographic data representing the effects of angiotensin-converting enzyme (ACE) inhibition with captopril in two post-MI patient groups: (i) those with MI and left ventricular ejection fraction (LVEF) <45% treated from 1 week for 1 year; and (ii) those with Q-wave MI treated from 24 to 48 h for 3 months. In both groups, captopril improved left ventricular (LV) function in comparison with the placebo groups (green arrows) who show further increases in LV end-diastolic volume index (LVEDVI) with stroke volume index (SVI) maintained (Based on data from refs 17 and 18).*

The beneficial effects of ACE inhibition on ventricular remodeling following myocardial infarction have been translated into improved clinical outcomes with long-term treatment. Large-scale studies have shown survival benefit when this treatment is applied generally to all patients with myocardial infarction (Fourth International Study of Infarct Survival [ISIS-4]),[16] or selectively in patients with left ventricular dysfunction (Survival And Ventricular Enlargement trial [SAVE])[19] or heart failure (Acute Infarction Ramipril Efficacy study [AIRE]).[20]

While different regimens can be adopted in terms of treatment initiation and patient selection, it is generally agreed and recommended that patients with left ventricular dysfunction or heart failure following myocardial infarction be selected and treated with an ACE inhibitor without undue delay. Alternatively, all patients could be treated initially for a period, with review of the need for continuation later on the basis of left ventricular function assessment. Whichever approach is used, there is clear evidence that ACE inhibition should be standard treatment for patients with left ventricular dysfunction following myocardial infarction. A selective, high-risk echocardiographic screening approach is well justified from the evidence presented in this context, although the community prevalence of asymptomatic ventricular dysfunction is certainly not sufficient to justify general population screening.

CONGESTIVE HEART FAILURE

The primary aims of treatment for congestive heart failure are to relieve symptoms of low cardiac output and congestion and improve long-term outcomes, particularly hospitalization and survival.

These aims may be met through different mechanisms, which are not necessarily associated *(Figure 4)*. Blockade of the renin-angiotensin-aldosterone system with ACE inhibition produces both hemodynamic and symptomatic benefit and improved survival. The survival benefit is associated with, and may in part be mediated through, improvement in ventricular remodeling.[21] However, in chronic heart failure, adverse ventricular remodeling may still progress in patients who are on standard treatment including ACE inhibition and considered "stable."[22] More complete neurohormonal blockade with β-blocker treatment in addition to standard treatment can improve ventricular remodeling[22] *(Figure 5)*. The principal benefit of β-blockade in heart failure appears to be improved survival. As with ACE inhibition, this survival benefit is associated with, and probably in part mediated through, improved ventricular function,[23] although other actions including anti-ischemic and antiarrhythmic effects may well contribute. Thus, ACE inhibition and β-blockade have complementary neurohormonal blocking effects that provide additive benefit for patients with congestive heart failure. Both agents improve ventricular remodeling and survival. Changes in ventricular function in this setting of therapy may provide a reliable surrogate for long-term outcomes.[23] In contrast, inotropic agents such as phosphodiesterase inhibitors, while able to produce short-term hemodynamic and symptomatic relief, may increase mortality in heart failure, possibly as a result of increased neurohormonal activation and adverse remodeling long-term.[24]
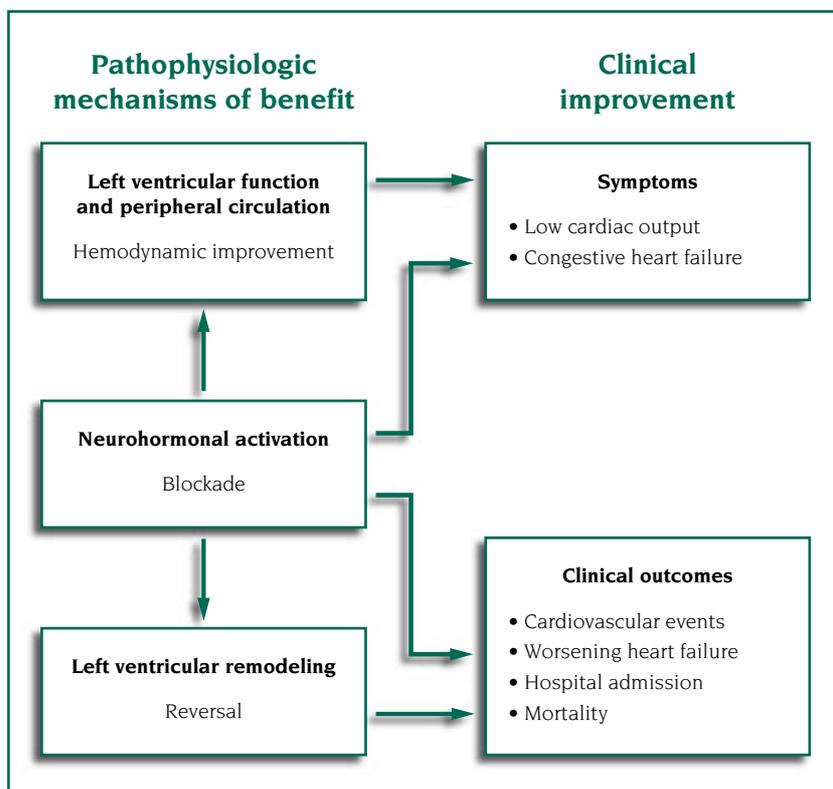
Figure 4. *Treatment aims in heart failure. The relationship between clinical aims of treatment and possible pathophysiologic mechanisms of benefit. Reversal of left ventricular remodeling achieved by neurohormonal blockade is associated with improved clinical outcomes.*
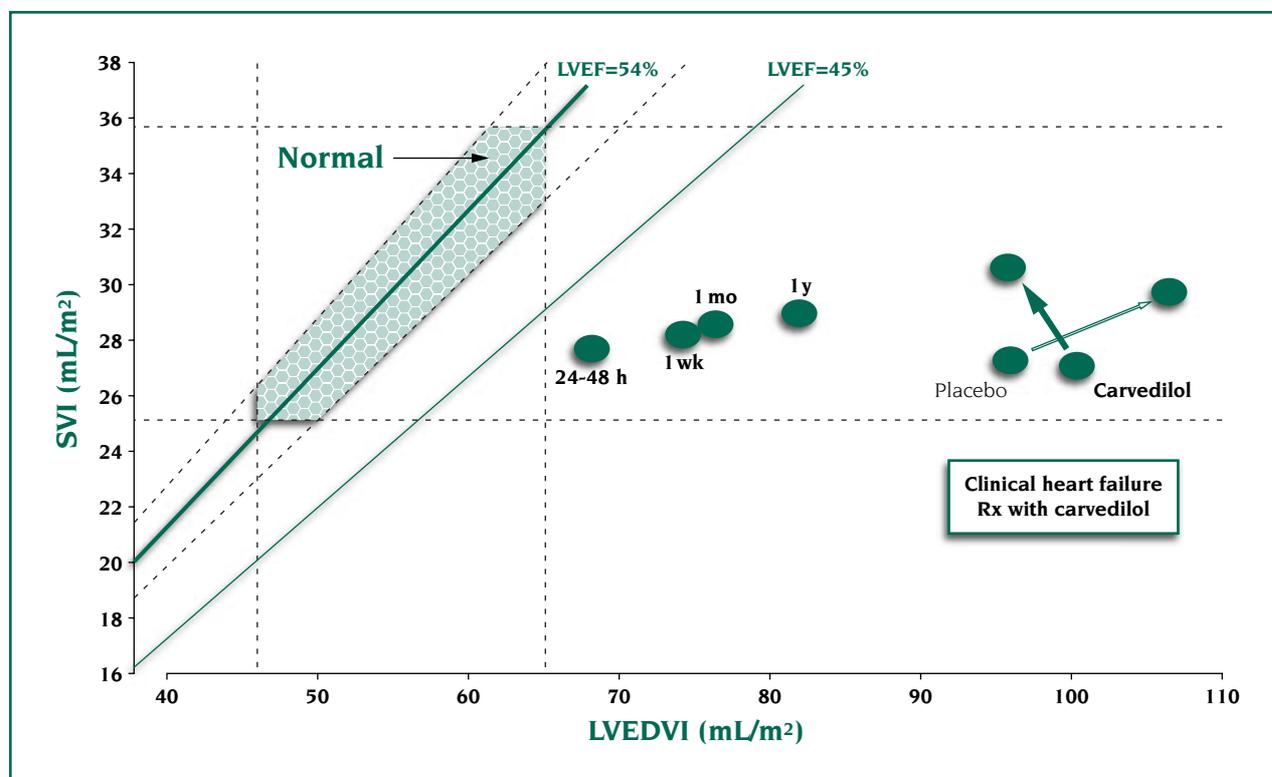
Figure 5. *Effects of carvedilol on left ventricular volumes in heart failure. Quantitative 2-D echocardiographic data from previous post–myocardial infraction (MI) study groups (refs 17 and 18) show progressive increases in left ventricular (LV) end-diastolic volume index (LVEDVI) at intervals up to 1 year with stroke volume index (SVI) maintained. Placebo patients from the Australia and New Zealand Heart Failure Collaborative Study (ANZ) heart failure study (ref 22) show further increases in LVEDVI, whereas during 1 year of treatment, carvedilol improves LV function and prevents LV dilatation.*

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Cardiac Remodeling

Summaries of Ten Seminal Papers

1

Influence of chronic captopril therapy
on the infarcted left ventricle of the rat

J.M. Pfeffer and others. *Circ Res*. 1985

2

Angiotensin I converting enzyme inhibitors
and cardiac remodeling

C. Van Krimpen and others. *Basic Res Cardiol*. 1991

3

Pathological hypertrophy and cardiac interstitium:
fibrosis and renin-angiotensin-aldosterone system

K.T. Weber, C.G. Brilla. *Circulation*. 1991

4

Effect of captopril on mortality and morbidity
in patients with left ventricular dysfunction
after myocardial infarction. Results of the
Survival and Ventricular Enlargement Trial

M.A. Pfeffer and others. *N Engl J Med*. 1992

5

Cells expressing angiotensin II receptors in
fibrous tissue of rat heart

Y. Sun, K.T. Weber. *Cardiovasc Res*. 1996

6

Structural basis of end-stage failure
in ischemic cardiomyopathy in humans

C.A. Beltrami and others. *Circulation*. 1994

7

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in the rat heart

J.P.M. Cleutjens and others. *Am J Pathol*. 1995

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Angiotensin converting enzyme and myofibroblasts
during tissue repair in the rat heart

Y. Sun, K.T. Weber. *J Mol Cell Cardiol*. 1996

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Angiotensin II receptor blockade after myocardial
infarction in rats: effects on hemodynamics,
myocardial DNA synthesis, and interstitial
collagen content

J.F.M. Smits and others. *J Cardiovasc Pharmacol*. 1992

10

Fibrosis, a common pathway to organ failure:
angiotensin II and tissue repair

K.T. Weber. *Semin Nephrol*. 1997

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Highlights of the years by **Dr P.B. Garlick**
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Influence of chronic captopril therapy on the infarcted left ventricle of the rat

J.M. Pfeffer, M.A. Pfeffer, E. Braunwald

Ligation of the left anterior descending artery of the anesthetized rat to produce a variable-sized myocardial infarction of the left ventricle, though first described by Fishbein in 1978, has become known to many as the *"Pfeffer model."* Initially, this experimental approach was utilized by Marc and Janice Pfeffer to study the effects of healed myocardial infarction on the diastolic compliance of the left ventricle in rats 26 days after infarction. Peak cardiac output and pressure-generating capacity were seen to be impaired in proportion to infarct size, correlating also with increases in diastolic volume. Similar relationships between infarct size, diastolic dilatation, heart failure, and survival outcome were already apparent to clinical scientists. Consequently, the *"Pfeffer model"* offered an opportunity to study the hemodynamic and survival effects of therapeutic intervention. Two key papers were published by this group in 1985 detailing the hemodynamic, structural, and survival effects of treatment with the angiotensin-converting enzyme (ACE) inhibitor captopril in rats after coronary ligation. In the first of these, captopril attenuated the left ventricular remodeling (dilatation) and deterioration in performance that were observed in rats with chronic myocardial infarction. In the second, survival times were reported to have increased.

Baseline left and right ventricular and systemic arterial pressures, aortic blood flow, maximal stroke volume, and cardiac indices attained during volume loading were measured in 59 anesthetized rats who had survived for 3 months after coronary ligation. Following removal of hearts, passive pressure-volume relations of the left ventricle were also determined and analyzed so as to characterize ventricular chamber stiffness. Overall, left ventricular volumes (in vitro) of captopril-treated rats were significantly less than those of untreated rats. In untreated rats, increasing infarct size correlated with increasing left ventricular end-diastolic pressures and a progressive decline in maximal pumping ability. For captopril-treated rats, filling pressure and peak stroke volume index remained within normal limits except in the presence of very extensive infarction. Furthermore, chronic captopril therapy reduced baseline mean arterial pressure and total peripheral resistance, yet maintained cardiac and stroke outputs in rats both with and without infarcts. The maintenance of forward output from a less dilated left ventricle also resulted in a higher ejection fraction for treated rats with moderate and large infarcts when compared to untreated rats with infarcts of similar size. Reductions in left ventricular chamber stiffness seen with increasing infarct size also appeared to be normalized by chronic captopril therapy.

In the first randomized, placebo-controlled survival study to be performed in rats, a total of 302 animals were given either placebo or captopril from 14 days after coronary artery ligation, and were followed for a 1-year period or until spontaneous death. In all cases, the size of myocardial infarction was determined from serial histologic sections of the left ventricle. In placebo-treated rats 1-year mortality was directly related to size of infarction, being 29% for rats without infarction and 92% for rats with large infarctions. Overall, captopril significantly (P=0.02) prolonged survival in rats with infarction, the more so as the infarcts were of a moderate size. Extension of these seminal studies into man has resulted in a series of investigations, which have collectively randomized over 100 000 patients with myocardial infarction to ACE-inhibitor or placebo therapy. Collectively, these have confirmed the beneficial findings first observed in rats, resulting in a major change in routine clinical practice.

1985

Gary Kasparov becomes the youngest
World Chess Champion, aged 22;
Live Aid concerts in the UK & USA raise
£40 million for Ethiopia;
and lyrical French painter Marc Chagall dies,
aged 97

Angiotensin I converting enzyme inhibitors and cardiac remodeling

C. Van Krimpen, R.G. Schoemaker, J.P.M. Cleutjens, J.F.M. Smits, H.A.J. Struyker-Boudier, F.T. Bosman, M.J.A.P. Daemen

One of the main controversies to emerge from the mortality trials of ACE inhibition after myocardial infarction stems from the findings of CONSENSUS II (COoperative North Scandinavian ENalapril SUrvival Study II). Early intravenous treatment of over 6000 patients with suspected myocardial infarction was not associated with an improvement in survival. The work of van Krimpen and others suggests one possible explanation for this disappointing outcome. Their findings suggest that there is a negative effect of early ACE inhibition resulting from interference with the adaptive responses of the heart to myocyte loss.

The left coronary artery was ligated in adult male Wistar rats rats to induce a myocardial infarction. A first group of animals received no treatment, a second subcutaneous (SC) captopril from 3 to 5 weeks, and a third SC captopril from 24 hours to 3 weeks after infarction. A fourth group of control rats received sham operations but no active treatment. Each animal was given an SC infusion of BrdU (5'-bromo-2'-deoxyuridine) to label cell nuclei as an indicator of DNA synthesis. All rats were sacrificed by deep ether anesthesia. Hearts were then removed and fixed, structural changes being investigated using a computerized morphometrical system. Infarct size and left ventricular volume were determined, and collagen content of multiple noninfarcted segments of myocardium ascertained using morphometric techniques aided by Sirius red staining.

Mean infarct sizes were reported to approximate 40% in all infarct groups regardless of the different times after infarction and treatment regimens. This represents a contrast to the earlier work of the Pfeffers who reported a range of infarct sizes and also some rats in which no infarction occurred after coronary ligation. In addition, most workers previously reported an early operative mortality of 40% to 60%. Early after ligation, the left ventricle was dilated in association with a marked, but transient DNA synthesis in the remaining left ventricle; the amount of collagen also increased. Early captopril treatment was associated with a decrease in DNA synthesis, collagen deposition, and a reduction in left ventricular volume of 15% among animals surviving to 3 weeks. Late treatment with captopril was reported to have no effect on DNA synthesis, collagen content, or left ventricular volume.

Importantly a parallel hemodynamic study conducted in the same rats by Schoemaker et al found that late captopril administration had much more favorable hemodynamic effects than did early use. Influenced also by a comparative study of hydralazine and captopril, van Krimpen et al conclude that: (i) induction of a myocardial infarction stimulates interstitial DNA synthesis and increases the collagen content in the noninfarcted areas of the heart; and (ii) interstitial DNA synthesis is dependent on the angiotensin I converting enzyme (ACE) in a direct manner, independent of afterload changes. However, later comparative studies with the AT_1 angiotensin receptor losartan suggested that the DNA synthesis–inhibiting effects of captopril are not dependent on AT_1 receptor–mediated mechanisms.

1991

The Empire State Building celebrates its 60th birthday; UK journalist John McCarthy is released after being a hostage in Lebanon for 1934 days; and eight people are sealed inside Biosphere II for a 2-year experiment

Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system

K.T. Weber, C.G. Brilla

Cardiologists are renowned for their focus on a single organ often to the exclusion of other vital related structures. In the 1970s, the importance of abnormalities in the peripheral vasculature to syndromes such as heart failure and hypertension started to be more fully recognized as increasing numbers of patients underwent cardiac catheterization. However, one research group more than any other has drawn clinical attention to noncardiomyocyte structures and cell types within the heart. Initially concerned with the fibrotic changes seen to accompany hypertensive heart disease, studies performed by Karl Weber and colleagues have since been extended to include other pathological conditions that share a final common pathway of cardiac fibrosis. In this one of a series of reviews, prior knowledge is collated and the regulatory role of the renin-angiotensin-aldosterone system introduced to a wider body of clinicians and cardiovascular scientists.

While the Framingham epidemiological study suggested that left ventricular hypertrophy (LVH) was the main cause of clinical heart failure, the explanation as to why this process should be pathological rather than adaptive was unclear. Much research effort was initially focused on the contractile function of the myocardium, while the abnormal accumulation of fibrillar collagen in the extracellular space received less attention. Weber advocated that fibrosis occurring first perivascularly and later throughout the interstitium accounted for abnormal myocardial stiffness and ultimately ventricular dysfunction, probably as a result of cardiac fibroblast growth and enhanced collagen synthesis. Consequently, research into collagen gene regulation, gene-switching events, and the control of collagen synthesis and degradation were considered important in order to develop a more complete understanding of the relation between the collagen network and heart disease.

This review emphasizes the important fact that excessive fibrotic change does not always accompany myocyte hypertrophy and LVH, suggesting that the stimuli for growth of myocyte and nonmyocyte cells are independent of each other. Evidence cited as supporting this belief comes from in vivo studies of experimental hypertension in which the abnormal fibrous tissue responses seen in hypertrophied left ventricle also occurred in normotensive nonhypertrophied right ventricles. Futhermore, initial localization of fibrotic changes to perivascular regions of the myocardium suggested that at least one circulating substance was implicated. Components of the renin-angiotensin-aldosterone system provide the focus for much of Weber's research and also of this review, though the precise logic that caused him at that time to suspect dominance of this system is not clearly apparent.

Weber and Brilla used different animal models, varying plasma concentrations of angiotensin II and aldosterone, and looked for alterations in morphometric and morphological findings. Systemic hypertension, combined with elevated circulating levels of aldosterone, was associated with increased cardiac fibroblast number and activity. However, the exact cellular mechanisms mediating increased collagen metabolism and mitosis of cardiac fibroblasts were considered to require further multidiciplinary investigation. Furthermore, it was suggested that prevention and possibly reversal of the fibrotic component of pathological LVH might be achievable using therapeutic interventions. Specifically, a key role for the angiotensin-converting enzyme inhibitors and aldosterone antagonists was suggested.

1991

South African Nadine Gordimer is awarded
the Nobel Prize for literature;
Sonic the Hedgehog streaks into the lead
over the Mario Brothers;
and Dame Margot Fonteyn,
British ballerina, dies, aged 71

Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial

M.A. Pfeffer, E. Braunwald, L.A. Moyé, and the SAVE Investigators

The SAVE (Survival And Ventricular Enlargement) trial, led by Marc Pfeffer and Eugene Braunwald, represents a landmark investigation for a number of reasons. Foremost among these is the fact that it was the first survival study to demonstrate the potential benefits resulting from angiotensin-converting enzyme (ACE) inhibition after acute myocardial infarction. While consistent with the previously reported CONSENSUS I (COoperative North Scandinavian ENalapril SUrvival Study I) and SOLVD-treatment (Studies Of Left Ventricular Dysfunction, treatment arm) trials of enalapril in patients with overt heart failure, the SAVE study extended the earlier experimental work of this group and others. Limitation of adverse remodeling of the left ventricle, denoted by progressive dilatation, did indeed appear to be a mechanism by which death after myocardial infarction might be effectively prevented. However, a surprising observation was that the likelihood of reinfarction occurring might also be attenuated.

In SAVE, 2231 patients with ejection fractions of 40% or less, but without overt heart failure or symptoms of myocardial ischemia, were randomly assigned to receive double-blind treatment with either placebo (1116 patients) or captopril (1115 patients) within 3 to 16 days after myocardial infarction, being followed for an average of 42 months. Death from all causes was significantly reduced in the captopril group (228 deaths, or 20%) as compared with the placebo group (275 deaths, or 25%); relative reduction in risk 19% (95% confidence interval [CI], 3% to 32%; P=0.019). The relative reduction in risk of developing severe heart failure was 37% (95% CI, 20% to 50%; P<0.001).

Importantly, benefits were observed also in patients who received thrombolytic therapy (33%), aspirin (59%), or β-blockers (36%), suggesting that treatment was producing an additional effect not otherwise achieved by these agents. However, it is pertinent to note that routine early use of thrombolytic and aspirin therapies only started to occur in the course of the investigation. In a much smaller though related study, this same group reported that anterior infarction leads to late ventricular enlargement, not as a result of progressive infarct expansion, but due to an increase in contractile segment length and a change in ventricular geometry. Furthermore, persistent occlusion of the infarct-related vessel was associated with an increased risk of late ventricular enlargement, which was attenuated by captopril.

Part of the pretrial rationale suggested that infarct expansion caused early increases in left ventricular volume and abnormal left ventricular geometry. Patients with large infarctions, those manifesting expansion, and also patients with a persistently occluded infarct-related artery were perceived to be at highest risk of progressive LV dilatation. Furthermore, there were data to support the belief that reperfusion of occluded vessels occurring too late for cardiomyocyte salvage might nevertheless preserve interstitial cells. It is highly significant that the simultaneously published CONSENSUS II trial of early enalapril therapy after suspected acute myocardial infarction failed to show a survival benefit. Increased deaths from left ventricular dysfunction probably resulted from an excess of hypotension-induced infarct expansion combined with inhibition of repair mechanisms.

1992

The Vatican formally admits, after 359 years, that Galileo was right; demonstrations mark the 500th anniversary of Columbus' arrival in America; and Jodie Foster wins a Best Actress Oscar for her role in "Silence of the Lambs"

Cells expressing angiotensin II receptors in fibrous tissue of rat heart

Y. Sun, K.T. Weber

Angiotensin II has been implicated in systemic hypertension and the death of patients with heart failure and after acute myocardial infarction. Angiotensin II is also considered to be prothrombotic, potentially imparting an increased risk of myocardial infarction. Inhibition of angiotensin-converting enzyme (ACE) has emerged as a valuable treatment strategy for prevention of secondary events in patients with established cardiovascular disease. Furthermore, three major trials are currently under way to assess the ability of these agents to prevent primary events. In this context, it is not surprising that one of the papers identified here as being seminal describes the presumed pathological role of angiotensin II in the infarcted heart. This represents a key, albeit complex issue. Sun and Weber have conducted a series of interrelated studies of the fibrotic healing process that occurs in the rat following coronary artery ligation and pericardectomy without myocardial infarction. Having previously noted markedly increased ACE expression and angiotensin II receptor binding at the site of myocardial infarction and within the fibrosed visceral pericardium, they wished to identify which cells were expressing angiotensin II receptors, both at the early and late stages of wound healing.

Myocardial infarction was experimentally induced in anesthetized 8-week-old male Sprague-Dawley rats. Those surviving were sacrificed at either 1 or 4 weeks (n=3 at each time). Control animals were those in whom no myocardial infarction occurred despite thoracotomy, pericardiotomy, and placement of silk ligature around the left coronary artery. These were used to study pericardial fibrosis. Hearts were removed, rinsed in cold saline, frozen, and then sectioned. Angiotensin II receptors were then identified by x-ray and emulsion autoradiography. Immunohistochemical staining of sections with an α-actin primary monoclonal antibody was used as an aid to identifying cell types. Additional sections were stained with either hematoxylin and eosin or collagen-specific Sirius red.

At week 1, a focus of necrotic cells was surrounded by granulation tissue that included macrophages, α–smooth muscle actin fibroblast-like cells (myofibroblasts, myoFb), fibrillar collagen, and new vessels. By week 4, scar tissue had formed and most remaining cells were myofibroblasts. In the pericardium, fibrosis myofibroblasts were evident at both 1 and 4 weeks, though, in contrast with the myocardium, there were no macrophages nor new vessel formation. Myofibroblasts were the predominant cell expressing high-density angiotensin II receptors at the site of myocardial infarction, while fibroblasts, macrophages and vessels demonstrated low-density angiotensin II receptor binding. Likewise, myofibroblasts were seen to express high-density angiotensin II receptor binding in pericardial fibrosis.

These data indicate that the dominant cell type in the late phase of infarct repair (myofibroblasts) expresses large amounts of the angiotensin II receptor. Together with the observed expression of ACE within these healing tissues, this observation suggests that angiotensin II may play a role in mediating the fibrogenic response of wound healing. The clinical result of inadequate scar tissue formation after anterior myocardial infarction is the development of an aneurysm, which predisposes to mural thrombus, arrhythmias, and left ventricular dysfunction. Cardiac rupture and late left ventricular dilatation may also be potential consequences of inadequate healing. The strategy of early, aggressive, generalized use of ACE inhibitors after acute myocardial infarction consequently seems unwise.

1996

The New York marathon is won by
an Italian policeman, Giacomo Leone;
The Booker Prize is awarded
to Graham Swift for "Last Orders";
and René Lacoste, tennis star
and sportswear entrepreneur, dies, aged 92

Structural basis of end-stage failure in ischemic cardiomyopathy in humans

C.A. Beltrami, N. Finato, M. Rocco, G.A. Feruglio, C. Puricelli, E. Cigola, F. Quaini, E.H. Sonnenblick, G. Olivetti, P. Anversa

Loss of irreplaceable cardiomyocytes is a key etiological factor in the development of heart failure, irrespective of whether it is classified as being of ischemic or nonischemic origin. While ischemic cardiomyopathy is characterized by myocyte loss, reactive cellular hypertrophy, and ventricular scarring, the relative contribution of these elements and also the contribution of programmed cell death (apoptosis) remain unclear. Traditional morphometric methods based on test grids for the study of pathologic hearts are time-consuming even for the study of small areas of the myocardium. Consequently, the detailed work reported in this descriptive pathological paper provides important insights into the histopathology of ischemic cardiomyopathy.

In the first of a series of similar investigations, Beltrami and colleagues examined 10 human hearts obtained from individuals with chronic/terminal coronary artery disease undergoing cardiac transplantation. Ten hearts collected at autopsy from patients dying of other causes formed a control group for morphometric studies of left and right ventricular myocardial tissues. Three measures showed an increased amount of left (LV) and right (RV) ventricular hypertrophy: (i) change in organ weight—LV 85%; RV 75%; (ii) aggregate myocyte mass—LV 47%; RV 74%; and (iii) myocyte cell volume per nucleus—LV 103%; RV 112%. Loss of cardiomyocytes (LV 28%; RV 30%) was held responsible for differences in myocyte hypertrophy at the ventricular, tissue, and cellular levels. Ventricular muscle cell hypertrophy was accomplished through an increase in myocyte diameter (LV 16%; RV 13%) and length (LV 51%; RV 67%).

Segmental replacement fibrosis within the interstitium accounted for a large proportion of left (28%) and right (13%) ventricular myocardial volumes. With potential repercussions for contractile function, the proportion of myocytes included in the thickness of the left ventricular wall was reduced by 36%. Loss of cardiomyocytes with replacement fibrosis, combined with lengthening and slippage of the remaining cells, was associated with a major increase in left ventricular cavity size.

These findings are consistent with the belief that ischemic heart failure results from sequential discrete cardiomyocyte loss (micronecrosis) as denoted by multiple foci of replacement fibrosis. Based on the findings of both these and also other investigators, interstitial fibrosis and eccentric hypertrophy, characterizing the condition at a macroscopic level, appear to represent a more generalized secondary response. This concept is consistent with the clinical observations of Pouleur and colleagues, who reported progressive increasing of diastolic compliance of the left ventricles of placebo-treated chronic heart failure patients included in SOLVD-treatment (Studies Of Left Ventricular Dysfunction, treatment arm). This suggests that, rather than being excessive, collagen deposition in these circumstances may actually be inadequate. It has further been suggested that angiotensin-converting (ACE) inhibitors, AT_1-angiotensin– and β-catecholamine–receptor antagonists may act to prevent sequential myocyte loss and thereby improve the prognosis of heart failure patients. Also pertinent to this hypothesis are the more recent observations of Beltrami and colleagues that programmed death of myocytes occurs in the decompensated human heart, potentially contributing to the progression of cardiac dysfunction.

1994

War erupts in Rwanda between Tutsi rebels
and the Hutu government;
Norwegian speed skater Johann Koss breaks
three world records in Atlanta;
and Kansai International Airport,
built on an artificial island, opens in Japan

Collagen remodeling after myocardial infarction in the rat heart

J.P.M. Cleutjens, M.J.A. Verluyten, J.F.M. Smits, M.J.A.P. Daemen

Within the myocardium, interstitial collagen networks are composed largely of type I and III fibrillar subtypes, which help to preserve tissue architecture and chamber geometry, while also being the major determinant of wall stiffness. Consequently, inadequate deposition or excessive degradation of collagen attachments probably results in a reduction in stiffness and distortion in tissue architecture, which can lead to chamber dilatation, wall thinning, and even rupture of the myocardium. The metabolic activity and regulatory control of interstitial collagen therefore represent key elements of the myocardial remodeling process, which have been convincingly linked to long-term prognosis in man.

After inducing left ventricular myocardial infarction in rats, Cleutjens and coworkers investigated the quantity and location of type I and III collagen and their mRNA as compared to sham-operated animals. Northern blotting of cardiac RNA and hybridization with cDNA probes for types I and III procollagens was performed on sections of the paraffin-embedded hearts taken from animals sacrificed at varying times. In the infarcted left ventricle, type III procollagen mRNA levels were increased from 48 hours after coronary ligation, remaining so for at least 3 weeks. Increases in type I procollagen mRNA were not seen until 96 hours after infarction, and were still elevated 12 weeks later. Overall, increases in collagen mRNA content were of the order of 10-fold. Procollagen mRNA–producing cells were identified within the surrounding necrotic cardiomyocytes by in situ hybridization using type I and III procollagen probes.

On day 4 after coronary artery ligation, both type I and type III procollagen mRNA levels were increased within muscle derived from the noninfarcted right ventricle. Within the noninfarcted left ventricular septum at 7 days, type III procollagen mRNA levels were raised. Furthermore, between weeks 1 and 3, a transient increase in type I procollagen mRNA was observed. Hybridization studies indicated localization of mRNA to the interstitial cells of the noninfarcted myocardium, no labeling being detected in association with cardiomyocytes. Increase in types I and III procollagen mRNA in both infarcted and noninfarcted myocardium was followed by an increased collagen deposition, measured by computerized morphometry on Sirius red–stained tissue sections as well as by the hydroxyproline assay. Combined in situ hybridization and immunohistochemistry suggested that collagen mRNA–producing cells in the infarcted myocardium had a myofibroblast-like phenotype in contrast with the fibroblasts detected within the noninfarcted left septum and right ventricle free wall.

In a relevant parallel investigation by this group, the expression and activity of matrix metalloproteinase (MMP-1) and tissue inhibitor of metalloproteinase (TIMP) were studied with mRNA expression by fibroblast-like cells, and were found to be transiently increased in infarcted areas after earlier activation of latent collagenase pools. However, while a balance between collagen deposition and lysis clearly exists in infarct zones, increased expression of metalloproteinases within noninfarcted segments was not apparent. This paper serves as a reminder that it is wrong to consider fibrous tissue to be biologically inert, particularly during the time during which it is first formed.

1995

South Africa wins the World Cup for rugby;
the Tokyo subway is paralyzed
by a sarin nerve gas attack;
and Alberto Fujimori is reelected as President of Peru

Angiotensin converting enzyme and myofibroblasts during tissue repair in the rat heart

Y. Sun, K.T. Weber

This study was designed to determine whether collagen-producing phenotypically modulated fibroblasts (myofibroblasts, myoFbs) were present following experimentally-induced myocardial infarction and following pericardectomy within the visceral pericardium as it healed by fibrosis. In addition, the presence of the angiotensin-converting enzyme (ACE) on the surface of these cells was examined.

Although ACE had previously been described within a range of tissues undergoing repair, including the infarcted myocardium and incised pericardium, expression of this enzyme on fibroblast-like cells contrasts with interstitial fibroblasts that do not usually express ACE. Typically, myofibroblasts are larger than normal fibroblasts, having prominent nuclei and α-actin microfilaments. The key importance of this cell type in collagen deposition and in the formation and contraction of granulation tissue had previously been described. Consequently, the question raised was as to whether the cells observed in healing myocardium and pericardium are in fact myofibroblasts.

Two groups of male Sprague-Dawley rats underwent left thoracotomy and pericardotomy with or without ligation of the left coronary artery. Animals surviving to 24 hours after surgery were randomized to one of 5 groups of 3, and were sacrificed at day 3, week 1, 2, 4, and 8. After rinsing in saline, hearts were frozen prior to immuno-histochemical labeling using primary monoclonal antibodies to α-actin and ACE. In the noninfarcted heart, smooth muscle cells in blood vessels labeled positive for α-actin. At day 3 after myocardial infarction, large numbers of inflammatory cells were seen to surround the necrotic area with a few myofibroblasts. By week 1, a central core of persisting necrotic cardiomyocytes were surrounded by numerous myofibroblasts. By weeks 4 and 8, necrotic myocytes had been resorbed and the dominant cell type was the myofibroblast. Within the healing pericardium, myofibroblasts appeared in groups arranged according to the long axis of collagen fibers. Myofibroblasts, both at

the site of myocardial infarction and pericardial fibrosis, were also positively labeled by the ACE antibody.

Sun and Weber speculate that myofibroblast ACE may play a role in the fibrogenic response of tissue repair in the rat myocardium by regulating local concentrations of substances involved in healing and matrix remodeling. Specifically, the local production of angiotensin II and the breakdown of bradykinin are suggested as potential intermediaries in the healing process. The significance of these findings relates to the most appropriate timing of ACE-inhibitor therapy in patients after acute myocardial infarction. Logically, it would appear that these agents should be absolutely contraindicated due to likely inter-ference with the healing process. While islands of fibrosis within the myocardium may impair diastolic relaxation and act as a substrate for arrhythmias, the suppression of repair mechanisms would likewise be predicted to have detrimental consequences. It would appear, therefore, that the key objective when giving chronic maintenence ACE-inhibitor therapy is to prevent ongoing loss of car-diomyocytes, thereby avoiding both replacement fibrosis and, more importantly, loss of myocardial contractility.

1996

Wallace and Gromit are lost for 48 hours
in a New York taxicab;
Winnie the Pooh celebrates his 70th birthday
(14th October);
and US comedian George Burns, dies, aged 100

Angiotensin II receptor blockade after myocardial infarction in rats: effects on hemodynamics, myocardial DNA synthesis, and interstitial collagen content

J.F.M. Smits, C. Van Krimpen, R.G. Schoemaker, J.P.M. Cleutjens, M.J.A.P. Daemen

Cardiac remodeling represents an alteration in the geometry of the heart, which may act as an adaptive or a pathological process. Enlargement of the left ventricle after myocardial infarction has been taken as a surrogate for mortality in trials of thrombolytic agents and angiotensin-converting enzyme (ACE) inhibitors. The beneficial effects of ACE inhibitors after acute myocardial infarction are thought to result primarily from inhibition of angiotensin II formation, and thus diminished angiotensin receptor stimulation. Consequently, the effects of AT_1-angiotensin–receptor antagonists on left ventricular hemodynamics, dilatation, and DNA and collagen synthesis represent important surrogates when seeking to predict possible effects on survival of humans after spontaneous infarction.

Following coronary artery ligation in male Wistar rats, Smits et al administered the angiotensin II AT_1-receptor antagonist losartan either from day 1 to day 21 or from day 21 to 35. This approach was adopted to evaluate the role of angiotensin II both during and also after completion of the repair phase of an acute myocardial infarction. A group of sham-operated rats were treated with saline. All groups were administered BrdU (5'-bromo-2'-deoxyuridine) in order to study DNA synthesis. Collagen deposition was measured by computerized morphometrics of Sirius red–stained samples. As previously observed, myocardial infarction reduced both resting cardiac output (CO) and also maximal CO reserve. Losartan treatment resulted in a rightward shift of the angiotensin II pressor dose-response curve by a factor of 32 to 40, indicating effective receptor antagonism. However, neither CO nor COmax was affected by losartan treatment after either early or late treatment. Although early treatment with losartan reduced cardiac hypertrophy measured as heart weight, DNA synthesis was reduced only slightly. In contrast, collagen deposition was inhibited completely. The results suggest that the effects previously seen after administration of captopril to rats after myocardial infarction may not be completely dependent on AT_1-receptor–mediated mechanisms.

In the discussion section of their paper, Smits et al mention the possibility of the AT_2 angiotensin receptor playing a role in mediating adverse sequelae of increased angiotensin II levels after myocardial infarction. However, potential mechanisms for such an effect are unclear. Of the two alternative theories considered, namely, an adverse effect mediated by an intracellular angiotensin II receptor or a beneficial bradykinin-mediated effect, it is only the latter for which additional evidence exists. Bradykinin inhibitors have been shown to attenuate the beneficial hemodynamic effects of captopril on left ventricular remodeling after experimental myocardial infarction. Simplistically, these data suggest that it would be wrong to assume that the clinical benefits seen with ACE-inhibitor therapy after acute myocardial infarction are necessarily going to be shared by the new angiotensin AT_1-receptor antagonists.

1992

Women in Afghanistan are banned
from appearing on television;
race riots erupt in Los Angeles over
the Rodney King verdict, leaving 58 dead;
and Quentin Tarantino's "Reservoir Dogs"
is screened

Fibrosis, a common pathway to organ failure: angiotensin II and tissue repair

K.T. Weber

In an earlier review *(see page 46)*, I commented on the role that the work of Karl Weber's group may have had in expanding the horizons of cardiologists and cardiovascular physicians beyond cardiomyocytes, the heart, and the cardiovascular system. Such a view is underscored by the content of this review addressing the role of fibrosis as a common pathway to organ failure. Indeed, there is an opening exhortation in favor of "tearing down barriers between specialties in search of such common ground." However, despite taking a more comprehensive view of fibrosis and its role in health and disease, a primary focus is still maintained on the effects and inhibition of the renin-angiotensin-aldosterone system.

Defining some of the different manifestations of the fibrotic process, we are introduced to four concepts: (i) parenchymal cell loss leading to *replacement fibrosis;* (ii) reactive fibrosis occurring perivascularly in the absence of parenchymal cell loss; (iii) collapse fibrosis following parenchymal cell atrophy without increased collagen deposition; and finally (iv) absolute fibrosis referring to increased collagen deposition resulting from synthesis prevailing over degradation without altered parenchymal cells. *Progressive fibrosis* necessarily denotes increasing proportions of collagen over time, while *regression of fibrosis* implies the reverse.

Tissue repair involves different inflammatory cells, including members of the monocyte/macrophage lineage, which are integral to initiating the repair process. Early accumulation of polymorphonuclear leukocytes, macrophages, and/or lymphocytes can be attenuated by glucocorticoid or cyclooxygenase inhibitors. However, while such therapy is thought to beneficially modulate the bleomycin model of interstitial pulmonary fibrosis, it may exacerbate left ventricular remodeling in experimental myocardial infarction. Myofibroblasts (myoFb) containing α-actin microfilaments appear during a second phase and, together with phenotypically transformed interstitial fibroblasts, are responsible for collagen turnover and fibrous tissue formation. In addition, myofibroblats may have a contractile activity producing fibrous tissue contraction. Fibrogenic cytokine transforming growth factor $\beta 1$ (TGF-$\beta 1$) is a strong candidate for inducing phenotypic conversion of fibroblasts to myofibroblasts as is seen experimentally, in contradistinction to platelet-derived growth factor and tumor necrosis factor. After creating a firillar fibrin-fibronectin scaffolding, myofibroblats lay down type III and then type I collagens, which make up most fibrous tissues. Endothelin-1, catecholamines, bradykinin, serotonin, and angiotensin II may each influence the process of fibrous tissue formation. However, the differential expression of matrix metalloproteinase (MMP-1) and tissue-inhibiting metalloproteinase (TIMP) as well as disappearance of myofibroblasts through apoptosis determine whether fibrosis is progressive or regressive.

Weber suggests a unifying paradigm of tissue repair in which angiotensin II via the angiotensin AT_1 receptor plays a key autocrine role in regulating expression of TGF-β and thereby collagen deposition. Consequently, it is suggested that angiotensin-converting enzyme (ACE) inhibition and AT_1-receptor antagonism may usefully prevent progressive tissue fibrosis. Experimental evidence in favor of this key role includes the dominant presence of AT_1 receptors and ACE in scar tissues, as well as the antifibrotic effects of ACE inhibitors and AT_1-receptor antagonists in the heart and to a lesser extent other organs. However, it is of concern that inhibition of collagen formation after MI has been associated with greater hemodynamic impairment.

1997

The Caribbean island of Montserrat
is devastated by a volcanic eruption;
the British Racing Pigeon Society
celebrates its centenary;
and James Stewart, Hollywood legend, dies, aged 89

Cardiac Remodeling

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