Br. J. clin. Pharmac. (1989), **28**, 141S–150S

Angiotensin and the remodelling of the myocardium

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1 From a morphologic standpoint, the myocardium has three compartments: cardiac myocytes; intramyocardial coronary arteries with a microcirculation; and an interstitium composed largely of fibrillar collagen. As long as intercompartmental equilibrium exists, myocardial mechanics and energetics and myocyte viability will each be preserved.
2 The hypertrophic process seen with left ventricular pressure overload secondary to renovascular hypertension alters this equilibrium because of the adverse remodelling of intramural coronary arteries and fibrillar collagen. The pathogenetic mechanism(s) responsible for the observed myocardial fibrosis, having reactive and reparative components, remains to be elucidated.
3 Attractive circumstantial evidence, however, has been obtained to incriminate circulating angiotensin II in this process. Five lines of evidence favouring the role of angiotensin II in promoting the reactive perivascular and interstitial fibrosis and the reparative fibrosis are presented, including the potential cardioprotective effects of angiotensin converting enzyme inhibitors.

Keywords angiotensin myocardium

Introduction

The myocardium consists of cardiac myocytes and a coronary microcirculation each of which is surrounded by and supported within the interstitial space where the major structural protein is collagen. Because of the balanced equilibrium that normally exists between the muscular, vascular, and fibrillar collagen compartments, the mechanical behaviour and energetics of the myocardium are preserved as is myocyte viability. A permanent disequilibrium between compartments, that accompanies the hypertrophy seen in response to a haemodynamic overload or excess hormonal stimulus (e.g., noradrenaline, angiotensin), would prove pathologic. Hence, the hypertrophic process must retain the balanced remodelling between compartments if it is to be adaptive.

Because the heart is a muscular pump, it is not unexpected that a major emphasis has been placed on deciphering the role of cardiac myocytes in the appearance of pathologic hypertrophy with heart failure. In particular, an abnormality of the contractile process has been sought (Wikman-Caffelt *et al.*, 1979). To date, however, no unifying concept has emerged to implicate such a biochemical defect in the appearance and progression of heart failure. A broader perspective has therefore been proposed (Weber *et al.*,1987, 1988). It considers a structural basis for pathologic hypertrophy and includes the adverse remodelling seen in the cardiac interstitium and coronary microcirculation. The purpose of this review will be to examine the structural remodelling of these two compartments in pressure overload hypertrophy, the potential role of circulating angio-

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tensin in mediating this remodelling, and the potential cardioprotective effects of angiotensin converting enzyme (ACE) inhibitors.

Pathologic remodelling of the myocardium

Left ventricular hypertrophy is the major risk factor associated with the appearance of symptomatic heart failure (Kannel *et al.*, 1987). Hence it would not seem unreasonable to assume that the origins of heart failure are rooted in the hypertrophic remodelling of the myocardium. A causal relationship between hypertrophy and the appearance of heart failure is most often found in patients with hypertension or coronary artery disease (Kannel, 1989). In the case of occlusive coronary artery disease with myocardial infarction, an overwhelming loss of cardiac myocytes and sequential reduction in contractile mass provides one explanation for the appearance of heart failure. It does not account for its progression over time. The mechanism accounting for the onset of heart failure in the hypertrophied myocardium seen with longstanding hypertension, where a segmental loss of cells is unlikely, may instead reside in the structural remodelling of intramyocardial coronary arteries and the collagen matrix of the interstitium. A continued remodelling of these compartments may have pathophysiologic consequences that account for a progressive deterioration in the mechanical behaviour and energetics of the myocardium.

It is important to note that while various pathophysiologic conditions may result in left ventricular pressure overload, their pathogenetic origin can be quite different. Hence, the mechanism responsible for the adverse remodelling of these compartments may be different in each case and in fact may be independent of ventricular pressure. We will therefore consider our working model of potential pathogenetic factors, but first the pathologic aspects of myocardial remodelling in left ventricular pressure overload hypertrophy will be examined.

Remodelling of the intramural coronary circulation

In their review, Anversa and colleagues (1981) indicate that the luminal volume and surface of myocardial capillaries are increased in chronic pressure overload hypertrophy and therefore suggest that myocyte oxygen availability is preserved.

Intramural coronary arteries, however, are structurally remodelled in the hypertrophied human myocardium that accompanies systemic hypertension (Tanaka *et al.*, 1987) and aortic stenosis (Naeyt & Liedtke, 1976; St John Sutton *et al.*, 1980). This can include the hypertrophy of vascular smooth muscle cells, the proliferation of endothelial cells, and an accumulation of collagen in the media and adventitia. Such remodelling may account for the abnormal vasomotor reactivity and impaired coronary vascular reserve that is frequently observed in patients with left ventricular hypertrophy due to hypertension (Marcus *et al.*, 1979; Strauer *et al.*, 1983). Furthermore, and similar to the rat with experimental or genetic hypertension, the perivascular fibrosis that surrounds intramyocardial coronary arteries (see Figure 1) is a progressive process (Jalil *et al.*, 1988; Michel *et al.*, 1986; Thiedemann *et al.*, 1983). From their perivascular location, collagenous septae radiate outward between neighbouring myocytes to create a perimuscular fibrosis. In man with aortic stenosis (Anderson *et al.*, 1979), these septae are found to fuse with the perivascular collagen of neighbouring vessels creating a

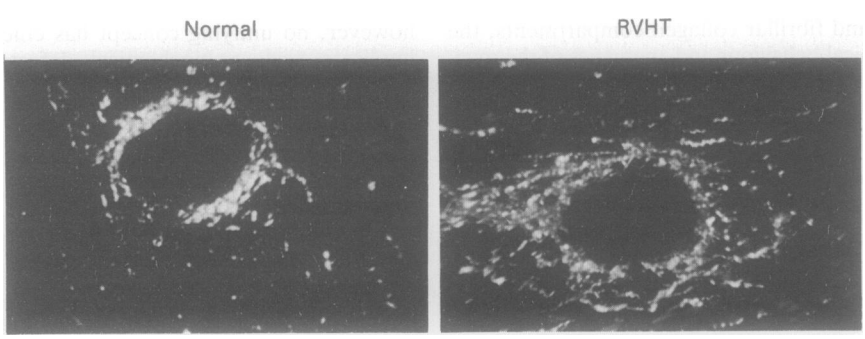

Figure 1 The perivascular fibrosis of intramyocardial coronary arteries is shown in the right panel and compared with the normal amount of fibrillar collagen that surrounds these vessels (left panel). Picrosirius-polarization technique. ×40.

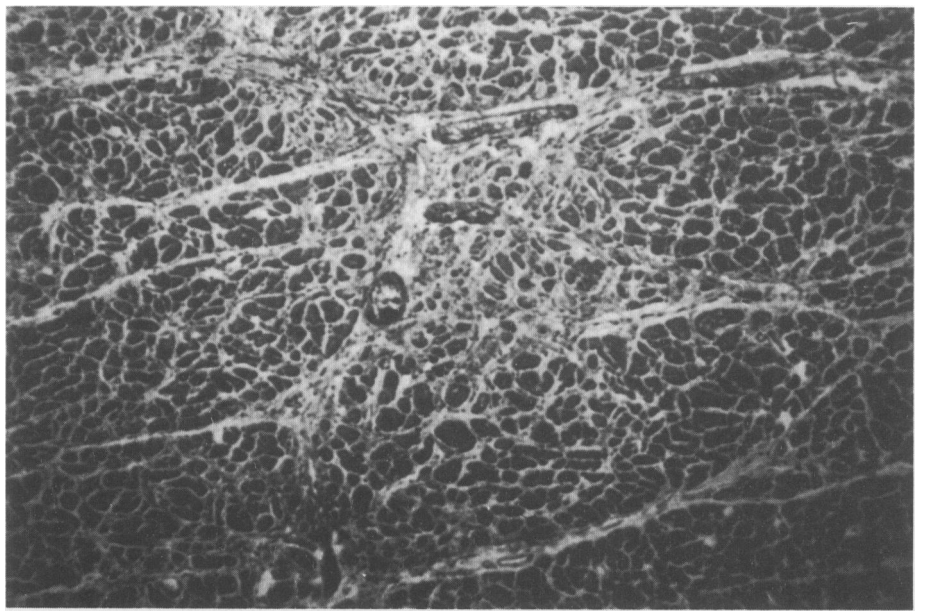

Figure 2 The interstitial fibrosis and lobulated appearing human myocardium seen in systemic hypertension is represented. Masson trichrome. ×4. Note also the variable size of muscle fibres contained within the dense areas of fibrosis.

lobulated-appearing myocardium. Such an interstitial fibrosis would offer a greater resistance to ventricular filling.

Remodelling of the collagen matrix

An impressive increment in the volume (or concentration) of myocardium occupied by collagen (see Figure 2) has been seen in adults with aortic valvular stenosis (Anderson *et al.*, 1979; Caspari *et al.*, 1977; Hess *et al.*, 1981; Oldershaw *et al.*, 1980; Schaper & Schaper, 1983; Schwarz *et al.*, 1978; St John Sutton *et al.*, 1980), children with congenital aortic stenosis or coarctation of the aorta (Cheitlin *et al.*, 1980), and adults with systemic hypertension (Pearlman *et al.*, 1982; Tanaka *et al.*, 1986). In each circumstance, the accumulation of collagen, or myocardial *fibrosis*, was not associated with epicardial coronary artery disease. Anderson *et al.* (1979) have categorized the fibrosis seen in aortic stenosis as consisting of an interstitial and perivascular accumulation of collagen, foci of reparative fibrosis, and a plexiform fibrosis associated with muscle fibre disarray.

In the nonhuman primate with gradual onset experimental hypertension studied over an extended period of time, it was possible to monitor the sequence to the remodelling of the collagen matrix. In established hypertrophy and using scanning electron microscopy, Abrahams and co-workers (1987) found an increased thickness of perimysial tendons and strands and an increased density of the perimysial weave surrounding myocytes. These features represent a reactive myocardial fibrosis in that cell necrosis with a reparative (or replacement) fibrosis was not seen. Pick *et al.* (1989) using the picrosirius-polarization technique to enhance collagen fibre birefringence, found several different patterns of myocardial fibrosis, based on the alignment of thick and thin collagen fibres to one another and to myocytes. They included: (a) a reactive interstitial fibrosis, where a greater number of intermuscular spaces were occupied by fibrillar often times thicker collagen; (b) a meshwork of collagen fibres that surrounded myocytes; and (c) in a late phase of established hypertrophy a reparative fibrosis that consisted of collagen fibres bridging the void created by myocyte loss.

The functional consequences of these various patterns of myocardial fibrosis have been examined in the rat (Carroll *et al.*, 1989; Doering *et al.*, 1988; Jalil *et al.*, 1989a,b). The findings of these studies emphasize the importance of collagen fibre configuration, alignment, and location (see Figure 3) on myocardial stiffness and myocyte loading. In each case, however, it is apparent that the remodelled collagen matrix can account for pathologic hypertrophy.

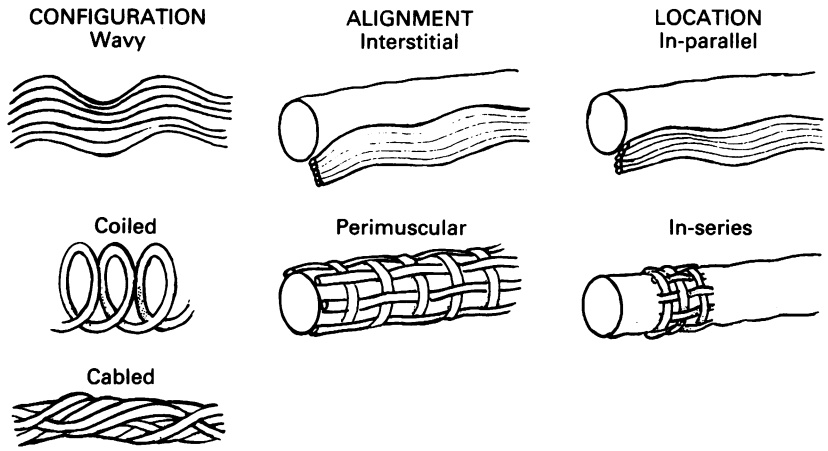

Figure 3 Myocardial stiffness and myocyte loading will not only be related to the concentration of collagen, but also the configuration, alignment, and location of fibrillar collagen with respect to cardiac muscle.

Unlike the fibrous tissue response seen in the pressure overloaded heart, an increase in collagen concentration is not seen in the volume overloaded ventricle secondary to an arteriovenous fistula (Michel *et al.*, 1986b), anaemia (Bartosova *et al.*, 1969), or atrial septal defect (Marino *et al.*, 1985). The explanation for this difference between the pressure and volume overloaded ventricle has not been elucidated. One attractive possibility may be related to the absence of elevated circulating angiotensin in these circulatory overload models. This hypothesis would explain the increased collagen volume fraction which we have seen in the dilated left ventricle secondary to rapid ventricular pacing (unpublished observations). Unlike the other volume overload models, where cardiac output is increased or the stimulus to heightened plasma renin activity is reduced, the pacing model of low cardiac output failure is associated with elevated plasma renin activity (Moe *et al.*, 1989). Riegger *et al.* (1984) have reported that the architectural remodelling of the rapidly paced ventricle and its impaired haemodynamic performance can be forestalled by pretreatment with the ACE inhibitor captopril.

In the sections that follow, the angiotensin hypothesis of myocardial remodelling of the coronary vasculature and interstitium will be considered.

Myocardial fibrosis: a model of potential pathogenetic mechanisms

Myocardial fibrosis is the result of enhanced collagen synthesis by existing cardiac fibroblasts or fibroblast proliferation, or because collagen degradation is reduced (Figure 4). Several potential pathogenetic mechanisms may be responsible for the accumulation of collagen. These include: (a) a direct relationship between ventricular chamber systolic pressure and collagen biosynthesis, much like stress-mediated bone remodelling; (b) a link between chamber pressure and collagen accumulation which is based on the release of 'growth factors' from within the myocardium (e.g. myocardial noradrenaline release); (c) circulating 'growth factors' that directly influence collagen accumulation, and which may (e.g. angiotensin) or may not (e.g. platelet derived growth factor) be associated with an elevation in ventricular pressure; and (d) an interaction of 'growth factors' contained within the vascular and interstitial spaces which occurs when the endothelial cell barrier is compromised.

Circulating angiotensin and myocardial fibrosis

Five lines of evidence will be reviewed.

Angiotensin infusion

In 1964, Giese (1964a,b) reported that both an intravenous infusion of angiotensin (AII) or experimental bilateral renal ischaemia increased the permeability of pancreatic and mesenteric arteries. Wiener and co-workers (Giacomelli *et al.*, 1976; Wiener & Giacomelli, 1973) reported similar findings, in these and other segments of the arterial circulation including intramural coronary arteries, and that this alteration in

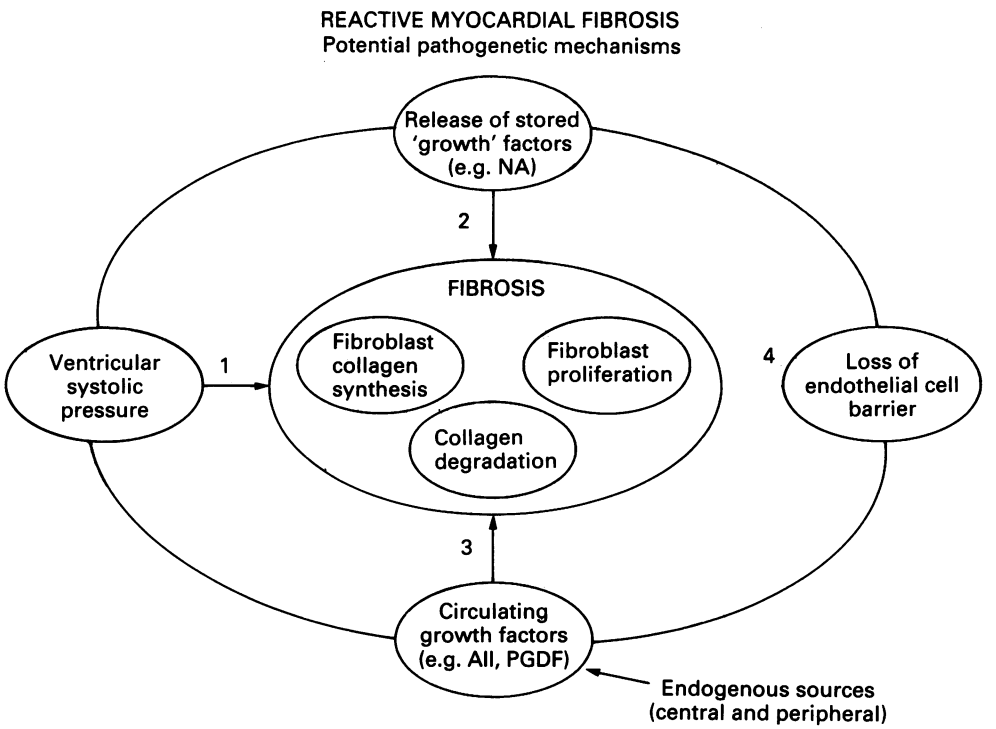

Figure 4 A working model of potential pathogenetic mechanisms involved in the appearance of myocardial fibrosis.

permeability was related to the formation of interendothelial cell clefts. As a result, plasma proteins were found within the media of intramyocardial coronary arteries. Vascular smooth muscle cell necrosis was also observed. In each of these studies, however, hypertensive doses of AII were administered and therefore it was not possible to differentiate the influence of AII from an elevation in arterial pressure on vascular permeability.

Using an osmotic minipump implanted in the peritoneal space of the rat, a dose of AII that did not raise arterial pressure for several days was administered (Tan *et al.*, 1989). Abnormal myocyte sarcolemmal permeability to antimyosin antibodies was seen throughout the myocardium on day one of the infusion. The detection of this abnormality in membrane permeability was interpreted to represent an early stage of myocyte necrosis. The fibroblast proliferation that followed, and which peaked on day 2 of the infusion, was consistent with this interpretation. The administration of AII for 14 days, however, did not lead to continued necrosis. Myocardial fibrosis that is characteristic of renovascular hypertension was noted after this long term infusion of AII. Hence, a reparative fibrosis is but one explanation for the accumulation of collagen that occurs in this setting and an elevation in arterial pressure is not a prerequisite for myocardial fibrosis.

Renovascular hypertension

On day 1 after the perfusion of the right kidney was compromised by abdominal aorta banding (Figure 5), evidence of antimyosin labelling of myocytes was found throughout the myocardium (Tan *et al.*, 1989). The quantity of necrotic myocardium has not yet been defined, but does not appear to be large. This necrosis was followed by fibroblast proliferation, as detected by radioactive thymidine labelling, which peaked on day 2 of renovascular hypertension. Thus, as with the AII infusion, a reparative fibrosis accounts, in part, for the myocardial fibrosis seen in this model of renovascular hypertension. Captopril pretreatment prevented the appearance of myocyte necrosis.

Using a less constrictive suprarenal aortic band, Lindy *et al.* (1972) found that prolyl hydroxylase activity rose promptly after the procedure and was immediately followed by enhanced proline incorporation into collagen. Relative to this

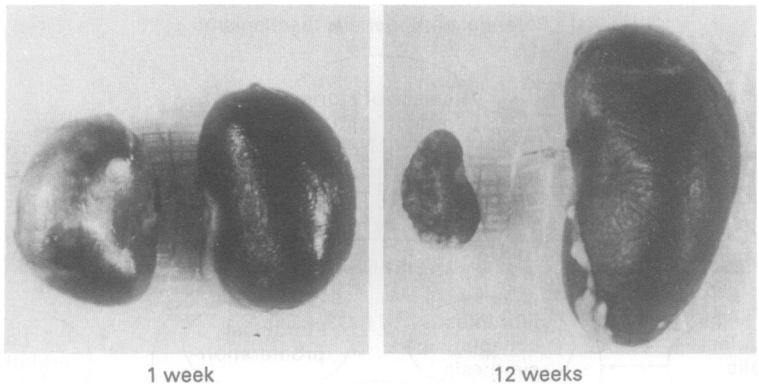

Figure 5 An abdominal aorta banding procedure is used to raise arterial pressure and to compromise the perfusion of the right renal artery. A progressive atrophy of the right kidney is seen at 1 (left panel) and 12 (right panel) weeks.

early rise in collagen synthesis, Morkin & Ashford (1968) observed a later proliferation of fibroblasts. These findings suggest that collagen synthesis rises first in existing fibroblasts and is accompanied thereafter by fibroblast proliferation. The disparity between the later fibroblast proliferation seen in this study and findings cited earlier, may be related to a more rapid and marked elevation in circulating AII that could accompany the more constrictive banding procedure.

In another model of renovascular hypertension (2 kidney/1 clip), studied in the rat at 4 weeks, Bhan *et al.* (1978) and Wiener *et al.* (1969) reported an abnormality in the permeability of systemic and intramural coronary arteries which resembled that seen with the AII infusion. They also observed an extravasation of platelets and plasma proteins into the adventitia of these vessels and the surrounding interstitium. After 4 weeks of renovascular hypertension in the dog, Laine (1988) found that coronary microvascular permeability and cardiac lymph flow were each increased. The interrelationship between enhanced permeability of the coronary circulation and the subsequent perivascular fibrosis of intramyocardial coronary arteries is uncertain. Nevertheless, the accumulation of collagen in the adventitia of these vessels and surrounding interstitium is progressive and envelops neighbouring myocytes. This same perivascular and streaky fibrosis was found in the rat myocardium following systemic microsphere embolization and the appearance of sclerotic glomeruli (Carroll *et al.*, 1989).

The collagen concentration of the myocardium in renovascular hypertension, as measured by either its concentration of hydroxyproline or its morphometrically determined collagen volume fraction, is elevated (Averill *et al.*, 1976; Bartosova *et al.*, 1969; Doering *et al.*, 1988; Jalil *et al.*, 1988; Michel *et al.*, 1986b; Sen & Bumpus, 1979; Thiedemann *et al.*, 1983; Weber *et al.*, 1988b). Thus, there is little question that collagen accumulation and its structural remodelling are an integral component of the pressure overload state that accompanies renovascular hypertension and which, in some yet undefined manner, may be related to elevated circulating angiotensin II. The role of ventricular pressure overload is considered below.

Right ventricular involvement

In keeping with the view that circulating AII is responsible for the remodelling of the myocardium, and not the rise in left ventricular pressure, one would expect that both the right and left ventricle would be remodelled in renovascular hypertension. This is indeed what we have observed (unpublished observations) in our model of renovascular hypertension in the rat. The right ventricular myocardium has an interstitial and perivascular fibrosis that is characteristic of the remodelling seen in the left ventricle even though its weight is not increased.

In cultured fibroblasts, AII induces cell proliferation (Ganten *et al.*, 1975). The mechanism responsible for this mitogenic effect is unclear. Turto (1977), however, found that the sodium-potassium ATPase inhibitor digitoxin, when administered prior to the suprarenal banding procedure, would attenuate the early rise in collagen synthesis and the degree of hyper-

trophy that accompanied this model of left ventricular pressure overload secondary to renovascular hypertension.

Nonrenovascular hypertension

In banding the abdominal aorta so that renal perfusion was not compromised, neither myocyte necrosis nor fibroblast proliferation were observed despite the pressure overload (Tan *et al.*, 1989). In preliminary studies, banding of the aorta in this manner for 4 weeks leads to left ventricular hypertrophy without myocardial fibrosis (unpublished observations).

Banding of the ascending aorta is associated with an early rise in collagen synthesis and fibroblast proliferation (Grove *et al.*, 1969; Skosey *et al.*, 1972). The clustered foci of fibroplasia are compatible with a reparative fibrosis.

Prevention of ACE inhibitors

Further evidence in support of the angiotensin hypothesis comes from observations where myocardial remodelling and fibrosis can be prevented with ACE inhibitors. Sen *et al.* (1980) found that when 3 week old rats with genetic hypertension were begun on a regimen of captopril in their drinking water the expected rise in myocardial collagen concentration seen 6 weeks later in untreated animals was not observed in the captopril group. In treating older (8 weeks) rats having established hypertrophy with oral captopril, this group found collagen content had declined significantly with the regression in hypertrophy. Unlike the genetic model, Sen *et al.* (1980) found that captopril would regress myocyte mass without altering collagen in rats with renovascular hypertension (2 kidney/1 clip) and as a result myocardial collagen concentration rose significantly.

Michel *et al.* (1986a) have reported that the perivascular fibrosis of afferent arterioles, seen in the kidney of rats with renovascular hypertension, could be prevented with perindopril. The response in myocardial collagen concentration and structure of intramural coronary arteries to this ACE inhibitor has not yet been reported.

As noted earlier, captopril pretreatment prevents myocyte necrosis in the rat with renovascular hypertension (Tan *et al.*, 1989). In a recently completed trial Jalil *et al.* (1989) found that the pretreatment of rats with captopril prior to inducing renovascular hypertension would also prevent the rise in collagen volume fraction and the appearance of the perivascular and interstitial fibrosis seen in the myocardium 8 weeks later. This effect of captopril was less dramatic when it was initiated several days after the banding procedure.

Future directions

The evidence presented is in keeping with a pathogenetic role of circulating angiotensin in the remodelling of the myocardium and particularly the appearance of myocardial fibrosis. This includes the appearance of a reparative fibrosis that follows myocyte necrosis and a reactive fibrosis represented by the accumulation of collagen in the interstitium and around intramural coronary arteries. Despite this attractive circumstantial evidence, further support for this hypothesis must be obtained and complemented by studies in which the interrelationship between AII and the collagen and vascular compartments is elucidated. This will, no doubt, require both *in vivo* and *in vitro* studies. The angiotensin hypothesis, however, must be clarified given the potential of ACE inhibitors to prevent or attenuate myocyte necrosis and the reparative and reactive myocardial fibrosis and thereby the appearance of pathologic hypertrophy with diastolic and/or systolic ventricular dysfunction.

This work was supported in part by NHLBI grant #R05-HL-31701.

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Discussion

Peter S. Sever (London): You clearly implicated AII in the pathogenesis of the collagen matrix remodelling. What are your views on other potential growth factors and vasoactive substances which have been implicated in the pathogenesis of myocardial hypertrophy and smooth muscle hypertrophy.

Karl T. Weber (Chicago): There are many substances which may be involved in the remodelling of the myocardium. I focussed on one of these. The adrenergic nervous system, which releases norepinephrine, is probably operative here as well, as is circulating AII and platelet-derived growth factor. My view is that the cardiac fibroblast, which is normally bathed in a host of growth factors, known as progression factors, does not proliferate until it is made competent by its exposure to one of these elements. Then the competence/progression model allows for their proliferation and collagen formation. So, clearly, the picture is very complicated. There are many potential 'growth factors' and AII is but one.