



REVIEW ARTICLE

ACE inhibition in aortic stenosis: dangerous medicine or golden opportunity?

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Conventionally angiotensin-converting enzyme (ACE) inhibitors are contraindicated in patients with aortic stenosis. Abundant evidence is now available showing that angiotensin II has a central role in the development of left ventricular hypertrophy (LVH), myocardial contractile failure and diastolic dysfunction in response to pressure overload. In animal models, ACE inhibitors have been shown to attenuate these pathological responses. In humans there is no such evidence available, however uncontrolled studies have shown that

these agents are not only tolerated but are associated with acute improvements in haemodynamics and diastolic function. Further studies are merited to assess the possible role of ACE inhibitors in aortic stenosis both before and after valve replacement. Potential benefits may include prevention of LVH, improved diastolic function, reduction of arrhythmias and preservation of left ventricular function.

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Introduction

Cardiologists are often able to practice evidence-based medicine as a result of the extensive data available from large, randomised clinical trials. However, the management of many common disorders continues to be guided by custom and belief based upon fundamental principles and anecdotal clinical experience. The avoidance of vasodilator therapy in patients with aortic valve stenosis is a good example of this practice. Although no controlled data exists, clinical experience suggests that vasodilatation in this condition carries the risk of severe hypotension and coronary hypoperfusion as a result of the inability of cardiac output to increase in the face of a fixed obstruction.¹ Sadly, such 'common sense' medicine is often used to justify only distantly related practices and it is possible or even likely that the avoidance of angiotensin converting enzyme (ACE) inhibitor therapy in aortic stenosis falls in to this category. Conventional clinical teaching and the current edition of the British National Formulary suggest that these drugs are contraindi-

cated in patients with aortic stenosis. This is presumably based upon their incorrect classification as vasodilators although they are neuro-hormonal antagonists with no intrinsic vasodilator action. In most patients ACE inhibitors are relatively weak vasodilators and it has long been recognised that their efficacy in chronic heart failure may have little to do with vasodilatation.² The activation of both circulating and tissue renin-angiotensin systems has been shown to exert diverse deleterious results in heart failure and the use of ACE inhibitors to inhibit angiotensin II formation is now a routine management strategy. Both tissue and circulating renin-angiotensin systems are also activated in patients with aortic stenosis and although the pathophysiology of ventricular dysfunction is distinct from heart failure due to systolic dysfunction, the effects of angiotensin II may be equally adverse (Figure 1). Indeed, far from being contraindicated on 'first principles', current knowledge of the role of the renin-angiotensin system in aortic stenosis would suggest that these drugs may be highly advantageous to patients with this valve lesion. Currently, no medical therapy is known to influence the natural history of aortic stenosis, a disorder that affects up to 10% of the elderly population³ and which without surgery inevitably results in premature death.

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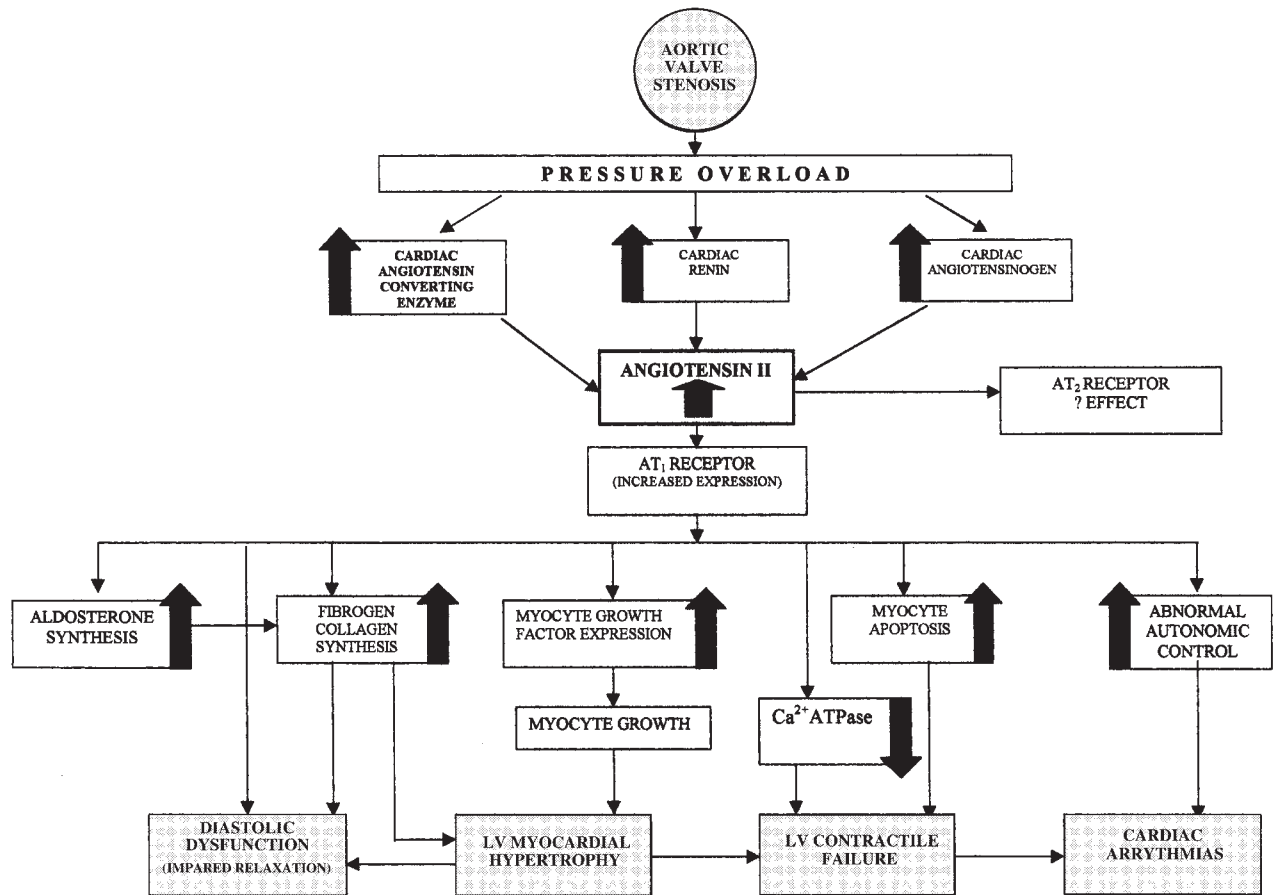


Figure 1 Angiotensin II in the pathophysiology of ventricular dysfunction due to aortic stenosis.

Role of the renin angiotensin system in aortic stenosis

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an inevitable consequence of aortic valve stenosis.⁴ Hitherto, this has been regarded as an important adaptation for preservation of pump function but it is now known that increased left ventricular (LV) mass of any cause is associated with substantially increased cardiovascular and all-cause morbidity and mortality.⁵ The mechanisms by which sustained pressure overload leads to compensatory cardiac hypertrophy in aortic stenosis are not clearly defined. There is however accumulating evidence for the role of neuro-humoral mechanisms and in particular angiotensin II as an effector peptide in this adaptive process.⁶ If it were possible to demonstrate that angiotensin II is produced in increasing concentrations as a response to haemodynamic load and then acts on specific receptors to stimulate myocardial growth then we would have a target for ACE inhibition in reducing the LV hypertrophic response to aortic stenosis. To some extent this evidence is now available.

Recent work has clearly demonstrated that rather than being solely a circulating system, components

of the renin-angiotensin system are produced and function locally in the heart and other tissues.⁷ Increased expression of both cardiac renin mRNA and cardiac angiotensinogen mRNA are seen under conditions of experimental chronic pressure overload in rats.^{8,9} Expression of the ACE has also been demonstrated to be upregulated within the myocardium of rats with pressure overload induced LVH.⁸⁻¹¹ These findings suggest that increased expression of ACE in the presence of increased local production of renin and angiotensinogen produce increases in angiotensin II, as a response to pressure overload or damage, in the left ventricle.^{12,13} This activation of the cardiac renin-angiotensin system occurs independently of systemic angiotensin II generation.

The cardiac receptors upon which angiotensin II acts, as a paracrine modulator, have been defined and divided into two functionally distinct types—AT₁ and AT₂—encoded by different genes.¹⁴ AT_{1a+b} receptors, expressed on cardiomyocytes and fibroblasts, mediate a cellular hypertrophic response.^{15,16} AT₂ receptors are found on coronary endothelial cells and fibroblasts⁷ and it has been proposed that they exert antiproliferative effects counteracting growth-promoting effects of AT₁ receptor stimulation.¹⁵ Distinct patterns of receptor upregulation have been demonstrated in animal models of LV

pressure overload. Left ventricular AT₁ and AT₂ receptor mRNA levels are both increased in hypertensive rats, whilst AT₂ receptors dominate in rats after aortic banding.^{17,18} In hearts with established LVH AT₂ receptor expression is increased and at the same time the new protein synthesis response to angiotensin II seems to be blunted. This may represent adaptive AT₂ receptor upregulation in order to prevent further inappropriate cardiac growth.^{15,16,19} To date it remains unclear exactly what effect alterations in receptor subtype density in humans have on response to angiotensin II in the context of LV pressure overload, although the development of specific AT₁ receptor-blockers is helping to elucidate this.¹⁵

Once cardiac angiotensin II has bound to local receptors a number of biological effects have been demonstrated using a cell culture model of ventricular cardiac myocytes from neonatal rats. Direct stimulation of myocyte culture systems with angiotensin II is seen to induce the transcription of proto-oncogenes (characteristic of foetal cardiac cells)²⁰ and expression of growth factors.²¹ These increases in growth factor and foetal gene expression can also be demonstrated in isolated perfused adult rat hearts in response to angiotensin II.²² Changes of this nature, such as increased expression of the beta-myosin heavy chain mRNA and insulin-like growth factor production, are similar to those seen in human cardiomyocytes with pressure overload induced hypertrophy *in vivo*.^{23,24} The pathological remodelling of the ventricle occurring in pressure overload is not however simply caused by increases in myocyte size, but also involves a progressive interstitial fibrosis. Angiotensin II binding to the AT₁ receptor has also been shown to be responsible for a significant increase in collagen synthesis by cardiac fibroblasts. Fibroblast growth and increased collagen synthesis can also be stimulated by the addition of aldosterone to cell cultures²⁵ and *in vivo* local cardiac aldosterone synthesis is increased as a result of angiotensin II binding to its cardiac receptors.²⁶ In the rat heart aldosterone acts on receptors found locally, both on fibroblasts and myocytes, promoting collagen mRNA expression and protein synthesis and accumulation thus contributing to the hypertrophic effect.²⁷ Interstitial collagen is degraded by the enzyme metalloproteinase-1 and the activity of this enzyme is inhibited by the presence of angiotensin II.²⁵ Alterations in the myocardium induced by angiotensin II binding to cardiac AT₁ receptors thus closely mimic those seen in response to pressure overload caused by aortic stenosis, and include an increase in myocyte size, change in myocyte contractile protein expression and an increase in interstitial fibrotic tissue.

There is further evidence that angiotensin II mediates the effects of mechanical stress upon the ventricular myocardium. In neonatal cell culture systems, in the absence of serum containing growth factors or hormones, passive mechanical stretch

itself results in a cardiomyocyte hypertrophic response.⁶ Once again this is reproducible in adult isolated beating heart models, using a LV balloon.²⁸ An increase in angiotensinogen mRNA, angiotensin II release and an upregulation of the number of angiotensin receptors is seen during this response suggesting that the local renin-angiotensin system does play a role in the response to mechanical stimuli.⁶ Consistent with this hypothesis angiotensin AT₁ receptor-blockers (whose influence *in vivo* is described below), partially blunt the myocyte hypertrophic response to mechanical stretch when added to the neonatal cell cultures.²⁸

Diastolic dysfunction

Filling curves in patients with aortic stenosis, LVH and early heart failure demonstrate impaired LV diastolic distensibility.²⁹ Few animal studies have specifically examined this phenomenon, but again there is some evidence linking the pathophysiology directly to the cardiac renin-angiotensin system. In isolated hypertrophied myocytes taken from hypertensive rats and to a lesser extent myocytes taken from control animals, angiotensin II was reported to delay and impair relaxation. These results suggest that the high levels of angiotensin II found in aortic stenosis may not only mediate a hypertrophic response but may actively potentiate impairment of relaxation.³⁰

Transition to heart failure

In both human patients and experimental models of aortic stenosis, following the adaptive hypertrophic phase, persisting pressure overload eventually leads to progressive ventricular dilatation and dysfunction. The pathophysiology of this transition remains unclear but is likely to be related to altered excitation contraction coupling at the level of the myocyte. These changes may result from altered gene expression in hypertrophied cells leading to a down-regulation of Ca²⁺-ATPase mRNA.^{20,31} Such a change has been demonstrated in aortic-banded guinea pigs, as they develop pressure-overloaded heart failure, and the decrease in Ca²⁺-ATPase expression can be attenuated significantly by 8 weeks of treatment with an ACE inhibitor.³² Neuroendocrine activity has also been implicated, in particular local production of angiotensin II, in the apoptosis hypothesis for explaining progressive alterations in chamber contractility. Myocyte apoptosis has been demonstrated to contribute in rats and mice to the transition from hypertrophy to early heart failure.^{33,34} The demonstrations that angiotensin II applied directly, or released in response to mechanical stretch, induced apoptosis in adult rat cardiomyocytes *in vitro*^{35,36} suggest a further pathophysiological role for the hormone in the progression of myocardial disease in aortic stenosis.

Animal studies of ACE inhibitors in aortic stenosis

Prevention of LVH by ACE inhibition

The effects of ACE inhibition on the postulated mechanisms for myocardial hypertrophy have been investigated extensively using a live rat model of ascending aortic stenosis.³⁷ Although the supravalvular location of the obstructive lesion, above the origins of the coronary arteries, in the rat model means direct comparisons with human aortic stenosis must be made with care, the progression through compensated LVH to dilation, systolic dysfunction and cardiac failure is well demonstrated.³¹ In addition, using this model, changes occurring within the heart in response to manipulation of the renin-angiotensin axis can be examined in the context of a fixed increased load on the ventricle.

In these rats, echocardiographically determined LV mass index was significantly elevated 4 weeks after banding of the ascending aorta and further progression of LVH was seen in untreated rats. However 6 weeks of treatment with the ACE inhibitor, ramipril, or with an angiotensin II receptor antagonist (losartan) caused a reduction in LV mass index compared to control. To demonstrate that this effect was unlikely to be due to the (~18%) reduction in systemic blood pressure, a similar chronic drop in blood pressure was achieved by hydralazine without any attenuation of the LV hypertrophic response.³⁷ Confirmation of this result was obtained by excision of the hearts after 12 weeks of ACE inhibition at which time it was shown that the LV-body weight ratio increase was blunted in the ramipril and losartan-treated rats 1.5-fold compared to hydralazine treated rats. In addition, individual myocyte widths which were higher in the untreated hypertrophied hearts than those in control rats, were no different from controls in the ACE inhibitor treated group. In these same rats with aortic stenosis, cardiac (but not serum) ACE activity was markedly increased with a close correlation between cardiac ACE and LV-body weight ratio. Ramipril treatment resulted in approximately 70% inhibition of cardiac ACE activity, returning levels in aortic stenosis rats to near normal.³⁷

The conclusions to these studies were that long-term blockade of the renin-angiotensin system arrested cardiac growth and even resulted in regression of established LVH in aortic stenosis. As a similar effect was seen with AT₁-receptor blockade the effect seems likely to be mediated by angiotensin II rather than other neurohormonal mechanisms influenced by ACE inhibitors such as bradykinin. The possibility that ACE inhibition and AT₁-receptor blockade were both blunting a trophic effect of angiotensin II mediated sympathetic stimulation cannot be excluded. The findings of an earlier study however, in which ACE inhibition with quinapril caused an 80% regression of LVH in a rat model of aortic stenosis, but similar benefits were not

obtained by lowering LV noradrenaline content by sympathectomy,³⁸ suggest that this mechanism is less likely.

As cardiac ACE was elevated in untreated aortic stenosis rats whilst circulating serum ACE and plasma renin activity were unchanged, it seems unlikely that ACE inhibitor mediated LVH regression is due to an effect on the circulating renin-angiotensin system. Ventricular systolic pressures were minimally affected by ramipril (~6% reduction) or losartan in this aortic stenosis model, and no benefit was observed with hydralazine treatment. Thus it is also unlikely that reduction of afterload is a major factor responsible for the regression of LV hypertrophy by inhibition of ACE.³⁷

ACE inhibitors and improvement in LV diastolic function

Echocardiographic studies of aortic-banded rats demonstrated a restrictive filling pattern, and this indicator of diastolic dysfunction has been examined after treatment with the ACE inhibitor fosinopril. Measurements of LV stiffness were significantly lower in treated compared with untreated rats, though not completely normalised when compared with rats with no valvular obstruction.³¹ Such improvement in diastolic function may have been due to the regression of myocyte hypertrophy and interstitial fibrosis over the ACE inhibitor treatment period. In the untreated rats however, between 6 and 18 weeks after aortic banding, LV wall thickness did not increase any further whilst the abnormal diastolic filling pattern did become more marked. The investigators therefore suggested then that ACE inhibition was directly enhancing relaxation in the hypertrophied hearts as a result of a reduction in cardiac angiotensin II levels.

ACE inhibitors and prevention of LV dilatation and remodelling

Whether ACE inhibition can attenuate the progression of LV dysfunction following pressure overload, or whether in fact the reduction of myocyte hypertrophy achieved, as described above, represents the loss of an adaptive mechanism for preserving systolic function, has been examined in the rat model. In order to dissociate the effects of ACE inhibition on systemic from local cardiac renin-angiotensin system, the same method of aortic clipping was used to produce a rat with fixed increased LV afterload. Rats demonstrated a stage of compensated concentric LV hypertrophy, 6–8 weeks after banding with elevated intracardiac ACE mRNA and angiotensin II generation.³⁹ This was followed by cardiac decompensation and premature death after about 20 weeks. Investigators hypothesised that if the activation of the cardiac tissue renin-angiotensin system contributed to the transition to cardiac failure in rats with established hypertrophy then chronic adminis-

tration of fosinopril would favourably modify this outcome. At the start of fosinopril treatment all aortic-banded rats already had established concentric LVH but had normal systolic function. At the end of the 12-week treatment period LV mass by echo was again returned towards the normal range by fosinopril treatment.³¹ In fosinopril-treated rats there was a modest reduction in arterial systolic pressure but LV systolic pressure was not different between treated and untreated groups. After 15 weeks, the untreated aortic stenosis rats showed a marked increase in LV systolic dimension and a corresponding reduction in function (via fractional shortening), which was not present in the fosinopril-treated group.³¹ Left ventricular contractile function in the isolated perfused hearts after removal was also better in the fosinopril-treated rats.³⁹

The benefit of ACE inhibition in ischaemic heart failure with a dilated ventricle,⁴⁰ was originally thought of as simply a result of modification of the haemodynamic responses to systolic dysfunction. By blocking systemic angiotensin II production, reductions in LV systolic load, systolic pressure and cavity dilation (by increased venous capacitance) occur. A fall in heart rate and contractility are also seen as a result of withdrawal of angiotensin II's actions on sympathetic and vagal activity.⁴¹ In contrast in aortic banded rats, the beneficial effects of ACE inhibition in preventing serial changes in LV end systolic or diastolic dimension or preserving ejection fraction did not depend on a reduction in LV systolic pressure or heart rate, which remained equivalent to those in the untreated rats. If the benefits in this model are not due to improved haemodynamics and the adaptive mechanism of myocyte hypertrophy has been lost, then alternative mechanisms by which ACE inhibition preserves contractility must be sought.

The fosinopril study examined developed pressure–calcium relation and found this to be significantly improved with a shift upwards and to the left in isolated perfused hearts from ACE inhibitor treated aortic stenosis rats.³⁹ Thus, an improved contractile response to extracellular calcium appears to be compensating for the regression of hypertrophy or loss of force bearing units. Confirmatory evidence comes from isolated myocyte models in which the calcium-shortening relation was significantly enhanced in fosinopril-treated rats compared to untreated rats with aortic stenosis.³⁹ Similar results have been seen with improvement of contractile response in chronic captopril treatment of post infarction heart failure rats.⁴²

There is also evidence of a role for ACE inhibition in the reduction of apoptosis in pressure overload ventricular hypertrophy. AT₁-receptor blockade (losartan) but not AT₂ blockade, was shown to prevent the five-fold increase in apoptosis caused by angiotensin II in rat cardiomyocytes.^{35,36} Thus, another possible target for the use of ACE inhibitors in aortic stenosis may be prevention of a reduction

in functioning cardiac myocytes due to angiotensin II mediated apoptosis.

Increased survival

The eventual outcomes of these seemingly beneficial alterations in pathophysiology are reflected in the animals' survival data. Rats in the fosinopril study showed a striking survival benefit over untreated rats with aortic stenosis: 3% vs 31% after 15 weeks of treatment ($P < 0.05$).³⁹ Initially premature deaths in the untreated aortic-banded animals were attributed to development of severe LV dysfunction and dilatation. Inspection of the hearts from animals that died prematurely however, did not support this hypothesis. Another possibility is that ACE inhibition prevented premature deaths from cardiac arrhythmia possibly triggered by myocardial ischaemia or by adverse changes in cardiac autonomic control.³⁹ Both sympathetic tone and cardiac vagal activity are known to be favourably modified by the reduction of circulating angiotensin II.^{43,44} In the ramipril-treated aortic banded rats, regression of compensatory hypertrophy was also paralleled by improved survival: 31% died in the placebo treated group during 12 weeks follow-up compared with 11% in the ramipril-treated group.³⁷

Angiotensin AT₁ receptor inhibition

The beneficial effects of ACE inhibition on hypertrophic remodelling have thus been attributed to the inhibition of cardiac ACE activity and reduced activation of AT₁ receptors. Although this hypothesis has been supported by the results of Bruckshelgel and colleagues using the AT₁-receptor blocker losartan,³⁷ it has been challenged by the results of another important investigation. Using identical methods to their fosinopril study Weinberg and colleagues³⁹ treated aortic-banded rats with the specific AT₁-receptor blocker irbesartan. They found no regression of LVH, no improvement in survival, and no change in contractile function compared with untreated rats. A further unexpected observation was that elevated LV ACE mRNA levels in aortic-banded rats were normalised by treatment with both the AT₁-receptor blocker and by amlodipine and this correlated with an improvement in LV end diastolic pressure. The investigators concluded that an increased cardiac ACE expression may not be critical for pressure-overload LV hypertrophy. Differences in pharmacological effects may also be explained by the ability of ACE inhibitors, in contrast to the AT₁-receptor blockers, to decrease activation of the AT₂ receptor whose role in the regulation of myocardial growth and function in cardiac disease states remains poorly defined.

Clinical studies

Potential benefits

Because of the persisting opinion that ACE inhibitors are contraindicated in patients with aortic stenosis there are very few clinical studies and no randomised-controlled trials in this group of patients. If we can use the evidence now available from these animal models, to design the appropriate clinical studies, we may reveal a number of possible roles for this group of drugs in the treatment of patients with aortic stenosis. Whilst there is little doubt that the only 'cure' for aortic stenosis is to relieve the obstruction by valve replacement, there are situations in which medical therapy could confer a benefit. The most common scenario in which they are currently considered (and then usually rejected) is in patients with co-existing hypertension. ACE inhibitors are well established antihypertensives and within this role they decrease cardiovascular morbidity and mortality.⁴⁵ In patients with a bicuspid aortic valve (~45–50% cases) evidence suggests that co-existing systemic hypertension increases the rate of progression of valvular stenosis.⁴⁶ In addition it is clear that in patients with aortic valve disease, a second stimulus to progressive LVH, a well established risk factor for all major cardiovascular events, is disadvantageous.⁴⁷ Hence effective treatments for hypertension in this patient group are a necessity and an agent, which by its effects on the local cardiac renin-angiotensin system, can also arrest cardiac growth and even result in regression of established myocyte hypertrophy and interstitial fibrosis⁴⁸ should be of further benefit.

The second scenario, in which prescription of an ACE inhibitor might now be considered, is in treating the adverse effects of aortic stenosis on the LV myocardium. In the large number of asymptomatic patients under follow-up, there are currently no treatment options which have been shown to reduce LVH or to alter morbidity and mortality. In symptomatic aortic stenosis valve replacement is urgently required, but for those who refuse or are refused for surgery on the grounds of extreme age or comorbidity there is no effective medical therapy.⁴⁹ Currently operative mortality stands at 2–4%, but rises to between 9 and 20% in the presence of extreme age or poor LV function.^{50–55} Whilst there is significant functional improvement in almost all survivors of aortic valve replacement, irrespective of age or ventricular function,^{52,53,56,57} long-term survival rates post aortic valve replacement depend on the absence of increased heart size or low ejection fraction preoperatively.^{58–60} In autopsies performed in 51 patients who died 0 days to 14 years after aortic valve replacement all hearts remained enlarged by heart weight index and measures of LV wall thickness, indicating that regression of hypertrophy is incomplete after surgery. The cardiac pathology was predictable by preoperative scores of ECG hypertrophy and cardiothoracic index.⁶¹ These

findings raise the possibility that treatment with an ACE inhibitor for patients with aortic stenosis may be of benefit both preoperatively to avoid irreversible structural remodelling of the myocardium, and postoperatively to aid regression of myocardial hypertrophy. In addition, a beneficial effect on autonomic function may reduce the risk of sudden arrhythmic death.

Safety, tolerability and haemodynamics

Before recommending a randomised controlled trial to evaluate the effects of these agents on this patient group, the possible adverse effects must be considered. When examining the animal data it must also be remembered that the different position of the supra-ventricular obstruction in the rat, relative to the coronary ostia, may be of importance. The clinical evidence for adverse effects of ACE inhibitors is however lacking.

There are no case reports published of acute hypotensive reactions attributable to the use of an ACE inhibitor in a patient with aortic stenosis. This lack of confirmed cases is found despite the observation that as many as 48% of cases of aortic stenosis go undiagnosed—only presenting at post mortem, and many more wait a considerable period of time from presentation with cardiac symptoms before the correct diagnosis is made.⁴⁶ Bearing in mind that approximately 15% of patients are being treated for co-existing hypertension and many more for pain attributed to ischaemic heart disease,⁴⁶ one might assume that a number of patients with aortic stenosis do receive an ACE inhibitor at some time. If this is the case then the incidence of adverse reactions is either negligible or simply goes unreported. The only published case reports describing chronic use of ACE inhibitors in patients with aortic stenosis both involve single patients, neither of whom experienced adverse effects on normal doses of an ACE inhibitor.^{62,63}

Cox *et al*⁶⁴ recently reviewed the only studies specifically addressing the question of ACE inhibitor prescription in aortic stenosis. The larger of the two published series concerns 22 patients studied in Mexico with critical aortic stenosis (mean gradient: 93 mm Hg \pm 38) who were given oral captopril.⁶⁵ Patients were monitored with a Swan Ganz catheter over 48 h and six doses (12.5 mg/8 mg). Seven of these patients fell into the higher risk group for hypotension having signs and haemodynamic measures consistent with heart failure. Results were a predictable fall in systemic vascular resistance, with a small fall in systolic blood pressure. Cardiac output (by thermodilution) was increased significantly; rather than remaining 'fixed' stroke volume increased from a mean of 47 to 64 ml even in the patients with heart failure. Mean pulmonary capillary wedge pressure fell from 19 to 16 ($P = 0.04$). All patients demonstrated improved haemodynamic parameters following acute dosing with no deleteri-

ous reduction in blood pressure. A further human study suggests that these acute improvements are due to changes in diastolic function. In 20 patients with LVH due to aortic stenosis, Friedrich *et al*⁶⁶ demonstrated improved ventricular diastolic distensibility when infusing enalaprilat into the left coronary artery. Left ventricular end-diastolic pressure dropped by 20%, and simultaneous changes in LV pressure and dimensions demonstrating a downward shift in LV pressure–dimension relations. These improvements in relaxation were confined to the anterior segments perfused with enalaprilat and systemic neurohumoral changes did not occur. There were no changes in heart rate, cardiac output or right atrial pressure with ACE inhibitor administration to explain the regional increases in peak filling rate. A group of patients with dilated cardiomyopathy failed to demonstrate these changes. The authors concluded that activation of the cardiac renin-angiotensin system occurs in patients with pressure overload LVH, that this contributes to impaired diastolic function and can be prevented acutely by ACE inhibition.

The effect of chronic ACE inhibitor therapy has been studied in eight patients with severe aortic stenosis and fluid retention despite diuretics. A pulmonary artery catheter was again used to observe the acute haemodynamic response to a first dose, but the treatment was continued.⁶⁷ After 6.25 mg oral captopril, six patients demonstrated a fall in LV end-diastolic pressure and an increase in cardiac output of 21%. Blood pressure did not change significantly. These patients were said to demonstrate an improved exercise tolerance and decreased fluid retention with chronic dosing although these uncontrolled results must be interpreted with caution. In the remaining two patients there was no significant acute haemodynamic response and no change in symptoms with chronic dosing.

It seems then that although the reluctance to prescribe ACE inhibitors in aortic stenosis is based on some logical concerns there are no substantive clinical data to support them. In addition the only clinical data we do have, although numbers are small and studies uncontrolled, show not only tolerability but acute haemodynamic improvement in keeping with the results of animal studies.

Conclusion

There is accumulating evidence that cardiac angiotensin II production may, at least in part, be responsible for the development of myocardial hypertrophy and diastolic dysfunction in hearts subjected to pressure loading. Prevention of angiotensin II mediated myocyte growth, interstitial fibrosis, impairment of relaxation and induction of apoptosis are some of the mechanisms by which blockade of the cardiac renin-angiotensin system (or its specific receptors) might benefit patients prior to surgical intervention.

The concerns regarding safety and tolerability of these agents in patients with aortic stenosis are based on the misclassification of ACE inhibitors as vasodilators rather than being founded on the results of clinical investigation. In those 30 patients who have been closely observed, the acute haemodynamic response to ACE inhibition has been beneficial in 28 and no adverse effects have been recorded.

Further tolerability and safety studies are needed but if initial results are confirmed, a randomised controlled clinical trial will be required to further investigate the effects of ACE inhibitors on symptoms, disease progression, LVH and survival. The choice of ACE inhibitor for such a trial cannot be based on clinical experience but logic would suggest that the maximal benefit and lowest risk might be associated with an agent with high tissue binding and minimal hypotensive effect.

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