Left ventricular hypertrophy and aortic stenosis: a possible role for ACE inhibition?

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Abstract

Aortic valve stenosis is a common cause of left ventricular hypertrophy (LVH). Severe LVH in association with aortic stenosis does not always regress following valve replacement surgery and is associated with a poor prognosis. The importance of angiotensin II in the hypertrophic process is increasingly recognised and the benefits of angiotensin-converting enzyme (ACE) inhibition in reducing LVH associated with hypertension are well established. Although ACE inhibitors are currently contraindicated in aortic stenosis (AS) on theoretical grounds there are very few data to support this. We have audited the current use of ACE inhibitors in a group of patients with AS and found that 27% of this group are currently taking an ACE inhibitor with no documented adverse effects. Trials to investigate the therapeutic benefit of ACE inhibition in preventing adverse left ventricular remodelling are merited but must be preceded by safety and tolerability studies.

Key words: aortic valve stenosis, left ventricular hypertrophy ACE inhibitors, renin-angiotensin system, safety/tolerability studies.

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Introduction

Mayet and Lane recently wrote on whether left ventricular hypertrophy (LVH) should be a target for treatment[1] and we fully endorse their comments. They correctly observed that the presence of LVH is a poor prognostic indicator which is independent of blood pressure (BP), and that drugs acting upon the renin-angiotensin system reduce left ventricular mass more effectively than other antihypertensive agents. This efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in reducing LVH appears to be independent of BP changes.[2] After hypertension, the most common cause of LVH is aortic valvular stenosis, which affects up to 3% of adults over 65 years of age.[3] Hypertrophy of the left ventricle occurs early in the course of the disease and is almost invariable by the time of valve replacement.[4]

Although widely believed to be a beneficial response resulting in reduced wall stress, we suggest that ventricular hypertrophy in aortic stenosis (AS) is better considered as adverse ventricular remodelling. The consequences of the development of LVH in AS may be just as adverse as those that have been so well documented when the cause of the hypertrophy is hypertension. Two independent studies have established that the presence of severe LVH in AS is associated with a poor outcome following valve replacement.[5,6] In many cases LVH does not fully regress after surgery and there is no reason to believe that the hypertrophic process with its deleterious effects on diastolic and systolic function and arrhythmic potential is in any way different to that occurring in hypertension. Failure of LVH to regress has been shown to be associated with a poor prognosis.[7] Could drugs acting upon the renin-angiotensin system be used to reduce LVH in patients with AS?

The case for ACE inhibition

The presence of aortic valve stenosis is widely believed to be a contraindication to treatment with ACE inhibitors and is listed as such in the *British National Formulary*. It is thought that there is a risk of severe hypotension as a result of vasodilatation in the face of fixed left ventricular outflow obstruction. This advice is based upon theoretical grounds, however, rather than published evidence. Cox *et al*. pointed out some time ago that there are no published reports of severe hypotension or other adverse effects of ACE inhibitors in AS.[8] The concern, in part, derives from the mistaken classification of ACE inhibitors as vasodilators rather than neurohormonal antagonists. Haemodynamic studies have shown that in patients with heart failure, ACE inhibitors are weak vasodilators compared to direct acting agents.[9]

Recent advances in our understanding of the pathophysiology of LVH provide grounds for postulating that inhibition of the renin-angiotensin system in AS might lead to similar benefits to those established in the treatment of patients with heart failure due to systolic dysfunction. The scientific rationale for this theory is that ACE inhibitors will provide effective inhibition of tissue – myocardial – ACE in patients with AS and thus reduce or prevent the development of LVH with minimal systemic haemodynamic effects. We have reviewed the evidence that the myocardial renin-angiotensin system is intimately involved in the hypertrophic

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Table 1. Angiotensin II in the pathophysiology of ventricular dysfunction due to aortic stenosis and the potential benefits of ACE inhibition

Known adverse effects of angiotensin II
Increases myocyte growth factor expression
Increases fibrogen collagen synthesis
Increases myocyte apoptosis
Alters excitation-contraction coupling
Impairs cardiac autonomic control
Potential benefits of ACE inhibition
Anti-hypertrophic effect
Reduction in diastolic dysfunction
Delayed progression to LV failure
Prevention of contractile failure
Protection against cardiac arrhythmia

Key: ACE = angiotensin-converting enzyme

Table 2. Clinical characteristics of patients with aortic stenosis attending cardiology clinics, subgrouped according to ACE inhibitor therapy

	All aortic stenosis patients	Not on ACE inhibitor	Subgroup on ACE inhibitor
Number of patients	92	67	25
Mean (±SD) age (years)	70 (13)	71 (14)	69 (13)
Mean (±SD) gradient (mmHg)	57 (28)	57 (28)	56 (30)
% with mild aortic stenosis (gradient < 30 mmHg)	18	19	16
% with moderate aortic stenosis (gradient 31–49 mmHg)	29	24	40
% with severe aortic stenosis (gradient > 50 mmHg)	52	57	44
% with LVH on echocardiogram	57	55	60
Mean (±SD) serum creatinine (µmol/L)	110 (29)	108 (31)	113 (26)
Mean (±SD) systolic pressure	141 (26)	140 (26)	145 (28)

Key: ACE = angiotensin-converting enzyme; SD = standard deviation; LVH = left ventricular hypertrophy

response to a pressure load, and that ACE inhibitors and ARBs reduce this hypertrophic response, elsewhere.[10] Potential mechanisms of action are given in table 1. Such prevention of adverse left ventricular (LV) remodelling by ACE inhibitors is, of course, a concept already established in the treatment of LV dysfunction following myocardial infarction.

Data in aortic stenosis

Before human studies of ACE inhibitors in AS can be contemplated it will be necessary to establish that these agents are safe and tolerable. There are few data available on this subject but the limited clinical studies that have been performed suggest advantageous rather than adverse haemodynamic effects – an increase in cardiac output and small effects on arterial pressure have been seen even in patients with severe stenosis and clinical heart failure.[11] Improved diastolic function in AS has also been demonstrated during intra-coronary infusion of enalaprilat.[12] We observed that a number of patients with severe AS presenting to our institution were on established treatment with ACE inhibitors with no apparent adverse effects. As a result we have audited the use of ACE inhibitors in a large group of out-patients with AS: 92 patients with significant (gradient > 25 mmHg) aortic valve stenosis were identified by interrogating ('find' function in Microsoft word) computer-held correspondence from cardiology clinics at our institution. The group comprised 46 males. The mean age was 70 (±SD13) years and median aortic valve gradient was 56 mmHg. Despite being listed as contraindicated in the *British National Formulary*, ACE inhibitor therapy was being taken by 25 patients (27% of total); another five were taking ARBs. Of the patients taking an ACE inhibitor, the majority 20 (80%) had been on this therapy for more than one year, with hypertension being the most common indication for therapy (84%). No adverse responses, including syncope or hypotension, to ACE inhibitor therapy had been recorded. Examination of records of systolic BP and serum creatinine or the presence of LVH on echocardiography revealed no significant differences between the treated and untreated groups (see table 2). Mean serum creatinine in the group on ACE inhibitors was within normal limits (113 µmol/L).

Key messages

- Left ventricular hypertrophy (LVH) is an inevitable consequence of aortic stenosis
- Severe LVH is associated with a poor prognosis following aortic valve replacement
- Angiotensin-converting enzyme (ACE) inhibitors are currently contraindicated in aortic stenosis on theoretical grounds
- Early treatment with ACE inhibitors might reduce LVH and preserve left ventricular function in aortic stenosis
- Trials to examine the efficacy of ACE inhibitors in aortic stenosis must be preceded by safety and tolerability studies

Conclusion

While these data are subject to the well known limitations of retrospective analysis, they do lend support to existing reports sug-

gesting that despite the concerns, ACE inhibitors may be well tolerated in AS. Further safety data are required and we suggest that prospective safety and tolerability studies of ACE inhibitors in AS should be initiated. Currently, aortic valve surgery is not recommended until symptoms develop allowing the uninterrupted progression of hypertrophic ventricular remodelling. This management may represent a lost opportunity; early treatment with ACE inhibitors might reduce left ventricular hypertrophy and preserve ventricular systolic and diastolic function with resulting clinical benefits both before and after valve replacement.

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