Left ventricular hypertrophy: a target for treatment?

Left ventricular hypertrophy (LVH) is more than just an adaptive response to the increase in left ventricular wall stress caused by hypertension. It has long been known that it is an indicator of a poor prognosis: the increased risk associated with LVH is independent of the blood pressure level.[1] LVH is commonly assessed in clinical practice using electrocardiography (ECG), chest radiography (CXR) or echocardiography. Each of these investigations can be used to predict prognosis but anatomical and ECG-LVH do not necessarily reflect the same thing. Data from the Framingham study show that the combination of cardiomegaly on CXR and ECG-LVH imparts the worst prognosis. A significant number of patients, however, had ECG-LVH but no cardiomegaly on CXR and vice versa. Each of these groups had a worse prognosis than the group of patients with neither.[2] ECG-LVH confers a worse prognosis than cardiomegaly on CXR although the ECG is a relatively insensitive tool for detecting LVH when compared with echocardiography.[3] Echocardiography can also grade the degree of LVH and it has been demonstrated that a direct relationship exists between left ventricular mass indexed for body size and prognosis.[1]

Antihypertensive therapy

A vast number of studies have shown that antihypertensive therapy with a variety of different agents can reduce LVH,[4-6] although most of these studies are small and not blinded. Initial meta-analyses were criticised because they included all of these imperfect studies. They did give a clue that angiotensin-converting enzyme (ACE) inhibitors may be the best agents at reducing LVH. A subsequent meta-analysis including only randomised, double-blind, controlled clinical studies has had similar findings, with ACE inhibitors followed by calcium antagonists as the best two agents at reducing LVH.[7] Since the publication of this meta-analysis, the Preserve study, a single, large, double-blind, randomised study has found that nifedipine and enalapril reduced left ventricular mass by a similar amount.[8]

The Heart Outcomes Prevention Evaluation (HOPE) study, a double-blind, placebo-controlled clinical trial, assessed the effects of ramipril in preventing adverse cardiovascular events in patients at high risk without known left ventricular dysfunction or congestive heart failure.[9] These were patients over 55 years with either known vascular disease or diabetes with at least one additional risk factor. Participants were randomised to ramipril or placebo; investigators were encouraged to use antihypertensive agents other than ACE inhibitors to treat uncontrolled hypertension. Patients were followed up for 4–6 (mean 4.5) years. They had a 12-lead ECG at baseline, at two years and at the study end. The Sokolow-Lyon criterion was used to diagnose LVH (SV_1 + RV_5/V_6 > 3.5 mV). There were 8,281 patients who each had two interpretable ECGs for comparison. At baseline, 321 patients in the ramipril group compared with 355 in the placebo group had ECG-LVH. Among those patients, 46.1% (148) of the ramipril group compared with 38.6% (137) of the placebo group had regression of ECG-LVH. This difference was just statistically significant and remained so after adjusting for possible confounding factors; the blood pressure being significantly lower in the ramipril group. Overall, 8.2% (336) of the ramipril group compared with 9.8% (406) of the placebo group had development or persistence of LVH by the end of the study. Again, this difference was statistically significant even after adjustment for possible confounding variables. Although both groups were treated with a variety of other antihypertensive agents, the findings of the study are consistent with the hypothesis that ACE inhibitors are the best agents to cause regression of LVH.

Some 925 (12.3%) of the 7,539 patients with regression/prevention of LVH had the primary outcome of the study (cardiovascular death, myocardial infarction or stroke), compared with 117 (15.8%) of 742 patients with development/persistence of LVH. This difference was statistically significant. These findings are consistent with two other studies that have addressed the prognostic implications of changes in LVH. In one study, subjects from the Framingham Heart Study with ECG evidence of LVH who were free from cardiovascular disease were assessed.[10] Subjects with a serial decline in ECG voltage were at lower risk than those with no decline and those with a serial increase were at greater risk of cardiovascular disease. The results were similar when adjustments for serial change in systolic blood pressure were made. In a separate study, echocardiography was used to serially assess left ventricular mass.[11] Patients with a decrease in left ventricular mass had fewer events than those with an increase. This difference was independent of baseline left ventricular mass, baseline blood pressure and blood pressure

reduction. Most recently the LIFE trial[12] investigated the effects of the angiotensin II antagonist, losartan, compared with a beta blocker, atenolol. In all, 9,222 patients with essential hypertension and LVH apparent on the ECG were studied. The mean baseline blood pressure was 174/98 mmHg and blood pressure lowering effects were similar between the groups (losartan 30.2/16.6 *vs.* atenolol 29.1/16.8 mmHg). There was significant regression of LVH in the losartan but not the atenolol group and a 13% reduction of the combined primary end point of death, myocardial infarction and stroke in the losartan compared with the atenolol group. In a separate analysis of diabetic subjects in the study, the benefits of losartan were even more marked. The question of whether these results are due to additional benefit from the angiotensin-II antagonist or whether they add weight to the suspicion that beta blockers may not be as efficacious as other antihypertensive agents will be debated. It is certainly possible that any additional benefit is mediated by the reduction in left ventricular hypertrophy.

The question of whether the greater reduction in left ventricular mass conferred by drugs acting on the renin-angiotensin system compared with other antihypertensive agents translates into improvements in morbidity and mortality is still debatable. Further large, double-blind, randomised studies are needed to confirm the findings from LIFE. Other studies comparing outcomes between antihypertensive agents exist. The NORDIL study compared diltiazem with diuretics and beta blockers;[13] it reported a similar outcome in terms of cardiovascular death, myocardial infarction and stroke between the groups. However, differences between ACE inhibitors and calcium antagonists have been noted in two studies on diabetic patients; both the ABCD trial comparing the long-acting calcium antagonist, nisoldipine, with enalapril,[14] and the FACET study comparing amlodipine with fosinopril[15] found a lower event rate in the ACE inhibitor groups. Whether these differences are confined to diabetic patients or translate to the hypertensive population as a whole remains to be seen. A recent meta-analysis aiming to address whether antihypertensive drugs offer cardiovascular protection beyond blood pressure lowering, suggested that calcium antagonists may provide more reduction in the risk of stroke and less protection from myocardial infarction compared with other agents.[16] However, the main conclusion of the study was the emphasis on the importance of blood pressure control.

Summary

In summary, there is some suggestion from the existing literature that drugs acting on the renin-angiotensin system may offer protection above blood pressure control. The greater regression of LVH conferred by these drugs may provide a mechanism to explain why these agents may be better (though the exact pathophysiological reasons for the poorer prognosis with LVH and improved prognosis with regression of LVH has not been clarified). However, further evidence is required before sweeping recommendations regarding antihypertensive treatment can be made. Three large studies, ASCOT,[17] ALLHAT[18] and VALUE[19] will provide further information over the next few years. The ASCOT study has a large sub-study that includes echocardiography, which should give some further insight into the consequences of LV mass changes in relation to outcome.[20]

A final issue in terms of LVH relates to ethnicity; Afro-Caribbean subjects have a greater degree of LVH for given levels of blood pressure compared with white Europeans.[21] This is not just related to the smaller thoracic size, and hence increased cardiothoracic ratio, in Afro-Caribbeans,[22] but is apparent also at echocardiography.[23] Although it is clear that an increased LV mass index in Afro-Caribbean patients also suggests an adverse prognosis,[24] whether similar degrees of LV mass in Afro-Caribbean and white European populations predict a similar prognosis is not known. Different classes of antihypertensive drugs have different effects in different ethnic groups[25] and the effects of regression in terms of prognosis in Afro-Caribbean patients is, as yet, unknown.

As to whether LVH should be a target for treatment above and beyond tight blood pressure control, the balance of evidence is not yet conclusive. This should become apparent as ASCOT and ALLHAT report over the next few years.

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