Echocardiographic Studies of Regression of Left Ventricular Hypertrophy in Hypertension

FETNAT M. FOUAD-TARAZI AND PHILIP R. LIEBSON

SUMMARY The availability of echocardiography has allowed direct determinations of left ventricular wall thickness and calculation of left ventricular mass. As a result, the past decade has witnessed a remarkable evolution in our understanding of structural changes in the heart. Moreover, cardiac hypertrophy was found to be reversible by some forms of therapy. In general, reduction of left ventricular mass became evident after 8 to 12 weeks of antihypertensive therapy. Sympatholytics (including methyldopa and reserpine), converting enzyme inhibitors (captopril and enalapril), and calcium entry blockers led to significant regression of left ventricular hypertrophy. On the other hand, arteriolar vasodilators (hydralazine, trimazosin, and minoxidil) were not associated with regression of hypertrophy despite adequate blood pressure control. Finally, data regarding diuretics and β-blockers are controversial. These differences in results among various antihypertensive drugs reflect the multiplicity of factors modulating left ventricular hypertrophy.

(Hypertension 9 [Suppl II]: II-65-II-68, 1987)

KEY WORDS • echocardiography • cardiac performance

THE past decade has witnessed a remarkable evolution in our understanding of structural changes in the heart and arterial system in hypertension. Not only was cardiac hypertrophy found to occur much earlier in hypertension than previously thought, but it was also clearly demonstrated to be reversible by some forms of therapy within a relatively short period of time. This advancement was made possible by the availability of echocardiographic techniques that allowed direct determinations of left ventricular wall thickness and calculation of left ventricular mass. The measurements were shown to be reliable and reproducible over time with adherence to such adequate safeguards as double blind readings, strict application of reading criteria, and use of internal checking measures.

The reversibility of left ventricular hypertrophy in humans has been repeatedly demonstrated by many centers. In general, reduction of left ventricular mass became evident after at least 8 to 12 weeks of antihypertensive therapy, but the ability to induce this regression varied markedly among otherwise equipotent antihypertensive agents. Secondly, most of the centers demonstrated either a lack of or a relatively poor correlation between the degree of blood pressure control and the regression of left ventricular hypertrophy. The correlation between mass and pressure reportedly improved by utilizing averages of 24-hour blood pressure recordings rather than casual blood pressure levels, but even then, the index of determina-

From the Cleveland Clinic Foundation, Cleveland, Ohio, and Rush Medical College, Chicago, Illinois.

Address for reprints: Fetnat M. Fouad-Tarazi, M.D., Heart and Hypertension Department, Research Institute of The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44106.

Methodological Considerations

Differences in methods may partially account for the diversity of the results among centers. These differences include: age and sex distribution, previous treatment with antihypertensive agents, modes of assessment of hypertrophy by echocardiographic techniques, degree of hypertrophy present at the beginning of the study, reproducibility of results, duration of therapy, presence of control groups, and patient compliance.

No significant data have emerged on the effect of age on regression of hypertrophy. Normally, left ventricular wall thickness increases in older persons as a consequence of decreasing left ventricular chamber size. Whether this has at least a subtle effect on wall stress and its moderation of the stimulus to hypertrophy and its regression has not been assessed. Wall stress has been considered a possible stimulus for the induction of hypertrophic changes. Of the 17 studies we have reviewed, only three assessed changes in calculated systolic wall stress. This calculation can be derived noninvasively using echocardiographic and blood pressure determinations; it has considerable utility for classification of left ventricular hypertrophy (wall stress maintained within normal limits or inappropriate), a differentiation previously made mainly in terms of the left ventricular radius/thickness ratio.

Treatment of hypertension before initiation of clinical studies may have some bearing on the degree of hypertrophy at the time of initial examination. The baseline blood pressure at that time
may not reflect the degree of hypertrophy present. This discrepancy may decrease the calculated correlations between baseline blood pressure, its evolution with subsequent treatment, and any degree of change in left ventricular mass. Reproducibility of echocardiographic results may be tenuous if rigid techniques for consistency of measurements are not utilized. These include angulation of the echo beam, location of measurement, the convention used for dimension measurement, calculation of wall mass or cross-sectional area, and the variables used to calculate systolic performance of the left ventricle. The use of different blinded observers and consistent technique both have a bearing on the results. The 17 studies we reviewed showed considerable heterogeneity in these methods. The absolute decreases in left ventricular wall thickness, from which calculated wall mass changes were derived, were usually in the order of 1 to 2 mm; this is close to the limits of variability due to measurement errors. Using paired data analysis, averaging the results of two observers, keeping the same technician, and assessing M-mode records from the two-dimensional long-axis view may optimize the reproducibility of serial results.

Few of the studies used only one mode of therapy, and some did not report the specific types or order of administration of antihypertensive agents. Duration of therapy varied from 1 month to 5 years. In only one study did a control group receive a placebo to determine serial changes in wall mass without treatment and in comparison with changes in the treatment group. Ethical constraints in treatment of hypertension may preclude such studies in hypertensive patients, but within the context of each laboratory, it would be beneficial to have data available about the reproducibility of wall measurements in serially studied control normotensive subjects. Only one study gave that information.

The use of M-mode echocardiographic data to assess global left ventricular systolic function is potentially treacherous, especially when segmental wall motion abnormalities are present. Although patients with cardiac disease associated with wall motion abnormalities were excluded from most of these studies, these findings are not assured unless appropriate two-dimensional visualization was used. Only two studies mentioned routine use of two-dimensional technique, and then only to direct the M-mode beam for diastolic measurements — not to determine systolic performance. Also, the evidence in other studies of asymmetric hypertrophy in hypertension suggests that M-mode study may not completely reflect the degree of hypertrophy and its regression in a minority of hypertensive subjects.

Evaluation of these studies suggests that large-scale institutional studies of hypertrophy using individual classes of antihypertensive agents are desirable and can be readily accomplished provided agreement on echocardiographic methodology is reached.

Regression of Hypertrophy and Antihypertensive Medications

Sympatholytics, including methyldopa and reserpine, have been found to be associated with significant regression of left ventricular hypertrophy (Table 1). A particularly important observation was that addition of small doses of methyldopa to diuretics led to significant reduction of left ventricular mass with little change in blood pressure. Converting enzyme inhibitors, such as captopril and enalapril, and calcium entry blockers have also led to significant regression of hypertrophy. On the other hand, vasodilators such as hydralazine and trimazosin were not associated with regression of hypertrophy despite adequate blood pressure control; exceptions were reported when a vasodilator was used with a β-blocker or methyldopa.

### Table 1: Reversal of Left Ventricular Hypertrophy by Antihypertensive Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Rat</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>—</td>
<td>— or</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Disputed</td>
<td>Disputed</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Methyldopa</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2) Reserpine</td>
<td>↓</td>
<td>Not available</td>
</tr>
<tr>
<td>3) α1-Blockers</td>
<td>Not available</td>
<td>↑</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>↑</td>
<td>Not available</td>
</tr>
<tr>
<td>Trimazosin</td>
<td>Not available</td>
<td>—</td>
</tr>
<tr>
<td>Converting enzyme inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Not available</td>
<td>↓</td>
</tr>
<tr>
<td>Calcium-entry blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>↓</td>
<td>Not available</td>
</tr>
<tr>
<td>Flopapine</td>
<td>↑</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Dashes indicate no change in left ventricular mass. Arrows indicate decrease (↓) or increase (↑) in left ventricular mass. *Available in reports about combined therapy. T0.2-Blockers alone not available (Labetalol [α1 + β blockade] was reported to reduce left ventricular mass).

Diuretics usually did not reduce left ventricular mass, except in isolated cases. As regards β-blockers, initial studies were controversial, but evidence is accumulating that they may indeed be effective. The reasons for the disparities among these studies have not been fully clarified.

Continued studies of these two forms of antihypertensive therapy are helping develop a better understanding of the balance of factors involved in regression of left ventricular hypertrophy. Most evidence from animal and human studies has revealed only minimal changes in left ventricular mass during diuretic treatment. More recent studies suggest, however, that this conclusion needs to be modified. Two factors seem relevant in that respect, the duration of treatment and, possibly, the mechanism of blood pressure control. Both factors also emerged in recent studies of β-blockers: reduced systemic resistance and a marked, sustained reduction in blood pressure may have particular relevance in the reversal of left ventricular hypertrophy. Modulating factors can accelerate or interfere with regression of left ventricular hypertrophy, but a marked and sustained decrease of left ventricular afterload could by itself lead to regression of hypertrophy if maintained for long periods of time and if predominantly due to a reduction of systemic resistance.

### Functional Aspect of Regression of Hypertrophy

In humans, most studies report that left ventricular ejection fraction and fractional shortening were unchanged by reduction of left ventricular mass following antihypertensive therapy. However, these studies do not clearly dissociate the effects of blood pressure reduction from those of regression of left ventricular hypertrophy. Further, adequate assessment of the functional consequences of a reduction in left ventricular mass must
consider not only variations in arterial pressure levels but also any concomitant change in left ventricular wall thickness and diameter since left ventricular wall stress is determined by all three variables.

Fortunately, a quantitative estimate of the interaction of these factors can be obtained from sequential, noninvasive studies in humans. $^{4,22-25}$ Simultaneous determination of auscultatory systolic arterial pressure and of echocardiographic left ventricular dimensions allows calculation of left ventricular systolic stress and pump performance. In fact, many investigators have repeatedly demonstrated a close inverse relationship between left ventricular end-systolic stress and left ventricular fractional shortening (Figure 1). This correlation could be utilized to determine whether alteration in cardiac performance concomitant with changes in left ventricular mass is appropriate to or goes beyond changes in left ventricular wall stress.

In our experience, the relationship between left ventricular end-systolic stress and left ventricular fractional shortening was basically unchanged during peak reduction in left ventricular mass, confirming that regression of hypertrophy was not associated with deterioration of left ventricular pump function (Figure 2). Although this conclusion is common to most reports in the field, more studies are needed to assess the effect of regression in left ventricular hypertrophy on ventricular performance under rapid increases in load (e.g., in response to exercise, exacerbation of hypertension, or recurrence of hypertension after initial blood pressure control).

References

17. Devereux RB, Savage DD, Sachs I, Laragh JH. Effect of blood pressure control on left ventricular hypertrophy and function in hypertension [Abstract]. Circulation 1980;62(suppl 3):36

Figure 1. Left ventricular wall stress-function relationship in 20 normal volunteers. Plot of left ventricular fractional shortening (%Sh) and end-systolic stress (ESS).

Figure 2. Left ventricular wall stress-function relationship with regression of left ventricular hypertrophy (LVH). Normal relationship between left ventricular fractional shortening (FS%) and end-systolic stress (ESS) before treatment and at the time of maximal change in left ventricular mass (LVM) 3-7 months of maintenance therapy. Each point of relation between FS% and ESS at baseline (asterisks) and during treatment is located within 95% prediction limits (broken lines) of the correlation obtained in normal volunteers. (Reprinted from Nakashima et al. with permission.)


27. Tarazi RC, Fouad FM. Reversal of cardiac hypertrophy in humans. Hypertension 1984;6(suppl III):III-140-III-146

28. Rowlands DB, Glover DR, Stallard TJ, Littler WA. Control of blood pressure and reduction echocardiographically assessed left ventricular mass with once daily timolol. Br J Clin Pharmacol 1982;14:89-95


Echocardiographic studies of regression of left ventricular hypertrophy in hypertension.
F M Fouad-Tarazi and P R Liebson

Hypertension. 1987;9:II65
doi: 10.1161/01.HYP.9.2_Pt_2.II65
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/9/2_Pt_2/II65

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/