Cardiovascular Hypertrophy in Hypertension
Arthur C. Corcoran Memorial Lecture
ROBERT C. TARAZI

The transition at the turn of the century, from studies of pathological anatomy to investigations of disturbances of function was a quantum advance in medical sciences. Concepts that were developed then still dominate much of our current thinking; they stressed the primacy of functional disorders over structural damages. In hypertension, hypertrophy and fibrosis of the arterioles were interpreted as late, largely irreversible lesions. In the absence of any obvious alterations in cardiac output, the heart was not thought to play any important role in hypertension; cardiac hypertrophy developed only in its later phases, usually the harbinger of decompensation and the leading cause of hypertensive morbidity and mortality.

It took the remarkable insight and exhaustive work of Folkow and his Goteborg school to readjust these extreme conclusions and demonstrate the dynamic role that hypertrophy of the resistance vessels can play, even early in the disease. Cardiac studies were slower in development, but they also confirmed his conclusions from vascular studies and demonstrated the multifaceted ways by which cardiac hypertrophy can influence the evolution of hypertension and, possibly, its initiation. These studies have revealed a surprisingly wide spectrum of structural changes in what was all too often assumed to be a stereotypical response to a pressure overload.

Dynamic Role of Cardiovascular Hypertrophy

Two questions are basic to assertions that cardiovascular hypertrophy plays an important role in the evolution of hypertension as well as in its initiation and response to therapy — namely, the rapidity with which hypertrophy can develop and regress and the temporal relationship of structural changes to the course of arterial pressures. Extensive evidence has developed in support of the first question. In experimental hypertension, where the imposition of the pressure overload can be timed precisely, cardiac and vascular hypertrophy can be demonstrated within 1 to 2 weeks. Studies of amino acid incorporation in the myocardium revealed even earlier changes; signs of increased incorporation in vascular and in cardiac protein were found within minutes to hours of the increase in pressure load. Conversely, regression of hypertrophy was demonstrated within weeks of blood pressure control, both in humans and in experimental animals.

In spontaneously hypertensive rats (SHR), where the development of hypertension is much more gradual and often difficult to time precisely, it is not surprising that conclusions are not as clear-cut. Many authors have reported definite evidence of cardiac hypertrophy in the "prehypertensive phase" of SHR; at the very least the structural changes and the rise in arterial pressure are not coincidental. Of particular importance in this respect is the work of Yamori et al. suggesting a marked genetic predisposition to a hypertrophic response in cultured smooth muscle cells (SMCs) in SHR as compared with normotensive strains of rats.

This rapid survey of an extensive field of investigation is meant to stress the rapidity with which hypertrophy can develop and regress and, therefore, the possibility for its substantially influencing the course of hypertension. As to whether cardiovascular hypertrophy could initiate hypertension as opposed to only modulating its course, much more needs to be demonstrated. On theoretical grounds, one could envision the way by which SMC hypertrophy in resistance vessels could initiate pressor rises; a similar role for cardiac hypertrophy would be much more debatable, in my opinion, since an increase in myocardial mass is not a likely cause for an increase in cardiac output.

The anatomical basis for cardiovascular "hypertrophy" has recently been discussed in many excellent reviews. This aspect of cardiovascular hypertrophy will therefore not be discussed here. Of particular importance, however, is the growing evidence for individual increases in SMC size rather than hyperplasia, as pointed out by Schwartz and others.
Heterogeneity of Cardiovascular Hypertrophy

One of the more striking features that has emerged from recent research is the marked heterogeneity of structural responses to hypertension. Cardiac hypertrophy had already been shown not to be a homogenous entity but to differ markedly in relation to its initiating cause (e.g., volume vs pressure overload). However, even within the same group of pressure overload, differences could be defined between such types as aortic stenosis or banding and hypertension. Even more surprising was the identification by our group of substantial differences among different models of hypertension as regards the relationship of arterial pressure levels to degree of hypertrophy, alterations in myocardial catecholamines, and disturbances in excitation-contraction coupling. These were not the only differences in cardiac response to hypertension. Another difference reported in humans and in SHR concerned the rate of incorporation of \([\text{H}^3]\)lysine into cardiovascular proteins. The Framingham study revealed important variations in types of cardiac hypertrophy among the initial cohort and the offspring of hypertensive patients. Asymmetric septal hypertrophy was found in 4% of the cohort population and in 2% of their offspring. Eccentric left ventricular (LVH) occurred almost as frequently as concentric hypertrophy (Table 1). This sizable incidence of eccentric hypertrophy, even in early hypertension, which was also described in SHR, marks a significant departure from the classic teaching of marked dominance of concentric LVH in hypertension. The reasons for variance in type of LVH among essential hypertensive patients are not clear; early reports describing a difference in myocardial catecholamine concentration between the septal and free left ventricular wall and relating the type of hypertrophy to that difference have yet to be confirmed.

The response of different segments of the cardiovascular system to hypertension appeared to differ within the same type (SHR) of hypertension. Incorporation of \([\text{H}^3]\)lysine into noncollagenous proteins of vasculature was closely related to arterial pressure levels in the mesenteric arteries and practically unrelated in the heart.

Various hypotheses, based more on conjecture than definite proof, have been advanced for some of the differences listed above, such as the differences in degree of hypertrophy or incidence of asymmetric LVH. The reasons or mechanisms for this impressive list of heterogeneity in cardiovascular hypertrophic response to hypertension are not evident, nor have they been systematically explored. They point to a new facet of the disease and to the need for clear distinction of both the models of experimental hypertension and the segment of cardiovascular system explored. It is not tenable to extrapolate findings from the heart to responses to the larger vessels or of the resistance vessels; the three segments differ from each other, particularly in response to therapy, either quantitatively or even qualitatively.

Excitation-Contraction Coupling in Different Types of Hypertension

Whereas a reduced inotropic left ventricular responsiveness to adenylyl cyclase-stimulating agents (isoproterenol, glucagon, and vasoactive intestinal peptide) was common to different models of hypertension (i.e., spontaneous, renovascular two-kidney, one clip (2K1C) Goldblatt, and deoxycorticosterone hypertension) the mechanism for the reduction was markedly different in two of those models, SHR and renovascular hypertensive rats (RHR). Both of these models showed the same general pattern: 1) a significant correlation between the level of left ventricular mass and reduction in responsiveness and 2) a restriction of that reduction to stimuli of the adenylate cyclase system while inotropic responsiveness to digitalis glycosides or to various levels of extracellular calcium was unchanged. This last feature appeared common to other forms of cardiac hypertrophy, for example, as reported by Newman et al. in aortic banding in dogs. A reduced response of adenylate cyclase to isoproterenol was reported by Amer et al. in both the heart and vessels of SHR.

Table 2 lists the differences documented to date in

<table>
<thead>
<tr>
<th>Variable</th>
<th>SHR</th>
<th>RHR</th>
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<tbody>
<tr>
<td>Phosphodiesterase</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>PK</td>
<td></td>
<td></td>
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<tr>
<td>Soluble</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Microsomal</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Sarcoplasmatic reticulum Ca^{2+} ATPase</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>β-Adrenergic receptors</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Nucleotide regulatory protein</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Adenylate cyclase</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>α₁-Adrenergic receptors</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

RHR = renovascular hypertensive rats; ↓ = decreased; N = normal; ↑ = increased.

*Compared to appropriate controls 15 weeks (SHR) and 10 weeks (RHR) after clipping.
some of the possible mechanisms underlying that same reduction of inotropic responsiveness to isoproterenol. Whereas reduction in myocardial β-adrenergic receptors was almost uniformly reported in SHR, β-adrenergic receptors in renovascular hypertension were variously reported as increased, decreased, or unchanged in RHR. Sequential follow-up of alterations in β-adrenergic receptors and in nucleotide regulatory protein by Kumano et al. showed that the first change in SHR was in the number of β-adrenergic receptors whereas nucleotide regulatory protein was first altered in RHR, followed later by a reduction in the catalytic subunit of the receptor complex. A diminished sarcoplasmic uptake of calcium in SHR was held responsible by Aoki et al. for changes in cardiac contractility and related by Limas to variations in cardiac mass, not to changes in the degree of blood pressure control induced by therapy. On the other hand, highly significant decreases in calcium uptake by the sarcoplasmic reticulum were found in RHR (2K1C) but not in SHR.

These observations are slowly drawing a map of local alterations in the pattern of cardiac responsiveness, each peculiar to a different model of hypertension. It appears reasonable to suggest that these differences, which are evident in the early stages of cardiac hypertrophy, may slowly progress to a similar pattern in advanced disease. These alterations, which are reversible with reversal of hypertrophy in early or established stages, may well become irreversible later on, as in the recently documented response to forskolin in 2K1C RHR.

In summary, whatever their ultimate mechanisms, the abnormalities in excitation-coupling imply the need for early reversal of cardiac hypertrophy, since end-stage cardiac disease has been associated with marked diminution of both cardiac β-adrenergic receptors and responsiveness to isoproterenol.

Consequences of Cardiovascular Hypertrophy . . .

Addendum

The foregoing manuscript was to be completed and mailed to Hypertension when my husband, Dr. Robert C. Tarazi, entered the hospital. Some of his colleagues suggested I complete it. However, I preferred to keep it “open-ended” to reflect a message for his survivors and colleagues. “The work we started has opened the path for future directions; please go on and continue the effort.” We will continue, Bob.

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