Historical note

The context: investigation into hypertension and cardiac hypertrophy

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1. Introduction

From the 1940s to the late 1960s, The Cleveland Clinic Foundation’s Division of Research was a hub of advanced laboratory and clinical hypertension studies. Irvine H. Page, M.D., first chairman of Research, whose “mosaic theory of hypertension” outlined the multifactorial cardiovascular aspects of hypertension, was concentrating on the renin–angiotensin system in Clinic patients with both essential and renal hypertension. Page (and the City of Cleveland) became central to scientific interchange by founding the National Foundation for High Blood Pressure (precursor to the Council for High Blood Pressure Research of the American Heart Association).

Page had recruited F. Merlin Bumpus, Ph.D., in 1949 to investigate angiotensin and its antagonists; then, when high blood pressure was thought to be a “good” response of the heart to stress, no one knew that the renin–angiotensin system was a control mechanism in hypertension. By 1969 Bumpus had synthesized angiotensin II, making that vasopressor peptide commercially available for all subsequent research. These studies of some 30 years ago ‘provided the basis for the development and application of major new classes antihypertensive agents, such as converting enzyme, and angiotensin II-receptor blockers.’

In 1968 I joined these world-class hypertension research efforts. American science was rapidly changing, with a most significant change being research funding. It was not until the 1970s that funding from the National Institutes of Health became the prime source of competitively awarded research funding. The Clinic’s laboratories, with proven scientific innovations, were well positioned to compete, and one of the first successful awards was made to the Cleveland Clinic group for hypertension research. In particular, our work was to find out why hypertensive humans showed normal cardiac output in the setting of increased vascular resistance. We were finding that hypertrophy occurred early in hypertension; we began to see the heart as an active participant, rather than only a passive site of injury, in the hypertrophic cardiomyopathy of hypertension.

2. Scientific assumptions behind the research

In the early 1970s, cardiac hypertrophy, with coexisting hypertension, was regarded as a secondary response to increased arterial pressure load. Some studies had concluded that a close parallelism had to exist between the degree of hypertrophy and the level of hypertension [1]. However, exceptions were also being found: Grant [2] for example, showed that at autopsy many patients with marked hypertension showed little or no hypertrophy, even though the duration and severity of the disease did not differ substantially from that seen in patients who showed clear clinical evidence of left ventricular hypertrophy [1,3–5]. All these data suggested that factors other than arterial pressure are involved in hypertension-associated cardiac hypertrophy. Hypertension in the spontaneously hypertensive rat (SHR) model develops genetically, without any experimental manipulation. The rat model is used because the rat heart is known to vary rapidly in weight in response to various experimental maneuvers [1,6,7], and the SHR provides a reliable model of a naturally developing pressure load akin to human essential hypertension [8].

In our first study [9] we investigated the relationship between heart weight and blood pressure, comparing SHRs 3 weeks to 6 months of age with age- and sex-matched normotensive controls. We quantified the ventricular weight and blood pressure and measured plasma renin activity to study if angiotensin II also affects myocardial protein synthesis [10]. We evaluated the effects of the antihypertensive drug alpha-methyldopa and the vasodilator hydralazine on blood pressure and cardiac weight in this model [9]. This experiment was performed both as a
Cardiac hypertrophy and antihypertensive therapy

Fig. 1. Ventricular weight (H.Wt.) in normal rats (NR) and spontaneously hypertensive rats (SHR). The results are expressed as mg/g body weight±SE. The horizontal axis gives both blood pressure and body weight. Blood pressures in rats of the 50-g weight group were too small to record with the present setup.

treatment study, that is, once hypertension and hypertrophy was established in this SHR model, and as a prevention study, to determine effects of antihypertensive drugs given to the animals from 3 weeks until 6 months of age [9]. Two unexpected results were obtained in this study: [1] a significant increase in ventricular weight was found in very young SHRs; and [2] a marked difference with regard to reversal or prevention of hypertrophy was seen between two equipotent antihypertensive drugs (Figs. 1–3).

The alteration in ventricular weight during the development or reversal of cardiac hypertrophy was not due to changes in water content since the dry weight to wet weight ratio was basically the same in all groups of rats investigated. The increase in ventricular weight was noticed before hypertension was recorded in the SHR. The expected parallelism between the rise in arterial pressure and the increase in cardiac weight had not occurred; this discrepancy could be accounted for by many factors, including an arbitrary definition of the hypertensive level. These observed differences might be important biologically, even though they were difficult to establish numerically. The increased cardiac weight in young SHRs would then be viewed as secondary to the increased pressure overload. These two observations opened up new doors in studying the relationship between blood pressure and cardiac mass and provided us with ideas to pursue this study further to dissect out the role of sympathetic outflow, plasma renin activity, and blood pressure in relationship to ventricular mass.

The other unexpected observation is the effect of two antihypertensive therapies on arterial blood pressure and ventricular weight, which confirmed the tentative conclusions drawn from the first part of the study, that is, the dissociation between the development of hypertrophy and hypertension. Methyldopa and hydralazine were equally successful in controlling blood pressure in the older rat or in preventing its development in the younger SHR. In fact, hydralazine was superior for both conditions, leading consistently to complete normalization of the blood pressure (methyldopa 149±10 mm Hg vs. hydralazine 133±10 mm Hg) (Fig. 2). Yet methyldopa reduced the ventricular weight of SHRs to almost control level, whereas hydralazine had no effect on established hypertrophy during either treatment or prevention therapy. The dissociation between actual pressure response to hydralazine and persistent cardiac hypertrophy has also been noted by other investigators in renal hypertension and tentatively ascribed to a cardiac stimulating effect. The difference between the two drugs could be due to their different hemodynamic effects, although it has been argued by some that chronic hydralazine treatment in men will not be associated with more rapid heart rate than treatment with methyldopa [11].

Obviously, our work dictated that further studies are needed to biochemically characterize the reversal of hypertrophy and its hemodynamic correlates. The plasma renin activity and its positive correlation with cardiac mass also suggested to be a good candidate and could be more

Fig. 2. Ventricular weight in untreated, α-methyldopa-treated, and hydralazine-treated spontaneously hypertensive rats. Results are expressed as mg/g body weight±SE. B.P.=blood pressure.

Fig. 3. Ventricular weight and preventive treatment. Results are expressed as mg/g body weight±BP=blood pressure.
than coincidental. The importance of hemodynamic factors in hypertensive heart disease is so obvious that a more subtle or permissive role of associated hormonal or metabolic factors should also be considered. All these observations prompted us to determine the possible involvement of factors such as: (a) hemodynamic changes, (b) hormonal changes, or (c) a combination of the sympathetic activity of both agents or their combined influence in the enlargement of cardiac mass. Thus, we designed the experiments performed in the cited article to evaluate the effects of various antihypertensive drugs with known mechanisms of action on cardiac mass. Accordingly, we studied the biochemical and humoral factors in SHRs and normotensive Wistar–Kyoto control rats before and following treatment with the vasodilator minoxidil and the β-blocker propranolol. We measured blood pressure, heart size, and kidney and plasma renin activity. Our data showed that minoxidil effectively controlled blood pressure despite marked and sustained increase in both plasma and kidney renin activity and that minoxidil not only did not reduce ventricular weight, but actually increased it. In contrast, propranolol did not reduce blood pressure in SHRs significantly but caused a reduction in ventricular weight ($P<0.05$), as well as lowering both plasma and kidney renin activity. Methyl dopa, on the other hand, which controlled pressure and lowered plasma renin activity, led to reversal of hypertrophy. We concluded that although blood pressure control is obviously important for reversing cardiac hypertrophy, it may not be the sole factor for the development and regression of cardiac hypertrophy.

3. Why the reported findings have been cited

Scientific research occurs against the socio-economic and political ground of the times, and the factors surrounding our day-to-day practice of research are much like the ‘mosaic’ that Page theorized. We built on discoveries of our forerunners. For the article chosen here, it was many years before the significance of our findings could be placed within the context of new findings that supported our model, our hypothesis, and our results.

I am glad for this opportunity to give a new generation some insight into our reasoning, and thus to give a voice to my co-authors Merlin Bumpus and Bob Tarazi and our guiding light Irv Page, all now deceased. My career, like any scientist’s, has seen trials of the scientific, political, and economic sort, but looking back, I cannot regret my choice to come to the Cleveland Clinic to contribute to the world’s hypertension research. Now as a senior investigator, I still find satisfaction in the quest, including our laboratory’s discovery of the novel protein myotrophin, and in the knowledge that I have introduced many younger minds to the excitement of science and to the value of becoming part of the endless interplay of thesis, antithesis, synthesis — and the oftentimes surprising paradigm shift — that is modern biomedical science.

References