Novartis Award

Left Ventricle and Arteries
Structure, Function, Hormones, and Disease

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Abstract—The observation in the 1970s that the performance of the dysfunctional left ventricle was under the influence of aortic impedance led us to exploration of the role of the renin-angiotensin system and other hormonal systems in the progression of heart failure. The apparent efficacy of vasodilator drugs led to the first randomized, controlled trial in heart failure that demonstrated that all impedance-lowering drugs did not exert the same long-term benefit. Differences on the structural remodeling process in the myocardium and arterial vasculature were shown to account for the differential long-term response. We now recognize that the remodeling process in the left ventricle may be inhibited by nitrates, converting enzyme inhibitors, and β-blockers, and this growth process leads to adverse outcomes. The impedance load on the left ventricle is influenced by vascular remodeling that also may be inhibited by drugs such as converting enzyme inhibitors. Thus, progression of cardiovascular disease is largely a consequence of structural changes that are hormonally mediated and may be inhibited by drug therapy. (Hypertension. 2001;37[part 2]:346-349.)

Key Words: myocardium ■ arteries ■ angiotensin-converting enzyme inhibitors ■ heart failure

I am deeply grateful to my colleagues in the Council on High Blood Pressure Research for honoring me with the Novartis Award for Hypertension Research. I shall try to recount for you the background of some of the studies that led to this award and our more recent work that has led us to new insights into the mechanisms of cardiovascular disease.

In the late 1960s, while pursuing studies on the renal and hepatic circulation, I frequently performed regional arterial catheterizations, using polyethylene tubing that I fashioned into appropriately curved catheters. One day, while faced with a patient who exhibited some cardiac symptoms, I fashioned a longer catheter with a tear-drop curve at its tip and passed the catheter under fluoroscopic guidance into the left ventricle. This provided a new opportunity to study left ventricular function, and on that day, I suppose, I became a cardiologist. The technique I had developed as a spin-off of our regional arterial circulatory studies led to the development of a bedside technique for safely catheterizing the left ventricle that allowed us to begin studying acutely ill patients. It was then that I began a life-long effort to marry the ventricle that allowed us to begin studying acutely ill patients.1 It was then that I began a life-long effort to marry the ventricle and the peripheral circulation to gain an integrated understanding of dysfunction of the cardiovascular system.2

At that time in the 1970s, left ventricular function usually was quantified by the Frank-Starling curve, which related left ventricular filling pressure to stroke volume or cardiac output.3 It was classical student teaching to describe heart failure as a condition in which the Frank-Starling curve was depressed downward and to the right and to describe a shift of the curve upward and to the left as a positive inotropic stimulus. Armed with our left ventricular catheter, we studied a group of patients with severe hypertension and found in a subgroup surprisingly high left ventricular end-diastolic pressure indicative of a shift downward and to the right of the Frank-Starling curve.4 We chose a drug devoid of cardiac effects to evaluate the response to a pure vasodilator stimulus. Sodium nitroprusside solution was prepared by dissolving the powdered chemical in a glucose solution and passing it through a micropore filter for sterility. Infusion of this homemade drug resulted in a striking reduction in the elevated left ventricular filling pressure and a shift upward and to the left of the Frank-Starling curve.4 It was clear, therefore, that a reduction in left ventricular outflow resistance or impedance could favorably affect the function of the left ventricle.5 It occurred to us at that time that the relation between impedance and stroke volume might best be described by a family of curves, depending on the severity of left ventricular dysfunction. We therefore undertook studies in a series of patients with acute myocardial infarction who displayed significant left ventricular dysfunction. In response to sodium nitroprusside, there was a striking reduction in left ventricular filling pressure and increase in stroke volume indicative of a marked improvement of the traditional Frank-Starling curve. The suggestion that severe left ventricular failure in the setting of acute myocardial infarction would respond favorably to vasodilator therapy was received with great skepticism by the medical community. Many thought that the concept was flawed and the intervention would be
The efficacy of vasodilator drugs, we theorized, might be related to an inappropriate increase in vascular resistance and impedance in the circulation in response to the failing heart. Neurohormonal activation was entertained as a mechanism for this inappropriate vasoconstriction. We therefore began measuring plasma hormone levels in patients with heart failure and identified a consistent increase in plasma norepinephrine levels, a striking but variable increase in plasma renin activity, and a doubling of the normal levels of arginine vasopressin. Since these three potent vasoconstrictor hormones were increased in this syndrome, it was attractive to postulate that the hormonal stimulation led to the vasoconstriction and further impairment in left ventricular function that could initiate a vicious circle, resulting in progressive impairment of the left ventricle and the syndrome of pump failure and premature death. If this was the mechanism of action of vasodilator therapy, we theorized, long-term administration of an effective vasodilator drug should reverse the course of heart failure and prolong life.

Our next search was for an effective vasodilator regimen that could be used to accomplish long-term therapy. We carried out preliminary studies with isosorbide dinitrate, a widely used vasodilator for angina pectoris, and found it produced a sharp and sustained fall in the elevated left ventricular filling pressure. When we combined this nitrate with oral hydralazine, a potent arterial dilator, the hemodynamic effects of the combination replicated the hemodynamic response to sodium nitroprusside. We therefore believed that we had found an oral equivalent to the potent intravenous nitroprusside, with which we had initiated our studies. On the other hand, if activation of the sympathetic nervous system was an important contributor to the syndrome, as suggested by the elevated plasma norepinephrine levels, it might be more physiologically rational to block the vasoconstrictor effect of norepinephrine directly. The 1-blocker prazosin had been subjected to preliminary short-term trials in heart failure and found to exhibit a favorable hemodynamic effect. We therefore undertook the first large-scale trial in chronic heart failure with 3 therapeutic arms added to standard therapy, which at that time included digoxin and diuretics. One group was to receive a placebo, one to receive the isosorbide dinitrate–hydralazine combination, and the third group to receive prazosin. Our initial studies with the nitrate–hydralazine combination demonstrated a duration of effect of between 4 and 6 hours and we therefore elected to use the drug 4 times daily. Because this was a Veterans Affairs Cooperative Study, we elected to include only men and the proposed sample size was only modest. In these early days of clinical trial technology, we did not power the trial to detect a preordained reduction in mortality rate but rather selected what we thought would be a realistic sample size to recruit from the limited number of centers participating in the study. Consequently, we calculated the power that this sample would give us to detect varying degrees of mortality rate reduction. Furthermore, we anticipated that both vasodilator drugs would exhibit similar favorable effects on outcome and therefore we randomized more patients to the placebo arm than to either of the vasodilator arms to maximally power our study to compare the combined vasodilator therapy with placebo.

The Data Safety Monitoring Board, appointed to oversee the conduct of the trial, noted at the early meetings of their group that the two vasodilator interventions were not tracking together. One was tracking with the placebo arm and the other exhibited a mortality benefit. This trend continued throughout the course of the trial, which was terminated at a prescheduled date. At that time, the nitrate-hydralazine arm exhibited a significantly favorable effect on mortality, whereas the prazosin group exhibited no benefit compared with placebo.

This rather surprising outcome in V-HeFT I taught us that all vasodilator drugs are not the same. In fact, we should have been prepared for the news that vasodilation alone was not the mechanism of a favorable long-term response in heart failure. In our earliest observations of the response to sodium nitroprusside, the normalization of the Frank-Starling curve of left ventricular dysfunction was clearly not indicative of normalization of left ventricular structure. Echocardiography had been carried out before and during the infusion of nitroprusside in a subset of the early patients we studied. In this patient group, the striking reduction, almost to normal, of left ventricular filling pressure, was accompanied by only a modest reduction in the markedly increased left ventricular end-diastolic volume. Therefore, normalization of pressure and flow could be viewed as a cosmetic response in a remodeled left ventricle. The left ventricle was still dilated and remodeled, even though the hemodynamic indexes had been restored toward normal. This remodeling process and not the impaired function could be viewed as fundamental to the course of heart failure, and vasodilator drugs that might improve function but without correcting remodeling would be expected to have no long-term benefit on the syndrome. Although left ventricular volume studies were not carried in V-HeFT I, serial measurements of ejection fraction by radionuclide techniques were carried out. A sustained increase in ejection fraction is indicative of regression of remodeling, with a reduction of end-diastolic volume. A transient increase in ejection fraction might result from the vasodilation alone, but in the absence of structural remodeling, this increase in ejection fraction would be modest and nonsustained. When examining the serial ejection fraction changes in V-HeFT I, the nitrate-hydralazine combination exhibited a significant increase that persisted throughout the 4 years of the study, whereas the prazosin exhibited only a transient increase, which then fell along with the placebo arm during the remainder of the study. Thus, the nitrate-hydralazine combination exhibited structural regression of remodeling of the left ventricle, whereas prazosin did not. Indeed, the recent ALLHAT study also concluded that an 1-blocker was not effective in the long-term prevention of cardiovascular events in hypertensive subjects.

These observations required a revision of our concept of the relation between neurohormonal vasoconstriction and progression of heart failure. It became necessary to add a
The role of the vasculature needed reexamination. Not only was vasoconstriction present in the vasculature, but it became clear that structural remodeling of the arterial system also contributed to the progression of cardiovascular disease. Furthermore, the hormonal stimuli identified to play a role in the structural remodeling of the left ventricle also appeared to be active in structural changes in the arterial system. These structural changes not only may contribute to the impedance against which the left ventricle must empty but also may directly relate to the vascular events that characterize progressive cardiovascular disease. Furthermore, the arterial control of impedance is not confined to the arterioles but is also a function of changes in the large conduit arteries and the smaller arteries that serve as sites for arterial pressure oscillations and reflected waves in the circulation.

Vascular changes in the wall of the arteries are usually associated with increased wall thickness and reduced arterial compliance. These changes are characteristic of aging but also are observed in atherosclerosis and may be a consequence of neurohormonal activation, including the sympathetic nervous system and the renin-angiotensin system. To evaluate the function and structure of these arterial segments, we developed a pulse-contour analysis technique with a third-order equation to analyze diastolic decay of the arterial pressure wave and a modified Windkessel model to describe the compliance, resistance, and inertial components of the peripheral vascular system. The modified Windkessel model consists of two compliances in parallel, the proximal one depicting the capacitive function of the large arteries and the distal one identifying the oscillatory component predominantly in the small arteries and at branch points of the circulation. By using this model system, we were able to identify that sodium nitroprusside exerts a striking effect on the large conduit and small oscillatory sites, in addition to a modest relaxation of the arterioles. Thus, the improvement in left ventricular output in response to sodium nitroprusside may be related largely to the impedance reduction produced by an increase in compliance of the arterial system not just reduction of vascular resistance. Indeed, drug effects on the wall of the arterial system may be important in the prevention of cardiovascular events in a wide spectrum of cardiovascular diseases that eventuate in atherosclerosis. The favorable effect of ramipril in the HOPE trial may relate to a favorable effect of ACE inhibitors on the arterial vascular wall.

Thus, the marriage of the left ventricle and the arterial system may now be consummated. Structural changes in the left ventricle and in the arterial vasculature may be critical to the progression of cardiac and vascular disease and may be preventable or reversible by effective drug therapy. This therapy may be appropriately directed at the neurohormonal mechanisms that appear to contribute both to the functional and structural alterations in the left ventricle and the arterial vasculature. Heart failure is just one syndrome in which these structural changes may shorten life expectancy and may be responsive to pharmacological intervention. Further research must be directed to identifying the cellular and molecular mechanisms that contribute to this progressive structural alteration so that therapy may be directed more specifically.
stage for remarkable new insights that may eventually lead not only to prevention of progression of cardiovascular disease but prevention of the disease itself.

References

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