Local Hemodynamic Changes in Hypertension
Insights for Therapeutic Preservation of Target Organs

Edward D. Frohlich

Abstract—As a result of antihypertensive therapy, there has been a remarkable decrease in morbidity and mortality from such cardiovascular endpoints as stroke, coronary heart disease, and major hypertensive emergencies. In contrast, there has been no relenting in the increasing prevalence of cardiac failure and end-stage renal disease (ESRD) associated with hypertensive cardiovascular disease. Recent experience in our laboratories that involved the natural development of the cardiac and renal hemodynamic alterations in spontaneously hypertensive rats demonstrated that the natural history and pathophysiological lesions associated with cardiac failure and ESRD may be vastly different from the heretofore more pressure-dependent brain and other cardiovascular endpoints reported in earlier years. These initial antihypertensive agents (eg, diuretics, β-adrenergic receptor inhibitors) had minimal anti-ischemic and antifibrotic effects on heart and kidney and did not exert the cardiac and nephroprotective hemodynamic effects of the newer classes of agents. The cardiac and renal endpoints resulting in organ failure today are more related to ischemia, intraorgan fibrosis, and aging. Our experimental studies summarized herein strongly suggest that the newer classes of antihypertensive drugs (ie, ACE inhibitors, angiotensin II type 1 receptor antagonists, certain calcium antagonists, and perhaps L-arginine) may reverse these(pathophysiological lesions through improving blood flow and flow reserve, their antifibrotic and other actions. To this end, we look forward to the results of ongoing, well-controlled, and prospectively conducted multicenter clinical studies designed to demonstrate prevention of cardiac and renal failure. (Hypertension. 2001;38:1388-1394.)

Key Words: rats, spontaneously hypertensive ■ ventricular ischemia ■ ventricular fibrosis ■ renal failure ■ angiotensin-converting enzyme inhibitors ■ AT1 receptor blockade ■ calcium antagonists

Large clinical outcome studies have demonstrated dramatically reduced morbidity and mortality from strokes and coronary heart disease (CHD) over the past 4 decades.1–4 However, in contrast to these remarkable therapeutic achievements, cardiac and renal failure continue to increase unrelentingly.1,4–8

Legitimate questions, however, may be raised from these experiences that suggest there may be important pathophysiological explanations for these disparate effects on the major target organs of hypertensive disease. Thus, the cerebral circulation, which is responsible for strokes in hypertension, may be more pressure-dependent,9 and it responded beneficially first and more dramatically in these trials2,3,10 with arterial pressure reductions. Indeed, in subsequent years, there has been a ≥70% reduction in deaths from strokes in the American and World Health Organization reports.1–4 The coronary circulation, however, is more complex; and its pathophysiological responses are more dependent on duration of treatment, drug actions, and doses used.11–13 Thus, for example, when the recommended thiazide dosage was reduced significantly (even in older patients), the predicted reduction in deaths from CHD were achieved,2,3 thereby emphasizing the multiplicity of factors involved (eg, pressure reduction, myocardial oxygen demand, complications from left ventricular hypertrophy [LVH], coronary arteriolar disease, endothelial dysfunction, side effects).12–14 On the other hand, despite adequate control of arterial pressure, risk associated with hypertensive heart disease and LVH related to cardiac dysrhythmias,15,16 sudden death,17 and cardiac failure6,7,14 may not have been adequate or sufficiently specific with the earlier antihypertensive drug classes to reduce all endpoints related to that risk.14

A similar line of reasoning may be raised with respect to end-stage renal disease (ESRD).8 Indeed, more recent controlled trials have pointed out the necessity for more rigidly controlled arterial pressure14,18 and the use of the newer drug classes to prevent or reverse this outcome.19–23 These compounds antagonize specific pathophysiological pressor mechanisms that promote glomerular efferent, as well as afferent, arteriolar, and renal interstitial tissue involvement by exacerbating the renal hemodynamic, glomerular dynamic, endothelial interstitial, and other hypertensive disease mechanisms.24,25

This discussion summarizes recent reports from our laboratory that have focused on naturally occurring hypertensive CHD and ESRD in elderly spontaneously hypertensive rats.
Coronary Hemodynamic Alterations

Each of the foregoing clinical endpoints of hypertensive heart disease may be explained by a variety of specific alterations that affect coronary hemodynamics and the myocardial function (Table 1). These factors are exacerbated by aging and co-morbid diseases. Among those structural alterations are factors that may reduce coronary blood flow through ventricular wall compression, epicardial arterial luminal atherosclerotic plaque obstruction, increased wall/lumen ratio of the coronary arterioles,33 and impaired autoregulatory control of coronary flow. Moreover, as in other local organ circulations in hypertension, there may be reduced left ventricular wall vascularity.34 Furthermore, associated with these adverse structural changes is increased collagen and protein deposition in the extracellular matrix and perivascularity that further impairs ventricular function and coronary hemodynamics.26,27,32,35,36 Functional left ventricular changes in hypertension relate to LVH impaired myocardial contractility or relaxation,30,31 and compromised resting coronary blood flow and flow reserve. These latter indices of coronary hemodynamics can be assessed experimentally37–39 and, more recently, clinically by physiological (ie, exercise testing) or pharmacological (ie, carbochrome, dipyridamole, adenosine) interventions.40–42 Therefore, the increased coronary flow demand thus imposed diminishes the increased coronary flow reserve and vascular resistance (expressed as minimal coronary vascular resistance), but not to normal indices. These local coronary hemodynamic changes, first introduced experimentally by Marcus and his associates,14 have been employed more recently in hypertensive patients.40–44 Moreover, in addition to these well-established interventions, recent studies have clarified our understanding of coronary arterial and other organ endothelial dysfunctions associated with naturally occurring pathological changes, which seem to be reversible with appropriate therapies (Table 2).35–50

TABLE 1. Cardiac Enlargement: Altered Coronary Hemodynamics

<table>
<thead>
<tr>
<th>Structural</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial compression, occlusion wall thickness</td>
<td>Increased oxygen demand: ↑ systolic pressure, ↑ diameter</td>
</tr>
<tr>
<td>Rarefaction: reduced vascularity, No. of vessels</td>
<td>Impaired autoregulatory reserve</td>
</tr>
<tr>
<td>Left ventricle chamber size: LVH, collagen, protein</td>
<td>Impaired coronary hemodynamics</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Diminished NO synthesis</td>
</tr>
<tr>
<td>Diminished participation of local renin-angiotensin system</td>
<td>Increased participation of kinin system</td>
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</table>

Hypertensive Heart Disease

Multicenter clinical trials in patients with hypertension have clearly demonstrated that cardiac deaths are related to a variety of endpoints, including unremitting angina pectoris, cardiac dysrhythmias, acute and chronic ventricular failure, hypertensive coronary arteriolar disease (eg, microvascular angina), sudden cardiac death, and endothelial dysfunction of the coronary vessels and endocardium,13,14,29 as well as those worthy of separate emphasis, ventricular failure and left ventricular enlargement (without atherosclerosis),33 and impaired autoregulatory reserve control of coronary flow. Moreover, as in other local organ circulations in hypertension, there may be reduced left ventricular wall vascularity.34 Furthermore, associated with these adverse structural changes is increased collagen and protein deposition in the extracellular matrix and perivascularity that further impairs ventricular function and coronary hemodynamics.26,27,32,35,36 Functional left ventricular changes in hypertension relate to LVH impaired myocardial contractility or

TABLE 2. Some of the Described Endothelial Dysfunctions and Putative Therapeutic Reversal

<table>
<thead>
<tr>
<th>Causation</th>
<th>Potential Therapy</th>
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<tbody>
<tr>
<td>Aging</td>
<td>ACE inhibition and L-arginine</td>
</tr>
<tr>
<td>Menopause</td>
<td>Estrogen replacement therapy</td>
</tr>
<tr>
<td>Smoking</td>
<td>Tobacco cessation</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ACE inhibition; AT1 receptor blockade, calcium antagonists</td>
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<tr>
<td>Diabetes mellitus</td>
<td>ACE inhibition</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Statins, ACE inhibition, calcium antagonists (?), exercise</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Statins</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Folic acid</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Ventricular compensation by ACE inhibition, diuretics</td>
</tr>
</tbody>
</table>

( ) or in younger adult SHR with L-NNAME (N\textsuperscript{\textdagger}-nitro-L-arginine methyl ester)—exacerbated endothelial dysfunction and nephrosclerosis.25 Both expressions of target organ involvement (ie, heart and kidney) in the SHR are inextricably related to specific pathophysiological alterations, their responses to the newer antihypertensive drugs, and aging. These observations in SHR will be supported by very recent clinical reports in patients with essential hypertension.10,13–23,26,27 These latter findings, we believe, underscore justification for the present thesis and prognosis that there is very real merit to our premise that prevention and reversal of target organ involvement of heart and kidney in hypertension is close at hand.28

Hence, in patients with hypertension, there are a number of potential causes and disease mechanisms for coronary vascular insufficiency and the associated ischemic heart diseases involving the larger arteries, the arterioles, and the endothelium. There may also be coincident obstructive atherosclerotic epicardial coronary arterial disease. However, ischemic CHD may also occur with pure hypertensive heart disease and left ventricular enlargement (without atherosclerosis), which may be exacerbated by aging and fibrosis, and there may also be coincident or endothelial dysfunction of the coronary arteries, arterioles, and endocardium. Each of these pathophysiological alterations may be associated with symptomatic (or asymptomatic) ischemic heart disease, sudden cardiac death, or other endpoints that can be attributable solely to hypertension and hypertensive heart disease. We have reported a series of studies that support these foregoing concepts and provide a clearer understanding of the coronary arterial insufficiency in experimental hypertension. These experimental findings have been supported by very recent clinical reports that provide new insights concerning specific hemodynamic abnormalities in clinical hypertensive heart disease, a distinct complication of hypertension that need not incriminate associated coexisting ischemic atherosclerotic heart disease.
Cardiac Involvement

Until recently, cardiac involvement in hypertension was generally thought primarily to be the development of LVH. Indeed, present-day dictum maintains that the clinical presence of LVH confers a severe risk of premature cardiovascular morbidity and mortality, a risk that even exceeds that of the height of either the systolic or diastolic pressure elevation. To my way of thinking, 2 critical questions have been raised since demonstration that the risk is attributable to LVH: first, what are the intrinsic factor(s) that account for this increased risk; and second, if effective antihypertensive pharmacotherapy diminishes the increased ventricular mass associated with LVH, is that risk actually reduced. Moreover, should that risk reversal be ascribed to reversed LVH, the diminished overall left ventricular mass, or coincidental therapeutic epiphenomena of therapeutically induced arterial pressure reduction (eg, improved coronary hemodynamics, antiarrhythmic actions, or other associated actions). My current thinking is that antihypertensive therapy will ultimately demonstrate that risk reduction, but those studies must also define the specific mechanisms that are involved.

Over 20 years ago, we enunciated the concept that the development and reversal of LVH involved nonhemodynamic as well as hemodynamic factors. Among the postulated factors are, obviously, pressure (and volume) overload, gender, race, age, comorbid pathophysiological entities (eg, atherosclerosis, obesity, diabetes mellitus), and a number of related growth and autocrine/paracrine perturbations. Perhaps the 2 more important factors that have been demonstrated (particularly in the elderly patient or in experiments) are fibrosis in the extracellular matrix and ventricular ischemia with reduced coronary flow reserve. Clearly, impaired myocytic contractile function is important but the importance of aging, ischemia, and fibrosis has not been emphasized adequately. To these end, recent findings from our laboratory will be emphasized in this report.

Aging

Normotensive rats (Wistar-Kyoto [WKY]) and SHR have demonstrated either normal or reduced resting coronary blood flow; but impaired coronary flow reserve associated with increased coronary vascular resistance and increased minimal vascular resistance occurs throughout aging, from 30 to 65 weeks and even older, in the SHR hypertrophied left ventricle. These very same left ventricular coronary hemodynamic alterations also exist in the nonhypertrophied SHR right ventricle as well as in the left and right ventricles of elderly (2 years old) WKY with isolated systolic hypertension. Thus, impaired left and right ventricular coronary hemodynamics involve the hypertrophied and nonhypertrophied SHR ventricles, and these derangements are exacerbated by the aging process. Of vital importance, associated with these coronary hemodynamic changes related to hypertension and aging (and to the progressive development of myocytic hypertrophy), is the deposition of hydroxyproline in the left and right ventricular wall of both the normotensive and hypertensive rats. These findings demonstrating ventricular fibrosis have also been shown in patients with essential hypertension. Therefore, in patients with essential hypertension and in SHR with naturally occurring hypertension, ventricular fibrosis complicates myocytic hypertrophy and the associated impairment of left and right ventricular coronary blood flow reserve. Moreover, in addition to the progressive development of myocytic hypertrophy in hypertension, the critically important complicating factors of aging, ischemia, and fibrosis play major roles in the hypertensive and normotensive rat and in the hypertensive patient.

Pharmacotherapy

As we have demonstrated repeatedly, impaired left and right ventricular coronary hemodynamic alterations associated with hypertension (and aging) may be detectable at rest and are similar to the changes that occur in any other organ circulation in hypertension, normal or reduced resting blood flow, and increased vascular resistance. Pathologically, the arteriolar wall is usually thickened and associated with an increased wall-to-luminal ratio. However, when the coronary circulation is stressed physiologically (eg, treadmill exercise) or pharmacologically (eg, carbochrome, dipyridamole, adenosine), both left and right coronary blood flow reserve diminish, and there is an associated increased minimal coronary vascular resistances.

Of great significance, the 2 pathophysiological alterations associated with hypertension (coronary ischemia and fibrosis) are improved significantly by the newer antihypertensive agents: ACE inhibitors or calcium antagonists. These observations in SHR have recently been shown to occur in essential hypertensive patients treated with ACE inhibitors. Moreover, we have shown that both left and right ventricular hemodynamics were markedly and synergistically improved by coadministration of an ACE inhibitor with an AT1 receptor antagonist. However, the AT1 receptor was not the sole factor relating to fibrosis, since coadministration of a AT2 receptor antagonist counteracted hydroxyproline concentration and content. Furthermore, administration of an ACE inhibitor with an β-adrenergic receptor blocking agent will augment the antihypertensive, hemodynamic, and hydroxyproline alterations.

Similar qualitative, albeit not necessarily quantitative, actions were shown with certain calcium antagonists. These agents also increased left ventricular coronary flow reserve and reduced minimal coronary resistance hydroxyproline content. However, unlike the ACE inhibitors, each calcium antagonist that we have studied reduced SHR left ventricular but increased right ventricular hydroxyproline content, and they all increased right ventricular wall thickness in man. However, the increased right ventricular collagen in SHR was prevented by the coadministration of an ACE inhibitor, although left ventricular collagen was not reduced further. The mechanisms for this later observation have not yet been explained.

Endothelium

We have recently learned that the hemodynamic changes associated with hypertension are complicated further by endothelial dysfunction. The endothelial dysfunction is
distinctly different from those changes associated with hypertensive arteriolar disease and many other naturally occurring pathological and clinical conditions (Table 2). Many of these other “endothelial dysfunctions” are responsive to a broad array of therapies, suggesting that there is a variety of endothelial dysfunctional states that seem to be observed through a variety of specific biological endothelial alterations. In this respect, it was most intriguing to learn in our experimental studies in SHR that the hydroxyproline content of the left ventricle was diminished, at least in part, by the NO precursor amino acid L-arginine (even though the age-related changes were not as responsive). It is possible that either the lesser responses we observed were in rats that may have been too old or the rats were not treated long enough. Thus, the point of these differing responses, at least temporally, may reflect differences in mechanisms brought about by hypertensive disease and by aging. Nevertheless, we also demonstrated additive hemodynamic and antifibrotic improvements with prolonged coadministration of an ACE inhibitor with L-arginine in WKY with isolated systolic hypertension with hemodynamic and ventricular functional changes that were similar to those of isolated systolic hypertension in the elderly, including diastolic function.

End-Stage Renal Disease

Another major outcome of hypertensive disease is ESRD. Diabetes mellitus followed by hypertension, particularly in black patients, are the major factors underlying this unrelentingly increasing prevalence of ESRD. Moreover, because hypertensive renal vascular disease is exceedingly common in patients with diabetes, it is clear that hypertension plays a critical role in this exceedingly important complication of ESRD. Furthermore, renal hemodynamic, glomerular dynamic, and the pathological changes are very similar in both diseases.

Thus, in addition to renal arterial and afferent arteriolar constriction, which diminishes total renal and glomerular blood flow, there is intense efferent glomerular arteriolar constriction that reduces glomerular flow egress and, thereby, promotes an increased intraglomerular hydrostatic pressure. These glomerular dynamic alterations favor protein and other large molecular translocation across the glomerular capillary wall, which facilitates hyaline deposition and glomerulosclerosis. The precise mechanisms accounting for these changes no doubt involve a number of pathophysiological factors, including involvement of the local renal renin-angiotensin system. Evidence supporting this concept has been provided by the therapeutic demonstration that ACE inhibitors retard, and most likely reverse, the pathophysiological alterations manifested in early and established ESRD in man. It therefore seems highly likely that we may now, at last, be at the threshold of witnessing a downturn in the long-standing increase in ESRD. These findings learned from well-controlled multicenter studies, and current therapeutic recommendations emphasize the necessity of reducing and controlling arterial pressure to levels <130 and 80 mm Hg, systolic and diastolic, respectively. Although the basis of these observations was demonstrated by the remarkable improvement in the expected outcomes of patients with diabetes mellitus and ESRD, it is not inappropriate to extrapolate these recommendations for patients with hypertension at risk to develop ESRD (even in those with high normal blood pressure levels). In this report, we summarize our recent hemodynamic, micropuncture, pathological, and general clinical findings learned in the very old SHR with naturally occurring ESRD and in much younger adult SHR having exacerbated hypertension and ESRD associated with prolonged administration of the nitric oxide synthetase inhibitor L-NAME. The renal hemodynamics, glomerular dynamics, and renal pathology of both experimental models of ESRD are very similar to those in essential hypertension. In addition, their responses to therapy are also similar. Therefore provide strong evidence that not only can the currently available newer classes of antihypertensive agents ameliorate the development and progression of ESRD, but they can even prevent the pathophysiological renal alterations once established, and they can even reverse those lesions once they have developed.

Our first report demonstrated that the 73-week-old SHR naturally developed all of the pathophysiological and clinical alterations that are associated with ESRD in patients with essential hypertension. These findings included elevated arterial pressure; reduced total renal blood flow and increased renal vascular resistance; increased afferent and efferent glomerular arteriolar resistance, elevated glomerular hydrostatic pressure, and a diminished renal filtration coefficient; reduced glomerular filtration rate; massive proteinuria; and the classical histopathological glomerular and renal arteriolar injury lesions of severe nephrosclerosis. Moreover, when these rats were treated for only 3 weeks with an ACE inhibitor, each of these pathophysiological alterations was significantly reversed or normalized. The systemic arterial pressure was reduced, albeit to suboptimal levels, and this was associated with a reduced total peripheral resistance and a normal cardiac output and heart rate. Total renal and afferent and efferent glomerular resistances were likewise reduced. Furthermore, these changes were associated with increased total renal and single nephron glomerular plasma flows, reduced filtration fraction, decreased glomerular hydrostatic pressure, and markedly reduced proteinuria; in addition, the histological glomerular and arteriolar injury score indices were dramatically reduced. Hence, in the naturally occurring hypertensive nephrosclerosis of elderly (73 week old) SHR, all of the pathophysiological indices were significantly and remarkably improved by only a 3-week course of ACE inhibitor treatment—despite suboptimal control of arterial pressure.

Earlier studies in our laboratory had involved much younger SHR (23 weeks), without impaired renal flow and function or abnormal intrarenal micropuncture indices of flow and function. Because it was not possible to procure very old SHR and because maintenance of younger rats for >1 year was neither cost-effective nor efficient, we developed a protocol that reproduced all of the pathophysiological indices of nephrosclerosis in the very old SHR. This was achieved by treating younger (20 to 23 week old) SHR with L-NAME for 3 weeks, and we reproduced all of the pathophysiological alterations associated with nephrosclerosis in
the 73-week-old SHR, except for increased glomerular hydrostatic pressure.72 Thus, despite increased efferent and the more severely intense afferent arteriolar resistance, total and single nephron glomerular plasma flows were so markedly reduced that the glomerular hydrostatic pressure did not increase.72

Having reproduced with L-NAME the findings that we observed in naturally occurring severe nephrosclerosis, we devised a series of studies in younger 23-week-old SHR that were designed to determine whether pharmacological therapy would either prevent or reverse the accelerated SHR/L-NAME–induced nephrosclerosis. We first learned that when the same ACE inhibitor was coadministered with L-NAME, we prevented the development of the pathophysiological structural and functional lesions of nephrosclerosis and hypertensive ESRD. Moreover, when that ACE inhibitor was administered for 3 weeks after the 3-week period of L-NAME administration, these same pathophysiological alterations were reversed.76 We then determined whether the responses produced by ACE inhibitor reversal of the L-NAME–induced SHR nephrosclerosis resulted from the pressure reduction induced by ACE inhibition. We administered hydrochlorothiazide with the L-NAME for 3 week,77 and arterial pressure was reduced to the same level but the renal hemodynamic, glomerular dynamic, and pathological alterations were severely and significantly exacerbated. Thus, these findings demonstrated that by secondarily stimulating both the systemic and the local intrarenal renin-angiotensin systems with thiazide, we aggravated the renal pathophysiological changes despite the similar reduction in arterial pressure achieved earlier with the ACE inhibitor.70,71,73,76

In our follow-up studies, we confirmed our findings with another ACE inhibitor,78 an AT1 receptor antagonist,78 and with l-arginine, the amino acid precursor of NO.79 We also demonstrated that when the bradykinin receptor antagonist icatibant was administered together with the ACE inhibitor, the renal hemodynamic and glomerular dynamic changes and the pathological lesions were no different from the responses observed when the ACE inhibitor was administered alone.78 Hence, we concluded that the augmented bradykinin, generated through ACE inhibition, failed to provide additional nephroprotection than that of the ACE inhibitor or AT1 receptor antagonist employed alone.78

Further, to determine whether the nephroprotection produced by ACE inhibition or angiotensin II receptor antagonism were unique to agents that only antagonized the systemic and intrarenal renin-angiotensin systems, we also investigated the same pathophysiological responses using various calcium antagonists (ie, felodipine, amloodipine, mibebradil, and cilnidipine).80–82 In these studies, whether we used an L-, T-, or N-calcium channel receptor inhibitor, each of these 4 calcium antagonists improved the systemic and renal hemodynamics, glomerular dynamics, and pathological changes produced by the L-NAME in 23-week-old SHR. They not only prevented but reversed the intraglomerular and arteriolar histological lesions and pathophysiological changes.80–82 There were some differences in responses among those 4 calcium antagonists; however, they did not differ with respect to their renal and intrarenal effects.

Thus, our studies in the naturally developing nephrosclerosis in very old SHR were remarkably similar to those responses observed in the L-NAME–induced and –exacerbated nephrosclerosis in younger (23 weeks) adult SHR. These responses to ACE inhibition, AT1 receptor antagonism, and l-arginine and to certain calcium antagonists not only prevented, but reversed, hypertension-associated nephrosclerosis and ESRD. It was of particular interest that these effects resulting from presently available antihypertensive compounds did so with only suboptimal reduction of arterial pressure (with the exception of the angiotensin II receptor blocker, which entirely normalized arterial pressure). These changes were exacerbated by the diuretic hydrochlorothiazide suggesting that when used alone, the diuretic was not capable of preventing or reversing the pathophysiological alterations of hypertensive ESRD because of their dissimilar local renal hemodynamic effects. Indeed, perhaps this observation explains the increasing prevalence of ESRD in patients, even while deaths from stroke and CHD are reduced.

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