The importance of hemodynamic considerations in essential hypertension

Hypertension is a major risk factor for cardiovascular morbidity and mortality. Antihypertensive therapy consistently reduces complications from stroke and congestive heart failure, whereas benefits from the treatment of ischemic heart disease events are variable. Several plausible explanations, including hemodynamic hypotheses, have been put forth to account for the failure of treatment to more favorably influence mortality from ischemic heart disease. The effect of hypertension on coronary heart disease is probably much more complex than a simple elevation of arterial pressure. Some of these complexities include the potential separate risks of high total peripheral resistance, high cardiac output, increased myocardial power that reflects pressure times flow, and several structural and functional vascular changes. These factors may act in concert to unfavorably alter the balance between myocardial oxygen supply and demand. Several of these factors will be highlighted in an attempt to offer alternative or adjunctive pathophysiologic examinations for the high-risk subgroups of obesity and the failure of antihypertensive therapy to normalize the rate of coronary heart disease events. (AM HEART J 1988;116:594.)

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Epidemiologic data provide evidence that elevated arterial blood pressure is associated with a significantly higher incidence of cardiovascular complications, including myocardial infarction.[1,2] Pharmacologic lowering of arterial pressure reduces total cardiovascular morbidity and mortality in hypertensive patients.[3-6] Although the overall event rate is reduced, specific ischemic cardiac events are not consistently prevented.[7] Numerous plausible explanations have been provided by various experts to account for this major shortcoming in several treatment trials (Table I).

This review focuses predominantly on the potential role of both early and late hemodynamic variables, including total peripheral (systemic) vascular resistance* (TPR) and cardiac output (CO), as well as their product, mean arterial (blood) pressure† (MAP), on morbidity and mortality from coronary heart disease. Although the review is based on a wealth of physiologically sound experimental observations, some less recognized pathophysiologic concepts are explored in an attempt to more fully account for incompletely explained epidemiologic data. The data include not only the failure of antihypertensive therapy to normalize the excessive incidence of coronary artery disease, but also the excessive cardiac risk accompanying borderline hypertension and obesity, particularly in younger men.

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*Total systemic resistance (TSR) in arbitrary units is equivalent to mean blood pressure divided by cardiac output (CO). Total peripheral resistance (TPR) equals mean arterial pressure minus mean right atrial pressure divided by CO. Since right atrial pressure is generally 0 to 4 mm Hg in most healthy subjects and is only a small fraction of mean arterial pressure, in practice there is little difference between TPR and TSR.[8]

†Mean arterial pressure (MAP, mm Hg) implies a value derived from integration of the area under the directly measured arterial pulse-wave form. Mean blood pressure (MBP, mm Hg) implies a calculated value derived from noninvasively measure systolic and diastolic blood pressure.

HEMODYNAMIC CONSIDERATIONS

Peripheral vascular resistance. Several observations suggest the predominant importance of TPR in explaining the cardiac complications associated with hypertension. First, increased resistance to blood flow is the hemodynamic hallmark of hypertension.[9,10] This conclusion is based on a continuously fixed pressure and constant flow model of circulation in which MAP = CO × TPR. However, the power generator for the cardiovascular system, the heart, is pulsatile. In a pulsatile system, the forces opposing ventricular ejection of blood are more appropriately termed impedance.[11] Unfortunately, the data needed to quantify impedance require considerably more sophisticated measurement techniques than those needed to obtain data for the calculation of TPR. Despite the limitations, the simpler steady-state pressure-flow paradigm has

provided a useful conceptual framework for interpreting innumerable hemodynamic studies and will serve as the predominant model in this discussion.

As noted, in most persons with elevated arterial blood pressure, CO is within the normal range, whereas calculated resistance in absolute units is high. In hypertensive subjects with increased CO, which occurs in a substantial proportion of borderline hypertensive and obese persons,[12,13] the absolute resistance is normal. However, the resistance in relative terms is higher at any specified level of CO for those with higher arterial pressure.[14]

The importance of this apparently semantic argument is highlighted by hemodynamic data from studies on predominantly young men conducted in Ann Arbor.[15] Subjects were divided into two groups on the basis of percentage over ideal body weight (IBW). One group was <20% over IBW, whereas the other (obese) was >20% over IBW. The obese subjects were characterized by higher blood pressure (BP) and CO but similar values for peripheral resistance in comparison to lean participants. Furthermore, in the overweight men BP was positively correlated to CO, but BP was not related to TPR. However, in the lean normotensive men, TPR decreased appropriately as CO increased so that BP remained normal.[14] These data are consistent with previously reported information that CO is elevated similarly in overweight normotensive vs both borderline and overweight mild hypertensive subjects.[13] Therefore the fundamental hemodynamic mechanism of elevated BP in both the lean borderline hypertensive and overweight borderline-mild subjects is an inappropriately high resistance for the prevailing level of blood flow. Additional studies performed in our laboratory indicate that an increase in vascular α-adrenergic tone is an important factor in the relatively high resistance to blood flow in overweight people.[16] These studies were conducted in young men who, as will be discussed, may be the group at greatest relative hemodynamic risk from being overweight.

Second, CO remains essentially unchanged across the spectrum of hypertension, from mild to severe levels. Consequently, a successive increase in TPR is the predominant explanation for the progression of hypertension. Therefore one could argue that the progressive rise in TPR is an important component of the higher cardiovascular complication rate in more severely hypertensive patients.

Third, antihypertensive compounds that initially reduce CO, namely, diuretics and β-blockers, have not consistently afforded primary prevention against coronary events,[3-6] although exceptions have been noted.[17] These comments are not intended to repudiate either the longer-term hemodynamic effects of diuretics or b-blockers, which, in fact, include reduction of TPR,[18,19] or the beneficial effects of these compounds on stroke rate,[5,6] but rather to suggest that pharmacologic approaches to reducing ischemic heart disease may be more hemodynamically complex than simply reducing arterial pressure.

Table I. Seven recommendations for improving the outcome of coronary artery disease in hypertensive patients

Lower BP more
Treat BP longer
Reduce BP less
Multiple risk factor intervention
Avoid electrolyte imbalances
Minimize SNS and RAS activity
Decrease TPR and not CO

SNS = sympathetic nervous system; RAS = renin-angiotensin system.

Finally, a study of elderly men observed significantly lower cardiovascular mortality in overweight compared with lean hypertensive subjects. The lower absolute TPR in overweight hypertensive subjects was cited as one potential explanation for their more favorable cardiovascular outcome.[20]

Cardiac factors in determining the cardiovascular complication rate. If cardiovascular mortality were simply an inverse function of absolute TPR, then obese normotensive subjects would have the lowest cardiovascular complication rate, which is not the case.[21,22] However, there is substantial evidence that obesity, which is accompanied by lower absolute values for TPR at any given level of arterial pressure, is an independent risk factor for higher rather than lower cardiovascular complication rates.[23] Furthermore, borderline hypertension, which is characterized by relatively normal absolute values for TPR,[12,13] is associated with a substantial increase in cardiovascular complications despite the minimal elevation of blood pressure.[24,25]

Hemodynamically, borderline hypertension and obesity are both characterized by elevated absolute values for CO.[26] In other words, at any given level of afterload, which is roughly reflected by higher MAP, venous return or preload is also higher.[27-29] Consequently, the heart is exposed to the double burden of both increased preload (venous return) and afterload (arterial pressure).[29]

The double hemodynamic load in overweight patients may explain some of the excessive incidence of heart disease. In the Framingham Study, persons >20% over ideal weight, when compared with subjects <20% overweight, were at threefold higher risk for subsequent hypertension.[30] Moreover, obese sub-

Table II. Hemodynamic power in various patient subgroups

Data = mean ± SE	*Lean NT*	*Lean BHT*	*Obese*	*HT*
No.	236	129	70	39
Age	25 ± 1	26 ± 1	30 ± 1	40 ± 1
% > IBW	0 ± 1	4 ± 1	23 ± 1	15 ± 2
SAP	118 ± 1	132 ± 1	134 ± 12	150 ± 13
DAP	63 ± 1	73 ± 1	76 ± 1	85 ± 2
CO (L/min)	5.6 ± 0.1	6.7 ± 0.1	6.7 ± 0.2	5.8 ± 0.1
Power	74 ± 1	101 ± 3	103 ± 34	98 ± 3

Results of ANOVA: $> p < 0.05$; $= p > 0.05$

Age: HT > obese > BHT = NT
% IBW: Obese > HT > BHT > NT
SAP: HT > Obese = BHT > NT
DAP: HT > Obese = BHT > NT
CO: Obese = BHT > HT = NT
Power: Obese = BHT = HT > HT

SAP = systolic arterial pressure, mm Hg; HT = hypertensive; DAP = diastolic arterial pressure, mm Hg; lean <20% over IBW; obese ≥20% over IBW; BHT = borderline hypertensive; ANOVA = analysis of variance; power = CO (cm^3/min) × MAP (1333 dyne/cm^2) × 10^{-7} joules/dyne (cm) = joules/min.

jects were at approximately 10-fold higher risk for hypertensive cardiovascular disease (HCVD), which is defined as left ventricular hypertrophy by either chest radiography or electrocardiography.

Data from the Australian Heart Foundation Study attributed as much as 30% of hypertension in men and women between 25 and 64 years of age to being overweight.[31] However, within the subgroup of men less than 45 years old, as much as 60% of hypertension was explained by weight. Therefore from a hemodynamic viewpoint, overweight younger men may be at the greatest relative risk. Consequently, an analysis of hemodynamic data in this high risk subgroup, as will be discussed, may prove enlightening.

The potential importance of cardiac power. As previously noted, the incidence of HCVD in overweight subjects substantially exceeds that predicted from the higher rates of hypertension. Consequently, it is possible that in obesity the double cardiac burden of both increased preload and afterload offers a more satisfactory explanation than pressure levels alone for the excessive HCVD. A prerequisite for initial examination of this hypothesis is a quantitative expression of that dual cardiac load.

Preload or venous return is reflected quite precisely by CO, since over time venous return and CO must be equal. Afterload is approximated by higher MAP. In the constant pressure-flow model of the circulatory system, the power the heart generates to overcome its load equals the product of CO and MAP.[11] Therefore cardiac power reflects components of both preload and afterload. Cardiac power is also a more comprehensive term than the two more commonly used measures: stroke work and pressure-rate product. Stroke work does not account for the frequency (heart rate) of work, whereas pressure-rate product does not include stroke volume.

An index of cardiac power was calculated from baseline data obtained in supine volunteers who participated in hemodynamic studies conducted in the Hypertension Division at Ann Arbor. One adjustment was made in the constant pressure-flow model in the calculations. Since the left ventricle generates CO only during systole, calculated mean systolic arterial pressure rather than MAP was used in the cardiac power calculation. Because left atrial pressure data were unavailable, no adjustment was made for this variable in the computation. Thus cardiac (left ventricular) power[32] was determined by the product of CO, as measured by indocyanine green dye dilution, and mean systolic pressure, calculated from systolic and diastolic pressures measured directly from a brachial artery catheter. The results are summarized in Table II. As shown, cardiac power was substantially higher in lean borderline hypertensive and obese subjects compared with lean normotensive persons. In fact, power in these two conditions was virtually identical to levels calculated in older subjects with established essential hypertension.

Consequently, cardiac power rather than BP may serve as a more useful predictor of age-adjusted cardiac complications in borderline hypertension and obesity. This hypothesis requires confirmation but may provide a partial hemodynamic basis for the independent contributions of overweight to cardiovascular disease.[21] Indirect confirmation for the potential use of cardiac power is provided by data obtained in children from Muscatine, Iowa.[33] Children with BP levels in the upper quintile had a higher left ventricular mass index compared with their cohorts with BP levels in the lowest quintile. Within the upper quintile of BP, children with higher COs (greater cardiac power) had the highest values for left ventricular mass.

Vascular Factors (structural vascular abnormalities). In the development of hypertension in the spontaneously hypertensive rat, a progression of structural vascular changes occurs. In 6- to 8-week-old spontaneously hypertensive rats, capillary rarefaction is followed by functional arteriolar rarefaction at 12 to 14 weeks and finally structural arteriolar rarefaction at 16 to 18 weeks.[34] Similarly, capillary rarefaction

Table III. Known and postulated effects of the hypertensive process on the balance between myocardial oxygen supply and demand

Increased demand	*Decreased supply*
↑BP	↑HR
↑HR	Functional vascular changes
↑Contractility (early)	↓Response to hypoxia
	↓EDV
↑Cardiac power	↑Myogenic tone
↑LVMM	↑α-Tone
Increased Supply	Structural vascular changes
	Rarefaction
	↑Wall:lumen
↑DBP	Diastolic dysfunction
	Coronary atherosclerosis (accelerated by HTN)

HR = heart rate; DBP = diastolic blood pressure; EDV = ends diastolic volume; HTN = hypertension; LVMM = left ventricular muscle mass.

has been reported in borderline hypertensive humans;[35] evidence for arteriolar rarefaction has been observed in established human hypertensives.[36] Interestingly, in borderline hypertensive subjects, the degree of rarefaction was not significantly related to arterial pressure, but rather was inversely related to CO. In other words, borderline hypertensive patients with the highest CO displayed the greatest degree of capillary rarefaction.[35] In contrast, elevated BP induces medial hypertrophy, [35] which predominantly involves arteries and larger arterioles.[37]

Functional vascular abnormalities. One of the most widely reported and recognized abnormalities of the arterial circulation in hypertension is an impaired vasodilator response to ischemia.[38-40] The reduced vasodilator response to 10 minutes of regional ischemia partially reflects structural vascular changes.[38-40] However, hypertensive vessels may maintain higher tone under some conditions, in part through decreased sensitivity to hypoxemia or its metabolic consequences.[41] Enhanced vasodilator responses to both calcium channel blockade[42,43] (an index of myogenic tone) and α-receptor antagonists[44,45] (an index of vascular α-tone) comprise other well-documented functional abnormalities of hypertensive vessels. Explanations for these functional abnormalities are numerous, but agreement on specific mechanisms is not uniform. A hypothetic schematic depicting the causes and effects of vascular changes in the development and progression of hypertension is shown in Fig. 1.

Potential relationship of the structural and functional vascular changes to ischemic heart disease. Diminished coronary vasodilator reserve has been demonstrated in the hearts of hypertensive men and animals subjected to pressure overload from either systemic hypertension or aortic stenosis.[46] The impaired vasodilator reserve in hypertensive subjects likely reflects some of the functional and structural vascular changes previously noted. More specifically, vascular rarefaction and an increased wall-lumen ratio (concentric vascular hypertrophy) could provide a structural component to the diminished flow reserve. Rarefaction, even in the presence of normal total coronary flow levels, would increase the mean diffusion distance from individual capillaries to adjacent myocardial cells.[47] Thus the myocardial cells at greatest distance from nutrient supply would be at increased risk for ischemia. Impaired vasodilator responses to ischemia[41] would further exacerbate the effects of the structural and functional vascular changes. An increased vascular wall-lumen ratio,[37] although not documented in the coronary circulation,[48] would accentuate vascular responses to all vasoconstrictor stimuli.[37,38,49,50] In other words, when compared with a normal vessel, equivalent degrees of smooth muscle contraction in a vessel characterized by greater wall thickness in

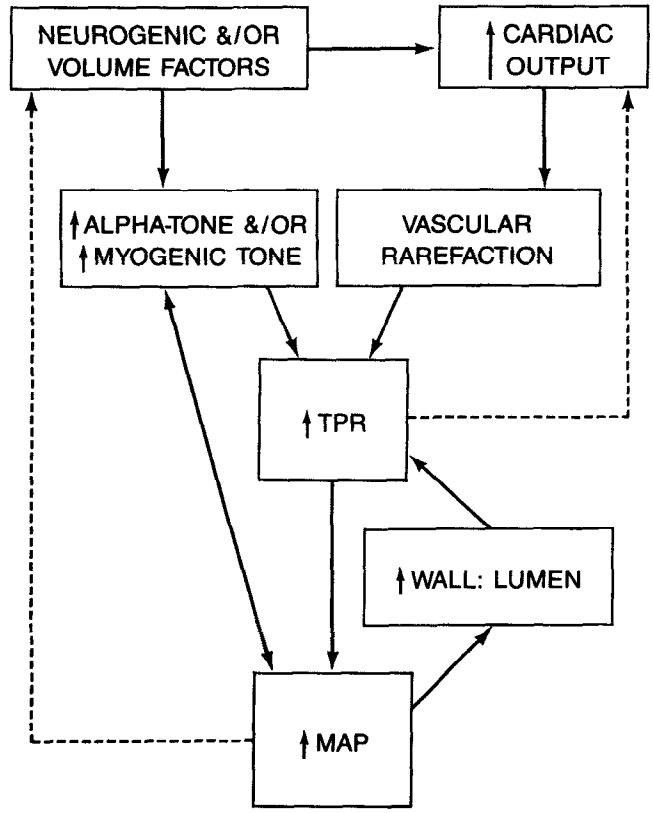

Fig. 1. Proposed causes and effects of vascular changes in hypertension.

relationship to luminal radius produce greater compromise of the lumen.[37] Since resistance varies inversely with the fourth power of the radius,[51] the increased wall-lumen ratio would enhance vascular resistance responses to all vasoactive compounds.[38] The enhanced vasoconstrictor responsiveness would include that reflecting impaired endothelium-dependent vasodilation in hypertension.[52] More specifically, the vasoconstrictor effects of several compounds, including thrombin, serotonin, and catecholamines acting as α_2-receptor agonists, are partially counterbalanced by endothelium-dependent vasodilation.[53-55]

The microvascular problems discussed previously would compound the adverse effects on myocardial perfusion of coronary macrovascular atherosclerosis, which is accelerated by hypertension. If the structural and functional abnormalities interact diabolically in the coronary circulation as postulated, then one can envision how these factors would, over time, produce ischemia-related events, including angina, infarction, arrhythmias, and cardiac decompensation. The multiple effects of the hypertensive process and the vascular changes in the balance between myocardial oxygen supply and demand are summarized in Table III. An extensive discussion of the separate risks of left ventricular hypertrophy exceeds the scope of this discussion, but the topic has been succinctly reviewed.[56]

CONCLUSION

The hemodynamic dysregulation that occurs in the development and progression of hypertension may contribute not only to elevated arterial blood pressure, but may also act in concert with the higher pressure levels to induce structural and functional cardiovascular changes. The anatomic and physiologic cardiovascular changes, which are not fully reversed by antihypertensive therapy, provide the substrate for subsequent complications. A greater understanding of the sequential hemodynamic pathophysiology of hypertension may permit the development of more effective treatment strategies. Although unproved, physiologically based treatment vs conventional approaches, which are targeted at correcting the underlying hemodynamic abnormalities in hypertension, may more effectively interrupt the sequence of events leading to cardiac morbidity and mortality.

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