Atherosclerosis Complicating Chronic Hypertension

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SUMMARY
The accelerating effect of hypertension on atherogenesis in the aorta and iliofemoral and coronary arteries is presented here as a graded function of elevated intraarterial pressure. Predilection of the abdominal aorta and iliofemoral arteries for atherosclerosis can be explained on the basis of pressure augmentation by reflected pressure pulse waves and the increase in hydrostatic pressure that is produced by standing. Wave reflection is intensified by vasoconstriction, which is a characteristic not only of hypertension but also occurs with upright posture. Standing also raises the hydrostatic pressure of blood in vessels below heart level. Coronary atherosclerosis seems likely to relate to the fact that the coronary vessels are located in an area of high pressure in the arterial system and that their intramyocardial branches are normally completely occluded during systole — a condition which could be accompanied by subtle differences in the pressure-volume characteristics of the epicardial vessels.
Evidence is presented from actuarial statistics, epidemiologic studies, and laboratory experiments to indicate that the level of arterial pressure has a measurable effect on the metabolism of arterial smooth muscle cells. Thus arterial pressure is viewed as having a metabolic determinant role in addition to its vital role in the circulation of blood.

Additional Indexing Words:
Cellular metabolism Arterial smooth muscle cells Arterial pressure

Although Dr. G. Lyman Duff's investigations into the genesis of atherosclerosis dealt primarily with the role of hyperlipidemia, he clearly recognized that other factors could well be important. Such has subsequently been proven to be the case and this 1973 Duff Lecture addresses itself to one, and perhaps the most important, of them — hypertension.

Hypertension and atherosclerosis are the two major diseases of the arterial system. They are intimately associated; hypertension begets atherosclerosis, and less frequently, atherosclerosis begets hypertension. On the one hand, hypertension causes premature death and disability by hastening the complications of atherosclerosis — heart attacks and strokes. On the other, atherosclerosis occasionally causes diastolic hypertension through development of renal arterial stenosis and frequently causes systolic hypertension by diminishing the elastic property of the aorta and large vessels.
Research efforts of the past 25 years have produced much enlightening information about both atherosclerosis and hypertension but have not begun to explain why hypertension plays such an important role in the pathogenesis of atherosclerosis and in its complications.

Evidence Relating Hypertension to Atherosclerosis
It is now incontestible that both clinical and experimental forms of hypertension are related to atherosclerosis. Actuarial studies of this relationship proved to be a milestone because they showed that with increasing levels of arterial pressure, beginning even in the so-called normal range, there was increasing mortality, and by 1959, when the Build and Blood Pressure Study appeared, it had become completely clear that the increased mortality results from arteriolar and arterial diseases. This supports Sir George Pickering's conclusion that hypertension is a quantitative deviation from the norm and suggests also (as will be detailed later) that intravascular

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pressure has a metabolic role in addition to its obvious importance in the circulation of blood.

Epidemiologic studies have shown that hypertension increases the risk of sudden death or of dying from coronary heart disease or stroke. It also increases intermittent claudication. These statistics could indicate that hypertension only promotes thrombotic complications of ordinarily occurring atherosclerotic lesions. However, the International Atherosclerotic Project found that at autopsy, hypertensives had a greater percentage of the intimal surface of aorta and of coronary and cerebral arteries affected by raised lesions than did normotensives. Thus, although hypertension may well predispose to thrombosis, it definitely accelerates atherogenesis. This acceleration has also been described in experimental animals when hypertension was superimposed on the stimulus of hyperlipidemia.

Effect of Antihypertensive Therapy on Complications of Atherosclerosis

At the present time there is no way of knowing whether good arterial pressure control with antihypertensive drugs has a decelerating effect on atherogenesis. Such information will be obtainable only when a simple, noninvasive method for detecting the presence of lesions in large arteries has been developed. There is, however, evidence indicating that therapy lessens the occurrence of strokes. The influence on myocardial infarction is less clear. The two Veterans Administration studies showed that for men with pretreatment diastolic pressures between 105 and 129 mm Hg, strokes occurred significantly less often in the treated patients than in the untreated but that there was no significant difference between the two groups with regard to myocardial infarction. Also, Beevers et al. who investigated the relationship in treated patients of the adequacy of arterial pressure control to strokes, myocardial infarction, and angina found that only the incidence of strokes was diminished in relation to the blood pressure reduction achieved by treatment and that myocardial infarction and angina occurred with equal frequency regardless of how well pressure was controlled. However, a report from a community study in Rochester, Minnesota, which involved about 1500 patients with ischemic heart disease, indicated that antihypertensive drug therapy reduced the occurrence of myocardial infarction.

Thus, the evidence to date does not show conclusively that treating moderately severe hypertension has a beneficial effect on all the complications of atherosclerosis, although it dramatically influences the arteriolar complications such as hypertensive encephalopathy, neuroretinopathy, congestive failure, and malignant nephrosclerosis. The finding that strokes occur less often with antihypertensive treatment does not necessarily mean that the complications of cerebral atherosclerosis are diminished; it may well reflect a lowered tendency of the microaneurysms typically found in hypertensives to rupture.

High Intravascular Pressure as a Cause of Atherosclerosis

While antihypertensive therapy has not been shown to effect a clear reduction of all atherosclerotic complications, it is indisputable that hypertension promotes development of atherosclerosis. Since hypertension is a hemodynamic abnormality, it is probable that hemodynamic factors are responsible for atherosclerosis, and perhaps also, its complications. Further, because in hypertension the entire systemic arterial bed is subjected to high pressure, the conclusion is inescapable that pressure itself, rather than other hemodynamic factors, is the primary determinant. Certainly, the circumstantial evidence is persuasive and bears repeating here.

The pulmonary artery pressure is normally low and atherosclerosis does not occur there except as a complication of longstanding pulmonary hypertension. However, in congenital coarctation of the aorta, lesions develop in the high pressure area proximal to the obstruction and are absent below the obstruction where pressure is low. A few persons with the left coronary originating from the low pressure pulmonary artery and the right coronary artery originating from the high pressure aorta have lived to middle age. At autopsy the right coronary artery is atherosclerotic while the left is free of lesions.

And finally, even in situations of marked hyperlipidemia, the veins are free of lesions yet localized phlebosclerosis occurs as a consequence of long-standing arteriovenous fistulae and veins of the hepatic portal system become sclerotic in portal hypertension. And phlebosclerosis is indistinguishable from fibrous lesions of arteries except that it has no lipid component.

Twenty-four years ago Moschowitz presented a convincing case for the causative role of high intravascular pressure in the pathogenesis of atherosclerosis, but the theory has received little attention recently. There is, however, work currently being done on other hemodynamic factors which Gessner reviewed. Gessner classifies the several theories concerning the hemodynamic determinants of atherogenesis under four headings: 1) flow separation, 2) turbulence related, 3) wall shear stress and 4) pressure related. They all, in one way or another, involve interaction of endothelium
with flowing blood. Even the pressure-related hypothesis does not require accompanying hypertension. Rather, it holds that atherosclerotic plaques develop as a response to endothelial injury in regions where relatively low pressure creates a suction and separates the endothelium from adjacent tissue. None of the theories take into consideration the fact that the entire wall of aorta and large arteries are continually involved in the events produced by contraction of the heart.

The foregoing discussion, although emphasizing the probable primacy of high intraarterial pressure, tells no more about possible mechanisms whereby it causes atherosclerosis than do the epidemiologic data. To attempt an insight into these, one must consider the pressure characteristics of the arterial system, how they are influenced by the arterial wall and modified in hypertension.

Some Characteristics of Arterial Pressure — Normal and Elevated

It is important to reemphasize here the fact, too often taken for granted, that the heart provides the energy for the circulation of blood. With each contraction the heart delivers about 70 ml of blood into a network system that is distensible and elastic, already contains a substantial volume from previous ejections, and has an outflow that, in comparison with inflow, is somewhat restricted. This sudden distension creates a pressure pulse (fig. 1). Left ventricular ejection rate is an important factor determining the speed of the upstroke, while the height of the systolic pressure depends on at least five variables — the speed of ejection, force of ejection, stroke volume, diastolic arterial volume, and elasticity of the aorta and proximal large branches. The level to which the pressure falls (diastolic pressure) depends to an extent on cardiac output and heart rate but is primarily determined by outflow resistance. In hypertension there is increased outflow resistance. Although some hypertension are characterized by increased cardiac output and normal resistance, arterial pressure still is elevated because resistance does not decrease as would normally occur under circumstances of increased flow. Thus although there are different combinations of cardiac output and peripheral resistance in the various types of hypertension, the basic fault is in the periphery.

The prime function of the aorta and its major proximal branches is to absorb some of the kinetic energy of each systolic thrust and distribute the force gradually during diastole to provide for diastolic flow. This is the function of elastic tissue. A rigid inelastic system has none of this property: each stroke volume produces a sharp rise in pressure and flow occurs only during systole (fig. 2). The normal elastic aorta absorbs some of this energy, dampens the pressure pulse, and by releasing the stored energy during diastole, promotes flow into the progressively narrowed arteries and arterioles. However, with aging, elastic tissue decreases and collagen increases; the aorta becomes more rigid, pulse dampening is diminished, and systolic hypertension results because of the decrease in aortic distensibility.

The function of distensibility can be expressed mathematically as the change in pressure with change in volume (dP/dV). An index of distensibility is ob-

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**Figure 1**

Aortic pressure pulses. See text for discussion of factors that determine the height of the pulse and its configuration.

**Figure 2**

Schematic representation of the energy-absorbing effect of distensible, elastic tube systems in contrast to the lack of pulse dampening by a rigid tube (reprinted from Folkow and Neil, with permission).
tained by using the formula: PP/SV (mm Hg/ml), where PP is pulse pressure and SV, stroke volume. The normal value found in our laboratory is 0.60 mm Hg/ml ± 0.19 (sd). As aortic rigidity increases the normal distensibility index is modified upward and systolic hypertension results.

Systolic hypertension can also reflect a large stroke volume with normal distensibility, as is often seen in labile hypertension in young people, or as an effect of aortic coarctation in which the dampening function is sharply diminished by the restricted size of the aortic compression chamber.40

These two points are exemplified by the data in table 1 taken from our ongoing study of the hemodynamics of hypertension. In both age groups of hypertensive patients (20–35 years and > 45 years) a pulse pressure of less than 60 mm Hg was associated with normal aortic distensibility; when it was greater than 60 mm Hg, the index was insignificantly increased in the younger age group, reflecting either an increased stroke volume or left ventricular ejection rate, but almost doubled in the older patients, presumably because of diminished elasticity with aging. Thus, a loss of elastic tissue and increased amounts of collagen beget hypertension just as hypertension begets the basic change that causes the loss of this function.

Pulse wave velocity is another circulatory characteristic that is largely determined by the arterial wall. With each cardiac cycle, the amount of blood ejected into the arterial system displaces an equal amount into the capillaries but three to four cycles are necessary before the blood of one stroke volume reaches the capillaries.37 In contrast, the pressure wave produced by each contraction travels in the arterial wall at a speed of 3 m/sec, and it becomes faster as arteries become more rigid (fig. 3).

The pulse wave is reflected at various sites where major branches originate and at the precapillary resistance vessels that act almost as a barrier to wave transmission.38 These reflected waves augment each primary wave and result in higher pressures in the lower aorta and distal branches (fig. 4). Further, the greater the peripheral vasoconstriction, the greater is wave reflection.

As will be detailed below, these arterial pressure and pulse wave characteristics may well be important determinants of aortic and iliofemoral atherosclerosis. (Cerebrovascular disease will not be discussed here because the application of these physiologic principles to that arterial bed seems less clear.)

**Aortic and Ilio Femoral Atherosclerosis**

The predilection of the abdominal aorta and iliofemoral arteries to development of atherosclerosis has long been recognized but never explained. If one accepts the premise that high intraarterial pressure by itself affects the function of cellular components of aortic and arterial walls in ways that promote atherogenesis, a plausible explanation begins to emerge.

In the abdominal aorta, wave reflection is such that there are brief moments during each cardiac cycle in which arterial pressure in this portion of the vessel is higher than pressure in the thoracic aorta (fig. 4).37 And this circumstance also obtains in iliac and femoral arteries. In the presence of hypertension, wave reflection, would, of course, amplify the already increased radial and longitudinal stress; however, the vasoconstriction of hypertension would serve to intensify

**Table 1**

<table>
<thead>
<tr>
<th>Pulse pressure (mm Hg)</th>
<th>PP/SV (mm Hg/ml)</th>
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<tr>
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<td>Age (yr)</td>
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<td>20–35</td>
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<td>&lt;60</td>
<td>0.67</td>
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<tr>
<td>&gt;60</td>
<td>0.75</td>
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<td>∆%</td>
<td>12</td>
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*PP/SV mm Hg/ml.

**Figure 3**

Simultaneously recorded central and radial pulses in a normal arterial system and one with diminished distensibility. In the latter condition, pulse wave velocity is increased so that time elapsed before the appearance of the peripheral pulse is shortened (from Wiggers,37 with permission).
wave reflection and thus raise intraarterial pressure proportionately higher. The effect of vasoconstriction on the pressure pulse in the femoral artery is presented schematically in figure 5. When peripheral vessels are widely dilated (right panel), there is no wave reflection; the proximal-distal pressure gradient is always positive, and because of this, there is only forward flow. In contrast, with vasoconstriction there is wave reflection (left panel); the pressure differential along the artery is not only diminished but also there are transient periods when distal pressure is higher than that proximally so the gradient is even reversed and backflow results.38

It seems likely, also, that upright posture plays an
important role in development of aortic and iliofemoral atherosclerosis as suggested by Wilens in 1951. With standing there is venous pooling and the resultant decrease in cardiac output reduces systolic pressure slightly. This stimulates carotid sinus and aortic arch baroreceptors and reflex vasoconstriction results. This, in turn, would enhance wave reflection in the abdominal aorta and iliofemoral vessels which would add to the hydrostatic pressure already substantially increased by gravitational stress. In this regard, it would be interesting to know whether tall people, who must have a greater gravitational increase in hydrostatic pressure on standing than short people, have more aortic and iliofemoral atherosclerosis, all other factors being equal.

Thus if one accepts the premise that intraarterial pressure is a determinant of cellular activities in the arterial wall, atherosclerosis will be greatest where pressure is normally the highest — the abdominal aorta and iliofemoral arteries. Accompanying hypertension would increase the normal influence of intraarterial pressure. The effect of gravity on intraarterial pressure would explain why atherosclerosis is much greater in the arteries of the lower extremities than in those of the upper.

**Coronary Atherosclerosis**

When considering the physiologic determinants of coronary atherosclerosis, it is immediately apparent that the heart is different from all other organs because it is self-perfused. This circumstance must have a major influence on coronary pressure-flow relationships, but at the present time, although there is a large amount of information about the flow, there is little about pressure.44, 45

There are at least two features of the coronary circulation that are unique and deserve consideration here. When the body is horizontal, the coronary arterial system is situated in the highest pressure area of all vascular beds of the body. The epicardial vessels course along the surface of the heart and send branches at nearly right angles into the myocardium; unlike any other vessels in the body, these branches become occluded during systole.

Although there has been little study of pressure-flow relationships in the coronary circulation (most contemporary emphasis being on flow), reference to a standard diagram (fig. 6) brings out some facts that seem important in regard to the physiologic determinants of coronary arterial disease. The diagram indicates that during isometric contraction when aortic pressure is relatively low and myocardial branches are completely occluded, there is even a slight backflow and this probably accounts for the rise in coronary artery pressure during that part of the cardiac cycle.

During the ejection phase as aortic pressure rises, coronary pressure rises also and there is a brief moment of forward flow, but this subsides again as aortic pressure falls, even though coronary pressure is nearly stable. During diastole, the myocardial vessels can fill and the major component of flow occurs at this time. Presumably the delayed fall in coronary arterial pressure during diastole results from the normal delayed fall in intraaortic pressure as well as from this relatively large blood flow that must be accommodated.

Hypertension is often accompanied not only by cardiac hypertrophy but also by prolonged systolic ejection. The former carries with it increased demands for myocardial flow while the latter shortens diastole, lessens the time available for myocardial perfusion, and probably results in a longer period of time that the coronary vessels are subjected to increased radial and longitudinal stress. It has been shown in hypertensive patients that coronary resistance is raised, but there is obviously great need for more information about pressure-flow relationships in this vascular bed. The possibility that arterial wave reflection may augment pressure in the coronary arteries, as it does in the aorta and iliofemoral vessels, has not been examined. However, it seems probable that the critical hemodynamic factors in the coronary arterial disease of hypertensive persons relate to the position of these vessels in a normally high pressure area, to prolonged systolic ejection with decreased time for diastolic filling and thus coronary flow, and to the possibility that a high level of intracoronary pressure may be prolonged.

There is also great need for information concerning coronary pressure-flow relationships during antihypertensive drug therapy. One can only guess how

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**Figure 6**

*Simultaneous recordings of flow in the left coronary artery (below) and pressure in the left ventricle, a peripheral branch of the left coronary artery, and the aorta (above) during one cardiac cycle.*

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These relationships might be modified if hypertension were treated by a drug that caused vasodilatation and compensatory increase in cardiac output as opposed to one that reduced cardiac output. In this regard, the results of the Veterans Administration studies of treating hypertension showed that death rate from coronary artery disease was not significantly affected.\textsuperscript{18, 19} If subsequent studies support this finding they would suggest that either the events set in motion by hypertension are not altered by treatment or that the stimulus still remains. If coronary heart disease is caused, in part, by arterial occlusion during systole and if the duration of occlusion is prolonged by hypertrophy, we must seriously look at the effects of antihypertensive drug treatment on cardiac hypertrophy. Does adequate treatment result in appropriate disuse atrophy of hypertrophied myocardium? This we do not know.

The ten-year mortality figures in the Peoples Gas Co. study\textsuperscript{19} indicates that a heart rate equal to or greater than 80 beats per minute compared with lower rates is a risk factor for sudden death or death from coronary heart disease. The fact that tachycardia does not seem to be a factor in cerebral atherosclerosis suggests that its primary effects are on coronary pressure-flow relationships. Tachycardia shortens diastole and therefore lessens the time available for coronary perfusion and could lead to subtle pressure-volume changes in the coronary bed. This would be particularly true if the tachycardia were associated with an increased cardiac output which increases demand for myocardial blood flow. Further, if both stroke volume and myocardial contractility were increased, as is characteristic of a hyperdynamic circulation with or without hypertension, the stress on the aorta and large vessels would also be increased because the larger volume would be ejected in a shorter period of time.

Arterial Pressure as a Metabolic Determinant

The foregoing discussion has presented the evidence for hypertension as a risk factor in development of atherosclerosis and has described the pressure characteristics of the circulation that may be responsible for the predilection of the coronary arteries, the aorta, and the iliofemoral arteries for atherosclerosis. But it has not been explained why high arterial pressure has such an effect on vessel walls. One possible explanation is that pressure, per se, has a profound influence on the multifunctional smooth muscle cells of the aortic and arterial walls. There is substantial evidence to suggest such an effect and teleologically the conclusion seems valid.

The function of aortic elastic tissue is to serve as an energy reservoir during systole and that of collagen is to provide strength. It would not be surprising, then, if under the stress of increased intraarterial pressure collagen production was increased in order to strengthen vessel walls. But it would seem of equal importance biologically for elastin production to increase in order to absorb the increased pressure of each systolic thrust. Apparently this does not occur, at least in an orderly fashion. Further, hypertension usually develops in the fourth or fifth decade and this is a time when age changes in fibrous protein production are already occurring. With aging, mucopolysaccharide production is increased but not elastin\textsuperscript{17} and the elastic fibers become broken and frayed.

The circumstantial evidence in support of the thesis that arterial pressure — both normal and elevated — has a metabolic effect came originally from actuarial statistics\textsuperscript{2} which showed a quantitative relationship between arterial pressure and mortality. Subsequently, both the Framingham Study\textsuperscript{6} and the Pooling Project\textsuperscript{9} have shown a graded influence of arterial pressure on death from myocardial infarction and stroke. Animal investigations have indicated that occurrence of atherosclerotic lesions in rabbits, rats, monkeys, and dogs fed atherogenic diets and made hypertensive is quantitatively related to the height of arterial pressure.\textsuperscript{13, 15-17} Since the production of raised lesions is a function of arterial smooth muscle cells,\textsuperscript{48, 49} both the clinical and experimental data suggest that arterial pressure, per se, is one of the factors which determines their metabolic activity. This conclusion is supported by the studies of Wolinsky,\textsuperscript{50, 51} who found production of fibrous proteins by rat aorta was positively correlated with calculated wall tension (which is partly determined by intraarterial pressure). In dogs with thoracic aortic coarctation, Hollander et al.\textsuperscript{52, 53} reported that in the vessel wall above the coarctation, collagen and elastin contents were increased but below the constriction these components were normal.

The relationship between pressure and cholesterol synthesis is less clear than that between pressure and fibrous protein production. Daly and Deming\textsuperscript{16, 54, 55} found that cholesterol synthesis was increased in the aortic wall of hypertensive rats and positively correlated with the arterial pressure level. However, Lehner et al.\textsuperscript{56} could not show this effect in hypertensive monkeys and suggested that the increases observed in rats were a function of age and reflected the medial hypertrophy that hypertension produced in growing animals. There is clearly a need for further studies. Not only would they improve our understanding of atherogenesis but they also could provide some insight into the therapy of hypertension by indicating whether reduction of arterial pressure to strictly normal levels, rather than effecting only
modest reductions, might be more effective in controlling atherogenesis. In this regard, Wolinsky has shown that “cure” of hypertension in rats by removal of a renal artery clip did not affect the thoracic aortic content of collagen and elastin although levels of non-collagenous, alkali-soluble proteins did return to normal. If future studies provide similar evidence this would make a case for early treatment of hypertension and the maintenance of arterial pressure at normal levels at all times.

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