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Invited Review Article

Elastic Properties and Windkessel Function of the Human Aorta

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Summary. **An understanding of the role of the aortic elastic properties indicates their relevance at several sites of cardiovascular function. Acting as an elastic buffering chamber behind the heart (the Windkessel function), the aorta and some of the proximal large vessels store about 50% of the left ventricular stroke volume during systole. In diastole, the elastic forces of the aortic wall forward this 50% of the volume to the peripheral circulation, thus creating a nearly continuous peripheral blood flow. This systolic-diastolic interplay represents the *Windkessel function,* which has an influence not only on the peripheral circulation but also on the heart, resulting in a reduction of left ventricular afterload and improvement in coronary blood flow and left ventricular relaxation. The elastic resistance (or stiffness), which the aorta sets against its systolic distention, increases with aging, with an increase in blood pressure, and with pathological changes such as atherosclerosis. This increased stiffness leads to an increase in systolic blood pressure and a decrease in diastolic blood pressure at any given mean pressure, an increase in systolic blood velocity, an increase in left ventricular afterload, and a decrease in subendocardial blood supply during diastole, and must be considered a major pathophysiological factor, for example, in systolic hypertension. The elastic properties of the aortic Windkessel can be assessed in vivo in humans in several ways, most easily by measuring the pulse wave velocity along the aorta. The higher this velocity, the higher the elastic resistance, that is, the stiffness. Other methods depend on assessment of the ratio between pulse pressure and aortic volume changes ($\Delta P/\Delta V$), which can be assessed noninvasively by ultrasonic or tomographic methods. All assessments of vessel stiffness have to take into account the direct effect of current blood pressure, and thus judgements about influences of interventions rely on an unchanged blood pressure. Alternatively, to derive the "intrinsic" stiffness of the aortic wall one has to correct for the effect of the blood pressure present. Recently reports about pharmacologic influences on the elastic properties of the aorta have emerged in the literature. Angiotensin-converting enzyme (ACE) inhibitors and nitric oxide (NO) donors seem to directly reduce the elastic resistance of the aorta. This effect, in addition to other effects on blood pressure and the peripheral circulation, could have major clinical relevance as an additional mechanism for unloading the left ventricle, improving coronary circulation, and reducing the pulsatile stress of the arterial system.**

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The role played by the aorta and large arteries in the physiology and pathophysiology is dual, incorporating both conduit and buffering functions (Safar et al., 1990). Arteries are not stiff tubes but are characterized by elastic properties. Elastic arteries are characterized by a high percentage of elastic fibers—up to 40% of the wall in the thoracic aorta, but this percentage decreases progressively as the vessels approach the periphery (Bader, 1983). Even within the human aorta, increasing stiffness from the proximal to the more distal parts has been documented in vivo (Mohiaddin et al., 1989).

With increasing intraluminal pressure, elastic vessels are distended, enabling them to act as buffering chambers (Bader, 1983). The distensibility of the aorta and other vessels is diminished when the intraluminal pressure is high and/or when the stiffness of the arteries increases in the course of aging and/or under pathophysiologic conditions. These changes have been attributed to structural changes in the aortic wall, alterations in blood flow in the vasa vasorum, and passive stretching of the aorta under high blood pressure (Stratos et al, 1992).

During the last few years, the elastic properties of the peripheral arteries have garnered increasing scientific attention (e.g., Simon et al., 1985, 1991; Safar et al., 1989, 1990, 1992; Perret et al., 1991; de Cesaris et al., 1992). In contrast to the great interest the elastic properties of the aorta had once received in classic physiology, in recent clinical presentations this topic has only occasionally been adequately acknowledged (O'Rourke, 1990; Opie, 1992). This seems to be due to confusion in nomenclature and difficulties in understanding the underlying physiologic and physical principles. It is the aim of this review to summarize some of the relevant knowledge on the aortic elastic properties.

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General Considerations of the Windkessel Function

During systole the left ventricle ejects a stroke volume of about 60–100 ml into the aorta and arterial system. Approximately 50% of the stroke volume is directly forwarded to the peripheral circulation (Figure 1). Peripheral resistance and elastic extension of the aortic wall are responsible for storage of the other 50% of the stroke volume, the storage volume (Bader, 1983). During diastole the aortic valve is closed and there is no further blood ejection. With a fall in aortic pressure, the aorta recoils slowly and the elastic forces of the aorta press the storage volume into the periphery of the circulation (Figure 1). Thus during diastole as well, pressure and blood flow are maintained and a nearly continuous peripheral flow of blood results in spite of the noncontinuous, rhythmic actions of the heart. Weber, in 1827, baptized this elastic function of the aorta, the *Windkessel* (Wiggers, 1962; Wezler, 1980). A *Windkessel* was an air- (top) and water- (bottom) filled reservoir similar to that behind the pump of an old-fashioned fire hose; its purpose was to transform the rhythmic water output of the plunger strokes into an almost continuous waterjet. Frank then developed the first *Windkessel models/theories* (1899, 1920) to describe the elastic storage effects of the aorta quantitatively. In modern physiology the Windkessel function is more a model for a plastic conception and didactic presentation of functional principles than a quantitative description of the physiologic events (Gebert, 1987).

One other mechanism important for maintenance of a relatively high diastolic pressure and blood flow should be mentioned here: In a healthy organism, the pulse wave velocity of the aorta and large vessels is

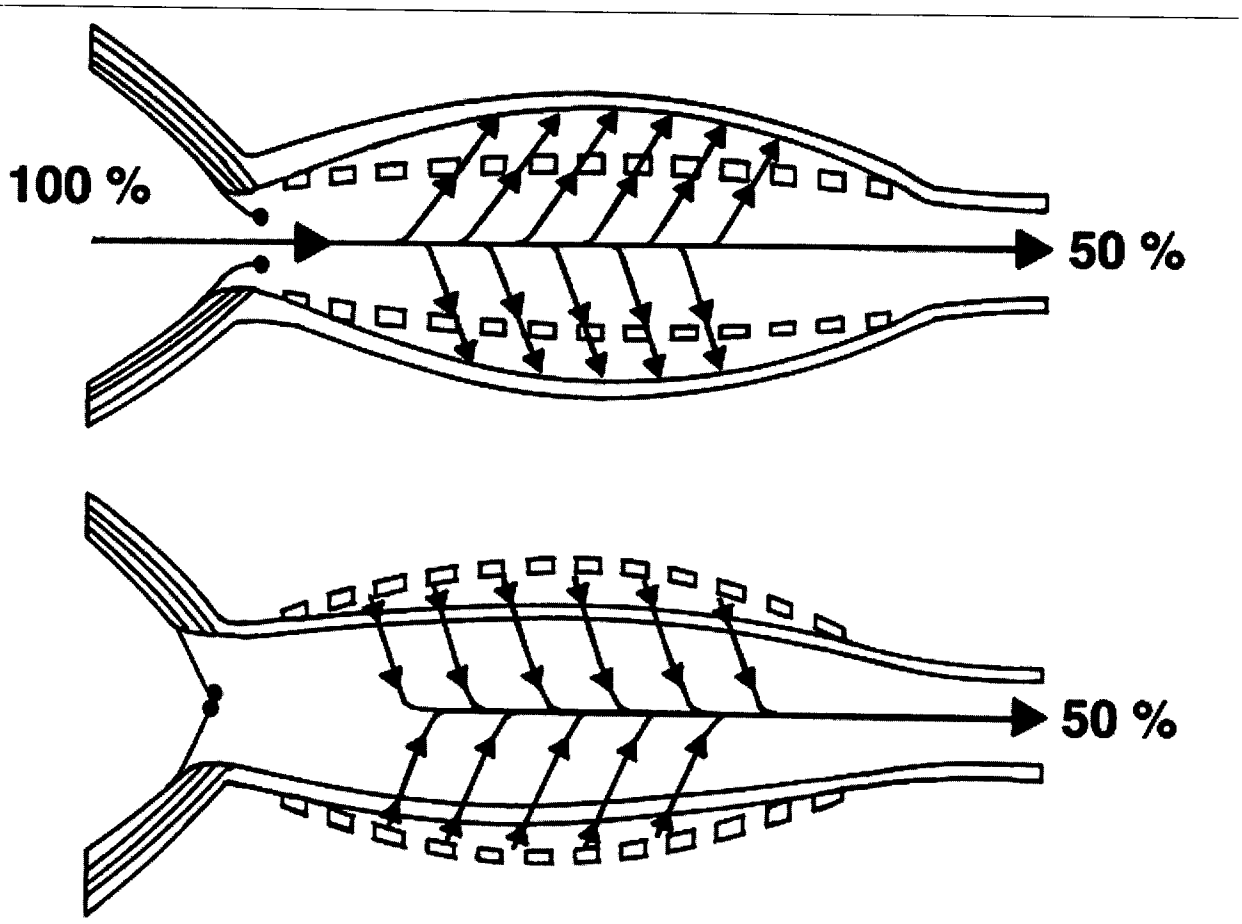

Fig. 1. *Windkessel function of the aorta. Upper panel: During systole the ventricle (left) ejects the stroke volume (100%) into the aorta; around 50% of the volume is directly forwarded into the peripherial circulation (right), and the other 50% leads to an extension of the aortic wall and is stored (storage volume). The energy needed to extend the wall is then available in diastole. Lower panel: During diastole the aorta passively contracts due to its elastic properties, and, utilizing the energy stored during systole, the other 50% of the stroke volume is forwarded into the peripheral circulation (including the coronary system). The rhythmic pulsations of intravascular volume, induced by the rhythmic actions of the heart, are buffered and converted into an almost continuous peripheral blood flow by these elastic properties of the aorta.*

relatively slow. When this wave is reflected in the peripheral circulation, it returns to the ascending aorta during early diastole, inducing the dicrotic wave (O'Rourke, 1990). This mechanism supports the elastic function of the aorta. It should also be noted that this second increase in pressure is dampened by the Windkessel function. For a detailed review of important aspects of wave reflections, refer to O'Rourke (1990).

The Windkessel function depends on the *elasticity* of the aorta (the word *elastic* is derived from the passive aorist form *elasthen* of the Greek verb *elauno*, which means "to drive on"). Physics defines deformable materials as elastic when after discontinuation of an external force they readopt their original shape. Any elastic body can store energy without loss of energy (Gobrecht, 1974).

During one heart action, the kinetic energy of the ejected stroke volume is first transformed into potential energy within the distended aortic wall. This stored potential energy is then reconverted into kinetic energy during diastole, when the aorta slowly recoils. Thus, in spite of the diastolic pauses of the heart, the column of blood within the peripheral arteries does not come to a diastolic stop and blood pressure does not drop to zero, as would happen in a system of stiff tubes.

Concepts of Elasticity, Stiffness, and Compliance

The elastic properties of the aorta incorporate both the property of dilating by increasing pressure *and* the property of recoiling slowly to its initial shape when blood pressure falls. *Elastic resistance* (= *elastance*), resembling *stiffness*, describes the resistance that the aorta sets against its distention when an additional volume is injected and the intraluminar pressure increases. Since there is a hysteresis in the pressure volume curve of the aorta, this definition contains some simplification. The inverse of stiffness is *compliance*, which describes the ease with which the aorta expands during systole. In this review the terms *elastic resistance* and *stiffness* are used preferably.

From a physical point of view, the change in volume induced by left ventricular blood ejection is the primary and independent variable. This change in volume causes an increase in pressure as the secondary and dependent variable. In physical equations it is usual to have the dependent variable in the numerator and the independent variable in the denominator. Consequently, $\Delta P/\Delta V$, indicating the elastic resistance or stiffness of the aorta, is the correct description of the causal relationship between the two variables. In addition, there are other physiologic arguments (O'Rourke, 1990), and preference for the term *stiffness* also takes into account the ambiguous use of the term *compliance* in medical science (e.g., compliance in relation to drug intake).

In physics, the elastic resistance of materials is characterized by the elastic modulus (= Young's modulus), E. E is the constant of a material, characterizing the resistance it sets against a deforming force; for example, the E of rubber is ~10 and that of steel is ~2,000,000 kp/cm^2 (Gobrecht, 1974). E is measured as the relation between the force applied and the distension achieved. To derive E of the aorta, the thickness of the arterial wall would have to be taken into account. According to Frank, the *coefficient of volume elasticity*, which is identical to the elastic resistance (= elastance), is defined as E′ (Wezler, 1980). In the human circulation we can assess E′ of the aorta or of other vessels from the changes in pulse pressure, that is, the difference between systolic and diastolic blood pressure (ΔP), related to the corresponding changes in volume (ΔV):

$$E' = \Delta P/\Delta V. \quad (1)$$

Compliance (C) can be regarded as the volume distensibility of a vessel, for example, the aorta, and is the reciprocal of elastic resistance:

$$C = 1/E' = \Delta V/\Delta P. \quad (2)$$

Relevance of the Aortic Windkessel Function

Windkessel function reduces the afterload

Theoretically, with complete abolition of the Windkessel function an exclusively systolic blood flow through the aorta would have to maintain the peripheral blood supply. For that to occur, the velocity of the systolic bloodstream would have to be increased by an increase in systolic blood pressure, but the diastolic pressure would drop to zero. Under clinical conditions, a deterioration in the Windkessel function consequent on stiffening of the aorta leads to a more or less pronounced increase in systolic blood pressure and a decrease in diastolic blood pressure at any given value of the mean arterial pressure. The systolic blood pressure is a major factor in left ventricular afterload.

One further consequence of stiffening of the aorta is increased pulse wave velocity. Thus, the peripheral reflection wave—usually located in early diastole—is shifted into late systole, boosting systolic blood pressure and afterload (O'Rourke, 1990; Simon et al, 1991). In addition, as the aortic blood slows (or stops) during diastole, the heart not only has to accelerate the blood mass of the actual stroke volume to the final flow speed, but also has to accelerate the blood mass within the aorta and arterial system. Thus an increase in the acceleration work of the heart will occur with

a decrease in the Windkessel function. The important contributions of all these mechanisms to a normal Windkessel function in reducing left ventricular afterload and vice versa are thus seen. The finding of a relationship between arterial stiffness and left ventricular hypertrophy (Darne et al., 1989) confirms the clinical relevance of this mechanism.

Windkessel function improves relaxation of the left ventricle

Ventricular relaxation, as characterized by the isovolumetric relaxation period (IRP) of the left ventricle, has recently been studied in humans aged 34–87 years (Ochi et al., 1991). Relaxation was prolonged with increasing aortic elastic resistance. Prolongation of IRP was also related to prominent tidal waves in the carotid pulse. These authors suggest that impaired left ventricular relaxation in patients with various cardiac diseases may be improved by pharmacologic adjustment of aortic elastic properties (Ochi et al., 1991).

Windkessel function improves coronary blood flow

In a recently published experimental study in dogs, stiffness of the aorta was increased by bandaging, which led to an expected increase in systolic blood pressure and a decrease in diastolic blood pressure (Watanabe, 1993). Subendocardial blood flow was distinctly decreased by this procedure, in spite of an increase in mean coronary flow, and it was shown that a chronic increase in aortic stiffness reduced transmural myocardial perfusion and aggravated subendocardial ischemia in the presence of coronary stenoses. The decreased diastolic blood pressure accompanying a stiff aorta was held to be responsible because subendocardial blood flow mainly depends on diastolic blood flow (Watanabe, 1993).

Since the blood flow during diastole is strongly dependent on the Windkessel function, it is conceivable that this physiologic principle has a direct influence on the blood flow in those parts of the left ventricle at greatest risk for ischemia, that is, the subendocardium.

Effect of the Windkessel function on peripheral arteries

A deterioration of the Windkessel function per se augments pulse pressure. That change will increase diastolic-systolic expansion in the peripheral arteries and maximal blood velocity at the vessel walls during systole. The ensuing pulsatile stress will promote development of vascular damage and arteriosclerosis (Fry, 1973; O'Rourke, 1982; Spence, 1983; Nichols and O'Rourke, 1990).

Which Variables Influence Aortic Elastic Properties?

Age and blood pressure

Arterial stiffness increases with increasing blood pressure because as the distending pressure rises, a greater proportion of the load is borne by the less extensible collagenous tissue than by elastic fibers of the aortic wall (Bergel, 1961; Learoyd and Tayler, 1966; Bader, 1967, 1983; Simon et al., 1991).

In vivo the increase in aortic stiffness was observed with aging and increased blood pressure by Bramwell and colleagues (1922, 1923) and was extensively evaluated by Böger and Wezler (1935, 1936, 1939). The age-related increase in elastic resistance was confirmed by studies using nuclear magnetic resonance (NMR) techniques in humans (Mohiaddin et al., 1989). In older studies, however, age and blood pressure dependencies were mixed. Schimmler (1965a,b) separated these effects and found aortic stiffness to be dependent on both age *and* blood pressure. Both variables were found to be more or less additive (Figure 2).

Hypertension also accelerates the effects of age on the rigidity of the arterial wall (Isnard et al., 1989). The increase in aortic stiffness with age is less apparent in populations with a low incidence of hypertension (Avolio et al., 1985), but it had also been found in societies where atherosclerosis is uncommon (O'Rourke, 1990). A recent study in normotensive, rigorously screened volunteers demonstrated an age-associated increase in aortic stiffness (Vaitkevicius et al., 1993). The large range of arterial stiffness at any one age can be explained at least in part by the effects of different blood pressures (see Figure 2).

Gender

Laogun and Gosling (1982) have demonstrated a clear dependence of aortic elastic properties on gender in vivo in humans. From birth to the age of about 10 years, both sexes had approximately the same values. In age groups between 20 and 50 years, elastic resistance in females was lower than in males. After menopause, these differences in sex were no longer observable. The sex differences were also evident when a blood pressure-independent index was used (Lehmann et al., 1993a).

Vascular diseases

Various diseases, such as atherosclerosis (Mohiaddin et al., 1989; Dart et al., 1991; Lehmann and Gosling, 1991; Athanassopoulos et al., 1994), diabetes mellitus (Lehmann et al., 1992b), familial hypercholesterolemia (Lehmann et al., 1992c,d), growth hormone deficiency (Lehmann et al., 1993b), generalized abnormalities of connective tissues and the Marfan syndrome (Handler et al., 1985; Hirata et al., 1991), and advanced renal failure (London et al., 1990, and

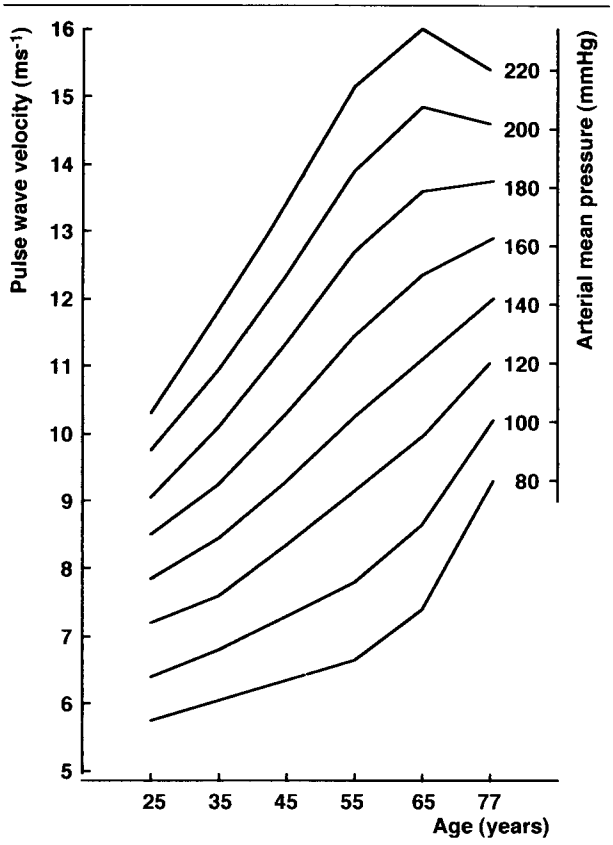

Fig. 2. *Relationship between the pulse wave velocity along the aorta, age (abscissa), and arterial mean pressures (from 80 to 220 mmHg). The underlying data were derived from 2500 patients (modified from Schimmler, 1965a). The velocity of the pulse wave correlates directly with the stiffness of the aorta.*

1992), are all associated with changes in aortic elastic properties, mostly with an increase in stiffness. Under pathophysiologic conditions, an accumulation of smooth muscle cells, calcium, and connective tissue, or a decrease in and/or an abnormal elastin, can be considered to be the underlying pathophysiologic cause for deterioration of the elastic properties of the aorta.

Pathophysiology of the Windkessel Function

With increasing age and under pathologic conditions such as hypertension, etc., the stiffness of the aorta is increased due to a loss of elastic fibers and an increase in collagen tissue (Bader, 1983). As a physiologic consequence of the reduction of the buffering function, the systolic blood pressure increases and diastolic blood pressure decreases at any given value of mean arterial pressure (O'Rourke, 1990). It is now increasingly recognized that isolated systolic hypertension is a most important indicator and/or contributor to cardiovascular morbidity and mortality (Kannel et al., 1981, 1986; Zanchetti et al., 1993). Development of isolated systolic hypertension is due to an increased stiffness of the Windkessel and much less on pathophysiology of the peripheral circulation, although the peripheral arteries have been shown to have reduced compliance under these conditions. In addition to the (central) Windkessel mechanism, increased arterial stiffness causes reflection waves from the periphery to return during systole, and thus to further augment the systolic pressure wave (O'Rourke, 1990).

Clinical Consequences of the Increase in Elastic Resistance (Stiffness) of the Aortic Windkessel

The pathophysiologic consequences of this have been discussed earlier. Clinically, an increase in stiffness of the aorta will lead to

1. An increase in systolic and a decrease in diastolic blood pressure, in pulse pressure, and in systolic blood velocity
2. An increase in left ventricular afterload (via various mechanisms)
3. A reduction in subendocardial coronary blood supply during diastole

There are only a few studies that relate aortic stiffness to strong (such as death) or weaker (such as stroke, myocardial infarction, etc.) endpoints. Therefore, at present the conclusion that stiffness indicates an increased risk is predominantly by analogy. It is based on results from the Tecumseh study (Gudbrandsson et al., 1992), on studies of populations with different nutritional habits (Hamazaki et al., 1988; Walhquist et al., 1989) and of systolic hypertension (Zanchetti et al., 1993). Additional strong arguments can be found in a study by Darne et al. (1989); these authors found the pulsatile component of blood pressure (pulse pressure) to be a possible risk factor (indicator?) independent of arterial mean pressure.

Studies in patients with isolated systolic hypertension (which can be regarded as an indicator of loss of the Windkessel function) clearly have shown that this disease has a major impact on death and morbidity (Emeriau, 1993; Zanchetti et al., 1993). On the other hand, studies on interventions to lower systolic blood pressure clearly showed a significant prognostic improvement (SHEP, 1991). The aortic elastic properties should at least have been passively improved by the reduction in intravascular pressure, but with some drugs there may even have been direct effects on aortic stiffness.

Assessment of the Windkessel Function In Vivo in Humans

Any direct method for measuring aortic elastic properties would require a system that is capable of measuring the diastolic-systolic changes in the pressure (ΔP) and luminal volume (ΔV) along the full length of the aorta (Handler et al., 1985), provided that the mechanical characteristics of the vessel are constant. Accurate measurement of aortic pressure can only be obtained by direct catheterization. A major problem with measuring blood pressure noninvasively at a given appropriate site is amplification of pulse pressure along the arterial tree. On the other hand, conventional measurement of brachial artery blood pressure under certain pathophysiologic conditions may underestimate pulse pressure (London et al., 1992). Indirect measurements at strictly standardized sites give estimates, which in clinical practice frequently must suffice.

For assessment of volume changes, several methodologies are available. The aorta can be surveyed with two-dimensional ultrasound, x-ray, or nuclear magnetic resonance (NMR) methods. Transesophageal echocardiography allows fairly accurate measurement of the aortic diameter and its diastolic-systolic variations; combination with pressure measurements by tonometry allows a direct assessment of regional aortic compliance (Slama et al., 1992). By ultrasonic measurement of aortic diameters, aortic elasticity can be obtained at given sites, but not along the complete aorta. When patients are to be followed up, relocation of the exact point of the previous insonation may prove difficult (Lehmann and Gosling, 1991). Furthermore, focal lesions in an arteriosclerotic aorta and distensibility evaluated at that specific site could greatly differ from a lesion-free area and vice versa, further compounding the difficulties in follow-up, especially in therapeutic studies (Lehmann and Gosling, 1991; Lehmann et al., 1992a).

Elastic resistance of the aorta can also be calculated from the relationship between pulse pressure and aortic storage volume. It is easily understood that the higher the E′, the greater the pulse pressure. On the other hand, the lower the E′, the higher the corresponding storage volume (Randall et al., 1986). A method to calculate E′ from the relationship between pulse pressure and storage volume of the Windkessel has recently been published (Breithaupt et al., 1992a). This method depends on measurement of blood pressure, stroke volume (Breithaupt et al., 1990), and systolic/diastolic time intervals.

One other approach is to estimate elastic resistance from the ratio between pulse pressure and stroke volume (Ferguson and Randall, 1986; Gudbrandsson et al., 1992). This method, however, negates the fundamental concept of the Windkessel function, which is storage of a fraction of the stroke volume within the distended aortic wall. Nevertheless, this parameter has been used clinically.

Alternate assessments of elasticity of the aorta depend on pulse wave velocity and analyses of the arterial pulse wave contour. These give an overall index of aortic elastic properties and do not focus on a localized arterial site where E′ might be changed (Breithaupt et al., 1992; Neutel et al. 1992). These global estimates of aortic elastic properties may be of great advantage in identifing individuals at high risk for cardiovascular disease. The aorta seems to have special relevance, since its natural history of fatty streaks tends to parallel that in the coronary arteries (Blankenhorn and Kramsch, 1989; Lehmann et al., 1993a).

Since the beginning of the century the pulse wave velocity along the aorta (C_w) has been used to assess the elastic properties of the artery wall. Systolic blood ejection into the aorta creates a pressure wave that travels through the arterial tree with a speed varying from 3 to 15 m/sec. In contrast to the higher speed at which pressure waves are propagated, the velocity with which the blood flows along this route ranges from only 0.14 to 0.18 m/sec (Wiggers, 1962). The speed at which the pulse wave travels along the vessel increases directly proportional to its stiffness. The relationship between the pulse wave velocity (C_w) and the coefficient of volume of elastic resistance (elastance, E′) was shown (Frank, 1920; Wezler-Böger, 1939; Sinn, 1956) to be

$$E' = C_w^2 \times \frac{\text{mass density of blood}}{\text{basic volume content of the aorta}}. \qquad (3)$$

It is evident from this formula that E′ is proportional to the square of the pulse wave velocity.

To assess the velocity of the pulse wave along the aorta noninvasively, two principles have been used: Sphygmometric methods apply two mechanical pressure pulse receptors, one on the skin over the carotid artery and the other over the femoral artery. The distance between the receptors and the time of wave transmission allow calculation of the wave velocity (Breithaupt et al., 1992a). By using the upstroke of the pressure waves in the carotid and femoral arteries, any bias from reflection waves can be excluded. A validation of this noninvasive approach has been performed in monkeys by simultaneous use of invasive assessments (Farrar et al., 1991), and a good correlation was shown ($r = 0.85$). Another approach to obtain the pulse wave velocity uses Doppler ultrasound, with one ultrasound probe insonating the left subclavian artery close to its root near the aorta, and the other probe insonating the abdominal aorta just proximal to the bifurcation (Lehmann et al., 1992a, 1993c).

Both methods to assess the pulse wave velocity use similar, but not exactly the same, phenonema. Therefore, some principle differences between the sphyg-

mographic and Doppler techniques should be kept in mind:

1. The Doppler method detects a flow wave, that is, the movement of erythrocytes, whereas the sphygmographic methods depend on propagation of a pressure wave. Theories of the pulse wave depend on the theory of pressure wave propagation and cannot be extrapolated to the movement of volumes without reservation (Wiggers, 1964).
2. The carotid-femoral method covers not only the aorta, but also some further distal parts of the Windkessel, such as the iliac artery.
3. The waves detected by sphygmographic methods are quite robust against artifacts, whereas ultrasonic methods are sensitive to a variety of possibly confounding factors, such as the angle of insonation.

It would be extremely valuable to obtain comparative results with different techniques to judge the pros and cons of both.

Another indirect approach to assessing E′ depends on the diastolic decay of the pressure pulse wave. Provided there is constant peripheral resistance, the stiffer the aorta (i.e., the higher E′), the more rapidly the diastolic pressure will fall. Whereas this approach is based on a static Windkessel model and does not take into account wave reflections, the pulse wave velocity methods do take these factors into account. Using the decay principle and a modified Windkessel model, it was shown that catecholamines, renin, lipids, and insulin are linked to an increase in aortic and peripheral elastic resistance (Neutel et al., 1992).

Influence of current blood pressure

Any assessment of vascular elasticity has to take into account the fundamental dependence of elastic resistance on current blood pressure. This means that the higher the intravascular pressure, and consequently the more the vessel wall is prestretched, the greater will be its resistance against further stretching and therefore its stiffness. This relationship has long been known, but has frequently been ignored. Values of elastic resistance or compliance under different conditions should, therefore, only be compared either after correcting for the actual blood pressure or at the same level of blood pressure. All statements on elasticity changes must be made with due reservation when there are simultaneous changes in pressure. Lehmann et al. (1993a) distinguish between (a) *operative compliance* of the artery wall, which represents the value observed at the actual blood pressure and is composed of both structural (e.g., atherosclerosis) and functional (e.g., blood pressure) variables and (b) *intrinsic compliance*, which represents elastic properties of the aortic wall structures. After correcting arterial compliance for the actual blood pressure effect, the intrinsic value (Cp) can be received, which is considered to represent the structural and functional elastic state of the aorta but without the influence of actual blood pressure.

Based on the same physiologic principles as the above-mentioned Cp, and resulting in the same information, Sinn (1956) described a pressure-independent exponent of diagonal distension as "2 m." This pressure-standardized distensibility index can easily be calculated as follows:

$$2\,\mathrm{m} = \frac{\mathrm{BP\ mean}}{\mathrm{C_w}^2 \times \mathrm{rho}} \qquad (4)$$

where BP mean = mean arterial pressure calculated according to Wezler and Böger (1939) as follows:

BP mean = 0.43 (systolic blood pressure − diastolic blood pressure) + diastolic blood pressure, C_w = pulse wave velocity and rho = specific density of blood = 1.06.

Diagnostic and Prognostic Implications

Several studies have shown the importance of high systolic blood pressure and pulse pressure (indicating a stiff aorta) as risk factors for cardiovascular morbidity and mortality (Rutan et al., 1988; SHEP, 1991). One could also consider that a stiff aorta is not only a risk factor, but also a risk indicator signaling the existence of pathophysiologic changes in the arterial system. Gudbrandsson et al. (1992) in the Tecumseh Blood Pressure study found that individuals in an otherwise normal population with the highest aortic elastic resistance not only had higher systolic and lower diastolic blood pressures, but also higher left ventricular wall thickness and higher fasting serum insulin compared with persons with a less stiff aorta. The authors concluded that there is an early association of increased aortic stiffness with anatomic, functional, and biochemical aberrations. They suggested that assessing elastic properties of the aorta might prove useful for prediction of cardiovascular complications.

In a study comparing volunteers of different age groups and different physical conditioning status, a higher physical status was correlated with a reduction in the age-associated increase in aortic stiffness (Vaitkevicius et al., 1993). Studies on the aortic elasticity using magnetic resonance imaging or echocardiographic and angiocardiographic techniques in patients with coronary artery disease showed that aortic elastic resistance was significantly increased when compared with normal controls (Stefanidis et al., 1987, 1990; Mohiaddin et al., 1989). The results were con-

firmed by measurements of the elastic properties of the aortic arch in symptom-free versus symptomatic patients, all of whom had raised serum cholesterol, revealing that assessment of aortic elastic resistance might be useful in identifying those patients with high cholesterol who should be treated more aggressively (Dart et al., 1991).

Also, pressure-corrected aortic distensibility was inversely related to total cholesterol in plasma (Lehmann et al., 1992d). London et al. (1990) found a small influence of HDL cholesterol on aortic stiffness. Curiously, a group of patients with hypercholesterolemia but no other features of coronary disease (Dart et al., 1991), as well as symptom-free young patients with familial hypercholesterolemia (Lehmann et al., 1992c), had fewer stiff aortas than the normocholesterolemic controls. In addition, a study by Avolio et al. (1985) questioned the stiffening effects of hypercholesterolemia. In the earliest phases of the development of atherosclerosis, accumulation of LDL cholesterol in the vessel wall, its oxidation, and the formation of foam cells could be the origin of an initial decrease in aortic elastic resistance. As soon as subjects grow older, the development of the sclerotic component (the increase in connective tissue, calcium accumulation, etc.) in the vessel wall induces a stiffening of the aorta, which could also be related to an endothelial mechanism, such as inhibition of nitric oxide (NO) release (Hopkins et al., 1993; Lehmann et al., 1992d). Strong evidence for stiffening of the aorta due to hypercholesterolemia comes from recent experimental studies (Farrar et al., 1991). Increased stiffness of the aorta has recently been reported in patients with atheromatous plaques in the aortic wall (Athanassopoulos et al., 1994). Measurements of elasticity of the aorta may be shown to be of high clinical relevance, since the natural history of aortic fatty streaks tends to parallel that in coronary arteries. These measurements may therefore offer a convenient surrogate estimate of coronary atherosclerosis (Anonymous, 1991) and could argue for the initiation or reenforcement of treatment of vascular risk factors.

Therapeutic Implications

Until now the influence of treatment, especially of drugs, on the Windkessel function has not received much attention. From cholesterol feeding experiments in monkeys, it was demonstrated that a functional improvement in the aortic elastic properties (measured from the subclavian to femoral pulse wave velocity) occurred with regression of diet-induced atherosclerosis (Farrar et al., 1980, 1991). In their most recent studies on monkeys using pulse wave velocity measurements, Farrar et al. (1991) found increasing aortic stiffness under a cholesterol-progression diet and a reverse of that process after the introduction of a regression diet. By comparison with morphometric data after the monkeys were sacrificed, it was shown that a combination of aortic pulse wave velocity, blood pressure, and total plasma cholesterol can be used to predict the severity of diffuse asymptomatic atherosclerosis. These experimental data in animals have to be seen as a challenge to clinical scientists.

O'Rourke (1990) concludes in a review that drugs, including nitrates, in humans have little or no direct effect on the stiffness of the various parts of the aorta or its major branches, but that wall stiffness decreases when blood pressure is lowered. In contrast, he states, most studies on peripheral arteries, such as the brachial or carotid arteries, have demonstrated that various drugs appreciably reduce arterial stiffness (O'Rourke, 1990). On the other hand, improvement in aortic compliance has been observed following acute nifedipine administration (Stratos et al., 1992) and following 1 month of nitrendipine (Asmar et al., 1992). It cannot be excluded that these effects predominantly account for the simultaneous effect of the calcium antagonist on blood pressure.

Safar's group presented data indicating that NO-donating nitrates improve the elastic properties of the aorta (Slama et al., 1992); we confirmed these findings in a study on healthy volunteers (data on file, 1993). An increase in stiffness of the aorta was seen after intravenous atropine (Breithaupt et al., 1992a). This drug reduces endogenous NO production via inhibition of the parasympathetic system. In another study we compared the effects of chronic therapy with the angiotension-converting enzyme (ACE) inhibitor cilazapril and the diuretic hydrochlorothiazide in patients with mild to moderate hypertension (Breithaupt et al., 1992b). At the same levels of blood pressure reduction, the ACE inhibitor induced a more intense slowing of the pulse wave velocity than the diuretic (Figure 3). ACE inhibitors, in addition to their effect on blood pressure, may well have additional beneficial effects on the aorta and large arteries (Thomas et al., 1991; Dzau, 1993). Although preliminary studies that indicate a direct drug influence on elastic properties of the aorta deserve further confirmation, they could open up new fields in the treatment of hypertension and other cardiovascular diseases.

The question remains open as to how to explain the influence of treatment on aortic elastic resistance. The passive effect following the drop in blood pressure is easily explained by physiology. Direct effects on the aortic wall, as suggested by results with atropine, nitrates, and cilazapril, could be mediated by direct or indirect drug effects on the vascular smooth muscle of the aorta. The fundamental importance of arterial smooth muscle on the elastic properties is well established (O'Rourke, 1990). Anatomically, in medium- and small-size arteries the muscles are in series with collageneous wall elements, but in parallel with the elastic fibers. Contraction of the vascular muscles

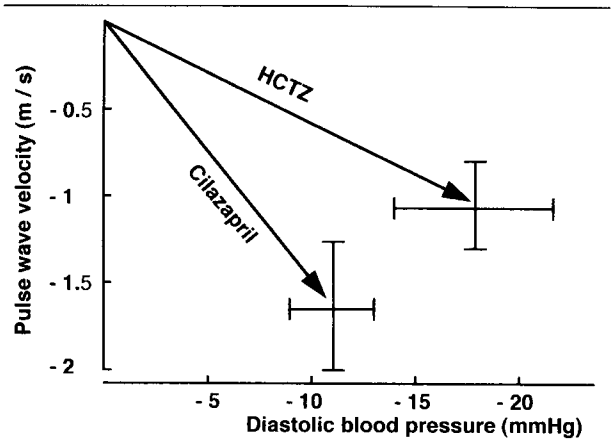

Fig. 3. Differential effect of cilazapril (5 mg daily) and hydrochlorothiazide (25 mg daily) on diastolic blood pressure and pulse wave velocity along the aorta. In spite of a somewhat less intense blood pressure–lowering effect of the ACE inhibitor cilazapril, the reduction in aortic elastic resistance (stiffness), as indicated by the reduction in the velocity of the pulse wave, was more pronounced (modified from Breithaupt et al., 1992b).

transfers stress from the elastic to the less extensive collagen fibers, thus stiffening the wall, and vice versa for relaxation of the muscles.

Whereas the effect of vasoactive drugs on the peripheral arteries is strong, the effects on the aorta are less. In experimental studies, the effects of vasodilating beta-adrenoceptor antagonists (Watkins et al., 1988a), calcium antagonists (Watkins et al., 1988b), and ACE inhibitors (Watkins et al., 1987) increased aortic compliance (or decreased stiffness) in dogs. The opposite effects were seen after administration of vasoconstricting drugs (Cabrera et al., 1988). Beyond the effects on aortic smooth muscle, other effects must also be considered, such as a change in the blood flow of the vasa vasorum of the aortic wall (Stratos et al., 1992; Stefanidis et al., 1993); changes in elastin, in smooth muscle cells and collagen, and in the calcium composition within the aortic wall (Kohno et al., 1987; Stratos et al., 1992), must also be considered. The latter would only be a possibility during chronic treatment. Data from the cholesterol-feeding study in monkeys support this view. It was obvious from the time course that some time, that is, around 1 year, was required before any beneficial effects of a dietary reduction in cholesterol showed a beneficial effect on aortic stiffness (Farrar et al., 1991).

It would be extremely valuable in future studies to examine whether interventions against or treatment of cardiovascular risk factors (such as hyperlipidemia, hypertension, or cigarette smoking) could normalize aortic elastic properties.

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