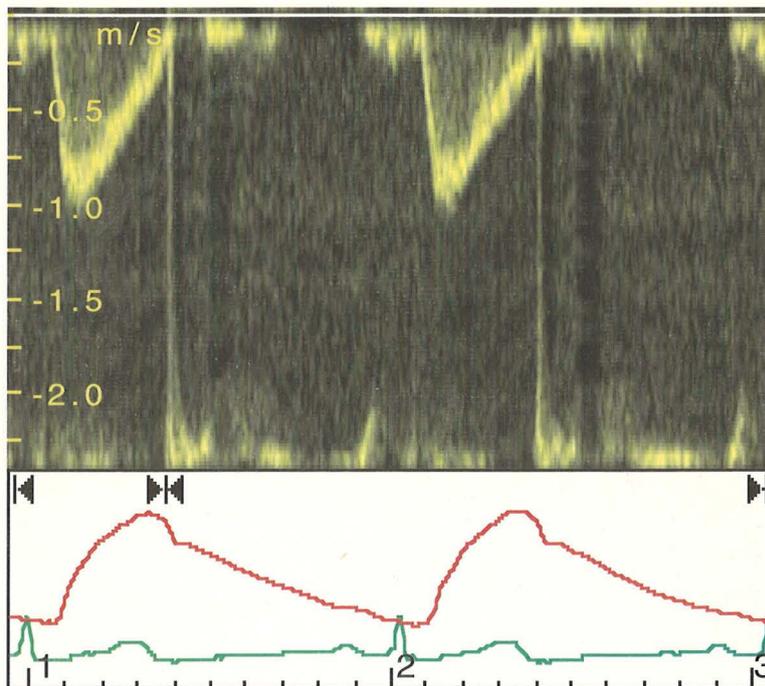


Interaction Between the Left Ventricle and the Systemic Arteries

By
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NORWEGIAN COUNCIL

ON CARDIOVASCULAR DISEASES



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Noninvasive Assessment of the
Interaction Between the Left
Ventricle
and the Systemic Arteries

in Normotensive Subjects
and before and during Drug Treatment in
Hypertensive Subjects

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List of papers

- I Soma J, Aakhus S, Dahl K, Slørdahl SA, Wiseth R, Widerøe TE, Skjærpe T.
Hemodynamics in White Coat Hypertension Compared to Ambulatory Hypertension and Normotension. *American Journal of Hypertension*. 1996;9:1090-1098
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Influence of Body Size and Left Ventricular Ejection Dynamics on Total Arterial Compliance Determined Using Doppler Echocardiography and Subclavian Artery Pulse Tracings in Healthy Humans. *Blood Pressure*. 1998;7:239-246
- IV Soma J, Aakhus S, Dahl K, Widerøe TE, Skjærpe T.
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- V Soma J, Angelsen BAJ, Aakhus S, Skjærpe T.
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Submitted

Introduction

Essential hypertension is an important risk factors for development of ischemic heart disease and cerebral stroke, which are leading causes of death and disability in the industrialised part of the world (1, 2). There is evidence that both hereditary (3) and ambient factors may play a role for the development of arterial hypertension (4), but the primary triggers are still unknown. In the absence of a specific pathogen, efforts are taken to avoid complications of arterial hypertension by recommending lifestyle changes and drug treatment according to prevailing recommendations (5). Antihypertensive drug therapy significantly reduces cerebral vascular strokes, but only modestly influences the complications of ischemic heart disease (6), the most important reason for cardiovascular morbidity and mortality in our society. One possible reason for the modest effect of antihypertensive drug therapy on coronary events is the metabolic syndrome associated with essential hypertension. Hence, an aggressive approach to reduce blood lipids in hypertensives has recently been suggested (7). Inadequate blood pressure control (8) or potential adverse consequences of drug treatment, for example by treating subjects who may not need drug treatment (9, 10), should also be considered.

Optimising treatment strategies in arterial hypertension may require a more precise hemodynamic characterisation, taking into consideration not only cardiac output and peripheral vascular resistance, but also a description of the interaction between the left ventricle and the systemic arteries based on the pulsatile nature of left ventricular ejection (11).

The study of pulsatile arterial hemodynamics is today possible by simultaneous recordings of blood flow velocities using Doppler ultrasound and tracings of the pressure pulse in the carotid or the subclavian artery (12-15). Time domain analysis using electric analogue models of the circulation (16) were used in the studies presented in Paper I - IV, but in Paper V arterial properties were also determined using frequency domain analysis (17).

Using noninvasive methods may reduce hemodynamic alterations due to mental stress and avoid risk associated with invasive procedures. The use of ambulatory blood pressure monitoring (18) may provide additional information concerning pathophysiology in arterial hypertension.

Aims of the studies

First, we wanted to evaluate feasibility and reproducibility of the noninvasive method (19) regarding hypertensive subjects. Second, we wanted to compare

hemodynamics in subjects with labile and sustained hypertension and in subjects with normotension and evaluate potential clinical implications of hemodynamic patterns in these groups. Third, we wanted to assess the effects of drugs on the interaction between the left ventricle and the systemic arteries.

Materials and Methods

Healthy subjects

We studied 87 presumably healthy subjects (39 males, 51 ± 15 years, and 48 females, 45 ± 19 years). The subjects were recruited from hospital staff and their friends. They were considered healthy on the basis of medical history, clinical examination, 12 lead ECG and echo Doppler examination. No subject used any drug. Selection aimed at recruitment of at least 10 subjects in each decade between 20 and 80 years.

Normotensive subjects

Healthy subjects with an arterial blood pressure $< 140/90$ mmHg, determined as the mean of the three measurements on the same day using a mercury sphygmomanometer.

Subjects with white coat hypertension

The 28 subjects in this group were recruited from the special ward for hypertension in this hospital and we used the same definition of white coat hypertension for inclusion in the study as that used in the ward, i.e. a diastolic pressure measured by the referring physician ≥ 90 mm Hg and ambulatory daytime pressures $< 140/90$ mm Hg. Two subjects who previously used antihypertensive drugs stopped treatment at least four weeks prior to inclusion into the study, the remaining 26 subjects were untreated. The mean age of the study group was 47 ± 13 years, range 18 - 67 years, and consisted of 16 males and 12 females. Smoking habits, cholesterol levels, and level of physical activity were not recorded neither in this, nor in any of the other groups.

Subjects with sustained (ambulatory) hypertension

Subjects with a diastolic pressure measured by the general physician ≥ 90 and < 115 mmHg, and an ambulatory daytime diastolic pressure ≥ 90 mmHg were defined as sustained hypertensive subjects. Previously untreated subjects (14 males and 9 females aged 48 ± 7 years) served as a control group for the comparison with white coat hypertensive subjects. Subjects who in addition to the criterias above had a

diastolic pressure measured by a nurse in the clinic ≥ 90 mm Hg (17 males and 13 females aged 49 ± 6 ; range 37 - 63) were included into a crossover study.

Exclusion criterias

Exclusion criterias were evidence of coronary heart disease, heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension, other major diseases, use of drugs, inappropriate echocardiographic window and/or inability to obtain a subclavian pulse trace.

Blood pressure measurements

General practitioners and a nurse in the special ward for hypertension in our clinic measured arterial blood pressures with the subject in the sitting position after at least 10 minutes rest using a mercury sphygmomanometer and a cuff on the right upper arm. Arterial pressures were derived by calculating the average of at least three measurements and averaging measurements obtained on different days.

During the echocardiographic examination arterial blood pressures were recorded with an automatic device (Dinamap 1846 SXP, Criticon Inc, Tampa, FL, USA) in all studies. The diastolic pressure recorded with this device was consistently lower than that recorded by a nurse in the clinic. This difference was mainly due to measuring blood pressures right upper arm with study subjects in the left lateral decubitus position, but characteristics of the oscillometric method (20) can not be excluded

There was a significant correlation between blood pressures measured with a mercury sphygmomanometer and with the oscillometric method. Whereas this correlation was stronger concerning systolic ($r = 0.72$, $p = 0.0001$) than diastolic ($r = 0.40$, $p = 0.04$) pressures in the group with white coat hypertension, there was stronger correlation between diastolic ($r = 0.62$, $p = 0.0003$) than between systolic ($r = 0.44$, $p = 0.02$) pressures in the group with sustained (ambulatory) hypertension. Ambulatory blood pressure monitoring was performed in all hypertensive subjects.

Echocardiography and Recording of Subclavian Artery Pulse Trace

The echocardiographic study was performed after the subject had been resting in the left lateral decubitus position at least 10 minutes. Standard recordings of two dimensional (2-D) and M-mode images of the left ventricle were obtained from the parasternal and from the apical window. The left ventricular apical 4-chamber, 2-chamber, long-axis and the parasternal short-axis view located at the tip of the papillary muscles were transferred to a computer (Macintosh II series, Apple computers Inc, Cupertino, California) as scanline data, that is without loss of ultrasound information,

providing a frame rate of 47 frames/second with the standard angle and depth. This provides an excellent condition for reviewing cine-loops at different speeds. The aortic annulus diameter was measured in the parasternal long-axis view between the insertion points of the valve leaflets by use of the trailing-to-leading edge method. M-mode echocardiograms of the left ventricle were obtained from the parasternal window, guided by 2-D echocardiography. Tracings from the level of the tip of the papillary muscles were transferred to the computer. It was required that the right and left endocardium of the septum and the endocardial and epicardial surfaces of the posterior left ventricular wall were recorded continuously in at least three cardiac cycles. Mitral and pulmonary flow velocities were recorded by pulsed Doppler technique, from the apical position, between the mitral leaflets and in the upper right pulmonary vein respectively. Data from at least five consecutive cardiac cycles were transferred to the computer. Doppler recordings of aortic root flow, using high repetition frequency pulsed Doppler, were obtained from the apical window. The brachial artery blood pressures were measured with an automatic device every 1 - 3 minutes during the study. A nurse recorded the subclavian artery pulse tracing during echocardiographic recordings.

Analysis of Data

The left ventricular endocardial surface in the apical 4-chamber view and the endocardial and epicardial surfaces in the para-sternal short-axis view were traced manually on end-diastolic and on end-systolic frames according to the convention by Wyatt et al. (21). The following parameters were determined from 2-D echocardiograms of the left ventricle: long-axis, short-axis, short-axis wall thickness, short-axis epicardial and endocardial areas, and left ventricular volumes, all in end-diastole and in end-systole. These dimensions served for calculating ejection fraction, fractional shortening, velocity of circumferential fiber shortening, and rate corrected velocity of circumferential fiber shortening (22, 23). Left ventricular meridional and circumferential end-systolic wall stresses were calculated according to Brodie et al (24) and Falsetti et al (25) respectively. Left ventricular mass was calculated according to Wyatt (26) on 2-D images and according to the Penn convention (27) on M-mode images.

The maximal velocity of at least three mitral and pulmonary venous Doppler flow velocity profiles was traced and averaged. From the mitral flow velocity tracings, early mitral flow peak velocity and deceleration time and peak velocity and duration of the late flow were measured. The peak velocity and time-velocity integral during systolic and diastolic pulmonary venous flow and the maximal velocity, velocity integral and duration of the flow reversion during atrial systole were measured.

The subclavian artery pulse tracing was calibrated with oscillometrically obtained systolic and diastolic pressures (14, 15) and the pulse transmission delay corrected by alignment of the pulse trace incisura to the end systole of the Doppler flow trace. The maximal flow velocities (i.e. outer envelope of the Doppler spectrum) of at least three cardiac cycles were traced manually and averaged according to the previously described computerised procedure (14). Ejection time was determined from the beginning of blood flow to the valve closure click. The time to peak aortic root flow was determined as the time from beginning of flow to peak aortic flow. Mean arterial pressure was calculated as the pressure integral over the total cardiac cycle. End-systolic pressure was determined at the incisura of the calibrated pulse tracing.

Total arterial compliance was estimated using the 3-element windkessel model (16) and a 2-element windkessel model (28). Aortic characteristic impedance was estimated by calculating the mean of the input impedance modulus between the second and 10'th harmonic (17), by calculating the ratio of the upstroke of the pressure and flow wave (29) and from the three-element windkessel model. Splitting of the pressure wave into its forward and backward components was obtained by the method of Westerhof et al. (30). In the frequency domain, the reflection coefficient was calculated as the ratio of backward and forward pressure waves. The modulus and phase of the reflection coefficients were calculated. Peripheral resistance was calculated according to the 3-element windkessel model (16, 14). Left ventricular total power was calculated from instantaneous pressure and flow (31).

Indexed variables were obtained by dividing with the respective body surface area calculated according to the method of Du Bois (32).

Additional considerations concerning the echocardiographic method

The methodology, including validity of the measurements and calculated variables, has been discussed in detail previously (19). Some few additional comments are given below.

The most obvious advantage of the noninvasive method is that it is not harmful. Consequently larger amounts of subjects may be examined and followed up. The examination is time consuming, but less than invasive procedures. Less resources are required. Although we have demonstrated that the arterial blood pressure increases in some subjects during the echocardiographic examination with regard to mean daytime ambulatory blood pressures (Paper I - II), there is reason to believe that the noninvasive method is less unpleasant compared to invasive methods.

It is underscored that in the present studies the properties of the arterial circulation is described by use of extremely simplified, lumped models which may give insight into physiologic and pathophysiologic mechanisms, but obviously only a part

of the picture and hopefully not the wrong picture. An additional deficiency of the method is that the brachial artery pressure does not take into account the pressure amplification from the proximal aorta to the periphery. The precision of blood pressure recordings, which do not exactly match the pulse tracings in time, could also be a problem. Although we did not use a high fidelity system, the frequency response of the pulse tracing (19) seemed to be adequate. The correction of the time delay of the subclavian pulse trace by aligning the incisura of the pulse trace to the aortic valve closure signal could, however, represent a problem. During analysis of the wave reflections in Paper V it was detected that this approach was associated with discrepancies in the timing of upstroke of flow and pressure in some cases. Correcting the time delay by aligning start of upstroke of flow and pressure, which was performed during analysis of the data in Paper V, seemed to provide more accurate results concerning the splitting of forward and backward pressure waves. It is possible that the time correction of the pulse trace could have influenced estimation of aortic characteristic impedance in the three-element vascular model during beta-blocker treatment (Paper IV). This is emphasised by the better agreement between aortic characteristic impedance determined in the frequency domain (77 ± 47 , 62 ± 30 , 54 ± 25 , 64 ± 30 , p -ANOVA = 0.002, baseline 1, baseline 2 and during treatment with atenolol and captopril respectively), and total arterial compliance during treatment with atenolol (Paper IV). Higher values of aortic characteristic impedance at baseline 1 (Paper IV) could be due to mental stress and consequently more rapid ejection of the stroke volume and stiffening of the aortic wall because of viscoelastic properties or inertance of the aortic blood column or a combination of these.

It is underscored that validity studies have not been performed for large ranges of arterial blood pressures. In about 5% of the population it may not be possible to obtain adequate pulse tracings and/or echocardiographic images.

Statistical analysis

Data were presented as mean \pm standard deviation and ranges. Paired and unpaired t-tests (two-tailed), and one way analysis of variance (ANOVA) were performed for univariate analysis. The Scheffé test used for post hoc comparisons is conservative and the possibility of type II error (33) should be considered.

Relationships between variables were tested with Pearson's coefficient of correlation and by use of multiple regression analysis. It is emphasised that correlations are not necessarily causal relationships. Another important deficiency of the correlation analysis is the influence of the range of values. Hence, the reason for the rather poor correlation between the time to peak aortic flow (acceleration time of aortic root flow) and total arterial compliance in Paper III could be due to narrow range of values of the

former. This effect could also influence the multivariate analysis in Paper III.

Reproducibility

Reproducibility was tested by calculating the coefficient of variation and the 95% limits of agreement (34). Intraobserver reproducibility was tested by comparing measurements from a group of 16 healthy subjects on two occasions at an interval of 14 days and by comparing measurements from a group of subjects with ambulatory hypertension at an interval of 8 weeks (Paper I - II). Similar values for reproducibility were obtained in hypertensives and in healthy subjects (Paper I - II). The coefficient of variation was 10 - 12% for stroke volume, cardiac output, total arterial compliance, and peripheral resistance but larger for the aortic characteristic impedance.

A large coefficient of variation for aortic characteristic impedance estimated in the three-element windkessel model could indicate poor reproducibility, but this variable seemed to be very sensitive for alterations in ventricular-arterial interaction (Paper V), and variation from one examination to another could represent biologic variation (Paper IV) as discussed above.

Summary of results

Paper I presents the results of noninvasive assessment of steady state and pulsatile hemodynamics assessed in 28 subjects with white coat hypertension, 23 subjects with previously untreated, ambulatory hypertension, and 32 normotensive subjects. The groups did not differ significantly concerning age, gender, body surface area, heart rate, stroke index and cardiac index, but total peripheral resistance index was increased and total arterial compliance reduced in the white coat group and the hypertensive group compared to the normotensive group. Subjects with white coat hypertension who had a systolic arterial pressure during echocardiography that was > 5 mmHg higher than the ambulatory daytime systolic pressure (n = 19) had increased cardiac index, increased total peripheral resistance, and decreased total arterial compliance compared to the normotensive group. There was a significant positive correlation between heart rate and mean arterial pressure in the group with white coat hypertension.

Paper II shows that the difference between clinic and ambulatory systolic blood pressures, in subjects with white coat hypertension, was positively related to the ratio of the systolic to diastolic pulmonary venous flow peak velocities and to the peak velocity of flow reversion in the pulmonary vein during atrial systole, and inversely related to the ratio of early to late mitral flow peak velocities. Left ventricular stroke

volume, ejection fraction and velocity of circumferential fiber shortening did not differ between subjects with white coat hypertension, previously untreated ambulatory hypertension, and normotension.

Paper III presents investigation of determinants of total arterial compliance in healthy humans. Thirty-seven males (27 - 76 years) and 45 females (20 - 77 years) were studied. Total arterial compliance correlated positively with body height ($r = 0.45$, $p < 0.01$) and acceleration time of aortic root flow ($r = 0.30$, $p < 0.01$) and inversely with age ($r = -0.34$, $p < 0.05$), heart rate ($r = -0.33$, $p < 0.01$), and mean arterial pressure ($r = -0.51$, $p < 0.01$). Multivariate analysis indicated that mean arterial pressure, height and heart rate, but not age significantly predicted total arterial compliance. After adjustment for height and heart rate total arterial compliance did not differ significantly between gender. These findings suggest that differences in body size, heart rate and mean arterial pressure should be considered when comparing total arterial compliance in different groups. Although not statistically significant, it was interesting that the older age groups showed a tendency to a more rapid ejection of the stroke volume. This could represent a mechanism for the decreased arterial compliance in the elderly.

Paper IV concerns the effect of selective β_1 -adrenergic receptor blocker (atenolol) and an angiotensin converting enzyme inhibitor (captopril) on total arterial compliance in subjects with ambulatory hypertension ($n = 30$). Although both drugs reduced arterial blood pressures significantly, total arterial compliance was significantly increased by atenolol (42%), but not by captopril.

Paper V presents the results of sublingual nitroglycerin on pulsatile hemodynamics in subjects with sustained (ambulatory) hypertension ($n = 25$). A reduction in mean arterial pressure was associated with a significant rise in heart rate, probably due to reflex sympathetic activation. Stroke volume was reduced, but pulse pressure did not change. Pressure wave reflections were delayed, but total arterial compliance did not change with nitroglycerin.

General discussion

Increased flow or increased peripheral resistance ?

It is widely accepted that an increased peripheral resistance is the hallmark for essential hypertension, but several studies (35, 36) have emphasised the contribution of increased cardiac output. Thus, early hypertension may be characterised by an increased cardiac output that converts to an increased peripheral resistance and normal or low cardiac output pattern with passage of time (37). The present studies support the importance of cardiac output, not only for transient elevations of the arterial blood pressure induced by mental stress during the medical examination, but also for sustained hypertension (Paper I, II, and IV). A more detailed comprehension of arterial blood pressures requires, however, the assessment of pulsatile hemodynamics.

Role of large arteries in arterial hypertension

Large arteries have, in addition to the conduit function, an important role in converting pulsatile to steady blood flow. Thus, the wall of the aorta and the large arteries is distended in systole and blood is propelled toward the periphery because of the elastic recoil during diastole. The compliance of large arteries is always reduced in hypertensives, simply because of the increased distending pressure combined with nonlinear elastic properties of the arterial wall. Accordingly, systolic pressure increases more than diastolic pressure with rising mean arterial pressure. The pulse pressure increases further, for each level of the mean arterial pressure, by increasing the stiffness of the arterial wall and by decreasing arterial cross sectional area (16) .

Difficulties in assessment and in interpretation of arterial compliance are important reasons for confusion regarding the significance of arterial compliance in hypertension. Thus, low arterial compliance has been suggested not only the principal mechanism for systolic hypertension in the elderly (38), but also an important mechanism in essential hypertension in general (39). Others have found increased large artery compliance in hypertensives compared to normotensives for comparable distending pressures (40). High arterial compliance in hypertensives could be due to increased arterial cross sectional diameter or a reduced elastic modulus of the arterial wall, both potential consequences of arterial remodelling. Similar phenomena could contribute to explain high values of total arterial compliance during treatment with atenolol in subjects with sustained hypertension compared to those found in normotensives, as discussed in Paper IV, but the effect of heart rate reduction may contribute to explain this phenomenon. In line with the traditional view, total arterial compliance seems to be a key factor determining differences between subsets of hypertensives like sustained and labile hypertension and predominantly systolic versus

predominantly diastolic hypertension.

Although arterial wall structure is an important determinant for large artery properties (41), left ventricular ejection dynamics (Paper III) may play a role. This is due to the dynamic nature of arterial compliance (Paper III - V). Consequently, it must be considered whether total arterial compliance is influenced by inertance of the aortic blood column and viscoelastic properties of the arterial wall (41), i.e. stiffening of the arterial wall may be induced by increased rate of delivery of the stroke volume. This is a possible mechanism for increased pulse pressure in elderly subjects (Paper III) as well as other conditions associated with increased adrenergic drive like left ventricular dysfunction. It is possible that the adverse effects of short and long term increased heart rates (42) may be partly ascribed to this effect.

Heart rate correlates reasonably well with total arterial compliance (Paper III - IV). The rather poor correlation between time to peak aortic flow (acceleration time of aortic root flow) and total arterial compliance (Paper III) may, as discussed above, be due to narrow range of values of the former. There is, however, reason to suggest that heart rate and time to peak aortic flow only partly reflect the aortic strain rate during left ventricular ejection. High resolution images (43) of the aortic wall pulsations could provide more appropriate assessments of aortic wall strain rate in future studies.

The implication of material viscoelasticity for total arterial compliance estimated in the models of the arterial tree has recently been challenged (44). According to these authors (44) total arterial compliance estimated in the vascular models is an apparent compliance which depends on wave reflections and heart rate, independent of alterations of the properties of the arterial wall. It is certainly correct to consider an influence of wave reflection phenomena on estimates of total arterial compliance since the arterial pressure used to calculate total arterial compliance is influenced by arterial wave reflections. Increased magnitude and early return of wave reflections do, however, increase the arterial pulse pressure, thereby tending to lower the estimate of total arterial compliance. The reason is that total arterial compliance is approximated by the ratio of stroke volume to pulse pressure (45, 46).

Some reflections on arterial wave reflections

Whereas wave reflections return late, and mainly in diastole, in subjects with compliant arteries, early return and increased amplitude of wave reflections are typical phenomena in subjects with stiff arteries, thereby contributing to increase the systolic pressure and the load on the left ventricle (47).

Modulus and phase of reflected pressure and flow waves depend on the frequencies of the waves (48). Thus, amplitude of the reflected wave depends, at least indirectly, on heart rate since left ventricular ejection time and acceleration of ejection

are related to heart rate. The fact that shorter left ventricular ejection time influences how much of the reflected wave returns in systole is possibly just another way of viewing the frequency dependency of wave reflections (Paper V). Delayed return of wave reflections indicates decreased pulse wave velocity. The mismatch between the proximal characteristic impedance and the input impedance at the reflection site affects the amplitude of the reflected wave. The input impedance at the physiological reflection site is affected by vascular parameters such as compliance and resistance.

Increased mean arterial pressure, combined with stiffened large arteries, as is often seen in elderly subjects, may have deleterious consequences for the cardiovascular system according to the preceding discussion. Hence, antihypertensive treatment may be even more important in elderly than in young hypertensive subjects.

Evaluation of left ventricular systolic function in arterial hypertension

An evaluation of left ventricular systolic function should not only take into consideration dynamics of left ventricular filling, but also the impedance to left ventricular ejection (31). The components of left ventricular afterload are, however, poorly defined. It has been suggested that aortic input impedance, comprising arteriolar resistance, arterial compliance, reflected pressure waves, inertia of the blood column and blood viscosity, provides the best representation of the external load on the left ventricle (49). In clinical practice afterload is commonly defined by systolic or end-systolic blood pressure, but it must be related to left ventricular wall thickness and geometry to determine the force on each myofiber, thereby emphasizing the significance of left ventricular end-systolic wall stress for the assessment of left ventricular systolic function (50). Since arterial compliance and pressure wave reflections contribute to determine the systolic blood pressure, they are important determinators of left ventricular function and energetics. Hence, the concept of left ventricular unloading (51) must take into consideration not only effects of drugs on arteriolar resistance, but also effect of drugs on large artery mechanics. Since our studies have indicated that beta-adrenergic receptor blockers may increase total arterial compliance and thus may improve aortic elastic properties, it is possible that these drugs should be considered vasodilating drugs. This may partly explain why beta-blockers show promising results in left ventricular failure (52).

It has been discussed whether increased left ventricular contractility is involved in early hypertension (53). Increased left ventricular contractility in hypertensives may, however, be caused by the white coat effect and thus probably by transient neuro-endocrine stimulation of the myocardium (Paper I - III). This is in accordance with increased cardiovascular reactivity in hypertensives. Evidence of increased left ventricular contractility in subjects with sustained hypertension (54) may also be due to

the confounding effect of left ventricular hypertrophy (55, 56), which emphasises the importance of an appropriate analysis of left ventricular mechanics (57) in hypertensives (Paper II).

Although the mechanisms for the development of heart failure in arterial hypertension (58) are intensively studied, the transition from normal function to heart failure is not completely understood (59). Left ventricular systolic performance in hypertensives deteriorates at some point of time, manifested by dilatation, reduced ejection fraction and clinical signs of heart failure (60). A common view is that after passing through the stages of left ventricular hypertrophy, the compensatory mechanisms are maladaptive in the long run, leading to myocardial degeneration and left ventricular failure. Although the development of left ventricular hypertrophy in hypertension is due to pressure overload, abundant evidence indicates a direct neuro-endocrine influence on the myocardium (56). An important reason for the lack of correlation between left ventricular hypertrophy and degree and duration of arterial hypertension is the confounding effect of white coat hypertension (Paper II). It should, in addition, be considered whether increased heart rates per se may contribute to the development of cardiomyopathy of overload (Paper III - IV).

It is important to realise that hypertensive cardiomyopathy today is a relative rare reason for left ventricular failure compared to the consequences of ischemic heart disease complicating the course of arterial hypertension.

Are alterations of left ventricular diastolic function the earliest sign of end-organ damage in hypertension ?

There is evidence that diastolic dysfunction of the left ventricle may occur before a decline in systolic function (61). The increased arterial pressure may induce a prolongation of the left ventricular relaxation (62). Left ventricular compliance may be reduced because of fibrosis of the myocardium. The relative impact of these changes may be assessed with Doppler ultrasound recordings of trans-mitral flow velocities, but the interpretation of mitral flow patterns are confounded by the influence of several other factors like age, heart rate, autonomic discharge etc. (63). The addition of pulmonary venous flow recordings may improve the diagnostic power of Doppler ultrasound recordings of trans-mitral flow velocities (Paper II).

Thus, although early alterations of left ventricular filling in hypertensives was believed to be mainly due to structural myocardial changes, several functional factors may disturb left ventricular filling and the analysis should always be performed in light of the interaction between left atrial contraction and left ventricular relaxation and compliance (Paper II). In this framework it is possible that early disturbances of left ventricular filling in hypertensives may be due to increased adrenergic drive or slight

elevations of the systemic arterial pressure or both. This may constitute a link between arterial compliance and alterations of left ventricular filling.

Neurogenic hypertension versus borderline hypertension versus labile hypertension versus white coat hypertension versus predominantly systolic hypertension. More similarities than differences ?

The study of subjects with anticipated early hypertension or borderline hypertension might give a clue to the understanding of the early hemodynamic derangements in hypertension (64). Borderline hypertension (65) is characterised by arterial blood pressures sometimes above and sometimes below a certain cut-off limit, commonly 140/90 mm Hg, which is a general accepted definition of hypertension (5). Some investigators (66) use the term labile hypertension in an analogue way. Because of evidence of involvement of the sympathetic nervous system (67-69) the term neurogenic hypertension has sometimes been applied to this kind of hypertension.

Recent technological developments has provided the possibility to monitor blood pressures intermittently during a 24 hour period. Ambulatory blood pressure recordings are performed with a cuff on the upper arm connected to a device carried on the chest. The measurements are performed automatically with an interval of one half to one hour during daytime and night-time respectively, thereby assessing a mean day and night-time blood pressure as well as blood pressure variations during normal workdays (70-72).

The term white coat hypertension (73) is used when normotensive subjects according to ambulatory blood pressure monitoring, have repeated blood pressures > 140/90 mm Hg measured with sphygmomanometer in the physician's office. Although there is general agreement concerning the blood pressure limits for office (casual or clinic) pressures, the definition of ambulatory normotension is controversial. Ambulatory normotension is accordingly by some defined as mean daytime ambulatory blood pressures < 140/90 mm Hg (74), but by others < 135/80 mmHg(9, 75, 5, 76). The prevalence of white coat hypertension has been estimated to 10 - 30% in a hypertensive population (77, 78, 75), but varies according to the definition used. It is thus of great interest, both for the individual patients and for the society, to clarify whether these subjects may need antihypertensive medication.

Our studies support the view that the discrepancy between ambulatory and casual blood pressure measurements is caused by mental stress since increased heart rate and increased cardiac output seems to play a role (Paper I). But the studies also showed evidence of a lack of vasodilatory capacity in these subjects. Low total arterial compliance in subjects with white coat hypertension could be due to a combination of increased arterial distending pressure, age-dependent arteriosclerosis, small body size

and increased rate of ejection of the stroke volume (Paper I - III).

A potential implication of small body size in white coat and systolic hypertension is indicated by the association between small body size and low total arterial compliance (Paper III). It can not be excluded that small body size may play a role for the increasing pulse pressure with ageing since there is a high prevalence of predominantly systolic hypertension (79) and white coat hypertension in elderly female subjects (80), but additional biologic and environmental mechanisms should be investigated.

Increasing arterial pulse pressure with increasing age is a typical phenomenon in the western society and has been associated with a poor prognosis (79). Systolic hypertension in the elderly may due to a combination of low arterial compliance and increased amplitude and early return of reflected pressure waves. Future studies should investigate whether a chronotropic insufficiency (81) may influence the balance between heart rate and left ventricular contractility in elderly subjects. Hence, it is possible that an increased adrenergic drive in elderly subjects (82, 83) may stimulate left ventricular contractility and the rate of left ventricular ejection, with only a modest increase in heart rate (Paper III).

Our studies support that systolic hypertension in the elderly to a large degree is a labile phenomenon (84) (Paper I - III). In other words, it seems to be a condition whereby even modest mental excitement such as visiting the doctors office may elicit a pressor response. This may have important implications for the management of this serious problem including the possible danger of over-treating these subjects (10). The absence of extremely hypertrophic left ventricles in elderly subjects with systolic hypertension may also be a consequence of this phenomenon.

Several studies (85-87) have recently demonstrated the effect blood pressure lowering drugs in systolic hypertension in the elderly. Ambulatory blood pressure recordings may serve to monitor treatment effect (76) and contribute to the choice of dosage and type of medication in systolic hypertension.

Prognostic significance of white coat hypertension and ambulatory blood pressure monitoring

The risk for cardiovascular complications associated with arterial hypertension is determined by the degree of blood pressure elevation (1, 2) and by the degree of end-organ damage, as for example the degree of left ventricular hypertrophy (88, 89). There is also evidence that blood pressure profiles like predominantly systolic hypertension (79) and increased pulse pressure (90) provide additional clues to risk assessment. Additional risk factors like atherosclerotic arterial disease, diabetes mellitus, smoking, heredity and lack of physical activity should also be considered.

Several studies have demonstrated that subjects with white coat hypertension have less end-organ damage than subjects with sustained hypertension (9, 91, 92) indicating a favourable prognosis, but it is underscored that white coat hypertension is associated with more end-organ damage than "normotension" (93).

Few follow up studies have selected subjects according to ambulatory blood pressure monitoring (94, 78). Perloff et al. (94) who followed 1076 hypertensive subjects in average five years found that those whose ambulatory pressure was low in relation to their clinic pressure were at lower risk of mortality. Verdecchia et al (78) followed 1187 subjects for three years and found that the prognosis was better for subjects with white coat hypertension than for subjects with sustained hypertension.

Although there is reason to suggest that white coat hypertension in elderly subjects with arterial atherosclerotic derangements may be associated with an unfavourable prognosis, the prognosis for young subjects with a hyperkinetic circulation (95, 96) in the physician's office and no evidence of atherosclerosis is possibly good. The possibility that white coat hypertension is a precursor of sustained hypertension should, however, be considered and general advice concerning lifestyle as well as routine blood pressure control is recommended (97).

Ambulatory blood pressure monitoring unquestionably contributes to the risk assessment of subjects with arterial hypertension and may contribute to selection of treatment strategy according to the overall risk (5).

Potential mechanisms linking arterial hypertension to myocardial ischemic events

Myocardial ischemia can be the consequence of either increased oxygen demand or deficient oxygen supply. Acute arterial hypertension may induce myocardial ischemia by increasing myocardial oxygen demand (98). Sustained arterial hypertension is associated with left ventricular hypertrophy (55, 56) which, although the load on each myofibril is "normalised", may induce a mismatch between oxygen offer and demand with consequent angina pectoris, myocardial infarctions and ventricular fibrillation. Hypertensive subjects have three times the risk of sudden death (99).

It is also possible that arterial hypertension may be associated with endothelial damage and ruptures of atherosclerotic plaques because of the mechanical stress on the plaque (100, 101) with subsequent coronary occlusion and myocardial infarction as well as ventricular fibrillation. Endothelial dysfunction in hypertensives could also predispose for coronary artery spasm.

Since arterial hypertension may influence the prognosis of coronary artery disease, or vice versa, by several mechanisms, different therapeutic approaches may

favourably influence this relationship such as reducing the blood pressure per se, improving the balance between parasympathetic and sympathetic nervous system activity, reducing and/or preventing left ventricular and arterial structural alterations and prevention of atherosclerosis.

How can the noninvasive assessment of ventricular-arterial interaction provide insight into pharmacodynamics ?

A more precise evaluation of influence of drugs on pulsatile hemodynamics is necessary. The most important contribution by us in this regard is the demonstration of an increased total arterial compliance during selective beta₁ receptor blockade. We believe that the increase in total arterial compliance during beta-blockade depends on inertance of the aortic blood column or viscoelastic properties of the arterial wall or both. This assumption is supported by the lack of improvement in total arterial compliance during treatment with nitroglycerin, which may be due to the reflex sympathetic activation (Paper V). Thus, the effect of beta-adrenergic blockade on left ventricular ejection dynamics favourably influences ventricular-arterial interaction which may contribute to the reduction in morbidity and mortality with beta-blocker treatment in conditions like ischemic heart disease (100), heart failure (102), aortic aneurysms (103) and the potential favourable effect of beta-blockers on atherogenesis (104).

Conclusions

A comprehensive approach to the assessment of hemodynamic derangements in hypertensive subjects is feasible with noninvasive methodology. These methods may be used to characterise hemodynamics in subsets of hypertensives and in individual subjects. Hemodynamics together with metabolic features, age and comorbid conditions may provide a basis for the establishment of a risk profile for more appropriate management of hypertensive subjects. Moreover, extended insight into mechanisms of drug actions may be provided by this methodology. It is emphasised that the present studies indicate that left ventricular and arterial mechanical properties influence each other in a reciprocal manner, thereby undermining the view that the aortic impedance spectrum depends only on arterial properties without influence of left ventricular dynamics.

Although reduced arteriolar dilatatory capacity seems to be a prerequisite for the development of arterial hypertension, increased cardiac output also seems to play a role, not only for the blood pressure response in the medical environment in young and in elderly subjects, but also in sustained hypertension. There is evidence that large arteries in sustained (ambulatory) hypertension are more or equally compliant as large

arteries in normotensives after correction for the distending pressure. White coat hypertension share several features with systolic hypertension in the elderly and is characterised by a low total arterial compliance possibly due to a combination of structural alterations of the arterial wall and increased adrenergic drive, but small body size may play a role.

The heterogeneity of pathophysiologic mechanisms involved in arterial hypertension provides a basis for a broad pharmacodynamic approach when drug treatment is indicated. Drugs with pure vasodilatory effects according to the traditional view may decrease left ventricular afterload by reducing arteriolar resistance as well as reducing magnitude of reflected pressure waves and delaying pressure wave reflections. Drugs that reduce left ventricular contractility and heart rate like beta-adrenergic receptor blockers and possibly some calcium antagonists seems to improve aortic elastic properties with a secondary favourable influence on left ventricular dynamics. Obtaining additional gain by combining treatment principles, taking into consideration the reciprocal influence of pathophysiologic mechanisms on each other, is expected.

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Paper I

Hemodynamics in White Coat Hypertension Compared to Ambulatory Hypertension and Normotension

Johannes Soma, Svend Aakhus, Ketil Dahl, Stig Slørdahl, Rune Wiseth, Tor Erik Widerøe, and Terje Skjærpe

Hemodynamic alterations associated with the blood pressure response in subjects with white coat hypertension may provide insight into the pathophysiologic mechanisms of this condition. Systemic arterial hemodynamics were investigated with a recently validated method based on noninvasive estimates of aortic root pressure and flow in 28 subjects with white coat hypertension (diastolic pressure ≥ 90 mm Hg measured by the general practitioner [GP arterial pressure] and ambulatory daytime pressures $< 140/90$ mm Hg), in 23 subjects with previously untreated, ambulatory hypertension (GP diastolic pressure ≥ 90 and < 115 mm Hg and ambulatory daytime diastolic pressure ≥ 90 mm Hg), and in 32 normotensive subjects. The groups did not differ significantly concerning age, gender, body surface area, heart rate, stroke index and cardiac index, but total peripheral resistance index was increased and total arterial compliance reduced in the white coat group and the hypertensive group compared to the normotensive group. The subjects in the

white coat group with a systolic arterial pressure during echocardiography that was > 5 mm Hg higher than the ambulatory daytime systolic pressure ($n = 19$) had increased cardiac index, increased total peripheral resistance, and decreased total arterial compliance compared to the normotensive group. The subjects in this group with a hemodynamic pattern characterized by a high ratio of cardiac index/peripheral vascular resistance were significantly younger than the subjects with the opposite pattern. Thus, the blood pressure increase in subjects with white coat hypertension is associated with increased cardiac output, increased peripheral vascular resistance, and reduced total arterial compliance, but the hemodynamic pattern may be influenced by age. *Am J Hypertens* 1996;9:1090-1098

KEY WORDS: White coat hypertension, ambulatory blood pressure, hemodynamics, Doppler echocardiography, calibrated subclavian artery pulse trace.

Subjects with white coat hypertension are characterized by elevated arterial pressures in the physician's office, but "normal" pressures at other times.¹ Several studies have indicated a good prognosis of this condition by demonstrating a

low degree of end-organ damage.² The consequence is that subjects with white coat hypertension, which may represent 20% to 60% of a hypertensive population,^{1,3} may have a confounding effect in studies of heart disease as well as in clinical practice. However,

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others have shown that subjects with this condition exhibit end-organ damage^{4,5} and metabolic characteristics^{3,6} that differ from normal. It is therefore controversial whether subjects with white coat hypertension need increased medical surveillance or treatment.

The aim of this study was to investigate the pathophysiological mechanisms that generate the white coat blood pressure response. To accomplish this, we used a recently validated method based on noninvasive estimation of aortic root pressure and flow.⁷⁻⁹ Subjects who were evaluated as hypertensives by the general practitioner, but who had "normal" ambulatory daytime arterial pressures,¹⁰ were recruited for this study. Arterial blood pressures were in addition measured by a nurse according to a standardized procedure and during the echocardiographic examination. Hemodynamic variables obtained during echocardiography were evaluated in relation to the blood pressure response achieved during that examination.

METHODS

Study Subjects The study comprised three study groups that were not significantly different regarding age, gender and body surface area (Table 1). The white coat group consisted of 28 subjects with diastolic pressure in the general practitioner's office (GP arterial pressure) ≥ 90 mm Hg and ambulatory daytime arterial pressure $< 140/90$ mm Hg (Table 1). The main reasons for referral to the special ward for hypertension in our hospital were a tendency to blood pressure variability, increased heart rate associated with measurement of arterial pressure, young age, or an unspecified wish from the patient or from the physician to obtain a thorough evaluation before the start of medical therapy. Subjects who fulfilled the inclusion criteria were consecutively referred for echocardiography for evaluation of inclusion in the study. Three of the referred subjects were excluded, one because of valvular heart disease and two because of a poor echocardiographic window. Two subjects used antihypertensive medication that was stopped at least 4 weeks before inclusion. The remaining 26 subjects were previously untreated.

The group with ambulatory hypertension (hypertensive group) consisted of 23 previously untreated subjects with GP diastolic pressure ≥ 90 and < 115 mm Hg and ambulatory daytime diastolic pressure ≥ 90 mm Hg. These subjects were recruited directly from general practitioners with the aim of participating in a study of hemodynamics in hypertension. Twenty-four subjects with previously untreated, ambulatory hypertension were referred for echocardiography. One subject was excluded because of an inappropriate echocardiographic window.

All subjects in our database of normotensive, healthy subjects in the same age range as the hypertensive group were selected as controls for this study. Most subjects in that age range entered the database by a random selection of employees in the hospital. The normotensive group consisted of 32 subjects with diastolic pressure < 90 mm Hg measured by a nurse in the clinic. This pressure was determined in accordance with the requirements for the clinic arterial pressure as described below, but was performed on one day only.

Exclusion criteria for all groups were evidence of coronary heart disease, heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension, other major diseases, use of drugs, inappropriate echocardiographic window, and the inability to obtain a subclavian pulse trace.

All subjects gave written informed consent to the investigation, which was approved by the regional ethical committee.

Arterial Blood Pressure Measurements *GP Arterial Pressures* GP arterial pressures were measurements of brachial arterial pressures obtained in the general practitioner's office by the physician. The requirements for recording and analysis of these pressures were in accordance with the guidelines from The Norwegian College of General Practitioners.¹¹ If several pressures were presented at admittance in the clinic, an average of these was calculated.

Clinic Arterial Pressures Clinic arterial pressures were measured in the clinic with a mercury sphygmoma-

TABLE 1. GROUP CHARACTERISTICS

	Normotension	Hypertension	
		White Coat	Ambulatory
Gender (men/women)	19/13	16/12	14/9
Age (years)	48 \pm 7	47 \pm 13	48 \pm 7
Body surface area (m ²)	1.90 \pm 0.20	1.90 \pm 0.18	1.95 \pm 0.17
LVMI (g/m ²)	90 \pm 20	103 \pm 36	121 \pm 24*

Values are mean \pm SD.

* $P < .05$ v normotension and v white coat hypertension.

LVMI: left ventricular mass index, which was suitable for analysis in 29 normotensive subjects, 25 subjects with white coat hypertension, and 21 subjects with ambulatory hypertension.

nometer by an experienced nurse. Korotkoff phase V was used to determine the diastolic pressure. These measurements were obtained with the subject in the sitting position after resting for at least 15 min. They were performed on 3 different days with 1 week in between measurements. The two lowest of the three readings on each day were averaged and the average of the two lowest averages determined the clinic arterial pressures.

An ambulatory 24-h arterial blood pressure recording (Oxford, Medilog ABP, Oxford Medical, Inc., Clearwater, FL, or Suntech Accutacker II, Suntec Medical Instruments, Inc., Raleigh, NC) was performed on a normal work day. Ambulatory 24-h arterial pressures were defined as the mean of half-hourly recordings from 7 AM to 11 PM and hourly recordings from 12 PM to 6 AM. The nighttime recordings were missing in one subject, whereas five recordings were missing in another subject and between one and three recordings in seven other subjects. Ambulatory daytime arterial pressures were defined as the mean of half-hourly recordings from 7 AM to 11 PM. The editing of ambulatory pressures were done automatically, but manually controlled.

Oscillometric Arterial Pressures Oscillometric arterial were measurements of brachial arterial pressures recorded during the echocardiographic examination as outlined below. Clinic arterial pressures were initially measured on both arms to exclude significant deviations of arterial pressures between the right and left arm. Clinic and oscillometric arterial pressures reported in the study are all from measurements on the right arm, but the latter were recorded with the subject in the lateral decubitus position and the former with the subject in the sitting position. Ambulatory pressures were measured on the left arm except for a few cases in which the right arm was used.

Because the diastolic arterial pressures during echocardiography were considerably lower than the diastolic pressures obtained in the sitting subject, systolic pressures were used for the comparison of blood pressure responses (the increase in arterial pressure with regard to the ambulatory daytime systolic pressure) achieved during measurements of clinic pressures (Figure 1) and during echocardiography (Figure 2).

Noninvasive Data Recording All echocardiographic recordings and analysis were performed by the same investigator. The recordings were obtained with the patient in the left lateral decubitus position, and started after the patient had been at rest for at least 10 min. An ultrasound scanner (Vingmed CFM 750, Vingmed Sound, Horten, Norway) with a duplex probe (3.25-MHz imaging / 2.5-MHz Doppler) was used. The aortic annulus diameter was measured in the parasternal long axis view between the insertion points of the valve leaflets by use of the trailing-to-leading edge method.¹²

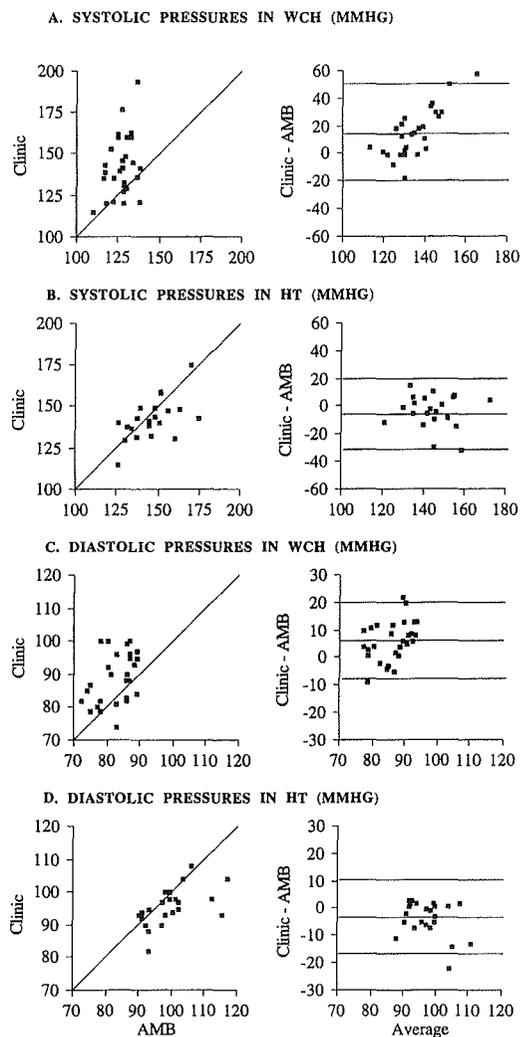


FIGURE 1. Plots show the association and the agreement between ambulatory daytime (AMB) pressures and the corresponding clinic arterial pressures (Clinic) for the white coat group (WCH) and the hypertensive group (HT). The equations for the regression line, the coefficients of correlation and the 95% limits of agreement were as follows: **A.** Systolic pressures in WCH: $y = 0.86x + 34$; $r = 0.33$, $P = .09$; 16 ± 36 . **B.** Systolic pressures in HT: $y = 0.54x + 63$; $r = 0.59$, $P = .003$; -3.5 ± 24 . **C.** Diastolic pressures in WCH: $y = 0.55x + 44$; $r = 0.38$, $P = .05$; 6 ± 14 . **D.** Diastolic pressures in HT: $y = 0.41x + 54$; $r = 0.56$, $P = .006$; -3.7 ± 14 . Horizontal lines indicate mean \pm 2SD.

The aortic annulus flow velocities¹³ were recorded by pulsed Doppler technique from the apical position with the sample volume positioned in the centre of the outflow tract just at the annulus, obtaining an optimal

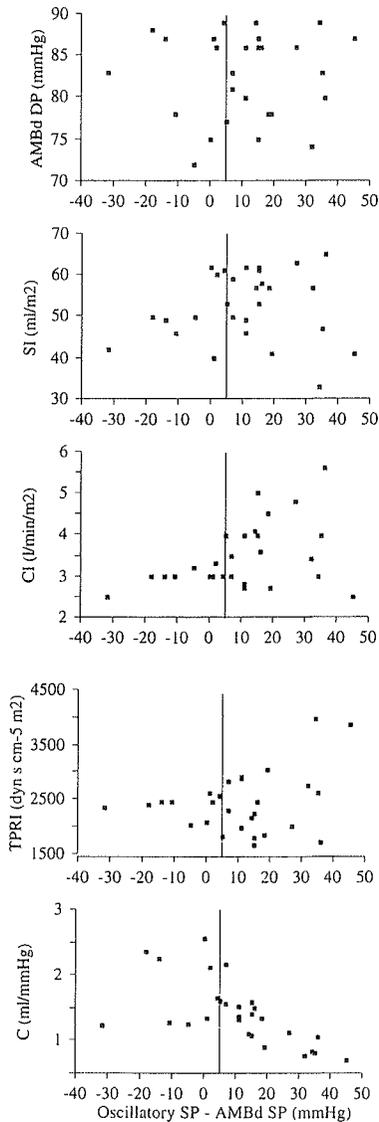


FIGURE 2. Plots show the distribution of hemodynamic variables in relation to the white coat blood pressure response during echocardiography (difference between oscillometric systolic and ambulatory daytime systolic pressure). AMBd DP: Ambulatory daytime diastolic pressure; AMBd SP: Ambulatory daytime systolic pressure; SI: stroke index; CI: cardiac index; TPRI: total peripheral resistance index; C: total arterial compliance. Vertical lines indicate a white coat response of 5 mm Hg (Group B is to the left and Group A to the right of this line).

flow velocity spectral profile and a distinct valve closure signal.

The subclavian artery pulse tracings were obtained

with a capillary damped funnel (Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery at its point of maximal impulse and connected to a strain-gauge transducer (model 120-0123, Irex Medical Systems, Ramsey, NJ) and displayed simultaneously with the Doppler velocity spectre on the monitor.^{9,14} Only pulse traces with a consistent wave morphology, a sharp deflection in early systole, and a minimal linear drift were used. Doppler recordings and pulse traces were obtained during a short period of apnea close to end-expiration. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiogram traces, to a computer for analysis (Macintosh II CI, Apple Computers Inc., Cupertino, CA).

M-mode echocardiographic images, guided by two-dimensional echocardiography, were obtained from the parasternal window and transferred to the computer.

Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP, Criticon Inc., Tampa, FL) every minute during the Doppler ultrasound study. The measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis.

Analysis of Echocardiographic Recordings Aortic root flow velocities and subclavian artery pulse traces were recorded and analyzed in all subjects ($n = 83$). The maximal velocity (ie, outer envelope of the Doppler spectrum) of at least three Doppler flow velocity profiles were traced manually and averaged. The subclavian artery pulse trace was calibrated with oscillometrically obtained systolic and diastolic pressures and the pulse transmission delay corrected by alignment of the pulse trace incisura to the end systole of the Doppler flow trace.⁸

M-mode recordings were suitable for analysis in 75 subjects (M-mode recordings were rejected in three subjects in the normotensive group, three subjects in the white coat group, and two subjects in the hypertensive group). It was required that the right and the left side of the endocardial septum and the endocardial and epicardial surfaces of the posterior left ventricular wall be recorded continuously in at least three cardiac cycles.

The examiner was blinded for the arterial pressures, but not for the category of the subjects.

Analysis of Data The flow and pressure traces were processed by specially designed computer software in which the properties of the arterial circulation were estimated according to a three element Windkessel model of the systemic arterial tree.⁸ In this model, the total arterial compliance represents the volume compliance of the arteries, characteristic impedance is an expression of the resistance to pulsatile flow in the proximal aorta, and peripheral resistance represents the arte-

riolar resistance. Heart rate was determined from electrocardiogram (ECG) recordings during the echocardiographic investigation. Mean arterial pressure was calculated as the pressure integral over the total cardiac cycle.⁸ Pulse pressure was defined as the difference in systolic and diastolic pressures. Stroke volume was calculated as the product of the Doppler velocity-time integral and the aortic cross-sectional area assuming a circular valve annulus.¹² Cardiac output was calculated as stroke volume times heart rate. The corresponding indices were obtained by dividing by the body surface area.¹⁵ Total peripheral resistance was calculated as the mean arterial pressure over cardiac output, multiplied by 80 for unit conversion. The corresponding index was obtained by multiplying by the body surface area.

Left ventricular mass was calculated from M-mode echocardiograms using the formula according to the Penn convention (Penn-cube LV mass)¹⁶:

$$1.04\{(\text{IVSd} + \text{LVIDd} + \text{PWTd})^3 - (\text{LVIDd})^3\} - 13.6,$$

where LVIDd is the end-diastolic left ventricular internal diameter, IVSd is the end-diastolic intraventricular septal diameter, and PWTd is the end-diastolic posterior wall thickness. The corresponding index was obtained by dividing by the body surface area.

Statistical Analysis Continuous variables are expressed as means \pm standard deviation (SD). Comparisons between the groups were performed with analysis of variance. Within group comparisons were performed with analysis of variance for repeated measurements. When the difference in the overall comparison of groups in the analysis of variance was significant ($P < .05$), post hoc comparisons were performed with the Scheffé test. Relationships between variables were tested with linear regression analysis and Pearson's coefficient of correlation. The coefficient of variation (%) was calculated as the standard deviation of the differences divided by the mean of the initial values. The 95% limits of agreement were calculated as the mean difference \pm the standard deviation of the differences $\times 2$.¹⁷ Agreement was illustrated by plotting the differences against their average.

Reproducibility Intraobserver reproducibility of the variables of the noninvasive method used in this study were assessed by comparing measurements obtained in 30 subjects with ambulatory hypertension on two occasions, 8 weeks apart. The results for the following variables comprises variability due to recording, analysis as well as biological variability. The aortic annulus diameter obtained at the first occasion was used for calculation of hemodynamic variables at both occasions, specifically, oscillometric systolic pressure (6%; 3 ± 18 mm Hg, coefficient of variation; 95% limits of agreement), oscillometric diastolic pressure (8%; 0 ± 13 mm Hg), mean arterial pressure (6%; 1 ± 13 mm Hg), Doppler velocity-time integral of aortic root flow

(7%; 0 ± 3 cm), left ventricular stroke volume (7%; -2 ± 15 mL), cardiac output (11%; -0.28 ± 1.5 L), peripheral resistance (11%; 27 ± 283 dyne/sec/cm⁵), total arterial compliance (11%; -0.04 ± 0.33 mL/mm Hg), and aortic characteristic impedance (34%; 16 ± 44 dyne/sec/cm⁵). Intraobserver reproducibility of the aortic annulus diameter was assessed by comparing measurements in 16 normotensive adults on two occasions 2 weeks apart (2.5%; 0.02 ± 0.11 cm). Interexaminer and interanalyzer reproducibility of the method have been reported previously.⁸

RESULTS

Arterial Blood Pressures Although the subjects with white coat hypertension had significantly lower clinic and oscillometric systolic and diastolic pressures than GP systolic and diastolic pressures, the clinic systolic and diastolic pressures and the oscillometric systolic pressure were significantly higher than the respective ambulatory daytime arterial pressures, indicating that these subjects had an arterial pressure response during measurement of arterial pressures by a nurse and during echocardiography (Table 2). During the measurement of clinic arterial pressures, 19 subjects (10 men and 9 women) had a > 5 mm Hg higher systolic pressure compared with their ambulatory daytime systolic pressure (Figure 1). While a corresponding blood pressure response was shown by an equivalent number of subjects (9 men and 10 women) during echocardiography (oscillometric arterial pressures), 14 subjects showed that degree of blood pressure response on both examinations.

There was no significant difference between the white coat group and the hypertensive group concerning GP, clinic, and oscillometric systolic pressures, but the corresponding diastolic pressures were significantly lower in the white coat group (Table 2), which indicates that the pulse pressures were wider in the white coat group on all three procedures.

Figure 1 illustrates the poor relationship and agreement between ambulatory daytime arterial pressures and clinic arterial pressures in the white coat group compared to the hypertensive group. It is interesting to notice that clinic arterial pressures tended to be lower than the ambulatory daytime arterial pressures in the hypertensive group.

Hemodynamic Characteristics of the Study Groups The study groups were not significantly different concerning heart rate, stroke index, and cardiac index (Table 3). In the white coat group, but not in the other two groups, there was a significant correlation between heart rate and mean arterial pressure ($r = 0.5$, $P = .009$). The white coat group was significantly different from the normotensive group, but not from the hypertensive group concerning total peripheral resistance index, peripheral resistance, aortic characteristic impedance, and total arterial compliance (Table 3).

TABLE 2. ARTERIAL PRESSURES

	Normotension (n = 32)	Hypertension		P
		White Coat (n = 28)	Ambulatory (n = 23)	
GP SP (mm Hg)		161 ± 21	160 ± 17	.8
GP DP (mm Hg)		100 ± 6	105 ± 5	.0002
Clinic SP (mm Hg)	118 ± 13	142 ± 16*	142 ± 12*	.0001
Clinic DP (mm Hg)	77 ± 6	89 ± 8*	96 ± 6*†	.0001
Oscillometric SP (mm Hg)	108 ± 12	137 ± 19*	140 ± 11*	.0001
Oscillometric DP (mm Hg)	61 ± 7	75 ± 11*	82 ± 9*†	.0001
MAP (mm Hg)	82 ± 8	103 ± 14*	108 ± 9*	.0001
AMB 24 h SP (mm Hg)		122 ± 7	142 ± 13	.0001
AMB 24 h DP (mm Hg)		80 ± 6	97 ± 7	.0001
AMB daytime SP (mm Hg)		127 ± 6	145 ± 13	.0001
AMB daytime DP (mm Hg)		83 ± 5	99 ± 8	.0001

Values are mean ± SD.

*P < .05 v normotension.

†P < .05 v white coat hypertension.

GP: general practitioner; SP: systolic pressure; DP: diastolic pressure; MAP: mean arterial pressure; AMB: ambulatory blood pressure.

Table 4 and Figure 2 shows characteristics of the subjects in the white coat group with (Group A) and without (Group B) a blood pressure response during echocardiography, as defined above. While age, heart rate, and cardiac index were significantly higher, total arterial compliance was significantly lower in Group A than in Group B, but there were no differences concerning stroke index and total peripheral resistance index. Moreover, cardiac index and total peripheral resistance index were both increased in Group A compared to the normotensive group ($P < .05$).

To study whether there were any characteristics associated with a high ratio of vascular resistance / cardiac output and vice versa, Group A was divided into groups according to total peripheral resistance index

below and above mean total peripheral resistance index ± 1 SD in the normotensive group (ie, below and above 2400 dyn/s/cm²). The 10 subjects (4 men/6 women) in the low vascular resistance group were younger (45 ± 10 v 56 ± 7 years, $P = .01$) and had significantly increased heart rate (77 ± 11 v 63 ± 11 beats/min, $P = .01$), stroke index (57 ± 5 v 48 ± 9 mL/m², $P = .01$) and cardiac index (4.5 ± 0.6 v 3.1 ± 0.5 L/min/m², $P < .0001$) compared to the other group. There were no differences between these groups concerning body surface area, left ventricular mass index, ambulatory blood pressures, clinic arterial pressures, oscillatory arterial pressures, blood pressure response during echocardiography, or total arterial compliance (all $P = NS$).

TABLE 3. HEMODYNAMIC CHARACTERISTICS

	Normotension (n = 32)	Hypertension		P
		White Coat (n = 28)	Ambulatory (n = 23)	
Heart rate (beats/min)	64 ± 8	67 ± 12	68 ± 6	.3
Aortic VTI (cm)	23 ± 4	24 ± 4	24 ± 4	.4
LVOT (cm)	2.34 ± 0.19	2.31 ± 0.21	2.34 ± 0.16	.8
SI (mL/m ²)	52 ± 11	53 ± 8	53 ± 7	.9
CI (L/min/m ²)	3.3 ± 0.8	3.5 ± 0.8	3.6 ± 0.5	.3
TPRI (dyne/sec/cm ⁵ /m ²)	2059 ± 370	2436 ± 565*	2458 ± 347*	.001
R (dyne/sec/cm ⁵)	1022 ± 206	1207 ± 305*	1186 ± 176*	.006
C (mL/mm Hg)	1.92 ± 0.51	1.42 ± 0.49*	1.57 ± 0.46*	.0006
Z (dyne/sec/cm ⁵)	69 ± 21	89 ± 36*	81 ± 22	.02

Values are mean ± SD.

*P < .05 v normotension.

VTI: Doppler velocity-time integral; LVOT: aortic annulus diameter; SI: stroke index; CI: cardiac index; TPRI: total peripheral resistance index; R: peripheral resistance; C: total arterial compliance; Z: aortic characteristic impedance.

TABLE 4. CHARACTERISTICS OF GROUPS WITH A BLOOD PRESSURE RESPONSE > 5 mm Hg (GROUP A) AND < 5 mm Hg (GROUP B)

	Group A	Group B	P
Gender (men/women)	9/10	7/2	.1
Age (years)	51 ± 10	39 ± 14	.02
Body surface area (m ²)	1.86 ± 0.19	1.99 ± 0.14	.08
LVMI (g/m ²)	98 ± 38	116 ± 24	.3
AMB daytime SP (mm Hg)	126 ± 6	127 ± 9	.8
AMB daytime DP (mm Hg)	83 ± 5	83 ± 6	.9
Clinic SP (mm Hg)	147 ± 19	134 ± 14	.06
Clinic DP (mm Hg)	90 ± 7	88 ± 9	.5
Oscillometric SP (mm Hg)	146 ± 14	119 ± 12	.0001
Oscillometric DP (mm Hg)	79 ± 7	68 ± 12	.0001
MAP (mm Hg)	109 ± 10	90 ± 11	.0001
Heart rate (beats/min)	70 ± 13	60 ± 8	.05
SI (mL/m ²)	53 ± 9	51 ± 7	.5
CI (L/min/m ²)	3.8 ± 0.9	3.0 ± 0.2	.02
TPRI (dyne/sec/cm ⁵ /m ²)	2463 ± 677	2380 ± 202	.7
R (dyne/sec/cm ⁵)	1243 ± 361	1133 ± 109	.4
C (mL/mm Hg)	1.25 ± 0.37	1.78 ± 0.54	.005
Z (dyne/sec/cm ⁵)	98 ± 38	71 ± 21	.06

Values are mean ± SD.

LVMI: left ventricular mass index; AMB: ambulatory blood pressure; SP: systolic pressure; DP: diastolic pressure; MAP: mean arterial pressure; SI: stroke index; CI: cardiac index; TPRI: total peripheral resistance index; R: peripheral resistance; C: total arterial compliance; Z: aortic characteristic impedance.

DISCUSSION

A definition of white coat hypertension that assumes a completely normal cardiovascular status during everyday life may implicate a lower ambulatory blood pressure cut-off than used in this study.¹⁰ However, since there is no general agreement on the definition of white coat hypertension, we used current procedures in this hospital for the selection of subjects with white coat hypertension, even though this may give access to subjects with borderline hypertension.

This study has shown that subjects who had an arterial systolic pressure during the echocardiographic examination that was > 5 mm Hg higher than the ambulatory daytime systolic pressure had increased vascular resistance as well as increased cardiac output compared to a normotensive control group. The subjects in this group who had an increased cardiac output/low peripheral vascular resistance pattern were younger than the subjects with the opposite pattern.

Increased sympathetic nervous system activity, which is considered to be an important pathogenetic mechanism in borderline hypertension,¹⁸ as well as in white coat hypertension,⁶ most appropriately explains the blood pressure response in subjects with white coat hypertension. However, the different hemodynamic patterns seen in individual subjects may indicate that activity of other neuroendocrine mechanisms, such as the renin angiotensin system⁶ and the parasympathetic system, may modulate the sympathetic activity.¹⁹

Different hemodynamic patterns with advancing

age may be due to an increased ratio of norepinephrine to epinephrine secretion,²⁰ but a different responsiveness to catecholamines²¹ may also play a role. The tendency toward increased vascular resistance and reduced cardiac output with advancing age,²² regardless of underlying etiology, will tend to reinforce this hemodynamic pattern because an increased afterload is imposed on the left ventricle with diminished contractile reserve,²³ thereby creating a vicious circle. However, to investigate whether hemodynamics associated with the white coat arterial pressure response convert from one pattern to another pattern with advancing age requires a follow-up study.

While cardiac output and peripheral vascular resistance determine the mean arterial pressure, the degree of large artery stiffness contributes to determining the arterial pulse pressure.²⁴ Although arteriolar resistance represents the major part of the total peripheral resistance, the resistance to pulsatile flow, determined by the large arteries, may have a relatively large impact on left ventricular function.²⁵⁻³⁰ Total arterial compliance and aortic characteristic impedance are variables that may be used to indicate the degree of large artery stiffness.³¹

The reduced total arterial compliance associated with the white coat arterial pressure increase in this study was probably due to increased arterial distension pressure, but an additional effect induced by large artery vasoconstriction cannot be excluded. In this regard it was interesting to notice that the white coat group tended to have wider pulse pressures than

the hypertensive group for similar arterial pressure levels, not only during the echocardiographic examination, but also during the examination by the general practitioner and in the clinic. If this represents an increased large artery smooth muscle tonus, it may indicate that these subjects have an increased vascular responsiveness.

However, alternative explanations for the difference in pulse pressure between the white coat group and the hypertensive group must be considered. The possibility of a reduced elastic modulus of the arterial wall in hypertension was discussed in a recent publication.³² Although there is large evidence that vascular remodeling in ambulatory hypertension will tend to decrease arterial compliance by increasing vascular wall thickness, studies in animals have provided evidence for the opposite.

The clinical significance of hemodynamics in borderline hypertension has been a matter of debate for years.^{33,34} Although white coat hypertension may be considered a special case of borderline hypertension and may serve as a model for the understanding of the pathophysiological mechanisms of early hypertension, the results of the present study may not simply be extrapolated to borderline hypertension as traditionally defined. Moreover, since most earlier studies on hemodynamics in borderline hypertension did not use ambulatory blood pressure monitoring for the categorization of subjects, hypertension in several of these subjects may have been due to an alerting reaction,³⁵ which complicates the issue considerably. However, we have shown that the evaluation of hemodynamics in hypertension with a completely non-invasive method is feasible. This method, which integrates simultaneous recordings of pressure and flow, may provide important information about the pathophysiology of hypertension and thereby contribute to the classification of subjects into groups with different disease mechanisms and possibly different prognoses.

Another important clinical implication of this study is that it may indicate that ambulatory blood pressure monitoring is required for the categorization of hypertensive subjects, since the subjects in the white coat group showed a pronounced white coat arterial blood pressure response even by the careful measurements of arterial pressures performed by a nurse and under the quiet circumstances during echocardiography.

CONCLUSION

The blood pressure response in subjects with white coat hypertension is associated with increased cardiac output, increased peripheral vascular resistance, and reduced total arterial compliance, but the hemodynamic pattern may be influenced by age. The reduced total arterial compliance is probably a consequence of passive distension of the arterial wall, but an in-

creased large artery smooth muscle tonus cannot be excluded.

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Paper II

Paper II

Left Ventricular Systolic and Diastolic Function Assessed With Two-Dimensional and Doppler Echocardiography in "White Coat" Hypertension

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Objectives. The aim of this study was to investigate left ventricular function in subjects with "white coat" hypertension, defined as office arterial diastolic pressure ≥ 90 and ambulatory daytime pressures $< 140/90$ mm Hg.

Background. The white coat arterial pressure response may, by influencing left ventricular function, have a confounding effect in studies of heart disease.

Methods. Two-dimensional and Doppler echocardiography, combined with the calibrated subclavian arterial pulse tracing, were used to assess variables of left ventricular function in 26 subjects with white coat hypertension, as well as 22 subjects with previously untreated ambulatory hypertension (office arterial diastolic pressure ≥ 90 and < 115 mm Hg and ambulatory daytime diastolic pressure ≥ 90 mm Hg) and 32 normotensive subjects.

Results. In subjects with white coat hypertension, systolic arterial pressure during the echocardiographic examination was

significantly higher than ambulatory daytime systolic pressure. This pressure response was positively related to the ratio of the systolic to diastolic pulmonary venous flow peak velocities and to the peak velocity of flow reversion during atrial systole; it was inversely related to the ratio of early to late mitral flow peak velocities. Left ventricular stroke volume, ejection fraction and velocity of circumferential fiber shortening did not differ in the study groups, but left ventricular external work and end-systolic wall stress were increased in the white coat group.

Conclusions. The arterial pressure response in subjects with white coat hypertension is associated with increased left ventricular external work, increased end-systolic wall stress and alterations of left ventricular filling but normal ejection fraction and velocity of circumferential fiber shortening.

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Subjects who have an exaggerated arterial pressure response in the physician's office but normal average 24-h arterial pressures are considered to have "white coat" hypertension (1). The prognosis in this condition, determined by assessment of end-organ damage, appears to be benign (2-4). However, even though the degree of end-organ damage is low, there are features that may indicate a need for careful medical surveillance of such subjects (5). Moreover, such subjects, who may represent 20% to 60% of a hypertensive population (1,5), may be considered as confounders in studies of heart disease as well as in clinical practice.

Information about left ventricular dysfunction is important because it may be a sensitive indicator of hypertensive heart disease (6-8). There are few reports (2,9) on left ventricular diastolic and systolic function in subjects with white coat hypertension.

The purpose of this study was to investigate left ventricular systolic and diastolic function assessed with two-dimensional and Doppler echocardiography in subjects with evidence of white coat hypertension and to compare the findings with those in subjects with untreated ambulatory hypertension and normotensive subjects. We recruited for this study subjects who, although evaluated as having hypertension by the general practitioner (physician arterial pressures), had "normal" ambulatory daytime arterial pressures (10). However, arterial blood pressures in these subjects were also measured by a nurse according to a standardized procedure on admission to the ward for hypertension in our hospital (clinic arterial pressures) and during the echocardiographic examination (oscillometric arterial pressures).

Methods

Study subjects. The study comprised three groups that did not differ significantly in age, gender and body surface area (Table 1). The *white coat hypertensive group* consisted of 26 previously untreated subjects with diastolic pressure in the general practitioner's office (office arterial pressure) ≥ 90 mm Hg and ambulatory daytime pressure $< 140/90$ mm Hg (Table 1). The main reasons for referral to the special ward for hypertension in

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Table 1. Group Characteristics

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
Men/women	19/13	14/12	13/9	0.9
Age (yr)	48 ± 7	46 ± 13	48 ± 7	0.8
Body surface area (m ²)	1.90 ± 0.20	1.90 ± 0.18	1.95 ± 0.17	0.6
Pressures (mm Hg)				
Office SP		159 ± 19	159 ± 17	0.9
Office DP		98 ± 5	105 ± 5	0.0001
Clinic SP	118 ± 13	143 ± 19*	141 ± 12*	0.0001
Clinic DP	77 ± 6	89 ± 8*	96 ± 6*†	0.0001
Amb 24-h SP		122 ± 7	142 ± 13	0.0001
Amb 24-h DP		79 ± 6	97 ± 7	0.0001
Amb daytime SP		127 ± 7	145 ± 14	0.0001
Amb daytime DP		83 ± 5	99 ± 8	0.0001

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. Data presented are mean value ± SD. Amb = ambulatory; DP = diastolic arterial pressure; SP = systolic arterial pressure.

our hospital were a tendency to blood pressure variability, increased heart rate associated with measurement of arterial pressure, young age or because the patient or his physician wanted a more thorough evaluation before initiation of medical therapy. Subjects who fulfilled the inclusion criteria were consecutively referred for echocardiographic evaluation for inclusion in the study. Five of the referred subjects were excluded: one with valvular heart disease, two with a poor echocardiographic window and two who had used antihypertensive medication.

The group with ambulatory hypertension (*ambulatory hypertensive group*) consisted of 22 previously untreated subjects with office diastolic pressure ≥90 and <115 mm Hg and ambulatory daytime diastolic pressure ≥90 mm Hg. These subjects were recruited from general practitioners, who had referred 24 subjects with previously untreated ambulatory hypertension for echocardiography; 2 were excluded because of inappropriate echocardiographic window.

The *normotensive group* consisted of 32 subjects with diastolic pressure <90 mm Hg measured by a nurse in the clinic. This pressure was determined in accordance with the requirements for the clinic arterial pressure as described later, but was performed on 1 day only. The subjects were randomly selected from healthy employees in the hospital and matched for age and gender with the hypertensive control group.

Exclusion criteria for all groups were evidence of coronary heart disease, heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension, other major diseases or use of drugs and inappropriate echocardiographic window.

All subjects gave written informed consent for the investigation, which was approved by the regional ethical committee.

Arterial blood pressure measurements. *Office arterial pressures* were measurements of brachial artery pressures obtained by the physician in the general practitioner's office. The requirements for recording and analysis of these pressures were in accordance with the guidelines from The Norwegian

College of General Practitioners (11). If several pressures were presented on admission to the clinic, an average of these was calculated.

Clinic arterial pressures were measured in the clinic by an experienced nurse using a mercury sphygmomanometer. Korotkoff phase V was used to determine clinic diastolic pressures. These measurements, obtained with the subject seated after >15 min of rest, were performed on 3 days, 1 week apart. The two lowest of three readings on each day were averaged and the average of the two lowest averages determined the clinic arterial pressures. Clinic arterial pressures were initially measured in both arms to exclude significant deviations of arterial pressures between the right and left arms. Later the right arm alone was used.

An ambulatory 24-h pressure recording (Oxford Medilog ABP, Oxford Medical) or Suntech Accutracker II, Suntec Medical Instruments) was performed on a normal workday. *Ambulatory 24-h pressures* were defined as the mean of half-hourly recordings from 7 AM to 11 PM and hourly recordings from 12 PM to 6 AM. *Ambulatory daytime pressures* were defined as the mean of half-hourly recordings from 7 AM to 11 PM. Whereas all clinic arterial pressures were measured in the right arm, ambulatory arterial pressures were measured in the left arm except for a few cases in which the right arm was used.

Oscillometric arterial pressures. Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP, Criticon) every minute during the Doppler ultrasound study. The two measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis.

Echocardiography. All echocardiographic recordings and analyses were performed by the same investigator. An ultrasound scanner (Vingmed CFM 750, Vingmed Sound, Horten, Norway) with a duplex probe (3.25-MHz imaging/2.5-MHz Doppler) was used. The study subjects rested >10 min before they were examined in a left lateral decubitus position. Recordings were performed in end-expiration. A specially designed computer software (Echodisp 4.0, Vingmed Sound) was used for analysis. Doppler, two-dimensional and M-mode echocardiograms were analyzed independently from each other and without knowledge of the arterial pressures, but the category of the subjects was known. Whereas two-dimensional and Doppler echocardiographic recordings of aortic flow were analyzed in all 80 subjects, M-mode echocardiographic recordings were suitable for analysis in 73 subjects and Doppler recordings of mitral and pulmonary venous flow in 75 and 72 subjects, respectively.

Aortic root pressure and flow. The aortic annulus flow velocities were recorded by pulsed Doppler technique from the apical position with the sample volume positioned in the center of the outflow tract just at the annulus, obtaining an optimal flow velocity spectral profile and a distinct valve closure signal. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiographic (ECG) tracings, to the computer for analysis. The maximal velocity (i.e., outer envelope of the Doppler spectrum) of at

least three aortic root Doppler flow-velocity curves were traced manually and averaged. The subclavian artery pulse tracings were obtained with a capillary damped funnel (Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery at its point of maximal impulse and connected to a strain gauge transducer (model 120-0123, Irex Medical Systems) and displayed simultaneously with the Doppler velocity spectra of the aortic root flow on the monitor (12,13). Only pulse tracings with a consistent wave morphology, a sharp deflection in early systole and a minimal linear drift were used. The pulse tracing was calibrated with oscillometrically obtained systolic and diastolic pressures and the pulse transmission delay corrected by alignment of the pulse tracing incisura to the end-systole of the Doppler flow tracing. The calibrated subclavian pulse tracing closely matches the aortic root pressure (12-14).

Two-dimensional echocardiography. The aortic annulus diameter was measured in the parasternal long-axis view between the insertion points of the valve leaflets by use of the trailing to leading edge method. The left ventricular apical four-chamber, two-chamber, long-axis views and the parasternal short-axis view located at the tip of the papillary muscles were transferred to a computer (Macintosh II series, Apple Computers) as scanline data, that is without loss of ultrasound information, providing a frame rate of 47 frames/s with the standard angle and depth. This provides an excellent condition for reviewing cine-loops at different speeds. The endocardial surface in the apical four-chamber view and the endocardial and epicardial surfaces in the short-axis view were traced manually on end-diastolic (the frame according to the R wave on the ECG) and on end-systolic (the frame before opening of the mitral valve) frames according to the convention of Wyatt et al. (15) and Vuille and Weyman (16). The papillary muscles were considered part of the left ventricular cavity. The following variables were determined: the left ventricular long axis (L) measured on end-diastolic (Led) and end-systolic apical four-chamber frames as the distance from the mitral annulus to the apex, the apical part of the end-systolic long-axis (a), truncated at the level of the tips of the papillary muscles, the short-axis end-diastolic (Ded) and end-systolic (Des) diameters, the short-axis end-diastolic (hed) and end-systolic (hes) wall thicknesses and the short-axis end-diastolic (A1ed) and end-systolic epicardial and end-diastolic (A2ed) and end-systolic endocardial areas.

M-mode echocardiography. M-mode echocardiograms of the left ventricle were obtained from the parasternal window, guided by two-dimensional echocardiography. Tracings from the level of the tip of the papillary muscles were transferred to the computer. It was required that the right and left endocardium of the septum and the endocardial and epicardial surfaces of the posterior left ventricular wall be recorded continuously in at least three cardiac cycles. The end-diastolic left ventricular internal diameter (LVIDd), the end-diastolic intra-ventricular septal thickness (IVSd) and the end-diastolic posterior wall thicknesses (PWTd) were determined according to the Penn convention (17).

Doppler echocardiography of mitral flow and pulmonary flow. Mitral and pulmonary flow velocities were recorded by pulsed Doppler technique, from the apical position, between

the mitral leaflets and in the upper right pulmonary vein, respectively. Data from at least five consecutive cardiac cycles were transferred to the computer. The maximal velocity of at least three mitral and pulmonary venous Doppler flow velocity profiles was traced and averaged. From the mitral flow velocity tracings, early mitral flow peak velocity and deceleration time and peak velocity and duration of the late flow were measured. The peak velocity and time-velocity integral during systolic and diastolic pulmonary venous flow and the maximal velocity, velocity integral and duration of the flow reversion during atrial systole were measured.

Analysis of data. Mean aortic pressure (MAP [mm Hg]) was determined as the pressure integral under the calibrated subclavian pressure tracing (12,13). Aortic end-systolic pressure (Pes [mm Hg]) was determined at the incisura of the calibrated pulse tracing. Instantaneous aortic flow ($Q(t)$ [ml·s⁻¹]) was calculated as the product of the instantaneous Doppler aortic blood flow velocity and aortic annular cross-sectional area (18). Mean aortic flow (Q [ml·s⁻¹]) was calculated as the integral of the instantaneous aortic flow. Left ventricular total power (\dot{W}_{tot} [mW]) was calculated from instantaneous pressure [$P(t)$] and flow [$Q(t)$] (19) as follows:

$$\dot{W}_{tot} = \frac{1}{T} \int_0^T P(t)Q(t) dt, \quad [1]$$

where T is the duration of the cardiac cycle. Steady power (\dot{W}_{std} [mW]) was calculated from mean aortic pressure and flow:

$$\dot{W}_{std} = MAP \times Q. \quad [2]$$

Oscillatory power (\dot{W}_{osc} [mW]) was calculated as

$$\dot{W}_{osc} = \dot{W}_{tot} - \dot{W}_{std}. \quad [3]$$

Left ventricular end-diastolic (Ved) and end-systolic volumes (Ves) were calculated from two-dimensional echocardiograms according to the following general formula (15,20):

$$V = \frac{5}{6} \times A_2 \times L, \quad [4]$$

where V is left ventricular volume, A_2 is the endocardial short-axis area, and L is the long-axis dimension in end-diastole and in end-systole, respectively.

Left ventricular mass was calculated according to an extended version of equation 4 (21-23):

$$LVM_{2D} = 1.05 \times \left\{ \frac{5}{6} \times A_{1ed} \times (Led + hed) - \frac{5}{6} \times A_{2ed} \times Led \right\}, \quad [5]$$

where LVM_{2D} = left ventricular mass by two-dimensional echocardiography, 1.05 is the density of the myocardium, A_{1ed} is the left ventricular epicardial short-axis area, Led is the long-axis dimension, hed is the mean wall thickness, and A_{2ed} is the endocardial short-axis area, all in end-diastole. Relative wall thickness (RWT [%]) was calculated as $200 \times hed/(Ded)$, where Ded is end-diastolic short-axis diameter. Sphericity index (%) was calculated as $100 \times Ded/Led$ (24). Left ventricular mass was also

calculated from M-mode echocardiograms according to the following formula (25):

$$LVM_{M-mode} = 1.04\{(LVIDd + IVSd + PWTd)^3 - LVIDd^3\} - 13.6, \quad [6]$$

where LVM_{M-mode} = left ventricular mass by M-mode echocardiography.

Heart rate was determined from ECG recordings during the echocardiographic investigation. Left ventricular ejection time (LVET [ms]) was determined from the beginning of blood flow to the valve closure click on the aortic Doppler velocity trace and rate corrected (LVETc [ms]) by dividing with the square root of cardiac cycle length. Left ventricular stroke volume (SV) was calculated as $V_{ed} - V_{es}$, where V_{ed} and V_{es} = left ventricular volumes in end-diastole and end-systole, respectively. Left ventricular ejection fraction (EF [%]) was calculated as $100 \times SV/V_{ed}$. Left ventricular fractional shortening (FS [%]) was calculated as $100 \times (D_{ed} - D_{es})/D_{ed}$, where D_{es} = the short-axis end-systolic diameter. Left ventricular velocity of circumferential fiber shortening was calculated as $10 \times FS/LVET$. Rate-corrected velocity of circumferential fiber shortening was calculated as $10 \times FS/LVETc$ (26,27). Left ventricular meridional (σ_m [kdyn·cm⁻²]) and circumferential (σ_c [kdyn·cm⁻²]) end-systolic wall stresses were calculated, respectively, as (28,29):

$$\sigma_m = 1.33 \text{ Pes} \left[\frac{\text{Des}}{4 \text{ hes} \left(1 + \frac{\text{hes}}{\text{Des}} \right)} \right], \quad [7]$$

$$\sigma_c = 1.33 \text{ Pes} \frac{\text{Des}}{4 \text{ hes}} \times \frac{8a^2 - \text{Des}^2}{4a^2 + \text{hes Des}}. \quad [8]$$

Indexed variables were obtained by dividing with the respective body surface area calculated according to the method of Du Bois and Du Bois (30).

Statistical analysis. Statistical analysis was carried out by using StatView 4.1 software (Abacus Concepts). Continuous variables are expressed as mean value \pm SD. Comparisons between groups were performed with one-way analysis of variance. Frequencies were analyzed by Kruskal-Wallis test. When the overall comparison of groups in the analysis of variance indicated significant differences ($p < 0.05$), post hoc comparisons were performed with the Scheffé test. Relations between variables were tested with Pearson's coefficient of correlation. The coefficient of variation (%) was calculated as the standard deviation of the differences divided by the mean of the initial values. The 95% limits of agreement were calculated as the mean difference \pm the standard deviation of the differences $\times 2$ (31).

Reproducibility. Intraobserver reproducibility was assessed by comparing measurements in 16 normotensive adults on two occasions, 2 weeks apart. Interexaminer and interanalyzer reproducibility of the noninvasive method have been reported previously (12).

Table 2. Left Ventricular External Work

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
Pressures (mm Hg)				
Oscillometric SP	108 \pm 12	137 \pm 19*	140 \pm 11*	0.0001
Oscillometric DP	61 \pm 7	75 \pm 11*	82 \pm 9*†	0.0001
MAP	82 \pm 8	103 \pm 14*	108 \pm 9*	0.0001
Pes	92 \pm 10	117 \pm 17*	122 \pm 10*	0.0001
LVOT (cm)	2.34 \pm 0.19	2.30 \pm 0.21	2.34 \pm 0.16	0.8
Aortic VTI (cm)	23 \pm 4	24 \pm 4	24 \pm 4	0.4
Power (mW)				
Total	1,360 \pm 436	1,858 \pm 580*	1,974 \pm 377*	0.0001
Steady	1,147 \pm 351	1,570 \pm 498*	1,677 \pm 319*	0.0001
Oscillatory	213 \pm 107	288 \pm 100*	296 \pm 81*	0.004

* $p < 0.05$ versus normotensive group. † $p < 0.05$ versus white coat hypertensive group. Data presented are mean value \pm SD. LVOT = aortic annulus diameter; MAP = mean aortic pressure; VTI = Doppler velocity-time integral; other abbreviations as in Table 1.

Results

In the white coat group the clinic systolic and diastolic pressures and the oscillometric systolic pressure were significantly higher than the respective ambulatory daytime pressures. These findings indicate that these subjects had a pressure response during measurements of arterial pressures by a nurse and during the echocardiographic examination (Tables 1 and 2). Additional support for a pressure response during echocardiography was provided by the increased left ventricular external work in this group (Table 2).

Left ventricular systolic function evaluated by stroke volume, ejection fraction and fractional shortening did not differ signifi-

Table 3. Left Ventricular Systolic Function

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
EDVI (ml·m ⁻²)	85 \pm 17	83 \pm 15	91 \pm 16	0.2
ESVI (ml·m ⁻²)	35 \pm 8	32 \pm 9	33 \pm 9	0.4
Stroke index (ml·m ⁻²)	50 \pm 13	51 \pm 13	58 \pm 14	0.07
Ejection fraction (%)	59 \pm 7	61 \pm 9	64 \pm 9	0.08
Fractional shortening (%)	27 \pm 6	28 \pm 7	31 \pm 11	0.08
Heart rate (beats/min)	64 \pm 8	69 \pm 12	68 \pm 6	0.1
LVET (ms)	310 \pm 20	308 \pm 24	296 \pm 21	0.06
LVETc (ms)	320 \pm 20	327 \pm 23	315 \pm 17	0.16
Vcf (circs ⁻¹)	0.87 \pm 0.19	0.93 \pm 0.21	1.06 \pm 0.27*	0.01
Vcfc (circs ⁻¹)	0.85 \pm 0.18	0.88 \pm 0.19	0.99 \pm 0.24*	0.04
σ_m es (kdyn·cm ⁻²)	65 \pm 10	78 \pm 23*	69 \pm 20	0.02
σ_c es (kdyn·cm ⁻²)	155 \pm 21	185 \pm 47*	168 \pm 36	0.009

* $p < 0.05$ versus normotensive group. † $p < 0.05$ versus white coat hypertensive group. Data presented are mean value \pm SD. EDVI and ESVI = end-diastolic and end-systolic volume index, respectively; LVET and LVETc = ejection time with and without rate correction, respectively; Vcf and Vcfc = velocity of circumferential fiber shortening with and without rate correction, respectively; σ_c es = circumferential wall stress; σ_m es = meridional wall stress.

Table 4. Left Ventricular Dimensions

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
MI, 2DE (g·m ⁻²)	102 ± 20	106 ± 21	126 ± 22*†	0.0003
DedI (cm·m ⁻²)	2.75 ± 0.35	2.73 ± 0.33	2.78 ± 0.30	0.9
hedI (cm·m ⁻²)	0.53 ± 0.07	0.56 ± 0.07	0.61 ± 0.08*	0.0008
LedI (cm·m ⁻²)	4.83 ± 0.47	4.73 ± 0.71	4.74 ± 0.39	0.7
Sphericity index (%)	57 ± 7	58 ± 8	59 ± 7	0.6
RWT (%)	39 ± 6	42 ± 7	44 ± 7*	0.05
MI, M-mode (g·m ⁻²)‡	90 ± 20	97 ± 25	121 ± 24*†	0.0001

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. ‡M-mode echocardiograms were analyzed in 29 subjects in the normotensive group, 23 in the white coat hypertensive group, 21 in the ambulatory hypertensive group. Data presented are mean value ± SD. DedI = end-diastolic short-axis inner diameter index; hedI = end-diastolic mean wall thickness index; LedI = end-diastolic long-axis index; MI, M-mode and MI, 2DE = mass index determined by M-mode and two-dimensional echocardiography, respectively.

cantly among study groups (Table 3). The velocity of circumferential fiber shortening was significantly higher in the ambulatory hypertensive than in the normotensive group, but it did not differ significantly between the white coat and normotensive groups. However, end-systolic wall stress was significantly higher in the white coat than in the normotensive group.

Left ventricular mass was significantly higher in the ambulatory hypertensive group than in the other two groups (Table 4). Sphericity index did not differ among groups.

The mitral flow pattern was not significantly different among groups (Table 5) except for a shortened deceleration time of early flow in the white coat group and a high peak velocity of late flow in the ambulatory hypertensive group. The peak velocity of diastolic pulmonary venous flow was higher in the white coat than in the ambulatory hypertensive group (Table 6), and the velocity-time integral of diastolic pulmonary venous flow was significantly lower in the ambulatory hypertensive than in the normotensive group. The peak velocity and the velocity-time integral of the flow reversion during atrial systole were significantly higher in the white coat than in the normotensive group. Variables of flow reversion during atrial systole in the ambulatory hypertensive group were intermediate between those in the other two groups.

Table 5. Left Ventricular Filling Variables: Mitral Flow

	Normotensive Group (n = 31)	Hypertensive Groups		p Value
		White Coat (n = 24)	Ambulatory (n = 20)	
E (cm·s ⁻¹)	64 ± 13	68 ± 14	71 ± 12	0.18
E-dec (ms)	201 ± 38	169 ± 28*	195 ± 49	0.01
A (cm·s ⁻¹)	55 ± 11	62 ± 16	65 ± 10*	0.03
E/A	1.19 ± 0.27	1.16 ± 0.32	1.12 ± 0.25	0.7
A-d (ms)	122 ± 29	117 ± 20	114 ± 23	0.5

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. Data presented are mean value ± SD. A = late mitral flow peak velocity; A-d = late mitral flow duration; E = early mitral flow peak velocity; E-dec = early mitral flow deceleration time.

Table 6. Left Ventricular Filling Variables: Pulmonary Venous Flow

	Normotensive Group (n = 30)	Hypertensive Groups		p Value
		White Coat (n = 23)	Ambulatory (n = 19)	
S (cm·s ⁻¹)	51 ± 11	59 ± 14	52 ± 9	0.05
S-vti (cm)	14 ± 4	16 ± 5	16 ± 4	0.2
D (cm·s ⁻¹)	47 ± 12	49 ± 10	40 ± 10†	0.01
S/D	1.17 ± 0.41	1.22 ± 0.29	1.34 ± 0.34	0.3
D-vti (cm)	11.2 ± 3.2	9.7 ± 2.8	8.3 ± 2.5*	0.004
PVa (cm·s ⁻¹)	21 ± 5	28 ± 6*	25 ± 6	0.0001
PVa-vti (cm)	1.79 ± 0.58	2.58 ± 0.94*	2.04 ± 0.92	0.003
PVa-d (ms)	101 ± 26	117 ± 32	100 ± 30	0.08

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. Data presented are mean value ± SD. D = peak velocity of diastolic pulmonary venous flow; D-vti = velocity-time integral of diastolic pulmonary venous flow; PVa = peak velocity of the flow reversion during atrial systole; PVa-d = duration of the flow reversion during atrial systole; PVa-vti = velocity-time integral of the flow reversion during atrial systole; S = peak velocity of systolic pulmonary venous flow; S-vti = velocity-time integral of systolic pulmonary venous flow.

Left ventricular filling variables were not significantly associated with left ventricular mass, velocity of fiber shortening and ambulatory daytime systolic pressure. The peak velocity of flow reversion during atrial systole correlated with heart rate (r = 0.34, p < 0.01) and the peak velocity of diastolic pulmonary venous flow correlated with ambulatory daytime diastolic pressure (r = 0.53, p < 0.01). Several variables of left ventricular filling were significantly related to arterial pressures recorded during the echocardiographic examination (oscillometric arterial pressures); however, although these correlations were pronounced in the white coat group and to some degree significant in the normotensive group, they were not significant in the ambulatory hypertensive group (Table 7).

Reproducibility. The coefficient of variability and the 95% limits of agreement for the following variables comprise variability due to recording analysis as well as biologic variability:

Table 7. Matrix of Correlation Coefficients (r) Between Oscillometric Arterial Pressures and Variables of Left Ventricular Filling in Subjects With White Coat Hypertension

	Osc SP (r)	Osc DP (r)
E (cm·s ⁻¹)	0.06	-0.31
E-dec (ms)	0.31	0.04
A (cm·s ⁻¹)	0.67†	0.43*
E/A	-0.72†	-0.79†
A-d (ms)	0.21	0.18
S (cm·s ⁻¹)	0.40*	0.45*
S-vti (cm)	0.33	0.39
D (cm·s ⁻¹)	-0.29	-0.49*
S/D	0.51†	0.68†
D-vti (cm)	-0.53†	-0.71†
PVa (cm·s ⁻¹)	0.40	0.45*
PVa-vti (cm)	0.13	0.31
PVa-d (ms)	-0.37	-0.33

*p < 0.05. †p < 0.01. Osc DP and Osc SP = oscillometric diastolic and systolic arterial pressure, respectively; other abbreviations as in Tables 5 and 6.

oscillometric systolic pressure ($6; 5 \pm 14$ [coefficient of variation; 95 limits of agreement]), oscillometric diastolic pressure ($7; 3 \pm 9$), Doppler velocity-time integral of aortic root flow ($10; 0.6 \pm 5$), aortic annulus diameter ($2.5; 0.02 \pm 0.1$), left ventricular total power ($17\%; 170 \pm 480$), steady power ($17\%, 128 \pm 393$), oscillatory power ($24\%; 42 \pm 116$), left ventricular end-diastolic long-axis ($7\%; -0.4 \pm 1.3$), short-axis diameter ($5\%; 0.12 \pm 0.5$), wall thickness ($14\%; 0.07 \pm 0.27$). Left ventricular end-diastolic volume ($21\%; 0.65 \pm 64$), end-systolic volume ($21\%; -2.5 \pm 24$), stroke volume ($16\%; 4 \pm 29$), ejection fraction ($8\%; 3 \pm 10$) and left ventricular mass ($18\%; 15 \pm 63$) all determined according to the cylinder-hemiellipsoid formula (Formulas 4 and 5).

Discussion

A definition of white coat hypertension that assumes a completely normal cardiovascular status during everyday life may implicate a lower ambulatory blood pressure cutoff point than that used in this study (10). However, because there is no general agreement on the definition of white coat hypertension, we used procedures current in this hospital to select subjects with white coat hypertension, even though this definition may include subjects with mild hypertension.

Our subjects with hypertension in the general practitioner's office but "normal" ambulatory daytime pressures had an arterial pressure increase during the measurement of arterial pressures by a nurse and during the echocardiographic examination. The pressure response during echocardiography was associated with increased left ventricular external work and left ventricular wall stress and alterations of left ventricular filling; however, left ventricular stroke volume, ejection fraction and velocity of circumferential fiber shortening were not different from values in a normotensive and an ambulatory hypertensive control group.

Left ventricular systolic function, whose final goal is the delivery of cardiac output, is determined by myocardial contractility, afterload, preload and heart rate (32). Variables like ejection fraction and velocity of circumferential fiber shortening, commonly used to evaluate left ventricular systolic function, are influenced by several of these determinants. When the aim is to evaluate myocardial contractility specifically, it has been recommended that these variables be related to end-systolic wall stress (33). Analyzed in this way, subjects with borderline and mild hypertension may have supernormal myocardial contractility (34,35). However, a thorough theoretic analysis of left ventricular mechanics showed that these results may be erroneous because left ventricular wall thickness differs between hypertensive and normotensive subjects (36-38). It has therefore been recommended that midwall instead of endocardial mechanics be used in such analyses. With this approach it was shown that subjects with apparently increased myocardial contractility had normal or depressed contractility, a finding more in accordance with results from studies on isolated myofibers from hypertrophic ventricles (39). This observation may have consequences for the interpretation of systolic function in the subjects with ambulatory hypertension

in the present study, who had increased left ventricular wall thickness. However, because left ventricular mass and wall thickness in the white coat hypertensive group were not significantly different from values in the normotensive group, increased left ventricular mechanics in this group may be interpreted as an expression of increased myocardial contractility. The most plausible explanation for this increased myocardial contractility is neuroendocrine stimulation to support the delivery of an adequate stroke volume against an increased external work load. It may also be important that the subjects with white coat hypertension had evidence of increased left ventricular end-diastolic pressure, as discussed later. However, their normal left ventricular end-diastolic volume indicates that the Frank-Starling principle was not an important regulating mechanism in this situation (40,41).

Previous studies (42) have obtained different results regarding factors related to alterations of left ventricular filling. The present study does not support the view that heart rate, ambulatory arterial pressures, left ventricular mass and velocity of circumferential fiber shortening are important in this regard. Arterial pressures recorded during echocardiography were correlated with the ratio of systolic to diastolic pulmonary venous flow peak velocities and inversely related to the ratio of early to late mitral flow peak velocities; however, these correlations were pronounced in the white coat hypertensive group, but were not significant in the ambulatory hypertensive group. These findings are in accordance with previous studies in which similar changes of filling patterns were observed after an acute increase in left ventricular afterload (43,44) and may be due to a slowing of myocardial relaxation (45,46).

The increased pulmonary venous flow reversal in the white coat group could be an indication of decreased ventricular compliance (43,44,47). However, because late mitral flow velocities also increased in these subjects, the findings might indicate increased atrial emptying during atrial systole. Increased left atrial pressure generation during atrial contraction due to neuroendocrine activation may have contributed to this change, but increased atrial preload due to redistribution of blood volume from early to late diastole may have played an additional role.

Methodologic considerations. All variables representing pressure-flow relations in this study were calculated by use of arterial pressures measured during the echocardiographic examination with the oscillometric technique. These pressures tended to be lower than the respective clinic arterial pressures because the former were measured with the subject in the left lateral decubitus position and the latter with the subject in the sitting position. Because all subjects were examined in the same position, we did not correct for the hydrostatic effect between cuff and aortic root.

Clinical implications and conclusions. This study emphasizes the potential confounding effect of the white coat arterial pressure response in studies on heart disease. It may also indicate the potential adverse effects of an acute elevation of arterial pressure in subjects with coronary heart disease. We believe that the arterial pressure response in subjects with white coat hypertension is associated with increased left ventricular external work, increased end-systolic wall stress, in-

creased myocardial contractility and alterations of left ventricular filling.

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Paper III

Paper III

Influence of Body Size and Left Ventricular Ejection Dynamics on Total Arterial Compliance Determined Using Doppler Echocardiography and Subclavian Artery Pulse Tracings in Healthy Humans

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The aim was to investigate determinants of total arterial compliance in healthy humans. Estimates of aortic root pressures and flow were obtained non-invasively with the calibrated subclavian artery pulse tracing and Doppler echocardiography in 37 males (27–76 years) and 45 females (20–77 years). Total arterial compliance, estimated using a three-element vascular model, correlated positively with body height ($r = 0.45$, $p < 0.01$) and acceleration time of aortic root flow ($r = 0.32$, $p < 0.01$) and inversely with age ($r = -0.34$, $p < 0.05$), heart rate ($r = -0.33$, $p < 0.01$), and mean arterial pressure ($r = -0.51$, $p < 0.01$). Multivariate analysis indicated that height and heart rate contributed most to the prediction of total arterial compliance. The inclusion of mean arterial pressure within the model significantly reduced the contribution of age, but not that of body height and heart rate. After adjustment for height and heart rate, total arterial compliance did not differ significantly between gender. Thus, total arterial compliance, as assessed in this study, seems to reflect both arterial capacity and viscoelastic properties of the arterial wall. Differences in body size, heart rate and mean arterial pressure should be considered when comparing total arterial compliance in different groups. *Key words:* age, arterial compliance, body size, heart rate.

INTRODUCTION

The arterial blood pressure is determined by the interaction between left ventricular contraction and arterial mechanics [1]. Although arterial mechanics have been most extensively studied using analysis of pressure and flow relationships in the frequency domain [2], description in the time domain using electric analogue models of the circulation [3] may be more suitable for analysis of the coupling between the left ventricle and the arterial circulation [4]. Such vascular models provide access to total arterial compliance [5] defined as a change in volume due to a given change in pressure.

We have recently gained experience with a three-element electric analogue model of the arterial tree [3] by studying subjects with coronary artery disease [6, 7], and subjects with hypertension [8]. These studies indicated that total arterial compliance was determined by body size and left ventricular ejection dynamics in addition to the better known influence of the arterial distending pressure [9] and age [10], but the number of subjects was relatively small and the age range narrow. Thus, the purpose of the present study was to evaluate the influence of body size and left ventricular ejection dynamics on total arterial compliance in healthy humans over a wide age range.

METHODS

Subjects

The subjects were recruited from hospital staff and their friends and relatives. They were considered healthy on the basis of medical history, clinical examination, 12-lead ECG and echocardiographic examination. None of the subjects used any drugs. Ninety subjects were included. Three were excluded because of a poor echocardiographic window. In addition, four females in the age range 10–17 were excluded in order to limit the study population to adult subjects. One male was excluded because he represented an extreme outlier as regards body size and body shape. The study population thus consisted of 37 males (52 ± 14 years, range 27–76 years) and 45 females (48 ± 18 years, range 20–77 years) (Table I). All subjects gave written informed consent to the investigation, which was approved by the regional ethics committee.

Non-invasive data recording

All echocardiographic recordings and analyses were performed by the same investigator. The recordings were obtained with the patient in the left lateral decubitus position, and started after the patient had been at rest for at

Table I. Characteristics of the study subjects according to age ($n = 82$)

	Age Groups (years)						p-ANOVA
	≤30	31 – 40	41 – 50	51 – 60	61 – 70	>70	
n	14	10	20	9	15	14	
Males (%)	3 (21)	4 (40)	10 (50)	7 (78)	7 (47)	6 (43)	
Height (cm)	172 ± 7	177 ± 7	172 ± 11	174 ± 10	168 ± 10	165 ± 6	0.03
Weight (kg)	65 ± 8	74 ± 11	75 ± 14	77 ± 12	71 ± 11	66 ± 9	0.03
BSA (m ²)	1.77 ± 0.13	1.90 ± 0.18	1.87 ± 0.21	1.92 ± 0.19	1.80 ± 0.19	1.72 ± 0.12	0.03
LVOT (cm)	2.19 ± 0.23	2.24 ± 0.22	2.35 ± 0.15	2.40 ± 0.26	2.25 ± 0.19	2.17 ± 0.15	0.03

Values are mean ± SD; post hoc comparisons did not reveal significant differences between the groups; BSA: body surface area; LVOT: aortic valve annulus diameter

least 10 min. An ultrasound scanner (Vingmed CFM 750, Vingmed Sound, Horten, Norway) with a duplex probe (3.25-MHz imaging/2.5-MHz Doppler) was used.

The aortic valve annulus diameter was measured in the parasternal long-axis view between the insertion points of the valve leaflets by use of the trailing-to-leading edge method [11]. The aortic root flow velocities were recorded by pulsed Doppler technique from the apical

position with the sample volume positioned in the centre of the outflow tract just at the aortic valve annulus, obtaining an optimal flow velocity spectral profile and a distinct valve closure signal (Fig. 1). The subclavian artery pulse tracings were obtained with a capillary damped funnel [12] (Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery and connected to a strain-gauge transducer (model 120-0123, Irex

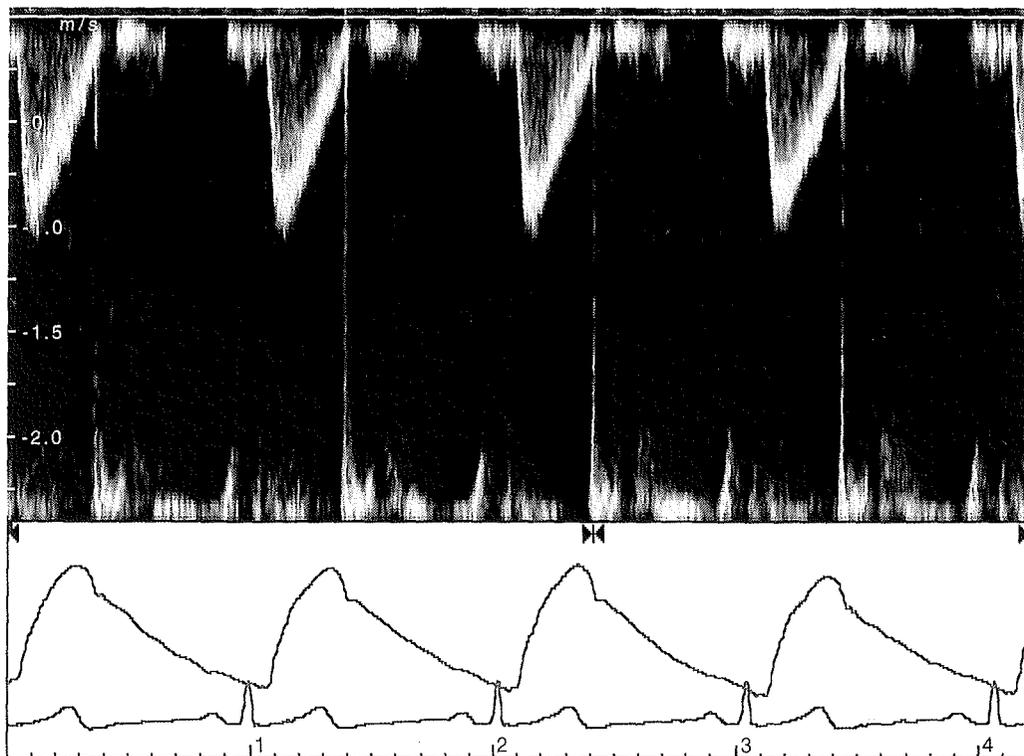


Fig. 1. Example of simultaneous recording of aortic root flow with pulsed-wave Doppler, subclavian artery pulse tracing (red trace), and ECG (green trace) in a 47-year-old female.

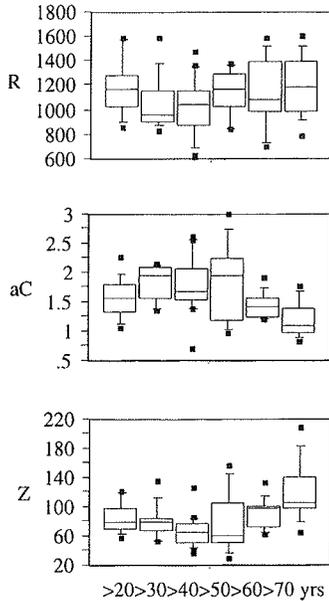


Fig. 2. Box plots show distribution of peripheral resistance (R), total arterial compliance (aC) and aortic characteristic impedance (Z) according to age groups. The boxes indicate the lower and upper quartiles, the centre line represents the median value. The bars below and above the boxes indicate the 10% and 90% values, respectively. Outliers are indicated as points.

Medical Systems, Ramsey, New Jersey, USA), and displayed simultaneously with the Doppler velocity spectre on the monitor [6] (Fig. 1). Only pulse traces with a consistent wave morphology, a sharp deflection in early systole, and a minimal linear drift were used. Doppler recordings and pulse traces were obtained during a short period of apnea close to end-expiration. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiogram traces, to a computer for analysis (Macintosh II CI, Apple Computers Inc., Cupertino, California, USA). Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP, Criticon Inc, Tampa, Florida, USA) every minute during the Doppler ultrasound study. The two blood pressure measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis.

Analysis of echocardiographic recordings and subclavian artery pulse tracings

The maximal aortic root flow velocities (i.e. outer envelope of the Doppler spectre) of at least three cardiac

cycles were traced manually and averaged according to the previously described computerized procedure [6]. Peak and mean velocities were determined from the aortic Doppler velocity trace. Ejection time was determined from the beginning of blood flow to the valve closure click. Acceleration of aortic root flow was determined from the beginning of blood flow to the peak velocity. Acceleration time was determined as the duration of aortic flow acceleration. The subclavian artery pulse trace was calibrated with oscillometrically obtained systolic and diastolic pressures [6, 13, 14] and the pulse transmission delay corrected by alignment of the pulse trace incisura to the end-systole of the Doppler flow trace.

Analysis of data

The flow and pressure traces were processed using specially designed computer software where the properties of the systemic arteries were evaluated by use of a refined estimation procedure [6] for solution of the three-element windkessel model [3]. In this model there is an element representing the aortic characteristic impedance (Z) in series with two elements in parallel, the peripheral resistance (R) and the total arterial compliance (aC) [3].

The governing equations for this model are as follows [3]:

$$aC \frac{dPa(t)}{dt} + \frac{Pa(t)}{R} = Q(t) \tag{1}$$

$$P(t) = Pa(t) + ZQ(t) \tag{2}$$

where P(t) is aortic pressure, Q(t) is aortic flow and Pa(t) is the pressure reduction over R and aC.

The general solution to these equations is:

$$P(t) = e^{-t/RC} \left\{ Pd + \frac{1}{aC} \int_0^t e^{\tau/RC} Q(\tau) d\tau \right\} + ZQ(t) \tag{3}$$

where Pd is aortic pressure at end-diastole (t=0). The model variables were first determined by use of a non-linear optimization algorithm using the least square method and then further refined by minimising the difference between the estimated and the measured pressure trace [15]. In this scheme the characteristic impedance was determined as:

$$Z = \frac{\int_{RR} P(\tau) d\tau}{\int_S Q(\tau) d\tau} - R \tag{4}$$

where RR is the total cardiac cycle and S the systole. Thus, total arterial compliance represents the volume compliance of the arteries, aortic characteristic impedance is an expression of the resistance to pulsatile flow in the proximal aorta, and peripheral resistance represents the arteriolar resistance.

Mean arterial pressure was calculated as the pressure integral over the total cardiac cycle. End-systolic pressure was determined at the incisura of the calibrated pulse tracing. Pulse pressure was calculated as the difference between the systolic and diastolic blood pressure. Stroke volume was calculated as the product of the Doppler velocity-time integral of aortic root flow and the cross sectional area of the aortic valve annulus, assuming a circular annulus. Cardiac output was calculated as the product of stroke volume and heart rate. Corresponding indexes were obtained by dividing with body surface area.

Statistical analysis

Continuous variables are expressed as means \pm standard deviation (SD). Analysis of variance was used to test the difference between age groups. If the overall difference between groups was significant ($p < 0.05$), post hoc comparisons were performed with a Scheffé test. The Fischer exact test was used to analyse the age distribution between gender. Simple linear and multiple regression analyses were performed to identify relations between age, body size, and haemodynamic variables. An analysis of covariance (ANCOVA) was used to test the impact of

gender on total arterial compliance. The level of significance was set at 0.05. Reproducibility of the haemodynamic variables has been reported previously [6].

RESULTS

The study population was divided into six categories according to age (Table I). Body height, weight, body surface area and aortic valve annulus diameter tended to be smaller in the youngest and the two oldest age groups compared with the groups in between. There was no significant difference in age distribution between genders.

Arterial systolic, diastolic, mean, and end-systolic pressures increased in the two oldest age groups (Table II). In these groups the velocity-time integral, the peak and the mean velocity and the acceleration of aortic root flow tended to increase, and the acceleration time of aortic root flow tended to decrease (Table III). Cardiac index tended to increase because of a slightly higher heart rate as well as stroke index in the two oldest age groups. Peripheral resistance did not differ statistically between the age groups (Table IV).

Total arterial compliance was significantly lower in the oldest age group compared to the groups between 30 and 70 years, but not significantly different from the youngest age group (Table IV and Fig. 2). A similar, but inverse age distribution was seen for aortic characteristic impedance.

Although age, body height, heart rate, acceleration time of aortic root flow and mean arterial pressure all correlated significantly with total arterial compliance (Table V and Fig. 3), multiple regression analysis indicated that height and heart rate contributed most to the prediction of total arterial compliance (Table VI). The inclusion of mean arterial pressure into the multiple regression model significantly reduced the contribution of age to total arterial compliance, but not that of body height and heart rate.

In females, age and height, but not heart rate ($r = 0.26$, $p = 0.09$) correlated significantly with total arterial compliance. Multiple regression analysis in females showed that when age and height were in the model together, neither variable seemed to contribute significantly. This may reflect the high inverse correlation between age and height in females ($r = -0.57$, $p < 0.0001$) which was stronger than the corresponding in males ($r = -0.38$, $p = 0.02$). In males, the addition of heart rate to the model increased the adjusted R^2 from 0.20 to 0.31, underscoring the contribution of heart rate to total arterial compliance in males.

Total arterial compliance was significantly higher in males than in females, but males were significantly taller than females (Table VII). After adjusting for height and heart rate in an analysis of covariance, total arterial

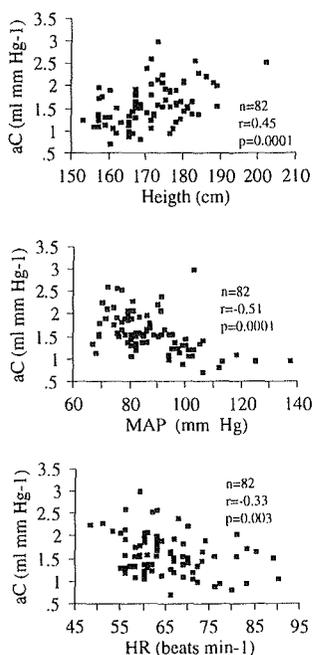


Fig. 3. Plots show the relationship between total arterial compliance (aC) and body height, heart rate (HR), and mean arterial pressure (MAP).

Table II. Arterial blood pressures (mm Hg) according to age (n = 82)

	Age Groups (years)						p-ANOVA
	≤30	31 – 40	41 – 50	51 – 60	61 – 70	>70	
n	14	10	20	9	15	14	
SP	103 ± 9	102 ± 7	106 ± 14	118 ± 15	128 ± 11 ^{*†‡}	139 ± 23 ^{*†‡#}	0.0001
DP	56 ± 7	58 ± 8	60 ± 7	67 ± 9	69 ± 7 [*]	71 ± 11 ^{*†‡}	0.0001
MAP	79 ± 7	79 ± 7	81 ± 9	90 ± 11	95 ± 8 ^{*†‡}	102 ± 17 ^{*†‡}	0.0001
ESP	89 ± 8	87 ± 7	92 ± 10	103 ± 13	109 ± 10 ^{*†‡}	117 ± 21 ^{*†‡}	0.0001
PP	47 ± 7	44 ± 9	46 ± 11	51 ± 11	58 ± 11	69 ± 14 ^{*†‡#}	0.0001

Values are mean ± SD; * $p < 0.05$ vs ≤ 30; † $p < 0.05$ vs 31 – 40; ‡ $p < 0.05$ vs 41 – 50; # $p < 0.05$ vs 51 – 60; § $p < 0.05$ vs 61 – 70; SP: systolic pressure; DP: diastolic pressure; MAP: mean arterial pressure; ESP: end-systolic pressure; PP: pulse pressure.

compliance was not statistically different between males and females ($p = 0.61$).

DISCUSSION

The present study reveals the complex relationship between age, body size, heart rate, left ventricular ejection dynamics, mean arterial pressure, and total arterial compliance in healthy humans. Total arterial compliance differs between males and females at least partly because of differences in body size.

Arterial stiffening causes an increase in the peak-systolic and a decrease in the end-diastolic blood pressure [1], as indicated in the present study by the increased pulse pressure in the oldest age groups. Although the disproportionate increase in the systolic compared to the diastolic blood pressure with aging in the industrialized countries [16, 17] is commonly attributed to degenerative alterations of the arterial wall with consequent stiffening of the large arteries, the present study may indicate that increased adrenergic drive contributes to the increased pulse pressure in elderly subjects. It should also be considered whether differences in body size can explain

some of the variance in pulse pressure between young and old subjects.

The relationship between systemic arterial haemodynamics and body size is as controversial as that between haemodynamics and age [18]. Although body surface area is accepted as a valid approximation of body size, body height may be more closely related to dimensions of the cardiovascular system [19, 20]. Since total arterial compliance is not solely determined by the properties of the arterial wall, but also by the arterial volume, an influence of body size on total arterial compliance was not unexpected.

The three-element electric analogue model of the arterial circulation used in this study was chosen because it has been well described previously, and has proved useful in experimental and clinical studies [3, 21, 22]. An important deficiency of this model is that it does not take into account the effect of propagation and reflection of pressure and flow waves [23]. It is, however, interesting that an influence of body size on the phenomenon of arterial wave reflection has been reported in several recent studies [24–26], indicating a possible relationship between wave propagation and total arterial compliance [27].

Table III. Doppler echocardiographic recordings of aortic root flow according to age (n = 82)

	Age Groups (years)						p-ANOVA
	≤30	31 – 40	41 – 50	51 – 60	61 – 70	>70	
n	14	10	20	9	15	14	
VTI (cm)	22 ± 3	22 ± 3	22 ± 3	22 ± 4	25 ± 5	25 ± 3	0.06
LVET (ms)	305 ± 18	304 ± 20	310 ± 21	313 ± 18	310 ± 22	315 ± 21	0.7
Vmax (cm s ⁻¹)	104 ± 12	106 ± 9	106 ± 12	100 ± 24	116 ± 24	116 ± 17	0.1
Vmean (cm s ⁻¹)	71 ± 8	72 ± 6	71 ± 8	67 ± 11	79 ± 14	81 ± 12	0.008
Acc (cm s ⁻²)	1286 ± 335	1330 ± 206	1320 ± 328	1200 ± 403	1667 ± 481	1729 ± 389	0.0009
Acc-t (ms)	84 ± 14	81 ± 11	83 ± 16	87 ± 12	71 ± 12	69 ± 12	0.002

Values are mean ± SD; post hoc comparisons did not reveal significant differences between the groups; VTI: velocity time integral of aortic root flow; LVET: left ventricular ejection time; Vmax: peak velocity of aortic root flow; Vmean: mean velocity of aortic root flow; Acc: acceleration of aortic root flow; Acc-t: acceleration time of aortic root flow

Table IV. Systemic arterial hemodynamics in healthy subjects according to age (n = 82)

	Age Groups (years)						p-ANOVA
	≤30	31–40	41–50	51–60	61–70	>70	
n	14	10	20	9	15	14	
HR (beats min ⁻¹)	62 ± 10	66 ± 9	65 ± 8	62 ± 8	68 ± 8	68 ± 9	0.3
SI (ml m ⁻²)	48 ± 10	46 ± 5	51 ± 8	52 ± 13	54 ± 11	54 ± 8	0.2
CI (l min ⁻¹ m ⁻²)	2.9 ± 0.5	3.0 ± 0.8	3.3 ± 0.8	3.2 ± 0.8	3.6 ± 0.7	3.7 ± 0.8	0.04
R (dyn s cm ⁻⁵)	1180 ± 226	1042 ± 223	1024 ± 229	1139 ± 194	1133 ± 292	1210 ± 214	0.3
aC (ml mm Hg ⁻¹)	1.57 ± 0.33	1.82 ± 0.31	1.80 ± 0.47	1.81 ± 0.68	1.44 ± 0.21	1.20 ± 0.30 ^{†‡#}	0.0002
Z (dyn s cm ⁻⁵)	84 ± 21	79 ± 23	66 ± 20	80 ± 41	91 ± 20	120 ± 40 ^{†‡}	0.0001

Values are mean ± SD; **p* < 0.05 vs ≤ 30; †*p* < 0.05 vs 31–40; ‡*p* < 0.05 vs 41–50; #*p* < 0.05 vs 51–60; §*p* < 0.05 vs 61–70; HR: heart rate; SI: stroke index; CI: cardiac index; R: peripheral resistance; aC: total arterial compliance; Z: aortic characteristic impedance.

Although the association between heart rate and total arterial compliance could be due to concomitant changes in the arterial distending pressure [28], it was recently shown in an animal study [29] that heart rate may influence arterial compliance independently of the arterial pressure. Stiffening of the arterial wall due to shortening of the time available for recoil during increasing heart rates was suggested as an explanation [29]. A similar mechanism may be the reason for the inverse correlation between heart rate and arterial compliance found in the present study. It is, however, possible that increased rate of delivery of the stroke volume may contribute to reduced total arterial compliance during increased heart rates [28]. A potential difference between males and females in this regard needs further investigation.

A somewhat higher heart rate may thus have contributed to decrease total arterial compliance in the oldest age groups, underscoring the point that functional mechanisms may be involved in reducing arterial compliance in the elderly. It is also interesting that the rate of delivery of the stroke volume tended to be increased and that stroke volume was not reduced in these groups, despite the increased external load on the left ventricle. This may be in accordance with observations of increased plasma catecholamine levels [30] and a high prevalence of "white coat" hypertension in elderly

subjects [31–36]. Although the slight increase in cardiac index in the oldest age groups combined with a lack of increase in peripheral resistance is not in accordance with previous studies [37], the associated rise in mean arterial pressure may indicate a deficient vasodilating capacity in the elderly.

The modest contribution of age per se to the variation in total arterial compliance, i.e. after correction for body size, heart rate and mean arterial pressure, is intriguing since it contrasts with increased elastic modulus of the aortic wall in elderly subjects as found in several autopsy studies [38]. The explanation could be that age-related aortic dilatation tends to neutralize the effect of stiffening of the aortic wall. Hence, a large part of the age-related decrease in total arterial compliance could be due to functional mechanisms.

Since the multivariate model explained only 30% of the variation in total arterial compliance, explanatory factors other than those investigated in this study should be considered. Potential confounding effects of variables like smoking habits, physical activity, alcohol consumption, cholesterol level and hormonal changes [39] should be assessed in future studies, but it is underscored that a methodology different from that used in the present study is needed to investigate changes specific to the arterial wall [40–42].

Table V. Correlation between total arterial compliance (aC) and six potential explanatory variables

Variable	aC	Gender	Age	Height	HR	MAP	Acc-t
aC	1.00	0.23*	-0.34*	0.45**	-0.33**	-0.51**	0.32**
Gender		1.00	0.14	0.59**	-0.03	0.00	0.02
Age			1.00	-0.30**	0.23*	0.61**	-0.35**
Height				1.00	-0.11	-0.29**	0.19
HR					1.00	0.31**	-0.23*
MAP						1.00	-0.20
Acc-t							1.00

p* < .05; *p* < .01; HR: heart rate; MAP: mean arterial pressure; Acc-t: acceleration time of aortic root flow

Table VI. Multiple regression of four variables on total arterial compliance ($n = 82$)

Units	Coefficient (SEE)	Standard coefficient	t	p-value
Height /10 cm	0.17 (0.05)	0.36	3.6	0.0005
HR /10 beats min ⁻¹	-0.12 (0.05)	-0.23	-2.3	0.02
Acct-t /10 ms	0.05 (0.03)	0.14	1.4	0.17
Age /10 years	-0.04 (0.03)	-0.13	-1.2	0.24

Overall $R = 0.57$; $R^2 = 0.32$; adjusted $R^2 = 0.29$; RMS residual = 0.38; F-test 9.2; $p = 0.0001$; HR, Heart rate; Acc-t: acceleration time of aortic root flow

Standard coefficient is an estimate of the relative contribution of the predictors to the model.

Additional potential limitations of the present study should be considered. The echocardiographic examination, the recording of the subclavian pulse trace, and the recording of right brachial artery pressures were performed with the subjects in the left lateral decubitus position. Right brachial artery pressures were subsequently used for calibration of the subclavian pulse trace. Although this technique could underestimate aortic pressure because of the pressure amplification from aorta to the peripheral arteries [43], previous validation studies [14, 44] showed that the brachial artery pressures obtained with the oscillometric technique [45] gave a fair approximation of the pressures in the proximal aorta in adult subjects. All study subjects in the present study were examined in the same position and it is not likely that the position of the subjects accounts for the variance in blood pressures between

Table VII. Hemodynamics in males and females

	Males	Females
n	37	45
Age (yrs)	52 ± 14	48 ± 18
Height (cm)	177 ± 8	166 ± 7**
SP (mm Hg)	117 ± 18	115 ± 21
DP (mm Hg)	63 ± 9	64 ± 11
MAP (mm Hg)	88 ± 13	87 ± 14
ESP (mm Hg)	99 ± 15	99 ± 18
LVET (ms)	304 ± 21	313 ± 18*
Vmax (cm s ⁻¹)	105 ± 17	111 ± 17
Acc time (ms)	79 ± 15	79 ± 14
HR (beats min ⁻¹)	65 ± 8	66 ± 10
SV (ml)	98 ± 19	88 ± 19*
CO (l min ⁻¹)	6.4 ± 1.4	5.8 ± 1.4*
R (dyn s cm ⁻⁵)	1046 ± 204	1172 ± 262*
C (ml mmHg ⁻¹)	1.71 ± 0.49	1.51 ± 0.40*
Z (dyn s cm ⁻⁵)	86 ± 33	86 ± 37

Values are mean ± SD; * $p < 0.05$; ** $p < 0.01$ see Table 2, Table 3, and Table 4 for abbreviations; SV: stroke volume; CO cardiac output

subjects. It could also be of concern that the pulse pressure measured with the oscillometric technique was large. However, the same device was used in all examinations, which should warrant a high degree of repeatability.

CONCLUSION

Small body size and increased heart rate are predictors of a low total arterial compliance. This should be considered when comparing total arterial compliance in different groups.

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Paper IV

Paper IV

Total Arterial Compliance in Ambulatory Hypertension During Selective β_1 -Adrenergic Receptor Blockade and Angiotensin-Converting Enzyme Inhibition

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Summary: Aortic root flow and pressure estimates were obtained noninvasively with Doppler echocardiography and calibrated subclavian artery pulse tracing in 30 subjects with ambulatory hypertension in a randomized, crossover study with 4 weeks' treatment and washout periods. Total arterial compliance, assessed by use of a three-element Windkessel model of the arterial tree, increased 42% with atenolol (50–100 mg once daily), and 7% ($p = \text{NS}$) with captopril (25–50 mg twice daily). Atenolol reduced mean arterial pressure by 15%, heart rate by 22%, and cardiac output by 14%, and increased acceleration time of aortic root flow by 17% and stroke volume and ejection time each by 11%. Captopril reduced mean arterial pressure and total peripheral resistance each by 7%. Acceleration time of aortic root flow, ejection time, heart rate, stroke

volume, and cardiac output were not significantly changed by captopril. We conclude that total arterial compliance, at the operational blood pressure, increases during selective β_1 -adrenergic receptor blockade in subjects with ambulatory hypertension. Although the main mechanism may be a reduction in mean arterial pressure, it should be considered whether reduced heart rate may play an additional role. The nonsignificant increase in total arterial compliance during angiotensin-converting enzyme inhibition may primarily be a consequence of a modest reduction of the mean arterial pressure. **Key Words:** Hypertension—Ambulatory blood pressures—Arterial compliance—Ventricular vascular coupling— β_1 -Adrenergic receptor blockade—Angiotensin-converting enzyme inhibition.

The hemodynamic profiles of angiotensin-converting enzyme inhibitors, and of β -adrenergic receptor blockers, both commonly used in the treatment of arterial hypertension, are well documented (1), but less is known about the effect on large artery mechanics. This information is, however, important because the aorta and the large arteries serve not only to transport blood from the heart to the periphery, but also to convert pulsatile into steady flow (2). During left ventricular ejection, energy is stored in the arterial wall and is subsequently used to propel blood toward the periphery during diastole. Whereas little energy is lost in converting pulsatile to steady flow in compliant arteries, a large amount of energy is wasted in overcoming frequency-dependent impedance to flow in stiff arteries. Thus an increase in arterial compliance (3) may improve left ventricular function and energetics (4,5).

In this study we used a recently validated noninvasive method (6,7) to investigate the effects of a selective β_1 -adrenergic receptor blocker (atenolol) and an angiotensin-converting enzyme inhibitor (captopril) on total arterial compliance in subjects with ambulatory hypertension.

METHODS

Study subjects

General practitioners were requested in a letter and by a subsequent visit to refer subjects with recently diagnosed arterial hypertension in the age range 30–60 years to participate in a study of hemodynamics in hypertension assessed with noninvasive methods. Study subjects ($n = 66$) were referred for registration in the ambulatory ward for hypertension in our hospital. Subjects who were willing to participate in the study after a thorough introduction to the protocol ($n = 50$) were examined with ambulatory and clinic blood pressure measurements and echocardiography. Subjects with a diastolic pressure ≥ 90 and < 115 mm Hg, as measured by the general practitioner (office diastolic pressure), a diastolic pressure ≥ 90 mm Hg measured by a nurse in the clinic (clinic diastolic pressure), and an ambulatory daytime diastolic pressure ≥ 90 mm Hg, were considered for inclusion in the study ($n = 37$). Subjects who used antihypertensive drugs ($n = 14$) before evaluation for inclusion in the study discontinued treatment ≥ 4 weeks before the measurement of the blood pressures by the general practitioners. Subjects with evidence of coronary heart disease, congestive heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension, other major

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diseases, inappropriate echocardiographic window, or inability to obtain a subclavian pulse trace (or a combination of these) were not considered eligible for randomization ($n = 4$). Of the 33 subjects who met the inclusion criteria, three subjects were excluded after randomization: one because the echocardiographic recordings were damaged, another because of a clinic diastolic pressure <90 mm Hg at the start of the second half of the study (Baseline 2), and one subject because of side effects of atenolol. The analysis was based on 17 men and 13 women, aged 49 ± 6 years (Table 1). Subjects randomized to captopril ($n = 16$) and atenolol ($n = 17$) did not differ concerning baseline characteristics. Two of the excluded subjects were randomized to captopril, and one was randomized to atenolol.

All subjects gave written informed consent to the investigation, which was approved by the regional ethical committee.

Arterial blood pressure measurements

Clinic arterial pressures were measured in the clinic with a mercury sphygmomanometer by an experienced nurse. Korotkoff phase V was used to determine the diastolic pressure. These measurements were obtained with the subject in the sitting position after resting for ≥ 15 min. The two lowest of three readings were averaged. Clinic arterial pressures were measured at each baseline examination, at day 14 of each treatment period and at the end of each treatment period. The clinic arterial pressure measured at Baseline 1 was an average of pressures obtained on three different days.

An ambulatory 24-h arterial blood pressure recording (Oxford Medilog ABP, Oxford Medical, Inc., Clearwater, FL, or Suntech Accutracker II, Suntec Medical Instruments, Inc., Raleigh, NC, U.S.A.) was performed on a normal work day at the time of inclusion into the study. Ambulatory daytime arterial pressures were defined as the mean of half-hourly recordings from 7 a.m. to 11 p.m. The recording of ambulatory blood pressures was only performed at Baseline 1.

Oscillometric arterial pressures were measurements of brachial arterial pressures recorded during the echocardiographic examination as described later.

Study design

The study was a crossover study with two treatment periods of 4 weeks, and a 4-week washout period in between (Fig. 1). An echocardiographic examination was performed immediately before each treatment period (Baseline 1 and Baseline 2) and at the end of each treatment period.

TABLE 1. Characteristics of the subjects

Age (yr)	49 ± 6 (37–63)
Males (%)	57
Weight (kg)	79 ± 11 (62–120)
Height (cm)	172 ± 7 (160–192)
BSA (m^2)	1.92 ± 0.15 (1.67–2.34)
LVOT (cm)	2.34 ± 0.16 (1.96–2.68)
LVMI (g/m^2)	117 ± 37 (57–195)
Pressures (mm Hg)	
Office SP	157 ± 19 (120–200)
Office DP	104 ± 7 (90–115)
Ambd SP	147 ± 12 (130–174)
Ambd DP	102 ± 8 (90–118)

Values expressed as mean \pm SD (range).

BSA, body surface area; LVOT, aortic valve annulus diameter; LVMI, left ventricular mass index; SP, systolic pressure; DP, diastolic pressure; Ambd, ambulatory daytime blood pressure.

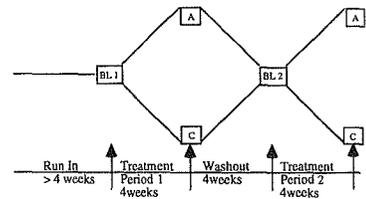


FIG. 1. Flow chart of the study design. The subjects were randomized to either atenolol (A), 50 mg once daily, or captopril (C), 25 mg twice daily, at Baseline 1 (BL 1). The drug dosages were increased to 100 mg once daily and 50 mg twice daily for atenolol and captopril, respectively, after 14 days of treatment if the diastolic pressure was ≥ 90 mm Hg (not indicated on the chart). Drug treatment was discontinued after additional 14 days of treatment. After a 4-week washout period, drug treatment was crossed over (BL 2) and the procedures for treatment period 1 were repeated. Arrows, data-acquisition times.

Drug treatment

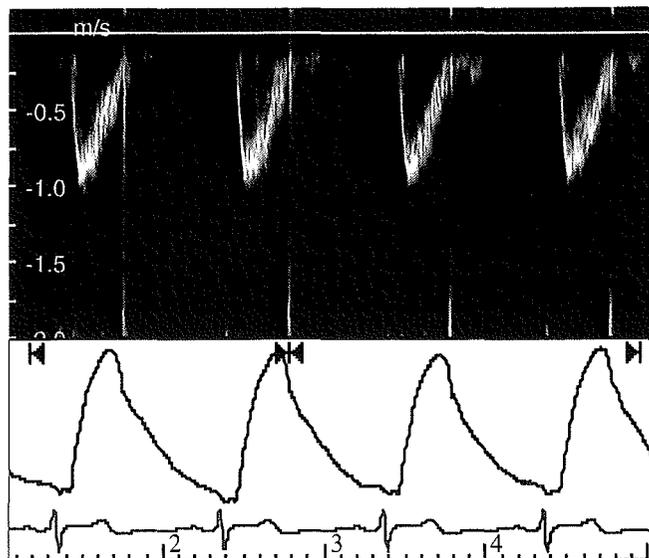
The subjects were randomized to atenolol, 50 mg once daily ($n = 17$), or captopril, 25 mg twice daily ($n = 16$), at the start of treatment period 1 (Baseline 1). The treatment was crossed over in treatment period 2 (Baseline 2). After 14 days on treatment, the dosages were doubled if the diastolic pressure was ≥ 90 mm Hg. The maximal daily drug dosage was administered to 10 subjects during treatment with atenolol and to 16 subjects during treatment with captopril. The captopril dosage was not increased according to the protocol in an additional three subjects. Study drugs were provided by Zeneca and Bristol-Myers Squibb and stored in the hospital pharmacy. The personnel in the ambulatory ward for hypertension delivered the appropriate amount and type of drugs to each study subject and monitored patient compliance with the drug regimen throughout the study.

Noninvasive data recording

All echocardiographic recordings and analysis were performed by the same investigator who was blinded to the drug treatment. The recordings were obtained with the patient in the left lateral decubitus position and started after the patient had been at rest for ≥ 10 min. An ultrasound scanner (Vingmed CFM 750; Vingmed Sound, Horten, Norway) with a duplex probe (3.25-MHz imaging/2.5-MHz Doppler) was used.

The aortic valve annulus diameter was measured in the parasternal long-axis view between the insertion points of the valve leaflets by use of the trailing-to-leading-edge method (8). The measurement of aortic valve annulus diameter at Baseline 1 was used in all subsequent analysis. The aortic valve annulus flow velocities were recorded by pulsed Doppler technique from the apical position with the sample volume positioned in the center of the outflow tract just at the annulus, obtaining an optimal flow-velocity spectral profile and a distinct valve-closure signal. The subclavian artery pulse tracings were obtained with a capillary damped funnel (9; Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery and connected to a strain-gauge transducer (model 120-0123; Irex Medical Systems, Ramsey, NJ, U.S.A.) and displayed simultaneously with the Doppler velocity spectrum on the monitor (Fig. 2). (6). Only pulse traces with a consistent wave form, a sharp deflection in early systole, and a minimal linear drift were used. Doppler recordings and pulse traces were obtained during a short period of apnea close to end-expiration. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiogram traces, to a computer for

FIG. 2. Example of simultaneous recording of aortic root flow with pulsed-wave Doppler, subclavian artery pulse tracing, and ECG (bottom trace).



analysis (Macintosh II CI; Apple Computers, Cupertino, CA, U.S.A.). Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP; Criticon, Tampa, FL, U.S.A.) every minute during the Doppler ultrasound study. The two measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis.

Analysis of echocardiographic recordings and subclavian artery pulse tracings

The maximal flow velocities (i.e., outer envelope of the Doppler spectrum) of at least three cardiac cycles were traced manually and averaged according to the previously described computerized procedure (6). From the aortic Doppler velocity trace, peak and mean velocities were determined. Ejection time was determined from the beginning of blood flow to the valve-closure click. Acceleration of aortic root flow was determined from the beginning of blood flow to the peak velocity. Acceleration time aortic root flow was determined as the duration of acceleration.

The subclavian artery pulse trace was calibrated with oscillometrically obtained systolic and diastolic pressures (6,7,10) and the pulse transmission delay corrected by alignment of the pulse trace incisura to the end systole of the Doppler flow trace.

M-Mode echocardiography

M-Mode echocardiograms of the left ventricle were obtained from the parasternal window, guided by 2-D echocardiography. Tracings from the level of the tip of the papillary muscles were transferred to the computer. It was required that the echoes of the right and left endocardium of the septum and the endocardial and epicardial surfaces of the posterior left ventricular walls were recorded continuously in at least three cardiac cycles. The left ventricular internal diameter, the intraventricular septal thickness, and the posterior wall thicknesses were determined in end diastole and in end systole according to the Penn convention (11) on M-mode echocardiograms.

Analysis of data

The flow and pressure traces were processed in a specially designed computer software where systemic arterial properties were estimated by use of an iteration procedure (6) for solution of the three-element Windkessel model (12). This model consists of an element representing the aortic characteristic impedance (Z) in series with two elements in parallel, the peripheral resistance (R), and the total arterial compliance (C) (12). The governing equations for this model are as follows (6,12):

$$C[dPa(t)/dt] + [Pa(t)/R] = Q(t) \quad (1)$$

$$P(t) = Pa(t) + ZQ(t) \quad (2)$$

where $P(t)$ is aortic pressure, $Q(t)$ is aortic flow, and $Pa(t)$ is the pressure reduction over R and C .

The general solution to these equations is

$$P(t) = e^{-t/RC} \left\{ Pd + \int_0^t e^{t/RC} Q(\tau) d\tau \right\} + ZQ(t) \quad (3)$$

where Pd is aortic pressure at end diastole ($t = 0$). The model variables were first determined by use of a nonlinear optimization algorithm by use of the least-square method and then further refined by minimizing the difference between the estimated and the measured pressure trace (6). In this scheme, the characteristic impedance was determined as

$$Z = \frac{\int_{RR} P(\tau) d\tau}{\int_S Q(\tau) d\tau} - R \quad (4)$$

where RR is the total cardiac cycle and S the systole. In this model, total arterial compliance represents the volume compliance of the systemic arteries, aortic characteristic impedance is an expression of the resistance to pulsatile flow in the proximal aorta, and peripheral resistance represents the arteriolar resistance. Mean arterial pressure was calculated as the pressure integral over the total cardiac cycle. End-systolic pressure was determined at the incisura of the calibrated pulse tracing. Pulse pressure was defined as the difference between systolic and diastolic pressure. Stroke volume was calculated as the product of the

Doppler velocity-time integral of aortic root flow and the aortic valve annulus cross-sectional area assuming a circular annulus. Cardiac output was calculated as the product of stroke volume and heart rate. Total peripheral resistance was calculated as the mean arterial pressure over cardiac output, multiplied by 80 for unit conversion. Left ventricular mass was calculated from M-mode echocardiograms by using the formula according to the Penn convention (11):

$$1.04\{(\text{IVSd} + \text{LVIDd} + \text{PWTd})^3 - (\text{LVIDd})^3\} - 13.6 \quad (5)$$

where LVIDd is the end-diastolic left ventricular internal diameter, IVSd is the end-diastolic intraventricular septal diameter and PWTd is the end-diastolic posterior wall thickness. The corresponding index was obtained by dividing with the body surface area.

Statistical analysis

Continuous variables were expressed as means \pm standard deviation (SD). Within-group comparisons were performed with an analysis of variance for repeated measurements. If the overall difference between groups was significant ($p < 0.05$), post hoc comparisons were performed with a Scheffé test. Percentage treatment effect was calculated with respect to an average of results at Baseline 1 and Baseline 2. The relation between variables was tested with linear regression analysis and Pearson's coefficient of correlation. Reproducibility of the method has been reported previously (6).

RESULTS

Atenolol reduced clinic and oscillometric systolic and diastolic pressures by 13–14% and the respective pulse pressures by 10 and 14% (Table 2). Captopril reduced clinic and oscillometric systolic and diastolic pressures by 7–8% and the respective pulse pressures by 3 and 6% (Table 2). Atenolol and captopril reduced the mean arterial pressure by 15 and 7%, respectively.

Atenolol, but not captopril, significantly increased the velocity-time integral and left ventricular ejection time (Table 3). Atenolol reduced the acceleration and increased the acceleration time of aortic root flow with respect to Baseline 1, but not with respect to Baseline 2. Neither atenolol nor captopril changed the peak and the mean velocity of aortic root flow.

Atenolol increased stroke volume by 11% and total arterial compliance by 42%, and reduced heart rate and cardiac output by 22 and 14%, respectively (Table 4). Figure 3 shows the relation between change in total arterial compliance and change in heart rate during treatment with atenolol. Peripheral resistance was not significantly changed by atenolol.

Captopril significantly reduced total peripheral resistance by 7% (Table 4). Total arterial compliance, heart rate, stroke volume, and cardiac output were not significantly changed by captopril.

Aortic characteristic impedance did not differ during treatment with atenolol and captopril, but there was a significant difference between baseline values (Table 4).

DISCUSSION

The study shows that, in subjects with ambulatory hypertension, total arterial compliance increases significantly during a 4-week treatment period with atenolol in daily dosages of 50–100 mg, but not during treatment with captopril (50–100 mg daily).

The marked effect of atenolol on total arterial compliance was surprising because it does not agree with some earlier studies (13–15). This may partly be due to methodologic differences. It is not unlikely that the arterial compliance of peripheral arteries, like arteries in the forearm (13) and the carotid artery (15) differs from the volume compliance estimated in the lumped model of the arterial circulation as used in our study (3,6,12,16). Thus total arterial compliance seems to reflect the properties of large, mainly elastic arteries (17), which may differ from peripheral arteries with predominantly muscle structure, possibly because mechanical influences on peripheral arteries are counterbalanced by vascular smooth-muscle constriction or dilatation.

Although contrasting effects of drugs on arterial mechanics may be due to different sites of action, specific drug actions and duration of treatment may play a role. Thus it should be recognized that the assessment of arterial mechanics during acute β -receptor blockade with a nonselective β -blocker (14) may differ from hemody-

TABLE 2. Arterial blood pressures (mm Hg) at baseline and during treatment

	Baseline 1	Baseline 2	Atenolol	Captopril	p (ANOVA)
Clinic SP	147 \pm 12 (130–178)	150 \pm 13 (127–175)	130 \pm 16 (124–136) ^{a,b}	139 \pm 19 (132–146) ^{a,b,c}	0.0001
Clinic DP	100 \pm 6 (92–115)	104 \pm 7 (90–120)	88 \pm 9 (85–91) ^{a,b}	94 \pm 10 (91–98) ^{a,b,c}	0.0001
Clinic PP	47 \pm 11 (33–80)	46 \pm 12 (25–73)	42 \pm 12 (37–46) ^a	45 \pm 13 (40–49)	0.02
Osc SP	147 \pm 13 (115–175)	144 \pm 15 (116–182)	125 \pm 15 (120–131) ^{a,b}	135 \pm 17 (129–142) ^{a,b,c}	0.0001
Osc DP	86 \pm 9 (65–102)	86 \pm 7 (72–98)	74 \pm 8 (71–77) ^{a,b}	79 \pm 9 (76–83) ^{a,b,c}	0.0001
Osc PP	61 \pm 9 (38–77)	58 \pm 10 (41–88)	52 \pm 12 (47–56) ^a	56 \pm 13 (51–61)	0.0009
Osc MAP	113 \pm 11 (94–139)	113 \pm 10 (92–135)	96 \pm 10 (92–99) ^{a,b}	105 \pm 12 (101–110) ^{a,b,c}	0.0001
Osc ESP	129 \pm 13 (102–159)	128 \pm 12 (105–151)	112 \pm 13 (107–117) ^{a,b}	121 \pm 14 (116–126) ^{a,b,c}	0.0001

Values expressed as mean \pm SD; range is in parenthesis for baseline values and 95% confidence interval is in parenthesis for outcome values.

Osc, oscillometric; SP, systolic pressure; DP, diastolic pressure; PP, pulse pressure; MAP, mean arterial pressure; ESP, end-systolic pressure.

^ap < 0.05 vs baseline 1.

^bp < 0.05 vs baseline 2.

^cp < 0.05 vs atenolol.

TABLE 3. Doppler echocardiographic recordings of aortic flow at baseline and during treatment

	Baseline 1	Baseline 2	Atenolol	Captopril	p (ANOVA)
VTI (cm)	24 ± 4 (18–32)	25 ± 4 (18–33)	27 ± 4 (26–28) ^{a,b}	25 ± 4 (23–26) ^c	0.0001
LVET (ms)	296 ± 24 (250–350)	293 ± 25 (240–345)	327 ± 37 (314–341) ^{a,b}	293 ± 25 (283–302) ^c	0.0001
V _{max} (cm/s)	116 ± 16 (85–159)	118 ± 15 (91–144)	117 ± 14 (112–122)	118 ± 19 (111–125)	0.9
V _{mean} (cm/s)	80 ± 10 (57–98)	83 ± 10 (65–111)	82 ± 10 (78–86)	84 ± 12 (80–89)	0.1
Acc (cm/s ²)	1,901 ± 487 (1,300–3,120)	1,748 ± 375 (1,120–2,470)	1,584 ± 417 (1,428–1,739) ^a	1,787 ± 353 (1,655–1,918)	0.008
Acc time (ms)	63 ± 11 (41–85)	69 ± 11 (52–91)	79 ± 14 (72–82) ^a	67 ± 11 (63–72) ^c	0.0001

Values expressed as mean ± SD; range is in parenthesis for baseline values, and 95% confidence interval is in parenthesis for outcome values. VTI, velocity time integral of aortic root flow; LVET, left ventricular ejection time; V_{max}, peak velocity of aortic root flow; V_{mean}, mean velocity of aortic root flow; Acc, acceleration of aortic root flow; Acc time, acceleration time of aortic root flow.

^ap < 0.05 vs baseline 1.
^bp < 0.05 vs baseline 2.
^cp < 0.05 vs atenolol.

dynamic changes that occur after long-term selective β_1 -receptor blockade. Thus although 6 weeks' treatment with atenolol did not increase total arterial compliance in one study (18), a significant increase in arterial compliance was demonstrated after 6 months' treatment in another study (19). It is possible that different effects on the arterial distending pressure may account for some of the discrepancy between these studies.

Arterial mechanics determined *in vivo* should always be evaluated in relation to the concomitant changes in the arterial blood pressure. A change in arterial compliance could be a simple effect of a change in the distending pressure with a shift on a given pressure–volume curve, or it can be due to a change in the elastic modulus of the arterial wall, inducing an upward or downward shift of the curve (20). Thus, it cannot be excluded that a higher dosage of captopril in our study could have induced a more pronounced effect on the arterial blood pressure with an increase in total arterial compliance comparable to that of atenolol. It should, however, be considered whether additional factors may have contributed to the differential effects of atenolol and captopril on total arterial compliance.

Drugs may alter the elastic modulus by modulating structural components of the arterial wall after long-term (i.e., years) treatment, but it is not likely that this occurred in our study because of the relative short treatment

period (21,22). The effect of reducing vascular smooth-muscle tone on large artery compliance is also somewhat controversial because a transfer of load from elastin to the stiffer collagen fibers may occur during vasodilatation (23). Although not a relevant mechanism during treatment with atenolol, it could contribute to explain the weak effect of captopril on total arterial compliance in this study. However, because vascular smooth muscle is relative scarce in large elastic arteries, the effect of captopril on total arterial compliance may be mainly pressure dependent, thereby explaining the difference between this study and studies that have shown increased compliance of peripheral, predominantly muscular arteries in animals (24) and in humans (25) during angiotensin-converting enzyme inhibition.

An influence of heart rate on arterial mechanics, with greater effects on elastic than on muscular arteries, was recently demonstrated in an animal study (26). This may occur because of the viscoelastic properties of the arterial wall (20,27). In other words, materials with viscoelastic properties may stiffen by increased rate of stretching and vice versa. It should be considered whether atenolol may influence total arterial compliance by reducing heart rate and rate of delivery of the stroke volume (28), as indicated by the prolonged acceleration time and reduced acceleration of aortic root flow. However, changes in the time available for diastolic recoil has also been proposed

TABLE 4. Hemodynamics at baseline and during treatment

	Baseline 1	Baseline 2	Atenolol	Captopril	p (ANOVA)
HR (beats/min)	69 ± 10 (54–95)	70 ± 12 (49–94)	55 ± 10 (51–59) ^{a,b}	68 ± 12 (63–72) ^c	0.0001
SV (ml)	103 ± 14 (70–137)	106 ± 16 (84–147)	115 ± 19 (108–122) ^{a,b}	106 ± 15 (100–112) ^c	0.0001
CO (L/min)	7.1 ± 1.1 (5.8–9.9)	7.3 ± 1.4 (5.0–11.0)	6.2 ± 1.0 (5.9–6.6) ^{a,b}	7.1 ± 1.0 (6.7–7.4) ^c	0.0001
TPR (dyn·s/cm ⁵)	1,309 ± 175 (1,007–1,678)	1,267 ± 199 (889–1,741)	1,252 ± 190 (1,181–1,323)	1,203 ± 112 (1,161–1,245) ^a	0.03
R (dyn·s/cm ⁵)	1,230 ± 166 (926–1,586)	1,204 ± 197 (839–1,637)	1,188 ± 173 (1,124–1,253)	1,144 ± 105 (1,105–1,183)	0.05
C (ml/mm Hg)	1.44 ± 0.36 (0.90–2.44)	1.47 ± 0.30 (0.89–1.98)	2.08 ± 0.73 (1.81–2.35) ^{a,b}	1.56 ± 0.42 (1.40–1.71) ^c	0.0001
Z (dyn·s/cm ⁵)	80 ± 30 (31–145)	65 ± 22 (26–122) ^a	65 ± 28 (55–76) ^a	61 ± 26 (51–71) ^a	0.03

Values expressed as mean ± SD; range is in parenthesis for baseline values, and 95% confidence interval is in parenthesis for outcome values. HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; R, peripheral resistance; C, total arterial compliance; Z, aortic characteristic impedance.

^ap < 0.05 vs baseline 1.
^bp < 0.05 vs baseline 2.
^cp < 0.05 vs atenolol.

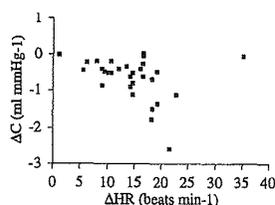


FIG. 3. Plot shows the change in total arterial compliance (ΔC) versus the change in heart rate (ΔHR) induced by atenolol ($r = -0.31$, $p = 0.09$). After exclusion of the outlier, the correlation coefficient was $r = -0.56$, $p = 0.002$.

as a mechanism for heart-rate dependence of arterial compliance (26). It is tempting to speculate that the properties of proximal large arteries are adapted to optimize ventricular-vascular coupling (29).

The complex influence on total arterial compliance (16) may explain the contrasting effect of atenolol on total arterial compliance and on aortic characteristic impedance (30), which is the impedance of the system in the absence of wave reflections (31). It is, however, emphasized that the estimation of aortic characteristic impedance is difficult (30) with conflicting results in previous studies (32-34). The interpretation of this variable should be performed with care.

The exact mechanism by which β -receptor blockers reduce the arterial blood pressures has been poorly understood (35,36). A reduction in cardiac output that persists even after long-term β -receptor blockade is of possible significance (37). An increased total arterial compliance may represent an additional mechanism. Because an increased total arterial compliance may indicate improved ventricular-vascular coupling (29), this could also contribute to explain some of the remarkable hemodynamic effects of β -receptor blockers, such as an increased ejection fraction and an increased stroke volume (38-40) that occur despite the negative inotropic effect on the myocardium of these drugs.

The possibility that characteristics of the study population may have influenced the results of the study should be considered. We encouraged the general practitioners to refer subjects with recently diagnosed arterial hypertension for a thorough evaluation with ambulatory blood pressure recordings and an echocardiographic examination. Several of the subjects were, in fact, recently identified as hypertensives in connection with a population screening of cardiovascular disease in 40-year-old subjects in this region (41), but it is not known if the study population is representative of subjects with essential hypertension in this area. The remarkable effect of β -receptor blockade may indicate the involvement of an increased adrenergic drive in the genesis of hypertension in these subjects.

It is also possible that the use of the diastolic, and not the systolic blood pressure as inclusion criteria, may have contributed to characterize the study population. The former method may allow selection of subjects with a low

pulse pressure and a high arterial compliance (42). This view is supported by the fact that total arterial compliance in the group of hypertensive subjects during treatment with atenolol was similar compared with a group of normotensive subjects of similar age and body size, earlier reported by us (43). The use of ambulatory blood pressure monitoring for the selection of study subjects may be an additional explanation for the contrasting results with other studies.

In this study we measured the arterial blood pressures during the echocardiographic examination on the right upper arm with the study subject in the left lateral decubitus position. All the subjects were examined in the same position with the same instrument. It is also underscored that the subclavian pulse trace calibrated with brachial artery pressures is accepted as a fair approximation of aortic root pressure (7,44). Because this was a crossover study, the subjects acted as their own controls, eliminating the influence of between-subjects variation. The four-week washout period should be sufficient to avoid any significant carry-over effect as indicated by similar arterial pressures at Baseline 1 and Baseline 2.

We conclude that total arterial compliance, at the operational blood pressure, increases during selective β_1 -adrenergic receptor blockade in subjects with ambulatory hypertension. Although the main mechanism may be a reduction in mean arterial pressure, it should be considered whether reduced heart rate may play an additional role. The non significant increase in total arterial compliance during angiotensin-converting enzyme inhibition may primarily be a consequence of a modest reduction of the mean arterial pressure.

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Paper V

Paper V

Sublingual nitroglycerin delays arterial wave reflections, but does not influence total arterial compliance in subjects with sustained hypertension

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Venodilation with consequent reduction in left ventricular filling and end-diastolic wall stress is an important mechanism for the beneficial effects of nitroglycerin in ischemic heart disease and in left ventricular failure. The effects of sublingual nitroglycerin on arterial pulsatile hemodynamics are less well defined. Doppler echocardiography and the calibrated subclavian artery pulse tracings were used to assess arterial pulsatile hemodynamics in subjects with sustained arterial hypertension ($n = 25$) before and 5 - 10 minutes after sublingual deposition of 0.5 mg glyceryl-trinitrate. Aortic characteristic impedance was calculated by averaging the modulus of the input impedance (ratio of pressure to flow) at high frequencies and by calculating the ratio of pressure and flow increments during upstroke. The pressure wave was split into forward and backward components, and the reflection coefficient (the ratio of backward to forward pressures) was calculated.

Parameters of the arterial bed were estimated using a two- and a three-element Windkessel model. Nitroglycerin delayed the return of arterial wave reflections (17%, $p = 0.02$), and increased aortic characteristic impedance (20%, $p = 0.01$), but did not influence total arterial compliance. Mean arterial pressure decreased 7%, $p = 0.0001$, but pulse pressure did not change. Stroke volume and acceleration time of aortic root flow decreased by 13%, $p = 0.0001$ and 8%, $p = 0.01$, respectively. Cardiac output decreased (7%, $p = 0.01$), despite an increase in heart rate (10%, $p = 0.0001$). Peripheral resistance tended to decrease (4%, $p = 0.06$). Thus, in subjects with sustained hypertension, sublingual nitroglycerin dilate peripheral, predominantly muscular arteries with subsequent delayed return of reflected pressure waves. Reflex activation of the sympathetic nervous system with consequent increased rate of left ventricular ejection seems to counteract the effect of reduced mean arterial pressure with respect to aortic compliance.

KEY WORDS: Arterial viscoelasticity, heart rate, pulse pressure, vasodilatation, ventricular-vascular coupling.

Venodilation with consequent reduction in left ventricular filling and end-diastolic wall stress is an important mechanism for the beneficial effects of nitroglycerin in ischemic heart disease and in left ventricular failure.¹ The effects of nitroglycerin on the systemic arterial circulation are less well defined.²⁻⁴ These effects are, however, important because the stiffness of the proximal elastic arteries is a determinant of resistance to pulsatile flow and contributes to determine the rise of the systolic blood pressure during left ventricular ejection and accordingly the load on the left ventricle.^{5,6} Peripheral, predominantly muscular arteries may influence the systolic blood pressure by attenuating the amplitude and the timing of arterial wave reflections.^{7,8} Hence, an increase in aortic compliance, reduced amplitude, and delayed timing of arterial wave reflections may improve left ventricular function and energetics.⁶ Although nitroglycerin seems to have a favourable effect on large artery function in coronary artery disease³ and in heart failure,⁴ few have studied the hemodynamic effects of nitroglycerin in subjects with arterial hypertension.^{9,10} To our knowledge no studies have been performed in sustained hypertension as defined by ambulatory blood pressure recordings.

Thus, using noninvasive methodology^{11,12} the present study investigates the acute effects of sublingual nitroglycerin on systemic hemodynamics in subjects with sustained hypertension. Since it has been suggested that choice of algorithm may influence the estimation of systemic hemodynamics,¹³ different models were used.

MATERIALS AND METHODS

Subjects were recruited as part of a study of hemodynamics in hypertension reported previously.¹⁴ Inclusion criterias were diastolic blood pressure ≥ 90 mm Hg as measured by the general practitioner (office diastolic pressure), diastolic blood pressure ≥ 90 mm Hg measured by a nurse in the clinic (clinic diastolic pressure), and ambulatory daytime diastolic pressure ≥ 90 mmHg, as well as willingness to participate in the study. Exclusion criterias were evidence of ischemic heart disease, congestive heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension,

other major diseases, inappropriate echocardiographic window and/or poor quality of the subclavian pulse tracing. Characteristics of the study subjects are given in Table 1. All subjects were off antihypertensive medication and other drugs at least four weeks before the investigation. All subjects gave written informed consent to the investigation, which was approved by the regional ethical committee.

Noninvasive Data Recordings All echocardiographic recordings were performed by the same investigator just before and 5 - 10 minutes after sublingual deposition of 0.5 mg glyceryl-trinitrate. The recordings were obtained with the patient in the left lateral decubitus position, and started after the patient had been at rest for at least 10 minutes. An ultrasound scanner (CFM 750, GE Vingmed Ultrasound, Horten, Norway) with a duplex probe (3.25-MHz imaging/2.5-MHz Doppler) was used. The aortic valve annulus diameter was measured at baseline in the parasternal long axis view between the insertion points of the valve leaflets by use of the trailing-to-leading edge method.¹⁵ The aortic valve annulus flow velocities were recorded from the apical position using high repetition frequency pulsed Doppler technique. The subclavian artery pulse tracings were obtained with a capillary damped funnel¹⁶ (Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery and connected to a strain-gauge transducer (model 120-0123, Irex Medical Systems, Ramsey, NJ, USA) and displayed simultaneously with the Doppler velocity spectrum on the monitor. Only pulse traces with a consistent wave morphology, a sharp deflection in early systole, and a minimal drift were used. Doppler recordings and pulse traces were obtained during a short period of apnea close to end-expiration. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiogram traces, to a computer for analysis (Macintosh II CI, Apple computers Inc., Cupertino, CA, USA). Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP, Criticon Inc, Tampa, FL, USA) every minute during the Doppler ultrasound study. The two measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis. M-mode

echocardiograms of the left ventricle were obtained from the parasternal window, guided by 2-D echocardiography. Left ventricular mass was calculated from M-mode echocardiograms using the formula according to the Penn convention.¹⁷

Analysis of Doppler-Echocardiographic Recordings and Subclavian Artery

Pulse Tracings All analysis were performed by the same investigator. The subclavian artery pulse trace was calibrated with oscillometrically obtained systolic and diastolic pressures^{11, 12, 18} and the pulse transmission delay was corrected by alignment of the upstroke of the pressure trace and the Doppler flow trace. The maximal flow velocities (i.e. outer envelope of the Doppler spectrum) of at least three cardiac cycles were traced manually and averaged according to the previously described computerized procedure.¹¹ Ejection time (LVET) was determined from the beginning of blood flow to the valve closure click. The time to peak aortic root flow (Acc-t) was determined from beginning of flow to peak aortic flow by use of an automatic, computerized procedure. Mean arterial pressure (MAP) was calculated as the pressure integral over the total cardiac cycle. End-systolic pressure (ESP) was determined at the incisura of the calibrated pulse tracing. Pulse pressure (PP) was defined as the difference between systolic and diastolic pressure. Stroke volume (SV) was calculated as the product of the Doppler velocity-time integral of aortic root flow and the aortic valve annulus cross-sectional area assuming a circular annulus. Cardiac output (CO) was calculated as the product of stroke volume and heart rate. Total peripheral resistance (TPR) was computed as mean pressure over mean flow.

The characteristic impedance (Z_c) was calculated as the mean of the modulus of the input impedance (ratio of pressure to flow) between the second and the tenth harmonic, and as the ratio of the pressure and flow increments during upstroke (Z_t).¹⁹

The pressure was split into forward and backward components by the method of Westerhof et al.⁷ The forward wave is defined as $P_f = (P + Z_c Q)/2$, while the backward wave is defined as $P_b = (P - Z_c Q)/2$, where P and Q denote pressure and flow, respectively (Figure 1). The pulse pressure of the forward (PP_f) and backward wave (PP_b) was calculated as

the difference of the peak and nadir pressures.

The reflection coefficient Γ was obtained as the ratio of backward to forward pressure waves, i.e. $\Gamma = P_b/P_f$. The reflection coefficient is a complex, dimensionless quantity containing information about both amplitude and phase of this ratio at each harmonic. Note that the first harmonic corresponds to 1/heart rate, i.e. a heart rate of 60 beats per minute corresponds to a first harmonic of 1 Hz. For each patient, the reflection coefficient for the data set with the lowest heart rate (normally the pre nitroglycerin set) was interpolated at a frequency corresponding to the first harmonic (1/heart rate) of the data set with the highest heart rate (normally the post nitroglycerin set). This was done to make allowance for comparison of the reflection coefficient of the two data sets at a given frequency, as the reflection coefficient is known to decrease in magnitude as a function of frequency and since intake of nitroglycerin increases heart rate (and thereby the first harmonic) significantly (Figure 2). The reflection coefficient depends on heart rate, aortic compliance, and peripheral impedance. By calculating a heart rate interpolated reflection coefficient (Γ_{hr}) it is possible to separate the effect of increased heart rate from the other effects.

Parameters of the arterial bed were estimated using the two-element Windkessel model and the three-element Windkessel model.²⁰ The compliance (C_{wk}) of the two-element Windkessel was estimated by the pulse pressure method,²¹ while the parameters of the three-element was estimated by minimisation of the squared differences between the measured pressures and the pressures predicted by the models (the Nelder-Mead algorithm). The parameters estimated in the three-element Windkessel were total arterial compliance (C_{wk3}) and aortic characteristic impedance (Z_{wk3}). After the model estimation, the peripheral resistance (R_{wk3}) was calculated as total peripheral resistance minus the characteristic impedance ($TPR - Z_{wk3}$).

Statistical Analysis Continuous variables were expressed as mean \pm standard deviation (SD). Group differences were tested with a paired t-test. Relations between variables were tested with Pearson's coefficient of correlation. The coefficient of variation for noninvasive

estimates of aortic pressures and flow has been shown to be in the range 6 - 10%.²²

RESULTS

Nitroglycerin reduced systolic, diastolic, mean and end-systolic blood pressures by 7 - 10 %, but did not significantly reduce pulse pressure (Table 2). Heart rate increased significantly in response to nitroglycerin, and left ventricular ejection time, time to peak aortic root flow, stroke volume and cardiac output decreased (Table 3). Although arteriolar resistance (Rwk3) tended to decrease ($p = 0.06$), total peripheral resistance (TPR) was not significantly influenced (Table 3).

Whereas the modulus of the reflection coefficient determined for the first harmonic (Γ -modulus) decreased significantly, the reduction of the modulus of the heart rate interpolated reflection coefficient (Γ_{hr} -modulus) was not statistically significant ($p = 0.1$) (Table 4). The corresponding phase angles (Γ -phase and Γ_{hr} -phase) were both more negative after nitroglycerin. The ratio of the pulse pressure of the backward to the pulse pressure of the forward pressure wave (PPb/PPf) was significantly reduced (Table 4).

Total arterial compliance, determined by use of the three-element windkessel model (Cwk3) and by use of the two-element windkessel model "pulse pressure method" (Cwk) did not change with nitroglycerin (Table 5).

Aortic characteristic impedance, determined by use of frequency analysis (Z_c) and calculated as the ratio of pressure and flow increments during upstroke (Z_t), increased significantly in response to nitroglycerin (Table 5). A similar tendency, although not statistically significant ($p = 0.08$), was shown for aortic characteristic impedance determined by use of the three-element windkessel model (Z_{wk3}). The percentage change in heart rate induced by nitroglycerin correlated significantly with the corresponding changes in aortic characteristic impedance and total arterial compliance estimated in the two element windkessel model (Table 6).

DISCUSSION

The study shows that, in subjects with sustained hypertension, sublingual nitroglycerin significantly delays the timing of reflected pressure waves. Aortic characteristic impedance increases, but total arterial compliance is not influenced, despite a reduction in the mean arterial pressure. The study shows, in addition, that subjects with sustained hypertension may have a tendency toward reflex sympathetic activation with increased heart rate and increased rate of ejection of the stroke volume after intake of sublingual nitroglycerin, indicating a well preserved baroreceptor function. This effect is not reported in all previous studies.²³ The use of concomitant medication such as beta adrenergic antagonists at the time of the investigation may explain the absence of increased heart rate after intake of nitroglycerin in some earlier studies.²⁴ It is underscored that the subjects in the present study were off all medications at least four weeks before the investigation.

Effect of Nitroglycerin on Arterial Wave Reflections Modulus and phase of reflected pressure and flow waves depend on the frequencies of the waves.²⁵ Thus, amplitude of the reflected wave may, at least indirectly, depend on heart rate since left ventricular ejection time and acceleration of ejection is related to heart rate. Shorter left ventricular ejection time also influences how much of the reflected wave that returns in systole, i.e. the smaller ejection time the larger portion of the reflected wave returns in diastole. Delayed return of wave reflections indicates decreased pulse wave velocity. The mismatch between the proximal characteristic impedance and the input impedance at the reflection site affects the amplitude of the reflected wave. The input impedance at the physiological reflection site is affected by vascular parameters such as compliance and resistance.

For each patient in the present study, the reflection coefficient for the data set with the lowest heart rate was interpolated at a frequency corresponding to the first harmonic of the data set with the highest heart rate. This was done in order to investigate whether the reduced amplitude of reflected pressure waves induced by sublingual nitroglycerin was due

to an effect on the arterial wall or if the effect could be explained by an increase in heart rate only. Thus, a reduced amplitude of the backward pressure wave after nitroglycerin seems primarily to be an effect of increased heart rate and less because of a direct effect on the arterial wall since the modulus of the heart rate interpolated reflection coefficient (Γ_{hr}) did not decrease significantly.

Although the reduced amplitude of the reflected pressure waves seemed mainly to depend on increased heart rate, the more negative phase angle of the reflection coefficient after nitroglycerin corresponds to delayed return of wave reflections and indicates dilatation of peripheral arteries according to Yaginuma et al.³ It is interesting that Yaginuma et al in their study, which was performed with invasive methodology, observed similar changes in wave reflections as well as in total arterial compliance and heart rate, i.e. no change in total arterial compliance associated with a slight increase in heart rate, as in the present study. Hence, nitroglycerin reduces the arterial systolic pressure in subjects with sustained hypertension because of delayed return and reduced amplitude of reflected pressure waves,^{2, 3, 24} and because of reduced stroke volume.

Effect of Nitroglycerin on Arterial Compliance A reduction in blood pressure without an effect on total arterial compliance may indicate increased arterial wall stiffness or reduced arterial cross-sectional area, or simply that the reduction in distending pressure is too small to significantly influence arterial wall properties. Against the latter argument is the tendency of stiffening of the aorta after nitroglycerin as indicated by increased aortic characteristic impedance and a tendency to decreased total arterial compliance, suggesting mechanisms counteracting the effect of reduced distending pressure may play a role. This mechanism could be represented by an increased vascular smooth muscle tone, which is not likely since nitroglycerin reduces vascular smooth muscle tone and because of small amount of vascular smooth muscle in the aorta. It should, however, be considered that total arterial compliance depends on the strain that accompanies a periodic, time-varying stress, i.e. a dynamic compliance.²⁶ Consequently, total arterial compliance is influenced by viscoelastic

properties of the arterial wall, i.e. stiffening of the arterial wall may be induced by increased rate of stretching secondary to increased rate of delivery of the stroke volume.^{14, 27} This may occur due to reflex activation of the sympathetic nervous system after nitroglycerin, with increased inotropic support of the left ventricle. A similar effect may also occur in relation to changes in heart rate induced by the parasympathetic nervous system because increased myocardial contractility accompanies increased heart rate, and vice versa, because of the force frequency relationship (Bowditch effect or "Treppe effect").²⁸ Other explanations for the association between changes in heart rate and estimates of aortic impedance and compliance should be sought in future studies.

Although reduced arterial cross sectional area, because of reduced arterial distending pressure, could contribute to explain the lack of effect of on total arterial compliance and the increase in aortic characteristic impedance after administration of nitroglycerin,²⁹ reduced cross-sectional area of peripheral, predominantly muscular arteries does not agree with the expected effect of nitroglycerin.³ The net effect of vasodilatation of muscular arteries, the most plausible effect of nitroglycerin, with respect to compliance of these arteries may be difficult to predict,³² but increased compliance is the most likely effect. Hence, increased compliance of peripheral arteries is the most plausible reason for the prolonged arterial wave propagation time induced by nitroglycerin.

Clinical Implications The study demonstrates that nitroglycerin may have differential effects on different parts of the arterial bed. The delay of reflected pressure waves because of dilatation of peripheral, predominantly muscular, arteries is desirable because it contributes to diminish left ventricular afterload. The reflex activation of the sympathetic nervous system after intake of nitroglycerin, which seems to counteract the effect of reduced distending pressure on proximal elastic arteries, is not desirable. Hence, use of a beta-adrenergic receptor blocker is recommended in conjunction with the need for sublingual nitroglycerin in subjects with sustained hypertension.^{14, 30}

Another implication of the study concerns the use of nitroglycerin as long term

antihypertensive medication. It has been questioned whether the increased peripheral resistance, which is the hallmark of arterial hypertension, is a consequence of a mismatch between endothelial derived vasoconstricting and vasodilating factors.³¹⁻³³ The fact that arteriolar resistance as well as the amplitude of reflected pressure waves both tended to decrease with sublingual nitroglycerin, may support this hypothesis, but higher dosages may be needed for a significant, direct influence on the arteriolar smooth muscle tone in subjects with sustained hypertension. The concomitant reduction in left ventricular filling and the resultant reflex activation of the sympathetic nervous system would, however, limit the clinical benefit of that approach, unless the subjects have high left ventricular filling pressures. An additional limitation for use of nitroglycerin as long term antihypertensive medication is the tendency to development of tolerance.³⁴

Methodological Considerations The study must be interpreted in light of the noninvasive methodology that was used. The subclavian artery pulse tracing calibrated with brachial artery pressures is, despite pressure amplification from central to the peripheral arteries, certainly accepted as a fair approximation of aortic root pressures,^{12, 35} but it should be considered whether the pressure amplification could have influenced the results.³⁶ Correcting pulse transmission delay by aligning upstroke of pressure and flow instead of aligning the incisura of the pulse trace with the aortic valve closure signal, as performed in previous studies,¹⁴ seems to provide more reliable estimates of aortic characteristic impedance. The automatic procedure for calculating time to peak flow (Acc-t) used in the present study may account for the slightly higher values compared to previous studies^{14, 27} where a manual procedure was used.

The hemodynamic effects of sublingual nitroglycerin are transient and the time window to perform recordings is accordingly short, requiring high precision in the collection of data. Blood pressure lowering drugs that induce reflex activation of the sympathetic nervous system may, however, serve to investigate the relative influence of frequency and pressure on arterial mechanical properties. Thus, controlled, randomized,

blinded studies comparing adequate dosages of drugs that reduce blood pressure, but have opposing effects on heart rate, such as beta-blockers versus some calcium antagonists, should be performed in the future to evaluate this important topic.

Conclusion In subjects with sustained hypertension, sublingual nitroglycerin dilate peripheral muscular arteries with subsequent delayed return of reflected pressure waves. Reflex activation of the sympathetic nervous system with consequent increased rate of left ventricular ejection seems to counteract the effect of reduced mean arterial pressure with respect to the compliance of the aorta and large elastic arteries.

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TABLE 1. CHARACTERISTICS OF THE SUBJECTS

Age (years)	50 ± 8 (31 - 67)
Males (%)	66
Weight (kg)	80 ± 11 (61 - 110)
Height (cm)	172 ± 7 (161 - 192)
BSA (m ²)	1.93 ± 0.16 (1.64 - 2.30)
LVOT (cm)	2.33 ± 0.16 (1.96 - 2.68)
LVMI (g m ⁻²)	124 ± 33 (70 - 187)
Pressures (mm Hg)	
Office SP	161 ± 17 (140 - 200)
Office DP	104 ± 8 (90 - 120)
Ambd SP	150 ± 13 (130 - 174)
Ambd DP	102 ± 8 (91 - 117)
Clinic SP	147 ± 16 (130 - 191)
Clinic DP	99 ± 6 (90 - 110)

*Values are mean ± SD; (range)
BSA, body surface area; LVOT, aortic valve
annulus diameter; LVMI, left ventricular
mass index; SP, systolic pressure; DP,
diastolic pressure; Ambd, ambulatory daytime
blood pressure*

TABLE 2. OSCILLOMETRIC ARTERIAL BLOOD PRESSURES (MM HG) PRE- AND POST NITROGLYCERIN

	pre-nitroglycerin	nitroglycerin	% change	p-value
SP	149 ± 18	139 ± 19	-7	0.0001
DP	86 ± 10	77 ± 12	-10	0.0001
PP	62 ± 12	62 ± 14	0	0.9
MAP	114 ± 13	106 ± 14	-7	0.0001
ESP	129 ± 16	118 ± 17	-9	0.0001

Values are mean ± SD

SP, systolic pressure; DP, diastolic pressure; PP, pulse pressure; MAP, mean arterial pressure; ESP, end-systolic pressure.

TABLE 3. HEMODYNAMICS PRE- AND POST NITROGLYCERIN

	pre-nitroglycerin	nitroglycerin	% change	p-value
HR (beats min ⁻¹)	70 ± 10	77 ± 10	10	0.0001
LVET (ms)	298 ± 24	270 ± 26	-9	0.0001
Acc-t (ms)	86 ± 13	79 ± 12	-8	0.01
VTI (cm)	24 ± 4	21 ± 3	-13	0.0001
SV (ml)	103 ± 16	90 ± 16	-13	0.0001
CO (l min ⁻¹)	7.2 ± 1.1	6.7 ± 0.8	-7	0.01
TPR (dyn s cm ⁻⁵)	1295 ± 180	1269 ± 196	-2	0.3

Values are mean ± SD

HR, heart rate; LVET, ejection time; Acc-t, time from beginning of aortic flow to peak flow; VTI, velocity-time integral of aortic root flow; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance.

TABLE 4. REFLECTION PARAMETERS PRE- AND POST NITROGLYCERIN

	pre-nitroglycerin	nitroglycerin	% change	p-value
Γ -modulus	0.56 ± 0.10	0.51 ± 0.10	-9	0.02
Γ -phase (rad)	-0.80 ± 0.29	-1.00 ± 0.36	-25	0.002
Γ_{hr} -modulus	0.54 ± 0.10	0.51 ± 0.10	-6	0.1
Γ_{hr} -phase (rad)	-0.86 ± 0.30	-1.01 ± 0.36	-17	0.02
PPb/PPf	0.66 ± 0.09	0.56 ± 0.09	-15	0.0001

Values are mean \pm SD

Γ , reflection coefficients determined at the frequency of the first harmonic; Γ_{hr} , reflection coefficients determined at the frequency of the first harmonic interpolated for heart rate; PPb and PPf, pulse pressure of the backward and forward pressure waves.

TABLE 5. PARAMETERS OF THE ARTERIAL TREE PRE- AND POST NITROGLYCERIN

	pre-nitroglycerin	nitroglycerin	% change	p-value
Zc (dyn s cm ⁻⁵)	92 ± 44	110 ± 42	20	0.01
Zt (dyn s cm ⁻⁵)	88 ± 37	112 ± 40	27	0.001
Zwk3 (dyn s cm ⁻⁵)	96 ± 29	104 ± 30	8	0.08
Cwk (ml mmHg ⁻¹)	1.12 ± 0.32	1.02 ± 0.37	-9	0.08
Cwk3 (ml mmHg ⁻¹)	1.51 ± 0.43	1.53 ± 0.60	1	0.8
Rwk3 (dyn s cm ⁻⁵)	1193 ± 173	1147 ± 178	-4	0.06

Values are mean ± SD

Zc, aortic characteristic impedance estimated using frequency analysis Zt, aortic characteristic impedance calculated as the ratio of pressure and flow wave during upstroke.

Cwk, total arterial compliance according to the pulse pressure method.

Cwk3, Zwk3, and Rwk3, total arterial compliance, aortic characteristic impedance and peripheral resistance according to the 3-element windkessel model.

TABLE 6. CORRELATIONS OF PERCENTAGE CHANGE IN HEART RATE AND MEAN ARTERIAL PRESSURE WITH CORRESPONDING CHANGES IN ESTIMATES OF AORTIC IMPEDANCE AND COMPLIANCE (n=25)

	$\% \Delta \text{HR}$	$\% \Delta \text{MAP}$
$\% \Delta Z_c$ (dyn s cm ⁻⁵)	$r = 0.21, p = 0.32$	$r = 0.05, p = 0.8$
$\% \Delta Z_t$ (dyn s cm ⁻⁵)	$r = 0.39, p = 0.05$	$r = 0.12, p = 0.6$
$\% \Delta Z_{wk3}$ (dyn s cm ⁻⁵)	$r = 0.41, p = 0.04$	$r = 0.17, p = 0.4$
$\% \Delta C_{wk}$ (ml mmHg ⁻¹)	$r = -0.49, p = 0.01$	$r = -0.16, p = 0.5$
$\% \Delta C_{wk3}$ (ml mmHg ⁻¹)	$r = -0.23, p = 0.28$	$r = -0.13, p = 0.5$

Z_c , Z_t , Z_{wk3} , aortic characteristic impedance estimated using frequency analysis, the ratio of pressure and flow wave during upstroke and the 3-element windkessel model respectively. C_{wk} and C_{wk3} , total arterial compliance according to the pulse pressure method (2-element windkessel model) and the 3-element windkessel model.

Fig. 1

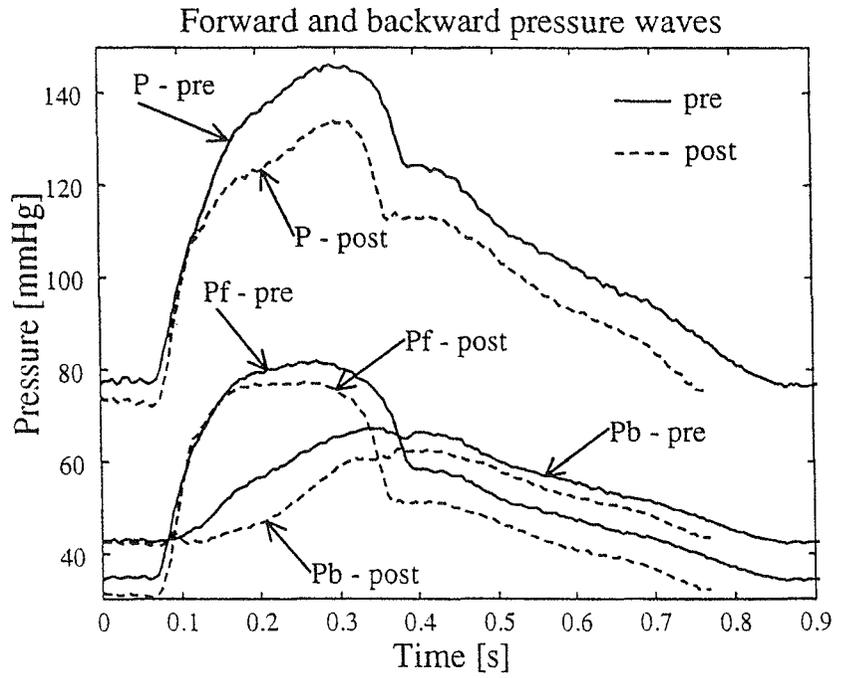
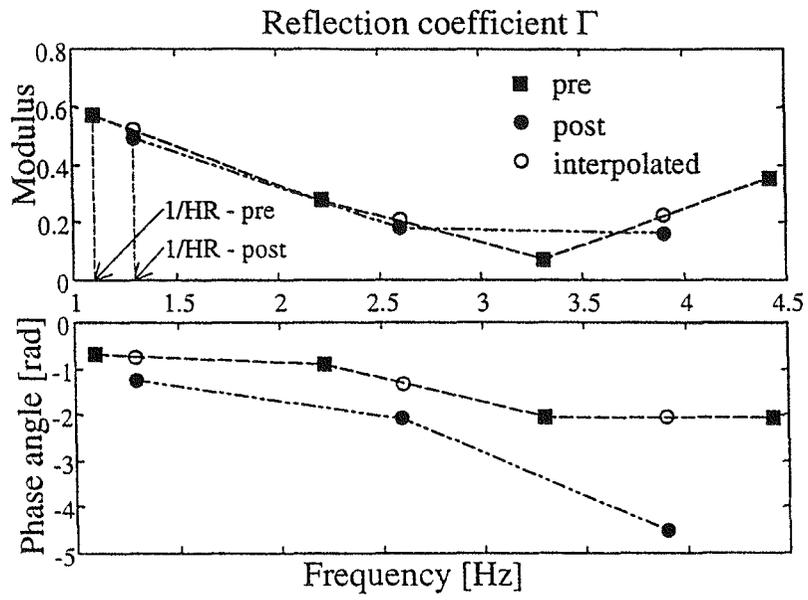


Fig. 2



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