Cardiol.

THE HEART IN HYPERTENSION

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INTRODUCTION

The search continues for a unitary cause of primary hypertension. A large number of candidates have been identified, including various neurohumoral and renal mechanisms and cellular and subcellular abnormalities of sodium and calcium handling (Haddy et al. 1980; Lau and Eby, 1985). These factors modulate the clinical course of the disease but primary hypertension is still a cardiovascular condition of uncertain etiology. Most antihypertensive measures remain symptomatic approaches to a lower arterial pressure (Tarazi, 1983).

The heart has a major dual role in arterial hypertension: maintaining the elevated pressure and suffering its consequences. This review presents a summary of current concepts, including the effects of essential or primary hypertension on cardiovascular mortality and morbidity, on systemic and regional hemodynamics, and on left ventricular structure and function. The discussion emphasizes human pathophysiology and clinical studies. The endocrine function of the heart and the cardiac natriuretic peptides deserve a separate review and will not be covered.

CARDIOVASCULAR COMPLICATIONS

Increased arterial pressure can be caused by inappropriate increases of systemic flow or resistance, or both. The relative contributions vary with the type and stage of hypertension but a common denominator is the development of structural and functional cardiovascular adaptations. These adaptations support the elevated pressure and cause most complications.

Table 1 documents the incidence of major cardiovascular complications in patients with (a) mild or moderately severe and (b) severe hypertension. The pooled data from the control groups of several large therapeutic trials show that even patients with mild hypertension have significant rates of clinical cardiovascular events. The data for the severe category were drawn from a single small series, a 1967 VA cooperative study. The general applicability of the results is questionable. Some of the patients had evidence for end-organ damage at entry. On the other hand, it is extremely unlikely that additional long-term follow up data will become available from untreated patients with equally severe hypertension. The cumulative incidence of major events during an average follow up period of 16 months included development of either accelerated hypertension, cerebral hemorrhage, severe congestive heart failure (CHF), or azotemia in 24%. Another 9% of the patients suffered myocardial infarction, mild CHF, cerebral thrombosis, or transient ischemic attacks.

More detailed information on the relative risks and the relationship between arterial pressure and cardiovascular morbidity and mortality has been derived from long-term follow data from a large general population during the course of the Framingham study (Kannel 1980). The annual incidence of cardiovascular disease in middle-aged men and women increases progressively with increasing systolic pressure without any apparent threshold. The overall disease rate increases by 30% for each 10 mm Hg increase in pressure or doubles

TABLE 1. MORTALITY AND MORBIDITY IN UNTREATED PRIMARY HYPERTENSION

ANNUAL INCIDENCE, PER CENT

	DIASTOLIC PRESSURE, mm Hg	
	90-114	115-129
CORONARY DISEASE		
FATAL	.3	.8
NON-FATAL	1.5	2.3
CONGESTIVE HEART FAILURE	.3	2.3
CEREBROVASCULAR DISEASE	.7	12.3
RENAL FAILURE	.2	2.3
TOTAL MORTALITY	.6	4.6
PATIENT YEARS OF OBSERVATION	2,386	91

The incidence data in the 90-114 mm Hg Group represent weighted averages from the control groups of the VA Cooperative Study (1970), the USPPS Hospital Study (1970), the Australian Therapeutic Trial (1980), and the Oslo Study (1980). The 115-129 mm Hg data are from the 1967 VA study. Modified from Staessen et al. (1983) and Kaplan (1982).

for each 33 mm Hg increase in the 45 to 64 year age bracket (Figure 1). The risks associated with high blood pressure are independent of other known risk factors for cardiovascular mortality and morbidity, e.g., age, sex, smoking, and blood lipids. The incidence of all major types of cardiovascular diseases (sudden death, ischemic heart disease, chronic congestive failure, stroke) is directly related to pressure but strokes tend to be disproportionately more prevalent at the higher blood pressure levels and at older ages. Similar trends are apparent in most Western populations (Wilhelmsen, 1984).

Electrocardiographic signs of left ventricular hypertrophy (LVH) have been identified as major predictors of cardiovascular morbidity and mortality (Kannel and Sorlie, 1981). About 30% of all deaths and 45% of all cardiovascular deaths in the Framingham cohort were preceded by a finding of LVH by ECG (Table 2). Definite LVH, defined as increased QRS voltage associated with STT abnormalities, was linked to an 8-fold increase in total cardiovascular mortality and 6-fold increase in coronary mortality and sudden death. The relative risks were lower for LVH without the STT abnormality but still 2 to 3 times higher than in subjects without LVH.

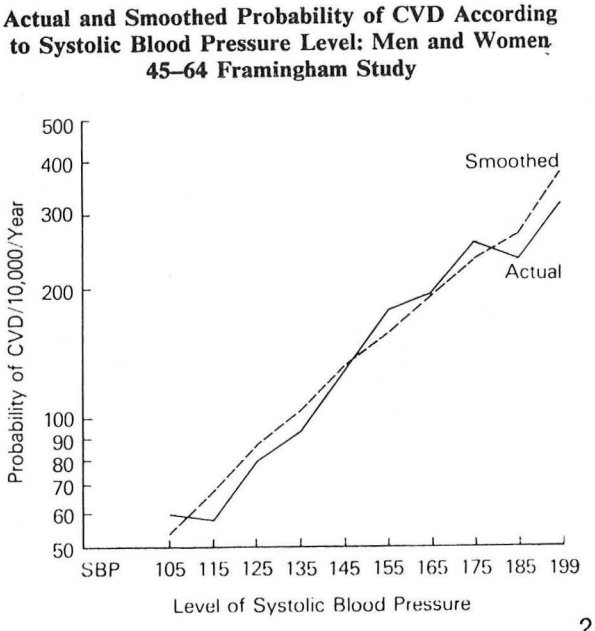


Fig. 1. Actual and smoothed probability of CVD according to systolic blood pressure level: Men and women 45–64. Framingham study.

From Kannel (1980).

TABLE 2. RELATIVE CARDIOVASCULAR MORTALITY IN THE PRESENCE AND ABSENCE OF ECG SIGNS OF LVH

	SUDDEN DEATH	ISCHEMIC HEART DS	TOTAL CARDIOVASCULAR
DEF. LVH/NO LVH	5.8	5.9	8.5
POSS. LVH/NO LVH	2.4	2.4	3.0

Definite LVH = increased QRS voltage and STT abnormality.
Possible LVH = high QRS voltage only.

Data from Kannel and Sorlie (1981).

The Framingham study is widely used as a reference point but some of the data were collected more than 20 years ago. The treatment of hypertension was then less frequent and less effective than today. Improved detection and treatment of high blood pressure can account for a major portion of the large gradual decline in total and cardiovascular mortality that has occurred in the United States starting during the late 1960's (Kaplan 1982). There are no detailed epidemiologic data that quantitate the effect of treatment on the relative distribution on specific causes of mortality and morbidity but Table 3 is based on the combined data from seven major therapeutic trials with treatments ranging from beta blockers alone to step care (Staessen et al., 1983). Total mortality and both fatal and non-fatal coronary events were reduced by about 20%. There was a larger reduction in cerebrovascular accidents, i.e., by almost 50%.

TABLE 3. MORTALITY AND MORBIDITY IN TREATED AND UNTREATED ESSENTIAL HYPERTENSION DURING SEVEN THERAPEUTIC TRIALS

	TREATED	CONTROL	P
TOTAL MORTALITY	48	61	<0.001
CARDIOVASCULAR MORTALITY			
TOTAL	26	36	<0.001
CVA	4	9	<0.001
ASHD	18	22	0.08
FATAL AND NON-FATAL EVENTS			
CVA	18	34	<0.001
ASHD	40	57	0.05

Total number of cases. Treatment modality and observation period non-uniform.
Data from Staessen et al. (1983)
CVA = Cerebrovascular Accident, ASHD = Arteriosclerotic Heart Disease

SYSTEMIC AND REGIONAL HEMODYNAMICS

Hemodynamic loading conditions are critical in the progression of hypertension and in the development of clinical complications.

Systemic hemodynamics at rest.

Early direct hemodynamic studies by Bolomey et al.(1949), Werkö and Lagerlöf (1949), and Varnauskas (1955) showed that the majority of hypertensive patients without congestive heart failure had normal or low cardiac output and increased peripheral resistance. However, about 1/3 of the subjects in these series had normal resistance and increased cardiac output. Within a few years during the late 1950's and early 1960's, several investigators had presented data indicating that increased cardiac output with normal resistance was the dominant hemodynamic pattern in young patients with mild or labile hypertension (Hejl, 1958; Widimsky et al., 1957; Eich et al., 1962). Stroke volume was normal but heart rate increased. Subsequent work by many groups have verified that primary hypertension usually progresses from a hyperdynamic systemic circulation in early hypertension, particularly in young patients, toward a low cardiac output and high resistance in older patients with a long duration of the disease. Nevertheless, there are frequent deviations from this pattern. Excellent, detailed, and current hemodynamic reviews are available (Lund-Johansen, 1980; Folkow, 1982; Tarazi, 1983).

The prominent inter-individual hemodynamic variations, particularly in the middle age groups, and the dominant trend from a high output to a high resistance are both well illustrated by the data published by Lund-Johansen (1977).

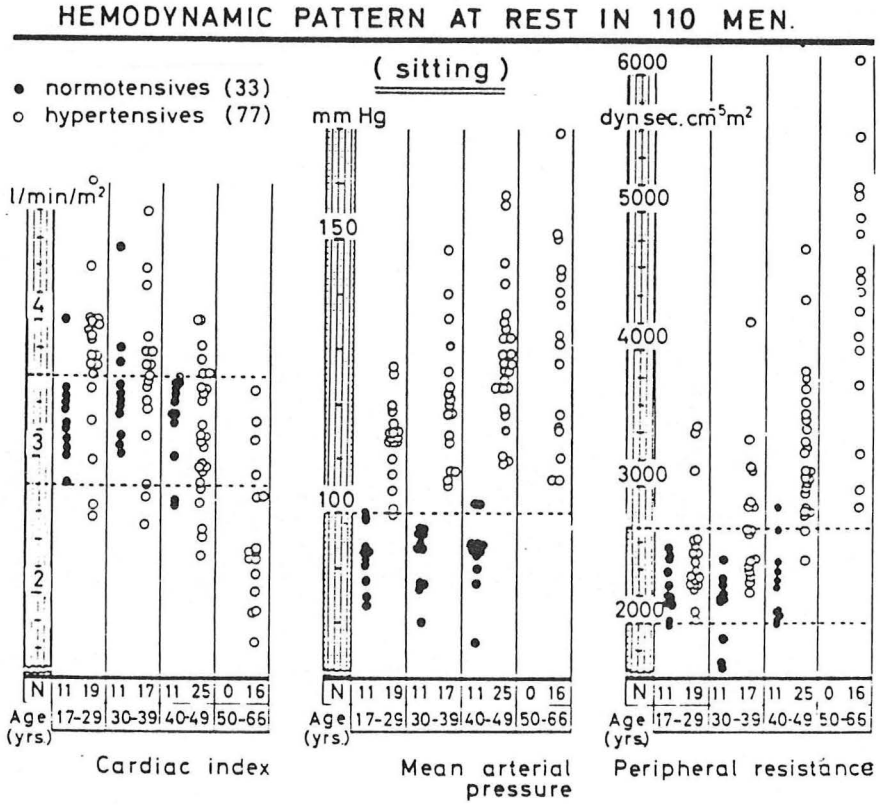


Figure 2.
Hemodynamic measurements in untreated primary hypertension.

From Lund-Johansen (1977).

Figure 2 shows age-specific hemodynamic patterns in untreated men with primary hypertension and in normal controls. Peripheral resistance was normal in almost all patients less than 30 years old and abnormal in all 50 and older. Mean cardiac output decreased progressively and total peripheral resistance increased. Corresponding longitudinal results are shown in Figure 3. Mean arterial pressure increased only slightly over a 10-year period but stroke volume and cardiac output decreased and total peripheral resistance increased in the vast majority of the patients. Similar results have been reported by 6 different groups of investigators who using direct hemodynamic techniques re-examined a total of 172 patients after a mean interval ranging from 2 to 12 years (Eich et al., Eliasch et al., Birkenhager et al., Weiss et al., Lund-Johansen, and Julius et al., reviewed by Lund-Johansen, 1980 and by Silvertsen, 1984). Each series showed a decrease in mean cardiac output and an increase in resistance with only minor changes in arterial pressures.

Exercise.

Dynamic exercise. The normal hemodynamic response to treadmill or bicycle exercise is characterized by an increase in cardiac output that is closely linked to the increase in systemic oxygen demand. An arterial O_2 content of about 200 cc/1 liter blood and a 5-6 liter increase in cardiac output for each liter increase in O_2 uptake correspond to a 1:1 match between changes in O_2 demand and O_2 transport. An efficient redistribution of blood flow is achieved by progressive systemic α-adrenergic vasoconstriction, opposed in active tissues by metabolic vasodilation. The metabolically mediated vasodilation in skeletal muscles dominates systemic hemodynamics. Total peripheral resistance reaches its minimum during maximal exercise when plasma norepinephrine levels, largely representing overflow from vascular α-receptors, are maximal (Lewis et al., 1983).

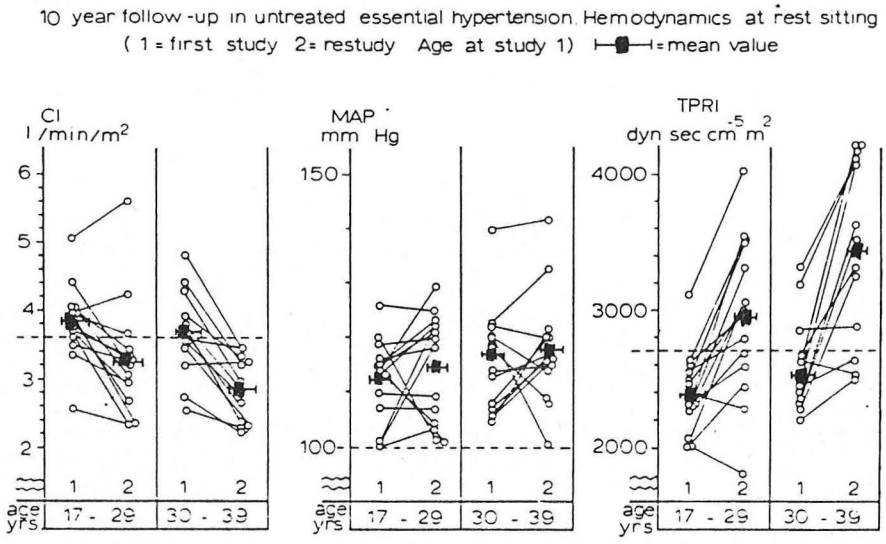


Fig. 3. Cardiax index (CI), mean arterial pressure (MAP) and total peripheral resistance index (TRPI) at rest sitting. Study 1 in 1965–66, study 2 10 years later.

From Lund-Johansen (1977).

The normal 1:1 relationship between the increase in systemic O_2 demand and O_2 transport is maintained during submaximal exercise in hypertensive patients without congestive heart failure, including patients with early or labile hypertension and abnormally high cardiac output at rest. However, most patients, including those without any clinical evidence for end-organ damage and normal or even low total peripheral resistance at rest fail to decrease resistance normally during exercise (Sannerstedt, 1966; Lund-Johansen, 1977, 1980). Systolic, mean, and diastolic pressures are consistently higher than in normal subjects at all levels. The slope of the relationship between arterial pressure and oxygen uptake is essentially normal but the y-axis intercept, i.e., arterial pressure at rest, is increased. The relative lack of capacity to vasodilate (Figure 4) becomes more prominent with increasing age and duration of the hypertensive state (Sannerstedt, 1966; Lund-Johansen, 1977, 1980). This is consistent with significant and progressive structural vascular adaptations. Increasing age and duration of hypertension are also associated with decreasing stroke volume and cardiac output of maximal and near maximal workload levels (Lund-Johansen, 1977).

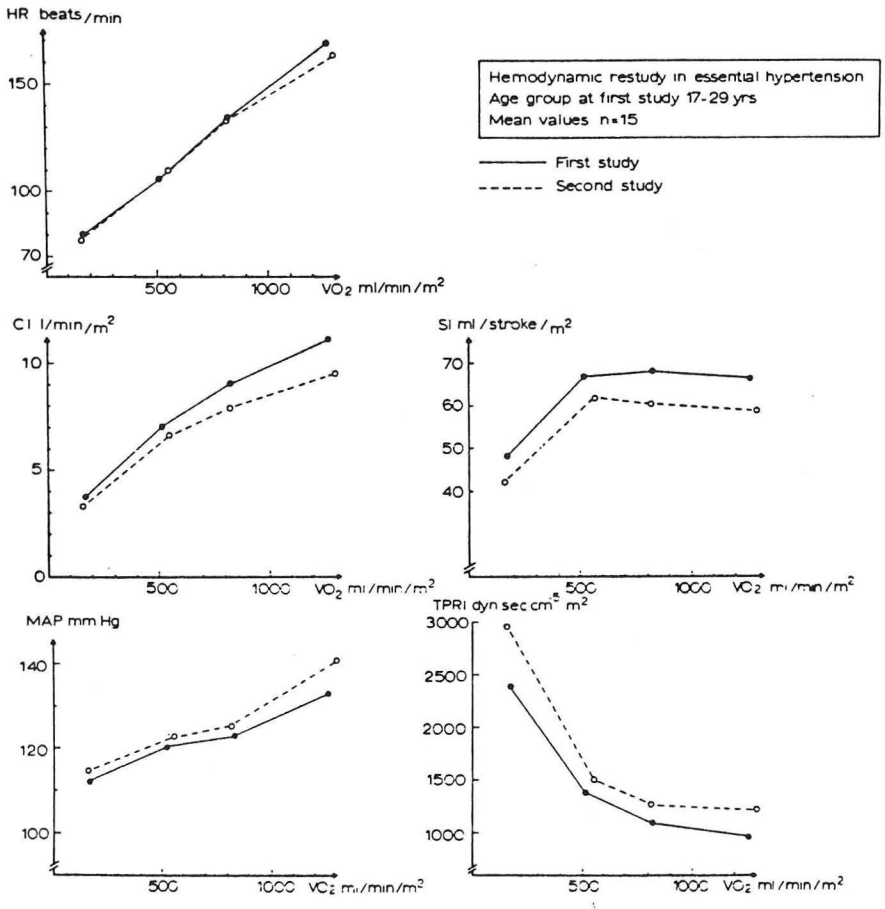


Figure 4. Longitudinal changes in the hemodynamic response to exercise. From a 10-year follow-up study by Lund-Johansen (1977).

Heavy static or isometric efforts can cause very high arterial pressures in hypertensive patients. Patients without left ventricular dysfunction produce the elevated pressures primarily by an increase in cardiac output with little change in peripheral resistance whereas patients with depressed left ventricular dysfunction achieve the pressor response primarily by vasoconstriction (Ewing et al., 1973).

Diurnal variations

Direct and continuous long-term recording of intra-arterial pressure in unrestricted subjects has been made possible by a device developed at Oxford by Bevan et al. (1969). A long series of publications by the Oxford group (Littler et al., 1975, 1978; Millar-Craig et al., 1978; Goldberg et al., 1978; Mann et al., 1980) have established a characteristic diurnal pattern in most normal subjects and in hypertensive patients. Arterial pressure is substantially lower and more stable during sleep than during active hours. Pressures during the day often show sharp transients (Figure 5) and the amplitude of the transients tend to be positively related to the level of the arterial pressure. There is only a tenuous correlation between changes in heart rate and changes in arterial pressures. This implies that different daily life stimuli may produce blood pressure increases primarily by increases in heart rate and cardiac output, by increases in peripheral resistance, or by a combination of both.

Standard clinical approaches have emphasized the importance of using of basal blood pressures as measures of the severity of hypertension and as predictors of complications. However, data from the Framingham study have demonstrated that systolic pressure is a more accurate predictor of cardiovascular events than diastolic pressure and that minimum, maximum, and mean pressures

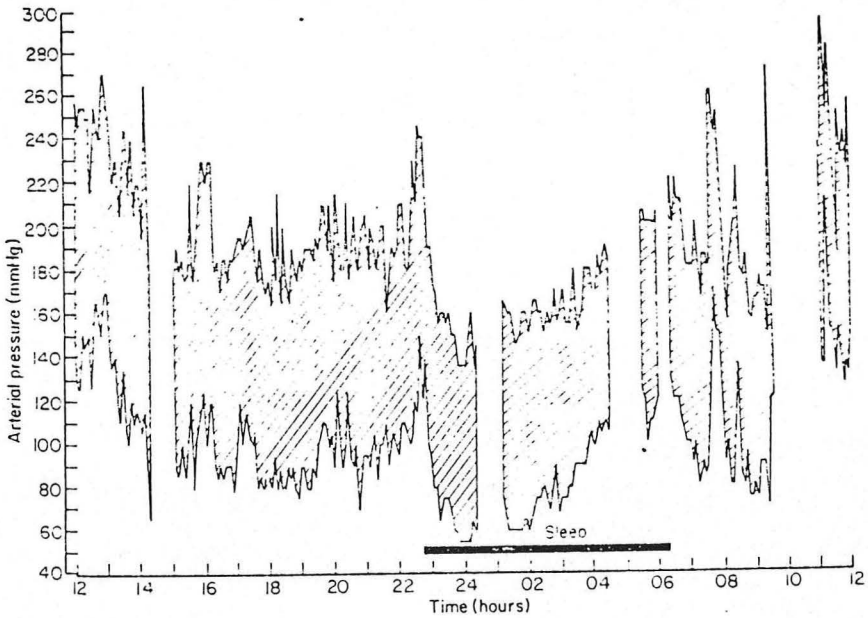


FIG. 5. Arterial pressure, plotted at 5 min intervals, of subject E.L. The period of sleep is shown by the horizontal bar. E.L. had the greatest fall in pressure during sleep of the group of patients with essential hypertension in the benign phase.

From Bevan et al. (1968).

as measured during a 1-hour observation period are equally effective markers of future cardiovascular complications (Kannel et al., 1980a and b). Recent studies have used echocardiographic estimates of left ventricular mass and shown that left ventricular hypertrophy in patients with primary hypertension is more closely related to systolic blood pressures during stress or activity than during basal conditions (Rowlands et al., 1982, Devereux et al., 1983, Ren et al., 1985). The technology is now available for non-invasive extended monitoring of arterial pressure (Weber and Drayer, 1984) but the clinical utility remains to be established (Sleight, 1985; Pickering, et al., 1985).

Regional hemodynamics.

General aspects. Blood flow to the skin and to skeletal muscle at rest, and flow rates in the renal, splanchnic and hepatic circulations show only a tenuous relationship to the rate of oxidative metabolism. These regions provide the primary substrate for changes in local resistance and flow subservient to the systemic regulation of arterial pressure. Cardiac output is poorly controlled at rest. There is usually at least a 25% fall in systemic flow on the transition from supine to standing whereas mean arterial pressure changes very little. Vasoconstriction in non-critical areas maintains an adequate perfusion pressure to the brain and myocardium that both are critically dependent on blood flow (Blomqvist and Stone, 1983). The narrow tolerance limits for arterial pressure and the wide limits for cardiac output make teleological sense. Only a fraction of the normal cardiac output is required to supply the brain and the heart but the perfusion pressure is critical.

In general, the flow and resistance in the regional circulations (excluding the brain and myocardium) tend to parallel systemic patterns at rest. (Messerli et al., 1978, Lund-Johansen 1980). The renal circulation is a special case. It participates passively in the systemic short-term regulation of blood pressure. At the same time, changes in regional flow rates and the interactions between neuro-humoral control mechanisms and renal flow patterns are likely to be major contributors to the long-term maintenance of an elevated arterial pressure (Hollenberg, 1980).

Pulmonary circulation. Early direct hemodynamic studies (Werkö and Lagerlöf, 1949; Varnauskas, 1955) demonstrated that most patients with primary arterial hypertension have normal right-sided central pressures unless significant left ventricular dysfunction and congestive heart failure are present. However, a minority of patients without heart failure had increased pulmonary artery pressure and pulmonary vascular resistance. The significance of this subset was not appreciated until much later when Atkins et al. (1977) examined 110 patients with diastolic arterial pressures $\geq$ 90 mm Hg. Pulmonary capillary wedge pressures exceeded 12 mm Hg only in 13% but 25% had mean pulmonary artery pressures $\geq$ 20 mm Hg. There was a significant correlation between systemic and pulmonary vascular resistance (r 0.39, $p < 0.001$ (Figure 6)) and mean pulmonary vascular resistance was well above the upper limit of normal.

Olivari et al. (1978) and Ferlinz (1980) have confirmed the relatively frequent occurrence of increased pulmonary vascular resistance and pulmonary artery pressure in the absence of congestive failure. Ferlinz (1980) attributed

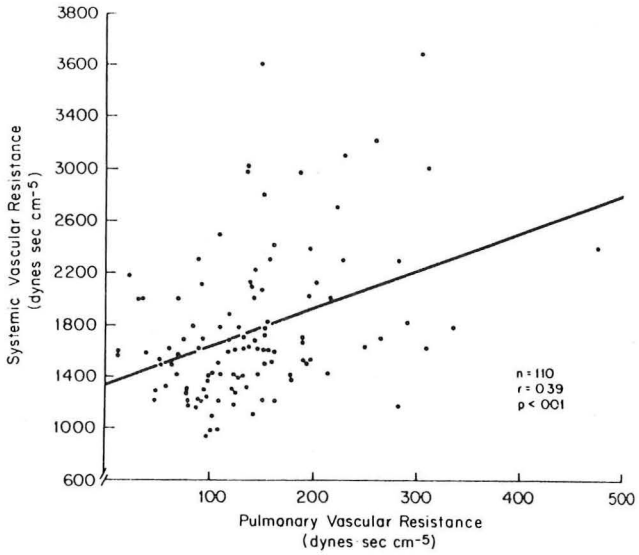


FIGURE 6. Relation of pulmonary vascular resistance to systemic vascular resistance ($r = 0.39$, $P < 0.001$).

From Atkins et al. (1977).

a decreased mean right ventricular angiographic ejection fraction in his series of patients with primary hypertension (59% vs a normal mean of 68%) to an increased right ventricular pressure load. A study by Fiorentini et al. (1985) has recently demonstrated pulmonary vascular hyperreactivity to stimuli that also cause systemic vasoconstriction. Together, these data strongly suggest that the pulmonary vasculature is affected by many of the same agents and conditions that influence the systemic circulation and that the right ventricle is often subjected to an increased pressure load.

Coronary circulation. Adaptive changes associated with left ventricular hypertrophy occur at several levels in the coronary circulation. The capillary reserve is diminished. Decreased capillary density is a characteristic of pathological hypertrophy. The primary limitation of the capacity to deliver oxygen may be the relative decrease in capillary surface area and mean transit time rather than an increased diffusion distance (Honig and Gayeski, 1983). Measurements in different experimental models of ventricular hypertrophy have generally shown that myocardial blood flow is within normal limits at rest but measurements during stress reveal inadequate perfusion rates. As a consequence, experimental coronary occlusion produces a relatively larger infarct size and higher mortality than in control animals (Bache and Vrobel, 1983; Marcus et al., 1983).

There is decreased coronary vasodilator reserve even in mild disease. An increase in left ventricular mass of as little as 30% is associated with attenuated vasodilator responses (Figure 7) in the absence of large coronary arteries lesions (Strauer, 1979, 1980 and 1984; Marcus et al., 1983).

Studies of the cerebral circulation in patients with hypertension have usually shown flow rates within the normal range of 50-60 mm/100 grams (Tarazi, 1983). The capacity for autoregulation of cerebral flow over a wide mean

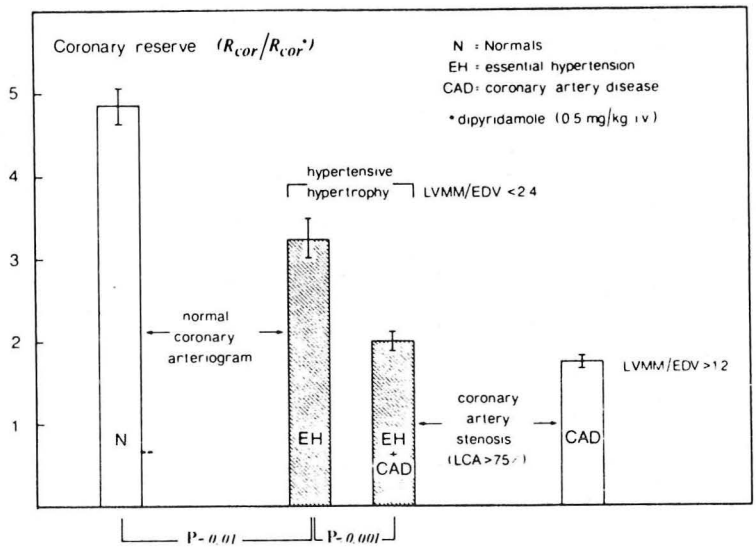


Fig. 7. Coronary reserve, defined as the ratio of coronary resistance (R_{cor}) under control conditions and coronary resistance under maximal coronary dilatation (R_{cor}), in normal subjects (*N*), in those with essential hypertension (*EH*) with a normal coronary arteriogram, in those with essential hypertension with coronary arterial stenosis, and in normotensive patients with coronary artery disease (*CAD*). Note the decreased coronary reserve even in hypertensive hypertrophy with normal coronary arteriogram. *LCA*, left coronary artery; *LVMM/EDV*, left ventricular mass to volume ratio; *P* = probability

From Strauer (1979).

pressure range is retained but basal cerebral resistance and the autoregulatory pressure operating point have moved upward (Strandgaard et al., 1973). This protects the patient against further increases in mean arterial pressure but may increase the vulnerability to sudden blood pressure drops (Figure 8). Occasional patients with occlusive cerebrovascular disease are critically dependent on perfusion pressure for adequate regional blood supply. The resetting of the autoregulatory range and the increased incidence of anatomical arterial lesions (Sandok and Whisnant, 1983) combine to produce the increased incidence of clinical cerebrovascular disease in patients with hypertension.

FACTORS MODULATING THE HEMODYNAMICS OF HYPERTENSION

Autoregulation and body fluid volumes.

The classical hemodynamic concept of hypertension includes a progression from a hypervolemic initial stage with renal fluid retention and increased cardiac output through autoregulation to prevent excessive tissue perfusion toward a late stage with increased peripheral resistance and increased arterial pressure (Borst and Borst-DeGeus, 1963; Ledingham and Cohen, 1963; Guyton et al., 1971).

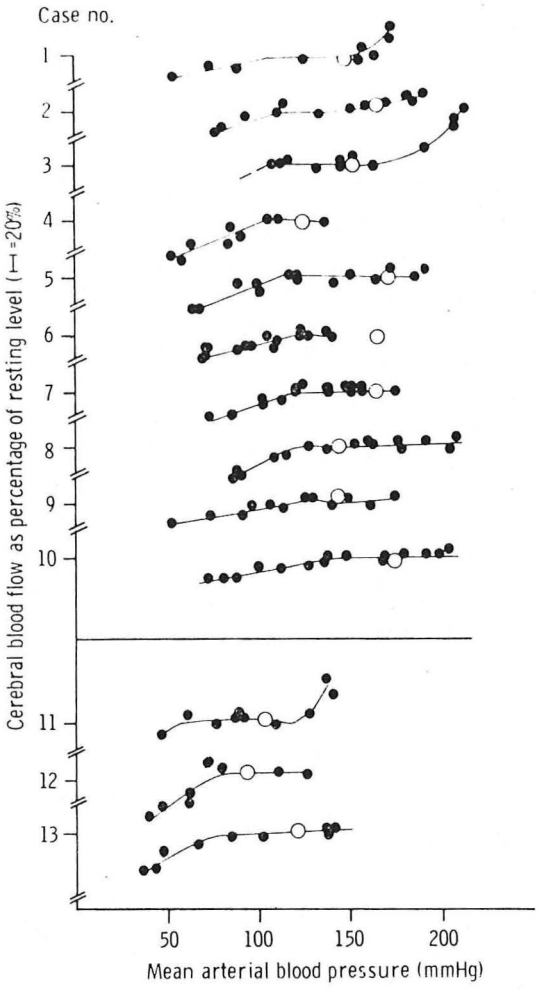


Figure 8. Autoregulation curves of the cerebral circulation in normotensive (*lower panel*) and hypertensive (*upper panel*) subjects. The points of breakdown of the autoregulatory phenomenon (the flat portion of the curve) are obviously displaced to higher pressure levels in the hypertensive subjects. (*From S Strangaard et al.*

Experimental renal hypertension and clinical renal vascular hypertension generally conform to this pattern but there are many reasons why the autoregulatory concept is unacceptable as a universal model of primary hypertension. Ferraro and Page (1978) have noted that cardiac output may be chronically increased without producing a secondary increase in peripheral resistance and in blood pressure. In other experimental models, arterial hypertension may develop without changes in cardiac output but with an initial primary increase in resistance.

As previously noted, clinical primary hypertension also tends to progress from a high cardiac output to a high peripheral resistance but there are frequent exceptions. Ibrahim et al. (1975) had described a group of patients with long-standing severe hypertension but chronically elevated cardiac output. Messerli et al. (1978) demonstrated that mild or borderline hypertension represents a spectrum of hemodynamic findings. Cardiac output, peripheral resistance, blood volume and extracellular fluid volumes range from low to high.

The relationship between body fluid distribution and hemodynamics in primary hypertension is complex. Total blood volume correlates positively with cardiac output. There is a closer inverse relationship between total peripheral resistance and blood volume that applies to both the normotensive and hypertensive subjects (Tarazi, 1976,1983). This is consistent with the classical autoregulatory pattern of progression but there are again frequent exceptions. Tarazi has described a group of patients with hypervolemia and normal cardiac output and high resistance (Figure 9). Furthermore, the inverse correlation between blood volume and peripheral resistance is apparent also in patients with low arterial pressure and orthostatic hypotension (Gaffney and Blomqvist, unpublished data). The combined findings make it tempting to speculate that blood volume changes represent adaptations to changing vasomotor states. The data do not seem to support the role of volume expansion or contraction as a primary means of controlling cardiac output. However, venoconstriction paralleling vasoconstriction is likely to increase central circulatory pressures and may activate ANF and inhibit the production of ADH and aldosterone. The cardiopulmonary baroceptors (Mark and Mancia, 1983; Bishop et al., 1983) may have a significant role.

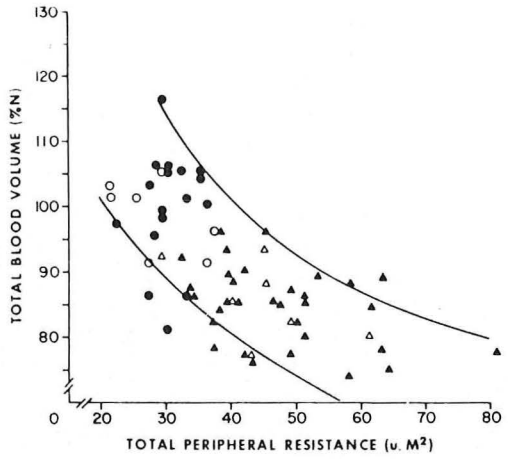


Figure 9A Relation between total peripheral resistance and total blood volume in 25 normotensive subjects and 38 patients with essential hypertension associated with normal or contracted plasma volume. Total blood volume is expressed as a percentage of normal to allow inclusion of both men and women despite sex differences in intravascular volume. Total peripheral resistance is expressed in arbitrary units corrected for body surface area. The correlation coefficient for patients with essential hypertension was significant ($r = -0.445$, $p < 0.02$); data from the normotensive subjects fitted well with those from the hypertensive and increased the correlation coefficient for the whole group ($r = -0.603$, $p < 0.001$). Solid circles represent normotensive men and open circles represent normotensive women; triangles represent hypertensive men and open triangles represent hypertensive women.

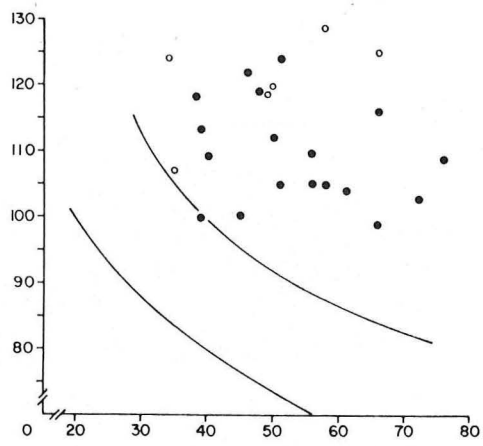


Figure 9B. Hypervolemia with essential hypertension is best defined in relation to level of total peripheral resistance; values for total blood volume in these 24 patients (solid circles = 18 men; open circles = 6 women) fall outside limits of relationship defined in 9A.

From R. C. Tarazi (1976).

The principal hemodynamic effect of changes in total blood volume is to influence ventricular filling. The compliance of the vascular bed is a major co-factor. There is evidence that both total effective vascular compliance, measured as changes in central venous pressure for rapid infusion of given fluid volumes (London et al., 1978) and peripheral venous compliance (Takeshita and Mark, 1979; Mark, 1984) are decreased in primary hypertension. These adaptations may provide hypertensive patients with a means of responding to stress with adequate ventricular filling even in the presence of a relative hypovolemia and to overcome the decreased compliance of the left ventricle that is associated with hypertrophy.

Neurogenic mechanisms.

General aspects. Neurogenic mechanisms are crucial for short-term control of arterial pressure. Adrenergic mechanisms also interact with renal and humoral mechanisms for major contributions to the long-term control of blood pressure and body fluid volumes. A hyperadrenergic state probably exists in many patients with mild or labile primary hypertension. Hemodynamic and metabolic findings at rest include increased heart rate, contractile state, cardiac output and systemic O_2 uptake. The total A-V O_2 difference remains within normal limits (Sannerstedt, 1966; Lund-Johansen, 1980; Tarazi, 1983; Frolich, 1983). There is also evidence that young patients with early hypertension have decreased parasympathetic activity and increased reactivity to adrenergic agonists (Phillip et al., 1978, Julius et al., 1980).

A large number of studies, reviewed by Goldstein (1980,1983) have examined plasma catecholamines in hypertensive patients. A majority have demonstrated elevated mean values in younger patients with mild or labile hypertension and normal levels in groups older patients with established disease. The data on plasma catecholamines are consistent with the predominant hemodynamic patterns but there is considerable disagreement regarding the strength of the quantitative relationship between sympathetic nerve activity and plasma catecholamines. Plasma levels are thought to represent primarily an overflow from vascular receptors but the regional distribution of sympathetic efferent traffic is non-uniform. In response to different stimuli there is a highly differentiated pattern of efferent sympathetic activity, often with markedly different impulse flow rates to skin, muscle, and to the renal or splanchnic area (Wennergren, 1975; Wallin, 1980; Abboud and Thames, 1983). Different local re-uptake rates also contribute to regional differences in plasma concentrations. Plasma norepinephrine levels may reflect most closely the activity in vasoconstrictor fibers supplying skeletal muscle (Folkow et al., 1983; Goldstein, 1981 and 1983; Goldstein et al., 1983).

Bühler et al. (1983) have studied extensively adrenergic function over a wide age range in hypertensive patients. In this series, plasma epinephrine but not norepinephrine levels were elevated in the patients at rest and during exercise. The patients had enhanced peripheral vasodilator responses to prazosin, an α_1-adrenergic antagonist. This is consistent with increased α-mediated vasoconstrictor activity. β-mediated tachycardia and peripheral vasodilator responses decreased with increasing age in normal subjects and this trend was enhanced in primary hypertension. However, measures of β-adrenergic receptor density and function in mononuclear leukocytes did not show any age-related changes.

Buhler et al. (1983) suggested that the hemodynamic evolution of primary hypertension from an increased cardiac output to an increased peripheral resistance reflects progressive dominance of α-adrenergic activity, caused by progressive attenuation of β-adrenergic functions. The apparent dissociation between estimates of receptor density and function and the physiological responses does not necessarily invalidate this concept. The reactivity to adrenergic stimuli may be modified by several factors including sodium balance, humoral factors, and structural adaptations (Folkow, 1982).

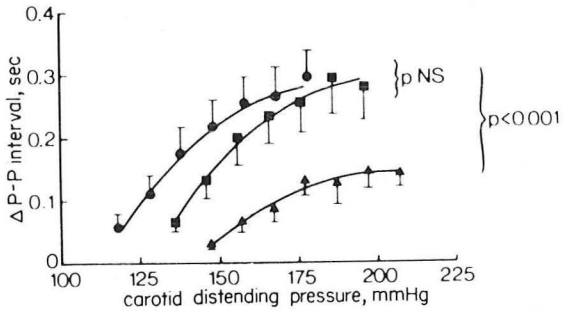


FIG. 10. Sinus node responses of subjects with normal blood pressure (●) and milder (■) and more severe (▲) borderline hypertension to brief (0.6-s) neck suction. Curves depict combined average responses of 10 subjects in each group. Carotid distending pressure was considered to be the absolute sum of systolic arterial pressure and neck-chamber pressure. Brackets indicate SEM.

From Eckberg (1979).

Reflex regulation. The arterial baroreflexes form the principal mechanism for short-term control of arterial pressure. The receptors sense deformation of the carotid sinus and aortic wall. Increased afferent traffic with increasing pressure and distension of the vascular wall enhances parasympathetic and inhibits adrenergic efferent impulse traffic. This produces bradycardia, decreased contractile state, and vasodilation. The opposite occurs when pressure decreases.

The human arterial baroreflexes have recently been reviewed in detail by Mancia and Mark (1983). The classical method of study has been infusion of vasoactive agents and correlation of changes in heart rate or R-R interval and arterial pressure. A new ingenious noninvasive method also has provided important information. Use of an air-tight neck collar makes it possible to apply negative and positive pressure pulses to alter carotid transmural pressures and to change the degree of deformation of the carotid baroreceptors without perturbing systemic blood pressure. Baroreceptor control of heart rate is diminished in primary and secondary hypertension (Figure 10), including early or mild stages (Korner et al., 1974; Eckberg, 1979). There is decreased sensitivity, i.e., less heart rate change for a given change in blood pressure and also a progressive resetting to a higher operating pressure (Mancia and Mark, 1983). This resetting may be caused by factors affecting afferent, efferent, or central reflex components, acting singly or in combinations. Zanchetti and Mancia (1984) have noted that the resetting of the operating point is associated with a change in the relative magnitude of responses to increases and decreases in pressure. Normal subjects tend to respond more vigorously to decreases in arterial pressure, but hypertensive patients are more sensitive to increases.

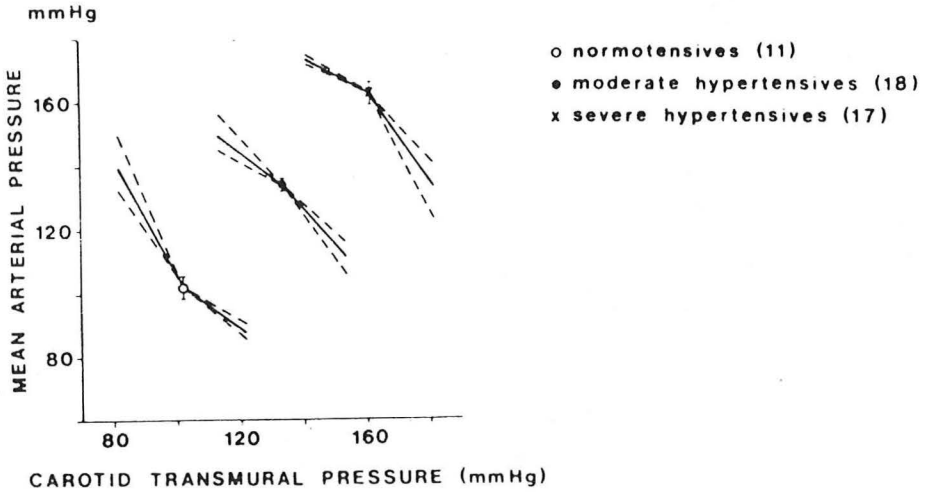
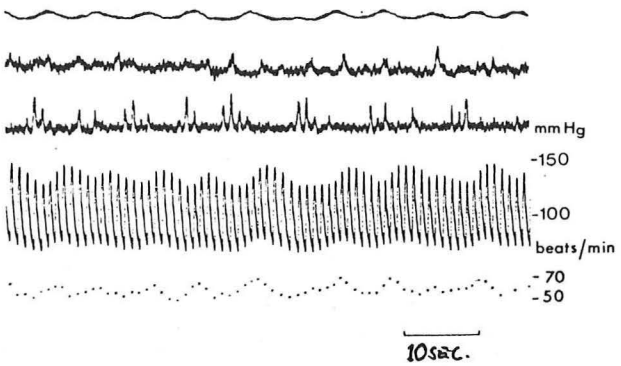


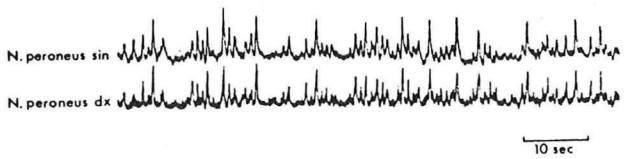
FIG. 11. Relationship between absolute values of carotid transmural pressure and absolute values of mean arterial pressure in normotensive moderate and severe hypertensive subjects.

Mancia and Mark, 1983.

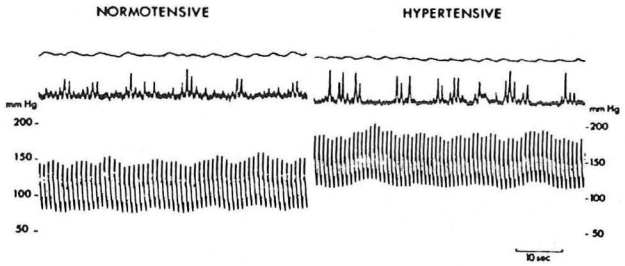
Despite these major changes in the heart rate limb of the baroreflex, most hypertensive patients maintain a largely normal overall ability to modulate systemic pressure in response to changes in carotid sinus transmural pressure (Figure 11). Zanchetti and Mancia (1984) have suggested that vascular adaptations may account for the attenuated heart rate response and the implied increased importance of the vasomotor responses. Diminished vascular compliance limits carotid sinus deformation. This reduces the afferent impulse traffic and the magnitude of the change in heart rate. However, similar structural peripheral vascular adaptations with medial hypertrophy enhance vascular reactivity and increase the effectiveness of the vasomotor limb of the baroreflex. This enables the patient to maintain an essentially normal total reflex gain. Increased reliance on the vasomotor component of the baroreflex to regulate arterial pressure may also be a feature of increasing age in normal subjects. (Gaffney et al. 1985).



Comparison of the patterns of skin and muscle nerve sympathetic activity at rest and their relationships to spontaneous blood pressure variations. Simultaneous recordings from two nerves with skin nerve sympathetic activity in the left peroneal nerve and muscle nerve sympathetic activity in the right peroneal nerve. **Top:** *Respiratory movements (inspiration upwards).* **Second:** *Integrated skin nerve sympathetic activity.* **Third:** *Integrated muscle nerve sympathetic activity.* **Fourth:** *Blood pressure recorded in the left brachial artery.* **Bottom:** *Heart rate.*



Examples of records from simultaneous recordings of muscle nerve sympathetic activity at rest from the left and the right peroneal nerves



Example of the relationship between muscle nerve sympathetic activity and spontaneous blood pressure fluctuations.

Fig. 12. From Wallin et al., 1973.

Reflex regulation of arterial pressure has recently also been examined using direct recording of sympathetic nerve activity. An essentially atraumatic microneurographic technique was initially developed by Hagbarth and Vallbo (1968) and has been later applied extensively to the study of cardiovascular physiology by Wallin and others (Wallin et al. 1973; Wallin 1981; Mark et al., 1985). The peroneal and median nerve are relatively easily accessible. A thin tungsten electrode is inserted into a nerve fascicle supplying either muscle or skin. The impulse pattern with pulse-synchronous bursts respond in response to changes in blood pressure identifies a muscle nerve (Figure 12). Studies based on this technique have provided strong support for the concept of a highly differentiated adrenergic traffic in response to different stimuli and also contributed to the understanding of baroreflex regulation. Measurements of muscle nerve activity (Wallin et al., 1973) have shown similar changes in impulse traffic to a given change in arterial pressure in patients and normal subjects. However, there was a significant upward displacement of the operating point in the patients. These data are consistent with an intact vasomotor limb as suggested by Zanchetti and Mancia (1984).

The role of the cardiopulmonary or low-pressure baroceptors in hypertension is still poorly defined. Data from spontaneously hypertensive rats have demonstrated a resetting of the operating point of the left atrial receptors (Thoren et al., 1978) which in turn may have significant effects on renal sympathetic traffic and volume regulation (Mancia and Mark, 1983). The resetting of the receptors may enable the hypertrophied stiff left ventricle to operate at appropriately increased filling pressures.

Structural vascular adaptations.

Many aspects of the structural cardiovascular adaptations and their physiological consequences are governed by two simple physical principles: the laws of Laplace and Poiseuille. The law of Laplace states that tension (T) per unit wall layer is proportional to the product of pressure (P) and inner radius r_i and inversely proportional to wall thickness w, i.e.:

$$T = P \cdot r_i/w \quad \text{(Laplace)}.$$

This means that--if wall tension is to be kept constant--any increase in pressure must be met by a decrease in internal radius, by an increase in wall thickness, or by a combination of the two. Reciprocal changes in internal radius and wall thickness is the hallmark of the vascular structural adaptations in primary hypertension. The law of Laplace is also crucial in the development of cardiac hypertrophy.

Any change in radius and vascular cross-sectional area has major effects on flow. Poiseuille's law states that the flow rate (v) of a liquid through a tube is proportional to the fourth power of the internal radius (r_i) and to the pressure gradient (P). Flow rate is inversely proportional to the length of the tube (l) and to the viscosity of the liquid (n), i.e.,

$$v = Pr_i^4/8ln \quad \text{(Poiseuille)}.$$

The relationship between cardiovascular function and the structural changes induced by the pressure overload in various forms of hypertension have been explored extensively by Folkow and associates (Folkow 1978 and 1982, Folkow et al., 1984). The onset of structural cardiovascular adaptation in experimental renal hypertension in rats lag only a few days behind the increase in blood

pressure. Adaptations are complete in 2-3 (Figure 13) weeks even if the increase in pressure load is not fully established until after 7-10 days (Lundgren et al., 1974).

Mark (1984) and Sivertson (1984) have recently reviewed data on human vascular adaptations in borderline hypertension. Renal biopsies have shown anatomical arteriolar abnormalities in a sizable minority of patients. Physiologic studies have also demonstrated decreased vasodilator capacity in young patients with mildly elevated blood pressures. Decreased sensitivity of the heart rate limb of the arterial baroreflex, perhaps also reflecting increased vascular stiffness, has also been reported in young patients.

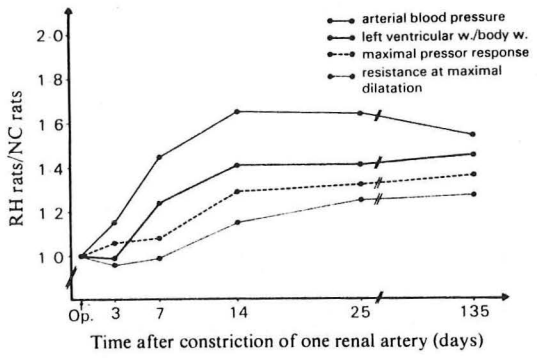


FIG. 13. Time course and extent of cardiovascular structural adaptation in normotensive rats made hypertensive by renal artery constriction, with day after artery constriction on the abscissa and, on the ordinate, the ratio between renal hypertensive rats (RH rats) and normotensive control rats (NC rats) concerning (1) mean arterial pressure during awake conditions, (2) left heart ventricular weight/body weight, (3) maximal pressor response reflecting the contraction strength of the media, i.e. its relative thickness, and (4) resistance at maximal dilatation reflecting the structurally determined average internal radius of the resistance vessels. Note that the adaptive structural changes of the left heart ventricle and the systemic resistance vessels are largely completed in RH rats in 2–3 weeks, even though the increased pressure load is not fully established until 7–10 days. The reduced blood pressure ratio at 135 days is due to a slight increase of NC rat blood pressure (From Lundgren *et al.*, 1974).

These observations are consistent with the concept that even mild and intermittent blood pressure increases can initiate a positive feedback interaction between functional and structural elements. Figure 14 shows the relationship between systemic resistance and the degree of shortening of vascular smooth muscle in normotension and hypertension. Because of the Poiseuille relationship, a very small increase in the degree of shortening causes a large change in resistance and systemic pressure. An increase in wall thickness with a decrease in internal radius will further enhance the effect on systemic resistance of any given change in the degree of smooth muscle shortening. Established hypertension is in this model associated with a 6-7% average decrease in internal arteriolar radius and a 30-40% increase in wall thickness, caused by hypertrophy of the media. The normal operating point of the vascular smooth muscle is between 10 and 15% active shortening. For the same activity level, the resistance is twice as high in the hypertensive subject. Equally important, any change in the degree of shortening will in the hypertensive patients cause a much larger change in resistance than in the normal subject. Thus, there is a purely structural basis for an enhanced vascular reactivity.

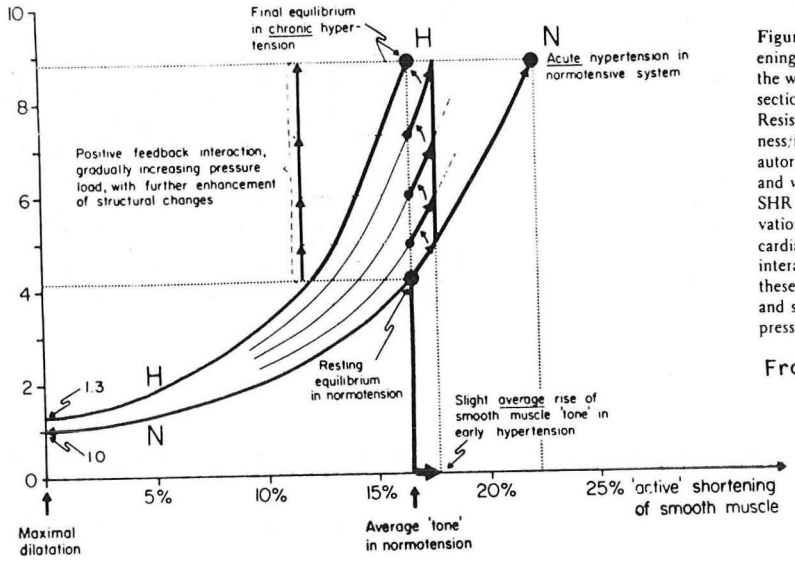


Figure 14. Principles of the changed relationship between degree of smooth-muscle shortening and resulting increase of systemic flow resistance, when medial hypertrophy increases the wall thickness in association with a reduction of inner radius in the precapillary resistance section, as a local response to an increased average pressure load ("structural autoregulation"). Resistance curve N represents a normotensive precapillary resistance vessel with wall thickness/inner radius around 0.2 at complete relaxation. Curve H represents a fully "structurally autoregulated" vessel in established hypertension, with inner radius reduced by 6 to 7 percent and w increased by 30 to 40 percent, which closely reflects the situation in both human and SHR hypertension when MAP is elevated by 40 to 50 percent. Note how the triggering elevation in pressure load caused by a slight increase in average smooth-muscle tone (and/or in cardiac output at unchanged resistance) needs to be only marginal, because of positive feedback interaction between this functional excitatory influence and structural autoregulation. Both these reinforce each other with respect to pressor effects, with a gradual transfer toward steeper and steeper resistance curves as the extent of structural adaptation grows ≈ Mean arterial pressure at unchanged cardiac output.

From Folkow (1978).

There is experimental evidence (Figure 15) that after relief of hypertension cardiovascular structural and functional abnormalities regress as rapidly as they develop (Lundgren, 1974). Human data on the vascular properties, including measurements of systemic and regional resistance and vasodilator capacity are much less convincing. Improved vasodilator capacity has been shown in the hand and forearm after normalization of blood pressure but not in the lower leg (Hanson and Sivertson, 1984; Trimarco and Wikstrand, 1984).

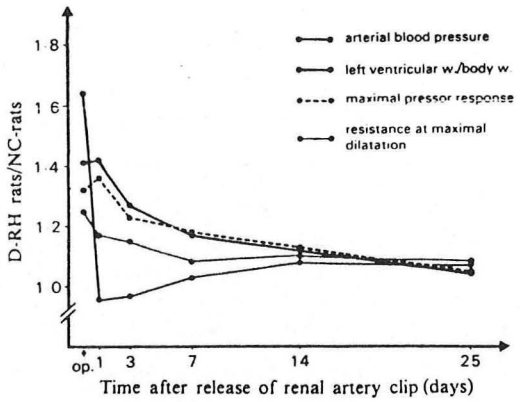


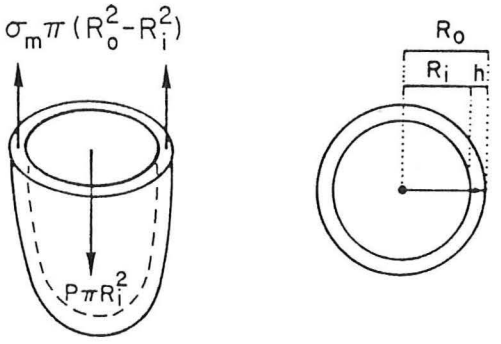
FIG. 15. Time course and extent of regression of the hypertensive changes in cardiovascular design after reversal of renal hypertension of 3–4 weeks duration. Days after unclipping are plotted along the abscissa, and along the ordinate, the ratios between renal hypertensive rats (RH rats), before and after (D-RH rats) unclipping and matched normotensive controls (NC rats), concerning (1) mean arterial pressure, (2) left ventricular weight/body weight, (3) maximal pressor response and (4) flow resistance at maximal dilatation (compare Fig. 5). The cardiovascular system still displays a largely unchanged adaptation one day after unclipping, but rapid regression then occurs with normalization after about 3 weeks.

From Lundgren (1974).

CARDIAC ADAPTATIONS

Stimuli initiating myocardial hypertrophy.

Cardiac hypertrophy (excluding the hypertrophic cardiomyopathies) usually develops in a pattern specific to the hemodynamic loading conditions, particularly in response to those that exist during systole (Linzbach, 1960; Grossman et al., 1975,1983). A pressure overload leads to a concentric hypertrophy in which there is an increase in myocardial mass relative to chamber volume. A volume overload produces an eccentric hypertrophy with a balanced increase in mass and volume. Eccentric refers to the leftward displacement of the center of the heart and not to any asymmetry in the distribution of myocardial mass.



$$\sigma_m \pi (R_o^2 - R_i^2) = P \pi R_i^2$$

$$\sigma_m = PR_i / 2h(1 + h/2R_i)$$

FIGURE 16. Diagrammatic representation of an idealized LV chamber in coronal section, looking from the front (left) and above (right). Wall thickness (h), inner radius (R_i), and outer radius (R_o) are required to calculate meridional wall stress (σ_m). This is accomplished by equating the meridional wall forces ($\sigma_m \times \pi[R_o^2 - R_i^2]$) to the pressure loading ($P\pi R_i^2$), since these must be exactly equal if the ventricle is to hold together. The same calculation applies for either an ellipsoidal or a spherical model.

From Grossman et al. (1975).

The mechanisms that control both normal cardiac growth and responses to changing hemodynamic loads are believed to respond to mechanical rather than to humoral stimuli. Grossman et al. (1975,1983) have examined different hemodynamic states in terms of end-systolic and end-diastolic wall stress. Figure 16 illustrates the principles for estimating meridional wall stress in the left ventricle. The forces acting on the endocardial surface are balanced by the tension developed by the ventricular wall. The second equation in Figure 16 is the equivalent of the simple Laplace relationship as applied to the analysis of vascular adaptations.

The essence of the cardiac adaptation is a change in the wall thickness/radius ratio in direct proportion to the change in pressure to maintain systolic wall stress within the normal range (Figure 17). A consequence of this response is to generate in left ventricular pressure overload an increased diastolic w/r ratio with a decrease in chamber compliance. This may combine with alterations in muscle characteristics to cause clinically significant diastolic dysfunction. Pressure overload is associated with parallel addition of new myofibrils as a basis for the wall thickening. Volume overload with an increase in diastolic stress leads to addition of new sarcomeres in serious and chamber enlargement. There is a secondary adjustment with a small increase in wall thickness to compensate for the increase in volume and to keep wall stress constant. Similar structural adaptations to pressure and volume overload develop also in response to physiological stimuli, e.g., athletic activity (Maron et al., 1986).

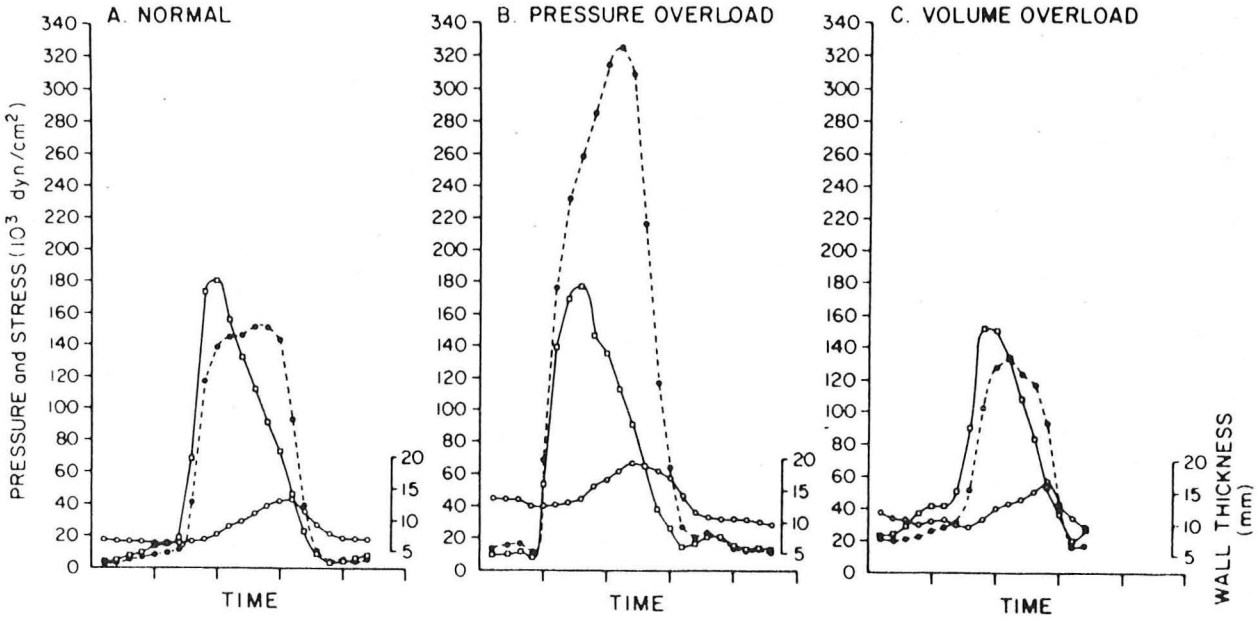


FIG. 17. A comparison of changes in left ventricular pressure *(solid dots)*, wall thickness *(open dots)*, and wall stress *(open squares)* throughout the cardiac cycle for representative normal, pressure overloaded, and volume overloaded left ventricles. In the pressure-overloaded ventricle **(B)** the markedly elevated systolic pressure is exactly counterbalanced by increased systolic wall thickness, with the result that wall stress remains normal. In the volume-overloaded ventricle **(C)**, peak systolic stress is normal, but end-diastolic stress is increased. From Grossman et al. (1975).

Quantitative clinical assessment of the degree of cardiac hypertrophy.

Access to accurate and convenient methods for the quantitation of cardiac dimensions is particularly important in hypertension. As previously noted, the complication rate is greatly affected by the presence of left ventricular hypertrophy (Kannel and Sorlie, 1981). Furthermore, the wide range of therapeutic agents that may be used to control arterial pressure offers unique opportunities to examine the interactions between hemodynamic loading conditions and factors involved in the maintenance and resolution of ventricular hypertrophy.

Electrocardiography. The classical approaches to evaluation of cardiac hypertrophy, chest x-rays and electrocardiography, are both insensitive (Panidis et al., 1984). All conventional ECG criteria for LVH underestimate the presence of an anatomical LVH. Romhilt et al. (1969) examined 33 different ECG sets of LVH criteria by anatomical correlation with a large autopsy series. Anatomical LVH was defined as a weight exceeding 175 or 200 grams depending on body size. The widely used Sokolow-Lyon criteria ($SV_1 + RV_5$ or $RV_6 > 35$ mm) had a sensitivity of 43% at a specificity of 95%. Most other criteria showed a similarly low sensitivity at a lower specificity but the Romhilt-Estes point score system had a slightly better performance with a sensitivity of 54% and a specificity of 97%. Similar or slightly worse diagnostic accuracy of the electrocardiographic criteria are apparent when the estimates of ventricular mass are based on M-mode echocardiography (estimated LV weight exceeding 125 grams/m^2) rather than on autopsy data (Devereux et al., 1984).

The relative poor performance of the various ECG criteria is hardly surprising. Many different factors modify the relationship between myocardial mass and body surface potential, including extracardiac conditions, some of which are related to age and obesity (chest impedance, heart-electrode distance). Cavity size should theoretically influence the surface voltage by the Brody effect but this is of doubtful clinical significance (Devereux et al., 1983).

TABLE 4. ACCURACY OF ECHOCARDIOGRAPHIC ESTIMATES OF LEFT VENTRICULAR MASS. HUMAN STUDIES BASED ON AUTOPSY DATA

AUTHORS	TECHNIQUE	N	MASS RANGE, GRAMS	r^2	S.D., GRAMS
Devereux et al., 1986	M-Mode, cube-Penn	52	96-625	0.85	43
	M-Mode, cube	52	96-625	0.81	47
	M-Mode, cube, vol. correction	52	96-625	0.71	60
Reichek et al., 1983	M-Mode, cube-Penn	18	77-454	0.74	59
	2-D, area-length	21	77-454	0.72	31
Parra et al., 1986	Modified Watanabe. In vitro.	20	80-174	0.88	8

Echocardiography. An array of non-invasive cardiac imaging methods are now available and several have been successfully applied to the quantitation of ventricular mass. Echocardiography is the most economical and most easily accessible of the current cardiac imaging techniques. Early studies (Devereux and Reichek, 1977; Salcedo et al., 1979) indicated that M-mode echocardiography can produce accurate estimates of septal and left ventricular posterior wall thickness, particularly if the endocardial echoes are allocated to the ventricular cavity volume (Penn convention). M-mode-based estimates of total left ventricular mass are much less reliable. In general, M-mode methods average septal and posterior wall thickness measurements obtained at a level just below the mitral leaflets. Mass is then estimated as the difference between the cubed external and cubed internal diameters of the left ventricle, with or without a volume correction according to Teichholz. It is assumed that the ventricular long axis is twice as large as the short axis and that the wall thickness is uniform. Both approaches overestimate ventricular mass. Table 4 shows that the M-mode measurements can nevertheless generate high coefficients of determination over a wide range of actual left ventricular weights; however, the confidence limits of the estimates are very wide.

Salcedo et al. (1979) and Wyatt et al. (1979) and, more recently, Schiller et al. (1983) and Fitzgerald et al. (in print) have demonstrated experimentally that accurate measurements of left ventricular mass can be obtained by two-dimensional or cross-sectional echocardiography, particularly by combining a measurement of the longitudinal axis (distance from the aortic or mitral valve to the apex) and one or more short axis estimates of myocardial cross-sectional area. Experimental errors of estimates of less than 10% have been recorded, i.e., an accuracy similar to that achieved with angiography (Rackley et al., 1964). Clinical data based on these methods (Reichek et al., 1983) are superior

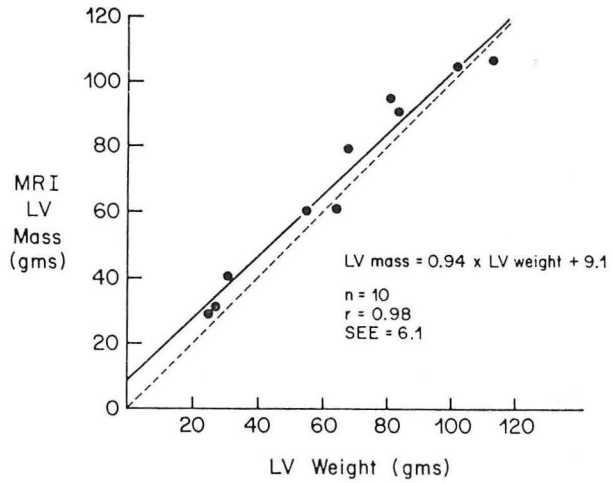


Figure 18. Relation between left ventricular mass determined from gated nuclear magnetic resonance imaging (MRI LV Mass) (**vertical axis**) and left ventricular weight (LV Weight) after formalin fixation (**horizontal axis**) for all 10 animals. The **dashed line** indicates the line of identity, whereas the **solid line** is the linear fit observed by least squares regression analysis.

From Keller et al. (1986).

to M-mode data but the error is still quite large. New approaches are capable of a much better accuracy but at the cost of analysis of multiple images (Parra et al., 1986).

Magnetic resonance imaging has recently been tested experimentally in a canine model by Keller et al. (1986) and Florentine et al. (1986). Gated MR images have excellent resolution. The accuracy is also superior with coefficients of determination of 0.90 or better and standard errors of estimate of about 10% of the mean (Figure 18). Performance characteristics at a level between that of two-dimensional echocardiography and MRI have been achieved experimentally using SPECT or single-photon emission computed tomography with thallium-201 (Wolfe et al., 1984).

TABLE 5. ECHOCARDIOGRAPHIC FINDINGS IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS.

From Hammond et al., 1986. Means and Standard Deviations.

MEASUREMENT	NORMOTENSIVE	HYPERTENSIVE	
		BORDERLINE	SUSTAINED
NUMBER OF SUBJECTS	160	145	316
WALL THICKNESS (CM)			
SEPTUM	0.94±0.17	1.07±0.18*	1.11±0.21*
POST. WALL	0.84±0.15	0.93±0.17*	0.98±0.17*
LV END-DIAST. DIAM. (CM)	4.81±0.53	4.95±0.57	4.99±0.54
LV MASS (GRAMS)	155±50	189±54	208±71*
END-SYST. WALL STRESS $X10^3$ (dynes•cm^{-2})	63±21	70±28*	77±27*
FRACTIONAL SHORTENING, %	35±6	37±7	37±7

*Significantly different from the normotensive mean.

Left ventricular mass in clinical series of patients with hypertension. Structural cardiac adaptations have been observed very early in primary hypertension. Culpepper (1983) has recently reviewed 4 different series of measurements in adolescents with mildly elevated blood pressures. Echocardiographic evidence for left ventricular hypertrophy, defined as increased left ventricular wall thickness mass or both, was present in 10 - 15%.

Savage et al. (1979) examined a series of ambulatory patients with mild to moderate primary hypertension and no clinical evidence of coronary disease. Arterial pressures ranged from the mean of 137/91 in the third decade to 167/95 in the seventh decade. The 12-lead ECG was abnormal in only 3% and the chest x-ray showed LVH in 5%. In comparison, the septal and/or posterior wall thickness was abnormal in 61%.

Table 5 illustrates the distribution of a wide range of M-mode measurements in a more recent study of normal subjects and patients with borderline or mild sustained hypertension (Hammond et al., 1986). Borderline hypertension was defined as resting systolic pressures of 140-159 and/or diastolic pressures of 90-94 mm Hg and sustained hypertension systolic pressure 160 or greater and diastolic pressure 95 or greater. Echocardiographic left ventricular hypertrophy was defined as a mass index of $\geq$135 grams/m^2 in men and 111 grams/m^2 in women (Devereux et al., 1986). These criteria had a specificity of 97% and identified 12% of the patients with borderline and 20% of the patients with sustained hypertension as having LVH.

An increased right ventricular wall thickness (Figure 19) is also often present in left ventricular pressure overload. There is a significant correlation between right and left ventricular wall thickness (Gottdiener et al., 1985). This represents the structural equivalent of the correlation between systemic and pulmonary vascular resistances described by Atkins et al. (1977).

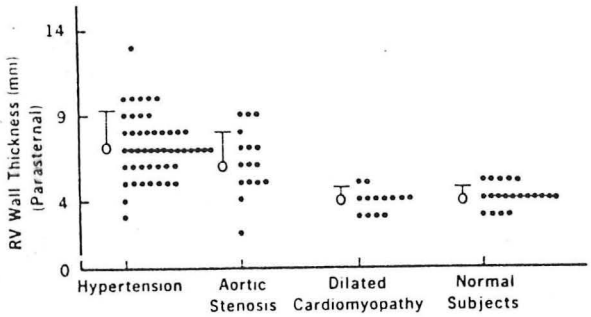
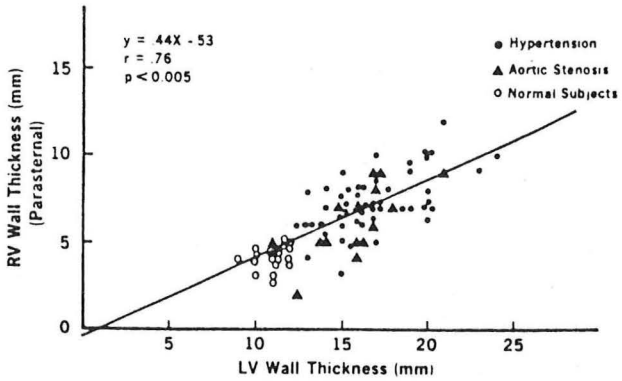


Figure 19. Right ventricular (RV) wall thickness obtained from the parasternal view in patients with hypertension, compared with patients with aortic stenosis, dilated cardiomyopathy and normal subjects. Right ventricular wall thickness is significantly greater in patients with hypertension or aortic stenosis than in normal subjects or patients with dilated cardiomyopathy.



Relation of right ventricular (RV) and left ventricular (LV) wall thickness, showing significant linear correlation (r = 0.76) in normal subjects, patients with aortic stenosis and patients with hypertension.

From Gottdiener et al. (1985).

Left ventricular function.

Most aspects of mechanical ventricular function and cardiac muscle function can be accurately defined by analysis techniques considering simultaneously fiber length, tension, and time. Less demanding approaches examine bi-variate relationships. One of the most informative and useful methods is the analysis of instantaneous ventricular pressure-volume relationships as defined by Suga and Sagawa (1974). Systolic functional capacity is measured as the maximal pressure that can be generated at any given ventricular volume or fiber length. The end-systolic pressure-volume relationship, which is linear function, also defines the extent of shortening or the stroke volume that can be achieved from a given end-diastolic volume. Figure 20 illustrates that an increase in end-systolic pressure can be accomplished only at the expense of an increased end-systolic volume and a decreased stroke volume (A). A normal stroke volume can be maintained at the higher systolic pressure if end-diastolic pressure and volume are increased (B) or if contractile performance is enhanced by inotropic agents (e.g., isoproterenol, calcium) or by chronic adaptations that produce an increase in ventricular muscle mass (C). Alternative (C) is predominant in hypertension in the absence of ischemic disease. An increase in muscle mass enables the ventricle to maintain within normal limits both systolic wall stress and the extent and velocity of shortening.

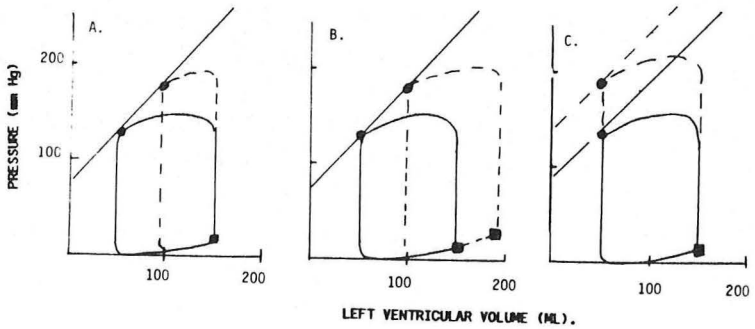


Fig. 20. NORMAL LEFT VENTRICULAR PRESSURE-VOLUME RELATIONSHIPS AND RESPONSES TO INCREASED END-SYSTOLIC PRESSURE.

A. No adjustment - increased end-systolic and decreased stroke volume.
B. Increased end-diastolic and end-systolic volumes, normal stroke volume restored.
C. Increased contractile state with all volumes restored to normal.

(Circle - end-systole, Square - end-diastole).

The application of echocardiography combined with non-invasive measurements of arterial pressure, has made it feasible to construct measures of systolic and diastolic function that are both physiologically correct and relatively easy to use. Such measures take into account the effect of changes in afterload and the reciprocal relationship between tension development and shortening. Velocity of circumferential fiber shortening (expressed as circumferences per second) and per cent fractional shortening (the decrease in ventricular diameter during systole expressed as a percentage of end-diastolic diameter) are linearly related to end-systolic wall stress (expressed as grams/cm^2 or dynes/cm^2). Basic measurements can be obtained from M-mode recordings (Quinones et al., 1980; Reichek et al., 1983; Borow et al., 1985).

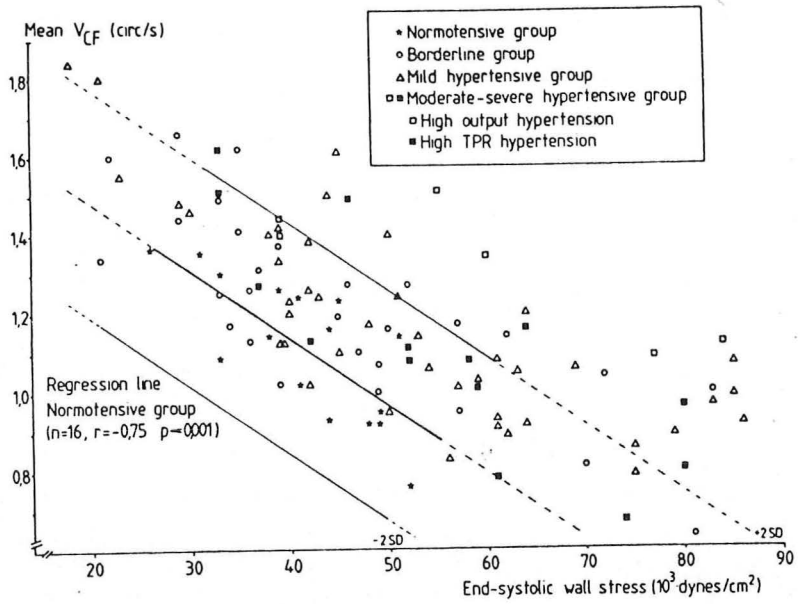


FIGURE 21. *Relationship between LV end-systolic wall stress and mean velocity of circumferential fiber shortening (mean V_{CF}) in four blood pressure groups* (for explanation, see text). *The linear regression line ± 2 standard deviations is given for the normotensive group. Note that no hypertensive subjects are characterized by a lower than expected mean V_{CF} for any end-systolic wall stress, but a higher than expected mean V_{CF} is seen in several hypertensive subjects. TPR = total peripheral resistance; SD = standard deviation*

From Wikstrand et al., 1984.

Wikstrand (1984) recently reviewed 8 echocardiographic and radionuclear studies of left ventricular function in primary hypertension. Without exception, systolic function as quantitated by various ejection phase measurements was judged normal or increased. Representative data are presented in Figure 21. Borer et al. (1983), Francis et al. (1983) and Inouye et al. (1984) have all reported normal left ventricular ejection fraction by radionuclide angiography performed at rest and during exercise in patients with primary hypertension in the absence of evidence for ischemic heart disease. Guazzi et al. (1979) also noted large mean stroke volumes in relation to right and left ventricular filling pressures in subgroups of patients with hypertension.

There is no obvious explanation for the apparent supranormal systolic function in many patients with primary hypertension. Wikstrand (1984) has pointed out that many patients have some increase in left ventricular end-diastolic dimensions but supranormality is evident even when evaluation of

systolic function is based on the velocity of circumferential fiber shortening, a measure that is insensitive to variations in preload (Nixon et al., 1982). It is tempting to speculate that a hyperadrenergic state may contribute or that there is abnormal myocardial calcium handling that affects both systolic and diastolic function.

The strong evidence for normal or enhanced systolic function in most patients with hypertension is balanced by equally strong evidence for a high incidence of left ventricular diastolic dysfunction. Wikstrand (1986) reviewed 6 studies that all indicated subnormal left ventricular filling rates in patients who had normal or enhanced systolic function. Further support has been provided by recent studies by Inouye et al. (1984), Colan et al (1985), Smith et al. (1985). Decreased filling rate and delayed relaxation as measured by echocardiography or radionuclide angiography is apparent even in early primary hypertension. Increased wall thickness can count only partially for the altered filling pattern. Some patients with normal wall thickness have grossly abnormal filling rates. Furthermore, physiological hypertrophy produced by athletic activity does not affect filling rates (Colan et al., 1985; Granger et al., 1985). Possible mechanisms in addition to the contribution from increased wall thickness include abnormalities in sarcoplasmic reticulum calcium transport and uptake or increased myocardial collagen content (Smith et al., 1985).

Abnormal diastolic function is likely to be the primary cause of the decrease in stroke volume in cardiac output that occurs over time in most patients with primary hypertension (Lund-Johansen, 1980). Clinical episodes of frank heart failure are also known to occur in patients who have maintained adequate systolic function. Calcium channel blockers are a logical therapeutic choice and clinical trials are being conducted. Improved diastolic filling is also likely to be one of the principal benefits of successful long-term treatment of high blood pressure.

Mechanisms involved in the development, maintenance, and regression of cardiac hypertrophy.

General aspects. The response of the heart to an increased workload depends on the age at which the stress is imposed. Increased load during fetal or early neonatal life produces cardiac enlargement by hyperplastic growth of all cardiac elements. Later onset of an abnormal load results in cardiac hypertrophy by enlargement of cardiac myocytes and hyperplasia of all other components, e.g., connective tissue and vascular elements (Oparil, 1985).

The mechanisms linking the hemodynamic or mechanical events to increased protein synthesis and eventually to cardiac enlargement are still incompletely understood. Changes in the rate of protein catabolism have minor effects except in the development of thyrotoxic hypertrophy (Crie et al., 1983). Cohn and Nath (1983) have recently reviewed the various stimuli that may initiate hypertrophy. Possible signals include increased energy requirements and increased blood flow. Angiotensin and perhaps also sodium may have direct effects that are dissociated from their effect on hemodynamic conditions. Prostaglandins may enhance contractility and myocardial growth by increasing the availability of calcium. Locally produced humoral factors (chalones, tissue hormone growth stimulator) have also been implicated but there is little evidence to indicate that they have a major role.

Adrenergic mechanisms. Most current work on the initiating factors has been focused on adrenergic mechanisms. The basic hypotheses is that increased levels of circulating and cardiac norepinephrine and increased β-receptor activation with release of cAMP produce the increased protein synthesis that forms the foundation for cardiac hypertrophy.

A seminal experimental study was published by Laks et al. in 1973. In dogs, infusion over 6-63 weeks of subhypertensive doses of norepinephrine produced a significant increase in mean left ventricular weight. The finding upon which many subsequent studies were based, was probably erroneous and caused by a dissection artifact (Ostman-Smith, 1981). The increase in left ventricular weight was completely offset by decreases in septal and right ventricular weights for no change in total cardiac weight. Nevertheless, several strong lines of evidence have since been established to support the role of cardiac sympathetic activity as the final common pathway in the induction of hypertrophy.

Most investigators have viewed β-adrenergic activity as the salient stimulus to hypertrophy. However, Simpson recently (1985) suggested that there is a dual adrenergic pathway with α_1 receptors regulating growth and β_1 receptors regulating the development of contractile function. The type of hypertrophy may at least in part be determined by the balance between α_1 and β_1 activity.

TABLE 6. Antihypertensive Therapy and Cardiac Hypertrophy in Spontaneously Hypertensive Rats (SHR)

Group	Blood Pressure (mm Hg)	Ventricular Weight (mg/g)
Normal	120	2·6
SHR	188	3·4
Methyldopa	149	2·7
Hydralazine	123	3·4
Minoxidil	130	3·8

Results of antihypertensive therapy indicate that reversal of cardiac hypertrophy is not dependent on blood pressure control alone.

From Tarazi (1983).

Chemical sympathectomy with large doses of guanethidine can prevent the physiological hypertrophy that otherwise occurs in swimming rats (Ostman-Smith, 1981). Adrenergic function clearly also modulates the development and regression of cardiac hypertrophy in clinical and experimental hypertension. Sen (1983) and Tarazi (1983) examined the effect of various pharmacological agents on blood pressure and the development of cadiac hypertrophy in spontaneously hypertensive rats (SHR) as compared to normotensive controls of the Wistar Kyoto (WKY) strain (Table 6). Alpha-methyldopa produced a modest reduction in blood pressure but normalized heart weight whereas hydralazine and minoxidil had more powerful antihypertensive action but no effect on the degree of hypertrophy. These data, which indicate that the hemodynamic changes and the effects on the degree of hypertrophy can be dissociated, are consistent with an important role adrenergic mechanisms. Monotherapy with hydralazine or minoxidil produces a significant secondary increase in catecholamine levels, heart rate, contractile state, and cardiac output.

Data from several clinical series have recently been reviewed by Tarazi and Fouad (1984), Trimarco and Wikstrand (1984), and by Amodeo et al (1986). Human data on single-agent treatment with vasodilators are not available but regression of hypertrophy has been documented after treatment using a wide range of pharmacological agents. Regimens include diuretics as first line drug with adrenergic antagonists as second line and also first line treatment with various β-blocking agents or calcium channel blockers. All these regimens produce significant antihypertensive effect and significant reduction in mean left ventricular wall thickness and/or estimated mass.

A detailed analysis of echocardiographic data (Trimarco and Wikstrand, 1984) suggests that treatment with thiazides and with metoprolol produce a similar sequence of events. There is an initial decrease in end-diastolic volume and stroke volume followed after several months by a decrease in left ventricular wall thickness, an increase in end-diastolic volume, stroke volume, and ejection fraction. These data suggest that reduced afterload and increased diastolic compliance both contribute to the hemodynamic improvement (Figure 22).

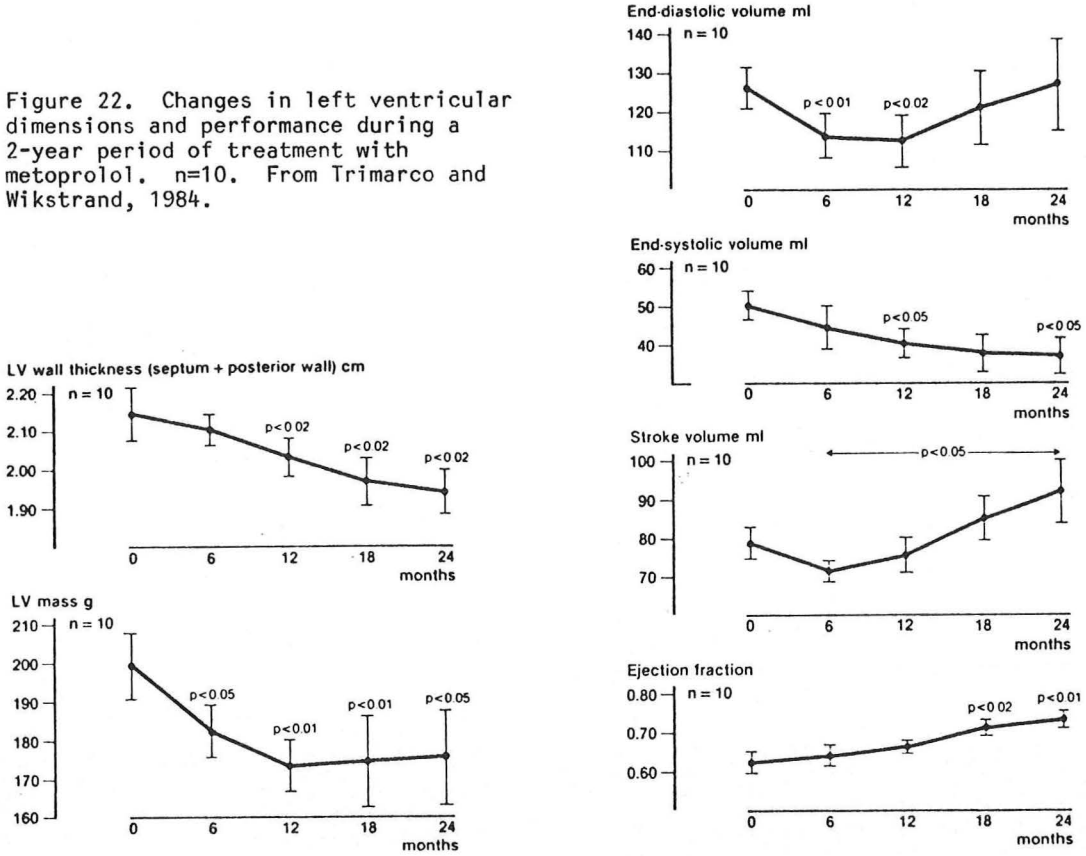


Figure 22. Changes in left ventricular dimensions and performance during a 2-year period of treatment with metoprolol. n=10. From Trimarco and Wikstrand, 1984.

Interaction between different stimuli to hypertrophy and the role of myosin polymorhism. Recent studies of the myosin isozymes in cardiac hypertrophy have provided new information on the biochemical correlates of contractile function. Hypertrophic cardiac muscle may exhibit a decrease in active tension development and the velocity of fiber shortening. This change can be correlated to change in the distribution of myosin isozymes. Three different types, referred to as

V_1, V_2, and V_3 have been isolated. They are listed in order of decreasing electrophoretic mobility and ATPase activity. There is a strong correlation between ATPase activity and contractile state. Light chain components are the same for all types whereas the heavy chain composition is different. Most experimental data have been obtained from rats. Increased thyroid activity is associated with an increase in the relative abundancy of the V_1 and on enhanced contractile state. On the other hand, a decreased contractile performance and predominance of the V_3 isozyme is a characteristic of chronic pressure overload and aging (Morkin, 1983).

Studies of myosin polymorhism have also provided intriguing information on the interaction between different stimuli to cardiac hypertrophy. Pfeffer et al. (1978) noted that spontaneously hypertensive rats subjected to physical training not only developed more prominent cardiac hypertrophy than sedentary SHR controls but also showed signs of improved cardiac pump performance. Scheuer et al. (1982) and Schaible et al. (1984) have reported that physical training (swimming) in rats with renal hypertension produces marked cardiac hypertrophy, i.e., +77% compared to +30% for swimming alone and +47% for hypertension alone. However, hypertensive swimmers had a markedly enhanced contractile performance relative to sedentary hypertensive rats. Analysis of the myosin isozymes showed a return to the normal predominant V_1 pattern in the hypertensive swimmers and a V_3 dominance in the hypertensive sedentary rats. Furthermore, coronary reserve also returned to normal in the hypertensive swimmers. Similar effects on myosin isozymes have been reported by Rupp and Jacob (1982).

This discussion of cellular and molecular mechanisms has only touched briefly on the role of different neurohumoral and pharmacological agents in the initiation and maintenance of myocardial hypertrophy and on the inter-relationship between hypertrophic stimuli, myosin polymorphism, and contractile performance. It should nevertheless be apparent that an exciting set of methods and procedures are now available. These tools are likely to help generate a much better understanding of cardiac function in hypertension and in other forms of hemodynamic overload and eventually provide a series of rational and specific therapeutic approaches.

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