Invited review

Central haemodynamics of hypertension

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Abstract

Invasive data on central haemodynamics in healthy normotensive subjects are scarce, and studies in hypertensives are limited as well. A summary of the available data on central haemodynamics in hypertensives and normotensives in the same age groups is presented. Hypertension reflects a disturbance in the balance between cardiac output (CO) and total peripheral resistance (TPR), ranging from a pattern of high CO and normal TPR in young age and early hypertension, to a normal-to-low CO and high TPR in more established hypertension. An early sign of impairment of cardiac pump function in hypertension is most readily seen in stroke volume, particularly during exercise. Drug therapy may reduce blood pressure in hypertensives by reducing CO, TPR, or both. Ideally a perfect antihypertensive agent should be able to reduce blood pressure to normal level by reducing TPR and restoring normal cardiac pump function both at rest and during exercise. But so far, no ideal drug has been found that can fully normalize the haemodynamic disturbance of hypertension.

Key words: blood pressure, central haemodynamics, hypertension.

Central haemodynamic variables

The pressure in the arterial system – the blood pressure (BP) – is the combined result of the pumping of blood from the heart into the arteries (cardiac output – CO), and the resistance against the blood flow through the vascular system (total peripheral resistance – TPR). The relationship between blood pressure, cardiac output, and total peripheral resistance may be expressed as:

$$BP \approx CO \times TPR \quad \text{(equation 1)}$$

or, since the cardiac output is the product of the blood volume ejected by each stroke (stroke volume – SV) and the number of strokes per time unit (heart rate – HR), as:

$$BP \approx SV \times HR \times TPR \quad \text{(equation 2)}.$$

A large group of vascular, humoral, hormonal, neural, and other factors all interact *via* the components of the haemodynamic equation in their collective control of blood pressure.

In the steady state blood pressure shows a slight oscillating pattern due to respiration and reflex mechanisms but the overall level of blood pressure during an undisturbed resting situation is still quite stable. Conditions such as change in body position, physical activity, respiration, mental stress, transition from sleep to wakefulness, and effects of nicotine or drugs may lead to instant and large changes in blood pressure. At the end of physical and/or mental excitement the blood pressure rapidly returns to its usual level. Thus, as actually emphasized by the inventor of the sphygmomanometer, Scippione Riva Rocci in 1896, a clinically useful blood pressure must be recorded under strictly standardized conditions [1].

The blood pressure may also increase more slowly to reach an abnormal high level, i.e. hypertension, either by known or by unknown mechanisms (secondary or primary hypertension). However, any change in blood pressure, whether acute or chronic, must be expressed by a change in one or more of the three components on the right side of the equation sign in equation 2: SV, HR, or TPR. Thus, hypertension can be defined as a haemodynamic disorder which reflects a disturbance in the balance between cardiac output and total peripheral resistance.

Methods of central haemodynamic measurements

For haemodynamic purposes the most precise measurement of blood pressure is obtained by intra-arterial recording using a pressure transducer which permits detection of immediate beat-by-beat pressure changes, e.g. during physical exercise or by other interventions.

The most reliable methods of cardiac output measurements are the dye dilution and the thermodilution techniques [2, 3]. One advantage of the dye dilution technique using cardiogreen (indocyanine) is its usefulness both at rest and during exercise, with repeatability in the order of 5% [3]. Limitations are that the technique is invasive and gives the mean value over 10 to 30 s (not beat-to-beat values). Cardiac output is expressed as volume per time unit, usually l/min, and may in turn be used to calculate the stroke volume when the heart rate is known (preferably by electrocardiogram):

$$SV = CO/HR \quad \text{(equation 3)}.$$

Total peripheral resistance is derived by calculation as the ratio between the mean arterial pressure and cardiac output:

$$TPR = BP/CO \quad \text{(equation 4)}.$$

The total peripheral resistance in equation 4 is usually transformed by a constant (1332) to be expressed by the unit•dyn•s•cm^{-5}. Indexed values for TPR, CO and SV, allowing comparison of results between different trial populations and between different laboratories, are obtained by relating data to body surface area (BSA). The corresponding variables are designated cardiac index (CI), stroke index (SI), and total peripheral resistance index (TPRI).

The exact nature of total peripheral resistance is still uncertain. Strictly, calculation of total peripheral resistance according to equation 4, which is based on Poiseuille's law, is only applicable to a steady, non-pulsatile flow through rigid tubes. It is presumed that vascular resistance is mainly determined by the diameter of the arterioles and that changes in resistance reflect changes in cross-sectional vascular area. As discussed by Folkow, even minute changes in diameter may cause large differences in resistance [4]. Mulvany and co-workers have been able, in isolated arterioles, to directly study factors that may be of importance in the control of arteriolar diameter [5].

Central haemodynamics of normotension

Invasive central haemodynamic measurements have been carried out only in a limited number of small-scale studies in healthy, normotensive subjects, mostly in men aged 20-40 years [6-12]. The total number of individuals in these studies is approximately 200. The weighted mean values of the haemodynamic variables in the resting supine position from these studies are shown in Table I.

Cross-sectional studies from most industrialized countries have shown that blood pressure, particularly systolic arterial pressure, increases with age [13-15]. There is also some increase in diastolic arterial pressure but it reaches a peak at the age of 60 and then levels off or even tends to fall slightly. The pattern of increasing blood pressure with age is modified by factors such as obesity and physical activity and it is also slightly different between the two genders, with more marked increase in systolic arterial pressure in women compared with men after the age of 50 [15, 16]. Most invasive

Table I. Central haemodynamics at rest supine in normotensive subjects. Mean values from 7 studies

Mean arterial pressure (MAP*) [mm Hg]	85.6
Cardiac index (CI) [l/min/m^2]	3.30
Total peripheral resistance index (TPRI) [dyn•s•cm^{-5}•m^2]	2118
Heart rate (HR) [beats/min]	66.7
Stroke index (SI) [ml/stroke/m^2]	51.1

**MAP = DAP + 1/3 (SAP – DAP); in invasive studies MAP is obtained by electrical damping of the intra-arterial pressure curve [7]*

studies have shown that the increase in blood pressure at higher age is due to an increase in total peripheral resistance, while stroke volume and cardiac output are reduced [7, 17-21]. However, in normotensive subjects between the ages of 18 to 50 years haemodynamic data from cross-sectional studies are rather similar in young and older age groups. Age-related changes in central haemodynamic variables from a cross-sectional study in normotensive and hypertensive subjects from our laboratory are shown in Figure 1 [7].

In agreement with the cross-sectional data, a study from Sweden in young men showed that there were virtually no changes in blood pressure, heart rate, cardiac output, or total peripheral resistance over a 5-year follow-up period [7, 12].

Exercise is used in clinical practice for evaluation of cardiac pump function. However, systematic haemodynamic studies in normotensive subjects using invasive techniques during exercise are scarce. In a study in 33 normotensive men aged 19-49 years (mean 31) from our laboratory there was found an increase in systolic arterial pressure (SAP) of 34.3 mm Hg at a steady state dynamic (bicycle) work load of 100 W compared to the resting sitting situation [7]. The corresponding increase in diastolic arterial pressure (DAP) was 3.8 mm Hg. Cardiac index increased by 6.0 l/min/m^2, SI 28.4 ml/stroke/m^2, and HR 53 beats/min. The TPRI fell by 1308 dyn•s•cm^{-5}•m^2 (Figure 2).

Central haemodynamics of essential hypertension

In nearly all the studies performed in middle-aged subjects with established, uncomplicated hypertension, the cardiac output during rest has been normal or slightly reduced while the total peripheral resistance has been increased. Increased total peripheral resistance is referred to as the hallmark of hypertension, and the resistance has been found increased in all vascular beds (renal, cerebral, pulmonary, myocardial, splanchnic, muscular and skin) in clinical as well as in experimental hypertension [22-30].

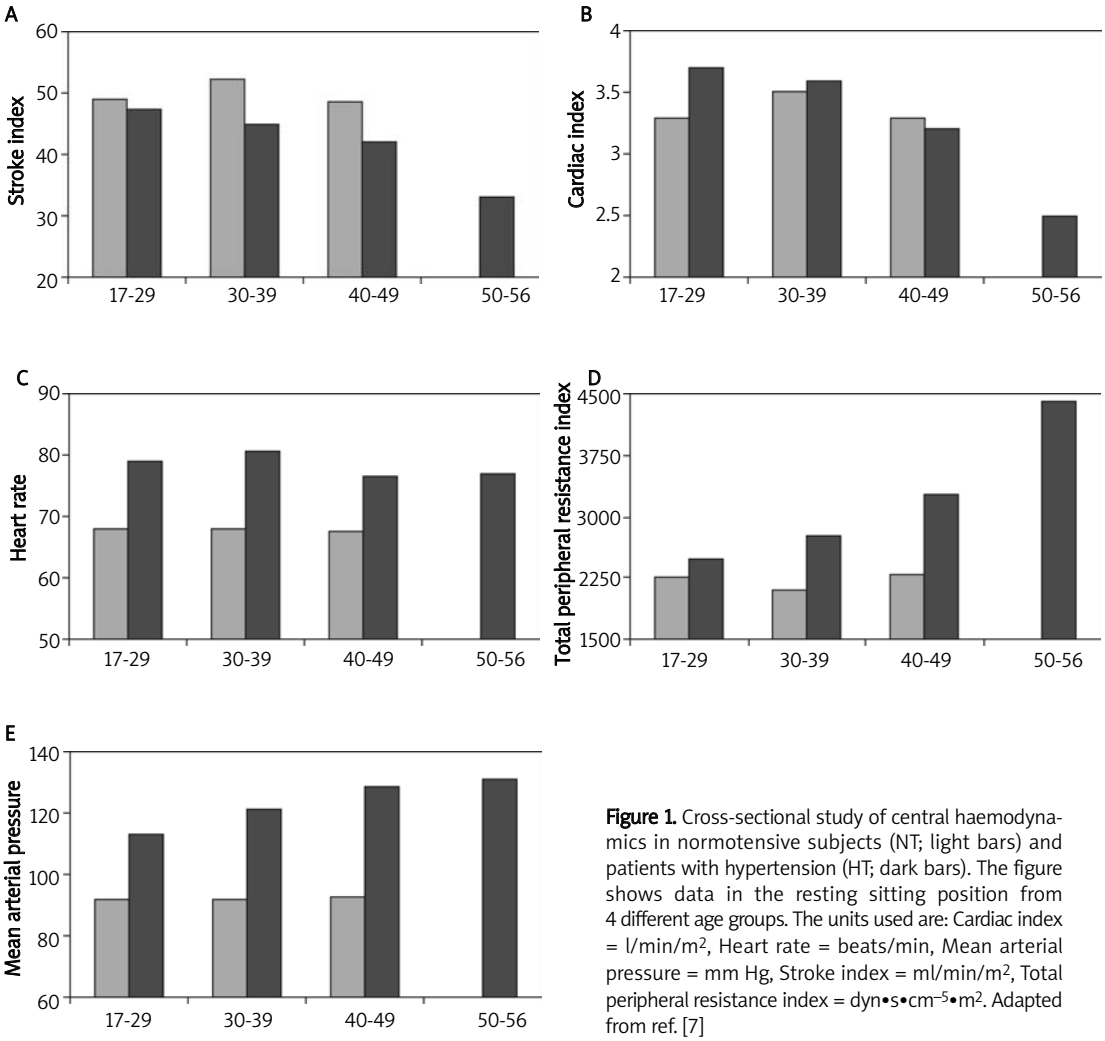

Figure 1. Cross-sectional study of central haemodynamics in normotensive subjects (NT; light bars) and patients with hypertension (HT; dark bars). The figure shows data in the resting sitting position from 4 different age groups. The units used are: Cardiac index = l/min/m^2, Heart rate = beats/min, Mean arterial pressure = mm Hg, Stroke index = ml/min/m^2, Total peripheral resistance index = dyn•s•cm^{-5}•m^2. Adapted from ref. [7]

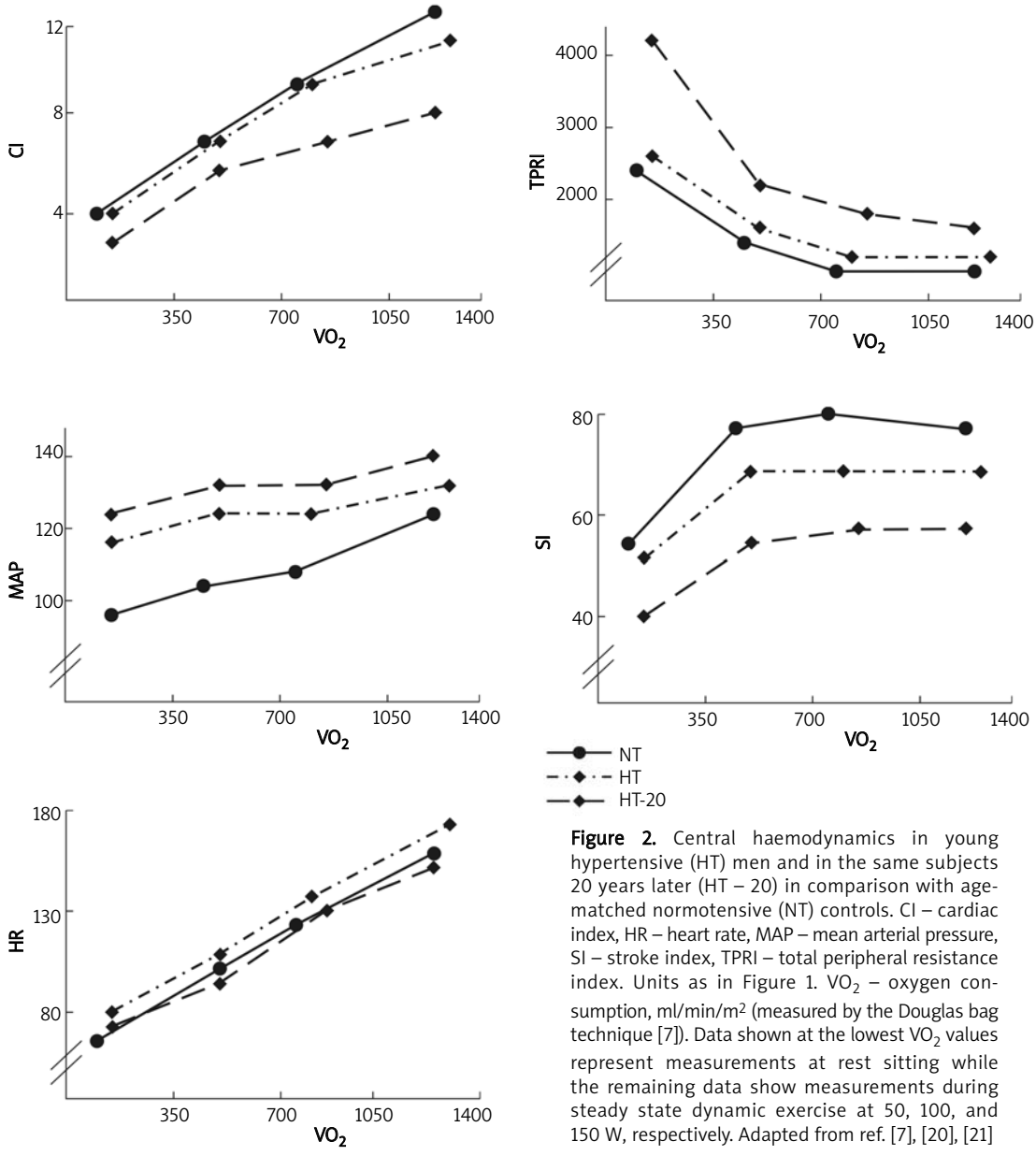

Figure 2. Central haemodynamics in young hypertensive (HT) men and in the same subjects 20 years later (HT – 20) in comparison with age-matched normotensive (NT) controls. CI – cardiac index, HR – heart rate, MAP – mean arterial pressure, SI – stroke index, TPRI – total peripheral resistance index. Units as in Figure 1. VO_2 – oxygen consumption, ml/min/m² (measured by the Douglas bag technique [7]). Data shown at the lowest VO_2 values represent measurements at rest sitting while the remaining data show measurements during steady state dynamic exercise at 50, 100, and 150 W, respectively. Adapted from ref. [7], [20], [21]

Regarding the starting phase of essential hypertension most invasive studies in young men (18-30 years) have demonstrated an increased cardiac output (about 15% higher than in age-matched normotensive controls) due to increased heart rate and normal stroke volume (Figure 3) [6-12]. These haemodynamic disturbances are thought to be due to hyperactivity in the sympathetic nervous system [31, 32].

In children with different blood pressure levels there is no consistent evidence for an increase in cardiac output in those with the highest pressures – so it is still uncertain whether the increased cardiac output seen in young males with blood pressure above 140/90 mm HG really represents the cardinal haemodynamic disturbance in the early phase [33-35].

Age: cross-sectional data

The age-related increase in mean arterial pressure in hypertensives is due to a progressive increase in total peripheral resistance, which at the age of 50 may be almost twice the value seen at the age of 20 (Figure 1). Cardiac output, which in the resting condition often is increased by 15-20% in young hypertensives, is reduced at higher age. The progressive decline in cardiac output with age in patients with hypertension is associated with reduction in stroke volume, while heart rate remains increased by 6-10 beats/min compared with normotensive subjects up to the age of 50-60 years.

The true nature of the reduction in cardiac pump function over the years seen in hypertension is not

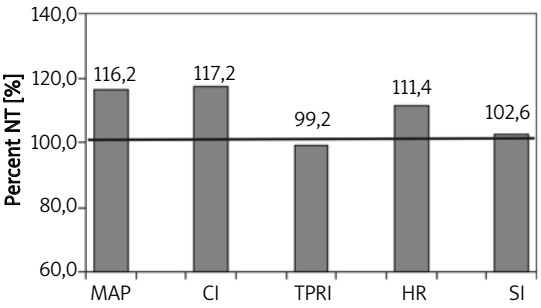

Figure 3. Central haemodynamic variables in young subjects with mild essential hypertension. Data are shown in percent compared with normotensive (NT) subjects (dotted line = 100%) and are the weighted mean values for the supine position at rest from 7 studies in a total of 189 normotensive subjects and 222 hypertensives [8-14]. Legends as in Figures 1 and 2

readily apparent. In a group of offspring (mean age 40) from parents who at a national health screening 27 years earlier had a blood pressure above 140/90 mm Hg, a shift of left ventricular diastolic filling from early to late diastole was seen when compared to offspring from parents who were normotensive both at the screening and at the time of the current study [36]. Similar findings have been made in other studies, suggesting increased left ventricular stiffness and reduced ventricular filling rate even before development of left ventricular hypertrophy [34, 37-39].

Age: longitudinal data

Most follow-up studies on spontaneous changes in central haemodynamics have been of short duration – typically 2-5 years [10, 12, 20, 21, 40-44]. Generally the blood pressure remained unchanged while the cardiac output decreased and total peripheral resistance in most cases showed an increase. Also during a longer follow-up period (10 years) similar results were found [20, 44]. As in the cross-sectional studies, the reduction in cardiac output was associated with a reduction in stroke volume in the order of 15% while heart rate was almost unchanged. Thus, the progressive decrease in cardiac pump function with age in hypertensives as suggested from the cross-sectional studies is also seen in longitudinal follow-up in individual patients.

A second restudy – with identical invasive methods as in studies 1 and 2 – after a total of 20 years from their first haemodynamic study – has also been performed in our laboratory [20, 21, 44]. The principal results were further increases in systolic and diastolic blood pressures associated with an increase in total peripheral resistance and further reductions in cardiac output and stroke volume (Figure 2) [21].

Exercise

Severe muscular exercise increases cardiac output by 300% or more, and dramatically changes the distribution of blood flow in the body – mainly by a large increase in the proportion of the blood flow to working muscles, including the myocardium. Thus, while it could be difficult to detect minor disturbances in the circulatory system in mild hypertensives vs. normotensive subjects in the rest situation, such haemodynamic differences could be more clearly unveiled during exercise – when the circulatory system is really challenged.

Several comparative haemodynamic studies during exercise between hypertensives and normal age-matched controls have been carried out in the past [7, 45-48]. In subjects between ages 18 and 30 years with mild or borderline hypertension, the rise in blood pressure during ergometer cycling with increasing loads was parallel to what was seen in the normotensive controls. The heart rate was slightly higher.

Surprisingly, in transition from rest to exercise (in the sitting position on an ergometer bicycle) the stroke volume did not increase to the same levels as in the normotensive controls [7]. In a study from our laboratory the stroke index in the hypertensive patients was approximately 15% lower than in normotensive controls during all exercise levels (50, 100 and 150 W). Thus, cardiac index during exercise was no longer higher than in normotensive controls, but actually significantly subnormal, particularly during strenuous exercise (150 W). The oxygen consumption was similar, and as a consequence the arteriovenous oxygen difference was increased. Total peripheral resistance, which was numerically normal in the youngest group at rest, was significantly higher than normal at all exercise levels and also in the older age groups (Figure 2).

Muscular exercise increases the workload on the heart and the myocardial oxygen need. The product of HR x SAP is a clinically useful index of myocardial oxygen demand [49]. When the rate-pressure product is compared in hypertensives and normotensives of similar age it is seen that in the hypertensive groups the rate-pressure product is similar at rest to what normotensives are exposed to during 50 W exercise (Figure 4) [50]. This illustrates the chronic increased burden on the hypertensive heart even at rest.

Hypertension is a well-known risk factor for heart failure. In subjects with very severe hypertension it was demonstrated that the cardiac index was markedly reduced compared to normotensive controls and also compared to subjects with mild hypertension [51]. When going from moderate to severe exercise, stroke index actually decreased. This was seen in subjects with

no clinical symptoms of heart failure, but these findings could be interpreted as an indication of incipient cardiac failure [7]. Studies from other laboratories have shown that the cardiac index in relation to the filling pressure is reduced in patients with relatively severe hypertension [48].

The most important conclusions from the exercise studies are that subclinical changes occur in cardiac pump function and vessel resistan-ce very early in subjects with mild, uncomplicated essential hypertension. As first pointed out by Tarazi et al., one mechanism responsible for the reduction in the pump function is reduced compliance of the left ventricular wall [52-54]. Studies of heart pump function at rest by echo-Doppler method in subjects with very mild hypertension have revealed a slight degree of left ventricular hypertrophy, and diastolic

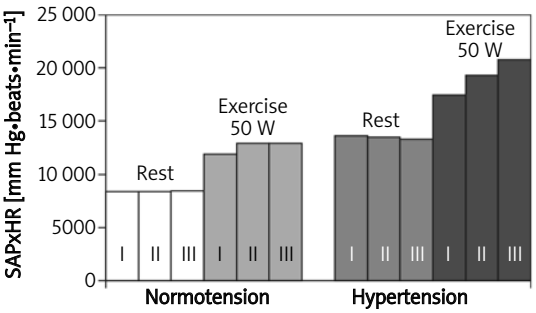

Figure 4. The rate-systolic arterial pressure product (SAPxHR) at rest (plain bars) and during steady state 50 W bicycle exercise (hatched bars) in normotensive subjects (light grey) and hypertensive patients (dark grey) in three age groups, respectively: I – 18-29 years, II – 30-39 years, III – 40-49 years. Adapted from ref. [50]

Table II. One-year central haemodynamic changes [%] induced by different classes of antihypertensive drugs or low sodium diet. Observations at rest sitting

	Number	MAP (130 mm Hg)*	TPRI (3905 dyn•s•cm^{-5}•m^2)	CI (2.73 l/min/m^2)	SI (37.4 ml/min/m^2)	HR (73.2 beats/min)
β-blockers	n=7, N=87	–12.8	12.9	–24.2	–3.0	–22.0
Low sodium diet	n=3, N=46	–2.5	7.4	–13.4	–3.5	–9.6
Diuretics	n=4, N=45	–17.7	–6.9	–11.5	–12.3	0.7
Multiple action	n=4, N=52	–15.6	–6.9	–9.9	2.5	–8.2
ACE inhibitors	n=3, N=43	–16.4	–13.9	–3.3	–0.9	–1.5
AT_1-blockers	n=1, N=28	–9.5	–11.5	0.9	3.6	–0.9
Ca antagonists	n=7, N=111	–13.9	–15.6	1.7	4.3	–2.8
α-blockers	n=3, N=38	–11.9	–17.7	5.5	5.7	0.6

n – studies, N – patients
**The data in parentheses show overall mean haemodynamic values before treatment in 450 patients with hypertension from 32 studies. Abbreviations as in Figure 2*

Table III. One-year central haemodynamic changes [%] induced by different classes of antihypertensive drugs or low sodium diet. Observations during 100 W dynamic exercise

	Number	MAP (147 mm Hg)*	TPRI (1695 dyn•s•cm^{-5}•m^2)	CI (7.07 l/min/m^2)	SI (54.7 ml/min/m^2)	HR (132.9 beats/min)
β-blockers	n=7, N=87	–12.3	6.6	–17.9	–6.2	–22.6
Low sodium diet	n=3, N=46	–2.6	0.0	–6.0	–1.5	–5.0
Diuretics	n=4, N=45	–14.7	–9.7	–7.0	–5.9	–1.8
Multiple action	n=4, N=52	–15.5	–5.1	–7.7	9.1	–15.9
ACE-inhibitors	n=3, N=43	–13.4	–6.0	–7.0	-5.4	–0.5
AT_1-blockers	n=1, N=28	–8.0	–14.5	6.1	9.1	–2.1
CA-antagonists	n=7, N=111	–11.3	–10.4	–2.2	2.0	–3.8
α-blockers	n=3, N=38	–11.5	–16.5	4.9	4.0	–0.9

n – studies, N – patients
**The data in parentheses show overall mean haemodynamic values before treatment in 450 patients with hypertension from 32 studies. Abbreviations as in Figure 2.*

dysfunction characterised by reduction in the E/A ratio. This indicates that the filling of the left ventricle is slightly reduced and more dependent on the atrial contraction in hypertension than in normals.

Pathophysiology of hypertension

The cause(s) of hypertension has been sought during the whole of the last century. Except for the limited group of patients in whom a defined disease process can be found to account for hypertension, most patients are still classified as having a form of hypertension without known cause: i.e. primary or essential hypertension.

According to the mosaic theory, originally proposed by Irvine Page more than half a century ago, primary hypertension may be caused by disturbance of one or more of a number of control mechanisms for blood pressure [55]. However, as discussed above, any mechanism or group of mechanisms that eventually may be shown to explain elevation of mean arterial pressure must be expressed by changes in either cardiac output and/or total peripheral resistance. Thus, central haemodynamic variables are cornerstones in the understanding of how hypertension may develop. Since a rise in total peripheral resistance seems to be of fundamental importance in the development of hypertension, research efforts have been directed towards components essential in the control of constriction and/or relaxation of arteriolar smooth muscles.

Antihypertensive drug therapy

Measurements of central haemodynamics have been a useful tool in understanding the mechanisms of action of antihypertensive agents [56, 57]. Conversely, by pharmacological challenging of haemodynamic variables drugs have been used to expose underlying haemodynamic mechanisms of hypertension and thus serve as tools to investigate the pathophysiology of the disease. Tables II and III show the overall data from 32 invasive studies in our laboratory on central haemodynamic changes at rest and during exercise at 100 W induced by 1-year treatment by the major drug classes of antihypertensive drugs. Data from studies on non-drug treatment by salt restriction are also included. The total number of patients in these studies is 450. In the tables the treatment regimens are ranked according to the cardiac index response at rest sitting.

The tables demonstrate that the modern selection of antihypertensive agents offers the possibility to modulate central haemodynamics of hypertension ranging from fall in blood pressure due to marked reduction in cardiac output, which is partly counteracted by some increase in total peripheral resis-tance, to vasodilatation with reduction in total peripheral resistance, and, in some cases, a small increase in cardiac output (Tables II, III). However, the tables also show that there is still a considerable gap between treated hypertension and normotension and thus that none of the available drug classes are even close to fully normalizing the central haemodynamic disturbances of hypertension.

Nine months of salt restriction induced a small reduction in blood pressure due to reduction in cardiac output, while total peripheral resistance actually tended to increase [58] (Tables II, III). This failure to normalize central haemodynamics might be due to the stimulating effect of sodium deprivation on the renin-angiotensin system and may serve as a counter-regulatory mechanism preventing excessive blood pressure fall [59, 60].

Some large-scale antihypertensive drug trials have shown that ACE inhibitors and angiotensin receptor-1 blockers are particularly effective in reducing left ventricular hypertrophy and also that development of congestive heart failure and other clinical end-points is reduced compared with other drugs [61]. However, full normalization of left ventricular geometry is usually not seen [62]. It is unknown whether this observation and the gap between normal and on-drug central haemodynamic pattern in patients with hypertension are linked, but from a haemodynamic point of view it is obvious that there is still a great potential for improvements in antihypertensive treatment.

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