STATE OF THE ART REVIEW

Haemodynamics in essential hypertension

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Introduction

The arterial blood pressure is mainly determined by the cardiac output and the total peripheral resistance. The blood pressure and the cardiac output are measured and the total peripheral resistance is calculated by dividing mean arterial blood pressure by cardiac output. This calculation is valid only for laminar flow in rigid straight tubes, but still this calculation is currently used to estimate the complex total peripheral resistance in man, although this means a rough approximation (Peterson, 1961).

In an extensive review of the haemodynamics of hypertension, Freis (1960) stated that according to the prevailing concept the primary and cardinal haemodynamic disturbance in practically all forms of hypertension was an increase in total peripheral resistance, probably caused by neurogenic or humoral mechanisms. The cardiac output was normal as long as heart failure was not present and, from a pathogenetic point of view, the heart was not of much interest.

However, in the late 1950s and the early 1960s a few observations in experimental and human hypertension seemed to indicate that increased cardiac output could play an important role in the starting phase of hypertension. The total peripheral resistance could become increased later as a sort of autoregulatory phenomenon. Ledingham & Cohen (1963) demonstrated that in some rats with experimental renal hypertension the cardiac output was increased when the pressure started to rise, although the total peripheral resistance was still normal. After some time the cardiac output fell and the total peripheral resistance increased, maintaining the elevated arterial pressure. From Czechoslovakia, Hejl (1957), Widimsky, Fejfarova & Fejar (1957) and Fejar & Widimsky (1961) reported increased cardiac output in the majority of young patients with essential hypertension. The calculated total peripheral resistance was numerically normal.

These observations generated great interest in the haemodynamics of essential hypertension, and today it is well documented that the haemodynamic pattern varies and depends upon the age of the subject and the stage of the hypertensive disorder (reviews: Frohlich, Tarazi & Dustan, 1969; Sannerstedt, 1970; Lund-Johansen, 1973; Birkenhager & Schalekamp, 1976). In recent years, functional disturbances of the heart and resistance vessels together with morphological changes in the left ventricle (diagnosed by echocardiography) have been demonstrated surprisingly early, e.g. in subjects in their twenties with mild hypertension.

This review will first discuss the function of the heart and the resistance vessels during rest and various stress conditions, and then the pathophysiological mechanisms responsible for the alterations in function. Finally the possibility of reversing the haemodynamic abnormalities by drug therapy will be briefly reviewed.

Central haemodynamics at rest

Early hypertension

It is difficult to find subjects with documented early essential hypertension. Most studies have been made in young adults with 'borderline' (here defined as patients with some readings above and some below 90 mmHg) or mild hypertension. When groups of borderline hypertensive subjects are compared with age-matched normotensive controls, the cardiac index at rest supine is usually increased. The heart rate is also increased and the stroke index usually normal.
(Eich, Peters, Cuddy, Smulyan & Lyons, 1962; Bello, Sevy & Harakal, 1965; Julius & Conway, 1968; Kuramoto, Murata, Yazaki, Ikeda & Nakao, 1968; Frohlich et al., 1969; Frohlich, Kozyl, Tarazi & Dustan, 1970; Safar, Fendler, Weil, Idatte, Beuve-Mery & Milliez, 1970; Julius, Pascual, Sannerstedt & Mitchell, 1971b). The left ventricular ejection rate is increased (Frohlich et al., 1969, 1970). Only one study (in older patients with more severe, but labile, hypertension) demonstrated normal heart rate and increased stroke volume (Finkielman, Worcel & Agrest, 1965). The calculated total peripheral resistance is not significantly higher than in controls. Individual variations are great, however, and a continuous spectrum of cardiac outputs from high to low might be found (Messerli, de Carvalho, Christie & Frohlich, 1978). Also in young adults with established, but mild, hypertension [all readings above 140/90 mmHg, but without complications, in World Health Organization stage I (Expert Committee, 1962)] a similar haemodynamic pattern has been found (Sannerstedt, 1966; Lund-Johansen, 1967). Table 1 shows haemodynamic data from five different laboratories obtained in adults below 40 years with average mean arterial blood pressure 100-108 mmHg at the time of the study.

A high heart rate and cardiac index have also been demonstrated in a large proportion of adolescents (12-25 years) and children with mild, labile essential hypertension (Davignon, Rey, Payot, Biron & Mongeau, 1977; Dustan & Tarazi, 1977), but some subjects with high resistance are also found at this stage. The increased cardiac output and heart rate in patients supposed to be in the 'starting phase' of essential hypertension gave rise to the concept of the 'hyperkinetic' circulatory system, an important factor in the autoregulation theory (Guyton, Coleman, Cowley, Norman, Manning & Liard, 1973). However, four independent studies showed that the oxygen uptake during rest was increased as well (Eich, Cuddy, Smulyan & Lyons, 1966; Sannerstedt, 1966; Lund-Johansen, 1967; Julius & Conway, 1968), and when the cardiac output was plotted against the oxygen consumption it was found to be normal, and so was the arteriovenous oxygen difference. These results showed that there is really no true 'luxury' perfusion in 'early' essential hypertension and no need for any 'protection' of the tissues against overflow through increase in vascular resistance. (During muscular exercise the cardiac output is definitely not increased; see below.) A true hyperkinetic circulatory system has been demonstrated by Gorlin (1962) in subjects with tachycardia and 'cardiac awareness'. In these subjects the arteriovenous oxygen difference was abnormally low (2·9 vs 4·0 ml of oxygen/100 ml of blood in normals) and the cardiac index was 5·7 vs 3·9 l min⁻¹ m⁻² in controls. Some of these patients had slightly elevated blood pressure, but whether they developed hypertension later is not known.

In elderly subjects with mild hypertension the cardiac output is usually low (Lund-Johansen, 1980b), but exceptions are seen and Kuwajima (1979) has reported a selected group of elderly subjects with mild hypertension and cardiac index values above 4·0 l min⁻¹ m⁻².

**Late hypertension**

In adults with moderate essential hypertension of several years' duration and in WHO stage I or II, the dominating haemodynamic disturbance is an increase in total peripheral resistance. The cardiac output is usually lower than in normotensive controls and lower than in younger hypertensive stage I subjects. The heart rate is usually higher than in controls and the stroke volume is normal or low (Glazer, 1963; Bello et al., 1965; Bello, Sevy, Harakal & Hillyer, 1967; Amery, 1969; Frohlich et al., 1970; Frohlich & Pfeffer, 1975; Chau, Safar, Weiss, London,

Severe hypertension

In patients with more severe hypertension and complications (WHO stage III) the characteristic finding is a pronounced increase in total peripheral resistance and a markedly decreased cardiac output and stroke volume (Glazer, 1963; Bello et al., 1965; Sannerstedt, 1966; Bello et al., 1967; Lund-Johansen, 1967; Frohlich et al., 1969; 1970; Terasawa, Kurimoto, Lie Hon Ying, Suzuki & Kuramochi, 1972; Frohlich, 1973).

In patients with severe hypertension refractory to triple drug treatment very high resistance values were found (Anderson, Hansson & Sivertsson, 1978).

A few exceptions from this pattern have been reported with a high cardiac index in some patients with severe hypertension (Ibrahim, Tarazi, Dusart, Bravo & Gifford, 1975).

In patients with hypertension and left ventricular strain on ECG the cardiac index is decreased (Olivari, Fiorentini, Polese & Guazzi, 1978), and when heart failure is present, very low cardiac output and very high total peripheral resistance have been reported, together with increased pressures in the pulmonary circulation (Werka & Lagerløf, 1949; Varnauskas, 1955; Taylor, Donald & Bishop, 1957), and reduced left ventricular ejection fraction and circumferential fibre shortening (Strauer, 1979).

Regional circulation at rest

Large systematic studies of the circulatory pattern in various parts of the body in hypertensive subjects of different ages and in various stages are lacking. The increased calculated total peripheral resistance in established essential hypertension is not shared equally in all parts of the body (Brod, Fencl, Hejl, Jirka & Ulrych, 1962; Brod, 1973).

In early essential hypertension renal blood flow is increased (Hollenberg & Adams, 1971) and there is a correlation between cardiac output and renal blood flow (Messerli et al., 1978). In established hypertension the renal blood flow is usually reduced and the renal vascular resistance increased (Brod et al., 1962; de Leeuw et al., 1978; Messerli et al., 1978). In the splanchnic area the resistance is also increased, as in the rest of the body (Messerli, Genest, Nowaczynski, Kuchel, Honda & Latour, 1975; Messerli et al., 1978).

In the skeletal muscles the blood flow is increased in the early stage, and the total peripheral resistance is increased (Conway, 1963; Amery, Bossaert & Verbrugge, 1969), but there is no correlation between central and peripheral haemodynamics (Fantini, Nuzzaci, Padeletti, Michelucci, Arcangeli & Forti, 1977).

Hand blood flow during maximal vasodilatation (obtained by heating and exercise during ischaemia) is increased in young subjects (19–22 years) with mild hypertension. The resistance in the hand vessels is normal if cardiac output is increased, but elevated if cardiac output is normal (Sivertsson, Sannerstedt & Lundgren, 1976).

Strauer (1979) has demonstrated that the coronary reserve is reduced in patients even in the early stages of hypertension. In more severe hypertension a great reduction in the coronary reserve was found and an increase in coronary vascular resistance during rest.

Pulmonary circulation

As long as heart failure is not present, it has been assumed that the pulmonary circulation is normal in essential hypertension. However, recently it has been shown that even in patients with moderate hypertension without clinical signs of heart failure, there is often an increase in the pulmonary artery pressure as well, and vascular resistance is increased both in the pulmonary and the systemic circulation (Atkins, Mitchell & Pettinger, 1977; Olivari et al., 1978; Ferlinz, 1980). Also there is involvement of the right ventricle with reduced ejection fraction demonstrating functional disturbances on both the left and the right side of the heart (Guazzi, Fiorentini, Olivari & Polese, 1979).

Haemodynamics during sleep, exercise and stress

Haemodynamics during sleep

Continuous intra-arterial recordings have shown that blood pressure decreases markedly during sleep (Millar-Craig, Bishop & Raftery, 1978). Bristow, Honour, Pickering & Sleight (1969) found that the pressure fall was mainly due to a marked decrease in total peripheral resistance, and the cardiac output showed only a small decrease (6%). However, in another study by Khatri & Freis (1969) the dominant changes were in the cardiac output.

Studies in cats have shown that vasodilatation is mainly responsible for the fall in blood pressure (Zanchetti, Baccelli, Guazzi & Mancia, 1973).
The sensitivity of the baroreceptor reflex during sleep is increased (Bristow et al., 1969) and could possibly contribute to the reduction in pressure.

**Haemodynamics during dynamic exercise**

**Borderline and mild hypertension.** In patients with borderline hypertension the blood pressure increases during exercise, parallel to the rise in normotensive age-matched controls. Cardiac output is no longer increased, and rises as in normals. The total peripheral resistance falls, but not to the same low levels as in controls (Levy, Tabakin & Hanson, 1967; Julius & Conway, 1968).

We have studied central haemodynamics during standardized exercise on an ergometer bicycle at 50, 100 and 150 W in more than 200 males with mild to moderate essential hypertension, the majority in WHO stage I, and in normotensive age-matched controls (Lund-Johansen, 1967, 1973, 1980b). During exercise the 'hyperkinetic' circulatory pattern found in young hypertensive subjects (17-29 years) at rest disappears. The cardiac output is then no longer higher than in controls; on the contrary, it tends to be subnormal. At 150 W the cardiac output related to oxygen consumption is significantly lower than in age-matched controls. The heart rate during exercise is slightly increased and the stroke volume subnormal. The total peripheral resistance falls, but not to the same low levels as in normotensive subjects. In patients 10 years older a similar pattern is found.

**Late and severe hypertension.** In patients in WHO stage II and III, the cardiac output during exercise is markedly lower than in age-matched controls, mainly due to a subnormal stroke index. In these patients the stroke index is often already low at rest. The total peripheral resistance is markedly increased at rest as well as during exercise (Varnauskas, 1955; Taylor et al., 1957; Sannerstedt, 1966; Amery, Julius, Whitlock & Conway, 1967; Lund-Johansen, 1967).

**Haemodynamics during isometric exercise**

Isometric exercise induces marked increase in the blood pressure and heart rate (Chrysant, 1978). Patients with borderline hypertension and high cardiac output demonstrate greater increase in mean arterial pressure and heart rate than patients with low cardiac output (Messerli et al., 1978).

**Haemodynamics during emotional stress**

Brod (1974) has demonstrated that during emotional stress the blood pressure increase is associated with vasoconstriction in the kidneys, in the skin and probably also in the splanchnic area, whereas vasodilatation takes place in the muscles. The net balance between these vascular areas will determine the total peripheral resistance. Andrén, Hansson, Björkman & Jonsson (1980) have shown that industrial noise raises blood pressure through increase in total peripheral resistance.

**Long-term changes in central haemodynamics**

From cross-sectional observations it seems likely that the circulatory pattern in hypertension would undergo a change with time from the typical 'high blood flow-normal resistance pattern' in young age towards 'low blood flow-high resistance pattern' in old age.

Unfortunately there are few systematic follow-up studies in untreated hypertensive subjects. Table 2 summarizes the most important findings in six studies (Eich et al., 1966; Eliasch, Varnauskas & Werko, 1971; Birkenhager, Schalekamp, Krauss, Kolsters & Zaal, 1972; Lund-Johansen, 1977; Weiss, Safar, London, Simon, Levenson & Milliez, 1978; Julius, Quadir & Gajendragadkar, 1979). Only two include strictly untreated patients and have been performed with the same experimental conditions at both studies.

In our series (Lund-Johansen, 1977, 1979a) 77 patients who had been investigated haemodynamically in 1964-1966 were restudied clinically, and 33 of the 34 untreated patients also haemodynamically after about 10 years. The blood pressure during rest sitting was on average 150/92 mmHg in age group I (17-29 years) in the first study, and was not significantly increased during the follow-up period. Individual data showed that the blood pressure increase was seen mainly in the few patients who had a high total peripheral resistance in study I. During exercise at 150 W there was a significant increase in the mean arterial pressure in both age groups.

The oxygen consumption, which was originally increased in age group I, had fallen to values close to those seen in age group II 10 years before. The cardiac output had decreased 15 and 23% during rest in age groups I and II respectively (15 and 14% during 150 W exercise).

In both age groups there was decrease in stroke index of about 12%. The heart rate showed small changes in age group I; in group II there was a significant decrease at rest and also during exercise. The total peripheral resistance increased by about 24-35% in both groups.

Julius et al. (1979) reported rather similar
Haemodynamics in essential hypertension

Table 2. Haemodynamic follow-up studies in essential hypertension showing changes in cardiac output (CO) and peripheral resistance (TPR)

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Therapy</th>
<th>Experimental condition during study 1 and study 2</th>
<th>Follow-up time (years)</th>
<th>Haemodynamic changes in study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eich et al. (1966)</td>
<td>68</td>
<td>41</td>
<td>In some</td>
<td>Different*</td>
<td>About 4</td>
</tr>
<tr>
<td>Eliash et al. (1971)</td>
<td>83</td>
<td>20</td>
<td>Sympathectomy in some</td>
<td>Different† Rest only</td>
<td>8–17</td>
</tr>
<tr>
<td>Birkenhager et al. (1972)</td>
<td>15</td>
<td>15</td>
<td>In all</td>
<td>Same Rest only</td>
<td>1–4</td>
</tr>
<tr>
<td>Weiss et al. (1978)</td>
<td>37</td>
<td>37</td>
<td>0</td>
<td>Same Rest only</td>
<td>About 4</td>
</tr>
<tr>
<td>Lund-Johansen (1977) (untreated group)</td>
<td>34</td>
<td>35</td>
<td>0</td>
<td>Same Rest and exercise</td>
<td>9–10</td>
</tr>
<tr>
<td>Julius et al. (1979)</td>
<td>24</td>
<td>24</td>
<td>In nine</td>
<td>Same Rest only</td>
<td>5–6</td>
</tr>
</tbody>
</table>

*Study 1: ward patients (study 2: outpatients). †Study 2: heart catheterization (study 2: less-invasive methods).

findings in patients with mild borderline hypertension (blood pressure only 141/88 mmHg) followed for 5–6 years.

In five of our patients aged 40–49 years there was an increase in the blood pressure at rest as well as during exercise, together with marked increase in total peripheral resistance and decrease in cardiac output.

In conclusion, the follow-up studies have demonstrated a decrease in cardiac output and stroke volume and increase in total peripheral resistance with time in the young patients with borderline or mild hypertension. The blood pressure changed little, but with some increase in the few subjects with high total peripheral resistance. A 10 year follow-up period is probably too short to demonstrate rise in blood pressure in groups of young hypertensive patients. Widimsky & Jandova (1977) found that during 20 years 37 out of 70 young borderline hypertensive patients had become hypertensive.

In older patients with increased peripheral resistance a rise in blood pressure was found by Eich et al. (1966), and also in our study (Lund-Johansen, 1979b).

Whether the changes in flow and resistance are mainly due to the effects of aging or to the effects of hypertension is still unknown. Cross-sectional studies of central haemodynamics in normal subjects have shown that over several decades there is a decrease in cardiac output and stroke index (Amery, Wasir, Bulpitt, Conway, Fagard, Lijnen & Reybrouck, 1978). On the other hand, haemodynamic studies in subjects in their twenties, thirties and forties have usually not demonstrated significant differences between the groups (Lund-Johansen, 1967; Hanson, Tabakin & Levy, 1968).

Pathophysiological mechanisms inducing or maintaining haemodynamic alterations

Sympathetic nervous system

The increased cardiac output, heart rate and oxygen consumption during rest in patients with early essential hypertension could be due to overactivity of the sympathetic nervous system. To demonstrate such an overactivity has been difficult and the role of the sympathetic nervous system in the pathogenesis of essential hypertension is still unsettled (review in Chalmers, 1978). The excretion of catecholamines in 24 h urine is not increased in patients with essential hypertension studied under similar inpatient conditions as age-matched controls (Bing, Harlow, Smith & Townshend, 1977).

Elevated plasma catecholamines have been reported (Engelman, Portnoy & Sjoerdsma, 1970), but the difference between normal subjects and hypertensive patients could be due to differences in age (Lake, Ziegler, Coleman & Kopin, 1977).

Philipp, Distler & Cordes (1978) have studied plasma catecholamines at rest and during exercise in hypertensive patients and normotensive subjects (age 20–49 years), and also reactivity to infused noradrenaline. Increased resting plasma noradrenaline levels and increased reactivity to noradrenaline was found in
some but not all patients with essential hypertension. No correlation between basal plasma noradrenaline concentrations and blood pressure was found.

Julius and coworkers (Julius & Conway, 1968; Julius & Esler, 1975; Julius, 1976) have studied the central haemodynamics and the sympathetic nervous system in a large group of young males with very mild borderline hypertension and in control subjects (age 18–35 years). On the day of the study, the mean blood pressures were only 132/75 ± 14/10 mmHg (controls 112/63 ± 8/11 mmHg). When $\beta$-adrenoreceptor blockade was achieved (by propranolol) the increased cardiac output fell, but only after complete autonomic blockade with propranolol plus atropine was the difference between hypertensive patients and normotensive subjects abolished. The heart rate then became similar (about 100 beats/min), showing that the intrinsic activity of the sinus node was normal and that the increased cardiac output and the increased heart rate were due to an imbalance in the autonomic nervous system. Also increased stroke volume became normal after autonomic blockade. Thus the sympathetic tone to the heart is too high and the parasympathetic tone too low. The mechanism of this imbalance is unknown. The autonomic blockade also revealed an increased total peripheral resistance, which remained increased in a number of patients after $\alpha$-adrenoreceptor blockade with phentolamine, possibly reflecting structural changes already at this stage.

A subset of patients with mild essential hypertension and increased plasma renin activity has been demonstrated. This group showed other signs of increased sympathetic nervous activity: raised plasma noradrenaline and normal blood pressure by total autonomic blockade (atropine, propranolol and phentolamine) (Esler, Julius, Zweifler, Randall, Harburg, Gardiner & de Quattro, 1977). On psychometric testing, the patients exhibited suppressed hostility. It is possible that these patients have hypertension of psychosomatic origin. More or less opposite findings have been made in patients with low renin hypertension (Esler, Zweifler, Randall, Julius, Bennett, Rydelek, Cohen & de Quattro, 1976).

Thus, according to Julius and coworkers, most of the haemodynamic abnormalities during rest in borderline hypertension can be explained through neurogenic mechanisms.

Muiesan, Agabiti-Rosei, Alicandi & Fariello (1979) found a positive correlation between total peripheral resistance and plasma catecholamines, and after blockade of $\alpha$- and $\beta$-receptors with labetalol the reduction in total peripheral resistance was directly related to previous catecholamine levels.

Miura, Kobayashi, Sakuma, Tomioka, Adachi & Yoshinaga (1978) have reported a positive correlation between plasma noradrenaline and total peripheral resistance or cardiac index in patients with early essential hypertension.

Variations in sympathetic activity could be responsible for the variability of the blood pressure in hypertension. However, Clement, Mussche, Vanhoutte & Pannier (1980) did not find a correlation between pressure variability and plasma catecholamines.

**Baroreflexes**

These complex regulating systems will be mentioned only briefly. Studies in humans in whom blood pressure has been increased stepwise by injections of angiotensin have shown that the slowing of the heart is less in hypertensive subjects, even when hypertension is mild, reflecting less efficient baroreflex control. With increasing severity of hypertension the baroreflex is less efficient (Gribbin, Pickering, Slieght & Peto, 1971; Takeshita, Tanaka, Kuroiwa & Nakamura, 1975). Thus disturbances in the baroreflexes could play an important role in the maintenance of the elevated blood pressure in essential hypertension. This area is under current investigation also by new non-pharmacological methods, i.e. the pressure-neck-chamber (Mancia, Ludbrook, Ferrari, Gregorini & Zanchetti, 1978).

**Blood volume, its distribution and the capacitance vessels**

In the early phase of essential hypertension, an increased heart rate is partly responsible for the increased cardiac output. But since the afterload on the heart is elevated, an increase in cardiac contractility must also be an important factor. An increase in the total blood volume or changes in the distribution of the blood volume, with a larger fraction centrally (in the lungs and heart, the so-called cardiopulmonary blood volume), could also play a role. This would facilitate the filling of the heart and contribute to maintenance of normal cardiac output and stroke volume when the afterload is high (Julius, 1976; Safar, Weiss, London, Chau & Milliez, 1977; Dustan & Tarazi, 1978).

It has been demonstrated that the total blood volume is not increased in mild hypertension and in moderate or severe hypertension it is often
abnormally low (Frohlich et al., 1969; Julius, Pascual, Reilly, London & Arbor, 1971a; Dustan, Tarazi & Bravo, 1972; Tarazi, 1976). However, the cardiopulmonary blood volume is increased, indicating a shift of the blood from the peripheral veins to the pulmonary capacitance bed (Safar, Weiss, London, Simon & Chau, 1980), and a positive correlation between the cardiopulmonary blood volume and cardiac output has been found by Messerli et al. (1978).


The mechanism behind the suspected reduced distensibility of the total venous system in hypertension is unknown. Functional and/or structural alterations could be responsible (Ulrych, 1979). Simon, Franciosa & Cohn, (1979) have demonstrated a decreased venous distensibility in the forearm in patients with essential hypertension, but they found no correlation between the reduced distensibility and the haemodynamic parameters. Thus the pathophysiological role of this finding is uncertain, but obviously the forearm represents a very small part of the capacitance system and the results are inconclusive.

Structural changes in the left ventricle and in the resistance vessels

It has been shown in the spontaneously hypertensive rat that hypertrophy and reduced compliance of the left ventricle occur at a very early stage in the development of hypertension (Folkow, 1978; Hallbäck-Norlander, Noresson & Thoren, 1979; Yamori, Mori, Nishio, Ooshima, Horie, Ohtaka, Soeda, Saito, Abe, Nara, Nakao & Kihara, 1979). Based on ECG recordings and haemodynamic observations during rest, it seems that reduced compliance and left ventricular hypertrophy are rather late phenomena in human hypertension. However, when patients with mild hypertension exercise in the semi-sitting position with legs and thighs horizontally, facilitating venous return, the stroke volume does not increase to the same high levels as in normotensive controls (Lund-Johansen, 1967). This rather surprising finding was first interpreted as a sign of incipient cardiac insufficiency (Lund-Johansen, 1970b), but today restructuring of the left ventricle with reduced compliance would seem more likely (Tarazi, 1979).

Such a restructuring could also partly explain the reduction in the stroke index in untreated hypertensive subjects followed for 10 years.

Recent studies of the left ventricular wall by echocardiography have shown that increased wall thickness is often found in patients with relatively mild hypertension (WHO stage I and with a normal ECG) (Dunn, Chandrazatna, de Carvalho, Basta & Frohlich, 1977; Frohlich & Tarazi, 1979; Safar, Lehner, Vincent, Plainfosse & Simon, 1979b; Savage, Drayer, Henry, Mathews, Ware, Gardin, Cohen, Epstein & Laragh, 1979). Safar et al. (1979b) have found increased thickness of the intraventricular septum even in patients with borderline hypertension. With sustained hypertension increased thickness is found both in the intraventricular septum and in the posterior wall of the left ventricle.

An increase in the thickness of the arteriolar wall with a reduction in the arteriolar lumen is found in the spontaneously hypertensive rat even at an early stage (Folkow, 1978). In essential hypertension, the functional disturbances in the total peripheral resistance during exercise (Lund-Johansen, 1967) could well be explained by similar changes.

Lack of complete normalization of total peripheral resistance after \( \alpha \)-receptor blockade by phentolamine (Julius, 1976) or after combination of heating and exercise during ischaemia (Sivertsson & Hansson, 1976) could also be due to structural changes. So could the increase in total peripheral resistance with time in untreated patients. However, obviously this evidence is only indirect.

Regression or arrest of haemodynamic alterations by drug treatment

An important question is whether the functional and structural changes in the heart and in the resistance vessels found in hypertension are reversible. In hypertensive rats treated with \( \alpha \)-methyldopa, regression of left ventricular hypertrophy has been demonstrated (Ferrario, Spech, Tarazi & Doi, 1979), but somewhat surprisingly other antihypertensive agents also reducing the blood pressure did not induce such regression (Tarazi, 1979). Thus it is likely that factors other than blood pressure reduction alone are of importance (Frohlich & Tarazi, 1979).

In humans systematic studies of cardiovascular morphology are obviously lacking and only studies of function are available.
In subjects with secondary hypertension it has been shown that after removal of a kidney with a stenotic artery, or after correction of coarctation of the aorta, the haemodynamic abnormalities may be changed in the direction of normal (P. Lund-Johansen, unpublished results).

In essential hypertension, conventional drug therapy induced different haemodynamic responses. We have studied about 200 male patients with mild to moderate hypertension before and after 1 year on one of the commonly used antihypertensive agents (a few studies have also been made on drug combinations) (review in Lund-Johansen, 1978).

It is beyond the scope of this review to discuss these results in detail, and only a few findings will be mentioned.

**Thiazide diuretics.** In 15 patients treated with hydrochlorothiazide as the sole drug for 1 year, the haemodynamic restudy showed a 15% decrease in mean arterial pressure at rest and also during exercise, associated with a significant drop in total peripheral resistance. The heart rate was unchanged and so was the stroke volume and the cardiac output during exercise. Thus at least a partial correction of the haemodynamic abnormalities was achieved. Whether the induced reduction in total peripheral resistance is due to functional or structural changes is not known (Lund-Johansen, 1970a).

**Sympathetic nervous system inhibitors. (a)** \(\beta\)-Adrenoreceptor-blocking agents. The ‘beta-blockers’ induce a dramatic change in the function of the heart pump. Heart rate is reduced, often by 25–30% at rest and during exercise. Blood pressure is usually decreased 15–20%. On some beta-blockers, an increase in the post-treatment stroke volume has been observed, partly compensating for the marked decrease in the heart rate and as a consequence cardiac output during exercise is reduced less than the heart rate. However, on all seven beta-blockers (atenolol, metoprolol, alprenolol, bunitrolol, pindolol, timolol and penbutolol) studied in our laboratory there was a significant decrease in cardiac output, averaging 15–20% (Lund-Johansen, 1980a).

The calculated total peripheral resistance did not fall below pre-treatment levels either at rest or during exercise and sometimes it was increased. There appeared to be some differences between the cardioselective and non-cardioselective beta-blockers in this respect (Lund-Johansen, 1980a).

(b) \(\alpha\)-Adrenoreceptor-blocking agents. More recently \(\alpha\)-receptor blockers have been used with success in treatment of hypertension. The \(\alpha\)-receptor blocker prazosin, which mainly acts at the post-synaptic \(\alpha\)-receptor, induces a reduction in blood pressure through a significant decrease in total peripheral resistance. The results have been very consistent, with a reduction in resistance of about 22% at rest as well as during exercise. In contrast to effects of other drugs causing vasodilatation, the heart rate did not increase. The stroke volume is higher than before treatment and the post-treatment cardiac output is increased. Thus, the post-synaptic \(\alpha\)-receptor blocker prazosin changes central haemodynamics in the direction of normal (Lund-Johansen, 1978).

**Prolonged therapy for 5 years.** Since it might be possible that prolongation of treatment for several years could induce greater normalization of central haemodynamics, a group of patients who had been on atenolol as the sole drug for 5 years were restudied after 5 years. The results did not demonstrate any decrease in total peripheral resistance or increase in cardiac output when 1 year and 5 year results were compared (Lund-Johansen, 1979a).

All these results show that neither ‘beta-blockers’ nor diuretics induce complete normality of central haemodynamics in patients with mild to moderate hypertension on long-term treatment. The greatest improvement was seen on prazosin. It is, of course, impossible to tell to what extent these functional alterations reflect structural changes and how they will effect clinical prognosis.

**Conclusion**

In the 20 years which have passed since Freis’ (1960) review haemodynamics and cardiovascular structure have been followed almost from birth to death in the spontaneously hypertensive rats, the animal model showing many similarities with human essential hypertension. It has been demonstrated that left ventricular hypertrophy and increased total peripheral resistance occur very early and also that reversal of those changes is possible at an early stage (reviews in Folkow, 1978; Yamori et al., 1979).

In man with essential hypertension the question about the role of the cardiac output in the starting phase is still open to discussion. However, it is well documented that a large fraction of young patients with borderline or mild essential hypertension do have an increased cardiac output and heart rate (compared with normotensive age-matched controls), but the cardiac output is not increased when related to the oxygen consumption of the body. It is also uncertain whether the majority of these subjects...
develop manifest hypertension after several decades, although reduction in cardiac output and increase in total peripheral resistance have been demonstrated in 5–10 year follow-up studies. Thus, it is difficult to use the increased cardiac output as an argument in favour of total body autoregulation and as being the important factor for inducing an increase in total peripheral resistance (still the cardinal haemodynamic disorder in established essential hypertension). The increased cardiac output found in the early phase of essential hypertension is probably neurogenic, whereas the increased cardiac output in many types of experimental hypertension is usually of short duration and initiated by mechanisms very different from those in essential hypertension (Fletcher, Korner, Angus & Oliver, 1976; Dustan & Tarazi, 1978; Ferrario, Page & McCubbin, 1970; Ferrario & Page, 1978). The high cardiac output is an inconsistent finding and, for instance, in DOCA-hypertensive pigs blood pressure increase is sometimes caused by increase in cardiac output, sometimes by increase in total peripheral resistance (Miller, Bohr, Schork & Terris, 1979). An excellent review of cardiac output in experimental hypertension has been given recently by Liard (1979).

An increase in total peripheral resistance is an early phenomenon in essential hypertension and is clearly demonstrated in subjects in their twenties with mild hypertension, more recently also in some hypertensive children. Studies of the regional circulation have also unveiled increased resistance at an early stage, probably caused by structural changes.

In man it has been shown that the stroke volume during exercise is subnormal even at an early stage, probably reflecting reduced compliance in the left ventricle. Echocardiographic studies have demonstrated an increase in the left ventricular wall in early hypertension (with normal ECG and normal cardiac X-ray).

An increase in the cardiopulmonary blood volume possibly contributes to maintaining the resting cardiac output in spite of increase in the afterload.

The recent demonstration of a reduction in the coronary reserve in patients with mild hypertension is of great importance.

As a main conclusion, studies of the haemodynamics in hypertension over the last 20 years have indicated that at an early stage important disturbances are found in the heart as well as in the resistance vessels and possibly also in the capacitance vessels. Their cause is still unknown. Studies of the effects of various antihypertensive agents have demonstrated that these are able to normalize the haemodynamic abnormalities to different extents, but which of the different haemodynamic patterns will induce the best clinical prognosis is still unknown. This and many other important questions await an answer in the next 20 years.

References


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Fletcher, P.J., Korner, P.I., Angus, J.A. & Oliver, J.R. (1976) Cardiac output changes during experimental renal hypertension in the rabbit. Clinical Science and Molecular Medicine, 51 (Suppl. 3), 1375–1389.

Folkow, B. (1978) Cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clinical Science and Molecular Medicine, 55 (Suppl. 4), 35–225.


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SIPERTZTEN, R. & HARRIS, L. (1976) Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. Clinical Science and Molecular Medicine, 51 (Suppl. 3), 775–79s.


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