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ROUND TABLE 1

Cardiac output and volume in hypertension

Chairman: Professor F. GROSS
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The significance of volume and cardiac output in the pathogenesis of hypertension

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In the most simplified way, blood pressure is defined according to Ohm's law as voltage which is equal to the product of current multiplied by resistance. If applied to haemodynamics, current stands for flow, which is usually determined by cardiac output, thus resulting in the formula:

\[
\text{Blood pressure} = \text{cardiac output} \times \text{total peripheral resistance}
\]

Of these three parameters, only blood pressure can be measured precisely and continuously. The two components which determine the height of blood pressure are influenced by numerous factors composing a regulatory system, the complexity of which is only too often neglected in the interpretation of data from studies in which changes of isolated parameters have been measured. The situation becomes even more complicated when the time course of the regulatory processes is considered. Acute changes in blood pressure differ in various respects from long-term variations with respect to the significance of the mechanisms that are involved. This is especially the case with pathological deviations, which are the consequence of regulatory failure.

The most sophisticated approach to the understanding of the short-term and the long-term control of blood pressure and the pathogenesis of chronic hypertension is the application of the systems analysis, introduced into this field by Arthur Guyton and his associates and skilfully developed and extended by them over the years (e.g. Guyton, Coleman, Cowley, Manning, Norman & Ferguson, 1974). The undoubted merits of this approach have been the quantification of the various changes and the demonstration of their inter-relation as well as the distinction between the mechanisms responsible for the acute and chronic regulation of blood pressure. The diagrams of the systems analysis are attractive and convincing, but they may also confound the simple mind, not accustomed to disentangling the complex but logical network. Hence, it may be useful to put together the various components which modify stroke volume and heart rate and in this way influence cardiac output as well as the neurogenic, humoral, and structural factors affecting vascular resistance,
and to ascertain how these various components are controlled (Julius & Hansson, 1974) (Fig. 1).

It is obvious that such an intricate regulatory system as the one responsible for the control of blood pressure is liable to numerous disturbances, which may eventually lead to hypertension. Although the chronic elevation of blood pressure may be elicited by various mechanisms, which cause different patterns of haemodynamic changes, attempts have been made to establish a unitary hypothesis for the pathogenesis of hypertension. On the basis of studies in subtotally nephrectomized dogs, in which hypertension had been induced by salt loading, it has been claimed that the kidney is primarily responsible for the long-range control of blood pressure (Coleman & Guyton, 1969). By means of the systems analysis a ‘servocontroller’ function has been ascribed to the kidney, which maintains the fluid-electrolyte balance. This concept ‘denies that chronic hypertension can be caused by (1) a primary increase in total peripheral resistance, (2) a primary increase in cardiac drive, or (3) decreased venous or total vascular compliance’ (Guyton, 1977). In other words, the blood pressure has to rise in order to restore a primarily impaired kidney function.

Ferrario & Page (1978) have critically reviewed the data and arguments put forward in favour of an increase in cardiac output for the pathogenesis of hypertension. They characterized the haemodynamic patterns that are found in chronically elevated blood pressure as ‘(1) increased total peripheral resistance with normal to low cardiac output, (2) increased cardiac output with “normal” peripheral resistance, and (3) a transitional pattern of an early rise in cardiac output with a later progressive increase in peripheral resistance’. The latter sequence of events is considered the result of an ‘autoregulatory’ mechanism, which, badly defined, is needed to explain the change from the increased flow to the elevated resistance. One of the major shortcomings of the studies on the role that cardiac output may have in the chronic rise in blood pressure is the inadequacy and diversity of the methods used to determine stroke volume and cardiac output. Results obtained with different techniques may not be directly comparable with one another, and, in addition, most of the methods cannot be applied to small laboratory animals, e.g. rats below a body weight of 200 g. Furthermore, large spontaneous variations in cardiac output and heart rate have been measured in normotensive dogs, observed during prolonged periods, and these deviations from the mean include increases in cardiac output which have been considered a haemodynamic abnormality in the early phase of hypertension (Ferrario & Page, 1978).

**Different types of hypertension**

In the various types of experimental hypertension, the eliciting mechanisms can be standardized and
the conditions can be more easily controlled than in hypertensive patients. Haemodynamic variations have mainly been studied in the following three models of experimental hypertension: spontaneous hypertension of rats, renal artery stenosis and mineralocorticoid hypertension.

In rats with spontaneous or genetic hypertension, there is good evidence that the genetic factors responsible for the sustained elevation of blood pressure are unlike in various strains, and consequently the haemodynamic patterns differ. The salt-sensitive (S) rats of the Dahl strain respond to salt supply with other haemodynamic changes than the salt-resistant (R) rats (Ganguli, Tobian & Iwai, 1979). In the Milan strain, an early impairment of the renal handling of salt and water has been described, which elicits an increase in blood pressure (Bianchi, Fox, Pagetti, Caravaggi, Baer & Baldoli, 1975; Bianchi, Gatti, Ferrari, Picotti, Colombo, Velis, Cusi, Lupi, Barlassina, Bracchi, Gori & Mazzei, 1979). The primary role of the kidney was convincingly demonstrated in transplantation experiments, in which kidneys from spontaneously hypertensive rats elicited hypertension in normotensive animals (Bianchi, Fox, Pagetti & Giovanetti, 1974). In the stroke-prone strain of spontaneously hypertensive rats (Okamoto, Yamori, Ooshima, Park, Haebara & Matsumoto, 1972), a sodium retention was found in young pre-hypertensive rats, but no concomitant increase in blood volume, which is even reduced. In the early hypertensive phase, sodium intake and output are in balance and the blood volume has returned to normal, whereas, in long-term hypertension, a negative sodium balance may develop, with a reduction in blood volume (Dietz, Haebara, Schömig, Rascher, Berecek, Mann, Lüth & Gross, 1979). In 'chemically sympathectomized' rats, which had received 6-hydroxydopamine for 10 days immediately after birth, the increase in blood pressure was delayed by about 4 weeks, but afterwards rose in parallel with the blood pressure of rats which had not been given 6-hydroxydopamine (Fig. 2). The reduction in blood volume, observed in the early stage of hypertension, was abolished by pretreatment with 6-hydroxydopamine, and similarly the increase in packed cell volume was no longer demonstrable (Fig. 3). Sodium was even retained during this phase (Schömig, Dietz, Rascher, Ebser, Voss & Gross, 1979). These findings indicate that, in stroke-prone spontaneously hypertensive rats, changes in intravascular volume and probably also in cardiac output hardly account for the rise in blood pressure.

Further evidence for the insignificance of cardiac output in the pathogenesis of spontaneous hypertension has been obtained in studies in which rats received β-adrenoreceptor-blocking agents (propranolol, timolol) during all their life span. Cardiac output fell by about 30%, but the degree of hypertension in the treated rats was just the same as in the untreated spontaneously hypertensive rats (Nishiyama, Nishiyama, Pfeffer & Frohlich, 1978). Hence, it is improbable that an increase in cardiac output is of pathogenic significance at any time of the development of spontaneous hypertension.

In renal hypertension, the original claims of an initial rise in cardiac output in unilaterally nephrectomized rats with renal artery stenosis (Ledingham & Cohen, 1964) were later confirmed in part only (Ledingham & Pelling, 1967). In those studies, cardiac output rose by about 10%, whereas total peripheral resistance increased markedly right from the beginning, which led the authors to the conclusion that 'the raised blood pressure at all stages was mainly attributable to an increase in peripheral resistance'.

In dogs, 30 days after unilateral nephrectomy, the clamping of the remaining renal artery was followed by a marked initial rise in cardiac output,
with negligible increase in peripheral resistance and mild hypervolaemia. Despite the fact that cardiac output remained high, peripheral resistance rose by the third week and became mainly responsible for the sustained elevation of blood pressure (Ferrario, 1974). A transient increase in cardiac output was found in two-kidney, one-clip renal hypertension of dogs, but, simultaneously, peripheral resistance was elevated (Maxwell, Lupu, Viskoper, Aravena & Waks, 1977).

In mineralocorticoid hypertension, the intravascular volume is initially increased, but, in rats, no data on cardiac output are available. In pigs, a maintenance of high blood pressure by a rise in cardiac output was observed but, in the majority of the animals, the sustained hypertension had to be attributed to an increase in peripheral resistance (Terris, Berecek, Cohen, Stanley, Whitehouse & Bohr, 1976; Berecek & Bohr, 1978). Similar observations have been reported in dogs, in which an endogenous overproduction of mineralocorticoids was induced and which responded with an increase in cardiac output (Bravo, Tarazi & Dustan, 1977). With progressive hypertension, the intravascular volume becomes normal and possibly even reduced (Dustan, Tarazi, Bravo & Dart, 1973), especially if total vascular compliance is decreased as a consequence of structural changes in the resistance vessels.

All these data provide limited experimental evidence showing that a primary rise in cardiac output would be a significant haemodynamic mechanism in several forms of hypertension. The fact that cardiac output may be elevated in the prehypertensive or very early phase of hypertension does not mean that such a change is a condition which precedes or has to precede the sustained increase in blood pressure.

**Increased pressor response as a primary pathogenic mechanism**

**Spontaneous hypertension**

In stroke-prone spontaneously hypertensive rats an increased response to pressor substances was observed in the pre-hypertensive stage, in the vascular bed of both the isolated perfused kidney and the perfused hindlimbs of rats. At the same time an enhanced sympathetic activity was demonstrable, based on an increased plasma noradrenaline concentration, whereas adrenaline and dopamine concentrations remained normal (Schömig, Dietz, Rascher, Lüth, Mann, Schmidt & Weber, 1978). After 'chemical sympathectomy' with 6-hydroxydopamine, the response to noradrenaline was enhanced in the renal and in the femoral vascular beds. This corresponds to the increased sensitivity to exogenous pressor substances seen in adrenergically 'denervated' smooth muscle (Berecek, Rascher & Gross, 1979; Schömig et al., 1979).
In renal hypertensive rats, an initial increase in the sensitivity of the vascular bed of the hindlimb to noradrenaline has been observed only in the one-kidney, one-clip model (Lüth, Dietz, Schömig, Mann & Gross, 1977).

Mineralocorticoid hypertension

In rats which received DOCA implants and had a 1% sodium chloride solution to drink, the renal vascular resistance was studied in isolated perfused kidneys. After 4 days, when the blood pressure was still normal, the dose–response curves to various pressor agents (noradrenaline, vasopressin, angiotensin II) were shifted to the left, whereas the maximum response was unchanged (Fig. 4). After 6–10 weeks, the increase in sensitivity to vasoconstrictor agents was more marked (Berecek, Stocker & Gross, 1979). In addition, a higher maximum response was obtained as a consequence of structural changes similar to those observed in other types of prolonged hypertension of rats (Folkow, Hallbäck, Lundgren & Weiss, 1970). In isolated perfused hindlimbs, the shift of the dose–response curves to the left was much less marked than in the renal vascular bed, which is another indication for the complexity of vascular regulation.

These findings of early changes of vascular response in several types of experimental hypertension draw attention to the significance of vasoconstrictor mechanisms in the developmental phase of sustained hypertension. It may be presumed that under these experimental conditions a rise in cardiac output is of no importance at all for the development of high blood pressure.

The autoregulatory hypothesis

The autoregulation of cardiac output and peripheral resistance as the two haemodynamic variables which control blood pressure is the pivotal mechanism connecting these two parameters with each other. However, little is known of how an increase in cardiac output is eventually converted into an increase in total peripheral resistance, which may be responsible for a return of the elevated cardiac output to normal. A rise in cardiac output, which is the consequence of hyperpyrexia caused by the infusion of a fluid load and by a reduced renal mass, is haemodynamically not comparable with an elevated cardiac output subsequent to sympathetic stimulation. With the exception of the initial phases of experimental renal hypertension of the one-kidney, one-clip type and of mineralocorticoid hypertension, the various
forms of experimental or clinical hypertension are not associated with an increase in the intravascular volume to a degree which could explain the rise in blood pressure. In most cases of chronic experimental and clinical hypertension, the intravascular volume is even slightly reduced, which, in advanced stages of hypertension, may be the consequence of a decreased total vascular compliance. Autoregulation within the cardiovascular system is still far from being understood, and its role in the various forms of hypertension remains obscure.

Is high blood pressure a compensatory mechanism?

According to the systems-analysis approach, the important integral system for the control of blood pressure is the 'renal/body-fluid pressure control system' (Guyton, 1977). The urinary volume load and the relationship of arterial blood pressure to urinary volume load are considered the primary determinants of blood pressure. In the long-term control of blood pressure, a central role is ascribed to the kidney, which can only excrete a urinary volume load at a certain pressure. A well-functioning kidney handles an elevated urinary volume load without any need for a rise in pressure. When the renal mass is reduced, the blood pressure has to go up to cope with an increased urinary volume load subsequent to an excessive fluid and salt intake. In the case of the two-kidney, one-clip hypertension, as well as in the chronic stage of spontaneous hypertension, an adequate urine volume at normal fluid intake is achieved at an elevated pressure. At this high pressure, an increased urinary volume load can also be well eliminated (Norman, Enobakhare, deClue, Douglas & Guyton, 1978). Once the pressure threshold for the urinary volume load is shifted to the right, the kidney excretes urine regardless of the amount of fluid administered per day.

In the long-range control of blood pressure, the excretory function of the kidney determines the height of blood pressure. Increase or decrease in blood pressure is a compensatory mechanism to maintain renal function. In other words, an elevation in blood pressure is necessary to maintain volume homeostasis, or else the kidney is able to eliminate an increased intake of fluid and salt only, if the renal perfusion pressure is high; '... the change in arterial pressure will not stop until the pressure reaches that very precise point at which intake and output are equal' (Guyton, 1977).

The primacy of blood pressure regulation

In the systems analysis, the blood pressure is considered the main responsible factor to restore a primarily impaired kidney function. Consequently, the 'servocontrol' function of the kidney can only be maintained at an elevated pressure. Hence, the sequence of events would be that, subsequent to an incomplete excretion of a urinary volume load, the intravascular volume expands and cardiac output rises and induces vasoconstriction by means of an autoregulatory process. Total peripheral resistance increases, which causes the elevation of blood pressure necessary for the kidney to handle the sodium and fluid load. However, in view of the wide range of short-term variations of blood pressure, one wonders whether the blood pressure would be a suitable means for the control of renal function and how volume can be kept constant during marked changes in pressure. Teleologically, the maintenance of extra- and intra-cellular volume is too important a homeostatic mechanism to be left primarily regulated by blood pressure.

If, on the other hand, the stimulation of vasopressor systems and the vasoconstriction induced by neurogenic and humoral factors are considered to be mainly responsible for the regulation of blood pressure, most observations can be explained. Primary vasoconstriction causes an increase in total peripheral resistance and, subsequently, a rise in arterial pressure. The latter would induce pressure diuresis, but since the renal vascular bed is also constricted, fluid and salt loss are prevented. If pressure diuresis occurs, the intravascular volume will be reduced, which leads to a further stimulation of the vasopressor systems (Fig. 5). In stroke-prone, spontaneously hypertensive rats, fluid and salt balance is maintained for a long period, but may eventually fail, with the consequence of a negative sodium balance and a reduction in intravascular volume. In rats with two-kidney, one-clip renal hypertension, such a failure of volume regulation may occur within about 2 weeks, if the contralateral kidney is unable to retain enough sodium and water and an acute sodium-loss syndrome develops. In such a case, substitution of the volume by offering a 1% sodium chloride solution for drinking may be of benefit (Möhring, Möhring, Haack, Lazar, Oster, Schömig & Gross, 1975).

The vasopressor concept is based on the assumption that the intact kidney is protected against pressure diuresis, and that by such a mechanism the body-fluid volume is protected
against changes in blood pressure. In contrast to the hypothesis that volume is regulated by an increase in blood pressure, it is postulated that the maintenance of volume, which is of primary importance for the control of homeostasis, is independent of the height of blood pressure.

In conclusion, the volume and the vasopressor concepts differ with respect to the function that is ascribed to the role of the blood pressure in the maintenance of homeostasis. According to the volume concept, the blood pressure has to rise in order to restore an impaired renal function, which is considered the primary cause of sustained hypertension. The vasopressor concept attributes the increase in blood pressure to the increase in peripheral resistance, caused by the stimulation of one or several pressor systems (catecholamines, the renin–angiotensin system, perhaps vasopressin). The intrarenal vasoconstriction, which in general is more pronounced than that in other vascular beds, prevents or reduces the pressure-induced diuresis. In this way, the vasopressor concept includes the important role of the kidney in the regulation of blood pressure. Examples can be given for a more dominant role of either volume or vasopressor effect, and there are also 'intermediate' forms. The aim of these introductory remarks has been to present an alternative hypothesis to the volume concept and the systems analysis, which offers further possibilities to our understanding of the mechanisms related to the pathogenesis of hypertension.

**References**


DISCUSSION

Gross: Dr Guyton will now present his views.

Guyton: Such factors as peripheral vasoconstriction and nervous stimulation of the heart play an exceedingly important role in increasing the arterial pressure in most types of hypertension. However, one must distinguish between those mechanisms that raise the blood pressure and those mechanisms that determine the level to which the arterial pressure will rise. When the arterial pressure rises to a value that is too high, pressure diuresis and pressure natriuresis occur. The resultant loss of water and salt then returns the arterial pressure back to that value which will allow exact balance between fluid and salt intake and fluid and salt output through the kidneys. Thus, it is this kidney–volume–pressure mechanism that determines the value at which the pressure will stabilize. And, because this mechanism has infinite gain to make this determination of the stabilized pressure, it is this mechanism which in the long run must be altered if hypertension is to occur.

Gross: Thank you, Dr Guyton, for this slight modification of your earlier views. Is there any comment from the table on what Dr Guyton has just presented?

Korner: I think there is no theoretical exception one can take to the points raised. The general question with the overall approach is whether the model conforms to the actual data. I personally do not believe that there is such a thing as long-term autoregulation, whereby cardiac output is converted, so to speak, into an increase in resistance. I think volume and resistance changes can occur independently, as I hope to show later on. I think I will leave it there for the moment.

Lever: I like the idea after the minor modification, but I ask whether there is not, according to your theory, Dr Guyton, a circumstance in which a primary rise of blood pressure, caused by an agent which did not cause resetting, would be followed by a fall in blood pressure as a result of the pressure natriuresis.

Guyton: I think that there are a lot of data in the literature which actually deal with this. One of those is closure of an arteriovenous fistula that does raise the pressure but does not shift the renal function curve. The resistance stays higher for ever, but the pressure comes quickly back to normal, within 2 or 3 days.
Round Table 1: cardiac output and volume in hypertension

Gross: Is anybody in the audience who has an immediate question or comment to Dr Guyton?

Dietz: I want to ask what the role of sodium is in your concept? Does sodium really change blood pressure only insofar as it affects extracellular fluid volume? Or is there any other possibility for sodium to raise blood pressure?

Postnov: The problem is how the kidney prevents loss of water and salt during hypertension. There are two parts of the mechanism preventing water and salt loss. One is the autoregulation of cortical blood flow, and the other relates to the modification of functional variables of the renal medulla. The initial concentrating effect (single effect) in the countercurrent multiplier of the renal medulla is reduced in hypertension (this effect is achieved mainly by the ascending part of Henle's loop). Our group found (1972–1974) that in practically all types of chronic hypertension there is a selective depression of the Na + K-dependent-ATPase activity in this part of the nephron. This suggests that in spite of the high speed of multiplication in the countercurrent multiplier system, induced by the elevated systemic blood pressure (medullary blood flow is not autoregulated), the net effect on medullary excretory mechanism remains almost unchanged.

Guyton: We have some experiments which provide an answer to Dr Dietz’s question. In this experiment, Dr Norman in our laboratory changed the amount of exchangeable sodium in dogs by using haemodialysis, sodium chloride infusion, and other procedures. We found that, as long as we did not let the volume increase but only increased the sodium itself, we achieved a plasma concentration up to 172–173 mmol of sodium/l; there was very little rise in pressure. But when we then allowed the animals to drink water to go with the sodium, the pressure then rose very rapidly to hypertensive values within 2 or 3 days. So we believe that sodium works almost entirely through changes in volume.

Gross: May I just come in here with a short question. What about sodium distribution? Do you not think that an increased intracellular sodium concentration, I mean the shift from the extracellular compartment, might have anything to do with the vascular response and cause supersensitivity to pressor agents?

Guyton: I am not sure whether sodium has much to do with vascular response, but I am quite sure the redistribution between cells and extracellular space has a lot to do with the amount of sodium in the extracellular fluid. In experiments that Dr Young and Dr Lohmeier have done in our laboratory recently, quite a shift of sodium out of the cells occurred, when aldosterone was given, but what such changes do to resistance is very difficult to say.

Gross: I think the sodium story is a good link with what Dr Lever intends to say, and I will ask Dr Lever to present his paper.

(Note by Editor: The next paper (Davies et al.) presents work representing the substance of the verbal communication by Dr Lever.)