Role of cardiac output, volume and resistance factors in the pathogenesis of hypertension

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There has been much speculation about the role of cardiac output in the pathogenesis of hypertension since the discovery of Widimsky and colleagues that cardiac output tended to be high in young hypertensive patients (Widimsky, Fejfarová & Fejfar, 1957). Subsequently, Borst & Borst de Geus (1963) and Ledingham and colleagues (Ledingham & Cohen, 1964; Ledingham & Pelling, 1967) suggested that the rise in vascular resistance might be due to autoregulation of tissue blood flow that was inappropriately high in relation to tissue metabolic needs. As originally formulated and recently restated by Coleman, Cowley & Guyton (1974), this theory postulates that early in the development of hypertension the rise in blood pressure is entirely mediated through a rise in cardiac output and triggers a myogenic response in the resistance vessels. This produces a gradual ‘autoregulatory’ rise in total peripheral resistance (TPR) which leads to the restoration of cardiac output. Eventually the elevated blood pressure is maintained entirely through raised TPR. This important theory provides a ‘mechanistic’ explanation how an increase in body fluid volume early in hypertension might become transformed into a TPR-mediated rise in blood pressure. The process has been termed long-term autoregulation, which thus has a quite different time course from the short-term ‘whole-body’ autoregulation, which takes less than 1 h to bring tissue blood flow into harmony with the tissues’ metabolic requirements.

However, there are many studies which do not conform to the postulates of the autoregulation theory (see Korner & Fletcher, 1977). One notable example is the original study of Ledingham & Pelling (1967) in one-kidney hypertension in the rat, where the initial rise in arterial pressure was entirely due to a rise in TPR. The latter remained the major cause of the hypertension through the 4 weeks of the study. Cardiac output in the clipped rats did not exceed the volumes observed in sham-operated animals until more than 6 days after application of the clip. Moreover, the subsequent difference of about 10% in the cardiac output between the two groups remained constant for the duration of the study. The last point is contrary to the prediction of the autoregulation theory, which calls for a gradual restoration of cardiac output.

There has also been lack of agreement with the postulates of the autoregulation theory in two recent studies on steroid hypertension, in both of which a rise in cardiac output was the predominant initial haemodynamic factor in the elevation of the blood pressure (Bravo, Tarazi &...
Dustan, 1977; Shulkes, Coghlan, Denton, Fan, Robinson & Scoggins, 1974). In the study of Bravo et al. (1977) the high cardiac output was sustained for 8 weeks in five of 11 dogs without any compensatory rise in TPR and in only three of 11 dogs there was a haemodynamic pattern consistent with the autoregulation theory. Similarly, sustained elevation of cardiac output unrelated to TPR changes is a common pattern in the ACTH-induced hypertension in the sheep (B. A. Scoggins, personal communication).

Two studies performed in our laboratory suggest that although a phase of high cardiac output sometimes occurs during the development of hypertension, it is not an essential requirement. In one study serial changes in blood pressure, cardiac output (Doppler flow meter) and TPR were measured in rabbits (i) before and during slowly developing hypertension after bilateral cellophan wrapping, and (ii) before and after sham-operation (Fletcher, Korner, Angus & Oliver, 1976). Control observations were performed on 2 separate days. Then the animals were anaesthetized and bilateral renal cellophan wrapping or sham-operation (renal exposure) were performed alternately. The cardiac output responses over the first week were the same in each group with output increasing by about 10% ($P < 0.05$). This suggests that the rise was a non-specific consequence of the preceding operative procedure and played no role in the subsequent changes in blood pressure. Moreover, a rise in cardiac output was not observed in every animal, in either wrapped or sham-operated groups, and its occurrence or otherwise made no difference to the subsequent elevation in blood pressure and TPR. After the first week cardiac output fell gradually in the renal-wrapped rabbits, reaching a value of 75% of control by day 32, compared with a value of 95% at that time in sham-operated rabbits. The difference was partly, but not entirely, accounted for by the differences in body-weight responses between the two groups and when cardiac output was expressed per kg/body weight the differences were still significant though smaller (Fletcher et al., 1976). Throughout the 32 days of the study arterial pressure and TPR were each significantly higher in the renal-wrapped animals than in the sham-operated rabbits. This type of hypertension was thus TPR-mediated from the earliest stages. The rise in TPR increased with time but this was again independent of the early cardiac output changes (Fletcher et al., 1976). Conceptually this experimental model resembles one-kidney hypertension, with the main difference from uninephrectomized one-kidney models due to the fact that the renal mass is greater, so there is a more gradual increase in blood pressure.

We have also studied much more acute development of one-kidney renal hypertension in conscious dogs (Korner, Anderson, Johnston, Angus & Fletcher, 1978). At a preliminary operation an electromagnetic flow probe was inserted around the aortic root; one kidney was removed and an inflatable cuff placed around the renal artery of the remaining kidney. Catheters were placed in the renal artery distal to the cuff and in the aorta (Anderson, Johnston & Korner, 1979). The animals had been trained to lie quietly on a padded table. After 2 days of control observations the renal artery cuff was inflated with saline over a period of 30 s to lower distal renal artery pressure to either 60, 40 or 20 mmHg and cuff inflation was then maintained constant. The narrowing of the renal artery was increased by further infating the cuff every morning and afternoon over the next 3 days to lower renal artery pressure again to the specified value in each dog.

With increasing renal artery stenosis there were graded progressive increases with blood pressure over the next 3 days which correlated closely with the increased plasma renin activity (PRA) and arterial angiotensin II concentration (Korner et al., 1978). Increases in systemic blood pressure and PRA were related to the severity of stenosis. Distal renal artery pressure remained below control over the 3 day period. Plasma volume increased in all groups ($P < 0.05$) with the rises varying from 8 to 21% of control before stenosis. Rises in plasma volume were not progressive with time (Korner et al., 1978). At no time was there any significant increase in cardiac output in any group, although there was considerable individual variation in responses, with cardiac output either rising or falling slightly in the different animals. During the 3 days of renal artery stenosis the variance of the cardiac output measurements within animals was significantly greater than in another sham-stenosis group of dogs, which were taken to the laboratory and subjected to identical procedures except that the renal artery was not constricted (Korner et al., 1978). In these experiments progressive renal artery stenosis produced a hypertension that was entirely mediated through a rise in TPR. The progressive nature of the renal artery stenosis in this experiment ensured that the rise in systemic pressure did not fully compensate by 'pressure diuresis' for the renal artery stenosis, permitting maintained elevation of plasma volume. The
expected tendency for cardiac output to rise owing to increase in blood volume in this model has become masked by the systemic vasoconstriction due to the presence of a considerable amount of constrictor factors, evidenced from the progressive experimental hypertensicity (Korner et al., 1978). Possibly in the absence of the rise in blood volume cardiac output might actually have been reduced, owing to the presence of this constrictor agent, as has been observed recently during the induction of renal artery stenosis in severely salt-depleted dogs (Stephens, Davis, Freeman, De Forrest & Early, 1979).

We have recently completed a study for assessing the role of dietary sodium intake on the hemodynamic changes in established renal hypertension (P. I. Korner, J. R. Oliver & M. Fahim, unpublished work). Rabbits were subject to renal-wrap hypertension (five with wrap of one kidney and other kidney removed; five with bilateral wrap) or corresponding 'sham'-operation (five with exposure of one kidney and other removed; five with bilateral renal exposure). Six weeks after operation, when a stable increase in blood pressure had been established for 3–4 weeks in the renal-wrapped rabbits, the animals were maintained for 2 weeks on low sodium (average urinary excretion 0–5 mmol/day), for 2 weeks on normal sodium (5–5 mmol/day) and for 2 weeks on high sodium (37 mmol/day). To eliminate bias the order of giving the diets was according to a Latin square experimental design for each set of three renal-wrapped and three sham-operated rabbits. Both the hypertensive subgroups showed similar responses to the different diets, as did the two sham-operated subgroups. On the low sodium diet the mean arterial pressure of the hypertensive animals was on average 12 mmHg lower than when they were on normal and high salt diet ($P < 0.01$). This was entirely due to reduction in cardiac output, which averaged 604 ml/min on the low salt diet ($P$ for difference between other two diets = 0.05); cardiac output on normal salt diet was 705 ml/min, not significantly different from 737 ml/min with the animals on high salt diet. There was no difference in TPR, which averaged 21–4, 20–5 and 21–2 units on low, normal and high salt diets respectively. In the sham-operated rabbits dietary salt intake had no significant effect on mean arterial pressure, cardiac output or TPR. On the low, normal and high salt diets these variables were: (i) mean arterial pressure, 87, 90, 89 mmHg; (ii) cardiac output, 592, 636, 574 ml/min; (iii) TPR, 15–3, 15–5, 16–3 units. It is of interest that in the hypertensive animals cardiac output was 'normalized' by the low salt diet. In general, the findings suggest that once hypertension has been established an increase in 'volume' factors acts independently of 'resistance' factors and produces alterations in cardiac output without corresponding changes in resistance. Over the period of 2 weeks each on the normal and high salt regimens, some elevation in TPR might have been expected compared with the low salt value, if 'long-term' autoregulation had occurred.

In conclusion, a phase of high cardiac output does not appear to be an essential step in the evolution of many types of experimental hypertension. In severe acutely induced renal artery stenosis the early rise in blood pressure is entirely due to a rise in angiotensin II, which accounts for the entire TPR response early in hypertension. The eventual maintenance of elevated TPR may involve constrictor factors of as yet unknown origin. In the cellophan-wrap models elevation in TPR is more gradual and the constrictor factors are less clearly related to the renin–angiotensin system. In both instances the rise in TPR and the rise in blood pressure can occur in the absence of early elevation of cardiac output. Alterations in 'volume' factors in established hypertension produce sustained increases in cardiac output independently of the TPR changes. Although the nature of the resistance factors in many types of hypertension remains unknown the occurrence of long-term autoregulation as postulated by the autoregulation theory does not appear an adequate mechanism to explain these changes.

References


DISCUSSION

Gross: Thank you very much, Dr Lever and Dr Korner. Dr Davis will have some additional comments on Dr Korner's presentation.

Davis: First of all, I should like to say that I agree with Dr Korner on the role of cardiac output in hypertension. Some of you will recall that, a year ago, at the meeting in Paris, we presented observations which were very similar to the results now reported by Dr Korner. We originally began our studies without measuring cardiac output, but obviously this is the critical variable, so the present work focuses on cardiac output. We examined the possible role of cardiac output in whole-body autoregulation in a group of unilaterally nephrectomized dogs, which were sodium-depleted. In this situation, there is never volume expansion, so if hypertension develops, this should occur in the absence of an increase in cardiac output. Sodium intake was very low; then there was a marked increase in sodium excretion secondary to a diuretic, and this was followed by renal artery constriction. The question considered under the experimental conditions was: what happens to cardiovascular haemodynamics? After 2 days, which is the first time we measured arterial pressure, we found it elevated. We expected to see no change or an increase in cardiac output, but actually cardiac output fell for the first 4 days. Blood pressure became truly chronically elevated over the 28 days, and there was a slow gradual rise in cardiac output back to the control volume. During all of this time, total peripheral resistance was elevated and accounted fully for the increase in arterial pressure. Further analysis of these changes in haemodynamics revealed that it is decreased heart rate that was primarily responsible for the decrease in cardiac output. Now you might say: so what? You have really not challenged the peripheral arterioles nor given them a chance to regulate automatically, because body fluid volume was so reduced. We reasoned that the next thing that should be done was to challenge the peripheral arterioles and give the arterioles a real chance to autoregulate. We did this in the last part of the study. At this time, sodium intake was initially low and body fluid volume contracted. The sodium intake was then increased from 3 to 60 mmol/day. After sodium and volume repletion had occurred, we began our haemodynamic studies. Cardiac output increased back to the control volume, plasma renin activity fell to normal again. Much to our surprise, there was no change in arterial pressure. So what we observed here was that, under conditions in which the peripheral arterioles were challenged, they dilated rather than constricted. So to summarize, we found no evidence for whole-body autoregulation during sodium depletion; instead, the cardiac output fell. With sodium and volume repletion, cardiac output increased to normal, but autoregulation failed to occur.

Frohlich: Our studies probably agree with Dr Korner's concerning the implications of long-term autoregulation; our studies also agree with the concepts of Dr Gross and Dr Guyton. When one talks about increased vascular resistance and increased cardiac output, one must also look at a third segment of the circulation, which, I think, has been minimized in this discussion of the haemodynamics of systemic arterial hypertension, namely...
the veins and venoconstrictor tone. In our studies in man, with Dr Messerli and Dr de Carvalho, and those of Dr Julius, Dr Safar and others, increased cardiopulmonary volume was shown at the time that an increased cardiac output occurs. This strongly suggests a redistribution of blood from the periphery to the central circulation, which is produced by venoconstriction. These findings are compatible with Guyton’s concept of either an expanded volume or a reduced relationship of intravascular volume and vascular capacitance (the venous portion of the circulation). They are also supported by other current studies in our laboratory by Dr Trippods, Dr Yamamoto and Dr Ishise, who have shown, in the spontaneously hypertensive rat and in the two-kidney, one-clip Goldblatt rat, a normal intravascular volume, but increased mean circulatory filling pressures in these conscious rats. These findings give further support, I think, to the Guytonian idea that there need not be an expanded intravascular volume, but a diminished capacity of the circulation.

Gross: Dr Guyton, would you like to make a comment, especially on Dr Korner’s point?

Guyton: I understand quite well the results that Dr Korner has presented, and I also recognize that they do not prove that autoregulation occurs in his particular experiments during the onset of the type of hypertension that he produced. However, I would also like to suggest that the experiments do not disprove the phenomenon of autoregulation either. The reason for this is that the wrapped kidney is a ‘dirty’ preparation and gives results that are extremely difficult to interpret. A large number of different events take place after the kidneys are wrapped. These include transient periods of renin secretion, periods of renal ischaemia and presumably therefore sodium retention, compression of the kidney so that the blood flow might be compromised, and very often even diminished excretory capacity of the kidneys. With so many different variables, all changing in unknown ways, it is almost impossible to interpret the results. From the point of view of the autoregulation mechanism, let us consider only two of the different variables. In our laboratory, we have attempted to separate the effects of volume loading on arterial pressure from the effects of vasoconstrictor agents on arterial pressure. When we perform experiments in which we think that we have achieved pure volume-loading hypertension, we always get a sequence of events that begins with an increase in cardiac output and elevation of the arterial pressure and is then followed by return of the cardiac output almost all the way to normal, and the total peripheral resistance increases secondarily. It is this secondary decrease in cardiac output and secondary increase in total peripheral resistance that we ascribe to the autoregulation phenomenon. On the other hand, when we create what we would consider to be a pure vasoconstrictor type of hypertension, caused by infusion of angiotensin at a relatively high and constant rate for a period of several weeks, we find that the initial events are an almost immediate rise in arterial pressure but a decrease in cardiac output. In this case, there is no need for autoregulation, because peripheral vasoconstriction has already occurred and the cardiac output is too low, if anything, to supply adequate nutrition to the tissues. Therefore, in these experiments, autoregulation does not occur. Now, returning to the wrapped kidney preparation, there is no way that I know that one can tell which of the two mechanisms is prevailing. Therefore, I am not at all surprised at the results that Dr Korner has reported. However, I can see no way in which this type of experiment could be used to disprove the idea that autoregulation can cause the total peripheral resistance to rise in those types of hypertension that are elicited primarily by volume loading with an initial onset of increased cardiac output.

Gross: I see we come nearer to each other, but I am afraid that, in spontaneous diseases of men, there are more ‘dirty’ than clean preparations.

Korner: I do not exactly know how you define ‘dirty preparation’ in this kind of context, but let me say something in defence of it. It really has been quite a clean preparation on our hands, and one of the best criteria I believe is that the plasma renin concentrations and the renin responses to different types of dietary salt intake are exactly the same as those of normal animals. Kidney weight and renal blood flow are also uniform. These are really sensitive indicators of uniformity of renal function in this kind of model The second point I want to make, again in defence of the preparation, is that, with different dietary salt, the rabbit’s responses are almost identical with those observed in the conscious dog by Dr Davis. What I really believe is that the important point at issue is the problem of confounding several factors simultaneously in many of the experimental designs for studying different hypertension models. This has given rise to...
the notion that volume or cardiac output factors become converted into resistance changes. The only way that you can really find out whether these two factors are independent is in the type of experimental studies that we have just performed and that Dr Davis has reported. This involves establishing a steady-state level of resistance before testing whether or not volume and cardiac output are independent factors. That they are is suggested by our data, by Dr Davis' data, and by the work of others on steroid hypertension; for example, in the study of Bravo et al. and those of the group at the Howard Florey Institute in Melbourne, where hypertension has been maintained for indefinite periods through cardiac output alone.

Gross: Could we compromise by saying, instead of a 'dirty preparation', a 'complex preparation', which is not as ideal as your two 'clean' preparations in which you change mainly one factor?