THE FOURTH VOLHARD LECTURE

Cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension

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Introduction

The history of hypertension research contains many remarkable personalities, but Franz Volhard certainly ranks among the really great. At a time when hypertensive disease mainly evoked feelings of frustrated confusion among clinicians, Volhard and Fahr, in a unique combination of precise clinical observation and penetrating pathological analysis, brought clarity and systematic order by their classic publication of 1914. It serves to illustrate the immense complexity of the problem they ventured to tackle, that enough loose ends were left to keep the members of the International Society of Hypertension intensely busy up to this very day, more than 60 years after that remarkable study was published.

The accomplishment provided a clinical counterpart to Tigerstedt’s and Bergman’s pioneering experimental approach to hypertension in 1898, and set the stage for a rapid development where Volhard for decades dominated the clinical scene by virtue of his creativity and impressive personality. Over the years he contributed to almost every aspect of human hypertension. In particular he emphasized some functional aspects of essential hypertension which are directly related to the present topic.

Volhard was, of course, well aware of the structural changes that afflict the left heart, the systemic arteries and the arterioles in chronic hypertension. He therefore suggested that in essential hypertension, where he recognized the importance of heredity and age, altered elastic properties of the high-pressure vessels could be of great hemodynamic relevance. He particularly emphasized that a reduced arterial distensibility might considerably influence baroreceptor reflex control, decades before this particular consequence of structural cardiovascular adaptation in hypertension was experimentally elucidated. It is therefore appropriate to use this aspect of Volhard’s many contributions to hypertension research as an introduction to the present lecture in honour of his work.

Some historical landmarks

Not only has hypertension research attracted remarkable personalities, it also contains some lines of development which in retrospect appear strange. For example, well before arterial pressure was ever measured in man, structural alterations of the left heart, systemic arteries and arterioles were generally acknowledged thanks to Bright (1836), Johnson (1868), Gull & Sutton (1872), Ewald (1877) and others. Nevertheless, although these structural changes are perhaps the most obvious features characterizing hypertensive disease, almost a century elapsed before their functional consequences were explored and seriously considered in connection with pathogenesis. The reasons for this remarkable hiatus are complex, but evidently they are to a great extent psychological in nature.

It was, for example, widely assumed that structural vascular changes represented a late and largely irreversible complication associated with considerable wall rigidity, and certainly arterioles commonly appear in this way when examined post mortem. This, in turn, reflects the difficulties in quantifying morphological microvascular changes because of the very variable ratio between wall thickness and internal radius (w/r), secondary to shifts in smooth-muscle activity and wall distension. This left investigators without any fixed ‘reference point’ for their estimations, implying that
only really massive, more or less degenerative, microvascular changes could be safely identified. As will be further dealt with below, nearly a century elapsed before it was technically possible to provide such a fixed point needed for precise morphometric analyses of resistance vessels.

It was, on the other hand, noted quite early that resistance vessels readily dilated in hypertensive subjects. As this obviously harmonized poorly with prevailing opinions about 'sclerosing' structural arteriolar changes, it seemed even more natural to consider these latter as a late result of a longlasting functional disturbance. The possibility that, e.g., arteriolar medial hypertrophy might be so rapid in onset as to largely parallel the pressure elevation, and then allow for further accentuated functional adjustments, was commonly overlooked. This is hardly surprising as at that time no biophysical analyses of vessel behaviour were available to illuminate the issue, even though parallel concepts concerning what, for example, skeletal muscular hypertrophy implies for functional achievement, might have generated ideas in this direction.

It was generally accepted that only a raised vascular smooth muscle activity could explain the chronically elevated resistance and arterial pressure in hypertension. When later, Goldblatt's classical studies were published (Goldblatt, Lynch, Hanzal & Summerville, 1934) they had an enormous impact because of their indisputable evidence, simplicity and elegance, but also because they fulfilled long expectations, present even before the days of Tigerstedt & Bergman (1898). In fact, ideas about an accentuated vascular smooth-muscle tone in hypertensive disease can be traced more than 200 years back in time, to the young Berlin professor Samuel Schaarschmidt, who died almost exactly two centuries before Volhard, in 1747, when only 38 years old (Backer, 1953). This remarkable young professor had evidently a clear grasp of what we now call essential, or primary, hypertension, which he denoted 'spastic constriction of the arteries' in his posthumously published writings, thus anticipating acknowledged cardiovascular pathophysiology by at least a century. He also anticipated treatment, then by two centuries, by prescribing nitrates, venesection, sedatives and the elimination of mental 'stress'; thus embracing several modern therapeutic principles for hypertension: dilate resistance vessels, damp cardiac output, and reduce sympathetic drive. Schaarschmidt therefore knew that blood vessels in these hypertensive patients could dilate readily, and it is natural that he assumed that a 'spastic constriction' of the arterial vessels must be the key to the disturbance. This was barely a century after William Harvey by one masterstroke transferred the cardiovascular system from superstition into reality, and just a decade after Stephen Hales first measured arterial pressure in his famous mare. It is certainly a remarkable example of brilliant scientific intuition. Thus, Goldblatt’s most convincing experiments, coming at the appropriate psychological moment, led to such an enthusiastic search for mechanisms accentuating vascular smooth-muscle activity, such as might explain the elevated resistance in established primary hypertension, that little room was left for alternatives.

Yet, there were ideas and observations in other directions as will be illustrated by a few examples, though the authors had difficulties in reaching the final decisive steps and thus in evoking sufficient interest to be more widely considered. Thus, another countryman of Volhard, Ewald (1877) presented some most interesting ideas in a paper where he confirmed George Johnson’s histological demonstration of arteriolar medial hypertrophy. He suggested that initial pressure elevation might induce widespread autoregulatory constriction of systemic arterioles (compare these hypotheses with current concepts of ‘whole body autoregulation’) and, subsequently, generalized medial hypertrophy. This, he observed, should not hinder either vasocostriction or dilatation, and he was evidently on the verge of considering the raised resistance in hypertension as causally dependent on the altered design of arterioles. He did, however, not venture this final step in decisive terms, which is hardly surprising since vascular biophysics was still a virgin field with Poiseuille’s introduction of basic hydrodynamic laws just a few decades old.

During the nineteen thirties, largely coinciding with Goldblatt’s animal experiments, several investigators attempted to estimate directly regional resistance to flow in human hypertension (Pickering, 1936; Prinzmetal & Wilson, 1936; Stead & Kunkel, 1940; Wilkins & Eichna, 1941). They tried to produce vasodilatation by the influence of ordinary vasodilator metabolites although, to judge from the flow figures, they only rarely achieved complete relaxation in either hypertensive subjects or controls. However, it was noted that resistance remained proportionally raised in most of the hypertensive subjects compared with similarly treated controls. Pickering (1936), also showed that the raised resistance in the resting equilibrium of established hypertension could not be ascribed to accentuated sympathetic activity, and seriously
discussed whether structural vascular changes might, indeed, be responsible.

However, the concept of an entirely functional background to the elevated resistance evidently dominated current thinking to such an extent that the findings mentioned above were generally deemed to reflect the presence of a humoral pressor agent, so potent as to overcome even massive concentrations of vasodilator metabolites. The fact that this would call for a most peculiar substance, which must be capable of producing the same percentage shortening of arteriolar smooth muscles, whether they were in their usual humoral environment or exposed to maximal concentrations of competing vasodilator influences, was apparently overlooked. However, Pickering was evidently uncomfortable with the current interpretations, because in reviewing these problems in 1950 he wrote: "...for the present impasse in hypertension is probably chiefly due to the fact that certain fundamentally important aspects of vascular behaviour are appreciated by contemporary science either dimly or not at all". Further, he had in some most interesting experiments on rabbits with renal hypertension noted that a non-renal factor dominated the scene after only a few weeks of high pressure, and he strongly suspected the vessels themselves (Pickering, 1945).

Present studies concerning the haemodynamic consequences of structural cardiovascular adaptation

Below will be outlined the ideas and studies performed by the present writer and his co-workers. Without the latter this line of work could never have been accomplished.

Via some purely physiological studies in cats around 1950 I came almost accidentally in contact with problems that seemed to be potentially relevant to the haemodynamics of hypertension. I was, however, particularly aware of the characteristic structural changes in hypertension, simply because this had been the major question put to me during a tough M.D. examination in pathology a few years earlier, and such confrontations with professors are apt to remain vivid in the memory. One line of these cardiovascular studies in cats dealt with the neurohormonal cardiovascular adjustments evoked from the hypothalamic defence area (Eliasson, Folkow, Lindgren & Uvnäs, 1951), which suggested how psychogenic influences might affect the circulation. The other line dealt with mechanisms responsible for the basal tone in resistance vessels, and how this inherent tone was modulated in connection with blood flow auto-regulation (Folkow, 1949). This led on to the question of how such active adjustments interacted with passive vascular distensibility (Folkow, 1952), how they were affected by neurogenic influences (Celander & Folkow, 1953), and the role of vessel design and altered smooth-muscle activity in this interaction (Folkow, 1953; Folkow & Lofving, 1956). Particularly when comparing design as well as function of the ordinary arterial high-pressure and venous low-pressure compartments, the differences in both these aspects must be striking to any observer.

It thus appeared increasingly obvious that factors such as medial thickness in relation to inner radius must, according to Laplace's law and the expected dynamics of smooth muscle adjustments, greatly influence the behaviour of resistance vessels. Since ordinary pathology textbooks stated that arterioles in hypertension exhibit medial hypertrophy, but generally left it at that, it was of interest from a purely haemodynamic point of view to explore how such a strengthened and thickened arteriolar wall might influence resistance control. Simple calculations revealed that an increased w/ri due to smooth-muscle hypertrophy should not only make the wall stronger and less distensible, but also produce exaggerated luminal changes for given shifts in muscle activity and length. The reason is that an increased mass of tissue is now pushed inwards because of the more bulky medial coat, and its contraction is greatly dependent on the outermost muscle layer where all the constrictor neuro-effector junctions are concentrated. In other words, an increased w/ri should accomplish vascular hyperreactivity without necessitating any altered sensitivity or reactivity of the encircling contractile elements, this resulting in accentuated resistance increases for given degrees of active muscle shortening. Moreover, depending on the way the adaptive growth of the wall occurs, this might well also reduce the inner radius proportionally by encroachment, in which case resistance to flow would be elevated even at complete muscle relaxation. There would be no need to associate such a type of structural adaptation with any mural rigidity or sclerosis; on the contrary it would, if anything, widen the potential range of functional adjustments.

In this way, an entirely different resistance vessel is formed as a result of the adaptive changes, setting out from a raised baseline and also
producing exaggerated luminal changes which result in an elevated pressure-resistance equilibrium. So far everything could nevertheless have been beneficial, because a high arterial pressure is from a haemodynamic point not necessarily a disadvantage, but unfortunately both heart and vessels are in almost all species not designed to take an increased pressure load and therefore develop degenerative lesions, as was admirably outlined in Byrom’s Third Volhard lecture (Byrom, 1976). Virtually the only exception to this sad rule is the giraffe who is genetically designed to live with an immense mean arterial pressure (MAP) of some 250 mmHg which he badly needs to supply his modest brain, placed at tree-top level because of his feeding habits. Giraffes show a massive wall thickening in all cardiovascular high-pressure sections, and it would probably be futile to search for any great increases in renin or angiotensin concentrations or in sympathetic discharge to account for this very high pressure and systemic resistance. Evidently their cardiovascular system is built for this greatly elevated pressure equilibrium, and presumably they utilize ordinarily balanced neuro-hormonal control systems to allow for a normal range of modulations around this. Uncomplicated degenerative lesions, as was admirably outlined in Byrom’s Third Volhard lecture (Byrom, 1976). Virtually the only exception to this sad rule is the giraffe who is genetically designed to live with an immense mean arterial pressure (MAP) of some 250 mmHg which he badly needs to supply his modest brain, placed at tree-top level because of his feeding habits. Giraffes show a massive wall thickening in all cardiovascular high-pressure sections, and it would probably be futile to search for any great increases in renin or angiotensin concentrations or in sympathetic discharge to account for this very high pressure and systemic resistance. Evidently their cardiovascular system is built for this greatly elevated pressure equilibrium, and presumably they utilize ordinarily balanced neuro-hormonal control systems to allow for a normal range of modulations around this. Uncomplicated hypertrophy must in general be considered as a normal muscular adaptation to increases in load, though it may for quite special haemodynamic reasons have dangerous consequences for the cardiovascular system as will be outlined below. Further, considering the rapid development of hypertrophy in skeletal muscle when exposed to training and increased load, it would seem likely that the related process in cardiovascular muscles could be established within a fairly short time span.

These ideas and calculations could fortunately quickly be put to the test in man thanks to generous help by Professor Bertil Hood of the Department of Medicine, Göteborg, who had just started an extensive clinical programme for essential hypertension and was able to select suitable untreated cases. Plethysmographic analyses of forearm resistance to flow during rest and at enforced maximal dilatation showed that resistance was in both these situations elevated in the hypertensive subjects, and largely in proportion to their mean pressure increase, when compared with age-matched normotensive controls. Great care was here taken to achieve a complete relaxation of the resistance vessels. Thus, even the structurally determined ‘baseline’ for the resistance vessels was evidently raised in the hypertensive subjects. By contrast there was no comparable change in the ratio between the resistances at rest \( (R_e) \) and at complete smooth muscle relaxation \( (R_{\text{min}}) \), which ratio reflects the average degree of smooth-muscle activity in the resting equilibrium. In sharp distinction to these results in chronic hypertension, an induction of acute hypertension by noradrenaline infusion in normotensive subjects showed, as expected, an increase in the ratio between \( R_e \) and \( R_{\text{min}} \) that was proportional to the acute MAP elevation, while \( R_{\text{min}} \) remained largely unchanged compared with the control state.

This test principle, earlier used in evaluations of the extent of myogenic and superimposed neurogenic vascular tone in animal experiments (Folkow, 1949, Celander & Folkow, 1953), corresponds to that widely used by pharmacologists to compare activity levels in muscle strips by relating active length to resting length (or tension). However, resistance measurements offer the great advantage that the Poiseuille relationship between \( r_1 \) and \( R \) amplifies differences in average smooth muscle length to at least the fourth power. Further, such measurements automatically average the responses of the vast multitude of otherwise poorly accessible microvessels, which together comprise the true resistance section, and the measurements are also necessarily performed at the relevant levels of vascular distending pressure. None of the ingenious studies on isolated vessels in vitro or the various microvascular techniques can offer all these advantages and still deal with precisely that section of the vascular bed which really matters in this context.

Thus, these experimental results in hypertensive man almost precisely coincided with the mentioned computed predictions which were, in turn, largely based on experiences from quantitative physiological cardiovascular studies in animals. However, the largely unchanged \( R_e/R_{\text{min}} \) in chronic hypertension was quite contrary to the widely held, almost axiomatic, view that the elevated resistance should, in established hypertension, be due to an accentuated smooth-muscle tone. Indeed, the results were such that there was simply no room left for such additional functional excitatory influences in the resting equilibrium of these patients with established essential hypertension. On the other hand, the control experiments showed that, once such an accentuation of smooth-muscle activity really was present, it could be easily revealed as an increased \( R_e/R_{\text{min}} \). Had perhaps investigators of primary hypertension been ‘hunting a non-existent ghost’ during all these years by drawing too close parallels with early renal hypertension, and was the presently studied haemo-
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dynamic consequence of an altered vessel design the unknown element anticipated by Pickering in 1950? These results in man, first discussed in a lecture in London 1955, were also presented at a Wellcome symposium on 'Hypotensive Drugs' (Folkow, 1956) and in a final extended form a few years later (Folkow, Grimby & Thulesius, 1958).

In this latter paper it was also pointed out that the structurally based vascular hyperreactivity would tend to create a positive feedback interaction with functional excitatory influences: a given smooth-muscle activation in such altered resistance vessels produces an exaggerated resistance and MAP elevation and thereby furnishes the stimulus for additional structural \( w/r_i \) increase which, in turn, further accentuates the resistance and MAP response, and so on. This would imply that only marginal and perhaps intermittent accentuations of average vascular smooth-muscle tone, and/or frequent cardiac output increases if causing some elevation of average MAP over longer periods (e.g. repeated defence reactions to alerting stimuli), might gradually build up a substantial alteration of \( w/r_i \) in systemic resistance vessels, as shown in Fig. 1. To be really dominant, however, such a chain of events might require a specific predisposition involving either the functional or the structural component. We also discussed (Folkow et al., 1958) whether part of the genetic predisposition to hypertensive disease might be expressed as a modest accentuation of the normal ability of muscle cells to respond to increases in load with hypertrophy (or hyperplasia, particularly in early life). If so, even a normal range of functional excitatory influences on the MAP equilibrium might be enough to initiate the hypertensive process. Such a suggestion is no more remote from realities than the frequent suggestions of genetic alterations of effector sensitivity, noradrenaline turnover, cell-membrane equilibrium, sodium excretion etc. Somewhere within the cardiovascular system and its many control mechanisms the genetic deviations must come to a decisive expression, and any of the mentioned alternatives must fall back on a perhaps quite modest deviation of the design, and hence function, of some enzyme or related macromolecule. In the case of a genetically accentuated structural adaptation this might, for example, imply

![Fig. 1. Principles of the changed relationship between degree of smooth-muscle shortening and resulting increase of systemic flow resistance, when media hypertrophy increases wall thickness (w) in association with a reduction of inner radius (r_i) in the precapillary resistance section, as a local response to an increased average pressure load ('structural autoregulation'). Resistance curve N represents a normotensive precapillary resistance vessel, with \( w/r_i \) around 0-2 at complete relaxation; curve H a fully 'structurally autoregulated' vessel in established hypertension, with \( r_i \) reduced 6-7% and w increased 30-40%. Note how the 'triggering' elevation in pressure load, caused by a slight increase in average smooth-muscle tone (and/or in cardiac output at unchanged resistance) needs to be only marginal, because of positive feedback interaction between this functional excitatory influence and the 'structural autoregulation', both reinforcing each other with respect to the pressor effects, with a gradual transfer towards steeper and steeper resistance curves as the extent of structural adaptation grows.](image-url)
a facilitation of some key enzymatic link in the underlying biochemical processes within the muscle cells themselves. Alternatively, some extrinsic trophic influence on cardiovascular muscle via hormones or/and transmitters, might be genetically so altered as to facilitate the structural adaptation (Folkow, Hallback, Lundgren, Sivertsson & Weiss, 1972; Folkow, 1975, 1976). It is in line with such suggestions that later comparisons concerning the extent of structural adaptation in hereditary (spontaneously hypertensive, SH) and non-hereditary (renal; RH) hypertension in rats, indicate that somewhat more pronounced changes occur in SH rats than in RH rats at corresponding MAP levels (Lundgren, Hallback, Weiss & Folkow, 1974).

These initial results in man aroused quite modest interest, at least at first, and the intense search for mechanisms thought to explain the assumed increase in smooth-muscle tone seemed to continue largely undisturbed. However, in a thorough study some years later on a larger number of hypertensive subjects Conway (1963) arrived at the same results and conclusions, as did Sivertsson (1970) who studied the hand vascular bed. Sivertsson also explored the regional resistance responses to intrarterial noradrenaline infusions over a wide concentration range. The hypertensive subjects showed pronounced vascular hyperreactivity with much steeper constrictor accentuations, while smooth-muscle sensitivity to noradrenaline was hardly altered, to judge from largely unchanged noradrenaline ‘threshold’ concentrations compared with controls. Supersensitivity alone should rather have produced a parallel shift of the constrictor curve towards the left. Further strong support comes from analyses in vitro on strips of small arteries, taken during surgery from hypertensive and normotensive subjects (Horwitz, Clinesmith, Van Buren & Ommaya, 1974; Thulesius & Gjöres, 1975). This technique eliminates the geometric influence of an increased \( w/r_p \), while possible changes in smooth-muscle sensitivity or reactivity that are bound to the effector cells in terms of alterations in membrane equilibrium, in receptor characteristics, etc., should still be present. The strips from subjects with primary hypertension displayed a normal sensitivity to noradrenaline and a normal contractile strength per unit transverse section area. Thus, like the haemodynamic analyses, these results on vessels from hypertensive man strongly suggest that the dominant alteration behind the elevated resistance in established primary hypertension is of a structural nature.

Moreover, it had at this time become possible to perform precise morphometric analyses of hypertensive resistance vessels in man, thanks to ingenious techniques developed by Short (1958) and Furuyama (1962), and their data agreed very closely with the observed haemodynamic alterations described above. Thus, a considerable reduction in the structurally set \( r_I \) was noted by Short (1958); and for a given \( r_I \), the muscle coat was found to be thickened in close parallel to the MAP elevation throughout the precapillary vascular section, though tapering off towards the finest precapillary arborizations (Furuyama, 1962).

From these studies in man sufficient mutually supporting results seemed to be available to permit a tentative integration of the structural component into a wider framework, by taking into account the obviously multifactorial background of primary hypertension. Further, they could also form the natural basis for a formulation of some key questions that should be exposed to further quantitative analyses in animal experiments in a way which is impossible in man. For this purpose suitable variants of the several available rat strains with polygenetically transferred primary hypertension could be studied. For details concerning the characteristics of these rat models the reader is referred to a recent survey of the most important findings made by various investigators of these models (Folkow & Hallback, 1977). Each strain seems to have a unique pattern of genetic predisposing elements, illustrating how primary hypertension can, indeed, be initiated in different ways.

To deal with the first aspect, a greatly simplified (and perhaps erroneous) scheme may be formulated as outlined in Fig. 2. It puts the structural (III) component into its presumed relationships with the multifactorial genetic (I) and environmental (II) elements, which both probably exert their main actions via functional mechanisms. I and II may therefore be considered as triggering influences. This scheme emphasizes the close interactions and great mutual dependence of these three key components in primary hypertension, though their balance is likely to vary greatly between individuals in man, and between strains in the pure-bred rats. For example, the impact of II(a) would be greatly facilitated if the predisposing genetic elements are so balanced as to make the individual particularly susceptible to mental alerting stimuli, as seems to be the case for SH rats (cf. Folkow & Hallback, 1977). Likewise, the impact of II(b) would become particularly important if the organism is genetically sensitive to increased salt loads as
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PRIMARY HYPERTENSION

I. POLYGENETICALLY TRANSFERRED PREDISPOSITION, in man of individually varying balance; in hypertensive rat strains uniformized though differing between strains

II. ENVIRONMENTAL FACTORS, influencing and reinforcing I:
   a. Excitatory psychoemotional influences relative importance varies with the balance of I
   b. Increased salt intake

III. SECONDARY ADJUSTMENTS influencing I + II and very early initiated:
   a. Of reinforcing nature (introduction of positive feedback)
   b. Of stabilizing nature (resetting of negative feedbacks)
   c. Of counteracting nature (largely unaffected negative feedbacks)

PRINCIPLE: Chronic hypertensive state initiated and maintained by interactions between I + II + IIIa, b, where the balance differs between individuals but where IIIa, b increasingly dominates, while IIIc tends to counteract the development. Also IIIa, b may well be genetically "reinforced".

FIG. 2. Schematic outline of principal causative elements in primary hypertension and how they might interact, stressing the multifactorial nature of each principal element. With respect to pathogenesis this allows for a range of differently balanced patterns, which in man may vary between individuals and in genetically hypertensive rats between purebred strains.

In this context, access to the hypertensive rat models proved of the greatest value because there was a chance to answer the following questions concerning the structural adaptive changes, which would be most difficult to study in man.

1. With respect to the resistance vessels, have these structural changes important functional consequences for all parallel-coupled systemic circuits, and how are they then distributed along these circuits?

2. What are the key stimuli for this structural vascular adaptation; do they need to be continuous or is an intermittent stimulus sufficient? May there sometimes be a genetic predisposition that accentuates this structural adaptation to the eliciting stimuli?

3. How rapidly can the structural adaptation be established? If quite rapid in onset the changes would actively contribute at the earliest stages of the hypertensive state, the functional and structural aspects proceeding together.

4. Is the structural adaptation readily reversible and, if so, how is this reversibility affected by the duration of the hypertensive state?

5. Since the left heart and systemic arteries also show structural adaptation, how does this affect (a) cardiac performance and (b) the short-term barostat function of the high-pressure and low-pressure (volume) reflex mechanisms initiated by arterial and left cardiac mechanoreceptors?

6. If also the renal vascular bed is afflicted, how does this affect the long-term barostat function of the kidneys?

The word adaptation should here be stressed, because this line of studies deals only with the haemodynamic consequences of the normal ability...
of muscle cells to adjust their size, or/and number to compensate for changes in load. The fact that deterioration and damage occurs later on if cardiovascular tissues can no longer cope with high intraluminal pressure is highly important, as outlined by Byrom (1976), but this represents a later stage where true disease and lesions dominate the high pressure state. With these questions in mind, animal experiments were started about ten years ago and are still going on, using as models mainly SH rats, and to a lesser extent MHS. The main results of these studies will now be discussed in outline only; they have been dealt with in more detail in other surveys (Folkow, Hallbäck, Lundgren, Sivertsson & Weiss, 1972, 1973; Folkow, 1975, 1976) and, particularly, in the quoted experimental studies.

1. Structural resistance vessel adaptation

Concerning the first question, the structural adaptation is evidently generalized to largely all parallel-coupled systemic circuits, as could perhaps be expected. Thus the structurally set $R_{\text{min}}$ for the entire systemic circulation in SH rats is increased largely in proportion to the MAP elevation in established hypertension (Folkow, Hallbäck, Lundgren & Weiss, 1970a), just as was the case with the forearm and hand vascular beds of man. The same holds for the vascular beds of SH rat hindquarters (Folkow, Hallbäck, Lundgren & Weiss, 1970b), and the myocardium (Noresson, Hallbäck & Hjalmarsson, 1977). It is true also for the kidneys (Göthberg, Lundin, Ricksten & Folkow, 1978), if in this latter case only the truly vascular resistance is measured, thus avoiding the disturbing influence of renal tissue pressure.

Furthermore, the resistance responses to vascular agents in established SH rat hypertension were explored over the entire range, from maximal dilatation up to maximal constriction, showing very characteristic and consistent differences of these resistance response curves between SH rats and controls (NC rats). Moreover, they were closely proportional to the MAP difference between SH rats and NC rats, which was of the order of 40–50%. These differences between the experimental resistance curves coincided in detail with the calculated ones for two hypothetical resistance vessels if one of them had an increased medial thickness of

![Hypothetical Resistance Vessels](image)

**Fig. 3.** (a) Average 'resistance curves' for the entire resistance section of the hindquarter vascular bed in spontaneously hypertensive rats (SHR) and normotensive control rats (NCR), based on the results of fifteen paired experiments. (b) Mathematically deduced 'resistance curves' for two hypothetical resistance vessels, H and N, where H differs from N only in the respect that its media thickness is supposed to be increased 30%, encroaching on its lumen even at maximum relaxation. $w/r_i = \text{ratios of wall thickness to internal radius.} (\text{From Folkow et al., 1970b; for details see this paper.})$ Since in reality only the precapillary resistance vessels are altered in SHR (see Fig. 4) a nearly perfect fit to the experimentally obtained curves is obtained if average precapillary $r_i$ at maximal dilatation is reduced by 10% and the precapillary media thickness increased 40% in SHR, thus elevating average $w/r_i$ in the precapillary resistance section by about 50%. At this stage of early established SHR hypertension, SH rats and NC rats usually differ by 40–50% in resting awake mean arterial pressure.
earlier phases of life the extent of the structural changes in SH rats is closely parallel to the lower MAP level at that age, to judge from the resistance curves in 6 week old SH rats and NC rats (Folkow, Hallbäck, Jones & Sutter, 1977b) and the differences in left ventricular weight (Weiss & Lundgren, 1978).

More penetrating experimental analysis showed that these structurally based haemodynamic alterations were confined to the precapillary resistance section (Folkow, Hallbäck, Lundgren, Weiss, Albrecht & Julius, 1974; Folkow et al., 1977b), leaving the postcapillary resistance section largely unchanged as also were the capillaries with respect to surface area and permeability (Rippe & Folkow, 1977). Fig. 4 summarizes these differences between SH and NC rats in the form of pressure drop and resistance profiles at maximal vasodilatation and maximal vasoconstriction in constant flow-perfused hindquarter vascular beds.

In fact, no other type of vascular alteration except a precapillary structural increase, based on medial hypertrophy (or hyperplasia) and \( r_1 \) reduction, can satisfactorily explain the experimental findings (Hallbäck, Göthberg, Lundin, Ricksten & Folkow, 1976). Moreover, there are no signs of waterlogging in arterial walls of SH rats (Jonsson, Lundgren & Wennergren, 1975) and SH rat resistance vessels show a reduced distensibility of such a nature that only a structural increase can explain it (Hallbäck, Lundgren & Weiss, 1974). It results in a non-specific precapillary vascular ‘hyperreactivity’ to both vasoconstrictor and vasodilator agents, which is not seen in the postcapillary section. Further, it seems marked enough to explain fully the raised resting resistance in established SH rat hypertension without any need for altered smooth-muscle sensitivity or accentuated excitatory drive. The presence of such structural changes does, however, by no means exclude a concomitant presence of functional alterations in smooth muscle characteristics, but in that case their presence and functional relevance require to be established as independent entities apart from the effects caused by the structural component. For example, the SH rat resistance vessels appear to exhibit a secondary altered dependence on external calcium which can be distinguished haemodynamically even in the presence of the effects due to the structural alterations (Folkow et al., 1977b).

As the structural changes are mainly confined to the precapillary resistance vessels they can be called structural autoregulation as a morphologically based (and therefore more slowly developed) haemodynamic correlate of the well-known functional autoregulation which precapillary resistance vessels display as a local response to acute pressure elevations (e.g. Folkow & Öberg, 1961). They serve similar haemodynamic purposes in connection with chronic and acute pressure elevations, respectively, by protecting the capillary vessels from undue pressure elevations. Further, both are by nature positive

![Diagram](image-url)
feedback systems, and therefore potentially dangerous if not offset by competent negative feedback mechanisms, among them the baroreceptor reflex modulations. However, in chronic hypertension these reflexes, as well as several other negative feedback mechanisms, show a gradual resetting as outlined in Fig. 2, which is one of the most obvious dangers inherent in the structural cardiovascular changes, as will be further discussed below.

Quite recently these haemodynamic results, which reflect the altered structure of the precapillary vessels, were confirmed in quantitative details in elegant biophysical–morphometric measurements on isolated small arterial vessels (\( r_f \) at complete relaxation and distension around 80–100 \( \mu m \)) from SH rats and normotensive controls (Mulvany, Aalkjaer & Hansen, 1978). The SH rat vessels showed an elevation of maximal contractile strength in close proportion to the MAP elevation and to the directly observed increase in the ratio between tissues, being slightly more extensive in the gastrointestinal tract and kidney than in skeletal muscle and the central nervous system.

Mulvany et al. (1978) also made the interesting observation that the increased muscle bulk in small splanchnic arteries in SH rats is mainly due to hyperplasia, i.e. more muscle cells rather than enlarged ones. Whether this reflects a true genetic deviation in SH rats or simply the quite early development of this type of primary hypertension along with the phase of rapid body growth is not known, but muscle adaptation to increased load often seems to take the form of cellular multiplication early in life. To exemplify from the vascular bed, Bevan (1976) noted in young rabbits an increased mitosis rate in the media of small arteries which had been exposed to an elevated MAP by means of aortic coarctation. From the haemodynamic point of view it hardly matters whether an adaptive medial thickening occurs by hypertrophy or hyperplasia, but the possibility remains that the medial hyperplasia in SH rat arteries may reflect a genetic deviation affecting the cardiovascular effector cells themselves, as discussed above.

2. Main stimulus for structural cardiovascular adaptation

Numerous studies of muscle in general strongly suggest that the main stimulus for hypertrophy is constituted by the local load against which the muscle exerts its tension. Also intermittent increases in load are obviously efficient, at least in skeletal muscle, as exemplified by the effects of physical training. Here the extent of hypertrophy depends on the frequency, duration and average load during the periods of exertion. Physical constitution (i.e. genetics, and hormonal trophic influences) is also of great importance as can be exemplified from the world of modern athletics.

There are a priori good reasons to believe that this should be the case for cardiovascular muscle cells as well, implying that the functional trigger elements do not need to be continuous, if only repeated often enough for a suitable time period. This is most important for the correct evaluation of how cortical-limbic-hypothalamic structures can, via environmental alerting stimuli, act as a trigger influence, by imposing more or less intermittently a substantial excitatory drive on the cardiovascular system via, for example, the neurohormonal defence reaction (Folkow, 1960). This may well enough elevate the average daily load on the system.
to put the interaction outlined in Fig. 1 into operation, even if there are no or little signs of such trigger influences when the subject is in the resting state. A striking example of the efficiency of intermittently applied loads is offered by the veins in dependent body parts. They show an increase in \( w/r_i \), that is largely proportional to the hydrostatically elevated transmural pressure, but this altered design develops first when the upright position becomes habitual (Svejcar, Prerovsky, Linhart & Kruml, 1962). Obviously, however, people spend a considerable part of the day in the reclining position, thus demonstrating that an intermittent application of increased load nevertheless results in an adequate structural adaptation.

Concerning primary hypertension, it was noted that if the SH rat hindquarters were rendered hypotensive by aortic obstruction they rapidly adapted structurally and haemodynamically, within a few weeks showing an enlarged \( r_i \) and a reduced \( w \) (Folkow, Gurévich, Hallbäck, Lundgren & Weiss, 1971). It should be stressed that these hypotensive hindquarter vessels were still exposed to the same neurogenic and hormonal influences as the hypertensive vessels of the forequarters, thus demonstrating beyond doubt that the local transmural pressure is by far the dominant stimulus for adapting wall thickness to internal radius. The structurally set \( r_i \) dimensions appear to be influenced also by tissue nutritional demands, presumably via local chemical influences. This can be exemplified by the adaptation of maximal flow capacity to the degree of skeletal muscle hypertrophy that occurs on physical training. Evidently the structurally set \( w/r_i \) ratio of vessels is closely adjusted to the local wall tension, in turn determined by both the transmural pressure and the tube radius according to Laplace's law, where the elevated pressure dominates in hypertension.

This in no way excludes the possibility that so-called trophic influences, exerted by hormones or nerve transmitters, may come in as important modulating influences, as already mentioned. It thus appears as if the extent of the structural changes in for instance renal hypertension (RH rats), induced in genetically normotensive rats, is somewhat less pronounced than in SH rats for a given MAP level. This may reflect the influence of genetic elements, directly or indirectly facilitating the structural changes in SH rats (Lundgren et al., 1974). Furthermore, a less developed \( w/r_i \) increase in the resistance vessels implies that more of a functional excitatory drive should be needed in RH rats than in SH rats to maintain a given increase in resistance, because the amplifying lever furnished by the structural autoregulation is less pronounced and therefore less efficient. This may also help to explain why the blood pressure elevation in non-genetic renal hypertension seems to be more easily returned to normal than in SH rats when the trigger influence is suddenly removed or pharmacologically counteracted (see below).

3. Rate of structural adaptation

The rate at which cardiac and vascular muscles can adapt their design when exposed to abrupt changes in pressure is in this context of the greatest importance, and for obvious reasons. Only if this process is rapid both in onset and completion, will the structural component become in time intertwined with functional trigger influences and thus from the very start exert its important positive feedback interaction with these excitatory influences, as outlined in Fig. 1. If, on the other hand, the structural adaptation was late in appearance and slow in development, it would rather be a complication of chronic hypertension of slight pathogenetic interest compared with functional elements.

To elucidate this problem, renal hypertension was induced by means of a Goldblatt clamp applied to one of the renal arteries in normotensive rats. This approach has the great advantage for this particular question that the onset of an increased pressure load on the heart and vessels is quite rapid compared with the much more gradual MAP elevation characterizing most variants of primary hypertension. This is obviously necessary if the true rate of structural adaptation is to be revealed. At regular time intervals after renal artery clamping the extent of structural changes in the left heart and systemic resistance vessels was explored. Briefly, despite the fact that the MAP rise took about a week to reach its final level, the structural changes could be seen already after this first week and they were largely completed in 2–3 weeks for both heart and vessels (Fig. 5: Lundgren et al., 1974). Had the pressure elevation been immediate, the relationship between MAP rise and adaptive cardiac and vascular structural change suggests that it would take only 8–10 days for cardiovascular muscle hypertrophy to be nearly complete in rats.

In man, with a much slower metabolic rate than the rat, the process of adaptive hypertrophy is likely to be correspondingly slower, taking perhaps months instead of a few weeks. Skeletal muscle hypertrophy in man can, for example, be quite substantial after a few months of intense physical
Fig. 5. Time course and extent of cardiovascular structural adaptation in normotensive rats made hypertensive by renal artery constriction, with day after artery constriction on the abscissa and, on the ordinate, the ratio between renal hypertensive rats (RH rats) and normotensive control rats (NC rats) concerning (1) mean arterial pressure during awake conditions, (2) left heart ventricular weight/body weight, (3) maximal pressor response reflecting the contraction strength of the media, i.e. its relative thickness, and (4) resistance at maximal dilatation reflecting the structurally determined average internal radius of the resistance vessels. Note that the adaptive structural changes of the left heart ventricle and the systemic resistance vessels are largely completed in RH rats in 2–3 weeks, even though the increased pressure load is not fully established until 7–10 days. The reduced blood pressure ratio at 135 days is due to a slight increase of NC rat blood pressure (From Lundgren et al., 1974).

training. However, such a time course still implies a most rapid process of structural adaptation, compared with the commonly slow onset of human primary hypertension, which suggests that the trigger influences are here quite gradual and perhaps also intermittent in their mode of action. It follows that the structural component can, indeed, be so rapidly established, both in man and in rats when related to the respective time courses of primary hypertension, that it must be in time fully integrated with the functional trigger influences. Therefore, it can already early in the course of primary hypertension exert its important and gradually more efficient positive feedback influence. For example, observations on 18–20 year old military conscripts with modest MAP elevations, evidently in the first early phases of primary hypertension (because MAP levels were above the norm among their parents as well) indicate that structural vascular changes have already started. Thus, compared with controls they showed a $R_{\text{min}}$ elevation in the hand vascular bed that was largely proportional to the modestly raised MAP level (Sannerstedt, Sivertsson & Lundgren, 1976).

It thus appears as if only a marginal and perhaps often intermittent excitatory drive is enough in primary hypertension to produce a gradual but eventually marked resetting upwards of both systemic resistance and MAP. This is accomplished by a positive feedback interaction between functional and structural elements acting from the very start, as outlined in Fig. 1. This also explains why it has been so exceedingly difficult to identify the functional initiating elements in primary hypertension for which people have searched largely in vain for decades, and in this process have often tended to disregard the potential importance of central neurohormonal influences mainly because these are by nature intermittent in action. Anybody doubting this greatly variable engagement of sympathetic activity should study the continuous MAP recordings in man, showing a daily 2:1 range of alteration, which certainly reflects moment-to-moment variations in tonic sympathetic activity (Bevan, Honour & Stott, 1969; Pickering, 1968). Only little extra addition in average load might be needed to initiate the sequence, since the functional excitatory influences can utilize an increasingly efficient amplifying lever, inherent in the gradual arteriolar $w/r_i$ increase, which these functional influences help to build up in the course of the positive feedback interaction. This element of structural autoregulation therefore tends to dominate the scene in primary hypertension almost from the start and, because of the consequences of structural adaptation afflicting also the barostats and the left heart (see below), the structural component in Fig. 2 appears to constitute the key factor in this disturbance.

4 Reversibility of structural cardiovascular adaptation

The degree of reversibility of the precapillary structural autoregulation is of great theoretical and practical interest, since it largely determines the chances for a true reversal of primary hypertension, if the MAP elevation can be pharmacologically suppressed for a sufficient period of time. Again, this problem was studied in RH rats, simply because renal unclipping usually implies such a rapid MAP normalization in rats that the rate of structural regression can be easily followed. The rapid pressure fall in this type of secondary hypertension, where the extent of structural adaptation appears to be less pronounced than in SH rats, seems to be due to the fact that vascular smooth-muscle activity becomes markedly subnormal on the sudden elimination of a dominating
renal pressor influence when the previously ischaemic kidney becomes overperfused after unclipping. This dramatic alteration in the balance of excitatory influences on the activity of arteriolar smooth muscles evidently leads to a suppression of their tonic activity, reflected as a marked lowering of the ratio between $R_e$ and $R_{\text{min}}$, a type of undershoot reaction which is the converse of the overshoot reactions often displayed by cells suddenly released from a prolonged inhibitory influence (Y. Lundgren & M. Hallbäck, unpublished observations).

Whatever the background of the reduced vascular tone and the prompt pressure reduction in unclipped RH rats, the pressure fall is followed by a rapid and largely complete regression of both left ventricular hypertrophy and structural autoregulation, with full correction in 2–3 weeks (Fig. 6; Lundgren, 1974). This was so, however, only if the renal hypertensive state had lasted for not more than a month or two; the longer its duration the more sluggish and the less complete was the regression. It also proved more difficult to induce full regression of the structural changes in SH rats on correction of the high pressure by means of pharmacological treatment (Weiss, 1974), perhaps here in part due to the presence of muscle hyperplasia, according to Mulvany, Aalkjaer & Hansen (1978). It appears reasonable that it would be more difficult to get rid of existing cells than to cause regression in size of hypertrophied ones. By contrast, when instead early preventive treatment of hypertension in SH rats was maintained from weaning up to 8 months of age, the further course of hypertension was much milder, with a very slow pressure rise and with far less harmful effects in the long run, even though all pharmacological treatment had been stopped at 8 months of age (Weiss, 1974). Evidently, such an early period of preventive treatment implies an efficient brake on the positive feedback interaction between neurohormonal (and other) trigger influences in SH rats and the structural component during that period of life when hypertension in SH rats is ordinarily initiated and established.

The less complete regression of structural cardiovascular changes with increasing duration of hypertension probably to a great extent reflects the still slower addition of interstitial supporting material to arterial, arteriolar and cardiac walls, which to a great extent takes the form of collagen formation. Unfortunately such intercellular material shows far less regression than does muscle hypertrophy, even if MAP is kept efficiently lowered (Wolinsky, 1971, 1972). It appears as if both collagen and elastin molecules are synthesized and secreted by vascular smooth muscle when exposed to increased load, and then built into intercellular filaments (Udenfriend, Ooshima, Cardinale, Fuller & Spector, 1976).

This more slow addition of non-contractile supporting elements to the pressure-exposed walls may be regarded as a third line of defence, organized by the smooth-muscle effectors and providing a local support that helps to relieve them from part of the strain. Their first, and immediately available, line of defence for keeping flow and pressure in the all-important capillary section normal in the face of MAP elevations, is the functional autoregulation. The second line of defence, which can take only some weeks (in rats) or months (in man) to establish, is the structural autoregulation, based on muscle hypertrophy, and sometimes also hyperplasia.

From a local point of view all these three adaptive processes are most adequate for the given vessel and circuit, because the situation can thereby be kept almost normal in the capillary section, whatever happens upstream. However, when all systemic precapillary resistance sections are affected in this way it introduces the potentially serious positive feedback interaction outlined earlier,
because the generalized resistance elevation then affects MAP to about the same extent. Particularly unfortunate is the fact that there is far less of return from the third line of defence, and any further progression means outright degeneration with vascular and tissue lesions, as excellently described by Byrom (1976). Because of these circumstances antihypertensive treatment ought to be particularly rewarding if initiated before the structural adaptation of the precapillary resistance vessels has reached, or even surpassed, this third line of defence. Before this the chances for prompt regression ought to be good.

5. Consequences for cardiac and large artery function

The functional consequences of the related structural changes in the left heart and systemic arteries can be summarized as follows.

(a) Concerning left ventricular hypertrophy (and/or hyperplasia, which might contribute in SH rats) it implies a reduced diastolic compliance simply because a thicker wall is inevitably less distensible. In such a ventricle a given filling pressure causes a lower degree of end-diastolic prestretch of the average contractile element, displacing particularly the lower range of the Frank-Starling curve for the SH rat left ventricle to the right of that of the NC rat (Hallböck, Isaksson & Noresson, 1975; Hallböck, 1975). This should come as no surprise because in normotensive hearts also the more thick walled left ventricle always needs a higher end-diastolic pressure (5-8 mmHg) to produce the same stroke volume than does the right one (2-4 mmHg), which is designed for a low-pressure performance.

As a result, stroke volume would tend to be lower in SH rats than in NC rats once left ventricular hypertrophy is established, had there been no compensation in SH rats in the form of an elevated left ventricular filling pressure or/and an accentuated inotropic stimulation. Fig. 7 summarizes this, as studied by means of perfusions in vitro of SH and NC rat left ventricles in a set up designed for quantitative analyses of the Frank-Starling relationships (Noresson, Ricksten, Hallböck-Nordlander & Thorén, 1978). Further, direct measurements of left end-diastolic pressure in intact, awake SH and NC rats show that it is around 10 mmHg in SH rats but only about 5 mmHg in NC rats (Noresson et al., 1978). This in no way implies any relative failure of the clearly strengthened SH rat left ventricle, though an inevitable backward complication follows in the sense that the cardiovascular low-pressure compartment, initially in the venous end of the pulmonary circuit, becomes exposed to an elevated transmural pressure. These consequences of left ventricular hypertrophy may explain the tendency towards a slowly declining stroke volume in hypertension, particularly when an increased accretion of interstitial material further reduces diastolic compliance.

It has, for example, recently been shown that an accentuated neurogenic discharge to the splanchnic capacitance vessels is needed in SH rats to achieve the same stroke volume as in NC rats, reflecting the consequences of the reduced diastolic compliance of the SH rat left ventricle. In contrast, the SH rat resistance vessels display their characteristic vascular hyperreactivity to the vasoconstrictor fibre influence, resulting in greatly accentuated neurogenic resistance responses to given rates of sympathetic activity compared with NC rats (Folkow, Hallböck & Noresson, 1978). This illustrates how the hypertensive animal would greatly profit from a reduced sympathetic discharge to the resistance section in association with an accentuated discharge to the capacitance vessels, but it is highly
doubtful whether the bulbar sympathetic centres are capable of such a differentiated compensation. Instead, if a compensatory increase of activity is called for to adjust the capacitance volume compartment to the less compliant left heart, sympathetic discharge will increase also to the resistance side, still further accentuating the arterial pressure elevation.

The reduced diastolic compliance of the hypertrophied SH rat left heart also explains the clear resetting towards higher pressure levels of the left cardiac stretch (low-pressure or volume) receptors, firing in unmyelinated vagal afferents (Thorén, Ricksten & Noresson, 1978). Thus, the firing of these volume receptors, which exert most important depressor reflexes particularly influencing cardiovascular volume control (for ref. see Thorén, 1978), remains about the same as in NC rats despite a twofold higher filling pressure, reflecting the reduced diastolic compliance.

The same process of structural adaptation constitutes perhaps the most important element behind the resetting of the arterial high-pressure baroreceptors. The thicker wall of large arteries was well known already a century ago which, among other things, reduces the 'Windkessel' function of the conduit arteries, thus contributing to the elevated pulse pressure in hypertension. These changes led Volhard to suggest that the altered elastic properties must be important for reflex cardiovascular control in hypertension. The presence of a definite baroreceptor resetting at the peripheral level was experimentally shown more than 20 years ago by McCubbin, Green & Page (1956). However, it was particularly Aars (1969), by measuring simultaneously the alterations both in aortic nerve discharge and aortic diameter in the course of renal hypertension, who illustrated how the receptor resetting was closely linked to the structurally produced reduction in wall distensibility. This by no means excludes the possibility that other mechanisms can contribute but, considering the obvious structural wall changes, it seems inevitable that they are in established hypertension the major cause of the resetting of the short-term barostats, to use Guyton's terminology (Guyton, Coleman, Cowley, Manning, Norman & Ferguson, 1974).

It is striking, however, that largely all electrophysiological analyses of baroreceptor resetting have dealt with the myelinated afferents, which are greatly outnumbered by the functionally very important unmyelinated afferents (Kirchheim, 1976). The discharge rate of these latter fibres is much lower, but they produce most pronounced reflex effects even at quite low firing rates. A recent electrophysiological study in rabbits with renal hypertension (Jones &Thorén, 1977) has shown that, whereas the unmyelinated afferents in the normal situation fire first at somewhat higher pressures than the myelinated ones (Aars, Myhre & Haswell, 1978), they are less completely reset in the course of hypertension than the myelinated ones (Fig. 8). Consequently, the unmyelinated baroreceptor afferents may in the hypertensive animal exert a relatively more pronounced ‘braking’ influence, as their effective discharge range now tends to be somewhat below the prevailing MAP. If this is true for hypertension in general, this so far neglected though most important group may perhaps constitute one of the negative feedback mechanisms (in Fig. 2: IIIc) which continue to counteract the hypertensive state, simply because they are less completely reset in the process. If so,
they may help to explain why the hypertensive animal, despite the positive feedback effect at the resistance level and the resetting of several barostat mechanisms, does not develop fulminant arterial pressure rises more often.

6. Structural autoregulation and the resetting of the renal long-term barostat function

As also the renal vascular bed ought to be afflicted by structural autoregulation, this process may be of importance for the resetting of the long-term barostat function of the kidneys. According to Guyton et al. (1974), perhaps the most efficient way to achieve this would be by some interference with the glomerular filtration process. A most efficient way to do so would be to elevate the ratio between the pre- and post-capillary resistance, as this even more pronouncedly lowers the effective filtration pressure for a given MAP level (Fig. 9).

In a first series of haemodynamic analyses of the renal vascular bed in SH and NC rats (Folkow, Hallbäck, Lundgren & Weiss, 1971b), haemodynamic evidence was obtained for a structurally based increase of the renal resistance vessels in SH rats, but without differentiating between the pre- and post-glomerular sections. In this first study $R_{\text{min}}$ appeared to be reduced in the SH rat kidneys, in contrast to other circuits. However, a more recent study, taking into account both the pre- and post-glomerular resistances and the artifactual influence of passive autoregulation (via elevations of renal tissue pressure), revealed that the truly vascular resistance in the kidney is moderately higher in adult SH rats than in NC rats (Göthberg et al., 1978). Functionally more important was the finding that the structurally determined pre-/post-glomerular resistance ratio is considerably raised in established SH rat hypertension, but only marginally so in early borderline stages (Folkow, Göthberg, Lundin & Ricksten, 1977a). This is illustrated in Fig. 10 as a rightward, parallel shift of the curve relating arterial perfusion pressure to glomerular filtration rate in the maximally vasodilated, adult SH rat kidney compared with that of the NC rat. This phenomenon can only be explained by a raised pre-/post-glomerular ratio in SH rats whereas the parallel curves suggest that the glomerular filtration capacity is largely unchanged. The calculated rise in preglomerular resistance was, in fact, so pronounced in relation to the modest elevation of total renal vascular resistance that the structurally determined postglomerular resistance in SH rats must be slightly lowered.

The renal preglomerular resistance vessels are here the functional equivalent of other systemic precapillary resistance sections. Both are thus responsible for acute functional autoregulation in the respective tissues, serving to stabilize capillary flow and pressure, and both evidently also display the phenomenon of structural autoregulation in primary hypertension. Thereby the renal long-term barostat function becomes gradually reset to match the MAP elevation, as part of the structural adaptation within cardiovascular high-pressure sections. This may be so also in such variants of primary hypertension where the kidneys are not the site of any genetic predisposing elements, for which SH rats seem to be an example. Once the pre-/postglomerular resistance ratio becomes structurally elevated, the only chance of maintaining a normal glomerular filtration pressure is to keep MAP proportionally elevated, or to constrict the postglomerular resistance vessels, as illustrated in Fig. 9. However, this latter type of adjustment inevitably lowers renal blood supply correspondingly and also raises the filtration fraction, a type of
change which seems to occur in advancing human primary hypertension.

**General summary and conclusions**

Summarizing these quantitative haemodynamic analyses, dealing with the functional consequences of structural cardiovascular adaptation in primary hypertension of man and rats, the following conclusions may be drawn.

1. The same principle of structural adaptation to increased load proves in hypertension to affect greatly the haemodynamic pattern throughout the high pressure cardiovascular sections.
2. These adaptive structural changes are examples of a most appropriate local adjustment of design according to Laplace's law, increasing the muscle bulk (w) in relation to the inner radius (r), which latter becomes structurally somewhat reduced in the precapillary resistance vessels. Predominantly their proximal sections are thus affected according to morphometric analyses. The wall is thereby strengthened and becomes less distensible, while the w/r increase in the precapillary resistance section introduces a vascular hyperreactivity, for a given shortening of the contractile elements. Consequently, an elevated precapillary resistance to flow can be maintained without necessitating any accentuation of smooth-muscle activity. This explains why there is, in fact, no or little sign of any increased smooth-muscle activity in regional vascular beds in established human primary hypertension, and why the search for mechanisms that could explain such an accentuated smooth muscle tone has been largely unsuccessful.

3. If the pressure increase is prompt in onset, the process of structural adaptation is correspondingly surprisingly rapid in both onset and completion, taking a week or two in rats and probably a few months in man. It may therefore become involved from the early stages of primary hypertension, and also in secondary forms of hypertension. Concerning the precapillary resistance vessels the structural w/r increase, structural autoregulation, acts as a gradually more efficient amplifying and strengthening mechanism for the action of functional excitatory influences. Because of a positive feedback interaction between these two, with respect to overall resistance and mean arterial pressure, the functional trigger component needs to be only marginally elevated and may well even be intermittent in action, as usually characterizes for instance central neurohormonal influences. Nevertheless, marked elevations of resistance and pressure can in a relatively short time be established, since the amplifying effect rapidly grows in efficiency as it develops and may soon entirely dominate the haemodynamic pattern.

4. Another long-term effect, in the form of left ventricular-wall hypertrophy with a consequent reduction in diastolic compliance, results in a lower stroke volume and hence reduced cardiac output.
This shifts the Frank-Starling relationship to the right. Such a cardiac change calls for an accentuated constriction (or a structurally reduced capacitance) of the low-pressure filling side which helps to elevate the filling pressure. Compensation might also be accomplished by enhanced inotropism.

5. Another consequence of cardiac, arterial and arteriolar wall thickening is the gradual resetting of most short-term barostat functions, inherent in the cardiac low-pressure (volume) and arterial high-pressure stretch receptors and the associated negative feedback reflexes. Thus these important feedback mechanisms are adjusted to the raised pressure as that of the reflexes, the denotions 'short-term' negative feedback reflexes. Thus these important barostat functions, inherent in the reflexes, may occur as rapidly as that of the reflexes, the denotions 'short-term' and 'long-term' barostat functions are not entirely appropriate.

6. As a consequence, the element of structural cardiovascular adaptation, primarily based on simple muscle hypertrophy, emerges as the real key element behind the quantitative deviation from the norm that primary hypertension seems to represent. However, true disease may soon develop if the positive feedback interaction outlined above is allowed to lead to outright degenerative lesions, as unfortunately occurs in most species (but not in giraffes), since the cardiovascular tissues are not genetically designed to withstand prolonged gross pressure elevations.

7. Considering these potentially deleterious consequences of a normal tissue adaptation to load, because of an inbuilt positive feedback action and a resetting of most negative feedback mechanisms, it is in a way more surprising that the great majority of the population manages to stay normotensive throughout life than the fact that some 20% become with time hypertensive. This fact must reflect the considerable homeostatic resources of the cardiovascular system which evidently has at its disposal powerful negative feedback mechanisms tending to offset the positive feedback, even when pressure becomes chronically raised. Thereby retarding the development of severe hypertension and its adverse consequences. One of the most interesting and important physiological questions is to find out what these 'diehard negative feedbacks' are, and how they manage to stay in operation.

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The Fourth Volhard Lecture


B. Folkow