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Vasoconstriction and Increased Blood Pressure in the Development of Accelerated Vascular Disease*

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Summary. The pathogenesis of acute vascular lesions has been studied in two types of accelerated vascular disease. Firstly, vascular lesions were induced by a short-term (2 h) infusion of angiotensin II. Low doses of angiotensin II caused only a slight increase in blood pressure and non-destructive lesions. High doses caused a significant elevation of blood pressure and destructive vascular lesions. Secondly, in renovascular hypertension, renal vascular disease was induced by the removal of the stenosing clip from the renal artery. Incidence and severity of destructive vascular lesions were correlated with the calculated gradient between the pressure before and beyond the stenosis. Anaesthesia had a protective effect on the development of destructive vascular lesions in both models. Obviously, this effect is not related to a reduction of the systemic pressure, but rather to the suppression of abnormal vascular tone, characterized by focal constriction alternating with overdilation. Vasomotor changes, which cause a local overdilation, may be responsible for destructive vascular lesions even at normal to subnormal blood-pressure values. Destructive vascular lesions occur as a result of the exceeding of a critical wall tension. The necrosis of medial smooth-muscle cells in non-destructive lesions may be explained by an excessive contraction, which "surpasses" the metabolic capacity of the cells.

Key words: Vascular lesions – Vasoconstriction – Critical wall tension – Accelerated hypertension.

* Dedicated to Prof. W. Doerr on the occasion of his 65th birthday

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Introduction

The quantitative assessment of the relationship between the height of blood pressure and hypertensive vascular disease is difficult, since, besides the increase in blood pressure, various other factors may be involved in the pathogenesis of vascular lesions. Controversial opinions have been expressed of the significance of humoral pressor factors in the development of hypertensive vascular disease. The hypothesis that the renin-angiotensin system be involved in the pathogenesis of vascular lesions in malignant hypertension (Brown et al., 1971; Laragh et al., 1972; Gavras et al., 1974; Möhring, 1975) has been challenged by the observation that similar lesions occur when the renin-angiotensin system is suppressed by desoxycorticosterone (DOC) (Gavras et al., 1975; Dietz et al., 1976). However, it has been reported that at the onset of the malignant phase in DOC-hypertension the plasma concentration of vasopressin is markedly elevated (Möhring et al., 1977). Both angiotensin II and vasopressin can induce acute vascular lesions, if given in sufficiently high doses (Byrom, 1937; Giese, 1964; Nemes et al., 1977).

Attempts to determine the role of pressor substances in the pathogenesis of vascular lesions should discriminate between the consequences of direct vasoconstriction and the influence of an increase in blood pressure. To obtain further information about the significance of these factors, we used two different models of accelerated vascular disease: (1) The induction of primary vasoconstriction by the infusion of angiotensin II and (2) the direct mechanical load, imposed on the renal vascular bed by the sudden removal of a stenosis from one renal artery of rats with renovascular hypertension. By such a procedure it should be possible to get information about the significance of humoral and mechanical factors for the incidence and the pattern of hypertensive vascular lesions.

Materials and Methods

Male Sprague-Dawley rats, weighing between 140 and 160 g, were used. A standard pellet chow (ssniff®), containing 100 mEq/kg sodium and 210 mEq/kg potassium, and demineralized water were offered ad lib.

1. Angiotensin Infusion

Under light ether anaesthesia, one iliac artery and both femoral veins were exposed by incision, and a polyethylene catheter was inserted into each of the vessels. The catheters were placed subcutaneously and exteriorized through a dorsal neck incision. For continuous recording of the blood pressure the cannula in the iliac artery was connected to a pressure transducer (Statham Model P 23 Db). The infusion of Val_5-angiotensin II-amide (Hypertensin®, CIBA) was started after 1 h of recovery and was continued for 2 h.

In another series of experiments, the rats were anaesthetized with 50 mg/kg thiobarbital i.p. and s.c., respectively. Prior to the infusion of angiotensin II, 5 ml/kg sodium-Fe^{3+}-gluconate complex (Ferrlecit®, Nattermann) or 500 mg/kg horse ferritin (Serva) were slowly injected i.v.. Afterwards, angiotensin II infusions of 0.1 µg/kg/min or 1.0 µg/kg/min were given by means of a multi-speed infusion pump (Perfusor E, Braun Melsungen). In another group of rats, 10.0 µg/kg/min saralasin (1-Sar, 8-Ala-angiotensin, P 113), either alone or together with 1.0 µg/kg/min angiotenin II, were infused. After the infusion period of 2 h, the rats were decapitated under ether anaesthesia and organs were collected for histological examination.

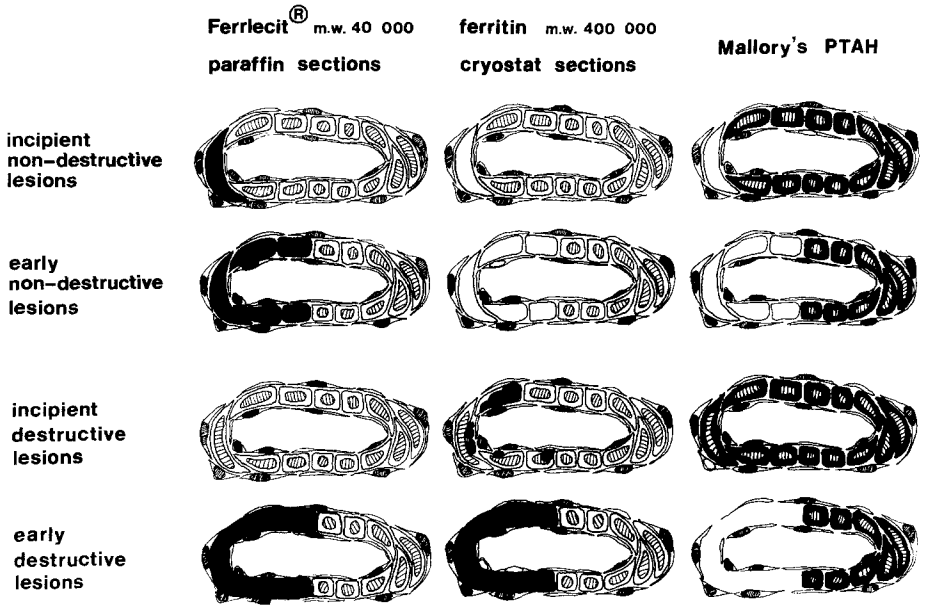


Fig. 1. Schematic drawing of the incipient and early phases of non-destructive and destructive vascular lesions as demonstrated by Ferrlecit-labelling, ferritin tracer, and Mallory's PTAH method, respectively

2. Removal of the Clip from One Renal Artery

Silver clips with a diameter of 0.2 mm were placed on the left or on both renal arteries. Unilateral clamping lasted 2 h, bilateral clamping was carried out for 3 days, 1 week, and 3 weeks, respectively, prior to declamping. The clip was removed from the left renal artery under light ether anaesthesia (Byrom, 1969). Sham-operation was performed by exposing the left renal artery through a lumbar incision. In conscious rats, the blood pressure was continuously recorded through a cannula placed in the iliac artery. Otherwise, the blood pressure was measured by tail plethysmography, under light ether anaesthesia (Byrom and Wilson, 1938). In a further group of hypertensive rats, 3 weeks after the induction of bilateral renal artery stenosis, the systolic blood pressure was reduced to 110 mm Hg by an infusion of sodium nitroprusside. The required level of blood pressure was maintained by continuous adjustment of the dose of sodium nitroprusside (between 0.25 and 1.0 μg/kg/min). Subsequently, the clip was removed under light ether anaesthesia during the infusion of the drug to prevent the sudden exposure of the renal vascular bed to high systemic pressure. Ferrlecit® (5 ml/kg) was injected i.v. just prior to the removal of the clip. Two hours after declamping, the rats were decapitated and organs were collected for histological examination.

Histological Techniques. The vessels of both kidneys, of pancreas, small intestine (duodeno-jejunal region), and mesentery were examined. In former studies (Nemes et al., 1977; Nemes et al., submitted), it was found that the lesions develop most frequently in these vascular beds. Buffered formalin was used for fixation, and cryostat or paraffin sections were prepared. The deposition of Ferrlecit-labelled plasma proteins or of ferritin in the vessel walls was demonstrated by Perl's reaction. Adjacent sections were stained with Mallory's acid-haematoxylin (PTAH) method (Pearse, 1968) to demonstrate the loss of cytoplasmic staining in the necrotic smooth-muscle cells.

Morphological Patterns of Vascular Lesions. In previous studies of acute vascular lesions in experimental hypertension (Nemes et al., 1977; Nemes et al., submitted), non-destructive and destructive vascular lesions were distinguished by means of tracer substances of different molecular weight (Fig. 1). Non-destructive vascular lesions were characterized by: (1) an intact vascular barrier to

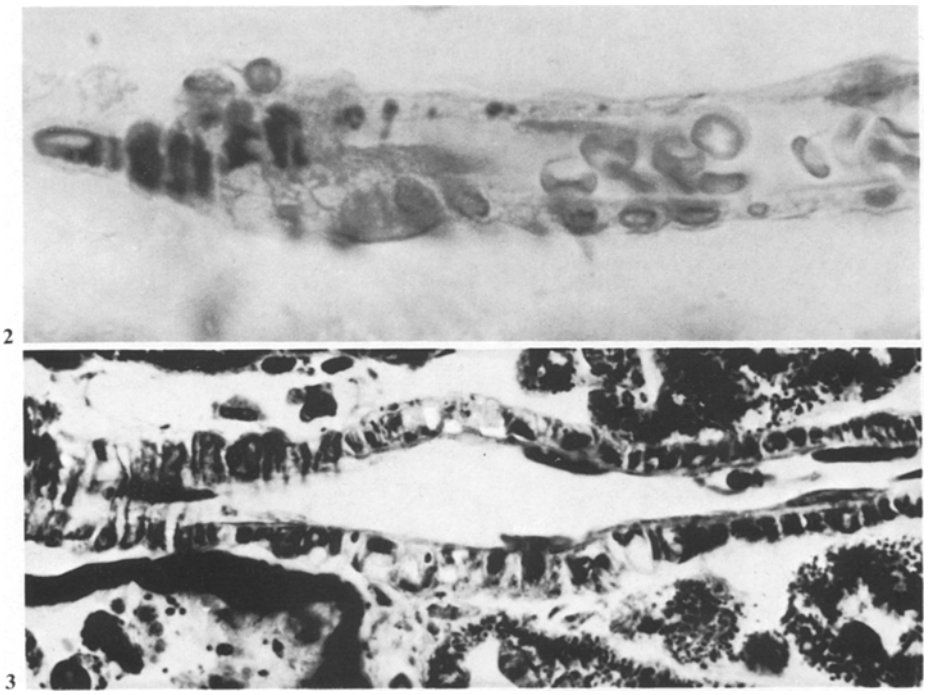


Fig. 2. Non-destructive vascular lesion (early phase) in a pancreatic arteriole of an anaesthetized rat after infusion of 1.0 μg/kg/min angiotensin II for 2 h. Intracytoplasmic deposition of Ferrlecit-labelled plasma proteins in necrotic smooth-muscle cells (left). Perl's reaction. × 800

Fig. 3. Non-destructive vascular lesion (early phase) in a renal arteriole of a conscious rat after infusion of 1.0 μg/kg/min angiotensin II simultaneously with 10.0 μg/kg/min saralasin for 2 h. Smooth-muscle cell necrosis is indicated by the loss of cytoplasmic staining with PTAH, corresponding to the region of focal vasodilation. Mallory's PTAH method. × 800

the macromolecular tracer ferritin (m.w. 400,000) and (2) necrotic smooth-muscle cells in the media, demonstrated by the intracytoplasmic deposition of Ferrlecit (m.w. 40,000). An increased permeability of the plasma membrane is the earliest morphological manifestation of cell injury (Köhler and Geyer, 1978; Geyer et al., 1979). The Ferrlecit-labelled plasma proteins penetrate the plasma membrane of injured smooth-muscle cells, and the subsequent aggregation and precipitation of these proteins in the cytoplasm of necrotic smooth-muscle cells can be visualized by Perl's reaction (Fig. 2). Smooth-muscle cell necrosis is also indicated by the loss of intense cytoplasmic staining with Mallory's PTAH method (Fig. 3).

Destructive vascular lesions were characterized by: (1) a breach of the vascular barrier to the macromolecular tracer ferritin and (2) a concomitant disruption of smooth-muscle cells in the media. The incipient phase of destructive lesions appears transitorily and shows multiple small dissecting aneurysms along still living smooth-muscle cells with ferritin labelling (Figs. 4 and 5). The disruption of smooth-muscle cells subsequent to the formation of dissecting aneurysms causes a confluent intra- and extracellular deposition of ferritin or Ferrlecit-labelled plasma proteins and a loss of detailed cellular structure (Fig. 6).

In the present study, the incidence and pattern of vascular lesions has been determined by Ferrlecit-labelling, which demonstrates all non-destructive lesions and the early phase of destructive lesions. The ferritin method used in the angiotensin II infusion experiments revealed that incipient

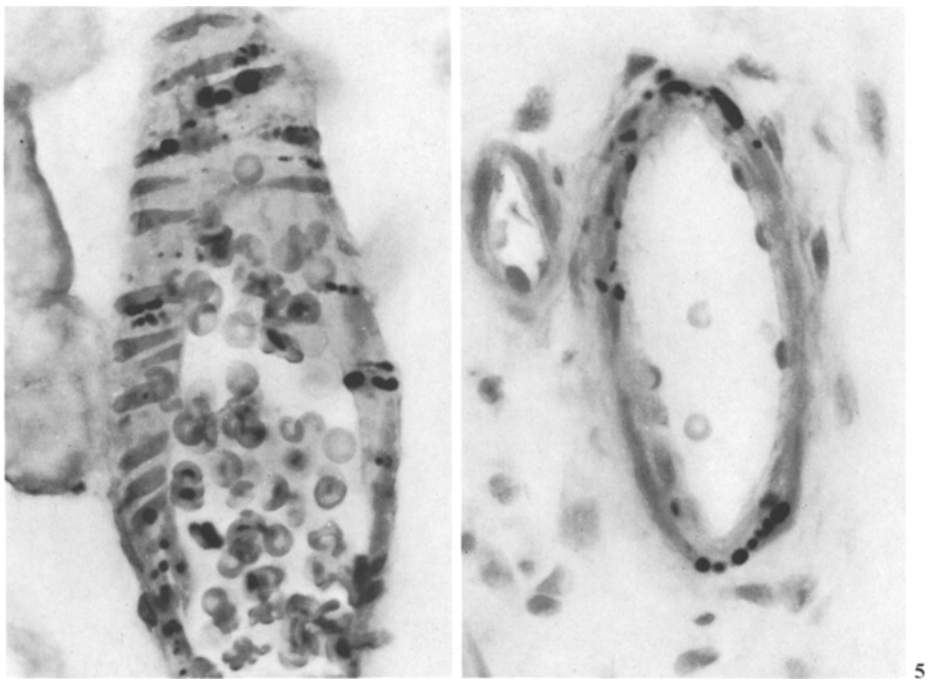


Fig. 4. Incipient destructive vascular lesions in a pancreatic arteriole of a conscious rat after infusion of 1.0 μg/kg/min angiotensin II for 2 h. Ferritin-containing droplets of plasma intruded into the basement membrane compartments of living smooth-muscle cells. The droplets tend to form linear arrays parallel to the long axes of smooth-muscle cells. Ferritin tracer method. Cryostat section. Perl's reaction. × 1,000

Fig. 5. Incipient destructive vascular lesions in a duodenal arteriole of a conscious rat after infusion of 1.0 μg/kg/min angiotensin II for 2 h. Small dissecting aneurysms resulting from the periodical injection of plasma into the ruptured media. Ferritin tracer method. Cryostat section. Perl's reaction. × 1,000

destructive lesions are transient phenomena in the course of destructive lesions and invariably occur together with early destructive lesions. Thus, it is justified to estimate the overall incidence of destructive vascular lesions by Ferrlecit-labelling.

Results

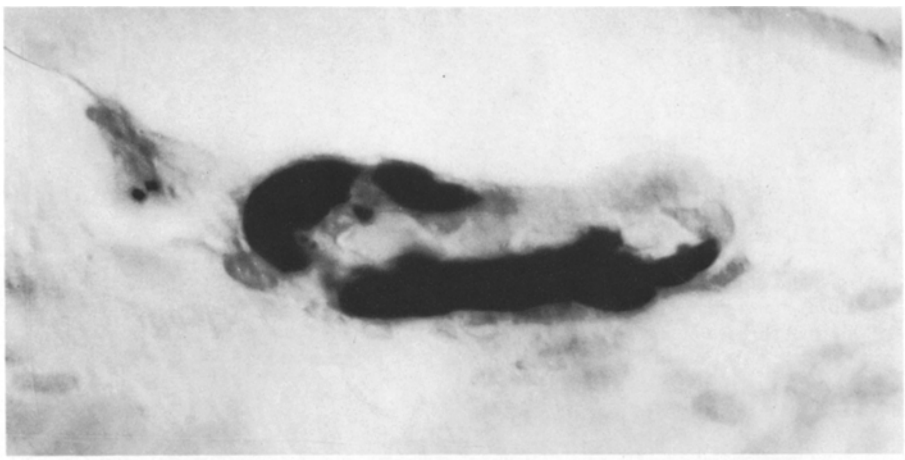
Vascular Lesions Induced by Angiotensin II

In anaesthetized rats, the infusion of 1.0 μg/kg/min angiotensin II caused acute vascular lesions in the pancreas and small intestine, but not in the kidneys (Table 1). The lesions were scarce and non-destructive, showing intracytoplasmic deposition of Ferrlecit-labelled plasma proteins in the necrotic smooth-muscle cells of the media (see Fig. 2).

When the same dose of angiotensin II was infused into conscious rats, the incidence and severity of vascular lesions increased markedly. In addition to

Table 1. Acute vascular disease and blood-pressure response induced by angiotensin II and saralasin

Infusion (2 h)	Anaesthesia		Number of rats showing acute vascular disease in		Elevation of systolic BP (mm Hg)
			kidneys	small intestine and pancreas	
angiotensin II amide 1.0 μg/kg/min	anaesthetized	*n*: 8	0	4	25.0 ± 2.3
	conscious	*n*: 3	3	3	36.0 ± 3.0
angiotensin II amide 0.1 μg/kg/min	conscious	*n*: 4	3	3	10 (0–35)
angiotensin II amide 1.0 μg/kg/min + saralasin 10.0 μg/kg/min	anaesthetized	*n*: 5	0	2	5 (–10–25)
	conscious	*n*: 3	2	1	10 (0–25)
saralasin 10.0 μg/kg/min	conscious	*n*: 4	2	1	1.25 (0–5)



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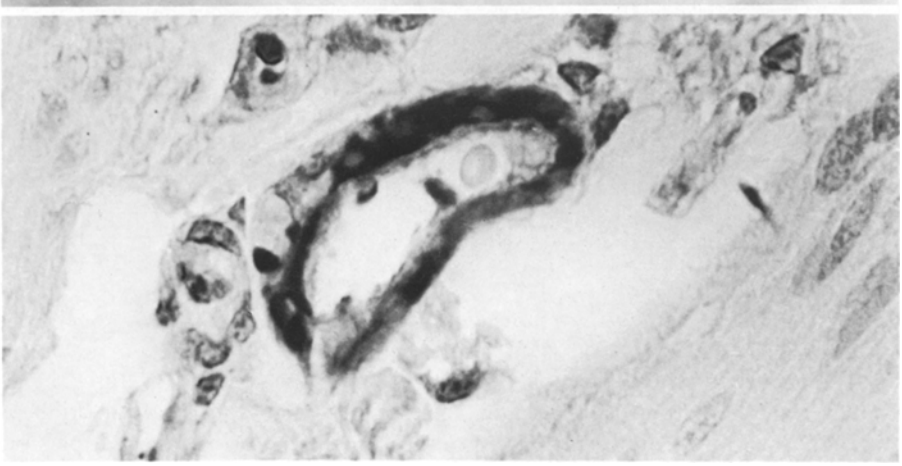

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Fig. 6. Destructive vascular lesion (early phase) in a duodenal arteriole of a conscious rat after infusion of 1.0 μg/kg/min angiotensin II for 2 h. Irregular focal deposition of Ferrlecit-labelled plasma proteins both intra- and extra-cellularly. The outlines of individual smooth-muscle cells are not discernible. Perl's reaction. × 1,200

Fig. 7. Severe destructive vascular lesion (early phase) in a duodenal arteriole of a conscious rat after infusion of 1.0 μg/kg/min angiotensin II. Red blood cells are seen as light spots in the dark media showing confluent deposition of Ferrlecit-labelled plasma proteins. Perl's reaction. × 800

Table 2. Incidence of acute renal vascular disease and blood-pressure response after removal of one clip from the renal artery

Localization and duration of the renal artery stenosis	Elevation of systolic BP prior to declamping (mm Hg)	Operation on the left kidney	Post-operative period (2 h)	Elevation of systolic BP 2 h after declamping (mm Hg)	Number of rats showing acute vascular lesions in the	
					left kidney	right kidney
left side 2 h	25 –40	none	conscious *n*: 2		0	0
left side 2 h	15 –35	declamping	conscious *n*: 2	0	2	1
bilateral 3 days	42.0± 5.1	declamping	conscious *n*: 5	21.7±19.6	2	0
	43.0± 6.0	sham-declamping	conscious *n*: 5	41.0± 5.6	0	0
bilateral 1 week	63.0± 8.8	declamping	conscious *n*: 5	8.0±15.2	3	0
	50 –60	sham-declamping	conscious *n*: 2	–10 –35	0	0
bilateral 3 weeks	127.5± 7.2	declamping	conscious *n*: 9	41.2±11.6	7	2
	82.5± 8.7	declamping	anaesthetized *n*: 9	5.0± 6.5	0	0
	110.0±15.3	sham-declamping	conscious *n*: 8	100.0±20.2	2	1
bilateral 3 weeks+	118.3± 8.9 reduced to 0	declamping	conscious *n*: 3	0	2	1
	84.6± 4.4 reduced to 0	declamping	anaesthetized *n*: 3	0	2	0

the intestinal and pancreatic vessels, the renal vessels were invariably affected. By means of ferritin, incipient destructive vascular lesions were detected as small dissecting aneurysms of the media (Figs. 4 and 5). These lesions were scarce as compared to early destructive vascular lesions which showed confluent intra- and extracellular tracer deposition in the media (Figs. 6 and 7). Non-destructive lesions were only occasionally observed.

In conscious rats, the infusion of 0.1 μg/kg/min angiotensin II produced less severe vascular lesions, but with a localization similar to that observed with the higher dose. Most lesions were of the non-destructive type, except for one rat which had destructive lesions in the kidneys.

Saralasin, when given simultaneously with angiotensin II, did not prevent vascular lesions, though it suppressed the elevation of blood pressure. In both anaesthetized and conscious rats, the lesions were of the non-destructive type. Saralasin alone also induced non-destructive lesions, similar to those caused by the simultaneous infusion of angiotensin II and saralasin.

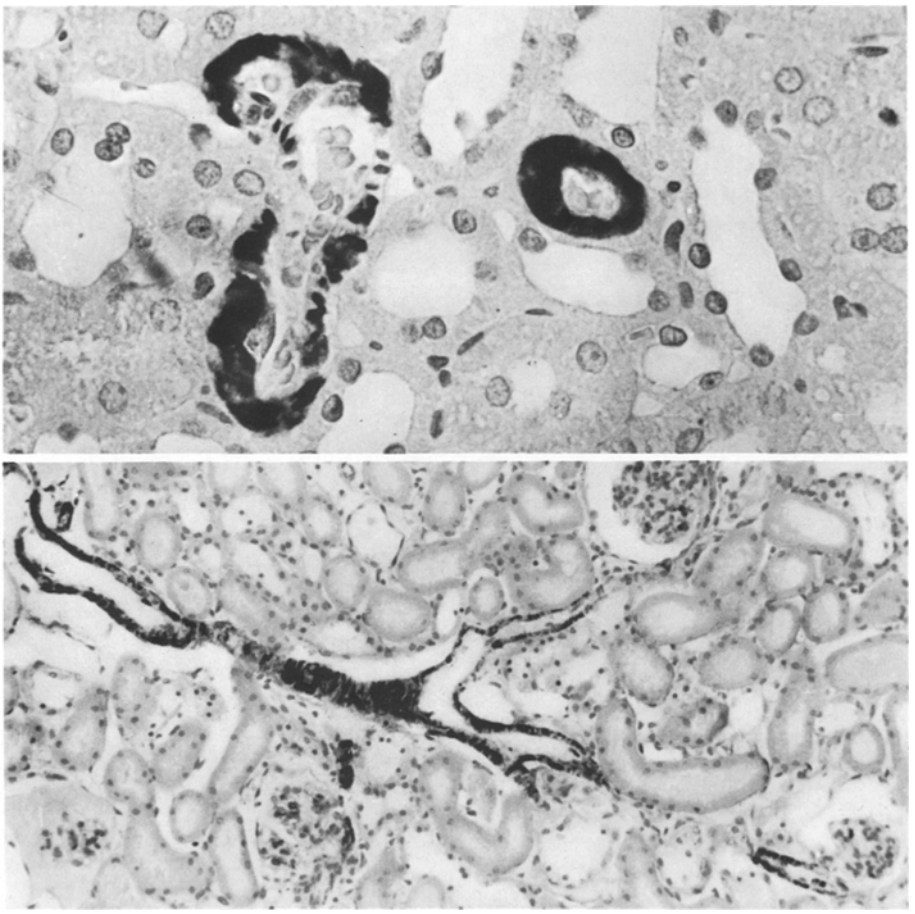

Fig. 8. Hypertension 3 weeks after induction of bilateral renal artery stenosis. Severe renal vascular disease in the kidney 2 h after the removal of the stenosing clip from the renal artery. Early destructive vascular lesions showing confluent deposition of Ferrlecit-labelled plasma proteins in the media and loss of cellular detail. Perl's reaction. ×400

Fig. 9. Hypertension 3 weeks after induction of bilateral renal artery stenosis. Widespread vascular damage of the renal arterial tree in the kidney 2 h after removal of the clip from its artery. Early non-destructive lesions are indicated by Ferrlecit-labelled necrotic smooth-muscle cells of the media. The outlines of individual smooth-muscle cells are preserved. Irregular dilation of vessels. Perl's reaction. ×250

Vascular Lesions After Declamping One Renal Artery

Two hours after the clamping of one renal artery, the removal of the clip resulted in severe destructive vascular lesions in the declamped kidneys and, in one case, also in the contralateral kidney (Table 2). When both renal arteries had been clamped for 3 days or for 1 week, the declamping produced less severe lesions in about half of the rats. The lesions were of the destructive type, but did generally not extend to the whole circumference of the vessels.

Three weeks after bilateral renal artery stenosis, the unilateral declamping resulted in severe vascular lesions of the declamped kidney in 7 out of 9 rats, when the rats were awake after declamping (Fig. 8). In 2 rats, lesions occurred also in the contralateral kidney, from which the clip had not been removed. The lesions were disseminated in the arterial tree, and usually the whole circumference of the vessels was involved. Generally, the lesions were of the destructive type, and only occasionally non-destructive lesions were found in the less severely affected parts of the kidney (Fig. 9). No lesions were seen when the declamping had been carried out under thiobarbital anaesthesia.

Sham-declamping 3 days or 1 week after bilateral renal artery stenosis caused no renal vascular damage, but after 3 weeks the same procedure resulted in lesions in 2 out of 8 rats at the site of manipulation. One of these rats had vascular lesions also in the contralateral, untouched kidney.

When, prior to the removal of the clip, the elevated blood pressure was reduced to normal values (110 mm Hg) by the infusion of sodium nitroprusside, severe destructive vascular lesions occurred in the declamped kidney of 2 out of 3 rats. One of these rats had destructive vascular lesions also in the contralateral kidney, the artery of which remained clamped. Whereas thiobarbital anaesthesia prevented the vascular damage both after angiotensin infusion and after declamping, no suppressive effect was observed when the declamping had been carried out during "normotension".

Discussion

In a previous study (Nemes et al., 1977; Nemes et al., submitted), non-destructive and destructive vascular lesions have been distinguished both in experimental hypertension and in accelerated vascular disease. Non-destructive lesions are characterized by focal necrosis of smooth-muscle cells, without destruction of the vessel wall. Destructive lesions, in turn, are initiated by small ruptures of the vessel wall that lead to the formation of multiple small dissecting aneurysms.

In the present study, non-destructive lesions were produced by the infusion of relatively low doses of angiotensin II (0.1 μg/kg/min), which caused only a small rise in blood pressure. Similar results were obtained, when the blood-pressure elevation, caused by a high dose of angiotensin II (1.0 μg/kg/min), was prevented by the simultaneous infusion of the competitive antagonist saralasin. Saralasin, in the dose given, induced only a minimal increase in systemic blood pressure, but produced also some non-destructive vascular lesions, probably as a consequence of its slight vasoconstrictor effect (Sen et al., 1974).

The mechanism responsible for the non-destructive lesions is most likely the vasoconstriction per se. Sustained, excessive contraction appears to be a possible explanation for vascular smooth-muscle cell necrosis and arterial endothelial cell necrosis observed in renal hypertension (Nemes et al., 1977; Nemes et al., submitted). Angiotensin II causes a sustained contraction of arterial endothelial cells (Robertson and Khairallah, 1972) and has also been reported to enhance myocardial contraction. The positive inotropic action of angiotensin II

has been ascribed to the release of catecholamines (Dempsey and Cooper, 1972; Bunag, 1974). Though excessive doses of catecholamines may produce myocardial cell necrosis (Szakacs and Cannon, 1958; Szakacs and Mehlman, 1960; Ferrans et al., 1964), it is doubtful that the amounts necessary for such an effect are released in severe renal hypertension. Nevertheless, it may be assumed that smooth-muscle cells and endothelial cells become necrotic, when sustained, excessive contraction "exceeds their metabolic capacity" (Wiener and Giacomelli, 1973). Sustained vasoconstriction can also result from a local myogenic "autoregulatory" response of the vessel wall to an increase in blood pressure. In such a way, high blood pressure can contribute to the development of non-destructive vascular lesions.

High doses of vasopressor agents, which cause a marked elevation of blood pressure, produce destructive vascular lesions, as have also been observed in the declamping experiments.

The change in the filling pressure of the renal vascular bed after declamping is not known. In the present study, the gradient between the pressure before and beyond the stenosis has not been measured. It is, however, known that, 3 days after the clamping of one renal artery, the pressure beyond the stenosis corresponds to about normal systemic blood-pressure levels (Kramer et al., 1971). Hence, the net increase in the filling pressure after declamping may roughly correspond to the difference between the basic and the hypertensive levels of blood pressure. Alternatively, 2 h after the placing of a clip on one renal artery, the pressure beyond the stenosis is lower than basic pressure. Thus, the gradient between the pressure before and beyond the stenosis may be higher in the case of early declamping (2 h) than after removal of the clip in renal artery stenosis lasting for 3 days or 1 week.

In conscious rats in which the clip was removed, the calculated pressure gradient correlated with the incidence and severity of destructive lesions. The occasional presence of destructive vascular lesions in the untouched kidneys after declamping the other kidney, or in one or both kidneys after sham-declamping, may also be related to a sudden increase in renal intravascular pressure. An acute rise in the pressure beyond the stenosis has been measured following manipulations of the renal hilus (Kramer et al., 1971).

The fact that anaesthesia protects the vessels against destructive lesions, induced either by angiotensin II or by declamping, does not seem to be related to the reduction in blood pressure. The systolic pressure of anaesthetized rats in which one clip was removed 3 weeks after bilateral clamping was higher than that of conscious rats which were declamped only 1 week after the induction of bilateral arterial stenosis (192.5 ± 8.3 mm Hg vs 173.0 ± 8.8 mm Hg), but destructive vascular lesions occurred only in the latter group. Hence, it is more likely that the protection by anaesthesia is related to a preventive effect on the induction of abnormal vascular tone subsequent to a sudden rise in blood pressure (Byrom, 1969). In severely hypertensive rats, Byrom (1954, 1969) demonstrated irregularities in the diameter of arteries: zones of constriction alternating with zones of overdilation. It has been shown, by means of in-vivo vascular labelling, that destructive vascular lesions occur mainly in the dilated segments of arteries and arterioles (Giese, 1964; Thorball and Olsen, 1974).

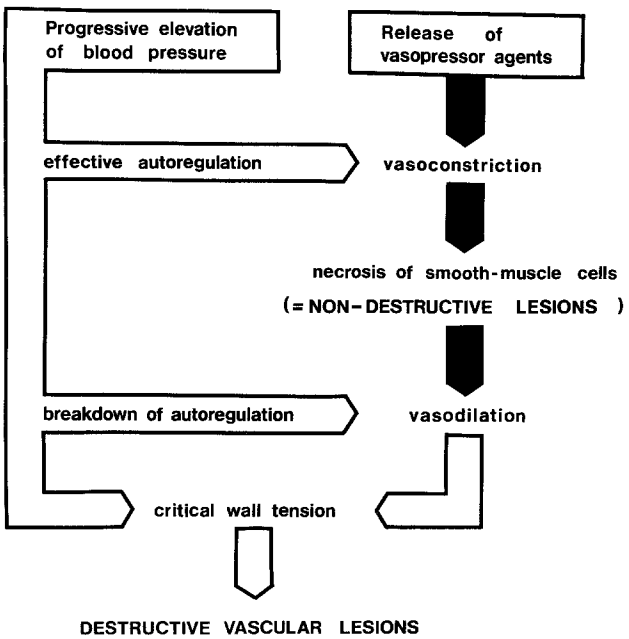

Fig. 10. Two pathways in the pathogenesis of vascular disease: The main pathway leads to the formation of destructive vascular lesions by a high pressure load and an abnormal vascular tone caused by the breakdown of autoregulation. The alternative pathway (indicated by black arrows) is initiated by an increased release of pressor agents that enhance the autoregulatory constriction of resistance vessels beyond the "metabolic capacity" of the cells. The resulting necrosis of smooth-muscle cells (= non-destructive vascular lesions) reduces vascular tone. The resulting passive vasodilation increases the local wall tension. When the wall tension exceeds the critical level, destructive lesions will be superimposed on the non-destructive lesions

Destructive vascular lesions could not be prevented by anaesthesia when, prior to declamping, the blood pressure was lowered to normal values by the infusion of sodium nitroprusside. Since, under these conditions, the removal of the clip from the renal artery could not cause an abnormal rise in intrarenal pressure, intraluminal pressure does not appear to be a decisive factor for the development of destructive lesions. Renal and extrarenal destructive vascular lesions have been found also in normotensive states (Zimmermann et al., 1977), and abnormal vasomotor changes seem to play a major role under these circumstances. On the basis of our findings and of in-vivo vascular labelling experiments (Giese, 1964; Thorball and Olsen, 1974), we presume that a critical wall tension is necessary for the formation of destructive vascular lesions. This hypothesis is also supported by the morphogenesis of vascular lesions (Nemes et al., 1977; Nemes et al., submitted). Multiple ruptures and small dissecting aneurysms in the vessel wall are the consequence of mechanical disruption, which is likely to result from an increased wall tension.

The non-destructive and the destructive vascular lesions represent different stages in the development of acute vascular disease (Nemes et al., 1977; Nemes et al., submitted). Non-destructive lesions occur first. The focal necrosis of smooth-muscle cells in the media leads to a focal reduction of the vascular

tone and a passive dilation of the affected vascular segments (see Fig. 3). Vasodilation corresponds to non-destructive vascular lesions and facilitates the formation of destructive lesions by increasing the wall tension which, according to Laplace's law, is the product of intravascular pressure and the radius of the vessel wall. However, this is only an alternative pathway in the development of destructive vascular lesions, which may also develop in intact vascular segments. The possible mechanisms underlying non-destructive and destructive vascular lesions are summarized in Fig. 10.

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References

Brown, J.J., Fraser, R., Lever, A.F., Robertson, J.I.S.: Hypertension: a review of selected topics. Abstracts of World Medicine **45**, 549–559 and 663–664 (1971)

Bunag, R.D.: Circulatory effects of angiotensin. In: Handbook of experimental pharmacology, Page I.H. and Bumpus F.M. (eds.), pp. 441–454. New York: Springer 1974

Byrom, F.B.: Morbid effects of vasopressin on the organs and vessels of rats. J. Pathol. Bacteriol. **45**, 1–16 (1937)

Byrom, F.B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. Experimental evidence from the hypertensive rat. Lancet **II**, 201–211 (1954)

Byrom, F.B.: The hypertensive vascular crisis. An experimental study. London: Heinemann 1969

Byrom, F.B., Wilson, C.: A plethysmographic method for measuring systolic blood pressure in the intact rat. J. Physiol. **93**, 301–304 (1938)

Dempsey, P.J., Cooper, T.: Pharmacology of the coronary circulation. Ann. Rev. Pharmacol. **12**, 99–110 (1972)

Dietz, R., Haebara, H., Lüth, B., Mast, G., Nemes, Z., Schömig, A., Szokol, M.: Does the renin-angiotensin system contribute to the vascular lesions in renal hypertensive rats? Clin. Sci. Mol. Med. **51**, Suppl. 3, 33–35 (1976)

Ferrans, V.J., Hibbs, R.G., Black, W.C., Weilbacher, D.C.: Isoproterenol-induced myocardial necrosis. A histochemical and electron microscopy study. Am. Heart J. **68**, 71–90 (1964)

Gavras, H., Brunner, H.E., Laragh, J.H.: Renin and aldosterone and the pathogenesis of hypertensive vascular damage. Progr. Cardiovasc. Dis. **17**, 39–49 (1974)

Gavras, H., Brunner, H.R., Laragh, J.H., Vaughan, E.D. Jr., Koss, M., Cote, L.J., Gavras, I.: Malignant hypertension resulting from deoxycorticosterone acetate and salt excess. Role of renin and sodium in vascular changes. Circ. Res. **36**, 300–309 (1975)

Geyer, G., Schmidt, H.P., Biedermann, M.: Horseradish peroxidase as a label of injured cells. Histochem. J. **11**, 337–344 (1979)

Giese, J.: Acute hypertensive vascular disease II. Studies on vascular reaction patterns and permeability changes by means of vital microscopy and colloidal tracer technique. Acta Pathol. Microbiol. Scand. **62**, 497–515 (1964)

Kramer, P., Rumpf, K.W., Ochwadt, B.: Hämodynamische Charakteristika einer experimentellen Nierenarterienstenose bei der Ratte. VIII. Symp. Ges. Nephr. (1971)

Köhler, B., Geyer, G.: A peroxidase exclusion test for cell viability. Acta Histochem. **63**, 261–264 (1978)

Laragh, J.H., Baer, L., Brunner, H.R., Bühler, F.R., Sealey, J.E., Vaughan, E.D.: Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Am. J. Med. **52**, 633–652 (1972)

Möhring, J.: Pathogenesis of malignant hypertension: experimental evidence from the renal hypertensive rat. Clin. Nephrol. **5**, 167–174 (1975)

Möhring, J., Möhring, B., Petri, M., Haack, D.: Vasopressor role of ADH in the pathogenesis of malignant DOC hypertension. Am. J. Physiol. **232**, F 260 (1977)

Nemes, Z., Mann, J.F.E., Dietz, R., Lüth, J.B., Gross, F.: Morphogenesis of early vascular lesions in experimental hypertension. Eur. J. Clin. Invest. **7**, 235 (1977)

Nemes, Z., Mann, J.F.E., Dietz, R., Lüth, J.B., Gross, F.: Morphogenesis of hypertensive vascular lesions (submitted).

Pearse, A.G.E.: Histochemistry. Theoretical and applied. 3rd Edn., Vol. 1, p. 642. London: Churchill 1968

Robertson, A.L., Khairallah, P.A.: Effects of angiotensin II and some analogues on vascular permeability in the rabbit. Circ. Res. **31**, 923–931 (1972)

Sen, S., Smeby, R.R., Bumpus, F.M.: Angiotensin antagonist and possible release of catecholamine. Proc. Soc. Exp. Biol. Med. **147**, 847–849 (1974)

Szakacs, J.E., Cannon, A.: L-norepinephrine myocarditis. Am. J. Clin. Pathol. **30**, 425–434 (1958)

Szakacs, J.E., Mehlman, B.: Pathologic changes induced by l-norepinephrine: Quantitative aspects. Am. J. Cardiol. **5**, 619–627 (1960)

Thorball, N., Olsen, F.: Ultrastructural pathological changes in intestinal submucosal arterioles in angiotensin induced acute hypertension in rats. Acta Pathol. Microbiol. Scand. Sect. A **82**, 703–713 (1974)

Wiener, J., Giacomelli, F.: The cellular pathology of experimental hypertension, VII. Structure and permeability of the mesenteric vasculature in angiotensin induced hypertension. Am. J. Pathol. **72**, 221–240 (1973)

Zimmermann, H.D., Maykemper, B., Dicker, D.: Intra- and extrarenal vascular changes in the acute renal failure of the rat caused by high-dose folic acid injection. Virchows Arch. A Path. Anat. and Histol. **376**, 47–73 (1977)

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