Experimental Production of Poststenotic Dilatation in the Carotid Arteries of Rabbits

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SUMMARY

Arterial dilatation distal to a stenosis has been known as poststenotic dilatation (PSD). This paper describes arterial constriction enough to produce PSD, time course of PSD, structural changes of the dilated segments and influence of hypertension on the development of PSD. These problems were studied in 2 experimental protocols. In protocol I, 87 carotid arteries of 45 rabbits were constricted by silver clip of 0.65 to 2.0 mm in diameter. The arterial diameter was measured at the sites both proximal and distal to the constriction after 3 days to 8 weeks. In protocol II, 22 carotid arteries of 12 rabbits with experimental one-or two-kidney Goldblatt hypertension were constricted and the development of PSD was compared with age matched controls. Remarkable PSD developed in arteries with moderate stenosis of 45 to 60% constriction. The degree of dilatation expressed as ratio of distal to proximal diameter reached about 1.5 at the end of the second week and remained unchanged thereafter. Destruction of the elastic fibers with intimal hyperplasia was observed in the dilated segments even at the early stages of the PSD. Both mild and severe stenosis failed to produce prominent PSD. In protocol II, the PSD averaged 1.18 ± 0.05 (mean ± SE) in hypertensive, and 1.32 ± 0.03 in normotensive animals (p<0.05). The result suggests that chronic hypertension decreases the distensibility of the arteries.

Additional Indexing Words:
Hypertension

ARTERIAL dilatation downstream to a stenosis has been known as poststenotic dilatation (PSD). For this curious and puzzling phenomenon many hypotheses have been proposed such as turbulence of the flow, vibration of the vasculature or increase in lateral pressure. These hypotheses have been partly confirmed by experiments in a rubber or a glass model. Using dogs, Roach11 produced PSD by constricting femoral or carotid arteries and con-

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cluded that PSD developed only if the arteries were constricted enough to produce distal turbulence. In her following study\(^2\) the dilated segments were found to have an increase in distensibility but to have minimal or no structural changes on histological examination.

The present experiments were designed first to produce PSD in carotid arteries of rabbits and second to study the influence of hypertension on the development of PSD. The results revealed quantitative relationship between degree of constriction and development of PSD. The PSD was less prominent in hypertensive than in normotensive animals.

**Methods**

*Production of PSD:* 
Stenosis was produced in 87 carotid arteries of 45 male rabbits weighing 1.8–2.6 Kg. Under sodium pentobarbital (30 mg/Kg i.v.) anesthesia, the carotid artery was exposed and gently dissected free from connective tissue and nerve. The external diameter of the exposed artery was measured by a magnifying-glass and then the artery was constricted by a silver clip of 0.65 mm to 2.0 mm in internal diameter and 3.0 mm in width. The degree of stenosis expressed as percent of proximal diameter was divided into 4 groups from mild to severe stenosis that were 30–35% in 10, 35–45% in 19, 45–60% in 42, and over 60% in 16 arteries. Nonstenotic clips were applied in 14 arteries of 9 animals as controls.

The clipped artery was reexposed under sodium pentobarbital anesthesia after various intervals to measure its diameter at both the proximal and distal segments of the stenosis. The intervals were 3 days in 12, 1 week in 10, 2 weeks in 39, 4 weeks in 8, and 8 weeks in 18 arteries. The degree of dilatation was expressed as a ratio of distal to proximal diameter. After measuring the diameter the animals were killed for the histological examination. Specimens of the carotid arteries were fixed with 10% formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin and elastica Masson’s stain.

*Hypertension and PSD:* 
Twenty-two carotid arteries of 12 chronic hypertensive rabbits were constricted and the PSD was compared with that of 20 carotid arteries of 10 age matched normotensive rabbits. Hypertension was produced by applying a silver clip in the left renal artery with or without contralateral nephrectomy. All these animals weighed 3.0–3.6 Kg and blood pressure measured on the central ear artery by an indirect method just before carotid constriction was 132±11 (SD) and 92±12 mmHg in hypertensive and normotensive animals, respectively. The PSD was produced by constriction of the carotid artery to 35–60% of its original lumen diameter and the animals were killed at the end of the 2nd week. The methods of production of stenosis and measurement of the diameter were the same as described above.
RESULTS

Fig. 1 shows a typical PSD in a rabbit. The PSD was fusiform and the maximum dilatation occurred about 7 mm distal to the stenosis. A turbulent flow was visible through the dilated arterial wall.

As later described, the degree of PSD reached a peak in 2 weeks and remained unchanged thereafter. Fig. 2 shows the relation between degree of stenosis and development of PSD on 79 carotid arteries of 59 animals in which arterial diameter was measured 2 weeks or more after constriction. Marked PSD developed in the arteries with moderate stenosis of 35-45% and 45-60%, and the degree of dilatation was $1.57 \pm 0.11$ (mean $\pm$ SE) and $1.45 \pm 0.05$, respectively. In arteries with severe stenosis over 60%, the degree of dilatation was $1.08 \pm 0.07$ which was less prominent than that of moderate stenosis ($p < 0.001$). Those of controls or mild stenosis less than 35% in diameter failed to develop PSD.

Time course of PSD was studied in 60 arteries with moderate stenosis of 35-45% or 45-60% (Fig. 3). The PSD began to develop within 3 postoperative days, and then the dilatation progressed rapidly. The degree of dilatation increased to $1.56 \pm 0.10$ in 2 weeks. Thereafter it remained almost unchanged up to 8 weeks, the maximum observation time of our experiments.
At the third postoperative day almost all cases developed only slight dilatation, but one artery of 53% stenosis developed marked dilatation to 2.08.

Histological examination showed that in the dilated segments the elastic and collagen fibers of the media were destructed and ruptured and subendothelial hyperplasia was present (Fig. 4).

The degrees of PSD in hypertensive and normotensive animals averaged 1.18±0.22 and 1.32±0.16, respectively (p<0.05, Fig. 5). In hypertensive animals the PSD was less prominent than in normotensives. The thickness of carotid arteries of hypertensive animals was increased both in proximal and distal segments. The increased thickness was due to expansion of the smooth muscle cell layers.
Fig. 4. Histologic section from the poststenotic segment. In this case the degree of stenosis was 51% in diameter and PSD was 1.22 times after 2 weeks' observation time. Elastic and collagen fibers represent marked destruction and mild intimal hyperplasia is observed.

Fig. 5. Effect of hypertension on PSD in rabbits. The constriction of arteries was 36-60% in diameter and duration of stenosis was 2 weeks in all cases. PSD in 22 arteries of hypertensive rabbits is less prominent than that in 20 arteries of normotensive rabbits.
DISCUSSION

Although the mechanisms of PSD are unclear, many hypotheses have been proposed. Holman\(^2\) felt that the high velocity jet of blood issuing from the stenosis was suddenly retarded by the slow moving stream distal to the stenosis, causing a local conversion of kinetic energy into lateral pressure. The local vibration of the vessel wall is also an important factor for developing structural fatigue of the vessels.\(^3\)–\(^5\) Bruns\(^5\) demonstrated that a dilatation could be induced in thin walled rubber tubes distended with water that was artificially vibrated in the absence of flow. But increase of lateral pressure or arterial wall vibration are parts of phenomena occurred in poststenotic area. In vivo, the arterial blood flow is pulsatile and arterial wall response to hydrodynamic changes is not only physical but also physiological. Roach\(^1\) produced PSD with moderate stenosis defined as the presence of a distal thrill or bruit in dog femoral arteries, and concluded that the presence of turbulence was a necessary condition for developing PSD. In other experiments by Fujiwara et al,\(^6\) abrupt reduction of flow was observed in dog thoracic arteries when the stenosis was increased to more than 55% in diameter.

The present study revealed that the moderate stenosis of 35 to 60% was most effective to produce PSD. In those with severe stenosis of more than 60% in diameter, PSD was less prominent and in some cases poststenotic collapse was observed. These result indicate that the development of prominent PSD results from only an optimal stenosis where adequate flow is kept. The turbulence was presumably present in the present study, but different from Roach’s experiments, carotic bruit or thrill were not detected. The degree of PSD in our experiments seemed to be marked compared to Roach’s results, where the maximum dilatation was 1.45 times in diameter. The explanation for these differences between our studies and those of Roach is that we used rabbits and measured the arterial diameter directly by a magnifying-glass, whereas Roach used dogs and measured the diameter roentgenographically.

PSD began to develop in 3 postoperative days and reached a steady state in about 2 weeks. The fact indicates that the physiological and histological vascular responses to the hydrodynamic changes begin extremely early, and vascular wall tension balances to the internal pressure in about 2 weeks. These early responses were also observed by Roach.

By histological examination of the vascular wall taken from patients with pulmonary stenosis, Robicsek et al\(^7\) revealed that the elastic elements of the media were defective in parts and showed extensive areas of increased fragility. This is in disagreement with the work of Roach\(^8\) who said that the elastic and
collagen fibers appeared normal. In the present study we showed pathological
changes chiefly occurred in the elastic fibers of the media. These changes
to the hydrodynamic stress were beyond physiological response, and were re-
results of destruction of the arterial wall architecture. These histological
changes were not progressive, but the arterial wall was balanced to the inter-
pressure by the dilatation.

The distensibility of human arteries decreases with increasing age9) and
hypertension may enhance the aging process. In our experiments, the PSD
in carotid arteries with chronic hypertension was less prominent than age
matched normotensive controls. The results indicate that hypertension de-
creases the arterial wall responsiveness to hydrodynamic changes with struc-
tural changes.

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