Perindopril Changes the Mesenteric Pressure Profile of Conscious Hypertensive and Normotensive Rats

Kent L. Christensen, Michael J. Mulvany

Abstract Information about how antihypertensive therapy affects the arterial blood pressure profile in conscious animals is at present not available. Here we report measurements of part of the pressure profile in conscious spontaneously hypertensive rats (SHR, n = 7) and Wistar-Kyoto (WKY, n = 7) rats before and after treatment with the angiotensin-converting enzyme inhibitor perindopril. The previously developed technique that we used, provided simultaneous measurements of the undisturbed arterial blood pressure at the base of mesenteric arcades (Paw; diameter, approximately 100 μm) and systemic mean blood pressure (MBP). The ratio Paw/MBP was 63 ± 2% (mean ± SEM) in SHR and 64 ± 3% in WKY rats. When a bolus of perindopril (0.8 mg/kg) was injected into the aorta, Paw/MBP fell within 2 minutes to 51 ± 2% (P < .05) for SHR and 56 ± 2% (P < .05) for WKY rats, and these levels were maintained for the next hour. In contrast, MBP did not change for approximately 5 minutes in either strain, whereas after 1 hour MBP still had not changed significantly in WKY rats, but MBP had fallen by 16 ± 2% (P < .05) in SHR. The experiments suggest that in the mesentery (1) the elevated resistance in the arterial system in SHR is present in both macroarteries and veins, (2) for at least 1 hour perindopril caused greater dilation of the macroarteries than the microarteries, and (3) these profound changes in the mesenteric blood pressure profile appear to occur independently of the fall in MBP, indicating that they are not directly associated with the blood pressure drop. (Hypertension. 1994;23:325-328.)

Key Words • angiotensin-converting enzyme inhibition • antihypertensive therapy • blood pressure • rats, inbred SHR • rats, inbred WKY

Although the action of antihypertensive drugs on systemic pressure (eg, mean blood pressure [MBP]) is widely studied, there is little evidence concerning the action of such drugs on the profile of the blood pressure through the vascular system. Current techniques do not allow such measurements to be made in humans, and in animal studies investigations have been prevented because the experimental procedures used could be made only in anesthetized animals. A notable exception is the study of Wiederhelm and Weston, who measured microvascular pressures in the wings of restrained rats, but the effects of drugs were not investigated. Because anesthesia and surgery can seriously affect the pressure profile, we have recently developed a technique that allows measurement of the undisturbed intra-arterial pressure at the base of the mesenteric arcade (Paw) in conscious rats. These arteries have a diameter of approximately 100 μm (N. Korsgaard, personal communication). The results showed that in Wistar rats approximately one third of the resistance of the mesenteric bed lay in macroarteries, ie, arteries proximal to the base of the mesenteric arcades. This has suggested that the peripheral resistance is located not only in the more distal microarterioles but that a significant portion resides in the macroarterioles, as indeed has been suggested in experiments made on anesthetized rats. Therefore, it has been of interest to determine whether the macroarterioles also contribute to the increased peripheral resistance seen in hypertension, as suggested by studies on anesthetized spontaneously hypertensive rats (SHR), and whether antihypertensive treatment acts through effects on the macroarterioles. We therefore have determined Paw in conscious SHR and Wistar-Kyoto (WKY) rats before and after treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril, a drug known to have a potent antihypertensive effect in SHR.

Methods

Animals

SHR and WKY rats were obtained from Mollegaard Breeding Laboratories. Catheters were inserted with rats under general anesthesia using the short-acting barbiturate drug derivative Brietal intraperitoneally (75 mg/kg plus approximately 20 mg/kg per 30 minutes of anesthesia). The surgery lasted 50 to 60 minutes, and after 6 to 7 hours of rest, the rats showed no signs of disease or discomfort. A stable baseline for blood pressure measurements was maintained throughout all subsequent measurements, which were initiated at this time. Because of the novelty of the procedure, the rats were not left overnight to recover but were at all times kept under close observation. Previous experience with Brietal anesthesia and surgery has shown complete recovery of all blood pressure parameters 4 to 5 hours after completion of the surgery. After induction of a second anesthesia, rats were killed by excising the heart. During measurements the rats could move freely and had free access to food and water. To prevent the rats from damaging sutures, the hind claws were cut. None of the rats died or developed signs of disease during the measurements. The experiments were approved by the Danish Com-
Perindopril
0.8 mg/kg

Time after perindopril (min)

![Graph showing effect of perindopril on systemic (Psys) and distal mesenteric arcade (Parc) blood pressures in a spontaneously hypertensive rat.](image-url)

**Fig 1.** Original traces show effect of perindopril on systemic (Psys) and distal mesenteric arcade (Parc) blood pressures in a spontaneously hypertensive rat.

mittee for Research Animals and were consecutive, being performed on one SHR and one WKY rat simultaneously.

**Measurement of Intravascular Pressure at the Base of a Mesenteric Arcade (Parc)**

The method used to measure Parc in conscious rats has been described previously. In brief, rats were anesthetized, the abdomen opened, and after a small proportion of the intestine was exposed, a small catheter was introduced into a first branch off the superior mesenteric artery. Side branches off this main arcade artery down to the base of the arcade were ligated such that the pressure measured at the catheter tip equaled the pressure at the arcade base (Parc). Normal hemodynamics in the unmodified half of this arcade were obtained by suturing circumferentially the wall of the intestine opposite the base of the arcade using 10 to 15 single 7-0 silk sutures, preventing all blood exchange and thus returning Parc to normal. The catheter was secured and extruded through the nape together with an aortic catheter introduced into the femoral artery using a dual-channel liquid swivel (375/D20, Scandidact) that allowed free movement of the rat, including rotation around the swivel axis. After surgery rats were allowed to recover for 6 hours, at which time they showed little discomfort. Heparin (20 IU/mL) was infused continuously at a rate of approximately 10 μL/min (in total, approximately 5 to 6 mL per animal) through the mesenteric catheter and also during all measurements. The rats were unrestrained, had free access to food and water, and were neither handled nor subjected to drugs other than perindopril and heparin. At autopsy, hyperemia was observed in the segment of intestine that was deprived of the direct blood supply, but necrosis was never observed, consistent with our previous observation that removal of the entire vessel segment from one arcade base to the next seldom interferes with the health status of the animals.

**Protocol**

After recovery, MBP and Parc were determined continuously for 30 minutes. After this, perindopril (0.8 mg/kg, Servier) was injected via the aortic catheter, and measurements were performed without handling or in any way disturbing the rats (see trace, Fig 1).

**Statistics**

Data are expressed as mean±SEM. Group means (SHR versus WKY rats) were compared by an unpaired t test (Fig 2). Changes in pressures or ratios (perindopril experiments) were tested using paired Student’s t tests (Fig 4) and a modified least significant differences test (using the spss program), taking into account the fact that multiple comparisons were made between the groups. Probability values of less than .05 were considered significant.

**Results**

For these experiments, seven SHR and seven WKY rats were used, all male and all 14 weeks old. The rats weighed 302±4 and 332±5 g, respectively. In the conscious, resting situation (Fig 2), SHR had 24% higher MBP and 23% higher Parc. However, there was no difference in Parc/MBP, which was 63±2% and 64±3%
FIG 3. Line graphs show time course of change in systemic mean blood pressure (MBP), small mesenteric artery pressure ($P_{arc}$), and $P_{arc}/MBP$ after injection of perindopril in spontaneously hypertensive rats (SHR) (A) and Wistar-Kyoto (WKY) rats (B). Values are group means ± SEM for seven rats of each strain.

In SHR and WKY rats, respectively, indicating that the percentage contribution of macroarteries and microarteries to the resistance of the mesenteric bed is equal in SHR and WKY rats.

Fig 3 shows the time course of the effect of perindopril injection in the SHR and WKY groups; Fig 1 shows typical traces. Fig 4 shows the individual data for measurements at the start and at 2 and 60 minutes after perindopril injection. During the first 2 minutes in SHR, $P_{arc}$ and $P_{arc}/MBP$ fell by 20% and 18%, respectively, whereas in WKY rats $P_{arc}$ and $P_{arc}/MBP$ fell by 6% and 13%, respectively. During the subsequent hour in SHR, MBP and $P_{arc}$ both fell gradually by another 16%, but $P_{arc}/MBP$ remained at the value achieved at 2 minutes; in WKY rats, no significant change in MBP was observed. Thus, in both strains bolus injection of perindopril rapidly reduced the ratio of the resistance of the microvessels (and veins) to the total mesenteric resistance to a level that was maintained for at least 1 hour, this effect being dissociated from the effect of the drug on MBP.

Discussion

The main findings of the present study are, first, that approximately one third of the increased peripheral resistance seen in conscious SHR is located in the macroarteries, at least as regards the mesenteric bed. Second, with acute bolus injection of perindopril in SHR, there is an immediate decrease in the ratio of the resistance of the microarteries to the resistance of the macroarteries, whereas the effect of the drug on MBP takes approximately 1 hour. In WKY rats the pattern was similar even though MBP did not fall significantly.

The finding that approximately one third of the mesenteric resistance resides in the macroarteries in conscious SHR is similar to previous findings in anesthetized animals in exteriorized vascular beds, including the mesenteric bed and other vascular beds. This suggests that anesthesia may not make important changes in the pressure profile and thus in our view strengthens the data previously obtained by others under such conditions. The proportion of resistance in the macroarteries of SHR is similar not only to that seen here in the conscious WKY rats but also to that seen previously by us in conscious Wistar rats. This suggests that approximately one third of the increase in peripheral resistance seen in SHR is located in the macroarteries, at least in the mesenteric bed.

Our finding that acute bolus injection of perindopril caused a drop in $P_{arc}$ of approximately 20% without a change in MBP suggests that perindopril is acting differently on the resistance of the macroarteries and microarteries. This observation corresponds to previous findings in which bolus injection of angiotensin II caused an acute rise in the $P_{arc}/MBP$ ratio of the mesenteric bed of Wistar rats. As we did not measure flow, we cannot determine whether the differential effects of perindopril are due to preferential dilation of the microarteries, to preferential constriction of the macroarteries, or to a combination of these. Given that the MBP did not fall immediately, the last of these alternatives seems the most likely. The suggestion that the angiotensin system is more important in the smallest arteries has been suggested by in vitro experiments.

The comparatively slow drop in blood pressure after bolus injection of perindopril is similar to the finding of
Cachofeiro et al., who observed that an intravenous bolus injection of ramiprilat (2 mg/kg) caused a fall in MBP that took 30 minutes to reach a maximum. The work of Richer et al. shows that 180 minutes after bolus injections of perindopril, the forearm resistance is reduced. Therefore, our finding that after 60 minutes the ratio $P_{ac}/MBP$ was still at the level reached after 2 minutes suggests that even at this stage perindopril is causing a greater dilation of the microarteries than of the macroarteries.

The present experiments do not allow us to determine the mechanism of the observed difference in reaction to ACE inhibition in microarteries and macroarteries. One possibility is that the mechanisms of vasodilatation that ACE inhibitors are known to potentiate through acetylcholine, nitric oxide, or bradykinin may be balanced differently and change in importance and function along the vascular tree.

Extension of the present findings to other vascular beds may be difficult, because chronic treatment with ACE inhibitors such as perindopril is found to reduce organ-related vascular resistances in SHR heterogeneously. In the mesenteric circulation, the reduction in resistance is equal to that in total peripheral resistance; but in 25-week-old SHR previously treated with ACE inhibitors at a young age, kidney resistance was lowered more than total peripheral resistance, whereas the coronary circulation hardly exhibited any reduction in vascular resistance.

In summary, macroarteries (>100 μm) carry a large fraction of the total mesenteric resistance and are responsible for a substantial fraction of the increase in mesenteric resistance seen in the SHR. The contribution of the resistance of the macroarteries increases promptly in response to acute ACE inhibition, even though MBP does not fall. The increased contribution of the macroarteries is maintained even after the hypertensive effect of ACE inhibition on MBP has taken effect. The results are consistent with ACE inhibition causing a greater dilatation of microarteries compared with macroarteries.

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