Acute Hypertension Selectively Potentiates Constrictor Responses of Large Coronary Arteries to Serotonin by Altering Endothelial Function In Vivo

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We tested the hypothesis that acute coronary artery hypertension may damage vascular endothelium and alter vasomotor responses to humoral agents. We examined effects of intracoronary infusion of the endothelium-dependent agent serotonin and two endothelium-independent agents, angiotensin II and methoxamine, on large coronary artery diameter in the blood perfused dog heart. Responses were examined before and 30 minutes after brief periods of coronary hypertension (200 mm Hg for 10 seconds to 15 minutes). In open-chest anesthetized dogs, the left anterior descending coronary artery was perfused at constant pressure. Coronary diameter (D) was measured with piezoelectric crystals. At a control perfusion pressure of 80 mm Hg, serotonin produced dose-dependent constriction of the large coronary artery (mean±SEM; ΔD = —22 ± 10 μm at 5 μg/min; —108 ± 50 μm at 50 μg/min). Increasing perfusion pressure to 200 mm Hg increased flow 515 ± 79% and coronary diameter 509 ± 9 μm. After 15 minutes of hypertension, when coronary diameter had returned to baseline values, the constriction of the large artery to serotonin was potentiated (ΔD = —89±33 μm at 5 μg/min; —207 ± 45 μm at 50 μg/min; p<0.05). Hypertension for 1–5 minutes potentiated constrictor responses of large coronary arteries for at least 2½ hours. Removal of endothelium prevented effects of hypertension on constrictor responses of large arteries to serotonin. Hypertension did not alter constrictor responses to angiotensin II (1 and 2.5 μg/min) or methoxamine (50 and 100 μg/min) or the dilator response to acetylcholine (40 μg/min). Acute hypertension altered endothelial morphology. There were small endothelial craters following 10 seconds of hypertension, and disruption of endothelial junctions with leukocyte adherence following 1–15 minutes of hypertension. We conclude that acute hypertension alters constrictor responses of large coronary arteries to serotonin by impairing endothelial function and not by directly affecting vascular smooth muscle. These effects of acute hypertension on vascular reactivity are selective in that they do not involve non-endothelium-dependent agents or the endothelium-dependent agent, acetylcholine. The effect of hypertension also persists long after pressure is restored to normotensive levels. (Circulation Research 1987;61:904–913)

Since Fuchgott and Zawadzki described endothelium-mediated vasodilation to acetylcholine in isolated vascular rings, endothelium-dependent responses have been demonstrated for many vasoactive substances in every vascular bed studied. The role of endothelium can be demonstrated by comparing vascular responses to a given agonist before and after removal of endothelium by mechanically rubbing the intimal surface or by perfusion with collagenase or hypotonic solution. Few studies have examined effects of pathophysiologic interventions on interactions of endothelium and vascular smooth muscle in the intact circulation.

Morphologic changes in vascular endothelium have been demonstrated following acute hypertension. Endothelial damage ranged from discrete endothelial lesions in pial arterioles and intestinal arterioles to disruption of cellular junctions and increases in vascular permeability in mesenteric vessels and focal areas of endothelial denudation and platelet adherence in mesenteric arterioles. In the cerebral circulation, acute hypertension not only damaged pial artery endothelium but also abolished dilation to acetylcholine and resulted in constriction of pial arteries to acetylcholine.

We have previously examined the role of endothelium on responses of large coronary arteries to vasoconstrictors in the intact circulation. Mechanical removal of endothelium selectively augmented constriction of coronary arteries to serotonin. The present studies were undertaken to test the hypothesis that acute hypertension results in altered vasomotor responses in the coronary circulation that persist beyond the duration of hypertension. We postulated that altered vasomotor responses are mediated by impaired endothelial function after hypertension. To test this hypothesis, coronary artery pressure was raised from 80 mm Hg to 200 mm Hg for brief periods. We examined responses of coronary arteries to two endothelium-dependent agents, serotonin and acetylcholine, and to two...
endothelium-independent agents, methoxamine and angiotensin II. The role of endothelium was tested by examining the effects of acute hypertension on coronary responses following removal of coronary endothelium.

**Materials and Methods**

**General Preparation**

Adult mongrel dogs of either sex (20–30 kg) were anesthetized with sodium Pentothal (25 mg/kg i.v.) and α-chloralose (80 mg/kg i.v.) and mechanically ventilated to maintain blood gases within physiologic ranges (pH 7.35–7.45, Pco2 35–45 mm Hg and Po2 100–125 mm Hg). A left thoracotomy was performed in the fifth intercostal space, the lungs retracted, and the heart suspended in a pericardial cradle. Heart block was produced by an injection of 37% formalin in the atrioventricular node by a modification of the technique described by Steiner and Kovalik, and the heart was paced at 100 beats/min.

Two 1–1.5 cm segments of the left anterior descending coronary artery were isolated. The proximal segment was used to cannulate and perfuse the artery from a pressurized reservoir. The second segment, at least 1 cm distal to the first, was used to measure coronary artery diameter using an ultrasonic dimension gauge. Two femoral arteries and a vein were cannulated for a pressurized reservoir. The blood leaving the reservoir passed through an in-line electromagnetic flow probe, and coronary flow was measured by a flowmeter (model 332, Carolina Medical Electronics, Winston-Salem, N.C.). The flowmeter was calibrated with the dog’s own blood, and mechanical zero flow was checked repeatedly during the experiment. Pressure was measured at the tip of the coronary cannula.

**Coronary Diameter Measurements**

The diameter of the left anterior descending artery was measured continuously with an ultrasonic dimension gauge. Two 7-MHz piezoelectric crystals were attached to opposing sides of a stainless steel clip (8 mm × 5 mm, spring constant 2.72 mN/min) to maintain the crystals in alignment throughout the experiment. A Dacron patch was attached to one side of the clip and 6-0 suture used to secure the device to the adventitial layer of the left anterior descending artery. The opposing crystal rested on the surface of the vessel. We have previously shown that diameter measurements obtained in this fashion are identical to those obtained with crystals sewn to the adventitia of the artery. Crystal alignment was confirmed when phasic diameter tracings paralleled phasic aortic pressure and maximal diameter measurements were obtained. Phasic and mean coronary diameter were monitored continuously by measuring the transit time of the ultrasonic signal between the crystals. Drift of the signal was less than 8 μm over a 7-hour period. Calibration of the sonomicrometer crystals was checked repeatedly throughout the experiment. Accuracy and resolution of the ultrasonic dimension gauge was determined by obtaining calibration curves comparing the sonomicrometer measurement to a mechanical micrometer. The accuracy as estimated by the variance calculation was 2.5 μm without significant bias, and the resolution was at least 10 μm.

**Coronary Perfusion**

After administration of heparin (500 U/kg i.v. followed by 250 U/kg every hour), the left anterior descending artery was cannulated with a stainless steel beveled tube (2.5–3.0 mm diameter) and perfused with blood from a pressurized arterial reservoir. The blood in the reservoir was maintained at 37° C, and the volume was held constant with blood pumped from the femoral artery. The blood leaving the reservoir passed through an in-line electromagnetic flow probe, and coronary flow was measured by a flowmeter (model 332, Carolina Medical Electronics, Winston-Salem, N.C.). The flowmeter was calibrated with the dog’s own blood, and mechanical zero flow was checked repeatedly during the experiment. Pressure was measured at the tip of the coronary cannula.

**Scanning and Transmission Electron Microscopy**

At the end of each experiment, the coronary artery was fixed at 80 mm Hg with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.2. We obtained samples of the artery (1–2 cm long) at the site of the sonomicrometer crystals and a segment of the left circumflex artery. After fixation in glutaraldehyde, a 1 mm section from the center of each vessel was taken for transmission electron microscopy. The intimal surface of the remaining arterial segments was exposed, and samples were mounted on copper tape attached to aluminum studs for scanning electron microscopy. Samples for scanning and transmission electron microscopy were prepared according to standard histologic procedures. A JEOL JSM 35C scanning electron microscope was used to examine the intimal surface of each vessel at 15 kV at a magnification range of 600 × . A Hitachi H-600 transmission electron microscope was used at 50 kV over a magnification range of 1,000–5,000 ×.

Scanning and transmission electron microscopy was performed to assess the morphology of the endothelium and vascular smooth muscle. Scanning electron microscopy in 5 animals confirmed that attachment of the sonomicrometer crystals did not disrupt the endothelial surface.

**Experimental Protocol**

**Group I.** Fourteen dogs were studied. After surgical preparation the animals were allowed to stabilize for a minimum of 30 minutes. No animal received more than two drugs, and the order of drug administration was randomized. Serotonin (5 and 50 μg/min, n = 7), angiotensin II (1 and 2.5 μg/min, n = 6), or methoxamine (50 and 100 μg/min, n = 6) was infused intracoronarily with coronary perfusion pressure maintained constant at 80 mm Hg. Each drug was dissolved in 0.9% saline. Hemodynamic and coronary artery diameter measurements were determined at steady-state levels of drug infusion (5 minutes). Animals were allowed a minimum of 30 minutes between infusions of different drugs. To minimize tachyphylaxis, 30 minutes was allowed between each dose of angiotensin II. Acetylcholine (40 μg/min, n = 6) was infused intracoronarily during the administration of the highest
dose of angiotensin II or methoxamine. Following the control infusions of drugs, the coronary perfusion pressure was elevated from 80 mm Hg to 200 mm Hg for 15 minutes and then returned to 80 mm Hg. Thirty minutes later, when coronary diameter was back to control values, infusions of serotonin, angiotensin II, or methoxamine were repeated with coronary perfusion pressure maintained at 80 mm Hg. Acetylcholine (40 \mu g/min) was administered again following constriction with angiotensin II or methoxamine.

**Group II.** In a separate group of 20 dogs, the effect of various durations of hypertension on the response of coronary arteries to serotonin was examined as well as the time course of altered responses. The animals were instrumented as previously described, and the experimental protocol was similar except that the duration of hypertension varied. Responses to serotonin were measured before and after coronary artery pressure was raised to 200 mm Hg for 10 seconds (n = 6), 1 minute (n = 7), and 5 minutes (n = 7). Responses to serotonin were measured 30 minutes, 90 minutes, and 2½ hours after pressure was restored to 80 mm Hg.

**Group III.** A separate group of 6 animals was studied to determine the effect of endothelium removal on the coronary artery response to acute hypertension. The animals were instrumented as described above. Serotonin (5 and 50 \mu g/min) was infused intracoronarily with perfusion pressure held constant at 80 mm Hg. Acetylcholine (40 \mu g/min) was given intracoronarily during infusion of serotonin (50 \mu g/min). The coronary endothelium was then removed in the region of the sonomicrometer crystals and proximal up to the cannula tip with two to three passes of a balloon-tipped Fogarty 4F embolectomy catheter. The animal was allowed to stabilize for a minimum of 30 minutes, and coronary responses to serotonin and acetylcholine were repeated. Coronary perfusion pressure was then elevated from 80 mm Hg to 200 mm Hg for 15 minutes. Infusions of serotonin and acetylcholine were repeated at least 30 minutes after the return of the coronary perfusion pressure to 80 mm Hg. Infusions of serotonin and acetylcholine were repeated at least 30 minutes after the return of the coronary perfusion pressure to 80 mm Hg. If the effects of acute hypertension on vascular responses are the result of endothelial dysfunction, then removal of endothelium prior to hypertension should abolish the effects of acute hypertension on vascular responses. If hypertension alters vascular responses following removal of endothelium, then this would suggest a direct effect of hypertension on vascular smooth muscle.

**Statistical Analysis**

All data are given as the mean ± SEM. Data before and after acute hypertension were compared using a two-way analysis of variance, followed by a least-squares mean analysis. The significance level was adjusted for multiple comparisons by the Bonferroni method.\(^{13}\)

**Results**

**Effect of Acute Hypertension on Baseline Hemodynamics and Vascular Morphology**

Raising coronary perfusion pressure from 80 mm Hg to 200 mm Hg for 15 minutes resulted in a 509 ± 79 \mu m increase in diameter of the left anterior descending artery and a 515 ± 90% increase in coronary flow (n = 14, Figure 1). After restoring pressure to 80 mm Hg, coronary artery diameter and blood flow gradually returned to control values over 30 minutes. Systemic pressure was not significantly altered.

Scanning electron micrographs of the intimal surface of all coronary arteries exposed to 15 minutes of hypertension showed disruption of endothelial junctions, separation of endothelium from the underlying basement membrane, and areas of endothelial denudation (Figure 2B). Numerous white blood cells were adherent to the vessel in the region of the damaged endothelium and platelets were adherent to the underlying basement membrane in denuded areas. In contrast, in the left circumflex artery, which was not exposed to hypertension, the endothelium was normal (Figure 2A).

In coronary arteries exposed to 1 and 5 minutes of acute hypertension, endothelial cell damage was similar; however, approximately half of the intimal surface was covered with intact endothelium. In all vessels endothelial cell junctions were disrupted with white blood cell adherence to damaged endothelium. Following 10 seconds of hypertension, although endothelial cell junctions were disrupted with adherence of white blood cells in all vessels, there was generally more intact endothelium (50–75%). Following 10 seconds of hypertension, small crater-like lesions...
in endothelium were observed in 4 of 6 arteries (Figure 2C). Transmission electron micrographs of vessels exposed to 15 minutes of hypertension showed granulocytes adherent to the basement membrane beneath endothelial cells (Figure 3A) and regions in which endothelial cells were separated from the basement membrane (Figure 3B). There was no morphologic evidence of damage to the underlying vascular smooth muscle in arteries exposed to acute hypertension.

**Effects of 15 Minutes Hypertension on Responses to Serotonin**

Intracoronary infusion of serotonin (5 and 50 μg/min, n = 7) resulted in a dose-dependent increase in coronary flow (Table 1) and a decrease in coronary...
FIGURE 3. A: Transmission electron micrograph of left anterior descending coronary artery following acute hypertension (200 mm Hg for 15 minutes). Granulocytes were adherent to the basement membrane beneath endothelial cells. B: Transmission electron micrograph of left anterior descending coronary artery following acute hypertension (200 mm Hg for 15 minutes) demonstrating endothelial cell separation from the underlying basement membrane with adherence of granulocytes to the basement membrane.
Table 1. Hemodynamics and Coronary Diameter (CD) During Intracoronary Serotonin Infusion in Dogs Before and After Acute Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5 µg/min</th>
<th>50 µg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>104 ± 5</td>
<td>105 ± 5</td>
<td>105 ± 5</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>29 ± 4</td>
<td>43 ± 4*</td>
<td>99 ± 14*</td>
</tr>
<tr>
<td>CD (mm) and ACD from control (µm)</td>
<td>1.77 ± 0.16</td>
<td>-22 ± 14*</td>
<td>-89 ± 30*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM, n = 1.

* p < 0.05 vs. corresponding control; † p < 0.05 vs. 5 HT, 5 µg/min; and ‡ p < 0.05 vs. before hypertension.

artery diameter (Figure 4). Mean arterial pressure was not altered (Table 1). Approximately 30 minutes after acute hypertension with coronary pressure at 80 mm Hg, mean arterial pressure, coronary flow, and coronary artery diameter did not differ from control (Figure 1). Following acute hypertension, the constrictor response of the large coronary artery to serotonin was markedly potentiated (Figure 4). Changes in coronary flow were comparable before and after hypertension (Table 1). We have previously shown that the constriction to serotonin during control conditions is reproducible over time.9

Effect of Hypertension on Responses to Angiotensin II

Since doses of angiotensin II (1 and 2.5 µg/min) were separated by a minimum of 30 minutes, responses to each dose were compared with the control values prior to each infusion. Intracoronary infusion of angiotensin II caused a reduction in coronary flow that was significant only before acute hypertension (control: 24 ± 4 ml/min; 1 µg/min: 19 ± 3 ml/min; control: 25 ± 4 ml/min; 2.5 µg/min: 22 ± 4 ml/min). Arterial pressure was not altered by angiotensin except at the high dose before hypertension (control: 99 ± 8 mm Hg; angiotensin: 117 ± 10 mm Hg). Angiotensin produced similar constriction of the large coronary artery before and after hypertension (Figure 5).

Effect of Hypertension on Responses to Methoxamine

Intracoronary infusion of methoxamine (50 and 100 µg/min) did not alter arterial pressure or coronary blood flow. Methoxamine produced a dose-dependent decrease in large coronary artery diameter that was not altered by hypertension (Figure 5).

Effect of Hypertension on Responses to Acetylcholine

The response to intracoronary infusion of acetylcholine (40 µg/min) was examined following constriction of the artery with angiotensin II (2.5 µg/min) or methoxamine (500 µg/min) (Table 2). We have found that constriction of the artery augments dilation in response to acetylcholine. The dilation to acetylcholine was similar in magnitude and unaffected by hypertension (Δ diameter before hypertension: 72 ± 39 µm; after hypertension: 99 ± 34 µm).
Table 2. Hemodynamics During Intracoronary Infusion of Acetylcholine (ACh) Following Constriction of Coronary Artery With Methoxamine (500 \(\mu\)g/min) or Angiotensin II (2.5 \(\mu\)g/min)

<table>
<thead>
<tr>
<th></th>
<th>Before hypertension</th>
<th>Methoxamine or angiotensin</th>
<th>Methoxamine or angiotensin with ACh (40 (\mu)g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>100 ± 8</td>
<td>115 ± 11</td>
<td>116 ± 13</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>25 ± 4</td>
<td>36 ± 16</td>
<td>92 ± 19*</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td>91 ± 10</td>
<td>90 ± 11</td>
<td>89 ± 14</td>
</tr>
<tr>
<td>Coronary flow (ml/min)</td>
<td>31 ± 9</td>
<td>38 ± 12</td>
<td>86 ± 28*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM, \(n = 6\).

*\(p<0.05\) vs. corresponding control.

Effects of Duration of Acute Hypertension on Responses to Serotonin

Intracoronary infusion of serotonin produced dose-dependent increases in coronary blood flow and decreases in large coronary artery diameter (Figure 6) that were comparable in each group of animals. The maximum increases in coronary diameter and blood flow during acute hypertension were similar to those observed during 15 minutes of hypertension (1 minute: Δ diameter = 404 ± 30 \(\mu\)m, Δ flow = 365 ± 44%; 5 minutes: Δ diameter = 407 ± 38 \(\mu\)m, Δ flow = 530 ± 73%). Thirty minutes following hypertension, control diameters were not different from control values before hypertension (10 seconds hypertension: before = 2.61 ± 0.13 mm; after = 2.61 ± 0.11 mm; 1 minute hypertension: before = 2.16 ± 0.15 mm; after = 2.15 ± 0.17 mm; 5 minutes: before = 1.55 ± 0.09 mm; after = 1.57 ± 0.10 mm).

Ten seconds of hypertension did not alter coronary responses to serotonin. The constriction of the coronary artery to serotonin was potentiated, however, after 1 and 5 minutes of hypertension (Figure 6).

Time Course of Enhanced Constriction to Serotonin Following Hypertension

In the 7 dogs exposed to 1 minute of coronary artery hypertension, responses to serotonin were examined at 30 minutes, 90 minutes, and 2½ hours following the return of pressure to normotensive levels. Enhanced constrictor responses of large arteries to serotonin observed at 30 minutes persisted for at least 2½ hours (Figure 7). Constrictor responses to serotonin were also enhanced following 5 minutes of hypertension for at least 2½ hours (\(n = 7\)).

Effect of Acute Hypertension Following Endothelial Removal

In 6 animals, we examined the effect of acute hypertension on the response to serotonin following removal of endothelium. Removal of the endothelium potentiated the constrictor response to serotonin at 5 \(\mu\)g/min (Δ diameter before removal: −24 ± 20 \(\mu\)m; after removal: −102 ± 48 \(\mu\)m; \(p<0.05\)) and at 50 \(\mu\)g/min (Δ diameter before removal: −119 ± 47 \(\mu\)m; after removal: −216 ± 76 \(\mu\)m; \(p<0.05\)). The dilation of the artery to acetylcholine (40 \(\mu\)g/min) following preconstriction with serotonin (50 \(\mu\)g/min) was abolished after removal of the endothelium (Δ diameter before removal: 43 ± 33 \(\mu\)m; after removal: −2 ± 5 \(\mu\)m; \(p<0.05\)).

Following removal of coronary endothelium the perfusion pressure was increased from 80 mm Hg to 200 mm Hg for 15 minutes. Arterial pressure and coronary flow during infusion of serotonin were similar before and after the hypertensive episode (Table 3). In contrast to effects of hypertension in the presence of endothelium, constriction of the artery in response to serotonin was not altered when the endothelium was removed prior to hypertension (Figure 8).

Discussion

The major finding of this study was that acute hypertension selectively potentiated constriction of large coronary arteries to serotonin. The data demonstrate that brief episodes of hypertension of as little as 1 minute duration can result in abnormal coronary vascular reactivity that persists for at least 2½ hours after pressure has been restored to normotensive levels.
Coronary Constriction Following Acute Hypertension

Several lines of evidence suggest that the effects of acute hypertension on coronary vascular responses to serotonin result from changes in endothelial function. First, there was morphologic evidence of damage to endothelium. Hypertension produced disruption of endothelial cell junctions and areas of endothelial denudation with deposition of white blood cells and platelets. Second, the potentiation of the constrictor response to serotonin following hypertension was comparable to that observed during normotension following mechanical removal of endothelium. Third, removal of endothelium prior to hypertension abolished the effects of hypertension on constrictor responses to serotonin. Since a dose-dependent vasoconstrictor response to serotonin was observed following removal of endothelium, the failure of hypertension to potentiate responses cannot be explained by maximum constriction following endothelial removal. Fourth, acute hypertension potentiated constrictor responses to serotonin, an endothelium-dependent agent but not to angiotensin II and methoxamine, non-endothelium-dependent agents.

Potentiation of Responses to Serotonin
At least four possible mechanisms may contribute to the enhanced constriction of the large coronary artery to serotonin following acute hypertension and damage to endothelium. First, endothelial cells act as a diffusional barrier to circulating humoral substances. Damage to endothelium and removal of a diffusional barrier to circulating humoral substances is probably not involved since responses to angiotensin II and methoxamine were not enhanced following acute hypertension.

Second, the endothelium is a site of serotonin metabolism via monoamine oxidase. Decreased metabolism of serotonin following damage to endothelium is also an unlikely explanation for the enhanced constriction because in vitro data have demonstrated that contractions of arterial rings are not affected by inhibition of monoamine oxidase.

The third possible mechanism for the enhanced constriction following hypertension may be related to platelet deposition. Platelets adherent to denuded areas of the vessel may release subthreshold amounts of serotonin, thereby increasing the concentration during dose-response curves following hypertension. This explanation is also unlikely since in vitro data have shown that threshold amounts of serotonin can potentiate constriction to angiotensin II. However, the response to angiotensin was not affected by hypertension. Also, threshold amounts of serotonin should shift the dose-response curve in a parallel manner. However, in a previous study in which platelets covered the entire proximal surface of the artery following mechanical removal of the endothelium, the constriction to serotonin was potentiated to a greater degree with increasing doses.

Finally, damage to endothelium during hypertension...
may decrease the release of vasodilator substances, such as prostacyclin and endothelium derived relaxing factor (EDRF). Release of prostacyclin from endothelium does not modulate constriction to serotonin, however, since inhibition of cyclooxygenase with indomethacin did not alter constriction of large arteries in vitro. Thus, it is most likely that damage to endothelium during acute hypertension results in a decreased release of EDRF by serotonin.

The observation that acute hypertension selectively potentiates constrictor responses of large coronary arteries to serotonin without impairing the dilator response to acetylcholine is of interest. The dilator response to acetylcholine is dependent on endothelium in isolated coronary artery segments and results from release of EDRF. Our results with acetylcholine before and after removal of endothelium in vivo confirm previous observations in isolated vessels and studies in the intact coronary circulation and the femoral artery. The preservation of acetylcholine-induced dilation after hypertension suggests that acute hypertension may impair coronary vasomotor responses to endothelium-dependent agonists in a selective manner. For example, EDRF released by serotonin may be altered by hypertension, while a different EDRF released by acetylcholine may not be altered. An alternative explanation is that the dose-response characteristics of EDRF release in response to serotonin and acetylcholine may differ. Thus, following hypertension, there may have been a sufficient number of functioning endothelial cells to produce maximal coronary vasodilation in response to acetylcholine, while synthesis and release of EDRF by serotonin may not be sufficient to inhibit the constrictor response.

Another explanation for the differential effects of acute hypertension on the coronary vascular response to serotonin and acetylcholine is suggested by recent work from Vanhoutte's laboratory. These investigators have demonstrated that endothelium may produce not only relaxant factor(s) but also constrictor substances in response to hypoxia in isolated coronary arteries and to arachidonic acid in isolated veins. In addition, Lüscher and Vanhoutte have suggested that serotonin causes release of an endothelium-derived contracting factor(s) in thoracic aorta of spontaneously hypertensive rats. We speculate that serotonin could also stimulate increased release of endothelium-derived contracting factor(s) following acute hypertension.

Mechanisms of Vascular Injury

Damage to coronary endothelium and altered vascular reactivity following acute hypertension may result from mechanical and/or chemical factors such as oxygen radicals. Mechanical factors that may alter vascular morphology during hypertension include elevated perfusion pressure, vascular distension, and an increase in shear stress that occurs during “breakthrough” of autoregulation. Studies by Fry have shown that both vascular distension and elevated shear stress can result in damage to arterial endothelium and increases in endothelial permeability. Presently, the relative importance of the increased pressure versus flow during acute hypertension in producing the observed endothelial damage is not known. While the magnitude of the induced pressure changes in these studies is probably rare in the intact, in vivo situation, mean arterial pressures in ambulatory subjects are highly variable and pressures as high as 160 to 190 mm Hg have been reported in subjects with mild to severe hypertension. The magnitude of hypertension and the rate of rise in perfusion pressure are also mechanical factors that may influence the altered vascular response.

Chemical factors such as oxygen free radicals generated during acute hypertension could also interfere with or inactivate EDRF or result in endothelial damage with decreased production of EDRF. In cerebral blood vessels, superoxide dismutase and catalase, which dismute free oxygen radicals to less reactive species, decrease the extent of endothelial lesions, prevent the decrease in responsiveness to hypercapnia and hypocapnia, and partially restore the vasodilation to acetylcholine following acute hypertension. Inhibition of the cyclooxygenase pathway also prevented the altered vascular responses following acute hypertension in the cerebral circulation. It is possible that acute hypertension may induce accelerated prostaglandin and free oxygen radical production, which may overwhelm the capacity of the vascular tissue to inactivate oxygen radicals via superoxide dismutase and/or catalase. An alternative source of oxygen free radicals is leukocytes that are adherent to damaged endothelium following acute hypertension. We speculate that generation of free oxygen radicals from increase arachidonic acid metabolism and/or leukocytes may be involved in the cellular damage and altered vascular responses to serotonin in the coronary circulation following acute hypertension.

Previous studies of vascular effects of hypertension have focused primarily on models of chronic hypertension. An increase in sensitivity to vasoconstrictor agents including norepinephrine and a decrease in responsiveness to vasodilator agents including acetylcholine, histamine, and adenosine, have been demonstrated in spontaneously hypertensive and deoxycorticosterone hypertensive rats. The role of endothelium in these altered vasomotor responses is not completely understood. Although the dilator responses to endothelium-dependent agents acetylcholine and histamine were reduced in chronic hypertension, the diminished responses were not due to a decreased release of EDRF as determined with a bioassay technique. These diminished responses may involve an impaired coupling between endothelium and smooth muscle. In addition, it has been suggested that there may be simultaneous release of a constricting substance from endothelium in chronic hypertension. The present study suggests that acute hypertension can damage coronary endothelium directly and produce alterations in vasomotor responses to serotonin that persist long after pressure is restored to normotensive levels.
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