Different Reactivity and Structure of the Prestenotic and Poststenotic Aorta in Human Coarctation

Implications for Baroreceptor Function

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SUMMARY
In eight humans with coarctation, fresh aortic tissue was examined pharmacodynamically. In four of these patients, and in 12 additional patients, the aorta above and below the coarctation was studied morphologically and compared with eight control aortas. By in vitro stimulation with potassium (127 mM), noradrenaline (18 µM), and prostaglandin F2α (28 µM), postcoarctational aortic ring preparations showed a significantly greater contractility than precoarctational rings (p < 0.05). Volumetric analysis showed significantly more collagen (p < 0.01) and less smooth muscle mass (p < 0.01) in the aorta above than below the coarctation. No significant differences were found between sections from the arch and distal to the ligamentum arteriosum in the normal aorta.

We conclude that the precoarctational aortic wall is more rigid than the postcoarctational wall. This may influence baroreceptors in the upper vascular bed in such a way as to tolerate a higher pressure. This would explain the preoperative proximal hypertension, the paradoxic hypertension and the frequent lack of normalization of blood pressure postoperatively.

THE HEMODYNAMICS of coarctation of the aorta is not understood well. Since the classic reports of Goldblatt and Kahn⁴ and Scott and Bahnson,⁵ coarctational hypertension has often been related to renal factors. Others have suggested a mechanical theory.⁶,⁷ None of these explanations are adequate, especially relative to postoperative paradoxic hypertension. In recent years, studies have focused on the function of baroreceptors in coarctation; but investigations have been performed only in experimental animals.⁸,⁹ In this study we assessed the area close to or in which baroreceptors are situated in man. The investigation was carried out by in vitro stimulation of fresh aortic tissue from patients with coarctation and by morphologic analysis.

Material and Methods

In Vitro Studies

Animals
Before the investigations of human vessels were carried out, the experimental procedure was tested on thoracic aortas from seven normotensive male Wistar rats (weight 250–300 g). From each aorta, four transversally cut ring preparations 4 mm long were taken, beginning at the aortic arch (ring 1) and progressing toward the diaphragmatic end (ring 4).

Humans
The aortic preparations were obtained from five males and three females, ages 6–35 years, undergoing operation for an isolated juxtaductal coarctation of the aorta. The patients were anesthetized with thiopental, nitrous oxide and halothane, and received pethidine, diazepam or atropine for premedication. During the operation, 2–3 cm of the coarctated aorta were removed to establish a normal, even lumen of the vessel. Five of the eight patients had an end-to-end graft. During the operations, the surgeon marked the proximal end of the removed aortic segments with a suture. The preparations were immediately placed in aerated Krebs solution (25–30°C) and transported to the laboratory, where they were cleaned of connective tissue and cut into rings. The macroscopically identified coarctation was isolated in one ring preparation, and two preparations of about the same weight were isolated above and below the stenosis.

Method
The isometric tension changes in both rat and human ring segments were recorded by the "ring" method described by Bevan and Osher⁷ and others.⁸—¹⁰ The ring preparations were mounted in 30-ml jacketed organ baths that contained Krebs solution (fig. 1). The temperature of the solution was maintained at 37°C and was constantly aerated with 95% oxygen and 5% carbon dioxide. The isometric contractions were recorded using Grass FT 03 transducers connected to a Beckman R611 polygraph.

During a 1–2-hour period, the resting length was adjusted (by stepwise depression of the rod) (fig. 1) to the level at which maximal contraction force by depolarization could be generated. During this period, anesthetics possibly left in the tissue were also washed out. The resulting resting length — and corresponding resting tension — for a ring preparation were kept constant throughout the experiment, and a drug was not applied before the resting tension was reached again.

The repeated isometric contractions were induced by potassium depolarization (127 mM) until responses were reproducible. Thereafter, the responses to supramaximum doses of noradrenaline (18 µM) and pros-
taglandin PGF$_{2a}$ (28 μM) were investigated. Tension was measured in mN (1 mN = 0.102 g [force]).

**Solutions and Drugs**

The Krebs solution, prepared on the day of the experiments, had the following composition (mM): NaCl 119, KCl 4.6, NaHCO$_3$ 20, CaCl$_2$ 1.5, NaH$_2$PO$_4$ 1.2, glucose 11 and pH 7.4. Double-distilled water and analytic-grade chemicals were used. The Krebs solution used for potassium-depolarization contained 127 mM KCl and no NaCl, but was otherwise of the same composition. Noradrenaline bitartrate DAK and prostaglandin F$_{2a}$ (Upjohn) were used. The drugs were injected into the organ bath in volumes of 0.03–0.3 ml. Concentration values refer to the active substance. Before the application of a vasoactive agent, the preparation was thoroughly washed out using normal Krebs solution until the resting tension was achieved.

**Histology**

In four of the eight patients from whom material was investigated pharmacodynamically, tissue was available for histologic examination. Twelve additional patients with coarctation of the aorta were included for microscopic evaluation alone. There were four females and 12 males, mean age 14.2 years (range 1 month to 37 years). The clinical data of these 12 patients are listed in table 1.

As controls, eight age-matched normal heart aortic preparations were obtained from the Institute of Forensic Medicine. The mean age was 17.6 years (range 3 months to 38 years). The cause of death was accident or suicide.

Rings of aortic tissue from immediately above and below the coarctation, and rings of the normal aortas from the aortic arch and from below the ligamentum arteriosum were fixed in buffered formalin. From each ring, 5–8-μm sections were cut on a base sledge microtome and stained with elastic van Gieson stain. This method stains collagen fibers red and elastic fibers black to silver-brown. Yellow-stained material is neither collagen nor elastin, and consists mainly of smooth muscle. Sections in which microscopic examination showed tissue of the coarctation or ductus/ligamentum arteriosum at any part of the circumference were excluded.

Quantitation was performed by point-counting volumetry using a square lattice of 25 points with a line density of 21.2 mm. Cross-points falling on red or yellow structures served as markers for the volumetric calculations. Ten to 20 random fields per section in the middle of tunica elastica were assessed at a magnification of 630× in at least three histologic sections per tissue ring.

**Statistical Evaluation**

The pharmacodynamic values are mean ±sd. Statistical significance was determined by t test. The Wilcoxon matched-pairs, signed-ranks test was used for the morphometric assessment, a pair being the proximal and distal ring (or specimen) from one patient. Statistical significance was at the p < 0.05 level.

**Results**

In rat thoracic aorta, no statistically significant differences in the contractile response between segments 1 and 4 were found (fig. 2). In human aortas, the amplitude of the maximum response to potassium, noradrenaline and PGF$_{2a}$ increased from the proximal to the distal segments (fig. 3). The reactivity of the isolated aortic segments from the different patients was rather heterogenous, but the isometric force/g aortic weight induced by all contractile agents was always higher in the poststenotic distal segments than in the prestenotic proximal segments. The reactivity of the coarctated parts of the aortas were higher than in the prestenotic segments but lower than in the poststenotic segments (table 2). These results are reflected by the histologic findings of more collagen tissue (points falling on red-stained fibers) in the proximal segment (6.2 ± 1.22) than in the distal one (4.5 ± 0.92). The amount of yellow-stained material (mainly smooth muscle fibers) was very different (4.2 ± 1.25 vs 6.1 ± 1.45) (fig. 4). The differences were statistically significant (p < 0.01). No significant differences, however, were found between proximal and distal aortic

**FIGURE 1.** The mounting of aortic ring segments for the determination of isometric contractions: (1) vascular ring segment, connected to specimen holder and hook by loops of surgical silk (6-0); (2) glass rod, lower fixed specimen holder; and (3) platinhook, upper specimen holder, connected to the transducer.
rings from the controls. The amount of elastin (black to silver-brown material) was the same in proximal (14.58 ± 1.28) and distal (14.38 ± 1.89) specimens from the patients and in the controls (14.23 ± 1.67 vs 14.43 ± 1.49).

In the prestenotic segments, the mean contractile response of the three agents correlated with the intraarterial systolic pressure in the brachial artery (or the systolic pressure gradient across the coarctation) preoperatively measured under local anesthesia: The greater the systolic pressure (or gradient), the smaller the response (fig. 5). No direct correlation was found with the age of the patients, and no correlations were found regarding the poststenotic segments.

**Discussion**

Hooker et al. showed that by applying the ring method we used in this study, almost twice as much maximal force was generated by noradrenaline in rabbit aortic rings as in spiral strips of equal weight.

Using a different technique and more vasoactive agents, Altura and Altura found that the reactivity in the thoracic aorta of rabbits decreases from the proximal to the distal part. They thought that this represented a decrease of the muscle mass rather than a reduction of the number of drug receptors. A similar trend was seen in our investigation of the thoracic aorta in normotensive rats by means of potassium, noradrenaline and prostaglandin F$_{2\alpha}$. These three agents were used because they induce isometric contractions in ring preparations, partly by different mechanisms, in human vessels.

Contrary to these studies on the experimental animal, we found a significantly reduced contractility above the coarctation compared with the aorta below. We do not believe that anesthetics left despite the washout period should have interfered with this result. Van Nimwegen and Dyer found no alterations in the response to noradrenalin of human uterine arteries in the presence of either halothane, nitrous oxide or lidocaine in concentrations normally used for anesthesia.

We also found an increased amount of collagen tissue and a reduced number of smooth muscle cells in the proximal compared with the distal segment. It is impossible to know whether the reduced preoccal tional reactivity was caused by a loss of drug receptors or by a replacement of smooth muscle by collagen, but a replacement seems to be more likely. It is also impossible to determine whether the morphologic changes in the prestenotic aortic segment may continue further centrally and involve the whole of the aortic arch and even the great brachiocephalic vessels in all patients.

More collagen was found several centimeters above the coarctation, i.e., the distal part of the aortic arch, central to the isthmus, than in specimens from well below the coarctation. (Specimens were obtained from

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**Figure 2.** Maximum response to potassium (127 mM), noradrenaline (18 μM) and prostaglandin PGF$_{2\alpha}$ (28 μM) in ring preparations 1-4 from the thoracic aorta of seven rats. Values are mean ±sd, calculated as mN/mg; zero represents the resting tension.

**Table 1. Clinical Data on the 12 Patients from Whom Specimens for Microscopy Were Obtained**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>Intraarterial upper BP (mm Hg)</th>
<th>Systolic gradient (mm Hg)</th>
<th>Type of operation (with/without graft)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>27 days</td>
<td>M</td>
<td>?</td>
<td>?</td>
<td>Died before operation; autopsy specimens; multiple intracardiac lesions</td>
<td></td>
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<tr>
<td>10</td>
<td>5 years</td>
<td>F</td>
<td>140/95</td>
<td>32</td>
<td>—</td>
<td>BP during general anesthesia</td>
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<tr>
<td>11</td>
<td>6 years</td>
<td>M</td>
<td>120/90</td>
<td>23</td>
<td>—</td>
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<tr>
<td>12</td>
<td>8 years</td>
<td>M</td>
<td>165/95</td>
<td>90</td>
<td>—</td>
<td>BP during general anesthesia; aortic stenosis</td>
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<tr>
<td>13</td>
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<td>M</td>
<td>116/72</td>
<td>43</td>
<td>—</td>
<td>BP measured perioperatively</td>
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<tr>
<td>14</td>
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<td>M</td>
<td>145/80</td>
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<td>+</td>
<td>Reoperation after 16 years</td>
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<tr>
<td>15</td>
<td>11 years</td>
<td>F</td>
<td>171/131</td>
<td>59</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>11 years</td>
<td>M</td>
<td>155/107</td>
<td>60</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>12 years</td>
<td>M</td>
<td>148/92</td>
<td>60</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>20 years</td>
<td>F</td>
<td>155/110</td>
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<td>—</td>
<td></td>
</tr>
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<td>19</td>
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<td>167/86</td>
<td>45</td>
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<td></td>
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<tr>
<td>20</td>
<td>37 years</td>
<td>M</td>
<td>177/87</td>
<td>35</td>
<td>+</td>
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Abbreviation: BP = blood pressure.
AORTIC DIFFERENCES IN COARCTATION/Sehested et al.

Figure 3. Isometric tension induced by potassium (127 mM), noradrenaline (NA, 18 μM) and prostaglandin (F$_{2\alpha}$, 28 μM) in isolated ring preparations from (A) prestenotic, (B) stenotic and (C) poststenotic parts of a human coarctated aorta.

Table 2. Maximum Response to Potassium (127 mM), Noradrenaline (18 μM) and Prostaglandin PGF$_{2\alpha}$ (28 μM) in Prestenotic, Stenotic and Poststenotic Parts of Coarctated Aorta

<table>
<thead>
<tr>
<th>Pt</th>
<th>K$^+$</th>
<th>NA</th>
<th>PGF$_{2\alpha}$</th>
<th>K$^+$</th>
<th>NA</th>
<th>PGF$_{2\alpha}$</th>
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<td>58</td>
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<td>140</td>
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<td>53</td>
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<td>140</td>
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<td>10</td>
<td>13</td>
<td>15</td>
<td>10</td>
<td>11</td>
<td>60</td>
<td>57</td>
<td>68</td>
</tr>
<tr>
<td>Mean</td>
<td>55.8</td>
<td>52.5</td>
<td>73.8</td>
<td>98.9</td>
<td>77.3</td>
<td>98.4</td>
<td>135.8</td>
<td>142.0</td>
<td>155.5</td>
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Values represent isometric force, calculated as mN/g tissue. The mean isometric tension induced by the vasoactive agents was significantly lower pre- than poststenotically ($p < 0.005$ for potassium [K$^+$]; $p < 0.05$ for noradrenaline [NA]; and $p < 0.05$ for prostaglandin F$_{2\alpha}$[PGF$_{2\alpha}$]).

Figure 4. (A) Histologic measurements in 16 patients with coarctation of the aorta. Amount of red-stained material (collagen) (I) and yellow-stained material (mainly smooth muscle cells) (II) in the aortic media proximal and distal to the coarctation. The circles indicate segments studied pharmacodynamically. (B) Histologic measurements in eight control persons in the aortic media proximal and distal to the insertion of the ligamentum arteriosum.
two patients who had a bypass graft 6 and 12 cm long, respectively [fig. 4]).

At the necropsy of two children, ages 1 year, 4 months and 1 year, 10 months, who besides an aortic coarctation had a ventricular septal defect and a patent ductus, and a common atrioventricular canal and Down's syndrome, respectively, aortic sections were obtained from the aortic arch, between the brachiocephalic artery and the left subclavian artery as well as from far below the poststenotic dilatation. At histologic examination, the relative amounts of collagen, smooth muscle and elastin showed exactly the same pattern between the pre- and postcoarctational aorta as mentioned above.

The composition with regard to collagen and smooth muscle tissue (and elastin) in the poststenotic aorta closely resembles that of the aortas from the control series. We did not investigate aortic distensibility directly in this study, but our findings of precoarctational hypertension, reduced contractility, an increased amount of collagen and a reduced amount of smooth muscle tissue suggest that the prestenotic aortic wall is more rigid than the poststenotic aortic wall. Furthermore, collagen is relatively inextensible, and with an increased amount of collagen, the distension is further diminished. At the same time, this process is influenced by the existing number of contractile smooth muscle cells, which exert a dampening effect on both stretch and release of stretch in the course of the cardiac cycle. This is supported by the recent finding of decreased distensibility of the aorta in hypertensive rats, and a direct relationship between the scleroprotein content (collagen and elastin) and the elastic properties of the vessel.

The baroreceptors placed in the prestenotic area may be influenced in such a way that, as stretch receptors, they will be activated less at a given pressure than receptors placed in vessels with normal distensibility. They will therefore permit or accept a higher pressure. The findings support the hypothesis of the role of baroreceptors in the postoperative paradoxical hypertension: By surgical establishment of a normal conduit from the thoracic aorta, the stress on baroreceptors drops to "unacceptably" low values. This drop of pressure may decrease receptor stimulation, and thus result in activation of pressor-active catecholamines and later stimulate the renin-angiotensin system. In the same way, an insufficient baroreceptor stimulation may explain the lack of a normalized blood pressure after surgical correction.

Several months after operation, an increased pulse frequency and plasma noradrenaline level may be found during work compared with preoperative values (unpublished observations). This could also be attributed to inadequate baroreceptor engagement, caused by a slow or absent reversibility of the vascular changes. The pharmacodynamic response in the prestenotic segments seems to be related more to hemodynamic conditions than to age. This might imply that the magnitude of preoperative blood pressure is as important as age in determining the postoperative course in patients with coarctation of the aorta.

References
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