Coarctation of the Aorta and Baroreceptor Resetting
A Study of Carotid Baroreceptor Stimulus-Response Characteristics before and after Surgical Repair in the Dog

FRANZ O. IGLER, LAWRENCE E. BOERBOOM, PAUL H. WERNER, JUDITH H. DONEGAN, E.J. ZUPERKU, LAWRENCE I. BONCHEK, AND J.P. KAMPINE

SUMMARY We studied baroreceptor function in dogs before and after surgical repair of coarctation of the aorta by direct recording of multifiber carotid sinus (CS) nerve activity (NA) during alteration of pulsatile arterial pressure with systemic phenylephrine and nitroprusside, and during static pressure changes using a CS pouch preparation. Coarctation was induced by banding the proximal thoracic aorta in ten 3- to 5-day old puppies. One and one-half years later, five of these coarctated animals were studied before, and five were studied 3-7 months after, surgical repair. Five adult animals also were studied 4-6 months after the proximal thoracic aorta had been banded. Controls were eight normal adult dogs. Threshold pressure at which NA began, saturation pressure at which NA reached a maximum, and slope (% Max NA/mm Hg) of the linear portion of the stimulus-response curve were determined. Pulsatile manipulations of pressure elicited normal sensitivity (slope) in dogs with coarctation but static nonpulsatile pressure changes showed depressed sensitivity compared to controls. After surgical repair, threshold and saturation returned toward normal; sensitivity determined with static pressure manipulations returned to control value. Coarctation reset CS baroreceptors to operate at higher pressures in both puppies and adult dogs and repair of coarctation returned function toward normal. We conclude that resolution of hypertension after repair of coarctation may depend upon baroreceptor readaptation.

SEALLY et al. (1957) suggested that the initial rise in systolic pressure following repair of aortic coarctation in children (paradoxical hypertension) may be due to resetting of systemic arterial baroreceptors to the chronically elevated pressure. Acutely unloading baroreceptor afferents by surgical repair would lead to an acute increase in sympathetic outflow and thus an increase in systemic arterial pressure. Rocchini et al. (1976) found that paradoxical hypertension after surgical repair of coarctation in children was biphasic in nature. An initial rise in systolic pressure within the first 24 hours after repair was related to increased sympathetic activity. The subsequent gradual rise in diastolic pressure was related to increased plasma renin activity. Upward resetting of the baroreflex heart rate response in the awake, adult canine with aortic coarctation from birth was demonstrated recently by Bonchek et al. (1976). The stimulus-response curve relating systemic arterial pressure to heart rate was shifted to the right with no detectable change in sensitivity (slope). Resetting of carotid and aortic baroreceptors to chronically elevated pressure in renal hypertension (Aarss, 1976; McCubbin, 1958; Salgado and Krieger, 1973), and in the spontaneously hypertensive rat (Nosaku and Wang, 1972; Sapru and Wang, 1976) has been demonstrated.
However, carotid sinus (CS) baroreceptor stimulus-response characteristics in experimental aortic coarctation have not been studied. In addition, the effect of age of onset (adult vs. neonate) and therapy (surgical repair) on baroreceptor function in aortic coarctation has not been elucidated. The purpose of the present study, therefore, was to describe baroreceptor stimulus-response characteristics in the adult canine with coarctation from birth, coarctation from adulthood, and after surgical repair.

Methods

Carotid sinus (CS) baroreceptor afferent nerve studies were performed under sodium pentobarbital (30 mg/kg, iv) anesthesia in 23 mongrel dogs intubated with auffed endotracheal tube and ventilated with 100% O2 using a Bird respirator. Four groups of animals were studied: (1) eight normal adults dogs served as controls; (2) experimental aortic coarctation was produced in five adult animals (adult coarctation) 4-6 months prior to CS baroreceptor studies; (3) coarctation was accomplished in five, 3- to 5-day-old puppies (pup coarctation), and 1½-2 years later, baroreceptor studies were performed; and (4) aortic coarctation was produced in five puppies (as above), and then 1½-2 years later, the aortic stricture was repaired surgically (pup coarctation repaired). Baroreceptor studies then were performed 3-7 months postoperatively.

Experimental Coarctation of the Aorta

Mildly constricting braided Dacron ligatures were placed around the aorta just distal to the brachiocephalic vessels in ten 3- to 5-day-old puppies. As these animals matured, significant relative narrowing of the descending aorta, hypertension proximal to the coarctation, and development of collateral circulation were observed (Bonchek et al., 1976). For comparison, adults mongrel dogs underwent banding of the aorta just distal to the left subclavian artery by use of a nylon locking tie (Code Laboratories) tightened sufficiently to give a systolic pressure difference across the stenosis of at least 50 mm Hg. Surgical repair of the aortic stricture was performed in five of the 10 dogs whose aortas had been banded when they were puppies. The aorta was cross-clamped just proximal and distal to the stenosis, the constricted segment was resected, and an end-to-end anastomosis was performed. The procedure usually required ligation of one or two collateral vessels just distal to the site of the aortic stricture.

Carotid Sinus Baroreceptor Stimulus-Response Characteristics

Carotid sinus baroreceptor function was studied by direct recording of multifiber afferent nerve activity from the peripheral end of the carotid sinus nerve which was divided at its junction with the
glossopharyngeal nerve, desheathed, placed across tungsten carbide bipolar electrodes, and immersed in a chamber filled with warm mineral oil (Fig. 1). Statham P23Db pressure transducers were used to monitor CS and femoral arterial pressure using stiff polyethylene cannulas filled with heparinized normal saline. Amplified and filtered nerve activity, carotid sinus pressure, femoral arterial pressure, and ECG were recorded on magnetic tape and displayed on a Grass model 7 polygraph and oscilloscope.

With the common carotid artery intact pulsatile arterial pressure was manipulated by intravenous infusions of 25 mg/100 ml phenylephrine (Neo-Synephrine HCl) in a 10- to 20-ml injection or sodium nitroprusside (Nipride) diluted with 5% dextrose and water to a concentration of 250 mg/100 ml in a 4- to 12-ml injection. Carotid sinus pressure was lowered to below threshold for nerve discharge by nitroprusside infusion and inflation of a balloon which was threaded into the inferior vena cava. Phenylephrine then was injected as a bolus and data collected as pressure increased. Using this technique, threshold pressure (the pressure at which distinct nerve discharge first began), saturation pressure (the pressure at which nerve firing no longer increased with increased pressure), and sensitivity (slope of the stimulus-response curve over its linear range) were determined under conditions of physiological pulsatile pressure contours over a wide range of CS pressures. Threshold was obtained by lowering CS pressure to a level at which nerve activity was no longer detected and then slowly increasing pressure by infusion of phenylephrine. Saturation was determined by noting the CS pressure at which nerve activity no longer increased with increasing pressure during infusions of phenylephrine. Several determinations of threshold and

![Figure 1](http://circres.ahajournals.org/lookup/fig/1)

**Figure 1** Carotid sinus pouch preparation used to determine static pressure stimulus-response characteristics: CS = carotid sinus, CSP = carotid sinus pressure, E.C. = external carotid, OCC = occipital artery, NA = nerve activity, CSN = carotid sinus nerve.
satisfaction were made for each animal and then averaged. In eighteen of the animals studied using the above method, the CS pouch preparation shown in Figure 1 also was used to manipulate pressure systematically. The external carotid, common carotid, and smaller arterial branches around the CS were ligated. Static, nonpulsatile changes in pressure were produced by changing the speed of a Sarns roller pump. An inverted bottle partially filled with air was used to eliminate pump pulsation artifact. CS pressure was increased in increments of 25 mm Hg and held constant for at least 1 minute, returning to control pressure (at or below threshold pressure) between steps. Data were considered for analysis only when base-line values of NA remained constant with time. The above techniques were used to manipulate CS pressure systematically, and baroreceptor stimulus-response characteristics were determined under conditions of unaltered (physiological) pulse pressure contours and under static step changes in which a nonpulsatile pressure waveform was used.

Data Analysis and Statistics

To quantify phasic data obtained during manipulations of pressure with phenylephrine and nitroprusside, nerve activity and CS pressure were digitized using a DEC PdP11 computer. NA was processed using a window discriminator and Schmitt trigger to produce a standard pulse for each nerve spike. The window discriminator was set just above noise level when CS pressure was below threshold for nerve discharge. The number of nerve impulses per cardiac cycle has determined using the R wave of the ECG to start and stop accumulation of data by a specially designed counting device and computer interface. The R wave of the ECG also was used to update and store data in the computer. CS diastolic, systolic, and mean pressure for each cardiac cycle were determined by a signal processor designed to determine electrically minimum, maximum, and mean values. To normalize nerve activity, all data points were divided by maximum nerve activity (average impulses/sec at saturation). A plot of CS pressure vs. percent of maximum nerve activity was made for data obtained during infusions of phenylephrine (i.e., as CS pressure increased) from threshold to saturation levels of pressure. Nerve activity obtained during nonpulsatile, static pressure manipulations was rectified and filtered by an active low pass filter to obtain electrically time-averaged activity at each level of CS pressure. This method of analysis has been used extensively to analyze these types of data (Irisawa and Ninomiya, 1967; Kirchheim, 1976). Nerve activity occurring 30 seconds after the initial rise in pressure was analyzed, representing the initiation of steady state or approximately complete adaptation of nerve activity (Franz et al., 1971). Nerve data here normalized by dividing all data points by maximum nerve activity (activity at saturation pressure) to obtain a plot of CS pressure vs. percent maximum nerve activity. Data at each pressure level for each group of animals were pooled and mean values were determined. Sensitivity (slope) was determined and compared using linear regression statistics on data points between 20% and 80% of maximum.

Comparisons between mean threshold pressures and mean saturation pressures were made using the unpaired t-test. Slopes were compared statistically using the F-test for differences between regression coefficients. Where appropriate, analysis of variance and Scheffe’s tests were applied. Significant differences were concluded when P ≤ 0.05 in two-tailed tests. Results are presented as mean ± se.

Results

Hemodynamic characteristics of experimental animals are presented in Table 1. Baseline carotid sinus and baseline femoral arterial pressures were obtained under anesthesia before infusion of vasoactive drugs. Pressure data from awake animals were presented previously (Bonchek et al., 1976). Significant pressure gradients were present across the aortic coarctation in both adult coarctation and pup coarctation groups. No significant pressure gradient was found in the pup coarctation repaired group. Carotid sinus mean systolic and diastolic pressures were significantly higher in animals with experimental aortic coarctation, as determined by t-test and Scheffe’s test. Pulse pressure in the pup coarctation group was significantly higher using Student’s t-test but not quite significant using Scheffe’s test. Pulse pressure was significantly higher than controls in adult coarctation using both tests. In contrast, pressures in pup coarctation-repaired animals were not significantly different from controls.

Carotid Sinus Baroreceptor Characteristics with Pulsatile Pressure Manipulations

An example of phasic nerve discharge obtained during infusion of phenylephrine is shown in Figure 2. Three levels of pressure are depicted. Both threshold and saturation pressures for the pup coarctation animal were higher than those of the control animals. Note the continuous nerve discharge throughout diastole at saturation pressure compared to the phasic nerve activity at the operating range of pressures depicted in the middle trace. It should be noted that at pressures at which nerve activity was saturated in the control animal there were still distinct bursts of nerve activity with each systole and minimal nerve activity during diastole in the pup coarctation animal. Figures 3 and 4 show scatter diagrams relating mean CS pressure and percent max nerve activity obtained from representative animals in control, adult coarctation, pup coarctation, and pup coarctation repaired groups. A shift of the stimulus response curve to
Table 1: Hemodynamic Characteristics of Experimental Animals

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 8)</th>
<th>Pup coarctation (n = 5)</th>
<th>Pup coarctation repaired (n = 5)</th>
<th>Adult coarctation (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS Femoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>132.5 ±4.03</td>
<td>207.0* ±8.30</td>
<td>163.0 ±13.38</td>
<td>214.0* ±16.08</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>102.5 ±4.43</td>
<td>149.0* ±8.12</td>
<td>115.0 ±7.91</td>
<td>144.0* ±6.60</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>112.0 ±3.99</td>
<td>169.0* ±6.43</td>
<td>130.9 ±9.07</td>
<td>172.2* ±7.90</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>31.7 ±3.3</td>
<td>58.0 ±9.82</td>
<td>48.0 ±9.43</td>
<td>70.0* ±10.37</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SE.

*P ≤ 0.05 compared to control using Scheffe’s test.

Figure 2: Typical example of phasic carotid sinus nerve activity (NA) at threshold (T), operating carotid sinus pressure (middle trace), and saturation pressures (top trace) for a control and pup coarctation. Pressure was lowered to threshold levels by infusion of nitroprusside and raised to saturation levels using phenylephrine. Note that the pressure scales for pup coarctation are double those for the control.

The right was evident in the pup coarctation and adult coarctation animals. After repair, the stimulus-response curve shifted back toward control (Fig. 4). Results from the experimental groups are presented in Figure 5. There was a significant elevation of mean threshold pressure and mean saturation pressure for pup coarctation (P ≤ 0.05) and adult coarctation (P ≤ 0.05) groups compared to controls. Pup coarctation repaired animals showed no significant difference in threshold or saturation pressures. No significant difference between sensitivities (slopes) was found with manipulations of pulsatile pressure. The above comparisons were also made utilizing diastolic and systolic pressure data. There was no difference in results obtained.

Baroreceptor Characteristics with Static Manipulations of Nonpulsatile Pressures

During manipulations of pressure using the CS pouch preparation, the level of nerve activity was determined 30 seconds after the initial rise in pressure. A continuous firing pattern at steady state pressures with an increase in averaged nerve activity at each step in pressure between threshold and saturation for a control and a pup coarctation animal is shown in Figure 6. The first increase in nerve activity occurred between 50 and 75 mm Hg for this control animal and 75 and 100 mm Hg for the pup coarctation animal. Saturation of nerve activity occurred at approximately 200 mm Hg for control and 225 mm Hg for pup coarctation animals. Figure 7 shows stimulus-response curves characterizing baroreceptor activity under static nonpulsatile step changes in CS pressure. The sensitivity (slope of the regression line determined over linear part of the curve) was 1.0 (% max/mm Hg) for controls, 1.00 for the pup coarctation repaired group, 0.65 for...
the adult coarctation group, and 0.68 for the pup coarctation group. There was no significant difference in slope between control and pup coarctation repaired groups or between pup coarctation and adult coarctation groups. Compared to controls and pup coarctation-repaired animals, there was both a significant decrease in slope (P ≤ 0.05) and a shift of the stimulus-response curve to the right in the pup coarctation and adult coarctation animals during nonpulsatile pressure studies.

Discussion

Hypertension is a well-recognized accompaniment of coarctation of the aorta in human beings (Keith, 1978) and in experimental animals (Habit and Nanson, 1968). Baroreflex characteristics in coarctation only recently have been studied. Bonchek and co-workers (1976) reported a shift of the stimulus-response curve relating blood pressure to heart rate to the right with no change in sensitivity (slope). Previous studies of baroreceptor function in renal hypertension (McCubbin, 1958; Salgado and Krieger, 1973) in the spontaneously hypertensive rat (Nosaku and Wang, 1972; Sapru and Wang, 1976) and in essential hypertension in the human (Bristow et al., 1969) also have shown upward resetting, but generally with decreased sensitivity. Reports of carotid sinus baroreceptor stimulus-response characteristics in clinical or experimental coarctation of the aorta have not appeared previously. The present study shows that resetting of carotid sinus baroreceptors to elevated pressure occurs in coarctation of the aorta, since both threshold and saturation pressures are increased significantly. Surgical repair results in "resets" toward a control operating range of arterial pressures. The sensitivity determined under pulsatile pressure manipulations was unaltered (Fig. 5). However, sensitivity determined under steady state, nonpulsatile conditions was decreased in animals with coarctation. The latter observation corresponds to changes in sensitivity observed in other hypertensive states (Bristow et al., 1969; McCubbin, 1958; Nosaku and Wang, 1972). The different pressure waveform of coarctated compared to control animals may account for the difference in results. An increase in pulse pressure in coarctation is well recognized (Keith, 1978; Kirkendall et al., 1959; O'Rourke and Cartmill, 1970; Sealy et al., 1957) and confirmed in the present study. A recent study by O'Rourke and Cartmill (1970) analyzed the pressure waveform in detail and showed that the amplitude of the proximal aortic pulse was greater than in normal controls; peak pressure was reached later in systole, and the anacrotic shoulder was closer to the foot of the wave than in controls. The importance of pulse

**Figure 4** Plot of mean carotid sinus pressure (CSP) vs. % max. nerve activity (NA) for a pup coarctation and pup coarctation-repaired animal. Note the shift of the curve to the left after repair. There was no significant difference in slope.

**Figure 5** Summary of data (mean ± SE) from the four groups of experimental animals showing baseline pressure (P) (pressure obtained before infusion of vasoactive drugs), threshold P, saturation P, and slope (% Max NA/mm Hg). All pressures are mean CS pressures. *Significant difference from control (P ≤ 0.05) using Scheffé's test.
pressure, dp/dt, and pulse frequency on baroreceptor nerve discharge has been reviewed extensively by Kirchheim (1976). It is clear that the slope of the stimulus response curve of carotid sinus pressure related to multifiber nerve activity is greater under pulsatile than under nonpulsatile conditions (Kirchheim, 1976, Koushanpour and McGee, 1969; Ninomiya and Irisawa, 1972). Gero and Gerova (1967) have shown that at a given mean pressure in normal dogs the heart rate response to carotid sinus pressure change increases with increases in pulse pressure. Results of Bonchek et al. (1976) and those of the present study obtained using similar methods to manipulate CS pressure (i.e., the vasoactive drug phenylephrine) both showed no change in sensitivity (slope). This may be due to differences in the pressure contour in coarctation rather than intrinsic baroreceptor characteristics, since standardized nonpulsatile pressure manipulations revealed a depressed slope.

Bonchek et al. (1976) suggested that cardiovascular parameters studied in experimental coarctation from birth (i.e., existing through growth and development) may be different from those studied in animals with coarctation produced after maturity. In this study, no difference in baroreceptor characteristics could be identified between aortic coarctation produced in adults and coarctation produced in puppies. This does not imply, however, that significant difference in other cardiovascular parameters do not exist.

Baroreceptor stimulus-response characteristics in surgically repaired animals tend to return to control after 3-4 months of recovery (Figs. 5-7). Studies in which pressure was therapeutically lowered to normal in the spontaneously hypertensive rat (Sapru and Wang, 1976) and in renal hypertension (Salgado and Krieger, 1973) have also shown return of baroreceptor stimulus-response characteristics to normal.

Results of the present study seem especially pertinent to the understanding of paradoxical hypertension seen after repair of coarctation (Bristow,
Aortic Coarctation and Baroreceptor Resetting

By guest on October 25, 2017


Goodall J, Sealy WC (1969) Increased sympathetic activity after surgical repair and resolution may depend on baroreceptor readaptation. Physiol Rev 56: 101–176


Sealy WC, Hasaus JS, Young GW, Callaway HN (1957) Paradoxical hypertension following resection of coarctation of the aorta. Surgery 42: 135–147

REFERENCES


1969, Goodall and Sealy, 1969; Ingomar and Terslev, 1961; Rocchini et al., 1976; Sealy et al., 1957). Unloading of reset baroreceptors was suggested as contributing to hypertension after surgical repair (Goodall and Sealy, 1969; Sealy et al., 1957). The present study shows that resetting to the increased pressure does occur to a significant degree and, after surgical repair baroreceptor function, returns toward normal. Rocchini et al. (1976) found that, during the first 24 hours post-operation in children, a significant systolic hypertension occurred which was associated with a diminished cold pressor response. Goodall and Sealy (1969) showed a significantly greater urinary adrenaline output after surgical repair of aortic coarctation than that of a control group in which surgical procedures were performed for other reasons. They hypothesized that an initial decrease in pressure after repair reduces the inhibitory influence of baroreceptors on the bulbar vasomotor centers and in turn increases sympathetic outflow. In light of the significant upward resetting demonstrated in the present study, it seems that an exaggerated sympathetic response following repair would not be surprising.

We concluded that age of onset of coarctation (i.e., adult vs. puppy) did not significantly influence CS baroreceptor resetting. Coarctation of the aorta leads to resetting of baroreceptors to operate a higher pressures with no difference in sensitivity determined under pulsatile (physiological) conditions but, a decrease in sensitivity as determined with static nonpulsatile pressure manipulations. It appears, therefore, that changes of intrinsic baroreceptor characteristics in coarctation are similar to those in other hypertensive states. Repair of coarctation returns baroreceptor function toward normal. Reset baroreceptors may play a significant role in the initial phase of paradoxical hypertension after surgical repair and resolution may depend on baroreceptor readaptation.
Coarctation of the aorta and baroreceptor resetting. A study of carotid baroreceptor stimulus-response characteristics before and after surgical repair in the dog.
F O Igler, L E Boerboom, P H Werner, J H Donegan, E J Zuperku, L I Bonchek and J P Kampine

doi: 10.1161/01.RES.48.3.365

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/48/3/365