Central Hemodynamics in the Developmental Stage of Spontaneous Hypertension in the Unanesthetized Rat

THOMAS L. SMITH, PH.D., AND PHILLIP M. HUTCHINS, PH.D.

SUMMARY The hemodynamic alterations associated with the developmental phase of high blood pressure were investigated in the spontaneously hypertensive rat (SHR). All hemodynamic measurements were made in unanesthetized, unrestrained SHR and Wistar-Kyoto (WKY) rats instrumented with chronic electromagnetic flow probes on the ascending aorta and arterial pressure catheters. Rats were studied at 30-41 days, 80 days and 120 days of age. Hemodynamics of SHRs and WKYs in the 30-41 day group were monitored daily. Spontaneously hypertensive rats demonstrated a higher cardiac index than WKYs (p < 0.05) from 32 through 41 days of age. Total peripheral resistance (TPR) was not elevated in SHRs at this time. Heart rate and stroke index were elevated in SHRs (p < 0.05) from 34 through 41 days, however, stroke volume was not. At 80 and 120 days SHRs had higher mean arterial pressure (MAP) and TPR than WKYs (p < 0.05), although cardiac index was not significantly different. This hemodynamic pattern of a hyperkinetic circulation prior to the development of hypertension supports the theory of total body autoregulation. A transient increase in cardiac index precedes an increase in TPR, which then normalizes cardiac index while elevating MAP.

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KEY WORDS • chronic instrumentation • electromagnetic flow probe • cardiac output • arterial pressure • total peripheral resistance • hemodynamics • spontaneously hypertensive rat

A n increase in cardiac index leading to a total body autoregulatory response may be an initiating factor in human essential hypertension. This autoregulatory response in the major vascular beds of the body provides for an elevation of total peripheral resistance which reduces cardiac index but increases mean arterial pressure. Frohlich and co-workers reported hemodynamic patterns in labile and established hypertensive patients which suggest that an autoregulatory mechanism may be involved in the development of essential hypertension. They report that labile hypertensive patients have elevations in cardiac index while peripheral resistance is normal. In general, these patients have a hyperkinetic circulation characterized by an increase in heart rate, cardiac index and left ventricular ejection rate. With sustained hypertension, however, cardiac index is reduced to normal levels as total peripheral resistance and mean arterial pressure are elevated.

The spontaneously hypertensive rat (SHR) is a generally accepted model for human essential hypertension. However, an early transient increase in cardiac index associated with total body autoregulation has not been demonstrated conclusively to be the initiating factor in the development of hypertension in the SHR.

This lack of definitive evidence can be attributed in part to studying animals at an age when the transient increase in cardiac index has already occurred. Albrecht and Trippodo and co-workers have shown that the SHR exhibits an elevated arterial pressure at less than 40 days of age. Thus, the most appropriate time to investigate changes in cardiac index associated with a total body autoregulatory response would seem to be at less than 40 days of age. Most investigators have studied SHR hemodynamics at older ages and have demonstrated that the SHR exhibits an elevated arterial pressure at less than 40 days of age. Thus, the most appropriate time to investigate changes in cardiac index associated with a total body autoregulatory response would seem to be at less than 40 days of age. Most investigators have studied SHR hemodynamics at older ages and have demonstrated that the SHR exhibits an elevated arterial pressure at less than 40 days of age. Thus, the most appropriate time to investigate changes in cardiac index associated with a total body autoregulatory response would seem to be at less than 40 days of age.
HEMODYNAMICS IN THE SHR/Smith and Hutchins

When autoregulatory mechanisms have presumably already been invoked.

Previous investigations of total body autoregulation in the SHR have often employed techniques that alter the hemodynamics being observed. These technical interventions include anesthesia, thoracotomy and positive-pressure ventilation. The direct Fick method of determining cardiac index avoids many of these observational alterations of hemodynamics, but the user sacrifices accuracy and the ability to detect transient changes in cardiac index during the observation period. Day-to-day measurements of cardiac index in the same rat using the direct Fick method have not been reported for the SHR.

Since many of the previous investigations of total body autoregulation in the SHR were done in the early 1970's, the proper control rat for the SHR was not employed. The Wistar-Kyoto rat (WKY), now the generally accepted control rat for the SHR, was not widely available at that time. The control rat used in earlier studies was the normotensive Wistar rat of European or American origin.

The purpose of this investigation was to document the presence or absence of a transient increase in cardiac index in unanesthetized, unrestrained SHR's before an elevation of total peripheral resistance. We utilized the SHR and its control, the WKY, instrumented with chronic electromagnetic flow probes and pressure catheters. This technique permits repeated hemodynamic measurements over a 2-week observation period. Recent advances in electromagnetic flowmetry technology made possible this improvement in methodology over that of previous investigations. In addition, the same rat could be studied throughout the entire time period, thus eliminating much of the variance among animals seen when a different rat is used for each observation.

Methods

The animal model used in this study was the spontaneously hypertensive rat (SHR) and its control, the Wistar-Kyoto rat (WKY) representing f40-42 and f14-16, respectively. Both strains came from a colony maintained in the laboratory animal care facility at Bowman Gray School of Medicine. The original breeding stock for this colony were descendants of the strains developed by Okamoto and Aoki, supplied by the National Institutes of Health. We housed all rats under identical conditions of temperature (20°C) and light-dark cycles (12 hours light:12 hours dark). Purina Rat Chow and water were available ad libitum.

To avoid possible sex differences in hemodynamics, we used only male rats in this study.

We studied the hemodynamics of SHR and WKY rats in three age groups: Group I, in which we monitored hemodynamics daily from 30-41 days of age; Group II, consisting of rats 79-83 days old; and Group III, consisting of rats 118-123 days old. There were seven rats of each strain in both groups I and II. There were six SHR and five WKY rats in group III.

Rats of both strains came from comparable litter sizes in each age group.

Carolina Medical Electronics (King, NC) supplied the chronic electromagnetic flow probes used in this study. Since our research required the implantation of these probes in small rats for periods of several days, the standard EP400 probe was found unsuitable and was therefore modified by the manufacturer. These modifications included a reduction in the size of the probe head, angling of the probe head relative to the cable, and a lighter saddle-shaped connector that could be sewn to the back. Modified probes are now commercially available from the manufacturer (EP100 series). Depending on the diameter of the aorta on which the probe was to be implanted, we used probes that were 5 mm or 6 mm in luminal circumference. Prior to the experiment, all probes were calibrated in vitro. Calibration was performed with rat aorta and whole blood using the stopwatch and beaker technique.

Chloral hydrate (400 mg/kg, intraperitoneally) provided surgical anesthesia for all implantation procedures and was selected because it produces little respiratory depression. All surgical procedures were performed using sterile techniques. Flow-probe implantation was via an intercostal thoracotomy at approximately the third right intercostal space. A rodent respirator (Model 680, Harvard Apparatus, Millis, MA) maintained adequate ventilation during the thoracotomy. We carefully dissected the ascending aorta free from its surrounding tissues and looped two 3-0 silk ligatures under it. Using these ligatures we gently lifted the aorta and placed the electromagnetic flow probe around it approximately 3 to 4 mm distal to the heart. A Silastic key secured the flow probe in place. The lifting ligatures were then removed and the thoracotomy was closed with 3-0 silk suture. Negative pressure applied through a chest tube aided re-inflation of the lungs and removal of fluids following closure of the thoracotomy. To prevent physical damage to the probe cable after recovery, we brought it subcutaneously to the back of the animal, where the saddle-shaped connector was sutured to the back of the neck. We fastened the connector to the neck with 4-0 synthetic polyfilament (Vetafil, Bengen) and reinforced the skin immediately beneath the connector with Mersiline mesh (RM53, Ethicon, Somerville, NJ) to prevent accidental tearing.

We also implanted a catheter in the abdominal aorta via the left femoral artery. The catheter was constructed of heparinized (TDMA Heparin, Poly Sciences, Inc.) silicone rubber tubing (Silastic, DowCorning, Midland, MI; 0.030" i.d. X 0.065" o.d.), except for the tip. The catheter tip was Teflon tubing (Small Parts, Inc.; 0.022" i.d. X 0.034" o.d.) drawn over heat and ligated inside the end of the silicone rubber tubing. The tips were 20 to 25 mm in length and had an average luminal diameter of approximately 0.5 mm. The Teflon tip seemed more resistant to clot formation and remained patent longer than polyethylene. The silicone rubber segment ran subcutaneously from the groin to the back of the...
neck. A predetermined volume of sodium heparin (1000 units/ml) filled the catheter and a stainless steel obturator plugged it. The catheter required daily flushing with physiologic saline (Normosol; Abbott Pharmaceuticals, North Chicago, IL) and refilling with sodium heparin.

Ascending aortic flow probes and arterial pressure catheters could be implanted in young rats (25 days old and weighing 49 g), an important feature since the SHR develops hypertension at a young age. The rat's movement and growth was not seriously impaired by the instrumentation.

We let the animals recover for 2 days following surgery before we utilized any hemodynamic measurements. Pilot studies showed that after 2 days body weight was at its pre-surgical level and the hemodynamic variables (cardiac output, blood pressure, heart rate) had plateaued. All rats gained weight throughout the experiment after the 2-day recovery period.

Clear plastic cages, 18.5 cm × 15 cm × 25 cm, housed the animals after they were instrumented. Recordings of mean aortic pressure and pulsatile and mean aortic flow could be made with minimal handling and without removing the animals from their cages. One drawback of working with unanesthetized animals is that they are sensitive to environmental stimuli and minimal handling is required if one hopes to measure hemodynamic variables accurately. We allowed the rats to reacclimate for several minutes after connecting them to the pressure and flow transducers before we made any hemodynamic recordings. The rats usually burrowed under shavings in the cage and remained quiescent. Rats exhibiting behavioral agitation and/or unusually high heart rates were monitored until such time that hemodynamic variables were stabilized. The incidence of agitation during transducer connection was minimal and equally distributed between strains. Animals which repeatedly became highly agitated were excluded from this study. Most recordings were made at the same time of day, between 9 and 11 a.m.

A square-wave electromagnetic flowmeter (Model 501D, Carolina Medical Electronics, King, NC) measured ascending aortic flow in the rat via a special lightweight connector cable suspended over the animal's cage. Also suspended over the animal's cage was a pressure transducer (MS 10-C, Ailtech, City of Industry, CA) that measured pressure via a short polyethylene connector plugged into the Silastic catheter on the rat's neck. Zero pressure was taken at midchest level. The pressure transducer and flowmeter connected to an amplifier and multi-channel oscillograph (Brush Instruments, Cleveland, OH). The entire recording system for aortic flow had a frequency response of approximately 80 Hz. The aortic pressure recording system monitored pulsatile pressures, but the frequency response was such that high fidelity recordings were attenuated at heart rates greater than 6 Hz. For this reason, only mean aortic pressures are reported.

The hemodynamic variables measured were pulsatile and mean ascending aortic flow and mean aortic pressure (determined by mechanical clamping). We recorded these at a paper speed of 10 mm/sec to obtain heart rates and then at 250 mm/sec to obtain accurate values of peak aortic flow velocity. Hemodynamic variables derived from the above data were cardiac output (ml/min, considered equal to ascending aortic flow), cardiac index (cardiac output/100 g body weight), stroke volume (ml/beat, cardiac output × heart rate⁻¹), stroke index (cardiac index × heart rate⁻¹), stroke work (mean arterial pressure × stroke volume), minute work (mean aortic pressure × cardiac output), normalized minute work (mean aortic pressure × cardiac index), and total peripheral resistance (mean arterial pressure × cardiac index⁻¹).

Instrumented animals were capable of producing pulsatile aortic flow data up to 21 days after surgery. Pulsatile aortic pressure could generally only be recorded for 8 to 10 days. After this period the pulse pressure became increasingly diminished until eventually mean aortic pressures were not reliable. This sequence of events limited practical measurements of pressure to 13 to 15 days. This allowed us to perform the study described but would limit the user to roughly a 2-week protocol. The construction of the electromagnetic flow probes also affected the longevity of their recording usefulness once implanted. Probes purchased early in our studies had only a silicone rubber covering over the probe wires. With repeated use these probes eventually fell prey to invasion of body fluids. Fluid infiltration would produce increasing amounts of electrical noise in the flow signal and this could be used as an indicator of expected longevity. When probes sheathed only in silicone rubber began to exhibit noise they were dried in silica gel for several days following their removal from the animal. Refinement of construction technique produced probes having an inner vinyl and an outer silicone rubber sheath over the probe wires. Probes with both vinyl and silicone rubber had somewhat stiffer cables but the longevity of recordings and overall probe life was improved.

The overall success ratio of the implantation procedure was approximately 80%. The primary cause of death in instrumented animals was aortic rupture. Upon autopsy it was found that extensive fibrosis surrounded the outside of the probe head and cable. There was no evidence of thoracic infection nor did there appear to be extensive fibrosis within the probe lumen. Aortic rupture usually occurred proximal to the probe head near the key-way. Heart rates in very young rats were high (380-480 beats/min). As a result, the ascending aorta was subjected to a constant rocking of the probe, which, after 2 to 3 weeks, would produce aortic rupture.

The data were statistically analyzed by two-way analysis of variance to detect age and strain differences. The data were also analyzed by Student's t test with unequal numbers and unpaired data to detect SHR/WKY differences at each age. Group 1 data were analyzed at 2-day intervals, with each data point representing mean values over the 2-day period.
Results

The hemodynamics of spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) in Group I (30–41 days of age) differed significantly. Spontaneously hypertensive rats had higher mean arterial pressures, cardiac indices, cardiac powers and normalized cardiac powers (figs. 1 and 3). In Group II (80 days of age) and Group III (120 days of age) SHRs had higher total peripheral resistance and mean arterial pressures than their age-matched WKY controls. Cardiac output, cardiac index, and heart rate did not differ between SHRs and WKYs of Group II nor did they differ between SHRs and WKYs of Group III. Both cardiac power and normalized cardiac power were higher in Group II SHRs, however, Group III SHRs had only higher values of cardiac power.

Body weights of the SHRs in Group I tended to be lower than those of WKYs (table 1), even though all animals came from comparable litter sizes. These weight differences were significant (p < 0.05) at ages 32 through 39 days. There were no differences in body weights between animals in Group II or animals in Group III, however. At all ages, mean arterial pressure was significantly higher in the SHR (p < 0.001) when compared to WKY rats (table 1, fig. 1). Arterial pressure increased from 30 to 80 days in both the SHR and WKY (fig. 1), but the rate of pressure increase was greater in the SHR. The average pressure for SHR and WKY rats in Group I was 107 ± 2.9 and 86 ± 1.9 mm Hg, respectively. The mean arterial pressure in SHRs 80 days of age was 147 ± 5 mm Hg while that of WKY rats was 105 ± 2 mm Hg. Group III SHRs had a mean arterial pressure of 139 ± 10 mm Hg while their WKY controls had a mean arterial pressure of 95 ± 3 mm Hg.

There was no difference in Group I cardiac outputs when SHRs and WKYs were compared on a daily basis, except at 38–39 days of age (table 1). When all observations of cardiac output for each strain over the entire age period were combined, there was a significantly (p < 0.05) higher cardiac output in Group I SHRs compared to Group I WKYs (52.3 ± 1.4 and 47.9 ± 1.6, respectively). There were no differences in cardiac output between Group II SHRs and WKYs. Similarly, Group III SHRs and WKYs did not have different cardiac outputs. Cardiac index was elevated in Group I SHRs (p ± 0.05) from 32 through 41 days (fig. 1). Cardiac index steadily declined in WKYS as they grew in size during the 30 through 41 day age period. However, SHRs exhibited a transient rise in cardiac index before it started to decline with increasing body size at 36 days of age (fig. 1). Cardiac indices in Group II were not different between strains, nor were those in Group III.

Total peripheral resistance was not significantly different between SHR and WKY rats in Group I (fig. 1). Total peripheral resistance increased in both SHRs and WKYs between 30 and 41 days (fig. 1). At 80 days of age, SHRs had a significantly (p < 0.05) elevated total peripheral resistance when compared to WKYS (4.27 ± 0.47 versus 3.13 ± 0.024 mm Hg • ml⁻¹ • min⁻¹, respectively). Group III SHRs had a similarly elevated total peripheral resistance compared to the WKY controls (5.02 ± 0.5 versus 3.24 ± 0.32 mm Hg • ml⁻¹ • min⁻¹ • 100 g; p < 0.01).

Heart rates in SHRs tended to be higher in all age groups studied (fig. 2). This increase was significant (p < 0.05) in Group I animals 34–41 days of age (table 1). Group II and Group III animals did not have significantly different heart rates between strains although their heart rates were lower than those of Group I, reflecting a slowing of heart rate with increasing age.

Stroke volume in SHRs of Group I was not different from that of the WKY (table 1), nor was it different between these two strains in Group II or in Group III. Stroke volume did increase with age, however, as evidenced by increased stroke volumes in Groups II and III compared to Group I. Stroke index (stroke volume normalized for body weight) was increased (p < 0.05) in Group I SHRs from 34–41 days of age (fig. 2). Elevations (p < 0.05) in stroke work were observed in Group I SHRs 34–41 days of age when compared to Group I WKYS (table 1). Stroke work was also significantly greater in Group II SHRs (p < 0.05), but not in Group III SHRs. Stroke work, like stroke volume, increased with age.

Minute work was greater (p < 0.01) in Group I SHRs aged 34 through 41 days than in WKY control rats (fig. 3). Minute work was also higher (p < 0.05) in SHRs of Groups II and III. Normalized minute work was elevated (p < 0.05) in the SHR throughout the Group I age period. Group II SHRs also had a significantly (p < 0.01) greater normalized minute work than the WKY control rats. Normalized minute work was not significantly different among Group III animals.

SHRs of Group I exhibited increased (p < 0.05) peak aortic flow velocities from 38 to 41 days of age when compared to the WKY rats of the same age (table 1). Group II rats did not differ in their peak aortic flow velocities, however, nor did they differ in Group III. Peak aortic flow velocity tended to increase in both strains of rat with increasing age (table 1).

Discussion

The basic hemodynamic disturbance in patients with established essential hypertension is an elevation of total peripheral resistance. Total peripheral resistance is one of two variables contributing to blood pressure. An increase in mean arterial pressure may also result from elevations in cardiac index. Frohlich et al., however, showed that in established essential hypertension (versus "labile" hypertension) cardiac index is not elevated above normal, non-hypertensive levels. A schema proposed by many researchers suggests that a hyperkinetic circulation, specifically an elevation of cardiac index, may be an initiating factor in the development of essential hypertension. This schema has been incorporated into the total body
autoregulation theory.\(^3\) Simply stated, this theory suggests that an initial increase in cardiac index results in overperfusion of the major autoregulatory beds of the body. These beds counter this overperfusion by increasing their resistance to flow. Cardiac index is thereby reduced to normal but with a resultant elevation of mean arterial pressure. Young labile hypertensive patients have been shown to have higher than normal cardiac indices,\(^4\)\(^4\) however, older, established hypertensive patients have cardiac indices no different than their age-matched controls.\(^4\)\(^4\)

Total body autoregulation is probably not a universal mechanism in the development of hypertension, however.\(^2\) Ledingham and Cohen,\(^2\) studying the developmental hemodynamics of one-kidney Goldblatt hypertension, found that some rats exhibited an initial increase in cardiac output while others had an increased arterial pressure with no changes in cardiac output. In a later study, Ledingham and Pelling\(^2\) were able to calculate total peripheral resistance in addition to measuring cardiac output with electronic flowmetry in conscious rats subjected to renovascular hypertension. In this latter study, increased mean arterial pressure was due primarily to a rise in total peripheral resistance but they also noted that an enhanced cardiac output was sometimes responsible for elevations in mean arterial pressure. Similarly, Terris and co-workers\(^2\) found that deoxycorticosterone hypertension in the pig was due primarily to increased total peripheral resistance. Terris and co-workers\(^2\) also reported that one of the seven pigs studied demonstrated an elevated cardiac output which preceded a rise in total peripheral resistance.

Steroid hypertension in metyrapone-treated dogs has also been studied.\(^30\) About half of the dogs developed hypertension due solely to increased total peripheral resistance. The other half exhibited elevations in cardiac output with little change in total peripheral resistance. If this enhanced cardiac output was reduced pharmacologically, hypertension was not prevented. Frohlich and Pfeffer\(^31\) also showed that chronic beta-adrenergic blockade in spontaneously hypertensive rats did not prevent the development of hypertension even though the cardiac output of these rats was significantly lower than those of control SHRs. Fletcher and co-workers\(^32\) found that in renovascular hypertension in rabbits the high blood pressure is apparently due only to increases in total peripheral resistance, although they note that elevations in cardiac output may participate in the development of hypertension in other species.

The relative roles of cardiac output and total peripheral resistance in the development of high blood pressure are difficult to determine, as evidenced by the disparate results in the above forms of hypertension. Ferrario and Page\(^33\) have written a review article which summarizes the difficulties in interpreting the many studies done on the hemodynamics of hypertension. They suggest that the experimental data cannot all be forced into a single hypothesis.

The most significant finding of the present study was a transient elevation in cardiac index (cardiac output/100 g body weight) in SHRs 32-41 days of age (fig. 1). This increase in cardiac index occurred when total peripheral resistance in the SHR was not different from that of the WKY (fig. 1). Heart rate was also higher in SHR by approximately 11% at

### Table 1. Central Hemodynamic Measurements in Unanesthetized Spontaneously Hypertensive Rats (SHR) and Wistar-Kyoto Rats (WKY) in Three Different Age Groups

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
<th>SHR</th>
<th>WKY</th>
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<tbody>
<tr>
<td>30-31</td>
<td></td>
<td></td>
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<tr>
<td>Body weight (g)</td>
<td>66 ± 2</td>
<td>75 ± 3</td>
<td>68 ± 2*</td>
<td>72 ± 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>78 ± 2</td>
<td>86 ± 3</td>
<td>100 ± 1*</td>
<td>106 ± 4*</td>
<td></td>
<td></td>
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<tr>
<td>Cardiac output (ml/min⁻¹)</td>
<td>48 ± 2</td>
<td>48 ± 3</td>
<td>48 ± 3</td>
<td>55 ± 3</td>
<td></td>
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<tr>
<td>Cardiac index (ml/min⁻¹·100 g⁻¹)</td>
<td>70 ± 4</td>
<td>63 ± 3</td>
<td>70 ± 2*</td>
<td>77 ± 3*</td>
<td></td>
<td></td>
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<tr>
<td>Total periph. resistance (mm Hg·ml⁻¹·min·100 g⁻¹)</td>
<td>1.19 ± 0.09</td>
<td>1.41 ± 0.07</td>
<td>1.45 ± 0.08</td>
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<tr>
<td>Heart rate (beats·min⁻¹)</td>
<td>437 ± 4</td>
<td>438 ± 10</td>
<td>411 ± 13</td>
<td></td>
<td></td>
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<tr>
<td>Stroke volume (ml·10⁻⁴)</td>
<td>10.4 ± 0.7</td>
<td>10.9 ± 0.8</td>
<td>11.8 ± 0.8</td>
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<tr>
<td>Stroke work (ml·mm Hg)</td>
<td>9.3 ± 0.5</td>
<td>10.6 ± 0.8</td>
<td>12.4 ± 0.9</td>
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<tr>
<td>Peak aortic flow velocity (ml·sec⁻¹)</td>
<td>2.38 ± 0.17</td>
<td>2.46 ± 0.15</td>
<td>2.55 ± 0.17</td>
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\(*p < 0.05. \#p < 0.01. \#\#p < 0.001.\)
HEMODYNAMICS IN THE SHR/Smith and Hutchins

Table 1. (Continued)

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
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<tbody>
<tr>
<td>36-37</td>
<td>38-39</td>
<td>40-41</td>
</tr>
<tr>
<td>90 ± 4</td>
<td>92 ± 4</td>
<td>100 ± 3</td>
</tr>
<tr>
<td>77 ± 2</td>
<td>81 ± 3</td>
<td>93 ± 4</td>
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<tr>
<td>86 ± 3</td>
<td>92 ± 2</td>
<td>91 ± 2</td>
</tr>
<tr>
<td>110 ± 3†</td>
<td>115 ± 4†</td>
<td>114 ± 8†</td>
</tr>
<tr>
<td>56 ± 3</td>
<td>43 ± 2</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>52 ± 5</td>
<td>53 ± 3†</td>
<td>54 ± 3</td>
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<tr>
<td>58 ± 4</td>
<td>49 ± 3</td>
<td>48 ± 3</td>
</tr>
<tr>
<td>73 ± 3†</td>
<td>65 ± 2†</td>
<td>62 ± 3†</td>
</tr>
<tr>
<td>1.58 ± 0.17</td>
<td>2.0 ± 0.17</td>
<td>2.04 ± 0.15</td>
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<tr>
<td>1.53 ± 0.07</td>
<td>1.69 ± 0.06</td>
<td>1.91 ± 0.14</td>
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<tr>
<td>414 ± 9</td>
<td>494 ± 9*</td>
<td>388 ± 15</td>
</tr>
<tr>
<td>450 ± 8†</td>
<td>439 ± 10*</td>
<td>436 ± 18*</td>
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<tr>
<td>12.5 ± 0.1</td>
<td>10.7 ± 0.6</td>
<td>11.6 ± 0.7</td>
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<tr>
<td>12.3 ± 0.6</td>
<td>11.8 ± 1.0</td>
<td>12.7 ± 0.7</td>
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<tr>
<td>10.9 ± 0.9*</td>
<td>9.9 ± 0.5</td>
<td>10.6 ± 0.7</td>
</tr>
<tr>
<td>13.7 ± 0.9*</td>
<td>13.9 ± 1.5*</td>
<td>14.3 ± 1.1</td>
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<tr>
<td>2.63 ± 0.19</td>
<td>2.33 ± 0.19</td>
<td>2.57 ± 0.18</td>
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<tr>
<td>2.95 ± 0.16</td>
<td>2.84 ± 0.17*</td>
<td>3.06 ± 0.17*</td>
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</table>

34-41 days, although stroke volume was not (fig. 2). Taken together, elevations in cardiac index and heart rate suggest the presence of a hyperkinetic circulation in young SHRs similar to that in patients with labile essential hypertension.4 24

Cardiac index was not elevated at 80 days of age in the SHR, but total peripheral resistance and arterial pressure were (p < 0.05 and p < 0.1, respectively, fig. 1). This observation was corroborated by the measurements at 120 days of age (fig. 1). These findings in Groups II and III confirm those of Pfeffer and Frohlich5 8 in anesthetized rats of similar ages. Additionally, the relationship between cardiac index and mean arterial pressure observed in 80- and 120-day-old SHRs is similar to that seen in human essential hypertensive patients with established hypertension.4 24

The findings of the present study also meet the criteria for total body autoregulation enumerated by Coleman and co-workers.9 There is a transient increase in cardiac index that returns to normal values when total peripheral resistance and arterial pressure increase (fig. 1). The present study provides the first evidence for a transient increase in cardiac index in unanesthetized SHR when compared to a WKY control. The demonstration of this early increase in cardiac index would be a prerequisite to total body autoregulatory adjustments resulting in increased peripheral resistance as observed in Groups II and III.

The initial increase in cardiac index proposed in the total body autoregulatory model could be due to enhanced sympathetic drive to the heart or elevated mean circulatory filling pressure (MCFP).2 Sympathetic nervous system (SNS) activity in the SHR has been studied extensively. Ablation of central nervous system centers24 or pharmacologic blockade of SNS activity10 in the SHR reduces arterial pressure. Similarly, chemical sympathectomy15 attenuates the development of hypertension in the young SHR. Investigations of sympathetic nerve spike activity16, 8 revealed enhanced levels of sympathetic firing in the SHR. Further, Judy et al.51 have demonstrated that SNS spike activity in the SHR increases with elevations in mean arterial pressure and with increasing age. Other researchers24, 52 however, have not found that SNS activity is elevated in the SHR.

The results of the present study tend to support the concept of enhanced sympathetic nervous system activity in the SHR. This is reflected by an elevation in heart rate in SHR at 34-41 days of age. This elevation in heart rate occurs when cardiac index is elevated and appears to be the major contributor to the increased cardiac index at this age. Further support for enhanced sympathetic activity in the SHR can be drawn from observed differences in stroke work, a quantity used by others as an indicator of myocardial performance.2 Stroke work was elevated (p < 0.05) in SHRs of Group I over the period of 34 through 41 days (table 1). This corresponded temporally with increases in cardiac index, heart rate, minute work and normalized minute work in the SHR (figs. 1-3). Minute work and normalized minute work can also be used to assess myocardial performance since they reflect the ability of the heart to maintain flow in the presence of increased afterload. In the present study minute work was significantly (p < 0.01) greater in SHR 34 through 41 days of age (fig. 3), even though SHRs were generally smaller than WKYs at this time.
FIGURE 1. Cardiac index, mean arterial pressure (MAP), and total peripheral resistance (TPR) in 30- to 41-day-old (Group I), 80-day-old (Group II), and 120-day-old (Group III) unanesthetized spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats. Each entry is a mean ± 1 SEM. In Groups I and II each mean is composed of data from seven animals. There were six SHRs and five WKYS in Group III. Mean values for Group I SHR and WKY reflect values for all rats in each strain averaged over a 2-day period. *0.01 < p < 0.05; **0.001 < p < 0.01; ***p < 0.001.

(table 1). Minute work remained elevated in the SHR at 80 and 120 days (p < 0.01). Peak aortic flow velocity has also been suggested as an indicator of myocardial performance. Spontaneously hypertensive rats had peak aortic flow velocities greater (p < 0.05) than those of the WKY rats at 38-41 days of age, again providing evidence supporting the hypothesis of a hyperkinetic circulation in Group I rats.

The role of mean circulatory filling pressure in the development of hypertension in SHR has not been as extensively investigated as SNS activity. Elevations in MCFP resulting in enhancement of cardiac index could be due either to increased plasma volume or decreased circulatory capacitance. Trippodo and co-workers studied fluid volumes in young (18-43 days) SHR and WKY rats. They found no difference in ex-

FIGURE 2. Heart rate and stroke index measurements in 30- to 41-day-old (Group I), 80-day-old (Group II), and 120-day-old (Group III) spontaneously hypertensive (SHR) and Wister-Kyoto (WKY) rats. For additional information, see figure 1 legend.

FIGURE 3. Minute work and normalized minute work in 30- to 41-day-old (Group I), 80-day-old (Group II), and 120-day-old (Group III) spontaneously hypertensive (SHR) and Wister-Kyoto (WKY) rats. For additional information, see figure 1 legend.
HEMODYNAMICS IN THE SHR/Smith and Hutchins

tracellular fluid volume or plasma volume between these two strains of rat. Simon investigated venous capacitance in the SHR and WKY. He found that the venous capacitance of the SHR is less than that of the WKY. Because venous compliance is some 30 times greater than that of the arterial system, any change in the expressed volume/compliance relationship (i.e., an effectively greater fluid volume in a less compliant vasculature) would most probably be due to changes on the venous side. Simon's findings support the idea that MCFP could be elevated in the SHR and produce an enhanced cardiac index. This study was done in 4- to 5-month-old rats, however, and may not reflect the vascular capacitance of young, prehypertensive SHR. If MCFP were the primary cause of increased cardiac index in young SHR, one might expect to see an increase in stroke volume or stroke index in SHR during the hyperkinetic period of 34–41 days. An enhanced stroke volume might also be indicative of increased myocardial contractility. In our study, stroke volume increases were not seen in SHR at 30–41 days (table 1), although stroke index was increased from 34–41 days. Therefore MCFP and SNS activity may both be involved in the elevation of cardiac index since both stroke index and heart rate were increased. Our findings suggest that more investigation is needed concerning two of these mechanisms in young, labile (less than 40 days old) SHR.

Previous investigations of the role of total body autoregulation in hypertension development in the SHR were less than conclusive due to differences in methodologies employed. One of the methodological differences among these studies was the strain of rat used for control measurements. The best available control for the SHR is the Wistar-Kyoto strain from which the SHR was bred. Earlier studies have often used the Wistar rat, although some researchers have used the WKY. Anesthesia can also alter hemodynamic comparisons in the rat to various degrees, depending on the anesthetic agent used and the strain of rat being investigated. studying the hemodynamics of the SHR under sodium pentobarbital anesthesia, found no difference in cardiac index (cardiac output per 100 g body weight) between SHR and Wistar rats at 4, 7, and 12–23 weeks of age. Mean arterial pressure was significantly elevated in the SHR at 12–23 weeks when compared to the Wistar rat (116 mm Hg vs 80 mm Hg for the two strains, respectively). Popovic and Kent and Salgado and Krieger have shown that pentobarbital significantly decreases cardiac output.

Pfeffer and Frohlich investigated the hemodynamics of SHR and Wistar rats under ether anesthesia at 63–84 days, at 126–231 days, and at 434–679 days of age. Significant differences in cardiac index were found between these two strains at 63–84 and at 126–231 days of age. Cardiac index values of approximately 28.0 and 24.5 were reported for SHR rats 63–84 and 126–231 days, respectively. Values of 23.5 and 22.0 were reported for Wistar rats in the same two age groups. Vidt et al. showed that the cardiac index in rats is higher under ether anesthesia than under pentobarbital anesthesia, an observation later confirmed by Pfeffer and Frohlich. Similarly, Walsh et al. and Salgado and Krieger reported that ether anesthesia in Wistar rats greatly enhances cardiac output and decreases total peripheral resistance when these variables were compared to those of the unanesthetized rat.

Albrecht studied SHR and Wistar male and female rats anesthetized by Inactin (thiobarbiturate) at many different ages (from 30 to 180 days of age). He found that male Wistar rats at 60 days of age had a cardiac index of 36.6 whereas male SHR of the same age had a cardiac index of 26.3, a significantly lower value. At 180 days of age, however, the SHR cardiac index was not different from that of the Wistar rat (25.7 versus 21.0, respectively). The cardiac index of Inactin-anesthetized SHR and Wistar female rats was not different at any of the age groups studied. The above studies suggest that the choice of anesthetic agent can greatly affect hemodynamic observations in the rat. Anesthesia may also have differential effects depending upon sex and animal strain.

The method chosen for cardiac output determinations can also alter the hemodynamic variables being studied. Methods employed by previous investigators of SHR hemodynamics include electromagnetic flowmetry, indicator-dilution technique as used in the study of the heart. Electromagnetic flowmetry is one of the most accurate methods of measuring phasic cardiac output (minus coronary flow) in the ascending aorta. The use of electromagnetic flow probes in acute studies requires anesthesia, thoracotomy and positive pressure ventilation. The effects of anesthesia on observed hemodynamics were noted earlier. Thoracotomy and artificial ventilation in the dog produce a 48% decrease in mean carotid artery flow as well as shrinkage of the heart. Pentobarbital anesthesia and thoracotomy in the rat produce marked decreases in cardiac output in both SHR and Wistar rats, as well as decreases in aortic pressure in the SHR. Thoracotomy alone can also reduce mean arterial pressure in the SHR up to 48%. Indication-dilution techniques as used in the study of spontaneous hypertension require anesthesia and are further limited by not being capable of measuring transient changes in cardiac output occurring over a short time period. The direct Fick technique is reproducible, but requires 10–12 minutes for determinations of oxygen consumption. Measurements, therefore, reflect a mean cardiac output for this period and do not detect phasic flow. Advantages of the direct Fick technique are that it does not require anesthesia during the measurement period, and it measures the entire cardiac output (electromagnetic flowmetry does not detect coronary flow). A disadvantage of the direct Fick is that it requires that metabolism be constant for a 10- to 12-minute period for the measurement to be valid. This technique also measures hemodynamic values 3 hours after recovery from surgical implantation of arterial and venous connections.
catheters when plasma catecholamines may still be elevated. The approach used in our study differs significantly from that of others. In an attempt to minimize observational influences on the data collection, we developed a technique for the implantation of commercially available chronic electromagnetic flow probes on the ascending aorta of a rat. These probes rendered absolute flow values and measured beat to beat changes in ascending aortic flow. We also implanted indwelling arterial catheters in the same rat. The animals recovered from the interventions for 2 days before any measurements were recorded. We could then observe ascending aortic flow and abdominal aortic pressure in unanesthetized, unrestrained rats up to 14 days after the implantation procedures. We had the capability of observing central hemodynamics in the same rat for relatively long periods of time.

In summary, the transient elevation in cardiac index in young, prehypertensive SHRs supports the concept of a hyperkinetic circulation characterized by an increased heart rate, stroke work, minute work, and normalized minute work. The hyperkinetic circulation, seen in 30- through 41-day-old SHRs, is likely antecedent to a total body autoregulatory response. This total body autoregulatory response is reflected by normalization of cardiac index and heart rate of SHRs at 80 and 120 days concomitant with elevations of total peripheral resistance and mean arterial pressure.

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T L Smith and P M Hutchins

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