SUMMARY. We wished to see if a maintained change in pressure at the baroreceptors leads to a maintained or a transient change in heart rate and total peripheral resistance, and if long-term changes in rate and resistance paralleled one another. In awake dogs with intact baroreceptors and complete atrioventricular block, ventricular rate was held alternately at high (90 beats/min) and low (50 beats/min) levels, each for 2 days. This cycle was repeated several times. Data were recorded for 1.5 hours each day. With this change in ventricular rate, there was a maintained change over 2 days in arterial (14.4 ± 1.0 mm Hg) and central venous (3.0 ± 1.2 mm Hg) pressures. These changes in pressure were accompanied by a maintained change in atrial rate of 41.1 ± 9.4 beats/min; peripheral resistance, however, changed only transiently. In three animals, the half-cycle length was 1 week. Changes in heart rate also persisted for this period. It appears from these studies that there is long-term control of heart rate, but not of peripheral resistance. Hypotheses to explain these results are presented. (Circ Res 54: 196-203, 1984)

ARTERIAL blood pressure is regulated over the short term by reflexes originating at arterial and cardiopulmonary baroreceptors. The concept that baroreceptors are responsible for long-term control of arterial pressure has been challenged (Cowley et al., 1973), based on two lines of evidence.

First, if the arterial baroreflexes are responsible for long-term regulation of pressure, arterial baroreceptor denervation should cause a large, sustained increase in blood pressure. Whereas several early studies demonstrated such an effect (Nowak, 1940; Thomas, 1944), in recent studies a sustained rise in pressure was not always seen (Cowley et al., 1973), and when pressure has risen, the rise has been modest (25 mm Hg or less) (Ito and Scher, 1981).

Second, in animals with chronic experimental renal hypertension, baroreceptor fibers discharge at a normal frequency despite a marked elevation in arterial pressure (McCubbin et al., 1956; Krieger, 1970; Coleridge et al., 1981). This "resetting" suggests that the baroreceptors adapt to prevailing mean pressure and that pressure is then regulated around that value.

Two reflex effects appear to originate from cardiopulmonary receptors. First, changes in heart rate follow changes in atrial pressure (Bainbridge, 1915; Coleridge and Linden, 1955). Second, when the vagus nerve is cut or blocked after the arterial baroreceptors are denervated, there is a peripheral vasoconstriction, indicating that a fall in pressure at the cardiopulmonary receptors will increase total peripheral resistance (Donald and Shepherd, 1978).

To examine functional resetting of reflexes due to arterial and cardiopulmonary baroreceptors, we studied awake dogs with complete atrioventricular (AV) block. In this preparation, increasing ventricular rate with an external pacemaker increases cardiac output and arterial pressure, and decreases central venous pressure. This results in a reflex decrease in atrial rate (Robinson et al., 1973) and in total peripheral resistance. We held ventricular pacing rate at alternately high and low values for either 2 days or 1 week. The time required for resetting to reach a plateau has been estimated at 2 days or less (Krieger, 1970; Cowley et al., 1980). If pressure changes are maintained over this period and if there is resetting of baroreceptor reflexes, neurally mediated changes in atrial rate and total peripheral resistance should disappear with time. These studies test the hypothesis that a maintained change in pressure at the baroreceptors leads to only a transient change in heart rate and total peripheral resistance.

The second general question concerns heart rate and total peripheral resistance, which usually change in a parallel fashion during short-term arterial baroreceptor responses (Kirchheim, 1976; Korner, 1978). These studies test the hypothesis that
long-term changes in heart rate will parallel long-term changes in total peripheral resistance as pressure at the baroreceptors changes.

Methods

Eight mongrel dogs, weighing about 20 kg, were trained to lie quietly in the laboratory. During an initial aseptic surgical procedure, both common carotid arteries were placed in skin tubes (Van Leersum loops), and the animals were then allowed to recover for at least 2 weeks.

In a subsequent surgical procedure, a thoracotomy was performed at the 4th right intercostal space. The pericardium was opened, and two or three Teflon-coated, stainless steel stimulating electrodes were sutured onto the right ventricle. Three to four recording electrodes were sutured to the right atrium. Heart block was produced by injection of formalin into the atrioventricular conduction system as described by Loeb et al. (1979). Verification of complete heart block was made from the electrocardiogram.

In five of these dogs, an electromagnetic flow probe (Zepeda Instruments) was placed around the ascending aorta. The pericardium was loosely apposed. Leads from the electrodes and flow probes were led out to the exterior in the interscapular region, and the chest was closed. A cardiac pacemaker was connected to the ventricular leads, and the animals were allowed to recover for at least 2 weeks. In three of these animals, at a subsequent surgery, a catheter was placed via the jugular vein into the superior vena cava at the junction with the right atrium for monitoring central venous pressure.

Recording Procedures

Data were recorded while the dogs were lying quietly on their sides. Arterial pressure was measured through a saline-filled Teflon catheter inserted into a carotid loop and connected to a strain-gauge transducer (Statham P23Db). Ventricular rate was determined from the stimulator. Bipolar atrial potentials were recorded and used to trigger a cardiotachometer. Aortic flow was measured with an electromagnetic flowmeter (Zepeda Instruments SWF-4RD). Flow measurements were calibrated before and after each study.

Data were displayed on a direct-writing oscillograph (Beckman Dynograph) and were edited on-line using a digital minicomputer as described previously (Wyss et al., 1982). The trigger signals from the stimulator and the cardiotachometer, as well as voltages proportional to all variables, were fed directly into the computer. The data-sampling frequency was 250 Hz per channel. For each heart beat, the computer calculated mean arterial pressure, mean central venous pressure, arterial pulse pressure, stroke volume, cardiac output, and peripheral resistance, as well as atrial and ventricular rates. All data were saved on digital magnetic tape.

Protocol

Atrial rate was variable and changed easily with external stimuli. This variability is larger than that in the dog without AV block (Cowley et al., 1973; Itó and Scher, 1981). To minimize the "noise" in this variable, extraneous stimuli were reduced by having the animals lie quietly, with minimal auditory and visual stimuli. Also, each dog was subjected to multiple pacing cycles; i.e., heart rate was held at a low rate (48–60 beats/min or, in two dogs, at the idioventricular rate) for 2 days, then at 90 beats/min for 2 days, and these cycles were repeated three to four times. A half-cycle of 2 days was chosen to allow us to complete three or four cycles within a reasonable amount of time, and because resetting of the receptors or of the reflex occurs within 2 days (Piereg, 1970; Cowley et al., 1980). In addition, in three animals, the high ventricular pacing rate was maintained for 7 days, followed by the low rate for 7 days, followed again by the high rate for 7 days.

Recording sessions were 1.5 hours in length and began at the same time each day. On days when the rate was changed (day 0), we recorded for 45 minutes at each of the two ventricular rates. One dog developed ventricular tachycardia after two cycles and subsequently died. The data from this animal for these two cycles were very similar to the data from the other dogs and are included in our results.

Data Analysis

Average values of all variables were computed for each session. The averaged daily data at each ventricular rate gave a number of 4-day cycles. These were combined into a single 4-day average cycle by combining all of the data on day 0 at the low rate, all of the data on day 1 at the low rate, etc. (Fig. 1). Statistical differences between days for the group of dogs were determined by two-way analysis of variance, using the Bonferroni method for multiple comparisons (Snedecor and Cochran, 1967; Wallenstein et al., 1980). All data are presented as the means ± SEM. When standard error bars are absent in the figures, the error falls within the data point.

Results

Data from a representative animal are shown in Figure 1. The left panel shows the session averages of mean arterial pressure, cardiac output, total peripheral resistance, central venous pressure, and atrial and ventricular rates. In the right panel, the data have been combined into a single average 4-day cycle. At the high ventricular rate, arterial pressure is elevated and central venous pressure is low. Total peripheral resistance and cardiac output show large changes on the days when ventricular rate is changed. Total peripheral resistance returns to the same level after 2 days when ventricular rate is low and when ventricular rate is high. By contrast, while atrial rate shows a decrease between days 0 and 1 at the low rate, there is a maintained difference in atrial rate between the last days of each half-cycle. Atrial rate remains high (70 ± 4) when ventricular rate is low, and remains low (24 ± 3) when ventricular rate is high.

Atrial Rate

Figure 2 shows the combined average data for a 4-day cycle for all eight dogs in which atrial rate changes were studied. Arterial pressure is inversely related to atrial rate, and significant differences (P < 0.001) in both variables are maintained over each half-cycle. Pulse pressure changes continuously over
FIGURE 1. Data from a 12-day experiment. Records were taken for 1.5 hours each day. Ventricular rate was held at 60 beats/min on day 0, was changed to 90 beats/min on day 1, was again lowered to 60 beats/min on day 3, etc. On the days when rate was changed, recording sessions were 45 minutes long at each ventricular rate. On the right, data are averaged by day (first day at the low rate is averaged, etc.) to make an average 4-day cycle. MAP = mean arterial pressure; CO = cardiac output; TPR = total peripheral resistance; CVP = central venous pressure; HRA = atrial rate; HRV = ventricular rate. Discussion in text.

Each half-cycle; it does not parallel either arterial pressure or atrial rate. The difference in atrial rate between days 0 and 2 at the low ventricular rate just fails to achieve statistical significance. This difference (112 ± 9 to 94 ± 10) is a 30% recovery of the change in rate that occurred on the day when ventricular rate was lowered (52 ± 5 to 112 ± 9). (The difference between days 0 and 1 is, however, significant, P < 0.05.) Average differences and statistical analysis for all variables are shown in Table 1. The most important results are: (1) there are no significant changes in arterial pressure within each half-cycle, and there is a maintained difference between the last days of each half-cycle of 14.4 ± 1.0 mm Hg (P < 0.001); (2) the difference in atrial rates between the last days of each half-cycle is large, 41 ± 9 beats/min (P < 0.001); (3) pulse pressure changes continuously within each half-cycle.

In three animals we maintained the alternating high and low pacing rates for 1 week (Fig. 3). Again,
atrial rate remains low at the high pacing rate and high at the low pacing rate. These changes occurred in all animals, despite the fact that arterial pressure at the high ventricular rate tended, in two dogs, to decrease in time. Nevertheless, the arterial pressures during the high and low half-cycles overlapped at only one pressure in one dog.

Peripheral Resistance Studies

We calculated peripheral resistance in five of the animals. These data are displayed in Figure 1 for a single animal and in Figure 4 as averaged data for all five animals. Changes in mean pressure were similar to those in the atrial rate studies (Fig. 2). The cardiac output measurements are quite reproducible from cycle to cycle. For the group, cardiac output was $1.3 \pm 0.15$ liters/min on the first day at the low ventricular rate, but increased to $1.7 \pm 0.18$ liters/min over the 2 days at the low rate. When the rate was changed to 90 beats/min, cardiac output rose to $2.4 \pm 0.21$ liters/min. Over the subsequent 2 days it fell to $1.9 \pm 0.15$ liters/min, which just fails to differ significantly from 1.7 liters/min on day 2 at the low rate (critical value for $P = 0.05$ is 2.59, and the calculated $t$-value was 2.50). Since the ventricular rate was constant in each half-cycle, these changes reflect stroke volume. Stroke volume averaged $26 \pm 3$ ml on day 0 at the low rate and $33 \pm 4$ ml 2 days later. With the increase in rate, stroke volume fell to $26 \pm 2$ ml, and over 2 days fell further to $22 \pm 2$ ml.

Total peripheral resistance was $70.4 \pm 6.8$ mm Hg/liter per min on the first day at the low ventricular rate, and fell to $52.1 \pm 5.2$ mm Hg/liter per min over 2 days. When ventricular rate was increased, it fell to $42.4 \pm 3.6$ mm Hg/liter per min, and then increased over 2 days to $53.3 \pm 4.7$ mm Hg/liter per min. (This does not differ significantly from the value of 52.1 mm Hg/liter per min at the low rate.) Immediately following a change in ventricular rate, resistance showed an opposite change. During the remainder of that recording session, resistance changed very little (a few percent of the 2-day change).

Central venous pressure was measured in three dogs (Fig. 4); it was $6.0 \pm 1.6$ mm Hg when ventricular rate was low and $3.0 \pm 0.5$ mm Hg when ventricular rate was high. These changes were sustained over each 2-day half-cycle, and differences on the last day of each half-cycle are significant at the 0.005 level.

The results of an analysis of variance are shown in Table 1. Total peripheral resistance returns to the same level over each half-cycle in the face of a maintained difference in arterial and central venous pressures and in atrial rate.

Discussion

In the dog with heart block, varying ventricular pacing rate stepwise for periods of 2 days produced stepwise changes in mean arterial and central venous pressures. Changes in atrial rate were present at the end of each half-cycle, but changes in resistance disappeared over 2 days. The persistence of the changes in atrial rate implies that baroreceptors operate over the long term, whereas the lack of long-term changes in resistance implies the contrary. Heart rate and resistance were not controlled in parallel.

Resetting

When receptors are subjected to maintained high or low pressures, the threshold and the operating point of the curve relating firing frequency to pressure are reset toward the new mean pressure level.
Heart rate is the criterion, reflex effects seem to reset hypertensives have normal or high heart rates. If however, suggest that there is a heart rate (30% of the maximal change) from day 0 to day 1. However, no such recovery occurs during the half-cycle at the high ventricular rate.

**Arterial and Cardiopulmonary Receptors**

At the low pacing rate, arterial pressure was low, and a high heart rate and peripheral resistance would be expected. In addition, central venous pressure was high (Fig. 4). This would increase heart rate through the Bainbridge reflex (Bainbridge, 1915; Coleridge and Linden, 1955). The low arterial pressure should cause vasoconstriction, while the high central venous pressure should oppose vasoconstriction (Donald and Shepherd, 1978). The opposite changes would be expected at the high pacing rate. Pressure changes at the two sets of receptors reinforce each other for heart rate but not for peripheral resistance. If changes in resistance represent competing effects from two receptor sites, it is remarkable that the effects after 2 days are opposite and equal.

If arterial baroreceptors reset, we must look for some other cause of the maintained changes in atrial rate. A possible cause is the rise in venous pressure (Bainbridge, 1915; Coleridge and Linden, 1955), acting on cardiopulmonary receptors. There is evidence that cardiopulmonary receptors reset (Thoren et al., 1979; Mifflin and Kunze, 1982). If there is complete resetting of cardiopulmonary receptors, it appears unlikely that the heart rate responses are due to the Bainbridge reflex. The Bainbridge effect is not clearly reflex, and stretch of the atria or volume infusion leads to increases in heart rate in intact animals with the vagi cut, in isolated perfused hearts, or after ganglionic blockade (Titsos, 1937; Keatinge, 1959; Jensen, 1971; Scher and Bennett, 1982). It is not clear that this response to stretch is large enough or of sufficient duration to account for the changes in rate that we see.

**Other Considerations**

Arterial pulse pressure and pulse frequency are effective stimuli to the baroreceptors (Angell James and DeBurgh Daly, 1971). The rising pulse pressure might account for the fall in atrial rate and peripheral resistance from day 0 to day 2 at the low ventricular rate. Similarly, the fall in pulse pressure...
**FIGURE 3.** Daily recording session averages for 1-week pacing cycles for three dogs. Abbreviations as in Figure 1. Results as in previous figures.
pears due to the rise in mean arterial pressure (pulse pressure falls), this seems unlikely. The frequency of the pulse wave changes in the same direction as mean pressure. It does not appear that this interferes with our test of reflex resetting.

Hypotheses to Account for the Differential Response

1. There is complete resetting of all baroreceptors over 2 days. Resistance, therefore, returns to the same level. The changes in atrial rate are due to some other factor.

2. There is not complete resetting of arterial and cardiopulmonary baroreceptors, and the observed responses are due to the summed effects from these two sets of receptors.

3. The baroreflexes do not reset completely. Changes in peripheral resistance involve baroreceptor regulation and some opposing mechanism which returns peripheral resistance to its control level.

The difference in the responses of atrial rate and peripheral resistance indicates that more than one mechanism regulates them, whether there is resetting or not. Our clearest finding is the lack of parallelism between changes in heart rate and total peripheral resistance. Guo et al. (1982) found such a separation between heart rate and hindlimb resistance following partial arterial baroreceptor denervation. They pointed out that use of reflex heart rate changes as indices of baroreceptor sensitivity may be erroneous. Our results indicate that heart rate and total peripheral resistance responses can be differential when all baroreceptors are intact.

We gratefully acknowledge the donation of cardiac pacemakers by Dr. Eugene A. Hessel, Dr. Andrew J. Martinis, the Cordis Corp., Intermedics Corp., and Medtronics. We thank Roger Scott for his expert technical assistance and Diane Clark for her editorial assistance.

Supported by Program Project Grant HL16910-09 (NHLBI), PHS/NRSA Fellowship HL05888-02, and Research Grant RR00374-16, National Institutes of Health.

Address for reprints: Dr. Allen M. Scher, Department of Physiology & Biophysics/S-40, University of Washington, Seattle, Washington 98195.

Received March 7, 1983; accepted for publication December 5, 1983.

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FIGURE 4. Averaged data for five dogs in which ventricular rate was cycled from 50 to 90 beats/min, and mean arterial pressure, cardiac output, and total peripheral resistance were measured. Shown on the lowest plot are the data for three dogs in which central venous pressure was also measured. Abbreviations as in Figure 1. ** P < 0.01 compared with day 2 low; † P < 0.05 compared with day 0 low; †† P < 0.01 compared with day 0 high. Other symbols as in Figure 2. Discussion in text.
INDEX TERMS: Arterial baroreceptors • Bainbridge reflex • Blood pressure control • Autonomic nervous system
Long-term responses of atrial rate and peripheral resistance to changes in ventricular pacing rate in awake dogs with atrioventricular block.
S J Fisher, A M Scher and C R Wyss

Circ Res. 1984;54:196-203
doi: 10.1161/01.RES.54.2.196

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