Effects of steps in cardiac output and arterial pressure in awake dogs with AV block

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O'LEARY, DONAL S., ALLEN, M. SCHER, AND JOHN E. BASSETT. *Effects of steps in cardiac output and arterial pressure in awake dogs with AV block.* Am. J. Physiol. 256 (Heart Circ. Physiol. 25): H361–367, 1989.—In awake dogs with atrioventricular block, we examined the responses in total peripheral resistance and atrial rate to square-wave changes in mean arterial pressure or cardiac output. We compared the responses 2–3 min after a step change with the responses 19–20 min after a step. With resetting of arterial pressure control, the compensatory responses should decrease as the baroreceptors reset to the prevailing pressure. With step changes in mean arterial pressure or cardiac output, the responses in both peripheral resistance and atrial rate increased from minutes 2–3 to minutes 19–20. The responses in peripheral resistance also increased in animals studied after bilateral vagal block. All of the above changes were significant in the majority of cases. In another experiment, the animals were "conditioned" by 20 min at imposed high or low pressure. When control was returned to the animal after conditioning at high pressure, arterial pressure was not significantly different ($P > 0.05$) from the initial control levels. When control was returned after conditioning at low pressure, arterial pressure was significantly greater ($P < 0.05$) than during the initial control period. These results indicate an absence of resetting of the entire arterial pressure control system.

resetting; baroreceptors; peripheral resistance; atrial rate

MCCUBBIN ET AL. (17) showed in 1956, that the relationship between pressure and arterial baroreceptor firing rate was reset in chronically hypertensive dogs so that a frequency of baroreceptor firing seen at normal arterial pressure in normal animals was observed at higher-than-normal arterial pressure in hypertensive animals. Subsequently, baroreceptor resetting during hypertension has been confirmed in many studies (1, 2, 23). For some time, baroreceptor resetting was considered to require days or weeks. Recently, it has been reported that both the baroreceptors and the baroreflex show substantial resetting over minutes.

Three methods have been used to investigate this rapid resetting. The first is observing the time course of baroreceptor activity after a step change in pressure at the baroreceptors. Munch et al. (20) observed an exponential decay of the initial increase in baroreceptor activity produced by a step increase in pressure at the baroreceptors. The second is generating baroreceptor or baroreflex function curves before and after conditioning the baroreceptors at high or low pressure. Several investigators have reported that after the baroreceptors are exposed to a conditioning pressure for a period of time (5–20 min), the curves relating pressure at the baroreceptors to baroreceptor activity or to an index of baroreflex responses (i.e., heart rate or systemic arterial pressure) are shifted in the direction of the conditioning pressure (5, 7, 9, 10, 12, 14–16, 19, 22). The third is determining the threshold of the baroreceptors or the baroreflex before and after conditioning the baroreceptors at an altered pressure. As in *method 2*, after the baroreceptors are exposed to a conditioning pressure, the threshold for activation of the baroreceptors or the baroreflex are shifted in the direction of the conditioning pressure (7, 9, 15, 16, 22).

Although rapid resetting of the baroreceptors and baroreflex responses has been widely demonstrated, rapid resetting was not observed in some studies (4, 26). In one recent report (6), resetting of the baroreceptors to elevated pressure was attenuated or prevented when pressure was pulsatile.

Short-term control of arterial pressure occurs mainly through changes in heart rate and peripheral resistance mediated by the baroreceptor reflex. A possible implication of rapid resetting of the baroreceptors and the baroreflex is that the entire arterial pressure control system may adapt to a maintained change in arterial pressure.

We have developed techniques for the control of mean arterial pressure and of cardiac output in conscious dogs with atrioventricular (AV) block (28). Using these techniques, we asked the following questions. *1*) If arterial pressure is moved to and held at a high or low level, which causes compensatory changes in peripheral resistance and heart rate, are these changes maintained for 20 min? If resetting of the entire arterial pressure control system occurs, then the responses should decrease as the system resets. This question is examined in *series 1A* below. The same question was asked (with larger changes in arterial pressure) about responses after imposed changes in cardiac output (*series 1B*) and about changes in cardiac output after vagal block when only arterial (carotid) baroreceptors are functional (*series 1C*). *2*) Does the "control point" of the arterial pressure control system change after a 20-min conditioning period at high or at low arterial pressure? (Control point here is the pressure level at which an animal voluntarily holds its pressure with no external perturbations.) A shift in the baroreflex function curve in the direction of the conditioning pressure is accompanied by a shift in the control point (*method 2* above). Thus, if resetting of the arterial pressure control system occurs, pressure subsequent to the conditioning period should shift from the initial control level toward the conditioning pressure.

In considering the questions above, we examined responses over 20 min after a change. In published studies, rapid resetting of reflex responses is substantial in the first 5 min after a pressure change and continues over 15 or 20 min (15, 16). Our procedures would have detected resetting of the arterial pressure control system over the first few minutes or at any time during the 20-min period.

METHODS

Surgical Preparation

Fourteen healthy mongrel dogs of either sex were prepared using standard aseptic techniques. In the first surgical session, the carotid arteries were placed in skin tubes bilaterally, and both vagi were brought to subcutaneous positions in the neck. At a second surgical session, a right thoracotomy was performed through the fourth intercostal space. The AV node was blocked by a modification of the technique of Steiner and Kovalik (24). An electromagnetic flow probe was placed on the ascending aorta to monitor systemic blood flow, and electrodes were sewn into the right atrial appendage and the apex of the left ventricle for recording atrial rate and stimulating the ventricles, respectively. The chest was closed, and the animals were allowed to recover for 2–3 wk. During this time, the ventricles were paced at 72–100 beats/min using an external pacemaker. Subsequently, Tygon catheters were inserted into a side branch of the femoral artery to monitor arterial pressure and near the atria-vena caval junction via the right jugular vein to monitor central venous pressure. The animals were allowed to recover for an additional week. All electrodes and catheters were exteriorized between the scapulae through subcutaneous tunnels.

Experimental Protocol

The animals lay on a padded couch. The ventricular electrodes were attached to a stimulator to control ventricular rate. The aortic flow probe was attached to a flowmeter (Zepeda Instruments) to monitor cardiac output. The arterial and central venous pressure catheters were connected to pressure transducers. The atrial electrodes were connected to a window discriminator that was triggered by each atrial depolarization. The output of the discriminator was fed into the computer (LM^2), which determined atrial rate. Arterial pressure, central venous pressure, aortic blood flow, and atrial rate were displayed on a pen recorder (Beckman Instruments). The arterial pressure, central venous pressure, and aortic flow signals were fed to a 12-bit analog-to-digital converter connected to the computer. The computer averaged each variable for each ventricular beat (27). These beat-by-beat mean data were stored on digital tape and were displayed on the pen recorder through 12-bit digital-to-analog conversion. Beat-by-beat data were averaged into 1-min samples. Total peripheral resistance (TPR) was calculated as TPR = (MAP − CVP)/CO, where MAP is mean arterial pressure, CVP is central venous pressure, and CO is cardiac output.

Series 1: Step Changes in Arterial Pressure or Cardiac Output

Series 1A: Control of arterial pressure (n = 5). The animal was usually allowed to control its ventricular rate, CO, and arterial pressure for 20 min (atrial depolarization triggered the ventricular stimulation; we refer to this as the "AV-linked" condition). We then switched to computer control of arterial pressure. The procedure is similar to that described previously for the control of CO (28). Ventricular pacing rate is varied so as to keep MAP at a target level. With this procedure, arterial pressure can be maintained at a selected level ±1 mmHg on a beat-by-beat basis, and step changes of ~10 mmHg can be achieved. Arterial pressure was held at a high or low level for 20 min. After this time, arterial pressure was switched to the opposite (low or high) level for 20 min. This switching was repeated for the duration of the experiment, usually 1–2 h.

Series 1B: Control of cardiac output (n = 5). The pressure changes we could impose in *series 1A* were limited (see DISCUSSION below). We therefore conducted a second series of experiments in which (through control of the animal's cardiac output) we were able to impose larger changes in arterial pressure than in *series 1A*.

The animal was allowed to control its CO for 20 min. We then switched to computer control of CO described previously (28). Briefly, the aortic flow is integrated in real time to yield stroke volume. The computer then calculates the interbeat interval necessary to maintain CO at the desired level. At the end of the proper interval, the ventricle was stimulated. With this procedure, CO can be maintained at the selected level on a beat-by-beat basis to within 1–2%. In addition, square-wave changes in CO can be imposed. CO was held at a high or low level for 20 min. After this time, CO was switched to the opposite (low or high) level for 20 min. This switching was repeated for the duration of the experiment, usually 1–2 h.

Series 1C: Experiments in animals without aortic or cardiopulmonary baroreceptors (n = 5). To determine whether the results of the above experiments might be influenced by resetting of cardiopulmonary baroreceptors, experiments with changes in CO (*series 1B* above) were conducted in animals with vagi acutely blocked by local anesthetic. This leaves only the arterial receptors in the carotid sinus. To block the vagi, 1–2 ml of lidocaine (2%) were injected bilaterally along each subcutaneous vagus. This was followed 2–5 min later by 2–5 ml of Marcaine (0.75%). Vagal block produced high and regular atrial rate without respiratory variation, slow deep respirations, and Horner's syndrome. Step changes in CO were imposed as described in *series 1B*.

Series 2: High and Low Pressure Conditioning ($n = 5$)

For the first 20 min, ventricular stimulation was triggered from atrial depolarization (AV-linked). At the end of this period, ventricular rate was increased to ~120 beats/min or decreased to ~40 beats/min to produce a maximal change in MAP, atrial rate (HRA), and TPR. Each rate was held for 20 min. After this time, the animal was returned to the AV-linked mode for 20 min. Thus the animal regained control over heart rate, CO, and MAP.

Analysis

Series 1. There were immediate reflex changes in TPR and HRA after the imposed step changes in arterial pressure or CO. In *series 1A* and *1B*, the changes in TPR and HRA in response to the step change in arterial pressure were averaged over minutes 2–3 (initial response) and over minutes 19–20 (final response). We ignored the first minute after the change to avoid transients. We then calculated the ratio of the change in resistance to the change in pressure (ΔTRP/ΔMAP) and the ratio of atrial rate change to pressure change for each of these periods. In *series 1C* the vagi were blocked. Therefore only the TPR responses were analyzed.

For all *series 1* experiments, the responses to increases and decreases in MAP and CO were analysed separately. For each animal, the above ratios for each change in MAP or CO were averaged to yield mean ratios for each animal. The average of the ratios during minutes 2–3 and 19–20 after a step change in CO were compared using Wilcoxon signed-rank test. If resetting of MAP control occurred over the first few minutes or thereafter, the above ratio would decrease over the 20 min.

Series 2. MAP and HRA during minutes 2–4 of the AV-linked periods after the 20-min conditioning period at high or low pressure were compared with the average levels during the initial AV-linked (control) and conditioning periods by analysis of variance and Newman-Keuls tests. If the arterial pressure control system had been reset by a period at high pressure, the animal would have maintained a higher pressure during the subsequent AV-linked period than that which maintained during the initial control AV-linked period. Similarly, the animal would have maintained a lower than control AV-linked arterial pressure after a conditioning period at lower arterial pressure. Average data are expressed as means ± SE.

RESULTS

Series 1A

In response to the maintained change in MAP, the compensatory responses in TPR and atrial rate increased over the 20-min period. The average change in MAP at the initial step up or down was 9.2 ± 0.6 mmHg. In response to a maintained decrease in MAP, the final changes in TPR and HRA were significantly greater than the changes during the initial period after the step change in MAP (0.27 ± 0.19 vs. 1.01 ± 0.27 TPR U/mmHg, $P < 0.05$; and 2.7 ± 0.5 vs. 5.4 ± 0.3 beats$\cdot$min$^{-1}\cdot$mmHg^{-1}, $P < 0.05$). In response to a maintained increase in MAP, the final change in TPR was greater than the initial change (0.40 ± 0.14 vs. 0.75 ± 0.22 TPR U/mmHg, $P = 0.05$). The average final change in HRA was greater than the initial change; however, this difference did not reach statistical significance (4.5 ± 0.6 vs. 6.8 ± 1.6 beats$\cdot$min$^{-1}\cdot$mmHg^{-1}, $P > 0.05$).

Figure 1 shows a *series 1A* experiment. In response to the imposed changes in MAP, the compensatory responses in TPR and HRA increased over 20 min. With resetting, the changes in TPR and HRA produced by the change in MAP would have decreased as the arterial pressure control system reset.

As indicated above, the compensatory changes in resistance grew larger as we attempted to hold pressure high or low for a 20-min period. These resistance changes oppose our attempts to maintain MAP at a high or low level. As resistance changes, the CO that is needed to maintain high and low pressure may become lower or higher than the range of our control. Therefore, our strategy was to set pressure at a level that could be maintained for 20 min. This forced us to use small pressure steps. When we attempted to impose large pressure steps, the animal would often "break out" of our control as described below. Since we can cause larger initial changes in MAP when we control CO, we conducted the experiments in *series 1B*.

Series 1B.

For the entire group of animals, CO during the high cardiac output period averaged 3.11 ± 0.48 l/min. When

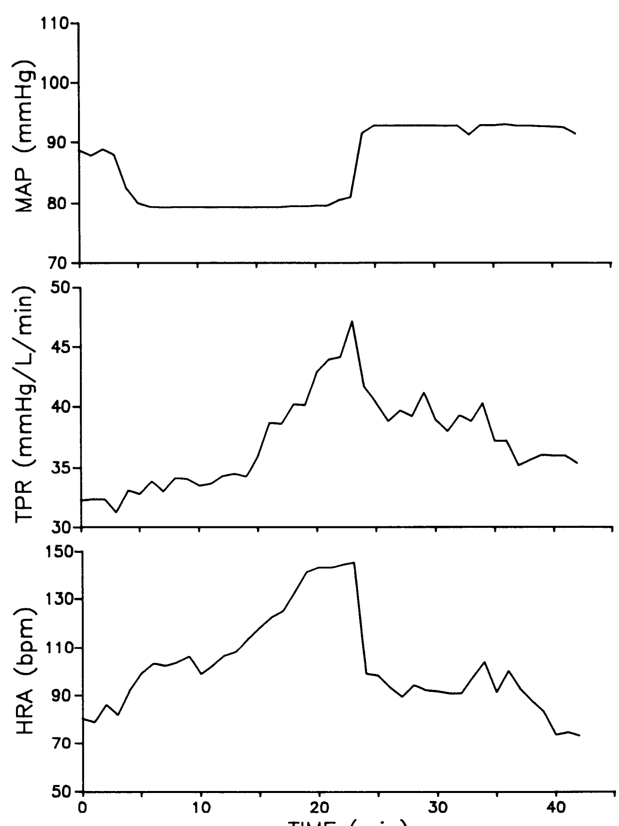

FIG. 1. Responses in total peripheral resistance (TPR) and atrial rate (HRA) to step changes in mean arterial pressure (MAP) from 1 animal. Compensatory responses in TPR and HRA increased over the 20 min imposed change in MAP.

we held CO at a low level, it decreased to 2.12 ± 0.28 l/min (P = 0.017). With the step changes in CO, MAP changes averaged 14.5 ± 0.7 mmHg.

In response to a decrease in CO, both the TPR and HRA changes per millimeter Hg change in MAP increased over the 20-min period. During the initial 2–3 min after a step decrease in CO, the TPR response averaged 0.56 ± 0.14 TPR U/mmHg, and the atrial rate response averaged 2.7 ± 0.5 beats$\cdot$min$^{-1}\cdot$mmHg^{-1}. Both were significantly less than the responses at the end of the 20-min period (1.01 ± 0.27 TPR U/mmHg, $P < 0.05$; and 5.4 ± 0.3 beats$\cdot$min$^{-1}\cdot$mmHg^{-1}, $P < 0.05$). A similar pattern was observed in response to an increase in CO. Again the initial responses in TPR and HRA were less than the responses at the end of the 20-min period (0.56 ± 0.14 vs. 1.45 ± 0.44 TPR U/mmHg, $P < 0.05$; and 3.8 ± 0.2 vs. 6.4 ± 1.4 beats$\cdot$min$^{-1}\cdot$mmHg^{-1}, $P < 0.05$).

Figure 2 shows a typical *series 1B* experiment. In response to changes in CO, the compensatory responses in TPR and HRA tended to increase throughout the 20-min period. If resetting of MAP control had occurred, the changes in resistance and atrial rate produced by the changes in pressure should have decreased as resetting occurred. In fact, they increased.

Series 1C

Step changes in CO (*series 1B* experiments) were repeated after bilateral vagal block, which eliminates

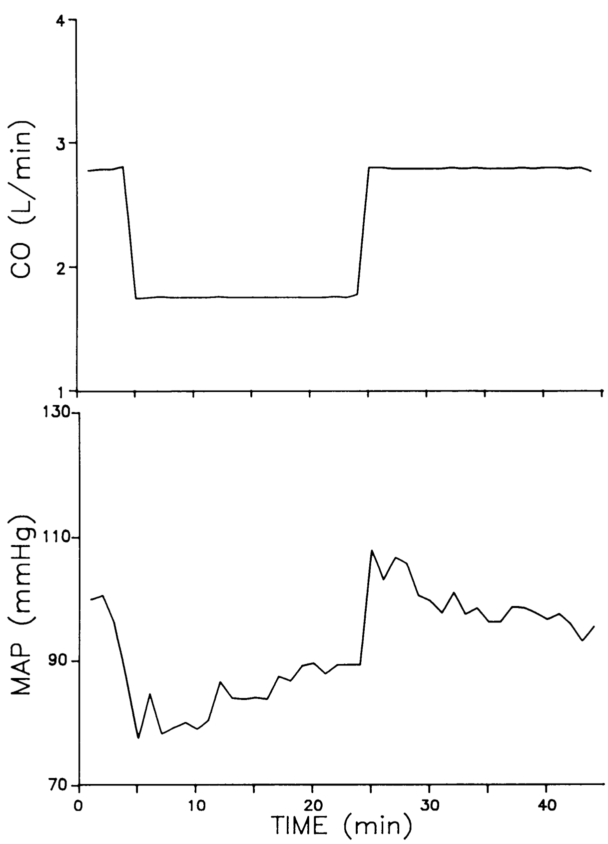

FIG. 2. Responses in mean arterial pressure (MAP) and atrial rate (HRA) to step change in cardiac output (CO) from 1 animal. In response to step changes in CO, changes in MAP decreased over 20 min, reflecting continued compensatory changes in peripheral resistance.

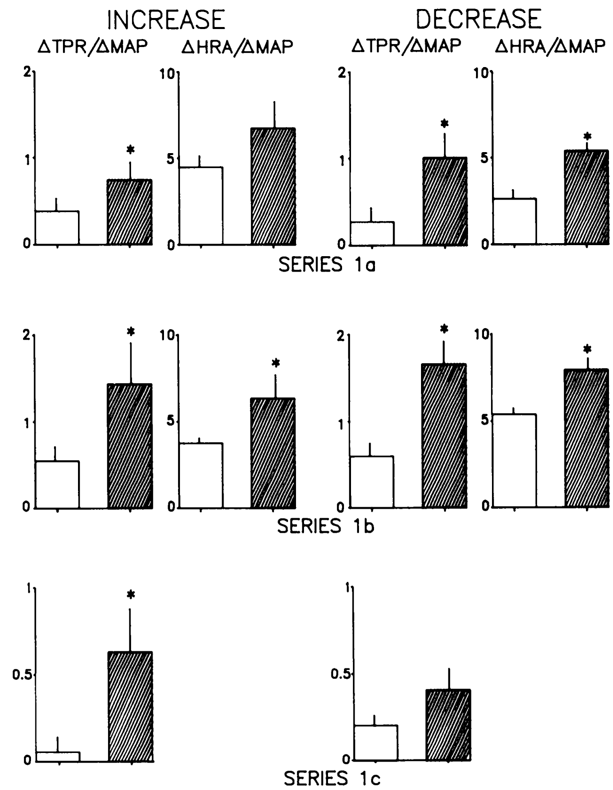

FIG. 3. Average responses in total peripheral resistance (TPR) and atrial rate (HRA) during initial (□) and final (▨) periods of 20-min increased or decreased mean arterial pressure (*series 1A*), cardiac output (*series 1B*), and cardiac output after vagal block (*series 1C*). * $P < 0.05$ vs. initial response.

aortic and cardiopulmonary receptors. Thus these experiments examine responses in animals with only arterial (carotid) receptors. As in *series 1B*, the ratio of resistance change to pressure change was used to determine the presence or absence of resetting of arterial pressure control.

During the initial period after decrease in CO, ΔTPR/ΔMAP averaged 0.21 ± 0.06 TPR U/mmHg. At the end of the 20-min period, the average ΔTPR/ΔMAP increased to 0.41 ± 0.12 TPR U/mmHg, however, this was not a significant change ($P > 0.05$). In response to an increase in CO after vagal block, the initial response in TPR was significantly less than the response at the end of the 20-min period (0.06 ± 0.08 vs. 0.64 ± 0.23 TPR U/mmHg, $P < 0.05$). Again the results show an absence of resetting of the arterial pressure control system.

Figure 3 summarizes the results from all *series 1* experiments. In response to an increase or decrease in MAP or CO, the compensatory responses in TPR and HRA increased over 20 min.

Series 2

These experiments were designed to test whether the (AV-linked) arterial pressure that the animal "voluntarily" holds is affected by a 20-min conditioning period at imposed higher or lower arterial pressure.

The average mean arterial pressure during minutes 2–4 after high arterial pressure and low arterial pressure were compared with the average MAP during the (AV-

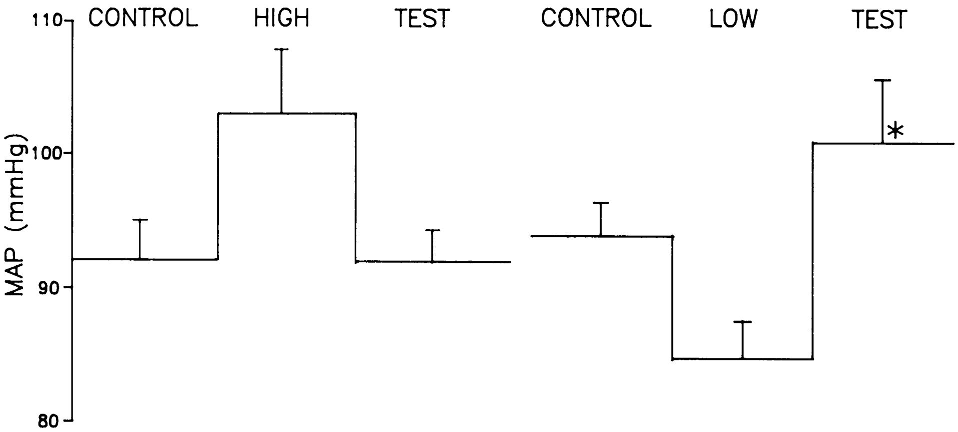

FIG. 4. Average results from *series 2* experiments. Animals were initially allowed to control their own arterial pressure for 20 min by triggering ventricular stimulation by atrial depolarization (Control). Arterial pressure was then increased (High) or decreased (Low) for 20 min by altering ventricular rate. Pressure control was then returned to animals (Test) to test whether resetting of arterial pressure control had occurred. MAP during Control, High, and Low represent average levels during respective 20-min periods, whereas MAP during Test represents average levels during minutes 2–4 after return of control to animal. * MAP significantly different ($P < 0.05$) during Test period from initial Control period.

linked) control period. The first minute after return to the AV-linked mode was excluded to avoid transients. In studies of the responses to increases in arterial pressure, arterial pressure during the AV-linked control period averaged 92.1 ± 3.3 mmHg and atrial rate averaged 72.2 ± 4.6 beats/min. During high-frequency ventricular stimulation, MAP increased to 103.1 ± 4.5 mmHg ($P < 0.05$), and HRA decreased to 42.4 ± 11.2 beats/min ($P < 0.05$).

MAP during minutes 2–4 after the conditioning period at high rate averaged 91.9 ± 5.3 mmHg and HRA averaged 74.5 ± 5.0 beats/min. Neither were significantly different ($P > 0.05$) from their respective control levels. For the responses to decreases in arterial pressure, MAP averaged 94.4 ± 2.4 mmHg, and HRA averaged 76.1 ± 5.8 beats/min during the initial 20-min AV-linked control period. When ventricular rate was lowered, MAP decreased to 85.1 ± 2.6 mmHg ($P < 0.05$), and HRA increased to 136.5 ± 9.7 beats/min ($P < 0.05$). MAP during minutes 2–4 after conditioning at low arterial pressure averaged 101.5 ± 4.2 mmHg, which was significantly greater ($P < 0.05$) than the average level during the initial control period. HRA averaged 77.1 ± 5.5 beats/min during the test period, which was not significantly different ($P > 0.05$) from the control level. Figure 4 shows the average results from *series 2* experiments. These results would not be expected if resetting of the arterial pressure control system occurred.

DISCUSSION

If resetting of the arterial pressure control system had occurred, the vasomotor and atrial rate changes caused by the changes in arterial pressure in *series 1* experiments would have decreased in time as resetting occurred. In *series 2*, pressure would have been maintained at a high level (compared with the control AV-linked period) after a 20-min "conditioning period" at high pressure and at a low level after a conditioning period at low pressure. In neither case were these results observed.

In *series 1*, when arterial pressure changed, the peripheral resistance initially changed in an opposite direction. Resetting of the arterial pressure control system would have led to a progressive decrease of this vasomotor response over the first 5–20 min. Previous studies (15, 16, 20) have shown substantial baroreceptor and baroreflex resetting in 5 min, which continues for 15 or 20 min. For either changes in pressure (*series 1A*), changes of output (*series 1B*) or changes in output when only carotid receptors are active after vagal block (*series 1C*), the changes in resistance increased over 20 min. The changes in atrial rate (*series 1A* and *1B*) behaved similarly. In all *series 1* experiments (Fig. 3), the responses in peripheral resistance and atrial rate were opposite to those predicted if resetting of arterial pressure control occurred. This occurred for both increases and decreases in arterial pressure. In response to maintained 20-min changes in arterial pressure or cardiac output, the compensatory responses in total peripheral resistance and atrial rate increased over the 20-min period, whereas resetting would predict a progressive decrease in the responses.

In *series 2*, we ask where does the awake animal maintain his arterial pressure after a 20-min "conditioning period" at high or low pressure? If resetting of arterial pressure control had occurred, the animal would maintain his pressure at a high level after 20 min at a high pressure and at a low level after 20 min at a low pressure. We compared the mean arterial pressure and atrial rate during minutes 2–4 of the (AV-linked) periods after forced high or low pressure to the average levels during the initial 20-min (AV-linked) control period. Resetting of arterial pressure control should have been most pronounced immediately on return of pressure control to the animal. Contrary to what would be expected with resetting, the levels of both mean arterial pressure and atrial rate during the AV-linked periods after 20 min at high pressure were not different ($P > 0.05$) from the AV-linked control values. In addition, after the 20-min conditioning period at low arterial pressure, arterial pressure was higher than the control level ($P < 0.05$), whereas atrial rate was not significantly different ($P > 0.05$) from the control level. It is possible that this increase in pressure was caused by the effects of circulating vasoconstrictor substances (i.e., vasopressin, angiotensin II, and/or catecholamines) that were released in response to the imposed decrease in arterial pressure.

A qualitative observation about resetting of the arterial pressure control system can be made from our unsuccessful attempts to impose changes in arterial pressure in *series 1A*. The computer algorithm attempts to maintain mean arterial pressure at a selected level by adjusting ventricular rate. If resetting of the arterial pressure control system occurred, and the changes in resistance caused by the pressure changes had decreased with time, it would be progressively easier to maintain the selected pressure changes. In actuality, as the animal continually attempted to maintain pressure, the opposite was true. For example, when we chose to increase mean arterial pressure by 20 mmHg, the initial change in pressure was easily imposed, but as time progressed, the reflex vasodilation due to the animal's attempt to correct pressure became greater, and further increases in cardiac output were needed to maintain pressure. Finally, the animal could not supply sufficient cardiac output and pressure fell. A similar limitation on imposed pressure changes was seen with decreases of pressure. Here attempts to maintain a low pressure failed when the required ventricular stimulation rate fell below the idioventricular rate. The fact that control did not reset limited our range of control of arterial pressure.

Evidence that rapid resetting of baroreceptor afferent nerve activity can occur in response to static pressure changes at the receptors is clear and unequivocal (7, 9, 20). As far as resetting of baroreflex responses are concerned, answers are mixed. Support for baroreflex resetting is provided in the work of Dorward et al. (9, 10) and Kunze (15, 16) but not by the experiments of Undesser et al. (26) and Aylward et al. (4).

There are two possible explanations for the absence of resetting of arterial pressure control in our studies. First, it is possible that we did not provide the proper stimulus for baroreceptor resetting. Second, it is possible that some other response obscured effects of baroreceptor resetting. Such a response might have nonneural aspects.

Concerning the stimulus for resetting, it is possible that *1*) there is a threshold for resetting, *2*) pulse pressure plays a role in resetting, *3*) changes in central venous pressure prevent or obscure resetting of arterial pressure control, *4*) the levels of systolic and diastolic pressure might have changed in some fashion that would counteract resetting, and *5*) changes in ventricular rate during the 20-min periods of mean arterial pressure or cardiac output control would counteract resetting.

We do not believe that a threshold for resetting has been demonstrated. The pressure changes we caused were of the order of 15 mmHg in the *series 1B* experiments, and in all experiments they were sufficient to cause substantial changes in atrial rate and peripheral resistance. If baroreceptor or baroreflex resetting does not occur with small pressure changes, that fact is noteworthy.

Concerning pulse pressure, the results of Chapleau et al. (6) indicate that resetting of baroreceptor afferent activity to increased pressure is minimized or absent if the pressure is pulsatile. In addition, we recently completed studies investigating the role of pulse pressure in baroreflex resetting, using the reversibly isolated carotid sinus preparation in conscious dogs (18). In response to a step increase in carotid sinus pressure to a high static level, substantial resetting of the depressor response was observed. However, when carotid sinus pressure was moved to a high level but remained pulsatile, resetting was abolished.

During step changes in arterial pressure and cardiac output, small changes in central venous pressure also occurred (~0.5–2 mmHg in the opposite direction to the arterial pressure changes). We were concerned that reflex responses originating from cardiopulmonary receptors (13), and possible resetting of these (19), might have obscured the resetting of arterial pressure control. In *series 1C*, step changes in cardiac output were performed after bilateral vagal block, which removes the cardiopulmonary and aortic receptors. Again, an increase in the compensatory resistance changes occurred throughout the 20-min step change in cardiac output. These results are consistent with those observed without vagal block and indicate that the apparent lack of resetting of arterial pressure control was not due to confounding effects from low pressure receptors.

Concerning systolic and diastolic pressure, both of these changed in the same direction as the mean pressure in all of the above studies. Thus none of these pressure-related hypotheses seems demonstrated.

During the 20-min periods of low or high mean arterial pressure or cardiac output in *series 1* experiments, ventricular rate was varied to maintain the controlled variable at the selected level. For example, ventricular rate tended to decrease over the 20-min period when mean arterial pressure was decreased (*series 1A*). The continual increase in total peripheral resistance made it necessary to decrease ventricular rate to maintain mean arterial pressure constant at a low level. This reduction in ventricular rate would not have been necessary had total peripheral resistance not continually increased. In addition, when cardiac output was controlled (*series 1B* and *1C*), the changes in ventricular rate over 20 min tended to be opposite to those in the mean arterial pressure control experiments. For example, in response to a decrease in cardiac output, mean arterial pressure initially decreased and then recovered as total peripheral resistance increased. As mean arterial pressure partially recovered, afterload increased requiring an increase in ventricular rate to maintain cardiac output constant at the low level. The changes in ventricular rate over 20 min were opposite in the mean arterial pressure and cardiac output control experiments, yet the results were the same. Thus we do not feel the changes in ventricular rate confound our results.

Concerning other possible responses, in these experiments pressure was changed throughout the entire cardiovascular system. In response to the imposed changes in cardiac output or arterial pressure, changes in the circulating levels of vasoactive substances (vasopressin, angiotensin II, catecholamine, etc.) may have occurred, and these may affect peripheral resistance or atrial rate either directly or through modulation of the baroreflex responses (3, 8, 11, 21, 25). Such effects may have acted to counteract or obscure resetting of the baroreflex. However, the question addressed in this study was whether the entire cardiovascular system behaves as if resetting of arterial pressure control occurs. In our experiments the system does not act as if resetting of arterial pressure control occurs.

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