Total Systemic Autoregulation in the Dog and Its Inhibition by Baroreceptor Reflexes

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ABSTRACT

Although many organs maintain constant blood flow despite changes in perfusion pressure, autoregulation in the total systemic circulation has only been reported in animals after destruction of the central nervous system. The present study examined the role of the baroreceptors in this autoregulatory response in open-chest dogs anesthetized with chloralose-urethane. Cardiac output was varied over nearly a twofold range by altering myocardial contractility with either inotropic agents or controlled myocardial ischemia. Cardiac output, determined by dye dilution, and mean aortic pressure stabilized within 3 minutes after the start of infusions of calcium (15-62 mg/min) into the cannulated left coronary artery or the reduction of coronary flow. With bilateral vagotomy and carotid sinus denervation, autoregulation of total peripheral flow was observed. Thus, changes in cardiac output evoked parallel changes in total peripheral resistance and wide variations in aortic pressure. However, with the baroreceptors intact, changes in cardiac output evoked inverse changes in total peripheral resistance which resulted in regulation of aortic pressure. We concluded that autoregulation in peripheral vascular beds could result in autoregulation of total peripheral flow after simple baroreceptor denervation. However, the baroreceptor reflexes normally achieved regulation of aortic pressure by inhibiting autoregulation in much of the peripheral circulation.

KEY WORDS: denervation of baroreceptors, myocardial contractility, cardiac output, aortic pressure, peripheral resistance, coronary blood flow, myocardial ischemia.

Autoregulation of blood flow has been described for many organs including kidney (1, 2), brain (3), skeletal muscle (4), myocardium (5), and mesentery (6, 7) in animals and brain (8) and kidney (9) in man. However, the summation of individual responses resulting in autoregulation of the total systemic circulation has only been described in animals after extirpation of their central nervous system and spinal cord (10). The present study was designed to reevaluate the pressure-flow characteristics of the periphery with reflexes intact and after selective denervation of the carotid sinus and the aortic arch baroreceptors. The selective denervation was performed primarily to allow maintenance of a more physiological animal preparation and evaluation of the role of the mechanoreceptors in masking or inhibiting an autoregulatory response of the total systemic circulation.

Methods

Left thoracotomies were performed in eight dogs weighing 21-29 kg (average 24.7 kg) following anesthesia with a mixture of chloralose (70 mg/kg) and urethane (700 mg/kg) administered intravenously. Positive-pressure respiration was maintained with 100% O₂. The main left coronary artery was cannulated with a Gregg cannula (11) and perfused with blood drawn from a femoral artery. A Sigmamotor pump was used to control coronary perfusion. Two polyethylene catheters were inserted into the descending aorta via the remaining femoral artery; the more centrally advanced catheter was connected to a Statham P23Db pressure transducer, and the more distally situated one was connected to a type 103 IR Gilford cuvette densitometer for determining cardiac output by the indocyanine green dye-dilution method. The sampling rate through the cuvette was held constant with a withdrawal pump at 46 ml/min. Accurate, repeated injections of 2 mg of green dye (volume 1.0 ml), using a Cornwall syringe pipetter, followed by 2-ml saline flushes were made directly into the left atrium through a small polyethylene catheter. Data analysis was facilitated by an analog computer which was programed to compute...
the area under the indicator curve associated with the primary circulation of the dye. This computation involved continuously summing the integral of the curve with a value for the remaining area under the curve predicted from the assumption of an exponential decay of the curve. Following control measurements, baroreceptor denervation was accomplished by infiltrating procaine amide intramurally into both carotid sinuses and bilaterally sectioning the vagi. Denervation was judged to be complete only when bilateral occlusion of the common carotid arteries failed to elicit a pressor response. Since the acute effects of eliminating moderator reflexes per se on peripheral resistance are fairly long (12), a 20–30-minute recovery period was observed following neuroablation to avoid these compensating fluctuations in vasomotor tone.

The protocol is illustrated by the records in Figure 1. Aortic pressure and cardiac output were recorded at various flow states before and after baroreceptor denervation. Cardiac output was varied (1) by underperfusing the cannulated left coronary artery, and thus establishing controlled myocardial ischemia and (2) by constantly infusing calcium chloride (15–62 mg/min) into the left coronary artery. Data were collected only after central aortic pressure had come to a steady-state value. In most instances, cardiac output curves at each pressure were determined in duplicate and were reproducible within ±5%. Cardiac output under control conditions was measured several times during each experimental procedure; the measured values were reproducible within ±13% in the worst case and typically were reproducible within ±5%.

**Results**

Figure 2 illustrates the time course to the new hemodynamic steady state following left coronary artery underperfusion in one dog. The data displayed in this figure were from a dog with its baroreceptors ablated, but the sequence was also representative of the intact state. As a consequence of coronary artery underperfusion, coronary pressure fell quickly to a new equilibrium in about 1–1.5 minutes. Central aortic pressure had a slightly larger time constant but equilibrated within 3 minutes. The close similarity in dye output values on repeated determinations indicated that cardiac output reached a steady state with a similar time course. These time responses were similar in all dogs. Aortic pressure and cardiac output remained stable when the duration of coronary artery underperfusion was extended to 10 minutes. However, to avoid ventricular fibrillation, cardiac ischemia was usually limited to 4 minutes.

Values of aortic pressure and cardiac output obtained at different steady states were plotted on a pressure-flow diagram (Fig. 3A). Data from intact and denervated dogs were fitted with straight lines by the method of least squares ($r = 0.95$ and 0.98, respectively). With reflexes intact, the periphery acted to hold pressure relatively constant over a twofold range of cardiac outputs. However, with baroreceptor denervation, pressure regulation was lost, and the periphery responded to hold flow relatively constant (autoregulation). The same data in Figure 3A were replotted in Figure 3B expressed in terms of peripheral resistance (aortic pressure/cardiac output). With reflexes intact, resistance varied inversely with cardiac output: vasoconstriction occurred at low cardiac outputs but lessened with increasing flow. Conversely, with...
denervation, resistance varied as a direct function of flow with progressive vasoconstriction at higher cardiac outputs.

Figure 4 illustrates that in some experiments flow regulation was limited to a central range of pressures and cardiac outputs. The end points were not included in the statistical analysis.

As noted in Figures 3 and 4, the pressure-flow curves with reflexes intact were characterized by a relatively steep slope (Δ cardiac output/Δ aortic pressure) and, when extended, had a negative y-intercept. Denervation caused the pressure-flow curves to have a much flatter slope and a positive y-intercept. A clear distinction between pressure and flow regulation is made based on the sign of the y-intercept. The data for all eight dogs are compared by slope and y-intercept in Figure 5. Criteria for pressure regulation—high initial slope values and negative y-intercepts—were observed in the intact state. With denervation, the slope was reduced and the y-intercept became positive in every case. The changes in slope and intercept were significant ($P < 0.01$), and the intercept differed significantly from zero ($P < 0.01$). Thus, the response of the total systemic circulation to a variation in cardiac output changed from one that regulated pressure to one that regulated flow when baroreceptor mediation was lost.

Discussion

The present study demonstrated that total body autoregulation occurred following ablation of the carotid sinus and the aortic arch baroreceptors. It also emphasized the importance of baroreceptor control in peripheral pressure-flow relationships.
Ablation of the baroreceptor reflexes changed the total body vascular bed from a pressure-regulating system to a flow-regulating system. The time required to achieve a new steady state for the pressure-flow adjustments in the denervated state was similar to that for autoregulatory responses observed in individual organs.

Levy and his co-workers (13) were the first to describe pressure-flow relationships for the systemic vascular bed in animals before and after carotid and aortic baroreceptor ablation. They concluded that, following reflex denervation, the periphery usually acted as a passive isoresistance system. Regression lines for their data intersected the pressure-flow coordinate axes very close to the origin. However, in some experiments, they noted positive flow intercepts after denervation, suggesting autoregulation. In the present study, positive flow intercepts occurred in every case after denervation. Reasons for this discrepancy are unexplained, but they may relate in part to the differences in animal preparation and experimental design.

Following the observations of Folkow (14), Granger and Guyton (10) were recently able to conclusively demonstrate whole-body autoregulation in animal studies. Emphasis was placed on the elimination of all extrinsic reflexes, both central and peripheral, by decapitation and spinal cord destruction to allow expression of intrinsic or local cardiovascular controls on the periphery. This procedure led to systemic hypotension requiring constant infusions of epinephrine and norepinephrine. The resulting autoregulatory responses were characterized by a prolonged time course to the new steady state, averaging 35 minutes for single-step acute pressure changes and 8 minutes for multistep slow changes.

In contrast to the experiments of Levy et al. (13) and Granger and Guyton (10), which used arterial reservoir bottles to vary systemic pressure, the present study varied cardiac output by changing myocardial contractility. A satisfactory range of cardiac outputs was effected by changing coronary artery perfusion and inotropic stimulation; this fact reemphasizes the influence of myocardial contractility in determining cardiac output (15-18). Blood pressure support was not required so that peripheral vasomotor tone was uninfluenced by pharmacologic intervention.

The present data indicated that complete neuroablation was not necessary to unmask whole-body autoregulation. Baroreceptor denervation was sufficient, and preservation of a more physiological preparation may explain why much shorter times, which were more consistent with autoregulation in individual organs, were required to achieve a steady state. On the other hand, the complete elimination of all extrinsic reflexes may account for the higher open-loop gains reported by Granger and Guyton (10) (3.32 vs. 0.58 calculated from the present data). This difference in gains suggests that the more extensive denervation in their preparation resulted in a more responsive autoregulation. However, differences in preparations between the two studies were large so that quantitative comparisons seem unwarranted.

Several studies of the distribution of cardiac output (19-21) have indicated that, depending on the species studied, 60-90% of the cardiac output perfuses organs capable of autoregulation. Consider the result for an animal with intact baroreceptors if 50% of the control cardiac output is distributed to organs in which flow does not vary over the limited range of pressures encountered in these animals: when the cardiac output is reduced by 50%, flow in the remaining organs would have to be zero. Since the range of cardiac outputs achieved exceeds this range, it is clear that, at least in some organs that are capable of autoregulation, neurogenic control of vasomotor tone predominates in the short-term regulation of blood pressure. Moreover, for some organs, such as the heart and the brain, to have relatively constant perfusion, other organs must undergo large variations in flow. It should be noted that the pressure regulation observed with intact reflexes has only been demonstrated as a short-term response. Further experiments are required, but it is conceivable with more prolonged interventions, particularly in settings of low cardiac output, that vasoconstriction in certain vascular beds may lead to ischemia. Local accumulation of metabolic products would then promote vasodilation with autoregulatory escape from neurogenic vasoconstriction, thus circumventing baroreceptor control.

The present data indicated that in the absence of baroreceptors cardiac output tended to be regulated and that variations in arterial pressure tended to be magnified. If a disturbance, such as an increase in venous return, caused an increase in cardiac output, the significant increase in arterial pressure would tend to limit the increase in cardiac output. In effect, the periphery would resist increases in flow. The effectiveness of this regulation would depend on the degree to which the output of the heart is
inhibited by an increase in afterload. If the output of the heart is insensitive to changes in afterload, changes in venous return might cause aortic pressure to vary beyond the range in which autoregulation occurs (about 60–150 mm Hg). The situation would be reversed when the buffer reflexes are intact. In that case, if a disturbance caused an increase in cardiac output, the periphery would dilate to accept more flow. Clearly, if cardiac output is regulated by the action of buffer reflexes, they must act through factors other than peripheral resistance, perhaps through effects on venous return or myocardial contractility.

References
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