Hemodynamic Components of a Cardiogenic Hypertensive Chemoreflex in Dogs

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SUMMARY The mechanical and hemodynamic components of a cardiogenic hypertensive chemoreflex were studied in 50 dogs. Within 6 seconds after a single injection of serotonin (100 µg/ml) into the left atrium, mean pressure (mm Hg) rose in the aorta from 103 to 197 and in the pulmonary artery from 21 to 34. Left ventricular dp/dt virtually doubled. There was an increase (75%) in peripheral vascular resistance that returned to control within 10 seconds. There was no significant change in pulmonary vascular resistance. Aortic and pulmonary arterial hypertension were associated with a profound depression (82%) in atrial force. Atropine transformed this negative isotropic effect on the atria into a positive isotropic action that averaged 65%. In contrast, ventricular force was always sharply increased, more in the right (95%) than in the left ventricle (50%). Bilateral stellectomy did not eliminate the reflex but it completely abolished the initial increase of cardiac contractility; a delayed increase in contractility persisted and was due exclusively to release of catecholamines from the adrenal glands. This cardiogenic hypertensive chemoreflex uses the vagus for itsafferent neural traffic and both the sympathetic and the vagus nerves for its efferent course. The brief and intense systemic vasoconstriction concomitant with an increase in cardiac contractility might represent a kind of "aortic cough." Some possible clinical implications are discussed.

INJECTION of small amounts of 5-hydroxytryptamine (serotonin) into either the left atrium or a small branch of the proximal left coronary artery activates a powerful cardiac chemoreceptor in the dog. This cardiogenic hypertensive chemoreflex is elicited by concentrations of serotonin that may readily occur during life in man. It is characterized by an immediate profound arterial hypertension and a profound increase in cardiac contractility, which might represent a kind of "aortic cough." Some possible clinical implications are discussed.

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time course and the mechanism of production of localized alterations of contractility.

Methods

Fifty mongrel dogs were prepared for these experiments with anesthesia produced by the intravenous administration of pentobarbital sodium (30 mg/kg). Positive pressure ventilation was maintained through auffed endotracheal tube, and ventilatory volume per minute was adjusted according to a continuously monitored end-tidai CO$_2$ concentration obtained with a gas analyzer (LB-2 Beckman). Central aortic, main pulmonary artery, and right atrial pressures were measured with transducers attached to catheters placed via the right carotid artery, the right ventricular outflow tract, and the right external jugular vein, respectively. Eight dogs, the left atrial pressure was measured with a transducer attached to a catheter introduced via a pulmonary vein. In 12 dogs, an artifact-free left ventricular pressure was obtained with a catheter-tip Millar micromanometer introduced through the apex into the left ventricular cavity and secured in place with a purse-string. The pressure so obtained was differentiated with a standard RC Hewlet-Packard differentiating circuit. In 20 dogs, an electromagnetic flow probe (14-16 mm in diameter; Biotronex Laboratory; BL 5140-E63 and BL 5160-D03) was placed around the ascending aorta (usually 2 cm above the aortic valve). In eight dogs, the same electromagnetic flow probe was placed around the pulmonary artery about 2 cm above the pulmonic valve. Because heart rate often is erratic at the beginning of the hypotensive response, both systemic arterial resistance (SAR) and pulmonary arterial resistance (PAR) are expressed as mm Hg·msec·ml$^{-1}$, according to the following derivation:

\[
\text{mean aortic pressure (mm Hg)} - \text{mean right atrial pressure (mm Hg)}
\]

left ventricular stroke volume (ml msec)

\[
\text{mean pulmonary artery pressure (mm Hg)} - \text{mean left atrial pressure (mm Hg)}
\]

right ventricular stroke volume (ml msec)

In 30 dogs, atrial (10 dogs) and ventricular (20 dogs) contractile forces were recorded with Walton-Brodie strain gauge arches sutured at the base of the right and left atrial appendages and over the two ventricular free walls. Care was taken to affix the gauges at approximately the same location and with the same orientation on each atrium and ventricle.

Bipolar electrograms were recorded from the right atrium near the sinus node and from the left and right ventricular surfaces; these electrograms were also utilized for computation, display, and recording of heart rate by a tachograph. In 10 dogs, His bundle electrograms were obtained with a standard pacing electrode catheter (5F or 6F) having a 10-mm interpolar distance and placed into the aortic root. Bilateral and bilateral stellectomy and/or cervical vagotomy were carried out in 25 dogs, as indicated. In selected experiments, atropine sulfate (0.1 mg/kg) was administered intravenously.

Serotonin (5-hydroxytryptamine) creatinine sulfate was prepared in Ringer's solution. To elicit the chemoreflex, serotonin was injected into the left atrium within 3-4 seconds with a hand syringe in 1- or 2-ml boluses (100 ng/ml). We have previously presented evidence that these left atrial injections activate a cardiogenic hypertensive chemoreflex in the same manner as selective injections into the coronary branch supplying the chemoreceptor. The results are expressed as means ± 1 SD. The significance of differences was assessed by Student's t-test; NS-not significant at P > 0.05.

Results

Effect on Aortic and Pulmonary Arterial Pressures

All injections of serotonin into the left atrium caused an immediate aortic and pulmonary arterial hypertension, but the onset of the two pressure increments was not simultaneous. Changes in aortic pressure occurred 6 ± 2 seconds after the beginning of injection and consistently preceded the increase in pulmonary artery pressure by 1-2 seconds (Fig. 1). The time required to achieve peak responses, however, was not significantly different, averaging 7 ± 2 seconds in both the pulmonary and systemic circulation. In 30 dogs, the mean aortic pressure rose from 103 ± 14 mm Hg to 197 ± 25 mm Hg (P < 0.001) whereas, in the same 30 dogs, the mean pulmonary artery pressure increased from 21 ± 6 mm Hg to 34 ± 8 mm Hg (P < 0.01).

Left ventricular dp/dt calculated for 12 dogs averaged 2250 ± 220 mm Hg/sec before serotonin in the left atrium, but 4 ± 1 seconds after the beginning of pressure rise the peak dp/dt had increased to 3950 ± 350 mm Hg/sec (P < 0.001). Progressive return to preinjection dp/dt was observed in each case within 5 minutes. In those same dogs, the control left ventricular end-diastolic pressure averaged 2.4 ± 0.2 mm Hg. Immediately after injection of serotonin and concomitant with the systemic increase in aortic and pulmonary arterial pressures, atrial fibrillation occurred in 13 of the 30 dogs (43%). The mean right atrial pressure (mm Hg) of 2.4 ± 0.2 mm Hg immediately after serotonin injection was significantly higher than the value before injection (1.0 ± 0.2 mm Hg, P < 0.001). The mean left atrial pressure (mm Hg) averaged 2.4 ± 0.2 mm Hg immediately after serotonin injection was significantly higher than the value before injection (1.0 ± 0.2 mm Hg, P < 0.001). The mean aortic pressure (mm Hg) of 21 ± 4 mm Hg immediately before serotonin injection was significantly lower than the value after injection (21 ± 7 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001). The mean pulmonary artery pressure (mm Hg) rose to 21 ± 4 mm Hg immediately after serotonin injection was significantly lower than the value before injection (21 ± 4 mm Hg, P < 0.001).
pressure rise and initial sinus bradycardia, the left ventricular end-diastolic pressure rose to 4.4 ± 0.3 mm Hg (P < 0.05). Three to four seconds later it began to diminish progressively and had returned to control in each dog within the following 10-20 seconds. In five dogs with profound initial sinus bradycardia (the magnitude of the initial chronotropic response varies), there was a left ventricular end-diastolic pressure rise from 2.8 ± 0.2 to 4.8 ± 0.4 mm Hg (P < 0.05). In three other dogs with less than 15% initial sinus bradycardia and in all dogs after treatment with atropine, left ventricular end-diastolic pressure actually decreased from 2.2 ± 0.3 to 1.9 ± 0.2 mm Hg. This change, however, was not statistically significant. Taken collectively, these observations suggest that the increase in left ventricular filling pressure before atropine is directly related to the amount of reflexly mediated sinus bradycardia.

Effect on Atrial Contractile Performance

In the absence of autonomic neural blockade, the reflexly induced aortic and pulmonary arterial hypertension was always associated with an immediate, brief but profound depression of atrial contractility (Fig. 2). The amount of depression in atrial contractile performance varied from dog to dog, and sometimes the right atrial force was slightly more depressed than the left. Since in any given dog the differences between the two atria were only minor, the changes in right and left atrial forces were computed together. In both, atrial contractility began to decrease 6 ± 2 seconds after onset of left atrial injection of serotonin, precisely at the same time as the beginning of the sinus bradycardia and the aortic pressure rise. Depression of atrial contractility was consistently apparent, with the very first heartbeat showing an increment in aortic pressure. This observation and the fact that systemic administration of atropine eliminated the decrease in atrial contractility suggest that this initial reduction of atrial forces was the result of a vagal discharge triggered by the chemoreceptor rather than by mechanoreceptor stimulation. In 10 dogs studied for their atrial inotropic responses, the maximal decrease of atrial contractility averaged 82 ± 15% (P < 0.001). Peak effect was observed within five seconds after onset; however, total duration was quite variable, in part because of the later onset of additional baroreceptor-mediated vagal effects. In most experiments the entire period of negative atrial inotropic response did not exceed 1 minute.

In all 10 dogs, the administration of atropine completely eliminated the vagally mediated negative inotropic effect on the atria during the chemoreflex. Atropine not only prevented the decrease in atrial contractile performance but it regularly unmasked a positive inotropic response. The increment in contractility averaged 65 ± 10% (P < 0.001) and began at the same time as the aortic hypertension (Fig. 2). This positive inotropic action lasted between 20 and 60 seconds and was followed by a transient and variable negative inotropic response that averaged maximally 42 ± 15% (P < 0.01) and lasted 1-2 minutes. The delayed type of negative atrial inotropic response was not vagally mediated since it persisted after treatment with atropine and is thus significantly different from the initial atrial depression which is entirely mediated by the vagus.

Effect on Ventricular Contractile Performance

In contrast to the marked initial decrease in atrial contractility observed in dogs untreated with atropine, ventricular contractility always increased promptly, with or without atropine. The increments in contractility (20 dogs studied) were greater in the right ventricle than in the left ventricle although the magnitude of this difference varied from dog to dog. Right ventricular contractility began to increase simultaneously with three other events: the sinus bradycardia, the decrease in atrial contractile force, and the aortic hypertension. Maximal responses for the positive inotropic effect were observed 6 ± 2 seconds later, and the peak increments averaged 95 ± 20% (P < 0.001). In two additional dogs not included in this computation but clearly illustrating the sequence and temporal relationships, the right ventricular force increased enor-
In each experiment the return to control isometric force was a steadily progressive process that was complete after 4 ± 2 minutes.

Increments of left ventricular contractility, which began exactly at the same time as in the right ventricle, amounted to 50 ± 15% (P < 0.001). Maximal effects were observed sooner in the left ventricle than in the right ventricle (about 1–2 seconds). Right and left ventricular contractile performance not only differed with regard to the magnitude and their respective time to peak effect, but the total duration of the positive inotropic action was much shorter for the left ventricle, averaging 2.5 ± 2 minutes. Systemic administration of atropine in 11 of those 20 dogs did not significantly alter the maximal initial increase in contractility of either ventricle (Fig. 4). In four other dogs, however, there was an 18 ± 5% (P < 0.05) increase in contractile performance after atropine. In each of those four dogs there was a marked increase in heart rate during the chemoreflex, suggesting that this augmented ventricular contractility might at least in part be due to the greater change in rate.

Bilateral stellectomy was carried out in 15 dogs after pretreatment with atropine. This procedure completely eliminated the initial part of the increase in contractility but it did not completely abolish the initial blood pressure rise (Fig. 5). In five other dogs, the same bilateral stellectomy was performed but the reflex was elicited in the absence of atropine (Fig. 6), to time the inotropic response relative to the chronotropic effect. During the reflex sinus bradycardia in those five dogs, there was no concomitant increase in ventricular contractility, nor was there as much though still significant aortic hypertension. In those five dogs, the mean pressure increased from 109 ± 10 to 146 ± 13 mm Hg (P < 0.01). In both groups of dogs, at 19 ± 4 seconds after completion of the injection there was also a secondary or delayed increase in ventricular contractility, concomitant with some further increase in aortic pressure. This positive inotropic effect was also observed in the atria. In eight dogs (four with and four without pretreatment with atropine), the arterial and venous blood supply of both adrenal glands was temporarily interrupted. After occlusion of the adrenal arteries and veins, serotonin in the left atrium did not cause the delayed increase in contractile force nor any changes at all in aortic pressure (Fig. 5); however, in the same eight dogs, this response promptly returned at a later time when serotonin was administered via the same route after restoring normal arterial supply and venous drainage of the adrenals. In each of those eight dogs, serotonin was later injected into the ascending aorta or into the proximal segment of the thoracic aorta. Within 19 ± 4 seconds, the same secondary or delayed increase in ventricular contractility was observed. Injections of the same amount of serotonin into the abdominal aorta below the level of the adrenal arteries, however, failed to produce this delayed positive inotropic effect.
FIGURE 5  From top to bottom, the channels represent heart rate (HR), aortic pressure (Ao), right ventricular force (RVf), and aortic flow (Ao_flow). Switch-averaged flow is scaled in liters/minute. Both switch-averaged and phasic (pulsatile) pressure and flow are recorded. Panel A illustrates a characteristic cardiogenic hypertensive chemoreflex response. Concomitant with aortic pressure rise, there is a sinus bradycardia and a brief decrease in aortic flow. The two components of increased contractility (numbered 1 and 2) are readily recognized in Panel A but not in Panel B, which is after atropine. There are comparable initial and delayed components in heart rate changes and in the aortic hypertension. After right stellectomy (Panel C), there is still the early component of reflex tachycardia and a reflexly mediated increase in right ventricular contractility. After bilateral stellectomy (Panel D), the early reflex tachycardia and increased contractility are both abolished, although some aortic hypertension still occurs. Panel E demonstrates that after temporary interruption of adrenal arterial supply and venous drainage there is no secondary tachycardia and no secondary increase in either right ventricular contractility or aortic pressure.
Effect on Peripheral and Pulmonary Vascular Resistance

Observations from 15 dogs are graphically presented in Figure 7 to illustrate the sequential change of systemic vascular resistance seen during a beat per beat evaluation of phasic aortic flow, mean aortic and right atrial pressures, as well as heart rate. Three seconds after onset of aortic hypertension there was an increase of 75 ± 20% in peripheral vascular resistance. This significant increment was of brief duration, however, since rapid return toward control peripheral resistance regularly occurred in the following few seconds. At the time of maximal hypertensive response, the aortic pressure had increased from 102 ± 10 to 199 ± 27 mm Hg (P < 0.001), while the right atrial pressure remained unchanged (3.7 ± 0.4 mm Hg). The left ventricular stroke volume rose from 13 ± 2 to 18 ± 4 ml (P < 0.01), whereas the heart rate went from 142 ± 16 to 159 ± 28 beats/minute (NS). Ten seconds after peak pressure was achieved, there was no longer any detectable increase in systemic resistance.

A corollary experiment was conducted in eight dogs to measure phasic pulmonary arterial flow, mean pulmonary arterial pressure, and left atrial pressure. There was no significant change in pulmonary vascular resistance in any of these eight dogs. At the time of the maximal aortic hypertensive response, the pulmonary arterial pressure had increased from 22 ± 4 to 33 ± 7 mm Hg (P < 0.01). The mean left atrial pressure rose from 2.5 ± 0.3 to 4.1 ± 0.4 (P < 0.05) and the heart rate increased from 140 ± 18 to 154 ± 26 beats/min (NS). These results indicate that the aortic hypertension is associated with a brief but important increase in peripheral vascular resistance, but that there is no comparable increase in pulmonary vascular resistance during the development of the pulmonary hypertension.

Figure 6 The cardiogenic hypertensive chemoreflex was elicited before and after bilateral stellectomy. Efferent vagal discharges are not affected by this maneuver, and the blood pressure increase that occurs during the reflex sinus bradycardia is due to systemic vasoconstriction.
Discussion

The hypertension of the cardiogenic chemoreflex elicited by serotonin is the net result of an initial, brief but significant increase in systemic vascular resistance combined with a concomitant marked (and more prolonged) increase in ventricular contractility. Stroke volume, though variable at the beginning because of important initial irregularity in heartbeats, also increases progressively; at the time peak pressure is recorded there is a significant increase in cardiac output. There is a very short time (at most a few seconds) between the onset of pressure rise and the maximal response in both the pulmonary and systemic circulation. Both the pulmonary hypertension and aortic hypertension are regularly abolished by vagotomy, indicating that both pressure changes are integral parts of this reflex. However, there is no significant increase in pulmonary vascular resistance; the pulmonary hypertension is caused mainly by an increase in pulmonary arterial flow due to increased right ventricular contractile performance. This observation necessarily implies that venous return must also be increased. Absence of any substantial calculated reflex increase in pulmonary vascular resistance is probably the explanation for the 1- or 2-second delay observed in the onset of pressure rise in the pulmonary artery. Since serotonin is one of the most potent constrictors of the pulmonary vasculature, we conclude that in our experiments only negligible amounts of serotonin reach the lungs on recirculation or through the bronchial arteries.

In contrast to the rather unresponsive pulmonary circulation during this chemoreflex, there is a marked increase in peripheral vascular resistance. Systemic arterial vasoconstriction began abruptly and was already maximal by 3 seconds after the onset of pressure rise. This increased systemic vascular resistance is of short duration, however, and lasts only a few beats or no more than 10 seconds. Increase in systemic resistance was somewhat less, especially; at the time peak pressure is recorded there is a significant increase in systemic vascular resistance. Calculations of changes in peripheral resistance were made on the basis of stroke volume instead of steady state cardiac output because of the brevity of the reflex response. Since there is a beat-to-beat increase in contractility with a concomitant more rapid and sudden ejection of blood into the aorta, the question arises whether estimates of increases in systemic vascular resistance are not significantly influenced by an aortic impedance factor.

By the same token one might also ask whether the greater compliance of the pulmonary arterial system is not in turn responsible for the absence of a significant change in calculated pulmonary vascular resistance. Since α-recepto

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one mechanism capable of ensuring a rapid and adequate increase in blood flow to the jeopardized left ventricle would be an abrupt increase in perfusion pressure to dislodge the offending platelets. This would in effect be an "aortic cough." That such a response could be triggered by the stimulation of a chemoreceptor conveniently located in the immediate vicinity of the proximal left coronary artery is ideologically attractive. Equally intriguing are the facts that there is no tachyphylaxis and that there is a simultaneous vagal and sympathetic efferent discharge. Thus, on the one hand ventricular contractility is increased while on the other hand the actual number of heart beats is diminished. Slowing the heart at just that moment would keep the energy expenditure of the increased contractile performance to a minimum. If these speculations are true, there may be great survival value in the hypertensive cardiogenic chemoreflex.

References
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