Analysis of Components in a Cardiogenic Hypertensive Chemoreflex

By Thomas N. James, M.D., James H. Isobe, M.D., and Ferdinand Urthaler, M.D.

SUMMARY
A cardiogenic hypertensive chemoreflex was studied in 38 anesthetized and three unanesthetized dogs. Serotonin (100 \( \mu \text{g/ml} \)) injected into either the left atrium or small branches of the proximal left coronary artery produced a maximal response, with 96 ± 15 mm Hg increment in mean aortic pressure within 6 ± 2 seconds, lasting about 1 min; a later phase of the same hypertension lasted 9 ± 5 minutes more and could partially be produced with serotonin injected into the thoracic aorta. Injections into the distal left coronary artery produced only the Bezold-Jarisch reflex. Concomitant with the immediate hypertension there were vagal and sympathetic efferent effects in both the sinus node and the atrioventricular (A-V) junction. Either of these effects could be selectively eliminated and the other augmented by direct local perfusion with an appropriate cholinergic (atropine 10 \( \mu \text{g/ml} \)) or adrenergic \( \beta \)-receptor (propranolol 10 \( \mu \text{g/ml} \)) blocking agent. Bilateral vagotomy markedly attenuated the Bezold-Jarisch reflex but did not eliminate the acute hypertension, it abolished both chronotropic and dromotropic effects. Phenolamine (2 mg/min i.v.) markedly diminished the hypertensive response. Guanethidine or reserpine pretreatment markedly diminished the hypertensive response; reserpine eliminated the electrophysiologic effects but guanethidine did not. Infiltration of serotonin around the main left coronary partially reproduced the reflex, but similar infiltration of xylocaine hydrochloride blocked the reflex. Serial section histologic studies of the region around the main left coronary artery in seven dog hearts and nine human hearts demonstrated the presence of a small structure resembling a chemoreceptor; its blood supply originated from the left coronary artery. Some possible clinical implications are discussed.

REGULATION OF THE CIRCULATION depends to a great extent on a number of cardiovascular reflexes. The afferent component of these reflexes begins with the activation of neural receptors which are primarily of two types, those which respond to mechanical stimuli such as stretch or other spatial deformation, and those which respond to chemical stimuli such as low oxygen tension or an acid pH. Among the more familiar baroreflexes are those caused by changes of arterial pressure which activate mechanoreceptors in the aortic arch or carotid sinus. Although chemoreflexes are probably best known as responding to hypoxia by activation of receptors in the carotid body, the literal definition of a chemoreflex only requires that it respond to a chemical stimulus. For over a century it has been known that veratridine and a variety of other compounds can elicit a chemoreflex from the heart, consisting of bradycardia, hypopnea and hypotension.\(^1,2\) The afferent component of this Bezold-Jarisch reflex courses in the vagus and its intracardiac egress is via a narrow funnel surrounding the main left coronary artery.\(^3\) Whether the Bezold-Jarisch reflex has either physiological or clinical significance or is simply a pharmacological curiosity has long been debated. Certain events during the course of acute posterior myocardial infarction in man closely mimic the experimental situation,\(^4\) but there are several possible nonreflex explanations of the human events.\(^5,6\)

Recently Eckstein and his colleagues have reported their observations on a chemoreflex which originates within the heart and which is excitatory in nature, a major response being arterial hypertension.\(^7\) The site at which the reflex originates was carefully examined in over 200 canine experiments. Although the location of this site varied slightly, it was most often within the first few millimeters of the proximal portion of the left coronary artery. Eckstein and his colleagues also reported the identification of tissue resembling carotid body in those locations but did not provide histological illustrations. A number of agents or procedures produced the reflex, including the creation of local hypoxia, but one of the more powerful stimuli proved to be serotonin (5-hydroxytryptamine). Serotonin is a naturally occurring material carried in the normal blood almost exclusively by the platelets.\(^8\)
The purpose of the present experiments was to investigate the components of the reflex produced by serotonin, and to conduct histological studies of possible sites of origin within the heart. By selective direct perfusion of either the sinus node or the atrioventricular (A-V) junctional tissues through their separate nutrient arteries in the canine heart intact \textit{in situ},\textsuperscript{8, 10} it was possible to eliminate exclusively either the cholinergic or adrenergic neural response in these areas of impulse formation and conduction, by the appropriate selective perfusion with either atropine or propranolol.\textsuperscript{11, 12} Such procedures served not only to identify local mechanisms but also to unmask different concomitant responses there or elsewhere in the heart or peripheral circulation. Following a description of the specific experiments below, the several different components of this cardiogenic hypertensive chemoreflex will be defined. Finally, by serial section studies of the proximal few centimeters of the main left coronary artery and its two major branches, a discrete histological structure has been identified in both canine and human hearts which resembles chemoreceptor tissue, and photomicrographs of this structure will be presented.

**Methods**

Thirty-eight dogs were anesthetized with sodium pentobarbital (30 mg kg intravenously), the trachea intubated for mechanical ventilation with room air, and the chest opened to expose the heart. Details of the methods for separate cannulations of the sinus node artery and of the A-V node artery\textsuperscript{10} have been published. Except for those two specific branches, the remainder of the coronary circulation was left intact unless other branches were cannulated in special experiments as noted. The entire normal innervation of the heart is routinely preserved in these preparations. To examine the response in awake dogs, three were prepared by placing an indwelling cannula in the left atrium during thoracotomy.

Eckstein and his colleagues demonstrated that the specific small artery perfusing the intracardiac chemoreceptor can be cannulated for selective direct perfusion with serotonin or other agents.\textsuperscript{7} We confirm the feasibility of this selective cannulation, with one typical example from four different dogs having their conus branch of the left coronary artery cannulated being shown in figure 1. However, injection of serotonin into the left atrium produces essentially the same response, is simpler to conduct and reproduce, and leaves the major coronary arteries and their neural supply undisturbed by dissection or local trauma. Additional comparative injections were made (five dogs) into the root of the aorta, the excluded peripheral component of both carotid arteries, the descending thoracic aorta, the right atrium and the main pulmonary artery; none of these produced the acute hypertensive response consistently occurring after injection into the left atrium. Injections into the distal two-thirds of either the left circumflex or the left anterior descending coronary artery did not produce the hypertensive reflex. These observations, coupled with the more meticulous anatomic searches of Eckstein and his colleagues,\textsuperscript{7} satisfy us that the site of origin is in the proximal coronary arterial circulation (therefore within the heart). For the sake of the advantages indicated above, most of our experiments were conducted with left atrial injections and any exceptions are indicated.

In selected experiments the vagi were cut in the neck, or the dogs were pretreated with intramuscular injections of reserpine (0.5 mg kg for each of two preoperative days) in three dogs or guanethidine (5 mg kg given on three successive days prior to study) in three other dogs. For generalized cholinergic blockade atropine sulfate 1 mg kg was administered intravenously. For selective local cholinergic blockade 2 ml of atropine 1 or 10 \(\mu\)g/ml was per-

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Characteristic examples of the hypertensive cardiogenic chemoreflex are illustrated. Left) the serotonin (STN) was injected into the conus branch of the left anterior descending artery; right) the same amount of serotonin was injected into the left atrium of the same dog. Pressures in the right atrium (RA) and aorta (Ao) are scaled in mm Hg, and heart rate (HR) is scaled in beats/min.
fused through either the sinus node artery or A-V node artery. Similar local blockade of the adrenergic beta-receptors was accomplished with propranolol hydrochloride 10 μg/ml. All injections into the sinus node artery or A-V node artery were 2 ml volume and delivered from a hand syringe within 5 to 10 sec. Every injection was made with a control administration of Ringer’s solution. All test substances were prepared in Ringer’s solution and included serotonin (5-hydroxytryptamine), histamine hydrochloride, norepinephrine bitartrate, acetylcholine chloride, physostigmine salicylate and prostaglandin (fractions E₁, E₂, A₂ and F₂α).

Results

Acute Arterial Hypertension

Each of 38 anesthetized dogs developed an immediate hypertension following the administration of 2 ml of serotonin 100 μg/ml into the left atrium (fig. 1). The average hypertensive response was 195 ± 20 mm Hg (mean aortic pressure) with a range of from 170 to 230 mm Hg. This represented an average increment of 96 ± 18 mm Hg above control level. The peak level of hypertension occurred within 6 ± 2 seconds, followed by a small drop for 30 to 60 seconds, after which there was a more gradual return to control level of blood pressure within 9 ± 5 minutes. There thus appeared to be two components to the hypertensive response: the immediate sharp rise in pressure which lasted 30 to 60 seconds, and a later less marked hypertension of longer duration. The latter was largely due to some nonreflex extracardiac effect and could in part be caused by injections into the descending thoracic aorta. However, the maximal levels of prolonged hypertension were only observed when the immediate marked pressor effect initiated the over-all response; e.g., the hypertensive produced by serotonin injections into the thoracic aorta (five dogs) reached a peak level only 30 to 40 seconds after injection, and exhibited a maximum increment of 25 to 30 mm Hg.

In the three unanesthetized dogs, 2 ml of serotonin (100 μg/ml) into the left atrium consistently produced an acute hypertensive response ranging from 48 to 73 mm Hg above control (fig. 2). The peak occurred slightly later than in anesthetized dogs, primarily due to an initial drop in pressure caused by an exaggerated immediate marked bradycardia, the nature of which is discussed in a subsequent section. In one of these three dogs serial injections of serotonin 20 min apart produced the same hypertensive and chronotropic effect each time. This dog was then anesthetized, following which serotonin in the left atrium caused essentially the same pressor effect as in the awake state.

In any given dog all characteristics of the pressor response were consistently reproducible. The acute pressor component was reproducible for long series of injections (six dogs), provided injections were at least 60 seconds apart. Injections in closer series, or a constant infusion of serotonin into the left atrium (three dogs) caused only the acute initial response without even prolonging the duration of the initial response. In nine dogs there was a dose-related increasing hypertensive response and in three of these a maximal response occurred with 25 μg/ml (fig. 3) while the other six required 100 μg/ml. In 12 dogs the immediate hypertensive response to serotonin was an increment of 88 ± 15 mm Hg mean aortic pressure before vagotomy, and 17 ± 6 mm Hg increment after both vagi were cut in the neck. In all 12 dogs the effect on heart rate was abolished by vagotomy and the later prolonged hypertension was attenuated.

Infiltration of the epicardial tissue surrounding the main left coronary artery with 2% xylocaine hydrochloride attenuated the pressor response (figs. 4 and 5) in three of four dogs but did not eliminate it. By contrast to the xylocaine effect, infiltration around the main left coronary artery with serotonin (100 μg/ml) consistently produced a small but distinct pressor response in three other dogs (fig. 6). While this effect was neither as prompt nor as marked as when serotonin was later administered into the left atrium.
of the same dogs, its very occurrence at all is considered significant. Infiltration of tissue around the main left coronary artery with Ringer’s solution alone had no effect on heart rate or blood pressure in five other dogs.

Pretreatment with either reserpine or guanethidine markedly diminished the pressor response to serotonin. Although pretreatment with intravenous bolus injections of phentolamine or dibenzyline (1.0 mg/kg) only slightly reduced the level of the acute hypertension, administration of the same amount of serotonin into the left atrium during a continuous intravenous drip of phentolamine (2 mg/min) markedly diminished the pressor effect. Intravenous administration of atropine 1 mg/kg in four dogs did not significantly alter the acute hypertension.

Injections of serotonin into the distal third of either the left circumflex or left anterior descending coronary artery in nine dogs failed to produce the hypertensive reflex. On the contrary, in seven of nine dogs there was a transient sinus bradycardia and aortic hypotension of 15 ± 5 mm Hg, lasting 7 ± 2 min and resembling the Bezold-Jarisch reflex (fig. 7). Direct perfusion of serotonin into the distal circumflex artery at a point proximal to the origin of the A-V node branch produced neither A-V block nor A-V junctional tachycardia (see later discussion). Control injections of 2 ml Ringer’s solution into any arterial branch where serotonin had caused either hypertension or hypotension failed to produce any significant effect on blood pressure or cardiac rhythm.

Effect on the Sinus Node

Serotonin itself directly produces a gradual slowing of the sinus node to a moderate degree. A delayed sinus bradycardia which appeared after injection of serotonin into the left atrium was due to recirculation and could be reproduced in the present experiments either by injection of serotonin downstream from the heart and coronary circulation or by direct perfusion of the sinus node itself in seven dogs.

Several effects on the sinus node occurred more immediately, however, and were concomitant with the initial acute hypertensive effect. In every dog there was an immediate reflex bradycardia at about the same time as the acute hypertension, and this could be selectively eliminated in 15 dogs either by prior selective perfusion of the sinus node with atropine or the intravenous administration of atropine (figs. 8 and 9). The reflex bradycardia was very brief, ending at a time when hypertension was still maximal. Furthermore, this immediate sinus bradycardia occurred in the three dogs pretreated with guanethidine even though little significant hypertension developed.

Both the magnitude and duration of the immediate sinus slowing could be augmented by prior administration of propranolol 10 µg/ml into the sinus node. In some anesthetized dogs (nine of 15 discussed here) there was a brisk and brief sinus tachycardia following the initial sinus slowing (fig. 1), and this tachycardia was regularly eliminated by prior treatment with propranolol selectively perfused into the sinus node artery. Sinus tachycardia was not observed in the three awake dogs, where only marked slowing occurred.

Finally, the administration of atropine either intravenously or selectively into the sinus node not only eliminated the immediate reflex sinus slowing after serotonin into the left atrium, but it also changed the response by the sinus node to one of immediate acceleration (fig. 8). This reversal in each of 15 dogs demonstrates that the initial efferent autonomic neural influence on the sinus node is mixed, being both adrenergic and cholinergic, but that in most dogs the vagal component initially predominates (for a few seconds) unless it is selectively eliminated. These various maneuvers concerning the chronotropic component of the reflex did not significantly alter the pressor component, which appeared to be essentially independent of the rhythm or rate changes.
Effect on the A-V Junction (A-V Node and His Bundle)

In the absence of selective autonomic neural blockade, the usual chronotropic and dromotropic responses after serotonin into the left atrium were an initial sinus bradycardia lasting only a few seconds, then a variable degree and duration of sinus tachycardia (never more than a minute), during either of which (slowing or acceleration) there was a variable minor degree of P-R prolongation but no higher grade of A-V block. In a few dogs (five of 38) the initial sinus bradycardia was followed by a brief period of A-V junctional tachycardia rather than sinus tachycardia; however, after prior selective perfusion of the sinus node with propranolol, A-V junctional tachycardia was observed in three of five dogs previously having only sinus tachycardia. These results suggest that sympathetic neural stimulation of the A-V junction is a usual efferent component of the reflex but that in most instances it is masked by concomitant effects elsewhere, particularly in the sinus node.

Prior selective perfusion of the sinus node with atropine not only insured the occurrence of maximal sinus acceleration after serotonin into the left atrium, but it also unmasked or augmented an initial brief period of negative dromotropic influence on the A-V junction during the sinus tachycardia (figs. 9 and 10). A concomitant negative chronotropic effect on the A-V junction was demonstrated by administering serotonin into the left atrium during A-V junctional rhythm (fig. 11). That this heart block was an efferent vagal reflex influence on the A-V junction is illustrated by two points: 1) the initial brief (few seconds) heart block could be abolished and prevented by prior selective perfusion of the A-V junction with atropine 10 μg/ml (four dogs), or by intravenous administration of atropine 0.1 or 1 mg/kg (three other dogs); and 2) the brief heart block did not occur when maximal sinus tachycardia was produced by selective perfusion of the sinus node with norepinephrine 0.1 μg/ml (eight dogs). Both the rate of acceleration and peak level of

Figure 4

The usual reflex response to serotonin (left panel) is altered by local anesthesia produced by infiltration with xylocaine hydrochloride 2% around the main left coronary artery. Such percutaneous anesthesia normally causes a slight bradycardia. There is marked attenuation of the hypertensive response (right panel, same dog) and elimination of the reflex bradycardia by this anesthesia.
tachycardia produced by norepinephrine in the sinus node were greater than during the cardiogenic reflex. The brief heart block was therefore not simply a failure of the A-V junction to keep pace with a rapidly accelerated sinus node, but must have been due to a direct negative dromotropic efferent vagal component in the initial period of the reflex.

Finally, since 2 ml injections of serotonin 100 \( \mu \text{g/ml} \) into the distal left circumflex artery proximal to the origin of the A-V node artery had no significant chronotropic or dromotropic effect on the A-V junction in nine dogs, it may be concluded that both the A-V junctional tachycardia and the brief heart block described in the preceding paragraphs must have been exclusively reflex in origin and not due to a direct local effect by serotonin on the A-V node or His bundle.

Figure 5

Right atrial electrograms recorded during each of the two experiments illustrated in figure 4 show that the local anesthesia around the main left coronary artery not only eliminated the reflex bradycardia but also the elevation of the P-T\(_r\) segment accompanying the bradycardia (see text). The first discernible P-T\(_r\) elevation in the upper panel is marked with an asterisk, but cardiac cycle length was prolonged two beats before that.

Figure 6

Local infiltration with serotonin around the main left coronary artery produces some hypertension and sinus acceleration.

Effect on Atrial Repolarization

Both the direct local administration (by perfusion of the sinus node artery) or the neural release of acetylcholine by vagal stimulation profoundly influence atrial repolarization, being clearly apparent in displacement of the P-T\(_r\) segment. Direct perfusion of serotonin into the sinus node artery has no significant effect on the P-T\(_r\) segment. In the present experiments a marked shift of the P-T\(_r\) segment of local right atrial electrograms was observed in most dogs immediately after left atrial serotonin (figs. 5, 9 and 10). Sudden displacement of the P-T\(_r\) segment is further evidence of an immediate vagal efferent component of the reflex, influencing atrial myocardium in general as well as the sinus node and the A-V node in particular.

Other Possible Chemical Stimuli for the Reflex

Eckstein and his colleagues demonstrated that serotonin was not the only agent which could elicit this reflex, although other substances were generally less effective. We tested the response to histamine (100 \( \mu \text{g/ml} \)), prostaglandin (fractions E\(_1\), E\(_2\), A\(_2\) and F\(_2\)\(_{10}\), all at 10 \( \mu \text{g/ml} \)), norepinephrine (0.1 \( \mu \text{g/ml} \)), and acetylcholine (1 \( \mu \text{g/ml} \)). In six dogs these agents were administered into the left atrium in the same fashion as the serotonin, while in four dogs they were administered into a branch of the main left coronary artery or its proximal rami which had previously been
shown to be sites where serotonin would cause a maximal hypertensive response. None of these naturally occurring vasoactive substances produced the cardiogenic hypertensive chemoreflex. Prostaglandin F$_{2\alpha}$ caused a minor degree of pressor effect, as did the norepinephrine, but of the same nature as when given into the aortic arch and never more than 10 mm Hg maximal aortic pressure increase. The fact that norepinephrine or acetylcholine did not elicit the chemoreflex may be especially important. Although it is not known whether there is a generally occurring sensory neurotransmitter, the two normal autonomic neurotransmitters released at postganglionic terminals have both been postulated as possible sensory neurotransmitters as well.\textsuperscript{16,18} If this is so, then they

Figure 7

When administered into the distal left anterior descending artery, serotonin produced only hypotension and bradycardia typical of the Bezold-Jarisch reflex. A control injection of the same volume of Ringer’s solution alone had no effect. The injections were made through a cannula inserted via a small distal branch of the left anterior descending artery with the tip pointed downstream in the distal third of the LAD. This is the same dog shown in figure 1 and the contrasting response depending on whether serotonin is administered proximally or distally in the LAD is clearly demonstrated.

Figure 8

Atropine eliminates the reflex bradycardia component of the chemoreflex and converts it to reflex tachycardia, but has no significant effect on the hypertensive component except making it a smoother response during the sinus acceleration.

Figure 9

Selective perfusion of the sinus node artery with 2 ml of atropine (ATR) 10 μg/ml eliminates the reflex bradycardia and unmasks the concomitant reflex negative dromotropic component. The reflex effect on atrial repolarization is still apparent, since perfusion through the sinus node artery does not influence cholinergic atrial innervation except for the sinus node and its immediately surrounding environs.
are presumably not the sensory transmitter agents for the origin of the chemoreflex in the present study.

Histological Appearance of the Possible Chemoreceptor

In seven dogs and in nine human hearts the region extending from the aorta through the first 5 mm of the two branches of the main left coronary was embedded as a whole with at least one centimeter of surrounding tissue. It was elected not to attempt serial sections of the entire aortic root region (including right coronary artery) because the specimen in the adult human and canine hearts was then too large for good infiltration and embedding. The embedded blocks were serially sectioned at 8 μ intervals with the slices essentially perpendicular to the long axis of the main left coronary artery. Every third section was saved and every tenth was stained with Goldner trichrome solutions. Thus, the examined sections represented approximately 80 μ steps. Five of the nine human hearts were from infants who died of unknown cause and the other four were from adults in the age range of 20 to 43 years, who died of noncardiac causes. Four of the seven normal canine hearts were from experiments in which the cardiogenic hypertensive chemoreflex had been studied, and three were from other experiments.

Figure 10

In three dogs a brief paroxysm of atrial fibrillation occurred during the chemoreflex. Here the period of reflex heart block (after selective perfusion of the sinus node artery with atropine) is demonstrated not only during unchanged sinus rhythm but also by slow ventricular response in the initial period of atrial fibrillation. The asterisk marks the onset of P-Tε elevation in the right atrial electrogram for a few beats prior to the onset of atrial fibrillation.

Figure 11

Simultaneous negative chronotropic and negative dromotropic action on the A-V junction during the chemoreflex is illustrated here during A-V functional rhythm (AVJR) which had been produced with sodium pentobarbital selectively perfused into the sinus node artery. Initially the His potential is present just before the superimposed atrial and ventricular complexes in the HBE record, and a uniform large complex is recorded in the right atrial electrogram from near the sinus node. Just after completion of the serotonin injection, the rhythm source immediately changes as first apparent in the right atrial electrogram. Over the next few cardiac cycles the location of the His potential and the form of the atrial complex in the HBE record also change, and then high grade A-V block appears. Note that both here and in the experiments shown in figures 9 and 10 the vagal reflex effects on cardiac electrical activity preceded the development of acute hypertension.

In two of seven dog hearts and in four of nine human hearts only fragments of tissue resembling a chemoreceptor were found. It is known that the chemoreceptor in the dog heart at least is variably located,7 including regions not examined in the procedure described above (e.g., proximal right coronary artery). However, in five of the seven dog hearts (including three of the four studied experimentally with serotonin) there was a distinctive structure which had all the histological characteristics of chemoreceptor tissue (figs. 12 and 13). This structure had the overall appearance of a stalk of grapes and was located directly adjacent to the main left coronary artery (less than 1 mm away), from which it received a distinct nutrient vessel. Virtually identical tissue was found in approximately the same location in five of the nine human hearts (figs. 14 and 15). These tiny neuroreceptors varied somewhat in size and shape, but none was more than 1 mm in maximal dimension. Numerous small vessels coursed throughout the structure indicating its rich vascularity. It was surrounded by a variety of other neural structures, including both myelinated and unmyelinated nerves as well as ganglia.
CAR diogenic Hypertensive Chemoreflex

Discussion

Three features of this cardiogenic hypertensive chemoreflex make it an exceptional phenomenon: the magnitude and speed of blood pressure rise, the fact that serotonin is a naturally occurring substance in the mammalian circulation, and the intracardiac origin of the reflex. To discuss the phenomenon we will consider the following: the evidence that it is a reflex, the anatomic origin of the reflex, its component physiological characteristics, and finally its possible clinical significance in man.

Evidence That the Phenomenon Is a Reflex

Both the pressor and electrophysiological effects were rapid in onset, the hypertension becoming maximal in 6 ± 2 seconds and the reflex chronotropic and dromotropic actions even sooner than that. The pressor effect was markedly diminished and the electrophysiological effects were abolished by bilateral vagotomy. All responses were significantly attenuated by prior local anesthesia around the main left coronary artery. None of the acute initial effects (pressor or electrophysiological) could be attributed to direct actions of serotonin outside the heart or within the heart on recirculation. Tissue which had the histologic appearance of a chemoreceptor was found in the appropriate regions of the heart (figs. 12, 14 and 15). These observations in the aggregate make it most logical that the events were truly reflex in nature. The fact that identical control injections (same volume and

Figure 12

The structure outlined with three black arrows in A was found in a canine heart directly adjacent to the main left coronary, the adventitia of which is seen at the lower right; one of several small nerves is labeled N. An experiment demonstrating the chemoreflex in this same dog is shown in figure 13. B is a higher magnification of the chemoreceptor which has histological features characteristic of the carotid body.

Figure 13

In the polygraph (top) the chemoreflex is elicited with serotonin in the same dog from which the photomicrographs are shown in figure 12; a control injection of Ringer’s solution into the left atrium produced no response. The right atrial electrogram (bottom) recorded at the same time as the experiment in the polygraph is also shown; the onset of reflex sinus slowing is indicated with the asterisk, and maximal P–T deflection is present in the very next beat.
speed) of Ringer’s solution into either a coronary artery or the left atrium failed to produce the response indicates that it is not due to activation of coronary mechanoreceptors.¹⁹

Anatomic Origin of the Reflex

The site of origin of this hypertensive chemoreflex must be from or near the proximal coronary arterial circulation, most often the first few millimeters of the left coronary or its immediate major branches. In addition to the nature of responses following injections of serotonin into appropriate extracardiac sites and the proximal or distal coronary circulation, three other observations support the site of origin as most often being the proximal left coronary artery. The first is the attenuation of the reflex by local infiltration of xylocaine around the main left coronary artery (fig. 4).

The second is production of hypertension by local extra-arterial infiltration with serotonin in this same site (fig. 6). The third is the histological demonstration of probable chemoreceptor tissue in this same location (figs. 12, 14 and 15). This tissue in both the canine and human examples in our study is virtually identical to neuroreceptor tissue described by others in carotid body and in aortic bodies.²⁰ ²⁶

Comroe²⁷ has demonstrated in both dogs and cats an excitatory chemoreflex which he attributed to activation of proximal aortic chemoreceptors. However, he also found that in four cats the blood supply of the chemoreceptors arose from the coronary circulation rather than the aorta, whereas in eight dogs it was from the aorta. In our experience and the much larger localizing study of Eckstein et al. in over 200 dogs,⁷ the blood supply in question comes predominantly from the coronary arteries and not from the aorta. We suggest that a chemoreceptor which receives its primary blood supply from the coronary arteries may be more logically considered a cardiac rather than aortic chemoreceptor.

Figure 14

The structure outlined with black arrows in A was located less than a millimeter from the main left coronary artery, and the small vessel penetrating it originated from the main left coronary artery of this 20-year-old man without known or apparent heart disease. One portion of a large nerve (N) and adjacent ganglion (G) are labeled. This human chemoreceptor is similar to that of the dog shown in figure 12. At higher magnification in B the resemblance to carotid body is illustrated by the number of capillaries (C) and whorls of cells, the nuclei of many of which (open arrows) contain characteristic clumps of chromatin.

Two different sections of the human chemoreceptor illustrated in figure 14 are shown here to demonstrate its organization about a small artery. These sections are 320 microns apart.

Figure 15
Physiological Components of the Reflex

Excitatory and depressor reflex responses to both chemical and mechanical stimuli delivered to the left ventricle or coronary arteries have been reported by many investigators. In both types of experiments attempts to relate these to possible events in acute myocardial ischemia and infarction have been a basis for discussion. There is evidence that some component of the sympathetic excitatory reflex during acute myocardial ischemia may course directly to the spinal cord and back, rather than to the brain. A similar "spinal reflex arc" may explain why bilateral vagotomy in our own experiments failed to eliminate all of the acute pressor response. However, there is no question that most of the acute hypertension (but not the delayed longer phase) and all of the immediate electrophysiological effects depended on the presence of intact vagus nerves.

In most respects this cardiogenic hypertensive chemoreflex resembles a mirror image of the Bezold-Jarisch reflex, the former being predominantly excitatory in nature while the latter is mainly depressor. However, while serotonin elicits the excitatory reflex when perfused selectively into certain proximal segments of the left coronary artery, it produces only hypotension when injected selectively into the distal left coronary tree (fig. 7). Serotonin may thus elicit either reflex from the heart, depending on the site of administration. When both areas are stimulated nearly simultaneously by serotonin, as after left atrial injection, the excitatory response clearly predominates.

Another feature shared by both the excitatory and depressor chemoreflexes is their alteration by local anesthesia directly around the main left coronary artery. Although hypertension was only attenuated by this procedure while the Bezold-Jarisch hypotension was eliminated, the excitatory reflex is clearly the more powerful and probably more difficult to suppress. More important, the anatomical site for interdicting either of these opposing responses appears to be essentially the same and it is in a very small region directly around the main left coronary artery. This region is also the location of what appears to be chemoreceptor tissue (figs. 12, 14 and 15). However, because the Bezold-Jarisch reflex is classically elicited from more distally located sites in the left ventricle, the demonstrated chemoreceptor tissue adjacent to the main left coronary artery may only be a consistent transit site or perhaps relay station for the depressor reflex. For the excitatory reflex, on the other hand, our own data and those of Eckstein et al. suggest that this chemoreceptor tissue may be the exact site of origin.

Of the several physiological characteristics of the serotonin chemoreflex, easily the most striking is the acute arterial hypertension. This represented a virtual doubling of the diastolic pressure within seconds, and the peak was followed by only a gradual return to control levels many minutes later. A relatively delayed hypertensive response to serotonin has been previously reported by others. Although some hypertension of the delayed type was also produced by serotonin injections into points downstream from the coronary arteries in our own experiments, this was neither as marked nor as prompt as when serotonin initially coursed through the proximal coronary circulation. This would suggest that whatever the mechanism of the prolonged hypertension, the immediate peak response acts to "set" it at a higher level than was found if the initial peak did not occur. Since the initial peak hypertension did not occur with extracardiac injections of serotonin, it is difficult to attribute the very first component of the pressor response to either a direct or indirect action by serotonin on peripheral arterial resistance vessels themselves. However, since alpha-receptor blockade with phentolamine virtually eliminated the hypertension, it is most likely reflex sympathetic peripheral vasoconstriction which is responsible for the acute hypertension. Because no hypotension of note occurred when serotonin was administered during the adrenergic alpha-receptor blockade, it seems unlikely that there is a significant concomitant peripheral vasodilator action of serotonin administered into the left atrium. The other well known effects of serotonin, such as pulmonary vasoconstriction, presumably played little role in the response to the left atrial injections, since the acute hypertension and electrophysiological responses did not occur when serotonin was injected intravenously. This also made unlikely the concomitant activation of any possible chemoreceptors within the pulmonary circulation to explain our present results.

Electrophysiological characteristics of the serotonin chemoreflex were best explainable by simultaneous dual autonomic efferent influence in both the sinus node and the A-V junction. For both regions the effects were almost immediate in onset and comparatively brief in duration. During the first few seconds, there was a profound vagally-mediated slowing of the sinus node (or of the A-V junctional pacemaker when it was dominant [fig. 11]), followed for about a minute by sinus acceleration (in five dogs this was A-V junctional tachycardia). Except with vagal blockade in the sinus node by selective perfusion with atropine, the concomitant negative dromotropic influence was generally masked. However, after selective vagal blockade in the sinus node, there was consistently a brief initial vagally-
mediated high degree of heart block. This suggests that in the first few seconds of the chemoreflex it is the vagal suppression of both the sinus node and A-V junction which predominates. Shortly thereafter the sympathetic influence becomes predominant, and it was the only apparent influence when local vagal effects were selectively blocked. Sympathetic reflex effect on the sinus node and on the A-V junction was simultaneous in onset and similar in duration for both sites. That this was truly neuroreflex in origin rather than due to local release of norepinephrine by serotonin is indicated by the lack of local stimulating action on either sinus node or A-V junction by direct perfusion with serotonin in either the present or previous experiments from this laboratory.

In addition to the mixed nature of autonomic efferent discharge influencing cardiac rhythm and conduction, there was also considerable individual variability from dog to dog as to which autonomic component predominated and its duration of effect. Comroe has previously emphasized the large degree of individual variability of chemoreflexes from dog to dog or cat to cat. There is also both anatomic and physiological basis for considerable variability in the incidence and magnitude of chemoreflex responses. In any given dog, however, both the pressor and electrophysiological responses were readily reproducible and consistent in all our experiments. Repeated injections of serotonin into the left atrium at suitable intervals reproduced virtually the same acute hypertension indefinitely, although the brief initial strong vagal suppressive effect on cardiac electrical activity tended to wane with successive injections. Whether this should be interpreted as tachyphylaxis for the vagal efferent response or not, the vagal afferent component which was responsible for the subsequent sympathetic efferent discharge must have remained reproducibly responsive. It would be useful to know whether dog-to-dog variability was due to physiological or anatomical (e.g. size or location of chemoreceptors) factors, but we have no data to answer this question.

Possible Clinical Significance of the Reflex

Serotonin is normally present in both canine and human blood (about 1 µg/ml) almost entirely contained in the platelets. If one considers the number of platelets normally present in a single milliliter of blood and then extrapolates to the probable volume of serotonin expected to be present in a solid milliliter of platelets (such as may be represented by a transient platelet aggregation along the vessel wall), the volume of serotonin should be at least several multiples of the concentration contained per milliliter of test substance injected into the left atrium during our experiments. This is without even allowing for the inevitable dilution of an experimental atrial injectate by the time it has reached the proximal coronary circulation. It would seem reasonable, therefore, to assume that concentrations of serotonin at least as great as those examined in our experiments could reach human chemoreceptors if a platelet aggregation occurred near the ostium of their nutrient vessel.

For many years it has been known that acute hypertensive episodes occur in some individuals during angina pectoris or in the very early stages of acute myocardial infarction. Although efforts have been made to attribute this to keen emotional stress and secondary sympathetic neural discharge, or to an increased concentration of circulating catecholamines, the level of hypertension which occurs is too often more than one would expect with either of those explanations. Furthermore, some have found that the hypertension is present a significant time before the onset of chest pain. On the other hand, if man has a cardiogenic hypertensive chemoreflex caused by serotonin, such as the reflex demonstrated here in dogs, then it is possible that recurring transient platelet aggregations may be forming on an atherosclerotic plaque or similar lesion located near the ostium of the chemoreceptor artery. It would be necessary for this to be a recurring dynamic renewable process for the hypertension to persist as it does in some patients for hours, but it is known that intracoronary platelet aggregations under experimental circumstances can continue to form for prolonged periods of time.

Under the hypothetical circumstances just described, the hypertension could be expected to end whenever 1) the platelet aggregation stopped reaccumulating, as might occur after a complete occlusion has taken place, or 2) if the local nidus became covered with cells or a substance which no longer caused platelets to aggregate there, or 3) when the chemoreceptor was itself no longer viable. At the other extreme, one may consider whether the postulated chemoreceptor has some tonic influence important to the normal maintenance of blood pressure. If so, then death of the chemoreceptor during some types of acute myocardial infarction may contribute to the pathogenesis of cardiogenic shock. This would be a difficult matter to investigate, since an occlusion which occurred near the ostium of most demonstrated locations of the chemoreceptor artery

*Estimating about 300,000 platelets/cu mm, and roughly considering one platelet to be 7 µm3 in volume. Platelet shape and dimension would of course change during the aggregating process at which time release of the serotonin might occur.

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would also be a proximal left coronary occlusion, with the loss of a very large volume of ventricular myocardium. Either of these consequences (large infarct or chemoreceptor inactivity) could contribute to cardiogenic shock. Teleologically, one might expect that the danger posed by an aggregation of platelets near the origin of the main left coronary artery would be so great that nature might provide a reflex response which could lead to dislodgement or disaggregation of those platelets by a sudden arterial hypertension.

One of the first to recognize the occurrence of unexplained hypertension and tachycardia in some patients with angina pectoris was Sir Thomas Lewis, who coined the colorful and apt term of "vasomotor storms"49 for these events. In preceding discussion we have hypothesized that such hypertension could become sustained by the recurring release of serotonin from reaccumulating aggregates of platelets. However, the mixture of autonomic neural events comprising the vasomotor storm may lead to critical malfunction of the heart during acute myocardial ischemia even if they are only of brief duration. Such events, for example, may account for some otherwise unexplained sudden deaths during myocardial ischemic attacks.50

These clinical speculations about patients with coronary disease seem sufficiently important so that several logical questions can be formulated to test them. For example, in those patients who do develop inordinate bouts of hypertension during angina or early infarction, it can be determined whether they have coronary lesions in sites potentially influencing the postulated chemoreceptor tissue. In fatal cases it would be feasible to search for such tissue in the periarterial environs of such coronary lesions, although it would be improbable that local platelet aggregations would have persisted long enough to be identified. If such investigations support the possibility that there is a cardiogenic hypertensive chemoreflex in man, at least two sets of further clinical investigations would be merited. First, surgical neurectomy in the appropriate location around the main left coronary artery may have some merit, for example in patients selected on other grounds to have coronary bypass surgery, and in whom acute hypertensive bouts had previously been documented during angina; this would be particularly worth considering if the coronary arteriographic anatomy demonstrated any lesion in the proximal part of the left main coronary system. Second, it would be useful to determine if intracardiac chemoreceptors play some role in other hypertensive states, such as essential hypertension or sudden acute malignant hypertension. For that purpose it would be useful to know from necropsy examination if there are more or larger structures resembling chemoreceptors in the hearts from patients who died with or from arterial hypertension.

Finally, it has recently been observed that many patients undergoing surgical replacement of the aortic valve develop subsequent arterial hypertension.51, 52 This unexpected finding has proven to be clinically important, since medical treatment of the hypertension significantly reduced the incidence of failure by homografted valves.52 Although a number of possible explanations were considered by these investigators, such as the sudden release of a previously pent-up powerful left ventricle, they concluded that the true cause of the hypertension was unknown. Whether either trauma during surgery on the aortic valve or some later postoperative cicatrical process somehow stimulates the cardiac chemoreceptor studied by us is not presently known. But the possibility is as intriguing as it is for a variety of other forms of unexplained hypertension and clearly merits further investigation.

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