Responses of the Sino-atrial Node to Change in Pressure in the Sinus Node Artery

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ABSTRACT

The sino-atrial node area was perfused selectively through the right atrial artery in 76 dogs. The relationship between changes in the blood pressure in this artery and sinus node rhythmicity was studied in 56 hearts in which the major blood supply to the sinus node artery came from the right atrial artery. A reciprocal relation was observed between changes of blood pressure in the sinus node artery and the sinus rate. Some characteristics were: (1) The negative chronotropic effect induced by raising the blood pressure was linearly related to the degree of pressure change and more prominent than the positive chronotropic effect induced by reducing the pressure. (2) This relationship was most prominent in a limited range between 20 and 100 mm Hg. (3) Dichloroisoproterenol, atropine, hexamethonium, reserpine and vagotomy did not modify these responses. It is concluded that this localized mechano-sensitivity of the sinus node to changes in arterial pressure may be responsible for the regulation of the heart rate in the lower range of blood pressure and that complete regulation of the heart rate is achieved physiologically in combination with the reflexes through the carotid and aortic nerves.

ADDITIONAL KEY WORDS

hexamethonium reserpine vagotomy dichloroisoproterenol atropine anesthetized dogs arteries to sino-atrial node regulation of cardiac rate mechanoreceptors

In the Langendorff dog heart-lung preparation and rabbit atrial preparations, Blinks (1) observed that the distension of the right atrium produced a substantial increase of the heart rate. Deck (2) confirmed this observation on isolated preparations of the sino-atrial node in cats and rabbits. There are numerous examples of a relationship between stretch and pacemaker activity and it is generally accepted that the mechanical distension of the pacemaker tissue decreases the diastolic potential, thus accelerating rate of discharge of the pacemaker cell (3). Recently, James and Nadeau (4, 5) arranged a unique preparation for perfusion of the sino-atrial node and observed the occurrence of sinus bradycardia when a large variety of test solutions was injected directly into the sinus node artery. He deduced that there is a stretch receptor mechanism closely related to a peculiar periarterial structure which operates as a sensing device for the distension of this artery, i.e., “slowing of the rate of the discharge by reducing the amount of stretch induced by arterial recoil.”

In this study we have examined the relationship between changes in perfusion pressure and pacemaker activity of the sinus node using modified methods and have discussed the physiological role of this response.

Methods

Seventy-six mongrel dogs, of both sexes, weighing 10 to 25 kg were anesthetized by intravenous injections of pentobarbital sodium (30 mg/kg). Heparin sodium was initially given in a single dose of 300 U/kg. A tracheal tube
was inserted and connected to a "Bird" respirator (Mark 8) with intermittent positive respiration. The chest was opened in the right fourth intercostal space and the heart was suspended in the pericardial cradle. The dorsal right atrial artery was carefully isolated from its origin for about 10 mm. A polyethylene tube (o.d. 3 mm) was tapered to fit a cannula, the tip of which was 0.5 to 1.0 mm o.d. The cannula was inserted into the dorsal right atrial artery and the tip was placed as shown at T in Figure 1 in the crista terminals. A pneumatic resistance (A) was arranged in parallel with the cannula. The arterial blood led from the femoral artery was driven by a Sigma motor pump to the cannula and to the pneumatic resistance (A) through which any excess of blood was shunted to the femoral vein. Perfusion pressure was regulated by changing the pressure in the pneumatic resistance.

The retrograde pressure was measured by the pressure transducer (D in Fig. 1), when the blood perfusion to the sinus node artery was closed by turning off the three-way stopcock (C in Fig. 1). The direction, but not the absolute values of blood flow during perfusion, was measured by a magnetic flowmeter (Nihon Kohden MF-2). Retrograde blood flow was measured in a graduated cylinder as it flowed from the central end of the cannula after it had been disconnected from the polyethylene tubing.

A multipurpose polygraph (Nihon Kohden 150-8) was used. The side pressure of the perfusion system (D) and the systemic blood pressure in the femoral artery were measured by pressure transducers. The heart rate was recorded by cardiotachograph which was triggered by the R wave of lead II of the ECG through a Nihon Kohden ME-20-TR. The epicardial lead was recorded simultaneously.

Drugs used were dichloroisoproterenol hydrochloride (0.1 and 1.0%), hexamethonium bro-
mide (0.5 and 5%) and atropine sulfate (0.1 and 1.0%). The drug solution (0.01 ml) was injected in a period of 4 sec into the rubber tube connected closely to the shank of the polyethylene cannula. For the accurate administration of a minute amount of solution, two types of micrometer syringes (Burrough Welcome & Co. and Jintan Co.) were used. Both injectors were quite satisfactory for the purpose. The plunger of the glass syringe was advanced in the cylinder by turning the screw of the microgauge in the former type, but in the latter the stainless steel plunger was moved directly in the closely fitted glass cylinder. An appropriate concentration of drug solution was obtained by dilution of the stock solution with saline. Saline (0.01 ml) injected in 4 sec had no effect whatever on the atrial rhythm. Reserpine (0.1 mg/kg) was given 24 hr in advance in 4 dogs in accordance with the procedure used by Waud, Kottegoda and Krayer (6).

| TABLE 1 |
|-----------------|-----------------|
| Retrograde blood pressure* (mm Hg) | Retrograde blood flow† (ml/min) |
| Mean | 41 | 0.27 |
| SE | ± 0.2 | ± 0.029 |
| Range | 14 to 80 | 0.2 to 0.38 |

*Ten experiments.  
†Six experiments.

Results

PATTERNS OF BLOOD SUPPLY TO THE SINUS NODE OF CANINE HEART (FIG. 2)

The blood supply to the sinus node was of two types. In type A, the dorsal right atrial artery originated from the right coronary artery, passed straight across the surface of

![FIGURE 2]

Patterns of the blood supply to the sinus node. Abbreviations as in Figure 1.

![FIGURE 3]

Typical curves of pressure-flow relationship in the perfusion through cannula open to the atmospheric pressure (A) and through cannula inserted in the dorsal right atrial artery (B). The retrograde pressure was 50 mm Hg.
the right atrium, turned to the crista terminalis intramurally and divided into branches, one of which passed through the sino-atrial node as the sinus node artery. Many arteriolar anastomoses were found between the dorsal right and the ventral left atrial artery which formed the vascular network around the caval funnel. Seventy-one of the animals (93%) belonged to this type; the dorsal right atrial artery was significantly dominant in 54 out of 71 type A hearts and the ventral left atrial artery was the major blood supply to the sinus node artery in the other 17.

In type B (5 dogs) the ventral left atrial artery came from the left coronary artery and passed through the sinus node from the opposite side. The dorsal right atrial artery was extremely small or it did not go to the crista terminalis. Because the ventral left atrial artery was quite difficult to approach beyond the auricular appendage, all perfusion experiments were done in type A hearts. Type A hearts with a dominant right atrial artery were the most useful for this study.

**Retrograde Pressure and Retrograde Blood Flow**

The retrograde pressure varied considerably from animal to animal; the retrograde blood flow varied relatively little. The retrograde pressure was measured in a static system; it was affected by various factors such as the systemic blood pressure and the extent of anastomosis, but not by resistance in the cannula and tubing. The retrograde blood flow was measured in a dynamic state and although it depended on the level of arterial blood pressure, it was also governed by arti-

![Figure 4](Image)

Typical tachograms caused by increasing and reducing the pressure in the perfusion system. PP = perfusion pressure; SBP = systemic blood pressure.

![Figure 5](Image)

Relationship between change of pressure in the perfusion system and rhythmicity of the sinus node. Numbers in parentheses represent number of experiments. The pressure changes are represented by bars with a square end (initial pressure) and a slanted end (final pressure).
facts such as the shape or the position of the tip of cannula; we could devise no better method to assess the amount of retrograde blood flow without any artifact.

When the pneumatic resistance (A in Fig. 1) was decreased to atmospheric pressure, all of the blood driven by the Sigma motor pump was shunted to the femoral vein; at this time blood from the cannula also flowed in retrograde direction into the shunt. When the pneumatic resistance was set at a level so that perfusion pressure exceeded the retrograde pressure, the blood flow in the cannula changed its direction promptly from retrograde to forward and the constant pressure perfusion to the sinus node artery was reestablished.

The approximate perfusion flow with constant pressure is illustrated in Figure 3B where the retrograde pressure was 50 mm Hg. Approximate values of the perfusion flow were from 2 ml/min at 100 mm Hg which was about 10 times greater than the retrograde blood flow. The perfusion flow through the cannula when open to the atmospheric pressure (Fig. 3A) was over 4 times larger than the actual perfusion volume to the dorsal right atrial artery at each level of perfusion pressure. Thus it is concluded that the resistance through the cannula is the factor controlling the perfusion pressure.

RELATIONSHIP BETWEEN CHANGES OF THE PERFUSION PRESSURE AND RHYTHMICITY OF THE SINUS NODE (FIGS. 4, 5 AND 6)

The typical time course of the chronotropic response of the sinus node to the sudden change of perfusion pressure is illustrated in Figure 4. The change in heart rate was attained within 15 sec and could then be stabilized at a certain level by either raising or reducing the pressure.

The maximal changes in the heart rate resulting from changes in the perfusion pressures were observed in 151 trials in 54 dogs. Average results are illustrated in Figure 5. At pressures above 150 mm Hg the number of experiments was limited, because petechiae appeared quickly along the perfused artery. Abrupt elevation of the perfusion pressure induced a decrease in the heart rate, while the abrupt reduction of the perfusion pressure...
Relationship between pressure and rhythmicity after administration of dichloroisoproterenol (DCI) (A, A'), hexamethonium (B, B'), atropine (C, C'), bilateral vagotomy (D, D') and reserpine (E). Doses of DCI, hexamethonium, and atropine were 100 ng, 50 fig and 10 iig respectively; 0.1 mg/kg of reserpine was given 24 hr in advance.

Caused an increase of the heart rate. The slowing produced by raising pressure was more prominent and linearly related to the degree of pressure change than the acceleration produced by the reduced pressure.

Greater chronotropic effects were observed from changes that began from or ended in the lower ranges of perfusion pressures. This was clearly demonstrated for the decrease in heart rate caused by raising the pressure, and also for the increase of heart beat by reducing the perfusion pressure.

The negative chronotropic responses to increments of 20 mm Hg from 0 to 200 mm Hg in two experiments are illustrated in Figure 6. The largest effect was usually obtained in the range from 20 to 100 mm Hg. Above this level the effect was small, and no response whatever was observed above 150 mm Hg. When the perfusion pressure was changed in decrements of 20 mm Hg, from 200 to 0 mm Hg, the positive chronotropic effect was greatest in the range from 100 to 20 mm Hg.

Effects of selected drugs on the chronotropic responses to changes of perfusion pressure (Fig. 7)

The intra-arterial administration of dichloroisoproterenol (10 and 100 μg) diminished and blocked the positive chronotropic effect of 0.1 μg of epinephrine. Atropine (10 μg) blocked completely the effect of acetylcholine (0.001 to 10 μg). Dichloroisoproterenol, atropine and hexamethonium (50 μg) did not modify the original response to increased pressure (Fig. 7, A', B' and C'). Bilateral vagotomy also had no effect (Fig. 7, D'). The negative and positive chronotropic effects in 4 reserpinized dogs were approximately the same as those in the control animals (Fig. 7, E). The reduction of perfusion pressure from 150 to 50 mm Hg.
caused an increase in the heart rate of about
15% in reserpinized animals while it was 12% in
the controls. Around 13% decrease was
obtained by increasing the pressure from 50
to 150 mm Hg in reserpinized animals while
the comparable value in controls was 12%.

ABSENCE OF A CHRONOTROPIC RESPONSE IN
PREPARATIONS OF LEFT CORONARY ARTERY DOMINANCE

In type B hearts, the size of the dorsal
right atrial artery was quite variable, ranging
from the thinness of a hair to the usual size.
These hearts did not respond to changes in
perfusion pressure in the right atrial artery.
This indicated that the relation between per-
fusion pressure and rhythmicity was medi-
atated in the very restricted area of the sinus
node.

Discussion

The right atrial artery described by James
(7) corresponds to the ramus atrialis dextra
intermedius reported by Meek et al. (8).
A blood supply corresponding to type A in
this paper (through the right atrial artery)
was found in over 90% of the canine hearts
examined by James (5), in 81% by Meek et
al. (8) and in 93% of the hearts we examined.
A majority of canine hearts of type A received
their main blood supply to the sinus node
from the right atrial artery, but some blood
came from the left atrial artery. When the
left atrial artery was dominant, chronotropic
responses to changes in perfusion pressure
through the right atrial artery were less. Thus
hearts in which right atrial arteries were
dominant (56 of 76 hearts) were selectively
used in our experiments.

The relationship between stretch and ac-
tivity of the sinus node observed in the per-
fusion experiment of the sinus node artery
must relate to a local mechanism in the sinus
node, because neither vagotomy nor hexa-
methonium treatment blocked the response.
The absence of a blocking action by atropine,
dichloroisoproterenol and reserpine indicates
that the response is probably not related to
autonomic nerve stimulation.

As James described in his histological
studies, the canine sino-atrial node must have
a unique structure so that a decrease of pres-
Sure in the sinus node artery causes the
stretching of sinus node fibers. It was found
in all preparations used in this study, how-
ever, that there was a limited range within
which changes in the perfusion pressure
causéd the prevailing effect on the rate of
impulse formation in the sinus node. This
was from 20 to 100 mm Hg. This range is
lower than that observed in the baroceptive
reflex of the canine carotid sinus which was
most prominent above 80 mm Hg in the ex-
periments reported by Heymans and Neil
(9). Quite recently, the same conclusion was
obtained in the aortic arch reflex (10). Pre-
vously, Blinks found the effective range of
stretch tension for the pacemaker activity
from 0 to around 100 mm H2O in a majority
of rabbit atrial preparations. Considering the
differences in species and methods for stretch-
ing, Blinks' observation probably corresponds
to those reported here, especially as the effec-
tive range was at rather low pressure level.

James and Nadeau (5) reported, in a brief
note, the determination of the pressure gra-
dient by double cannulation of the right
coronary and sinus node arteries. With an
input pressure of 400 mm Hg, they found a
very large pressure gradient of nearly 300
mm Hg. Thus, with their technique, the
effective pressure was about one fourth of
the input pressure. In the authors' arrange-
ment, the tip of the polyethylene cannula was
advanced in the artery to the crista terminalis
and there was no room for double cannulation
to measure the pressure gradient from the
input pressure. Thus it was not possible to
estimate the actual pressure in the artery
but there is much evidence against the ex-
istence of such a large pressure gradient. (1)
The direction of blood flow in the perfusion
system changed promptly when the perfusion
pressure was elevated above the retrograde
pressure. If the effective pressure in the ar-
tery was as low as one fourth of the input
pressure, 100 mm Hg pressure measured in
the input tube could not overcome 30 mm
Hg of retrograde pressure. Even with the
highest retrograde pressure of 80 mm Hg
observed in this study the blood flowed forward with 100 mm Hg of input perfusion pressure. (2) More than 150 mm Hg of perfusion pressure quickly caused many petechiae in the perfused area and it was practically impossible to use perfusion pressures greater than 200 mm Hg. (3) The blood flow from the cannula when it was open to atmospheric pressure was over 4 times larger than that through the dorsal right atrial artery at each level of perfusion pressure above the retrograde pressure. Thus, we have no reason to believe that a large pressure gradient exists across the cannula.

It may be concluded that a local, but minor, mechanism regulates the rhythmicity of the sinus node principally when the range of blood pressure is low while the major regulatory mechanism of heart rate through the carotid and the aortic nerves acts in the normal range of blood pressure. This minor, but local, regulatory mechanism may replace the regulation through depressor nerves when the systemic blood pressure goes down to an abnormally low level.

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