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DIRECT PERFUSION OF THE SINUS NODE: AN EXPERIMENTAL MODEL FOR PHARMACOLOGIC AND ELECTROPHYSIOLOGIC STUDIES OF THE HEART

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Studies of the chronotropic effect of drugs are in essence studies of the behavior of the sinus node. Because this structure is richly innervated and therefore subject to many extracardiac influences, it is often difficult in the intact heart to determine whether a drug has a direct or indirect effect on the cardiac pacemaker. If the drug additionally possesses inotropic effect, this further obscures any direct influence it may have on heart rate.

Figure 1

A vinylic cast of the coronary arteries and cardiac chambers of a normal dog; the pulmonary valves are seen in the right upper portion of the cast. The broad straight arrow indicates the location of the sinus node at the auriculocaval junction. The curved arrow indicates the usual site at which the catheter is introduced into the right coronary and passed up the sinus node artery, which is seen to ascend up the left margin of the photograph. Reproduced from James, T. N.: Anatomy of the Coronary Arteries, Paul B. Hoeber, Inc., New York, 1961, by permission of the publisher.

To facilitate the investigation of the chronotropic effect of drugs, an experimental model has been devised for selective perfusion of the canine sinus node through its own artery. With such localized perfusion it is possible to employ minute volumes of various drugs, observing their isolated effect on cardiac rate and rhythm. Moreover, the heart is preserved intact in situ, with its own blood supply and innervation.

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Method

Twenty dogs weighing 8 to 18 Kg. each were anesthetized with intraperitoneal pentobarbital (30 mg./Kg.), and the trachea intubated. Through a median sternal-splitting incision the heart was exposed and cradled in the pericardial sac. The right coronary artery and its immediate branches were dissected free. An arteriotomy was made in the right coronary artery proximal to the origin of the branch to the sinus node* (Figure 2). A small polyethylene catheter (0.7 mm. outside and 0.5 mm. inside diameters) was passed through the arteriotomy and into the sinus node artery (Figures 2-3). The main right coronary artery was then ligated just proximal and just distal to the arteriotomy, sacrificing a small amount of right ventricular myocardium. Any ventricular branches arising from the isolated segment were also ligated at their origin. The ischemia of this portion of right ventricular myocardium had no significant effect on cardiac rate, rhythm or pumping efficiency in 19 of the 20 dogs. In one dog ventricular fibrillation developed, but this responded promptly to counter-shock and did not recur. When the sinus node artery was too small to cannulate directly, the catheter tip was left in the main right coronary artery just proximal to the origin of the nodal artery; all the adjacent ventricular branches being ligated, the main artery acted as a conduit from the catheter to the nodal artery.

Figure 2

A drawing of the experimental model. A catheter is shown inserted into the right coronary artery, it was usually passed up the sinus node branch as far as the heavy black arrow. The small arrows indicate the route of flow to the sinus node (stippled area at the base of the superior vena cava). A is aorta, P.A. pulmonary artery, and S.V.C. superior vena cava. Note all the ventricular branches of the right coronary artery have been ligated to prevent ventricular perfusion. The inset illustrates the method of autoperfusion via a catheter from the femoral artery; a 3-way stopcock connects the catheters of the sinus node artery and femoral artery, and allows injection of test solutions.

After the catheter was satisfactorily placed, it was immediately connected to a large polyethylene catheter from the femoral artery. The femoral artery was preferred to a coronary, carotid or subclavian artery because of its size and accessibility and its paucity of neuroreceptors. A 3-way stop-cock joining the two catheters permitted the injection of drugs

Figure 3

A postmortem angiogram made after injection of contrast material into the catheter of the sinus node artery. The curved arrow indicates the site of the arteriotomy in the right coronary artery. The catheter tip is 8 mm. beyond this, lying within the sinus node artery. No contrast material appears in the region of the ventricles. The broad straight arrow at the top of the photograph indicates the location of the sinus node.
and other solutions directly into the sinus node artery. Both catheters and the stop-cock were rinsed in heparin with which the dogs were anticoagulated. The opposite femoral artery and vein were exposed for arterial and venous pressure measurements and for systemic injection of solutions.

Test solutions were delivered into the sinus node artery catheter through the 3-way stopcock, re-establishing autoperfusion from the femoral artery immediately at the end of the injection. Pressure by hand on a graduated syringe had to be slowly and gently applied to avoid injuring the small sinus node artery. For prolonged perfusion of the sinus node the solutions were dripped in from a suspended bottle.

To check the position of the catheter tip during the experiment a useful procedure was injection of acetylcholine, 0.1 to 0.5 mcg. (about 0.005 to 0.05 mcg./Kg.) delivered in 0.1 to 0.5 ml. within 1 to 15 seconds. This consistently produced a sinus bradycardia or sinus arrest, sometimes followed by brief atrial fibrillation (Figures 4, 5). Recovery of the sinus node following acetylcholine arrest was always prompt and sustained, whereas recovery following arrest with potassium or calcium injections was not only more prolonged but intermittent, recurrences of sinus arrest appearing unpredictably for several minutes. With further experience the catheter tip position was accurately determined by simple visual inspection and by observing the sinus node artery during injection, the blood disappearing from the artery as it filled with the injected solution.

When there was a negative or erratic response to acetylcholine, the following flaws in the preparation were usually responsible. 1. The catheter was falsely placed or had moved since proper placement. 2. With high injection pressure for test solutions, branches of the sinus node artery were occasionally ruptured, producing large atrial hematomata; this impaired consistency of delivery of solutions to the sinus node. 3. Small clots sometimes occluded either the sinus node artery or the catheter, if the injecting syringe and the perfusing system (3-way stopcock, femoral artery catheter) were not anticoagulated with heparin and cleansed regularly. 4. External rupture of the main sinus node artery was another cause for erratic response to acetylcholine, but was easy to detect on gross inspection. About 5 percent of dogs supply their sinus node from the left circumflex artery7 and in these the present method fails.

![Figure 4](image)
The results of an injection of acetylcholine into the sinus node artery is illustrated. This 1.0 ml. perfusion lasted 12 seconds (between arrows). The dose of acetylcholine (1.0 mcg./ml.) for this 18 Kg. dog was 0.055 mcg./Kg. It was rarely necessary to employ this large a dose (see Figure 5), but note that the return of normal sinus rhythm after the injection was prompt and sustained.

![Figure 5](image)
The results of a later injection of acetylcholine into the sinus node artery of the dog shown in Figure 4. Here the perfusion of 0.25 ml. (between arrows) took 17 seconds and an effect was apparent after approximately 0.1 ml., thus by a dose of 0.005 mcg./Kg., demonstrating the exquisite sensitivity of the preparation. This time, arrest of the sinus node was followed by transient atrial fibrillation.

At the conclusion of each experiment the heart was carefully removed with the catheter remaining within the sinus node artery. The catheter and artery were immediately irrigated with saline to wash out the blood and prevent permanent obstruction. Later the heart was weighed, the gross anatomy of the right coronary artery and its branches described, and the course and distribution of the sinus node artery determined by india ink and hypaque in-
jections with radiographs (Figure 3). This ascertained the precise location of the catheter tip, as well as the general distribution of the substances perfused into the catheter. In vivo the perfused area was likely even more localized to the sinus node, since there was some pressure in anastomoses in vivo but none there postmortem.

**DISCUSSION**

The principal value of this experimental model is provision of a means to deliver drugs and other solutions directly to the sinus node in a heart with its blood supply and innervation intact. Although intracoronary injections have been employed for such purposes before, these were associated with a significant amount of ventricular perfusion. For drugs with combined inotropic and chronotropic effects it was thus virtually impossible to separate these effects in the intact heart. In the present preparation the ventricles are not directly perfused, and it is unlikely that the recirculation of the minute volume of substances perfused into the sinus node has any significant effect on eventually reaching ventricular myocardium. It is also unlikely that an inotropic effect on the small amount of atrial myocardium perfused adjacent to the sinus node significantly affects the chronotropic response of the node.

Preparations utilizing heart-lung models, isolated hearts or atrial strips have all contributed greatly to our understanding of the chronotropic pharmacology of drugs, but it is uncertain how directly this information may be transferred to interpreting behavior of the intact heart. Topical application and subepicardial injection of drugs, especially in the region of the sinus node, have also contributed significantly to understanding cardiac pharmacology, but both these routes of delivery are unphysiological, and also introduce trauma and mechanical stimulation of the node and the surrounding atrial myocardium. Direct perfusion of the sinus node through its own artery provides a means of delivering substances to the node in a fashion virtually identical to that following systemic injections, but in a volume small enough not to cause a significant pharmacologic effect elsewhere in the body.

In addition to allowing the study of orderly chronotropic responses such as sinus tachycardia and bradycardia, this experimental model has also proven useful for studying atrial fibrillation and A-V nodal rhythm (Figures 4, 5). Both atrial fibrillation and A-V nodal rhythm so produced have the advantage of a normally responsive A-V node and avoidance of unphysiologic stimulation such as direct atrial trauma.

It is important to understand that the solutions injected enter an open system, since the sinus node circulation drains into the right atrium. With repeated injections one may eventually produce a cumulated systemic level which affects extracardiac receptor sites. More significantly, however, one must think of each injection not as a total delivered dose but in terms of concentration in the perfusate and duration of the perfusion.

Anastomoses of the canine sinus node artery are numerous and it is consequently difficult to produce experimental local hypoxia of the sinus node. How much the anastomoses influence the perfusion of substances into the sinus node artery is unknown, but it seems unlikely that a significant dilution of the perfusate
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by blood from anastomoses will occur since the mean injection pressure (about 100 mm. Hg) is probably higher than that presented by anastomoses.

Preparation of this experimental model is relatively simple. The only unusual requirement is a familiarity with the anatomy of the canine sinus node artery. AdapTABLEity of the model to variations such as cross-perfusion experiments, or systemic administration of a drug after prior perfusion of its antagonist through the sinus node, is readily apparent.

SUMMARY

An experimental model for studying the chronotropic responses of the intact canine heart is described. It provides direct perfusion of the sinus node, thus permitting observation of the specific effect on cardiac rate and rhythm by minute amounts of pharmacologically active substances.

REFERENCES
