OBSERVATIONS ON THE INNERVATION OF THE CORONARY VESSELS OF THE DOG

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It has been generally held in the past that the innervation of the coronary vessels of the mammal is peculiar with respect to the systemic blood vessels in that the parasympathetics, the vagi, were considered to be coronary vasoconstrictors and the sympathetic nerves, primarily coronary vasodilators. The evidence for this comes largely from work reported by Wiggers (1), Anrep and Segall (2), Hochrein (3, 4) and Rein (5). However, in the case of both the vagus and sympathetic nerves, contrary results have been reported. Coronary vasodilators in the vagus nerves have been reported to exist by Meyer (6), Martin (7), Drury and Smith (8), Greene (9), Danielopolu and Marcou (10), Hinrichsen and Ivy (11), Kountz et al. (12) and Klisiecki and Flek (13). The subject has been recently reviewed by Wiggers (14) and further details need not be given here. Recently, Greene (9) has presented evidence tending to show that some sympathetic vasodilator fibers are contained in the lower cervical portion of the vagus trunks. More recently Heymans (15) and his collaborators, Jourdan and Nowak (16), have claimed that the sympathetic fibers which are bundled in the vagus join the vagus within the skull and originate in the medulla. However, Kabat (17) has cast grave doubt upon the interpretation of Heymans and his collaborators.

It has been argued that the supposedly peculiar innervation of the coronary vessels serves to permit their needed dilatation when other systemic vessels are constricted as is the case in exercise. This argument is fallacious, since such adjustments of coronary flow actually occur through dynamic and humoral control and not because of the peculiarity of anatomical bundling of efferent vasomotor fibers.

The discrepancy between coronary innervation and innervation of systemic vessels has induced us to reinvestigate the subject. In order to evaluate accurately the active changes in coronary vessel caliber due to vasomotor nerves, it is necessary 1, to use a measure of coronary flow which

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gives a reliable index of total changes in coronary caliber, and 2, to eliminate other factors which may affect coronary flow, viz., changing driving force in the coronary arteries, changing extravascular forces acting on the vessels, and extrinsic humoral mechanisms. To fulfill these conditions we used a preparation consisting of a head and isolated heart with fibrillating ventricles, both perfused with defibrinated dogs’ blood at constant pressure and temperature. The method for the isolated heart perfusion has been described in detail elsewhere (18). This was modified by also perfusing

Fig. 1. Diagram of perfused head-heart preparation. A, cannula in aorta for perfusing head and heart; I, innominate artery; L.S., left subclavian artery; P, cannula in pulmonary artery for collecting and measuring coronary flow; V, drainage cannula in left ventricle; S.V.C., superior vena cava; I.V.C., inferior vena cava; V. A.z., azygos vein; C.S., mouth of coronary sinus. Blood from head and mediastinal structures is drained from S.V.C. and V. A.z. back to aerator and perfusion apparatus. In this preparation the ventricles are fibrillating.

the head, neck and mediastinal structures from the same reservoir through the aorta to keep alive the brain and the cardiac nerves. The venous blood from these areas was drained from the superior vena cava and azygos vein and returned to the common reservoir (cf. fig. 1). With this preparation, coronary driving pressure and extravascular forces are kept constant, and extrinsic humoral effects are eliminated. As an index of coronary vessel caliber, total coronary flow from the pulmonary artery was measured.2

2 We have found that an average of only 10 per cent of the total coronary flow
The direct effects of the vagi and sympathetic nerves were studied by stimulating the peripheral ends of the cut vagi and the stellate ganglia after double vagotomy. The tonic activity of the vagi and sympathetics was studied by observing the effects of vagotomy, spinal cord section above the level of the third cervical segment, and complete denervation of the heart, including the tying off of the blood supply to the head. Sodium barbital, nembutal, ether, or chloralosan were the several anesthetics used in these experiments. The type of anesthetic used had practically no effect on the nature of the results, although the last three anesthetics named yielded more reactive preparations than the sodium barbital.

Fig. 2. Coronary vasodilator effect of stimulating peripheral ends of cut vagi.

Fig. 3. Chart of coronary flow showing vasodilator effect of vagus stimulation and its abolition by atropine, and vasodilator effect of sympathetic stimulation and its persistence after atropine, demonstrating the cholinergic nature of former and adrenergic of latter.

**I. Effect of stimulation of the peripheral end of the cut vagus.** In 10 experiments it was found that stimulation of the peripheral ends of the cut vagi gave rise only to vasodilatation (cf. fig. 2). This dilatation was abolished or greatly reduced following the injection of 2.5 mgm. of atropine sulphate (cf. fig. 3). This indicates that the vagi contain cholinergic vasodilator fibers. In 25 experiments vagus stimulation gave no effect. No evidence was obtained at any time in the whole series of 35 experiments drains through the thebesian vessels into the left ventricle (21). Thus the flow from the pulmonary artery represents practically the total coronary outflow.
that stimulation of the vagi within the range of current strength available with the Harvard inductorium gave coronary constriction.

II. Effect of stimulating the stellate ganglia with the vagi cut. In 7 experiments stimulation of the stellate ganglia gave rise to coronary dilatation, and this dilatation was not abolished by atropine even in doses sufficient to abolish the vagus dilatation (cf. fig. 3). This indicates that there are adrenergic coronary vasodilators in the sympathetic nerves. In 5 experiments coronary vasoconstriction was obtained following sympathetic stimulation (cf. fig. 4). In 27 experiments a biphasic or doubtful response was obtained. We have not been able to test the effect of ergotamine or

![Diagram](http://ajplegacy.physiology.org/)

**Fig. 4.** Coronary vasoconstrictor effect of sympathetic stimulation.

**Fig. 5.** Chart showing vasoconstrictor effect of cutting both vagi, and further vasoconstriction after completely denervating the heart. Experiment was done after 10 mgm. of ergotamine tartrate were given.

the dioxane derivative F 933 upon this coronary constriction. Nevertheless, our results suggest that the sympathetics contain adrenergic coronary vasoconstrictors.

III. Effect of cutting the vagi in the innervated isolated fibrillating heart preparation. In 8 experiments it was found that cutting the vagi led to a decrease in coronary flow. This occurred in 1 preparation in which ergotamine (10 mgm. of tartrate) was first given (cf. fig. 5), and it occurred in 1 experiment in which the sympathetic pathways had been severed by sectioning the spinal cord above the level of the third cervical segment prior to cutting the vagi (cf. fig. 6). These results, therefore, confirm
the fact that the vagi contain only coronary vasodilator fibers, and indicate that these are under the tonic influence of centers in the central nervous system. Our results confirm our findings with nerve stimulation that these dilator pathways are not adrenergic fibers of sympathetic origin which are contained within the vagus trunks but are truly cholinergic fibers arising from a parasympathetic center.

IV. Effect of sectioning the sympathetic pathways to the heart in the isolated fibrillating heart. Twenty-three experiments were done. In 14 cases the effect of sympathetic denervation was studied by noting the consequence of completing the denervation of the heart after the vagi had been cut. In 9 cases the effect was studied by cutting the spinal cord above the level of the third cervical segment either before or after the vagi had been severed. In all instances where a change in coronary flow occurred, there was an increase (cf. fig. 7) confirming our previous results indicating the presence of sympathetic coronary vasoconstrictor fibers, and showing further that these fibers are under the tonic control of centers in the central nervous system.

In 2 experiments the denervation was performed after ergotamine (10 mgm. of tartrate) had been injected. In one of the experiments sympathetic denervation caused a decrease in coronary flow over and above that...
previously noted in the same preparation on severing the vagi (cf. fig. 5). This finding would indicate that the tonic vasoconstrictor influence of the sympathetic is adrenergic in character and that there is a weaker adrenergic tonic coronary vasodilator influence distinct from the cholinergic dilator influence propagated by the vagi. This tonic adrenergic vasodilatation appears to be less powerful than the adrenergic vasoconstriction, since it is masked when ergotamine is not administered. However, faradic stimulation of the sympathetic fibers with a Harvard inductorium in our experience appears to act more readily on these adrenergic dilator fibers than on the adrenergic constrictor fibers.

V. Significance of results. Our results are in accord with our previous observations on the action of acetylcholine derivatives and epinephrine (18) on this preparation of the dog, and appear to us to show conclusively that the innervation of the coronary vessels is similar to that of other systemic vessels as recently established, particularly by Burn (19). They show 1, that the vagi contain only cholinergic vasodilator fibers to the coronaries; 2, that the sympathetics contain both dilator and constrictor fibers of adrenergic type, and 3, that these fibers carry impulses from the central nervous system which exert a constant tonic effect regulating the caliber of the coronary vessels. Our results are not in accord with previous views on this subject and the discrepancy we believe is due to the different methods of study used. In previous work we believe the effects were masked by the action of these nerves on the aortic blood pressure, on the vigor of the contractions of the heart, on the secondary extracardiac humoral changes, on the development under certain circumstances of relative ischemia, and on the alterations in the distribution of coronary outflow between the coronary sinus and thebesian channels (cf. 20 and 21). Our method of study has avoided these pitfalls and has permitted evaluation of active changes in coronary caliber undisturbed by such extraneous factors.

The clinical importance of our work in relation to denervation of the human heart is apparent. If the coronary innervation in man is similar to that in the dog, then sympathetic denervation in man may not only interrupt afferent pain fibers but the only efferent vasoconstrictor fibers as well. This point of view has recently been put forth by Leriche and Fontaine (22) but without adequate evidence to support it. Our results supply the experimental evidence for this viewpoint.

SUMMARY

A method is described for determining the action of the sympathetic and parasympathetic nerves on the caliber of the coronary blood vessels in a preparation consisting of an isolated head and heart with fibrillating ventricles.
Evidence is presented showing that in the dog:

1. The vagi carry only cholinergic coronary vasodilator fibers which are tonically active. No evidence was obtained of cholinergic coronary vasoconstrictor fibers.

2. The stellate ganglia send to the heart adrenergic coronary dilator and adrenergic coronary constrictor fibers, both of which are tonically active.

3. The tonic action of the sympathetic nerves is predominantly vasoconstriction.

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