Cardiac Effects of Intracoronary Arterial Injections of Nicotine

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The effects of intracoronary arterial injections of nicotine on coronary blood flow, myocardial contractility, cardiac rhythm and the QRS-T complex of the electrocardiogram were studied in intact dogs. The results indicate that nicotine stimulates intrinsic cardiac structures producing parasympathomimetic, sympathomimetic and Bezold-Jarisch reflex responses. The role of these intracardiac receptors is discussed in relation to the circulatory effects resulting from the ingestion of nicotine.

In the preceding paper we have described a set of procedures by which it is possible to inject minute amounts of drugs into various coronary branches of dogs without opening their chests or interfering with perivascular nerves.

We chose nicotine as the first drug for systematic investigation by this method, for the following reasons: First, the actions of this drug on the heart are of considerable practical importance in view of the present widespread use of tobacco, and yet they are poorly understood in spite of extensive studies. Second, nicotine has been used for 50 years for elucidating autonomic nerve functions and has been responsible for many significant discoveries. The methods used in the present studies have the advantage of permitting the application of nicotine directly to various parts of the hearts of practically intact animals.

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METHODS

The experiments were performed on 33 normal adult mongrel dogs weighing 20 to 30 Kg., under light anesthesia by pentobarbital sodium (30 mg./Kg. intravenously). Systemic blood pressure was recorded from the femoral artery using a Sanborn electromonometer and a direct-writing Sanborn Polyviso recorder. The electrocardiogram was continuously monitored in the same recorder, using a precordial lead (V6). In some preparations, myocardial contractility was measured by means of a Walton strain gage sutured directly to the exposed surface of the ventricle in the area supplied by the coronary artery into which injections were made. The amplitude of the strain gage record is proportional to the force of contraction.1 The cardiomyogram was recorded in the same multichannel, Sanborn Polyviso recorder. In other preparations, coronary blood flow was measured as outflow from the coronary sinus. Catheterization of the coronary sinus was accomplished in the intact animal with a special coronary sinus catheter (modified Morn- witz cannula) inserted via the external jugular vein under fluoroscopic guidance, as previously described for a flexible cardiac catheter. The catheter was provided with multiple openings at the tip and an inflatable balloon for securing it in the coronary sinus. Catheterization of the main branches of the coronary arterial tree (right, left anterior descending, and left circumflex arteries) was also accomplished under fluoroscopic guidance. The chest was intact in all experiments except those involving the Walton myocardiograph.

This technique of coronary artery catheterization made possible localized drug injections into various sites in the heart. Thus a drug injected into the right coronary artery reaches the S-A node; injected into the left circumflex branch it strikes the A-V node; injected into the left anterior descending branch it affects neither of these two branches.
Fig. 1. Effects of nicotine and epinephrine injected into left anterior descending branch. The records (from above down) taken from two different experiments show: epicardial lead, myogram (strain gage attached to the anterior surface of the left ventricle), lead II and femoral arterial blood pressure. Top, note the marked increase in the height of contraction accompanied by ST-T wave changes in the electrocardiogram following nicotine injection. Bottom, shows that these effects of nicotine are essentially similar to the positive inotropic and electocardiographic effects of epinephrine when injected into the same site. Speed of recorder is 25 mm/sec.

rhythmic centers directly and local actions on the heart muscle are exhibited without complications (provided that the Bezold-Jarisch reflex is not elicited).

FIG. 2 Top. Effects of intracoronary arterial injections of nicotine on myocardial contractility. The graph represents 86 observations on 15 dogs. All nicotine injections were made into the left anterior descending branch. The smallest effective doses of nicotine in 6 of these animals elicited a negative inotropic effect. Larger doses resulted in a positive inotropic effect, and an intermediate dose between the depressant and stimulant dose elicited no response. Heart rate and blood pressure remained constant provided the Bezold-Jarisch reflex was not elicited (1.2 to 2.0 μg./Kg.).

FIG. 3 Bottom. Coronary sinus blood flow after coronary arterial injections of nicotine. The responses plotted in the graph represent the peak changes (increases) observed immediately after coronary arterial injections of nicotine. Left anterior descending injections of nicotine or atropine or vagotomy produced essentially no increase in coronary flow, however, after atropine or vagotomy, left anterior descending injections increased coronary artery flow. Left circumflex injections increased coronary artery blood flow. Heart rate and blood pressure remained constant during these effects of nicotine.

RESULTS

Effects on Myocardial Contractility. A total of 86 observations were made on 15 dogs. In most cases the strain gage was attached to the anterior surface of the left ventricle and
nicotine was injected into the left anterior descending branch. In all 15 dogs, injections of nicotine ranging from 0.2 to 2.2 μg./Kg. resulted in an increase in contractility (fig. 1) amounting to 40 to 90 per cent, with an average increase of 75 per cent. A similar increase in contractility was also observed in the right ventricle and in the posterior aspect of the left ventricle, when nicotine was injected into the corresponding artery (right coronary and left circumflex, respectively).* These findings are summarized in figure 2.

The increase in force of contraction produced by nicotine was accompanied by electrocardiographic changes consisting of ST-depression and T wave inversion. An increase in systemic blood pressure was also seen occasionally. All these results of coronary arterial injections of nicotine are essentially the same as the effects of epinephrine when similarly injected (fig. 1B). Tetraethylammonium chloride (TEA), when injected into the same site, completely prevented the stimulating action of nicotine on myocardial contractility as well as the accompanying electrocardiographic effects. The corresponding effects of epinephrine remained unaltered.

Effects on Cardiac Rhythm and QRS-T Complex. Intracoronary arterial injections of nicotine in 33 dogs produced changes in cardiac rhythm and alterations in the ST-T wave complex, depending on the site of injection and the dose of the drug.

Right Coronary Artery. Nicotine (0.2 to 1.2 μg./Kg.) when injected into the main right coronary artery in 6 dogs produced transient periods of sinus arrest, sinus bradycardia, atrial fibrillation and occasionally sinus tachycardia.

Left Anterior Descending Branch. Small doses of nicotine (0.2 to 1 μg./Kg.) in 13 dogs (36 observations) produced only alterations in the ST-T wave complex with no change in the rhythm. These electrocardiographic effects consisted of S-T depression alone, or S-T depression and inversion of the T wave. These changes are very similar to the effects of epinephrine when injected into the same site (fig. 1).

Left Circumflex Branch. In 13 dogs nicotine (0.2 to 1.2 μg./Kg.) caused ST-T wave changes and transient periods of complete A-V heart block with temporary cessation of ventricular beats, followed by nodal escapes.

Bezold-Jarisch Effect. Larger doses of nicotine (1.2 to 2 μg./Kg.), when injected into the anterior descending or circumflex branch of the left coronary artery, produced transient periods of sinus arrest or sinus bradycardia with or without A-V heart block; these effects were accompanied by hypotension. The A-V block always accompanied left circumflex injections and was a manifestation of the Bezold-Jarisch effect plus direct parasympathetic ganglion stimulation (i.e., it was reduced by vagotomy but abolished only by atropine). This was not true with left anterior descending injections, which produced A-V block only as a part of the Bezold-Jarisch effect (i.e., it was abolished by vagotomy alone). Occasionally the cardiac slowing and hypotension produced by injection of nicotine into the left circumflex branch were followed by nodal tachycardia even when the blood pressure had returned to the control level.

Blocking Procedures. Bilateral vagotomy completely abolished the Bezold-Jarisch effects

*An increase in myocardial contractility was elicited by nicotine in every animal and in all three coronary areas studied, and is clearly the characteristic effect of nicotine when injected into the coronary arteries of those preparations. It is noteworthy, however, that in 6 of the 15 dogs minimal effective doses of nicotine (0.04 to 0.8 μg./Kg.) similarly injected caused either a pure depression of myocardial contractility, or an initial depression followed immediately by an increase in this function. The effect could be elicited repeatedly by the same dose. Injections of equal volumes of saline were without detectable influence. Depressant effects of nicotine, when seen, were not accompanied by any changes in the electrocardiogram or blood pressure. Larger doses (1.0 to 2.2 μg./Kg.) had purely stimulant effects on myocardial contractility. In those animals in which minimal quantities had elicited a biphasic effect, doses somewhat larger than these, but insufficient to produce stimulation, had no detectable effect. We were unable to produce myocardial depression by any dose of nicotine in the other 9 animals. The significance of these observations is at present obscure.
resulting from left coronary arterial injections of nicotine. However, the A-V block accompanying left circumflex injections still persisted. Vagotomy did not alter the arrhythmias resulting from right coronary arterial injections. Atropine abolished all the cardiac inhibition induced by nicotine from right and left coronary arterial injections, but did not prevent the concomitant hypotension. TEA completely blocked all the effects of intracoronary injections of nicotine.

Effects on Coronary Blood Flow. A total of 64 coronary blood flow observations were made in 10 dogs. Each dog received 5 to 10 injections of nicotine (with at least 10 min. intervals between them) in doses ranging from 0.04 to 1 μg./Kg. Injections were given only when the coronary blood flow varied less than 5 per cent over a period of at least 5 min. Immediately following the response, sufficient time was allowed for the coronary blood flow to return to the preinjection rate. The results differed according to which coronary branch was injected and the presence or absence of change in heart rate, but in no case was there any sign of direct coronary vasocoustriction by nicotine.

Left Circumflex Injections. In the 5 dogs studied the coronary flow was increased by 8 to 42 per cent, with an average increase of 19 per cent (fig. 3). At the same time blood pressure and heart rate remained essentially unchanged except when the dose of nicotine elicited A-V heart block and/or the Bezold-Jarisch effect. In these cases there was a decrease in coronary blood flow and in blood pressure.

Left Anterior Descending Injections. These were made in 5 dogs. There were essentially no changes in coronary blood flow. Following atropinization or vagotomy in these preparations, injections of previously ineffective doses of nicotine produced increases in coronary blood flow of 10 to 46 per cent with an average increase of 20 per cent (fig. 3).

The increase in coronary blood flow following nicotine injections was abolished by TEA when given into the same coronary arterial bed.

DISCUSSION

The responses resulting from intracoronary arterial injections of nicotine in these experiments may be divided arbitrarily into three groups, parasympathomimetic, sympathomimetic and Bezold-Jarisch reflex.

Parasympathomimetic. The parasympathomimetic effects comprised decreased activity of the S-A and A-V nodes and occasional atrial flutter or fibrillation. These were completely blocked by atropine or by TEA. The effect of atropine establishes a parasympathomimetic (muscarinic) pattern, that of TEA implies an origin in autonomic ganglia. Our findings therefore support the current view, based on histologic evidence,6,8 that the heart contains parasympathetic (vagus) ganglia whose postganglionic fibers terminate in the S-A and A-V nodes. When nicotine was injected into the right coronary it reached ganglia which influence the S-A node and usually caused atrial slowing, occasionally flutter or fibrillation (parasympathetic effect). When introduced into the left circumflex, it reached ganglia which influenced the A-V node and produced A-V block (parasympathetic effect). Injections into the anterior descending branch apparently reached ganglia which influence neither of these special nodes and affected only the strength of myocardial contraction. The constant result of such injections was to increase the strength of ventricular contraction. In 6 of 15 animals the smallest effective doses elicited negative inotropic effects in the left ventricular muscle, and in these particular animals this effect was produced by smaller doses than those required for any of the other manifestations of nicotine. The inference—that the first cardiac effect to be expected from gradually rising blood levels of nicotine is a depression of the strength of ventricular contraction—must be drawn with caution until more is known about this particular action of the drug. As far as we know at present, it is a true nicotine effect, but we do not yet know why it was not seen in all the animals and why larger doses invariably had positive inotropic effects in the same preparations.
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**Sympathomimetic.** The sympathomimetic actions consist of positive chronotropic (only elicited from the right coronary and circumflex branch of the main left coronary, producing sinus and nodal tachycardia respectively) and inotropic effects, ST-T wave depression in the electrocardiogram, and increased coronary blood flow. Like the parasympathomimetic actions, these were totally blocked by TEA, which implies an origin in sympathetic ganglia. However, since TEA can block the chromaffin cells of the adrenal medulla, we cannot exclude an action by nicotine on chromaffin tissue in the myocardium, leading to liberation of epinephrine or norepinephrine. In our experiments the effects of nicotine, apart from the parasympathomimetic phenomena discussed above, were identical with those of the two catechol amines.

**Bezold-Jarisch Reflex.** The Bezold-Jarisch response consisting of transient sinus arrest or bradycardia, with or without A-V block and hypotension,* was elicited only by injections of relatively large doses of nicotine into the branches of the left coronary artery. Like the other effects of nicotine, these were completely prevented by TEA, indicating an origin in ganglia or ganglion-like tissue. Atropine prevented only the negative chronotropic effects. Bilateral vagotomy abolished all of the effects except the A-V block produced by injections into the left circumflex branch, which could be completely prevented only by atropine—evidence that it arose in part from direct stimulation of parasympathetic ganglia. Our findings confirm the conclusions of Dawes concerning the location of the cardiac receptors involved in the Bezold-Jarisch reflex.

We find no evidence that any dose of nicotine, injected into any of the three main coronary branches, can cause constriction of coronary arteries. Our measurements of coronary sinus outflow showed decreases only when the blood pressure fell as a result of marked ventricular slowing. Positive chronotropic and/or inotropic effects of nicotine invariably were accompanied by increases in coronary flow, even though the blood pressure did not rise. Insofar as these findings are applicable to the inhalation of nicotine from tobacco smoke by intact humans, the conclusion would be that anginal attacks associated with smoking are referable to increased cardiac work resulting from the sympathomimetic effects. The electrocardiographic changes produced in our animals by intracoronary injections of nicotine, epinephrine and norepinephrine are similar to those described in man after intravenous administration of nicotine and during cigarette smoking. We have already demonstrated that these changes are associated with an increased oxygen saturation in coronary venous blood and furthermore, in recent preliminary experiments, we have observed that these same electrocardiographic changes are associated with an increase in coronary blood flow, left ventricular oxygen consumption, and left ventricular work, after intravenous infusion of norepinephrine and epinephrine in dogs. Similar cardiac effects have been observed following intravenous infusion of nicotine in dogs and after cigarette smoking in man.

**SUMMARY**

Intracoronary arterial injections of nicotine in lightly anesthetized dogs elicited parasympathomimetic, sympathomimetic and Bezold-Jarisch responses.

The sympathomimetic effects consisted of increase in myocardial contractility and in coronary blood flow, ST-T wave changes in the electrocardiogram (ST depression and inversion of the T wave or deepening of a previously inverted T), and sinus or nodal tachycardia. These effects are qualitatively similar to those of epinephrine and norepinephrine when injected into the same sites.

The parasympathomimetic effects consisted of varying degrees of atrial and ventricular bradycardia and occasional atrial flutter-fibrillation. The Bezold-Jarisch effects consisted of transient periods of sinus arrest, sinus brady-
cardia with or without A-V heart block, hypotension, and apnea.

Tetraethylammonium chloride completely blocked the effects of nicotine on myocardial contractility, coronary blood flow, electrocardiogram and blood pressure. Atropine abolished all the cardiac inhibition induced by nicotine from the right and left coronary arterial injections, but did not prevent the change in blood pressure (hypotension) elicited from left coronary injections. Bilateral vagotomy completely abolished the Bezold-Jarisch effects resulting from left coronary arterial injections of nicotine but did not prevent the effects of injections into the right coronary and left circumflex branches of the S-A and A-V nodes respectively.

There was no evidence of coronary vasoconstriction as indicated by a decrease in coronary blood flow following intracoronary arterial injections of nicotine.

The results indicate that chemoreceptors, parasympathetic and sympathetic or sympathetic-like ganglia (chromaffin tissue) affected by nicotine are present in the heart and that the type of response depends on the predominant ganglia or receptor stimulated at the site of injection.

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SUMMARIO IN INTERLINGUA

Injections de nicotina intra le arterias coronari de levemente anesthesiata canes evocava responsas parasympathomimetic, sympathomimetic, e de Bezold-Jarisch.

Le effectos sympathomimetic consisteva de un augmento del contractilitate myocardial e del fluxo de sanguine coronari, de alteraciones del unda ST-T in le electrocardiogramma (depression de ST e inversion del unda T o approfundamento de un jam invertite unda T), e de tachycardia sinusual o nodal. Iste effectos es qualitativemente simile al effectos de epinephrina e norepinephrina quando iste compostos es inji-ite in le mesme sitos.

Le effectos parasympathomimetic consisteva de varie grados de bradycardia atrial e ventricular e a vices de flutter e fibrillation atrial.

Le effectos de Bezold-Jarisch consisteva de transienti periodos de arresto sinusal, de bradycardia sinusal con o sin bloco atrio-ventricular, de hypotension, e de apnea.

Chloruro de tetraethylammonium blocava completamente le effectos de nicotina super le contractilitate myocardial, le fluxo de sanguine coronari, e le pression de sanguine. Atropina aboliva completamente le inhibition cardiae inducite per nicotina injicite in le arterias dextero- e sinistro-coronari, sed illo non preveniva le alteration del pression sanguinea (i.e. le hypotension) effectuate per injectiones sinistro-coronari. Vagotomia bilateral aboliva completamente le effectos de Bezold-Jarisch resultante ab le injectiones de nicotina in le arterias sinistro-coronari, sed illo non preveniva le effectos de injectiones de nicotina in le brancaes dextero-coronari e sinistro-circumflexe del nodos sino-atrial e atrio-ventricular, respectivamente.

Post le injectiones de nicotina nitra le arterias coronari, nulle vasoconstriction coronari eseva manifeste in le reduction del fluxo de sanguine coronari.

Le resultados del studio indica que chimo-receptores—gangliones parasympathico e sympathico o sympathicoide (histro chromaffin)—que es aficite per nicotina es presente in le corde e que le tipo del responsa depende del predominante ganglion o receptor que es stimulate al sito del injection.

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BOOK REVIEW


Approximately one-tenth of the text is devoted to the pharmacologic response of the heart, blood vessels, blood and the hematopoietic system. Investigators doing cardiovascular research who desire to use this book as a reference may be disappointed on two scores. The documentation of certain facts is accomplished by listing the author(s) and year but the journal source is not always listed. In the chapter on digitalis, there are about 60 references cited in the text but the source of only 15 appear. The lack of distinction between trade names and generic names of some drugs is confusing. Investigators who desire to spend a few hours to review the present status of cardiovascular pharmacology may find this book useful. Two chapters are outstanding. The discussion of the response of the coronary vessels to drugs emphasizes the necessity to view coronary vasodilators not only in terms of their effects on coronary blood flow alone, but also in terms of their effect on the ratio of cardiac work to coronary flow. The discussion of pharmacologic agents in the treatment of hypertension is excellent. Each drug is analyzed in terms of its usefulness and limitations.
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