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THE EFFECTS OF ADRENALINE AND NORADRENALINE ON THE METABOLISM AND PERFORMANCE OF THE ISOLATED DOG HEART

BY

G. FAWAZ AND B. TUTUNJI

From the Department of Pharmacology, School of Medicine, American University of Beirut, Beirut, Lebanon

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In 16 dog heart-lung preparations modified to permit a more accurate measurement of coronary flow, adrenaline or noradrenaline was infused at a rate of 4 μg. base/min. After a 30-min. pause during which the increased oxygen consumption and heart rate, but not the coronary flow, returned to pre-infusion levels, the other sympathomimetic amine was infused for the same length of time. It was found that, mole per mole, noradrenaline is as effective, and probably more so, than adrenaline in raising the oxygen consumption of the heart-lung preparation. The positive chronotropic and coronary dilating action of both amines appear to be equal. It was observed that in any one experiment the second dose of the sympathomimetic amine was slightly more effective than the first dose in raising the oxygen consumption. The level of high-energy phosphorus compounds does not change after adrenaline or noradrenaline administration even at the time when the oxygen consumption rises to as much as 200%. During this period there are no signs of cardiac hypoxia, as can be judged by the good oxygen saturation of coronary venous blood. Single doses of 5 μg. adrenaline or noradrenaline have a consistent positive inotropic effect that lasts about 15 min. when tested on a failing heart. In 12 experiments on non-failing modified heart-lung preparations, a single dose of 5 μg. adrenaline fails to cause a measurable increase in oxygen consumption after 1, 3, 6, or 11 min. in spite of a mild positive chronotropic action. The significance of these findings is discussed and the suggestion made that, when noradrenaline infusions are effective in treating cardiogenic shock in man, part of this effect may be due to its positive inotropic action, thus correcting an element of heart failure that might exist.

The main actions of adrenaline on the heart are: positive inotropic and chronotropic effects, increased atrio-ventricular conduction, and increased excitability. In addition to these, there is the "calorigenic" effect. This is the increase in cardiac oxygen consumption which cannot be explained solely by the rise in heart rate and increase in work performed (for literature see Gollwitzer-Meier, Kramer and Krüger, 1936). All these effects of adrenaline need not have the same mechanism of action at the cellular or subcellular (enzymatic) level. Krayer (1949), for instance, has shown that the chronotropic action but not the inotropic action can be inhibited by veratramine. It is also conceivable that a certain dose of adrenaline would evoke one effect and not the other. The mechanism of the coronary dilating action of adrenaline is not completely understood and it is not clear to what extent the vasodilatation is due to the rise in cardiac metabolism.

In this study a comparison has been made between the "calorigenic," chronotropic, and coronary dilating actions of (−)-adrenaline and (−)-noradrenaline on the dog heart-lung preparation and the effect of these compounds on the phosphorus compounds of the heart. Furthermore, a study has been made of the effect of graded doses of adrenaline, to see if the inotropic action can be separated from the calorigenic action. This study appeared important in view of statements often encountered in the clinical literature that (*a*) adrenaline raises the blood pressure mainly by virtue of its action on the heart, increasing the cardiac output, whereas noradrenaline acts peripherally; (*b*) adrenaline is contraindicated in the treatment of cardiogenic shock as it increases myocardial oxygen consumption and produces symptoms of coronary

TABLE I

EFFECT OF ADRENALINE AND NORADRENALINE ON THE ISOLATED DOG HEART

Adrenaline added to reservoir at rate of 4 μg./min. for 15 min. followed by a 30 min. pause, then a 15 min. infusion period with noradrenaline. The next day the order was reversed, noradrenaline added first. The values at the end of the second 15 min. period are compared with those at 45 min. as a base line. The numeral (1) indicates at the start of the experiment, (2) after 15 min., (3) after 45 min., (4) after 60 min.

	Part 1								Part 2							
	Adrenaline				Noradrenaline				Adrenaline				Noradrenaline			
No. of expts. ..	16				16				8				8			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Heart rate	138	—	141	—	—	—	—	—	—	—	—	—	—	—	—	—
Mean±S.E. ..	(±4·8)		(±2·3)													
% change in heart rate	—	44·3	—	44·3	—	47·1	—	47·1	—	47·8	—	41·0	—	57·0	—	37·3
Mean±S.E. ..		(±3)		(±3)		(±4·5)		(±4·5)		(±4·6)		(±3·6)		(±5·9)		(±5·0)
Oxygen consumption (ml./100 g./min.) ..	6.67	—	—	—	6.67	—	—	—	—	—	—	—	—	—	—	—
Mean±S.E. ..	(±0·38)				(±0·38)											
% change in oxygen consumption ..	—	74·0	−3·7	74·0	—	112·0	−3·7	112·0	—	54·2	—	93·8	—	98·9	—	124·9
Mean±S.E. ..		(±11·6)	(±3·3)	(±11·6)		(±16·0)	(±3·3)	(±16·0)		(±9·9)		(±19·3)		(±27·5)		(±16·6)
Mean % change in work performed ..	—	−1·37	−8·1	−1·37	—	−0·8	−8·1	0·8	—	−2·35	—	−0·4	—	+2·2	—	−3·9
Coronary flow (ml./min.)	55	121	151	215	55	121	151	215	—	—	—	—	—	—	—	—
Mean±S.E. ..	(±6)		(±26)		(±6)		(±26)									
% change in coronary flow	—	—	—	—	—	—	—	—	—	113·6	—	78·9	—	130·7	—	49·4
Mean±S.E. ..										(±12)		(±20·8)		(±26·1)		(±20)
Phosphorus Compounds of Heart Muscle. Mean±S.E. (% Total Acid-soluble Phosphorus)																
Phosphocreatinine phosphorus		25·3 (±0·94)														
Inorganic phosphorus		17·8 (±0·87)														
Labile nucleotide phosphorus (2/3 of adenosine triphosphate)		27·7 (±0·62)														

TABLE II

EFFECT OF 5 μG. ADRENALINE ON THE ISOLATED DOG HEART

In the first five experiments adrenaline was added to the reservoir. In the next seven experiments adrenaline was injected into the venous cannula near the right heart, and in this series the first oxygen consumption measurement was made 45 sec. (4 experiments) and 1 min. after the injection; since the readings at 45 sec. and 1 min. were not different they were averaged together. Initial coronary flow was 56 (±6·6) in the experiments in which adrenaline was added to the reservoir, and 56 (±4·8) in those in which adrenaline was injected.

	Adrenaline Added to Reservoir						Adrenaline Injected					
No. of expts. . .	5						7					
Min. after injection . .	1	3	6	8	11	13	1	3	6	8	11	13
% change in heart rate	+13·5	+19	+15	+11·7	—	+11·0	27·0	+11·2	+10·4	—	+6·1	—
Mean±S.E.		(±2)				(±1·3)	(±5·9)		(±3·6)		(±2·4)	
% change in oxygen consumption . .	—	+3·8	—	−3·1	—	−2·2	+3·8	—	+3·0	—	−5·9	—
Mean±S.E.		(±1·8)		(±2·5)		(±3·1)	(±3·6)		(±2·7)		(±2·2)	
Mean % change in work performed	—	+4·4	—	+3·9	—	+2·7	+0·6	—	+0·6	—	+1·2	—
% change in coronary flow . .	—	+23·4	—	+38·6	—	+41·7	+11·9	—	+35·2	—	+45·3	—
Mean±S.E.		(±6·1)		(±12·3)		(±11)	(±2·3)		(±9·2)		(±11·2)	
Phosphorus Compounds of Heart Muscle (% of Total Acid-soluble Phosphorus)												
Phosphocreatine phosphorus . .				25·1 (±2·0)						26·0 (±0·8)		
Inorganic phosphorus . .				12·6 (±1·03)						13·9 (±0·89)		
Labile nucleotide phosphorus (2/3 of adenosine triphosphate) . .				30·3 (±0·86)						29·2 (±1·21)		

insufficiency, whereas noradrenaline does not increase cardiac oxygen consumption.

METHODS

Male and female dogs were used weighing about 12 kg. The techniques of preparing the heart-lung, of measuring coronary flow and oxygen consumption, as well as other experimental details have been described previously (Fawaz and Tutunji, 1959). Blood pressure was maintained at 100 mm. Hg, and an attempt was made to keep the left ventricular output constant. The average left ventricular output in this series was about 650 ml./min. Readings were taken at the start of the experiment, and then one of the sympathomimetic amines was added to the venous reservoir at the rate of 4 μg./min. for a period of 15 min. at the end of which measurements were again taken. After a period of 30 min. without infusion readings were taken again and an equimolar amount of the other sympathomimetic amine added over a period of 15 min.; after this the final readings were taken. The next day the order of adding the sympathomimetic amines was reversed. In all, 16 such experiments were performed over a period of a whole year. Each sympathomimetic amine was given 8 times during the first 15 min. and 8 times during the last 15 min. of the experiment. Experiments were terminated at the end of the second 15-min. infusion period and a piece of the left ventricle was excised for the determination of the phosphorus compounds.

The inotropic action of adrenaline and noradrenaline was tested on the classical Starling heart-lung preparation. Failure was produced in the course of about 15 min. by repeated additions of pentobarbitone until the systemic output fell to about half the original level with a corresponding rise in right auricular pressure. A single dose of 5 μg. of adrenaline or equimolar amount of noradrenaline was added to the reservoir or injected into the venous inflow tube near the right heart. The calorigenic action of this dose of adrenaline was tested on the modified non-failing heart-lung preparation by injection into the venous inflow tube, and the usual measurements were taken 45 sec., 1, 3, 6, 11, and 13 min. thereafter. The procedure for measuring oxygen consumption in these "acute" as well as in the infusion experiments was as follows: Coronary flow was measured during an interval of 15 sec., coronary venous and arterial blood samples were then collected simultaneously for the oxygen determination by the method of Van Slyke, a procedure that requires 5 sec., then a second coronary flow measurement was made, and the average was taken of the two coronary flow figures, which usually agreed very well.

RESULTS

Comparison of the Calorigenic, Chronotropic, and Coronary-dilator Actions of Adrenaline and Noradrenaline

It can be seen from Table I that during the 30-min. pause following the first 15-min. infusion period both the heart rate and the oxygen consumption return to pre-infusion levels. Yet we took not only the average of all 16 measurements for each of the sympathomimetic amines (part 1 of Table I), but made separate analysis of the 8 experiments during which each amine was given at the beginning or at the end (part 2 of Table I). We noticed early that the same amine, given at the end of the experiment, tends to have a greater calorigenic action and the same or slightly smaller chronotropic action than when given at the beginning of the experiment. We have no explanation for this finding, which may or may not be significant. Another reason for this separate analysis is because the coronary flow does not return to normal and may even decrease during the 30-min. pause.

"Calorigenic Action."—It is quite clear from the figures presented in Table I that one can speak of a "calorigenic" action of noradrenaline and adrenaline, for, in the absence of a change in work performed, a tachycardia with a 44 to 47% increase in rate cannot explain this rise in oxygen consumption. In a previous publication (Fawaz and Tutunji, 1959) we have shown that a tachycardia with about 65% increase in rate can result in not more than 23% increase in oxygen consumption. Our results indicate that the cardiac calorigenic action of noradrenaline is at least equal to, and probably greater than, that of adrenaline. There are marked variations in the response of different dogs to adrenaline and noradrenaline. The initial cardiac oxygen consumption, however, does not vary so much from one animal to another and in this particular series of 16 hearts it is 6.67 ± 0.38 ml./100 g./min. Due to these variations in response and the resulting high standard error it is not possible to compare the calorigenic actions of adrenaline and noradrenaline in a strictly quantitative manner. Gollwitzer-Meier, Kramer and Krüger (1936) and Gollwitzer-Meier and Witzleb (1952) have had the same experience regarding the variations in response to single doses of adrenaline and noradrenaline.

Chronotropic Action.—Our results indicate that adrenaline and noradrenaline infused at the rate of 4 μg./min. are equally effective in increasing the heart rate in the denervated heart-lung preparation. The heart rate rises rapidly and remains more or less steady during the infusion. Furthermore, we have found less variation from one animal to another in the chronotropic response to the sympathomimetic amines than in

the "calorigenic" response. Krayer (1949) and Krayer and Van Maanen (1949) have also found that the heart rate remains steady during a constant infusion of adrenaline or noradrenaline

Coronary Dilating Action.—Both adrenaline and noradrenaline given at the rate of 4 μg./min. have a definite coronary dilating action as can be seen from Table I. During the first 15 min. there was a gradual increase in coronary flow amounting, at the end of this period, to 113% in the case of adrenaline and 130% in the case of noradrenaline. It is known that coronary flow increases spontaneously in a heart-lung preparation, but the "spontaneous" rise in coronary flow during the first 15 min. is much less than that observed after the addition of sympathomimetic amines. This can be seen by comparing these values with results reported in a previous publication (Fawaz and Tutunji, 1959) and obtained under almost identical experimental conditions. These results, however, do not answer the question as to what extent the effect of the sympathomimetic amines is secondary to the marked increase in oxygen consumption.

The Inotropic Action of Adrenaline or Noradrenaline

If 5 μg. of adrenaline or noradrenaline is injected into the venous inflow tube near the right heart or into the venous reservoir in a classical Starling heart-lung preparation previously made to fail with pentobarbitone, the results are clear-cut and reproducible. There is a sudden drop of right auricular pressure almost to pre-failure level, then a gradual rise to pre-injection level in the course of about 15 min. Simultaneously there is an increase in output almost to pre-failure level followed by a gradual decrease to pre-injection level. The blood pressure rises suddenly to a high level during the first 15 sec. if the amine is injected near the heart and only slightly if injected into the reservoir. If the injection is near the heart the heart rate also increases by about 27% during the first minute and subsides to normal within 5 to 10 min. If now 5 μg. of the other sympathomimetic amine is injected the result is almost identical except that the correction of failure is not as complete. Adrenaline and noradrenaline behave identically in this respect. This experiment has been performed many times and is a student demonstration experiment. An illustration of this action can be seen in figure 12 of Krayer (1949) demonstrating the positive inotropic effect of 10 μg. of adrenaline in a failing heart-lung preparation treated with veratramine.

The Lack of Measurable Calorigenic Effect of 5 μg. of Adrenaline

The calorigenic effect of 5 μg. adrenaline was tested on the non-failing heart-lung preparation performed according to the modified procedure to allow a more accurate measurement of coronary flow (Table II). In 7 experiments, 5 μg. adrenaline produced no measurable increase in oxygen-consumption 45 sec., 1, 6 or 11 min. after injection. In another 5 experiments where 5 μg. adrenaline was added to the reservoir, a procedure known to produce definite inotropic effect, again no increase in oxygen consumption occurred after 3, 8, or 13 min.

The heart rate did increase in these experiments, by a maximum of about 27% in the first series, but this increase was not accompanied by a measurable increase in oxygen consumption.

The Effect on the High-energy Phosphorus Compounds of Heart Muscle

As can be seen from the tables, there was no change in the high-energy phosphorus compounds of heart muscle even in those experiments where the oxygen consumption rose to as much as 200%. During this period, however, the coronary flow was increased and there were no signs of cardiac hypoxia as can be judged by the high oxygen content of coronary venous blood.

Discussion

The results indicate that infusion of noradrenaline is as effective as adrenaline in raising the oxygen consumption of the isolated denervated dog heart. A quantitative evaluation of the actions of the two amines is not possible owing to the high standard errors resulting from the great individual variations in the response to the sympathomimetic amines from dog to dog. Gollwitzer-Meier and Witzleb (1952) are the only investigators who have studied the calorigenic effect of noradrenaline on the isolated denervated dog heart and they came to the opposite conclusion. They injected single doses of noradrenaline (20 to 40 μg.) and adrenaline (10 to 20 μg.). The maximum increase in oxygen consumption after noradrenaline was 21 to 154% (15 experiments) and 54 to 252% after adrenaline (6 experiments). They thus concluded that the metabolic action of noradrenaline was substantially less ("wesentlich geringer") than that of adrenaline. The experimental part of Gollwitzer-Meier and Witzleb's work was different from ours. In the first place, these authors used single injections of adrenaline and noradrenaline and noted the peak in oxygen

consumption. We, however, infused these substances at a constant rate of 4 μg./min. for 15 min. and measured the oxygen consumption at the end of this period. We have not measured the oxygen consumption during this 15-min. period. However, we have measured the heart rate during this interval and found it to be relatively constant, thus confirming the observations of Krayer (1949) and Krayer and Van Maanen (1949) with adrenaline and noradrenaline. There are also other differences in the experimental conditions of Gollwitzer-Meier and those of the present experiments. For example, in the methods for measuring coronary flow and oxygen content of the blood.

Our results also indicate that noradrenaline is at least as effective as adrenaline in increasing the heart rate and also the coronary flow. Whether or not the increase in coronary flow is secondary to the increased myocardial oxygen consumption cannot be decided from our experiments, which were not originally planned to answer this specific question. Even in experiments where single doses of 5 μg. adrenaline were given and found to be without measurable effect on oxygen consumption, the rise in coronary flow could not be distinguished from the "spontaneous" increase observed in heart-lung preparations. It has been known for some time that noradrenaline can cause coronary vasodilatation (see Lochner, Mercker and Schürmeyer, 1956), but no quantitative study has been made of its efficacy in comparison with adrenaline.

As was stated above, we found that single injections of 5 μg. adrenaline had no measurable effect on the oxygen consumption of the denervated heart-lung preparation. Here we find ourselves in complete disagreement with Gollwitzer-Meier *et al.* (1936), who state that doses of 5 to 10 μg. adrenaline increase the oxygen consumption of the denervated heart-lung preparation 100 to 250% and even 350%, the effect reaching a maximum 1 min. after injection and lasting 5 to 10 min. We have not found a measurable increase in oxygen consumption 45 sec., 1, 3, or 6 min. after injection, even when we injected the adrenaline into the venous cannula near the right heart as Gollwitzer-Meier *et al.* did. We believe that differences in experimental technique may account for this discrepancy in results. In the first place, the methods of measuring the coronary flow and thus the technique of preparing the heart-lung are different. Gollwitzer-Meier *et al.* employed a Morawitz cannula to measure coronary sinus flow and calculated from this the total coronary flow. In a previous publication (Fawaz, Hawa and Tutunji, 1957), we have given our reasons why we believe that the Morawitz cannula method cannot be relied upon to measure even total coronary sinus flow. Although both groups utilize the Fick principle for measuring oxygen consumption, we measure coronary flow and blood oxygen directly whereas Gollwitzer-Meier *et al.* use indirect methods for measuring coronary sinus flow (Weese's Stromuhr and Rein's Thermostromuhr) and blood oxygen content (Kramer's photoelectric method). We are not in a position to judge these indirect methods; however, all indirect methods have eventually to be calibrated by direct measurements with a graduated cylinder or a Van Slyke apparatus. The indirect methods have the general advantage of yielding continuous and instantaneous measurements. In this particular case there is no advantage in that, for knowledge of the oxygen content of coronary sinus blood at any one instant obviously does not tell us about the metabolic activity of the cardiac cell at that particular instant.

A dose of 5 μg. adrenaline did cause a measurable increase in heart rate, about 27%, after 45 to 60 sec., and theoretically an increased oxygen consumption is to be expected in view of the known effect of tachycardia *per se* in increasing metabolism (Laurent, Bolene-Williams, Williams and Katz, 1956; Berglund, Borst, Duff and Schreiner, 1958; and Fawaz and Tutunji, 1959). However, Laurent *et al.* found in the intact animal an 11% increase in oxygen consumption with a 27% increase in heart rate and a 5.5% increase in oxygen consumption with a 36% increase in heart rate. Badeer and Khachadourian (1958) observed no significant reduction in oxygen consumption when the heart rate was reduced from 153 to 110 beats per min. by applying a cold thermode to the sino-atrial node. Clearly, such changes in oxygen consumption are within the limits of experimental error.

The observation that small doses of adrenaline can have a positive inotropic action but no measurable calorigenic action may be of considerable interest. Noradrenaline has been used in recent years in the treatment of shock due to myocardial infarction (Binder, Ryan, Marcus, Mugler, Strange, and Agress, 1955), with the belief that noradrenaline acts peripherally to raise blood pressure whereas adrenaline acts mainly in the heart. The observation that adrenaline injections may sometimes produce symptoms of coronary insufficiency helped to support this hypothesis.

Perhaps if the clinicians had known that noradrenaline could raise the myocardial oxygen consumption to the same extent as adrenaline they would have hesitated to use it in cases of shock due to myocardial infarction. However, it is quite possible that, where noradrenaline is of use in cardiogenic shock, its efficacy may be due precisely to its cardiac (inotropic) action. The element of cardiac failure in shock—even haemorrhagic shock—has hitherto received little attention (for review of literature see Walton, Richardson, Walton and Thompson, 1959) and it may well be that the doses of noradrenaline used clinically have no effect on raising the cardiac oxygen consumption but produce a positive inotropic action, thus counteracting any existing element of cardiac failure. Noradrenaline is to be preferred to adrenaline in this treatment because the latter, by raising the basal metabolic rate—a property not shared by noradrenaline—indirectly puts an extra burden on the heart. The increase in cardiac output observed after adrenaline may thus be due to such a general metabolic action and be similar to the action of the thyroid hormones.

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