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Ole D. Mjøs, … , John K. Kjekshus, Jon Lekven

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Research Article

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OLE D. MJØS, JOHN K. KJEKSHUS, and JON LEKVEN

From the Institute for Experimental Medical Research, University of Oslo, Ullevaal Hospital, Oslo, Norway

ABSTRACT Increased delivery of free fatty acids raises myocardial oxygen consumption ($M\dot{V}O_2$) without influencing mechanical performance. The effects of norepinephrine on $M\dot{V}O_2$ and on the size of ischemic injury after acute coronary occlusion were therefore studied before and during inhibition of lipolysis with β-pyridylcarbinol. In spite of similar mechanical responses to norepinephrine, $M\dot{V}O_2$ increased by 57±11% before and significantly less, 31±6%, ($P < 0.01$) during inhibition of lipolysis. After coronary occlusion the ischemic injury associated with norepinephrine infusion, as evidenced by epicardial mapping of S-T segment elevation, was larger before (7.9±1.1 mV) than during inhibited lipolysis (2.8±0.4 mV; $P < 0.005$). Average S-T segment elevation associated with norepinephrine infusion during inhibited lipolysis (2.8±0.4 mV) was even lower ($P < 0.05$) than during control occlusion alone, before drug administration (4.4±0.7 mV). In conjunction with an antilipolytic agent, norepinephrine was shown to reduce the extent and magnitude of the myocardial ischemic injury produced by acute coronary occlusion; this could be due to an improved balance between myocardial oxygen supply and requirement.

INTRODUCTION

L-Norepinephrine has been widely used as a pressor agent in the treatment of cardiogenic hypotension (1). Although norepinephrine infusions of short duration are effective in raising peripheral vascular resistance and increasing myocardial contractility, the results of prolonged infusions have been less satisfactory (2–4).

There is reason to believe that agents altering the balance between myocardial oxygen supply and demand influence the extent and magnitude of ischemic injury after acute coronary occlusion (5). Thus, isoproterenol has been shown to increase the extent and magnitude of the ischemic injury (6, 7), probably due to raised myocardial oxygen demand out of proportion to oxygen supply. The hemodynamic effects of the naturally occurring catecholamine, norepinephrine, are not, however, comparable with those of isoproterenol in that norepinephrine is also a pressor agent. A rise in blood pressure alone has recently been shown to reduce the size of the ischemic injury after acute coronary occlusion in dogs (6), and this might be caused by a larger rise in oxygen supply than demand in the ischemic area.

Although catecholamine-induced changes in myocardial oxygen consumption ($M\dot{V}O_2$),[1] or oxygen demand, have usually been attributed solely to increased mechanical activity of the heart (8–10), recent investigations have shown that a major fraction of the rise in $M\dot{V}O_2$ effected by isoproterenol is related to excess release and consumption of FFA (11–13). Since norepinephrine probably produces a similar effect, the first purpose of the present study was to determine the norepinephrine-induced rise in $M\dot{V}O_2$ and the fraction related to excess myocardial utilization of FFA.

Secondly, we proposed to investigate whether the raised oxygen demand of norepinephrine infusion would lead to increased myocardial ischemic injury after acute coronary occlusion as evidenced by epicardial S-T segment elevation (6), and furthermore, whether norepinephrine-induced ischemic changes could be reduced

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[1] *Abbreviations used in this paper:* $\overline{AP}$, mean aortic blood pressure; CO, cardiac output; dP/dt; maximal value of first derivative of LVP; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; LVP, left ventricular pressure; LVSP, left ventricular systolic pressure; MF, myocardial blood flow; $M\dot{V}O_2$, myocardial oxygen consumption; $\overline{ST}$, mean of S-T segment elevation.

by inhibition of lipolysis, as shown for isoproterenol (7). If this should be the case, part of a mechanism by which sustained norepinephrine infusion exerts myocardial damage might be explained, and could be pertinent in evaluating its value in the treatment of cardiogenic hypotension in man pretreated with antilipolytic agents.

METHODS

Experiments were carried out in 14 mongrel dogs of either sex (15–25 kg body wt), fasted for 12–15 h. The dogs were anesthetized with sodium pentobarbital, 25 mg/kg body wt, followed by maintenance doses. Sodium heparin, 3 mg/kg body wt, given i.v. was used as anticoagulant.

The dogs were divided into two experimental groups.

Group I consisted of six close-chest dogs. Left ventricular pressure (LVP) was measured with a Statham P23Gb transducer (Statham Instruments, Inc., Oxnard, Calif.) connected to a radiopaque polyethylene tube introduced into the left ventricle from a carotid artery. The first derivative of LVP, dP/dt, was recorded continuously by means of a differentiator connected to the output from the pressure channel. Mean aortic blood pressure ($\overline{AP}$) was recorded from a femoral artery with a Statham P23Gb transducer (Statham Instruments, Inc.). Cardiac output (CO) was determined by the thermal dilution technique and calculated according to Fegler (14). Myocardial blood flow (MF) was measured polarographically by the hydrogen desaturation technique (15–17). A platinum electrode was advanced to the coronary sinus and placed 3–4 cm from the atrial outlet. H_2 was added to the tracheal tube, giving a concentration of about 2–5 vol/100 vol for 10 min, followed by ventricular infusion of 30–50 ml of saline saturated with dissolved H_2 for 30–60 s. The infusion time for each dog was constant. A rapid and reproducible arterial H_2 desaturation was thus established. Arterial H_2 concentrations were reduced to 10% of initial values within 10–30 s after stopping H_2 infusion (Fig. 1). Monoexponential coronary sinus desaturation curves were obtained in semilogarithmic plots, and MF was calculated from the monoexponential slope obtained. It is acknowledged that the use of monoexponential ratio constants is valid only if flow remains homogenous during the experimental conditions. Therefore, curves deviating from monoexponentiality above 10% of initial value (this occurred in two of eight dogs) were discarded. Repeated measurements of H_2 desaturation curves during steady state differed by less than 10% (17). The response time for the electrode was 2–3 s at 90% of full deflection (15). The tissue/blood partition coefficient was assumed to be 1.00 (15, 16). Arterial and coronary sinus blood samples were obtained simultaneously and analyzed for oxygen saturation by the method of Aukland (18). Hemoglobin was measured spectrophotometrically as cyanmethemoglobin. The concentrations of FFA in arterial and coronary sinus blood were determined by the method of Dole (19), as modified by Trout, Estes, and Friedberg (20). In vitro lipolysis was avoided by sampling blood in tubes precooled to 0°C and centrifuged immediately for 10 min at 2°C. Plasma was frozen until FFA analyses were performed.

Experimental procedure. After control registrations, constant i.v. infusion of norepinephrine was started at a rate of 2–3 μg/min to raise $\overline{AP}$ by an average of 50 mm Hg. Stable conditions were reached after 5–10 min, and new registrations and blood samples were obtained. 30 min after discontinuing norepinephrine infusion, lipolysis was inhibited by continuous i.v. infusion of β-pyridylcarbinol (5–10 mg/min; Ronicol, F. Hoffmann-La Roche & Co. A.G., Basel, Switzerland). Infusion of norepinephrine was repeated 15 min later. The infusion rate, although usually the same as in the first run, was adjusted so as to raise $\overline{AP}$ to the same level as before inhibition of lipolysis. This led to similar changes in all hemodynamic parameters measured. Stable conditions were reached within 5–10 min, and registrations and blood sampling were repeated.

Calculations. $M\dot{V}O_2$ (ml/min·100 g) was calculated from the myocardial oxygen extraction and MF, and myocardial uptake of FFA (μeq/min·100 g) as the product of arterio-coronary sinus differences of FFA and myocardial plasma flow. To evaluate differences, probability values (P) were obtained utilizing Student's t test for paired data (21), the dogs serving as their own controls.

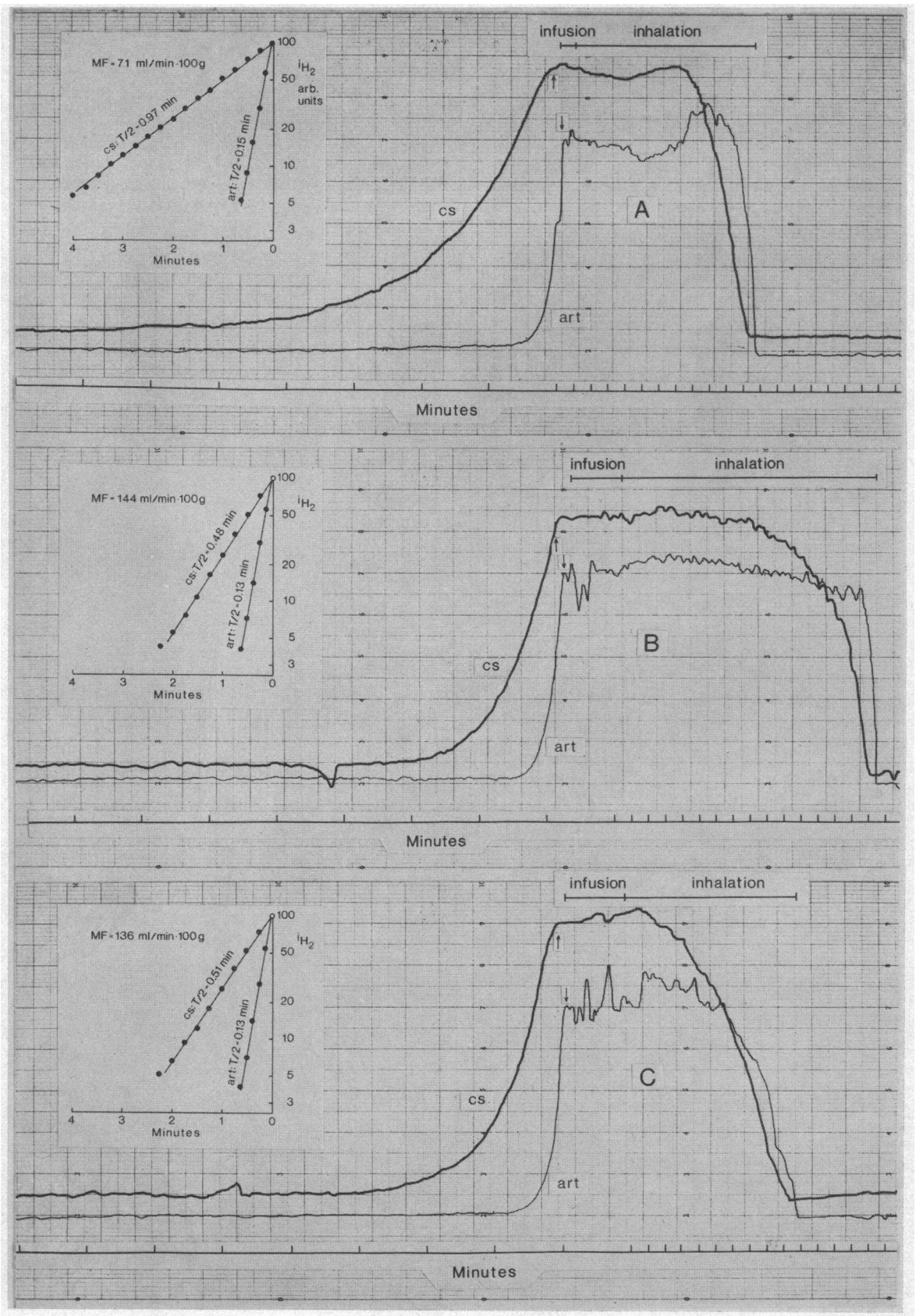
Group II consisted of six thoracotomized dogs. Ventilation was maintained with a Cyclator Mk. II respirator (The British Oxygen Company Ltd., London). The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. A branch of the left anterior descending coronary artery was dissected free and left *in situ* with a ligature (3–0) placed loosely around the vessel. A femoral artery and vein were cannulated for aortic blood pressure measurements and as a route for i.v. infusion. Aortic blood pressure was monitored with a Statham P23Gb transducer (Statham Instruments, Inc., Los Angeles, Calif.) and recorded on a Sanborn two-channel oscillograph (Sanborn Div., Hewlett-Packard Co., Palo Alto, Calif.).

An Elema Schønander (Stockholm, Sweden) electrocardiograph recorded limb leads and epicardial electrocardiograms (ECG). Epicardial electrocardiographic measurements were performed with a mobile cotton-wick electrode, as described by Maroko et al. (6). ECG from 10 to 14 anatomically recognizable sites of the myocardium supplied by the dissected coronary artery and from the surrounding left ventricular tissue were monitored sequentially at a paper speed of 25 mm/s. The sensitivity of the epicardial recordings was set at 1 mV/mm deflection. The sites at which the S-T segment elevation exceeded 2 mV were considered to be ischemic.

Irreversible myocardial injury does not occur in the first 20 min of myocardial ischemia (22, 23). S-T segment elevation has been shown to be reproducible after reocclusion of the vessel after a recovery period of 30 min. It is therefore possible to compare ischemic electrocardiographic changes during different interventions (6, 7).

As an overall index of the severity of the ischemic injury in any given animal, the mean of S-T segment elevation ($\overline{ST}$) from all recording sites in each animal at 15 min of coronary occlusion was used.

Experimental procedure. The coronary artery was occluded with a releasable Mayfield arterial clip. Epicardial ECG were recorded 5, 10, and 15 min after occlusion. The clip was then removed and a recovery period of 30 min was allowed for restoration of coronary blood flow, followed by i.v. infusion of norepinephrine 2–3 μg/min, to raise $\overline{AP}$ by an average of 50 mm Hg. An equilibration period of 5–10 min was allowed before reocclusion of the dissected coronary artery. Epicardial recordings were repeated at 5-min intervals for another 15 min; the occlusion was released, and infusion of norepinephrine was discontinued. Subsequent to a 30-min recovery period, lipolysis


infusion
inhalation
MF = 71 ml/min·100g
cs: T/2 = 0.97 min
art: T/2 = 0.15 min
$^{i}H_2$
arb. units
100
50
20
10
5
3
4
3
2
1
0
Minutes
cs
art
A
Minutes
infusion
inhalation
MF = 144 ml/min·100g
cs: T/2 = 0.48 min
art: T/2 = 0.13 min
$^{i}H_2$
100
50
20
10
5
3
4
3
2
1
0
Minutes
cs
art
B
Minutes
infusion
inhalation
MF = 136 ml/min·100g
cs: T/2 = 0.51 min
art: T/2 = 0.13 min
$^{i}H_2$
100
50
20
10
5
3
4
3
2
1
0
Minutes
cs
art
C
Minutes

was inhibited by continuous i.v. infusion of β-pyridylcarbinol at a rate of 5–10 mg/min. About 15 min later, infusion of norepinephrine was resumed at the same rate as before. The artery was reoccluded after an equilibration period of 5–10 min, and mapping of epicardial ECG was repeated, as previously described. The occlusion was then released, and infusions of norepinephrine and β-pyridylcarbinol were terminated. 3 h were allowed for recovery of lipolysis, as evidenced by raised plasma-FFA during norepinephrine infusion. The coronary occlusion and ECG mapping during infusion of norepinephrine alone were then repeated for control purposes. Arterial blood was sampled for determination of FFA after 15 min of occlusion.

In two additional experiments, after a control occlusion, norepinephrine infusion was begun and maintained during the rest of the experiment. The coronary artery was permanently occluded. 15 min later β-pyridylcarbinol was administered. Epicardial ECG and arterial blood samples were obtained as described above every 5 min.

RESULTS

Group I. Metabolic data before and after inhibition of lipolysis with β-pyridylcarbinol are given in Table I. Infusion of norepinephrine increased $M\bar{V}O_2$ in all experiments, both before and during inhibition of lipolysis; however, the augmentation was larger ($P < 0.01$) before than during inhibition (6.4±1.2 and 3.2±0.7 ml/min·100 g, respectively). MF increased similarly with norepinephrine before and after inhibition of lipolysis (Fig. 1). Administration of β-pyridylcarbinol did not change the arterial hydrogen desaturation. The smaller rise in $M\bar{V}O_2$, observed when norepinephrine was given with β-pyridylcarbinol, was therefore due to a reduction in myocardial oxygen extraction ($P < 0.01$). Although plasma-FFA and myocardial uptake of FFA were markedly increased with norepinephrine alone, these increases were largely abolished by inhibition of lipolysis.

Hemodynamic data before and during i.v. infusion of norepinephrine, with and without inhibition of lipolysis, are presented in Table II. Inhibition of lipolysis did not influence the norepinephrine-induced changes in mechanical activity as evidence by $\overline{AP}$, left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), dP/dt, heart rate (HR), and CO. When LVSP was raised by an average of 50 mm Hg in both sequences, LVEDP remained unchanged and dP/dt more than doubled, whereas HR and CO showed no consistent change.

Group II. i.v. infusion of norepinephrine, 2–3 μg/min, increased $\overline{AP}$ from an average of 104±5 to 156±4 mm Hg ($P < 0.001$), whereas HR remained unchanged or increased slightly (Table III). Coronary occlusion or infusion of β-pyridylcarbinol did not effect further alterations in blood pressure or HR.

Fig. 2 shows the results of one experiment. Under the influence of norepinephrine i.v., plasma-FFA, and average S-T segment elevation after 15 min of occlusion of a branch of the left anterior descending coronary artery were markedly higher than during control occlusion before drug administration. Pretreatment with β-pyridylcarbinol, however, blocked the norepinephrine-induced rise in plasma-FFA and S-T segment elevation after repeated occlusion became even less than during control occlusion alone, without drug administration. Approximately 3 h after discontinuing β-pyridylcarbinol administration, lipolysis had recovered, and with repeated occlusion during norepinephrine infusion, S-T segment elevation became nearly as high as when norepinephrine was infused before inhibition of lipolysis. No changes in S-T segments were observed in sites clearly outside the infarcted area.

A similar regression of S-T segment changes were obtained when β-pyridylcarbinol was administered after a permanent coronary occlusion and maintained norepinephrine infusion had caused extension of the ischemic area (Fig. 3). Plasma-FFA and S-T segment elevation declined in a parallel fashion and reached levels below that obtained with control occlusion alone after about 30 min.

In experiments with six dogs, infusion of norepinephrine increased average S-T segment elevation from 4.4±0.7 to 7.9±1.1 mV ($P < 0.005$), and the number of sites with ischemic injury from 6.2±0.8 to 8.5±0.5 ($P < 0.01$) (Table III). When β-pyridylcarbinol infusion was started before the norepinephrine administration, S-T segment elevation associated with subsequent coronary occlusion was markedly reduced, averaging 2.8±0.4 mV, compared to 7.9±1.1 mV during infusion of norepinephrine alone ($P < 0.005$). It should be noted that the S-T changes (2.8±0.4 mV) were even lower ($P < 0.05$) than during control occlusion before drug administration (4.4±0.7 mV). The number of sites with ischemic injury after coronary occlusion and norepinephrine infusion after pretreatment with β-pyridyl-

FIGURE 1 Polarographic recordings of H_2 desaturation curves from the coronary sinus (CS) and aorta (art). The curves are recorded from right to left. (A) Control; (B) during norepinephrine infusion; (C) during norepinephrine infusion after inhibition of lipolysis by β-pyridylcarbinol. Inserts are semilogarithmic plots of electrode current (i_{H_2}) in arbitrary units. MF was calculated from the half time (T/2) of coronary sinus desaturation curve. Myocardial equilibration was performed by adding hydrogen gas to the inspired air, followed by left ventricular infusion of H_2-saturated saline. Arrows indicate the start of desaturation; the pens are separated by the distance between arrows. The chart speed was 10 mm/min during H_2 breathing and 40 mm/min during H_2 desaturation. (dog 6).

TABLE I

*Metabolic Effects of Norepinephrine Infusion before and during Inhibition of Lipolysis with β-Pyridylcarbinol**

	Dog no.	Hydrogen infusion time	MF	O_2-extr.	$M\dot{V}O_2$	FFA a	FFA a-cs	FFA u
		s	*ml/min·100 g*	%	*ml/min·100 g*	*μeq/liter*	*μeq/liter*	*μeq/min·100 g*
Before inhibition of lipolysis								
	1	45	103	78.2	12.7	761	285	19.1
	2	40	112	43.7	7.6	263	63	5.5
Control	3	65	56	81.4	7.6	775	293	10.2
	4	35	144	78.3	19.3	524	63	5.0
	5	35	128	74.8	12.3	635	237	18.6
	6	55	71	70.4	7.7	221	44	6.6
	Mean±SEM		102±14	71.1±5.7	11.2±1.9	530±99	164±49	10.8±2.6
	1		132	82.8	16.3	1,970	330	28.5
	2		185	55.7	17.3	2,411	464	45.0
Norepinephrine	3		107	63.1	10.6	1,655	315	16.3
	4		193	77.5	23.8	2,130	195	20.5
	5		154	71.7	20.6	2,975	280	31.4
	6		144	75.4	16.8	774	176	52.6
	Mean±SEM		153±13	71.0±4.1	17.6±1.8	1,985±303	293±43	32.4±5.7
	P		<0.005	NS	<0.005	<0.005	NS	<0.05
Inhibition of lipolysis								
	1		88	87.4	10.8	280	90	4.8
	2		116	51.2	8.0	290	64	4.5
Control	3		69	82.3	7.2	293	0	0
	4		173	72.6	16.8	272	42	4.4
	5		114	63.6	12.1	285	42	2.9
	6		67	71.7	7.4	221	44	6.4
	Mean±SEM		105±16	71.5±5.3	10.4±1.5	274±11	47±12	3.8±0.9
	1		132	64.7	12.4	1,126	126	10.0
	2		163	47.6	12.3	181	63	5.7
Norepinephrine	3		107	55.6	8.5	314	8	4.0
	4		208	63.9	19.4	293	84	10.5
	5		173	52.7	17.5	598	138	15.2
	6		136	55.4	11.3	155	0	0
	Mean±SEM		153±15	56.7±2.7	13.6±1.7	445±151	70±24	7.6±2.2
	P		<0.001	<0.01	<0.005	NS	NS	NS

MF, myocardial blood flow; O_2-extr., myocardial oxygen extraction; MVO_2, myocardial oxygen consumption FFA, free fatty acids; a, arterial concentrations; a-cs, arterio-coronary sinus difference; u, myocardial uptake; *P*, probability values for comparison of paired data obtained with and without norepinephrine administration; NS, $P > 0.05$.

* Norepinephrine infusion, 2–3 μg/min; β-pyridylcarbinol, 5–10 mg/min.

carbinol was 5.3±1.2, compared to 8.5±0.5 during norepinephrine infusion alone ($P < 0.025$) and 6.2±0.8 during control occlusion before administration of β-pyridylcarbinol. Both the extent and magnitude of the ischemic injury induced by norepinephrine were thus markedly reduced by inhibition of lipolysis. After about 3 h, lipolysis had recovered and the S-T segment elevation associated with reocclusion of the coronary artery in the presence of norepinephrine averaged 5.0±1.0 mV, which was larger ($P < 0.05$) than could be induced by norepinephrine during inhibition of lipolysis (2.8±0.4 mV).

Infusion of norepinephrine i.v. raised plasma-FFA from 254±32 to 1,537±135 μeq/liter, but when norepinephrine was administered after pretreatment with β-pyridylcarbinol, plasma concentrations of FFA were only 318±80 μeq/liter. About 3 h after discontinuing β-pyridylcarbinol administration, lipolysis had recovered and plasma-FFA associated with norepinephrine infusion was 1,483±297 μeq/liter.

DISCUSSION

Norepinephrine-induced changes in $M\dot{V}O_2$ have been attributed to increased mechanical activity of the heart

TABLE II

*Hemodynamic Effects of Norepinephrine Infusion before and during Inhibition of Lipolysis with β-Pyridylcarbinol**

	Dog no.	$\overline{AP}$	LVSP	LVEDP	dP/dt	HR	CO
		mm Hg	*mm Hg*	*mm Hg*	*mm Hg/s*	*beats/min*	*ml/min·kg*
Before inhibition of lipolysis							
	1	165	175	0	2,900	195	137
	2	130	140	4	2,300	145	164
Control	3	105	115	2	2,000	160	104
	4	150	160	5	2,000	214	194
	5	145	155	3	1,500	194	127
	6	135	150	4	2,400	146	—
	Mean±SEM	138±8	149±8	3.0±0.7	2,180±190	176±12	145±16
	1	185	200	2	6,200	185	133
	2	170	195	4	6,400	150	210
Norepinephrine	3	170	175	2	4,000	146	147
	4	175	200	3	4,200	218	294
	5	190	200	3	2,500	171	168
	6	195	210	5	4,300	146	—
	Mean±SEM	180±4	197±5	3.2±0.5	4,600±600	169±12	190±29
	P	<0.005	<0.001	NS	<0.005	NS	NS
Inhibition of lipolysis							
	1	155	165	0	2,900	195	145
	2	130	135	5	2,000	130	170
Control	3	125	125	3	2,000	160	126
	4	148	160	2	2,000	214	175
	5	145	160	3	1,600	176	156
	6	130	140	3	2,200	140	—
	Mean±SEM	139±5	148±7	2.7±0.7	2,120±180	169±13	154±9
	1	185	200	2	6,300	185	151
	2	185	210	4.5	6,400	145	222
Norepinephrine	3	185	190	3	4,000	119	135
	4	173	200	3	3,500	194	278
	5	197	205	2	2,700	167	210
	6	195	210	4	4,400	130	—
	Mean±SEM	187±4	203±3	3.1±0.4	4,550±610	157±12	199±26
	P	<0.001	<0.001	NS	<0.005	NS	NS

$\overline{AP}$, mean arterial blood pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; dP/dt, maximal value of first derivative of left ventricular pressure; HR, heart rate; CO, cardiac output; Other abbreviations as in Table I.

* Norepinephrine infusion, 2–3 μg/min; β-pyridylcarbinol, 5–10 mg/min.

(8–10). The present study shows that the norepinephrine-mediated rise in $M\dot{V}O_2$ was reduced by 48% after inhibition of lipolysis, despite similar effects on the mechanical activity of the heart during both conditions as evidenced by LVP, dP/dt, CO, and HR. These data therefore corroborate the findings of other studies in which a significant fraction of the isoproterenol-induced rise in $M\dot{V}O_2$ was related to FFA (11–13) and extend the results to a naturally occurring catecholamine, norepinephrine.

The larger rise in $M\dot{V}O_2$ induced by norepinephrine before than after inhibition of lipolysis is shown by the present data to be associated with high myocardial uptake of circulating FFA. The fraction of $M\dot{V}O_2$ attributed to lipolysis is larger, however, than that observed for a similar rise in myocardial uptake of FFA induced by triglyceride emulsion and heparin infusion (24, 25). Increased endogenous lipolysis within the heart by catecholamines has also been suggested from in vitro experiments by Challoner and Steinberg (26, 27). It is therefore conceivable that increased myocardial lipolysis may also contribute to the rise in $M\dot{V}O_2$ by norepinephrine, in addition to the effect of circulatory FFA. The higher $M\dot{V}O_2$ effected by norepinephrine infusion

TABLE III

S-T Segment Elevation, Cardiac Hemodynamics, and Arterial FFA at Coronary Occlusions Alone (Occl), during i.v. Administration of Norepinephrine (Occl + Nor), or Additional Administration of β-Pyridylcarbinol (Occl + Nor + R)*

Dog no.	$\overline{ST}$				$\overline{AP}$				HR				FFA_a			
	Occl	Occl + Nor	Occl + Nor + R	Occl + Nor	Occl	Occl + Nor	Occl + Nor + R	Occl + Nor	Occl	Occl + Nor	Occl + Nor + R	Occl + Nor	Occl	Occl + Nor	Occl + Nor + R	Occl + Nor
	mV				*mm Hg*				*beats/min*				*μeq/liter*			
7	5.3	7.0	4.0	—	120	175	175	—	125	138	130	—	290	1,826	166	—
8	4.2	8.5	3.8	5.5	90	150	148	145	150	155	150	130	—	1,488	294	607
9	2.1	4.2	1.5	2.4	98	150	145	145	195	186	156	190	—	964	670	1,885
10	3.0	9.6	2.1	7.5	95	150	150	150	120	175	156	162	272	1,888	231	1,385
11	4.4	6.3	2.3	3.3	103	150	150	145	205	205	182	165	159	1,445	147	1,195
12	7.2	11.6	2.9	6.4	118	160	160	160	173	166	175	168	293	1,550	398	2,345
Mean	4.4	7.9	2.8	5.0	104	156	155	149	161	171	158	163	254	1,527	318	1,483
SEM	0.7	1.1	0.4	1.0	5	4	5	3	15	10	8	17	32	135	80	297
P	<0.01	<0.005	<0.05		<0.001	NS	NS		NS	NS	NS		<0.001	<0.005	<0.02	

$\overline{ST}$, mean value of S-T segment elevation at 10–14 epicardial sites; $\overline{AP}$, mean arterial blood pressure; HR, heart rate; FFA_a, arterial concentrations of free fatty acids; *P*, probability values for comparison of paired data listed in the adjacent columns; NS, $P > 0.05$.

* Norepinephrine infusion, 2–3 μg/min; β-pyridylcarbinol, 5–10 mg/min.

alone was mainly due to larger myocardial oxygen extraction before inhibition of lipolysis whereas coronary blood flow was similarly increased. This is in accordance with previous studies in which FFA concentrations were raised by triglyceride/heparin infusion (24, 28). The induced increase in $M\dot{V}O_2$ was obtained by an increase in coronary arterio-venous O_2 difference.

β-Pyridylcarbinol did not influence coronary flow in the present measurements although larger doses have been shown to reduce peripheral resistance in humans (29). This was probably not due to methodological errors in flow measurements since good correlation between coronary flow determination from H_2 desaturation curves and by electromagnetic flowmetry has been shown over a wide range of flow values (15, 30). Furthermore, previous experiments using electromagnetic flowmeters or collection of retrograde flow (28) are in accordance with the present findings.

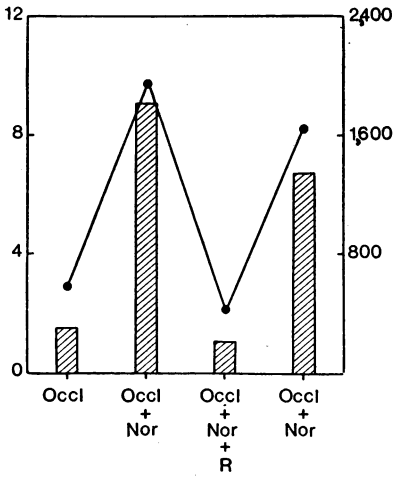


FIGURE 2 Average S-T segment elevation (mV) (●) and arterial plasma concentrations of FFA (columns) associated with 15 min of simple coronary occlusion alone (Occl) and under the influence of norepinephrine i.v. before (Occl + Nor), during (Occl + Nor + R), and after (Occl + Nor) inhibition of lipolysis with β-pyridylcarbinol (dog 4). Bars represent arterial concentration of FFA (μeq/liter).

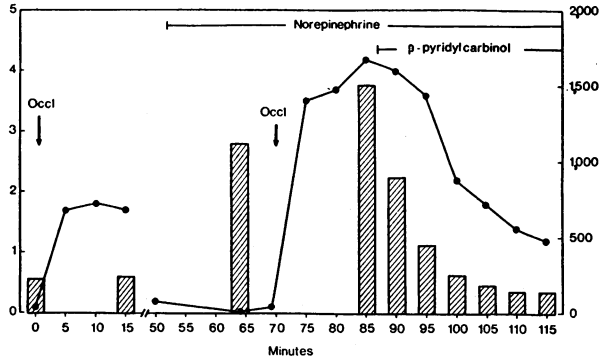


FIGURE 3 Average S-T segment elevation (mV) (●) and arterial plasma concentrations of FFA (columns) during two coronary occlusions in one dog experiment. The onset of occlusions is indicated by arrows. The first occlusion lasted for 15 min and served as control. The second occlusion was performed after 20 min of i.v. norepinephrine infusion (2.6 μg/min), and was maintained throughout the remaining experiment (45 min). Additional i.v. infusion of β-pyridylcarbinol (8 mg/min) was started 15 min after the second coronary occlusion. Bars represent arterial concentration of FFA (μeq/liter). See text for discussion (dog 13).

Whereas mechanical factors are by and large unchanged from prior control data, it should be noted that after inhibition of lipolysis, there is a substantial decrease in myocardial FFA uptake that is not translated into a decrease in $M\bar{V}O_2$. This probably indicates that under control conditions excess consumption of FFA does not take place, i.e., the substrate consumption equals the energy requirement. In a recent study it has been shown that the increase in $M\bar{V}O_2$ for a given rise in arterial pressure is dependent on the arterial levels of FFA (13). When $M\bar{V}O_2$ was increased by elevating FFA concentrations before the pressure rise, the subsequent pressure-induced increased in $M\bar{V}O_2$ was smaller than during pressure rise at control concentrations of FFA. Pressure loading increases the demand for substrate utilization. During increased uptake of FFA, available FFA are probably diverted into increased mechanical activity instead of being expended as heat only (31). Accordingly, it is only an increase in FFA over and above the substrate requirement set by the mechanical activity that will induce a change in oxygen consumption.

Although prolonged infusions of norepinephrine have been shown to produce myocardial necrosis and release of intracellular enzymes (3, 4), no conclusion has been reached concerning the influence of norepinephrine on the development of myocardial injury after acute coronary occlusion. From the present experiments it seems clear that before inhibition of lipolysis, norepinephrine administration increased the ischemic injury after coronary artery occlusion, and that this was due to a larger rise in oxygen demand—through raised contractility, blood pressure, and uptake of FFA—than in oxygen supply. These findings are in agreement with the studies of Maroko et al. (6) and Kjekshus and Mjøs (7), who showed that equivalent doses of isoproterenol (which do not produce ischemic injury in the normal myocardium) increased the extent and magnitude of S-T segment elevation and augmented the area of depression of creatine phosphokinase activity 24 h after coronary artery occlusion (6).

Pretreatment with β-pyridylcarbinol lowered the norepinephrine-induced oxygen consumption in normal dog hearts, and a marked reduction was observed in the norepinephrine-induced ischemic injury when lipolysis was inhibited. As these effects occurred despite similar changes in the mechanical activity of the heart, and as β-pyridylcarbinol has not been found to increase blood flow in the normal or ischemic heart (7), it is suggested that the lesser ischemic injury may partly be due to blockade of FFA release. It was of interest that when β-pyridylcarbinol was given after permanent coronary occlusion and norepinephrine infusion had extended the ischemic injury, there was a close and related decline in plasma-FFA and S-T segment elevation. These findings are in accordance with a recent study showing that the increase in myocardial ischemic injury induced by isoproterenol was markedly reduced, but not abolished, by pretreatment with an antilipolytic agent (7). It should be noted, however, that during inhibition of lipolysis the norepinephrine-induced ischemic changes became significantly less than during simple control occlusion without the drug, indicating that in this setting norepinephrine resulted in a smaller ischemic area than in control occlusion alone.

Increased aortic pressure is generally believed to raise myocardial oxygen requirements. However, it has been demonstrated that the extent and magnitude of acute myocardial ischemic injury can be reduced by raising aortic blood pressure; conversely, a fall in blood pressure will increase the size of the injury (6). The beneficial effect of raised aortic blood pressure is probably due to raised coronary perfusion pressure, and consequently increased collateral blood flow. The increased oxygen demand during the pressure rise thus encounters a larger rise in myocardial oxygen supply, resulting in reduced ischemic injury. This implies that in conjunction with β-pyridylcarbinol, norepinephrine raised myocardial oxygen supply, through increased collateral blood flow, more than the demand for oxygen was increased due to the rise in contractility and myocardial wall tension.

Although norepinephrine or isoproterenol induced essentially similar increases in $M\bar{V}O_2$ as well as in myocardial ischemic injury after acute coronary occlusion, important hemodynamic differences exist (11). $\overline{AP}$ was slightly reduced by i.v. infusion of isoproterenol, whereas norepinephrine in similar doses effected a 50 mm Hg rise. HR was found to increase more during isoproterenol than during norepinephrine infusion. A rise in HR has been shown to increase the size of a myocardial ischemic injury, probably due to increased oxygen demand (6).

With intact lipolysis, isoproterenol or norepinephrine effect the same directional increase in myocardial ischemic injury. When lipolysis is inhibited, however, the differences in the extent and magnitude of the ischemic injury induced by norepinephrine and isoproterenol were different, and probably determined solely by their hemodynamic differences. The reduced size of the ischemic injury by norepinephrine in this setting may therefore be explained by the rise in blood pressure. On the other hand, the rise in ischemic injury effected by isoproterenol during inhibition of lipolysis may be due to the combination of a fall in blood pres-

sure and increased HR and contractility. One explanation for the general reluctance to use sustained infusion of norepinephrine therapeutically is due to its untoward clinical effect which may be a result of unfavorable oxygen balance perhaps due to its lipolytic effect. When administered in conjunction with β-pyridylcarbinol, however, the effect of norepinephrine is to reduce oxygen demand and increase myocardial oxygen supply to an ischemic area. As a pure pressor and inotropic agent, norepinephrine may therefore be utilized successfully in cases of cardiogenic hypotension. Interventions that alter infarct size may ultimately have clinical importance. Since treatment before coronary occlusion is hardly clinically applicable it is interesting that S-T segment elevation was decreased also when β-pyridylcarbinol was administered after a permanent occlusion and norepinephrine infusion had caused extension of the ischemic injury (Fig. 3).

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