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Sympathetic Nervous System Activation in Postextrasystolic Potentiation: Role of Catecholamine Release in Enhancement of Ventricular Function

HERBERT J. GESCHWIND, MD, FACC, FRANÇOIS LHOSTE, MD, ANTONY J. I. SCRIVEN, MD, JEAN-FRANÇOIS DHAINAUT, MD, CATHERINE SABATIER, DANIEL LAURENT, MD

Créteil, France

The role of catecholamines in postextrasystolic potentiation was assessed in 30 patients during continuous coupled right ventricular pacing. Hemodynamic data were recorded in 15 patients (group 1); in the other 15 patients (group 2), coronary blood flow and metabolic variables, including catecholamines, were measured. Data were recorded in the control state and after 10 minutes of coupled pacing. Both groups had similar control pulse rates and mean aortic pressures: these variables decreased abruptly by 32 beats/min and 12 mm Hg, respectively, ($p < 0.001$ for each) after the initiation of coupled pacing. In group 1, all indexes of left ventricular function and contractility increased during coupled pacing ($p < 0.001$ for each), thus confirming postextrasystolic potentiation. In group 2, coupled pacing increased coronary blood flow, myocardial oxygen consumption and free fatty acid uptake ($p < 0.001$ for each) but not lactate extraction. Plasma epinephrine was unchanged, but norepinephrine levels increased in arterial (421 ± 27 to 576 ± 41 ng/liter) and coronary sinus plasma (611 ± 46 to 836 ± 46 ng/liter) ($p < 0.001$ for both). Indirectly calculated norepinephrine release within the myocardium increased from 25.6 ± 2.8 to 39.7 ± 5.2 ng/min (SEM) ($p < 0.05$), suggesting a sympathetic nervous system activation. It is argued that coupled pacing acutely lowered mean aortic pressure, leading to baroreflex sympathetic activation which may contribute to augmented cardiac contractility in postextrasystolic potentiation.

Postextrasystolic potentiation of myocardial contractility is known to result in marked enhancement of ventricular function during the cardiac contraction that follows an extrasystole. This effect is used in clinical investigation to assess left ventricular contractile reserve and identify segmental wall motion abnormalities in ischemic heart disease (1). The strength of the postextrasystolic contraction has been shown to be dependent on the prematurity of the extrasystole (2), but the fundamental mechanism of the potentiation is still uncertain. Current evidence (3) suggests that the enhanced myocardial contractility of postextrasystolic potentiation may be related primarily to increased availability of intracellular calcium at the contractile sites. The changes in preload and afterload that occur during the compensatory pause are now regarded as having a contributory rather than a major role in the enhancement of the contractile state (4). Since catecholamines are known to increase calcium influx by alteration of the cellular gating mechanism (5), the present study was undertaken to determine whether catecholamines have a role in the enhancement of ventricular function during postextrasystolic potentiation.

Methods

Patients. Thirty patients were studied during routine cardiac catheterization (Table 1). Five patients were routinely taking medication, but this was discontinued at least 24 hours before the study. All catheterizations were performed in the morning with the patient in the fasting state, supine and premedicated with 10 mg of diazepam intramuscularly.

Before the experimental study, all patients underwent diagnostic cardiac catheterization that included biplane left ventricular cineangiography and, when appropriate, coronary arteriography. Patients with coronary artery stenosis of greater than 50% or with a left ventricular ejection fraction of less than 0.45 were excluded from the study. For ethical and technical reasons, it was decided not to obtain hemodynamic, angiographic and metabolic data simulta-

From the Departments of Clinical Investigation and Clinical Pharmacology, and the Research Unit U 138 INSERM, University Hospital Henri Mondor, Créteil, France. Manuscript received November 28, 1983; revised manuscript received February 21, 1984, accepted March 29, 1984.

Address for reprints: Herbert J. Geschwind, MD, Catheterization Laboratory, Service d'Explorations Fonctionnelles, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France.

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Table 1. Patient Data

Case	Age (yr) & Sex	Diagnosis	NYHA Class	EF
		Group 1		
1	42F	MS	I	0.70
2	36M	CAD	II	0.61
3	18M	ASD	I	0.66
4	24M	ASD	I	0.52
5	35M	MS	I	0.56
6	34M	MS	II	0.52
7	53F	MS	I	0.56
8	41F	ASD	I	0.58
9	45M	CAD	I	0.64
10	42F	MS	I	0.70
11	40M	AI	I	0.73
12	41M	AI	II	0.45
13	55F	AI	II	0.54
14	39M	AI	II	0.51
15	35M	AI	II	0.51
		Group 2		
16	41M	CCM	I	0.48
17	30M	AI	II	0.58
18	42F	MVP	I	0.64
19	42M	AI	II	0.54
20	48M	PDA	I	0.55
21	33M	AI	II	0.49
22	39F	MS, MR	I	0.49
23	56M	AI	II	0.55
24	36F	MS	I	0.65
25	45M	CAD	II	0.45
26	31M	ASD	I	0.65
27	39F	MS	I	0.60
28	50M	MS	I	0.53
29	47F	MS, PHT	II	0.54
30	49F	MS	I	0.69

AI = aortic insufficiency; ASD = atrial septal defect; CAD = coronary artery disease; CCM = congestive cardiomyopathy; EF = ejection fraction; F = female; M = male; MR = mitral regurgitation; MS = mitral stenosis; MVP = mitral valve prolapse; NYHA = New York Heart Association; PHT = pulmonary arterial hypertension.

neously in all patients. Thus, although all patients had the identical protocol, 15 patients (group 1) had only hemodynamic and angiographic data recorded, while the remaining 15 patients (group 2) had metabolic and hemodynamic data recorded. This protocol was approved by the Human Research Committee of University Hospital Henri Mondor. Informed consent was obtained from all patients.

The ranges of age and sex, diagnosis and functional class were similar in both groups (Table 1); ejection fraction at rest was 0.58 ± 0.02 in group 1 and 0.56 ± 0.02 in group 2.

Procedure. After completion of the diagnostic study and the placing of additional catheters, patients from both groups rested undisturbed for 10 minutes, after which control data were recorded. Data were measured again after patients had undergone sustained coupled right ventricular pacing. The following data were obtained in the two groups.

Group 1: hemodynamic. These included aortic blood pressure, heart rate, peak first derivative of left ventricular pressure (dP/dt) and repeat cineangiographic ejection fraction and mean velocity of circumferential fiber shortening during coupled pacing.

Group 2: metabolic. These consisted of aortic blood pressure, heart rate, coronary blood flow and simultaneous aortic and coronary sinus blood samples for the determination of levels of norepinephrine, epinephrine, free fatty acids, lactate, hemoglobin, hematocrit and oxygen saturation.

Hemodynamic studies. In group 1, left ventricular pressure was continuously monitored with a 7F high fidelity microtransducer-tipped catheter equipped with a side hole for simultaneous aortic pressure recording (Millar Instruments). These data were recorded on a Bell and Howell recorder and stored in Syscomoram system computer (SNIAS, Bordeaux) for processing and retrieval. The same system

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was used for studies in group 2, but the catheter was positioned in the ascending aorta. Left ventricular volumes were computed from biplane cineangiograms using computerized Simpson's rule and ejection phase indexes (ejection fraction and mean velocity of circumferential fiber shortening) were derived from these values.

In group 2, coronary blood flow was measured in triplicate by a continuous infusion thermodilution technique using a constant infusion rate of 60 ml of 0.9% sodium chloride per minute for 30 seconds (6). A 7F two thermistor catheter (Wilton Webster) was inserted through the femoral vein and advanced to the coronary sinus. The position of the sensing thermistor was confirmed fluroscopically by small injections of contrast medium. In a previous series, we failed to observe any reflux of contrast medium from the right ventricle into the coronary sinus during right ventricular pacing (unpublished observations).

Continuous postextrasystolic potentiation was induced in both groups by sustained coupled right ventricular pacing using a bipolar electrode catheter (USCI) and a 5837 Medtronic pacemaker. Single electrical impulses triggered by the spontaneous QRS complex and adjustably delayed were applied to the endocardial surface of the right ventricle. The stimulus was moved progressively earlier in the cycle to achieve maximal prematurity. The stimulus could be brought as close to 280 to 310 ms, still yielding a coupled depolarization so that the second contraction was minimized. Thus, a minimal left ventricular pressure response to the stimulus was achieved while the effect of the potentiated beat was maximized, as was reflected by the increase in dP/dt without any significant change in peak systolic left ventricular pressure. The mechanical effect of the extrastimulus was observed as either a notch on the descending limb of the left ventricular pressure curve or a slight systolic pressure increase so that the peak pressure did not exceed 20 mm Hg. Since the contractile force of the extrasystole was insufficient to open the aortic valve and cause an increase in pressure in the aorta, the aortic pressure pulses were caused by the potentiated beats alone. Coupled pacing with the fixed interval was maintained for 15 minutes to secure a steady state of potentiation.

Biochemical studies. In group 2, blood samples were drawn for the estimation of hemoglobin, hematocrit, oxygen saturation, norepinephrine, epinephrine, free fatty acids and lactate. Oxygen partial pressures were determined by a polarographic method using a BMS 3 Radiometer apparatus. Oxygen binding capacity was measured using a LEX-02-CON apparatus (Lexington Instruments). Oxygen content was calculated from oxygen partial pressures, oxyhemoglobin saturation (MOS 1 Radiometer apparatus) and oxygen binding capacity. Norepinephrine and epinephrine were assayed in duplicate by a sensitive and specific double isotope radioenzymatic technique (7). Lactate and free fatty acids were assayed by conventional methods.

Catecholamine measurements. In our laboratory, average arterial plasma levels for norepinephrine and epinephrine in the resting state are 500 ± 50 and 40 ± 10 ng/liter, respectively. Estimates of inter- and intra-assay variation are 4.8 and 2.5%, respectively. Using calculations based on coronary blood flow data and plasma aortic and coronary sinus catecholamine concentrations, variables of myocardial catecholamine turnover were estimated.

Catecholamine influx. This refers to the rate of delivery of norepinephrine and epinephrine to the myocardium in the coronary arterial blood and is determined by:

$$\text{Influx (ng/min)} = \text{CBF} \times (\text{Cat})_{Ao} \times (1 - \text{hematocrit}),$$

where CBF = coronary blood flow and $(\text{Cat})_{Ao}$ = aortic catecholamine concentrations.

Catecholamine efflux. This refers to the total efflux of norepinephrine and epinephrine from the myocardium to the systemic circulation in the coronary venous effluent, and is calculated as:

$$\text{Efflux (ng/min)} = \text{CBF} \times (\text{Cat})_{CS} \times (1 - \text{hematocrit}),$$

where $(\text{Cat})_{CS}$ = coronary sinus catecholamine concentration.

Norepinephrine overflow. This refers to the net addition of norepinephrine to the blood flowing through the coronary circulation, and is determined by:

$$\text{Norepinephrine overflow (ng/min)} = \text{CBF} \times (\text{Cat})_{CS\text{-}Ao} \times (1 - \text{hematocrit}).$$

Myocardial catecholamine uptake. During their passage through vascular beds, catecholamines are continuously taken up from the plasma into neuronal and extraneuronal binding sites. The arteriovenous difference for epinephrine across all organs except the adrenal glands reflects tissue uptake alone because only the adrenal glands (outside the brain) can synthetize epinephrine (8). Thus epinephrine uptake is given by:

$$\text{Epinephrine uptake (ng/min)} = \text{CBF} \times (\text{E})_A - (\text{E})_V \times (1 - \text{hematocrit})$$

and

$$\text{Percent uptake} = \frac{(\text{E})_A - (\text{E})_V}{(\text{E})_A} \times 100,$$

where $(\text{E})_A$ and $(\text{E})_V$ = arterial and venous concentration of epinephrine, respectively. This method cannot be applied directly to norepinephrine uptake because norepinephrine is also released into the blood perfusing an organ. However, since norepinephrine (NE) and epinephrine (E) share the same uptake mechanism (9) and have been shown to have similar percent uptakes (10), norepinephrine uptake can be estimated indirectly according to: norepinephrine uptake (ng/min) = E% uptake × NE influx.

Myocardial norepinephrine release. This refers to norepinephrine that spills over from the synaptic cleft and dif-

fuses into the coronary blood. Although not a direct measure of the rate of neurotransmitter discharge, the spillover of norepinephrine from the synapse has been shown to correlate closely with changes in sympathetic nerve activity (11). Using an adaptation of the method of Levy and Blattberg (12), the quantity of norepinephrine (NE) appearing in the coronary venous blood (norepinephrine overflow) represents: NE influx + NE release − NE uptake. Thus: Myocardial norepinephrine release (ng/min) = NE overflow + NE uptake − NE influx.

Statistical analysis. Data are given as mean values ± standard error of the mean. Data obtained under control conditions and during coupled pacing were compared using the paired Student's *t* test; differences were regarded as significant when probability values were less than 0.05.

Results

Heart rate and blood pressure. In both groups, coupled pacing caused a profound decrease in the effective arterial pulse rate because only the potentiated (and not the extrasystolic) contractions opened the aortic valves. Thus, the control heart rate in group 1 was 77.1 ± 1.9 beats/min and this decreased to 42.8 ± 1.1 beats/min ($p < 0.001$); the decrease in group 2 was similar, from 73.5 ± 2.4 to 42.3 ± 0.8 beats/min ($p < 0.001$).

This was accompanied by immediate and significant decreases in mean (as a consequence of the lengthened interval between beats [Fig. 1]) aortic blood pressure from 85.2 ± 3.9 to 73.7 ± 2.9 mm Hg in group 1 and from 91.4 ± 2.6 to 79.4 ± 2.6 mm Hg in group 2 ($p < 0.001$ for both) (Tables 2 and 3). Thus, in both groups the decrease in mean aortic pressure was similar and due principally to a decrease in the diastolic component because systolic pressure did not change during coupled pacing.

Group 1: ventricular function data. In group 1, the ejection fraction, mean rate of circumferential fiber shortening and left ventricular peak dP/dt all increased significantly ($p < 0.001$) during coupled pacing. This response was observed for all three variables of left ventricular function in all patients (Table 2).

Group 2: metabolic and catecholamine data. Coronary blood flow increased in all patients during coupled pacing from a mean of 142.3 ± 11 to 176.8 ± 15 ml/min ($p < 0.001$). This was associated with an increase in myocardial oxygen consumption ($p < 0.001$) that was due in part to the change in coronary flow and in part to a small but significant ($p < 0.01$) increase in the arteriovenous oxygen difference (from 11.5 ± 0.5 to 12.5 ± 0.5 ml/min).

The mean basal aortic and coronary sinus plasma norepinephrine levels were 0.421 and 0.611 ng/ml, respectively, showing a net release of norepinephrine by the heart. During coupled pacing, these levels increased in all 15 patients to 0.576 and 0.836 ng/ml, respectively. Although these increases were relatively small (approximately 35%), they were highly significant ($p < 0.001$ for both) due to the uniformity of the response (Table 3). The mean venoarterial norepinephrine difference increased slightly, from 0.190 ng/

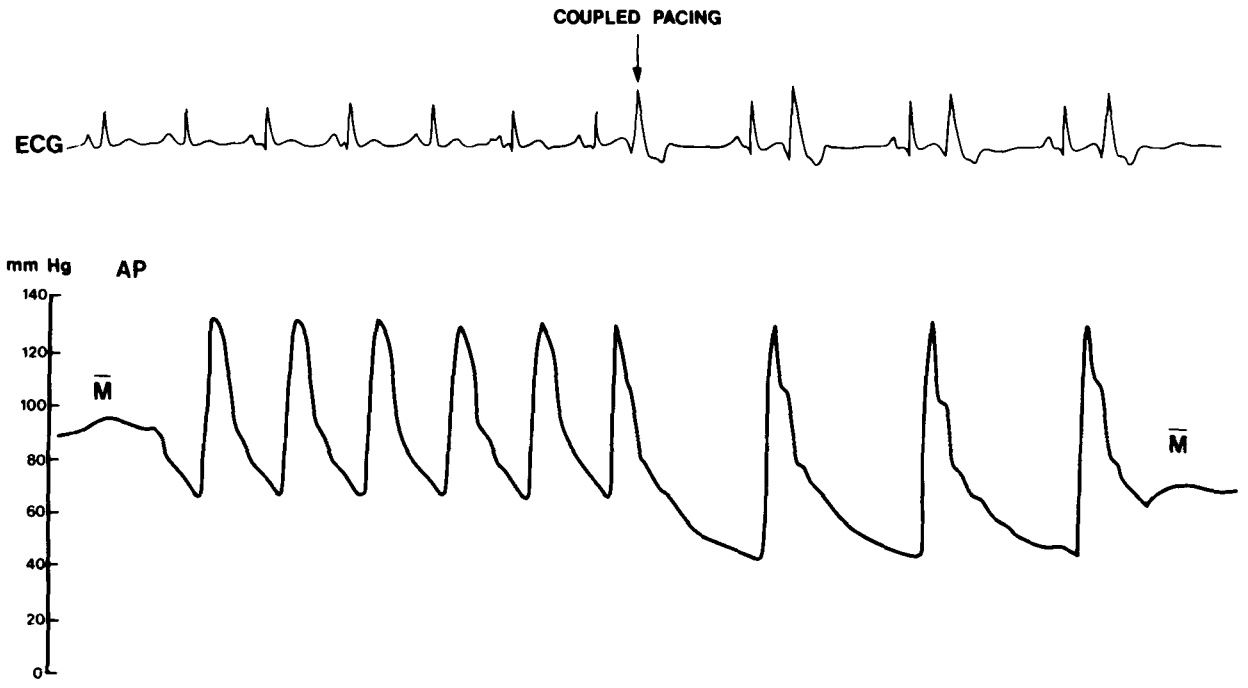

Figure 1. The characteristically abrupt decrease in aortic diastolic pressure at the onset of coupled pacing. AP = aortic pressure; ECG = electrocardiogram; M = mean aortic pressure.

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Table 2. Group 1: Hemodynamic Effects of Coupled Right Ventricular Pacing

Case	State	HR	Mean AoP	LV Peak dP/dt	EF	Vcf
1	C	85	100	1,700	0.70	1.6
	CP	43	70	3,000	0.79	2.1
2	C	88	92	1,800	0.61	1.3
	CP	45	82	3,800	0.77	2.0
3	C	76	89	1,500	0.66	1.6
	CP	40	71	3,000	0.72	2.1
4	C	83	95	1,500	0.52	1.1
	CP	41	92	3,000	0.64	1.5
5	C	76	80	1,400	0.56	1.4
	CP	49	73	3,100	0.72	1.8
6	C	70	74	1,800	0.52	1.3
	CP	38	61	2,600	0.76	2.1
7	C	67	74	1,700	0.56	1.1
	CP	42	57	2,700	0.83	2.5
8	C	75	105	1,900	0.58	1.5
	CP	43	98	4,200	0.77	1.8
9	C	80	93	1,700	0.64	1.5
	CP	44	79	2,100	0.79	1.9
10	C	94	93	1,700	0.70	1.6
	CP	52	83	2,600	0.74	2.1
11	C	72	82	1,400	0.73	1.6
	CP	45	73	2,000	0.77	2.0
12	C	71	71	900	0.45	1.0
	CP	34	61	1,550	0.71	1.5
13	C	69	70	1,000	0.54	1.1
	CP	39	65	1,300	0.60	1.5
14	C	75	81	1,200	0.51	1.4
	CP	44	71	1,550	0.66	1.7
15	C	76	79	1,000	0.51	1.0
	CP	43	70	1,500	0.72	1.1
Mean control		77.1	85.2	1,480	0.586	1.34
± SEM		1.9	3.9	83	0.02	0.06
Mean coupled		42.8	73.7	2,530	0.733	1.85
pacing ± SEM		1.1*	2.9*	222*	0.02*	0.09*

*$p < 0.001$. AoP = aortic pressure (mm Hg); C = control; CP = coupled right ventricular pacing; EF = ejection fraction; HR = heart rate (beats/min); LV Peak dP/dt = peak first derivative of left ventricular pressure (mm Hg); Vcf = mean velocity of circumferential fiber shortening (circumferences per second).

ml during basal conditions to 0.260 ng/ml during coupled pacing. However, because individual responses were more variable (11 subjects with increased and 4 with reduced venoarterial difference during coupled pacing), this increase was not significant. For the same reason, although the mean overflow of norepinephrine from the myocardium increased by 68% during coupled pacing (from 15.1 ± 2.5 to 25.5 ± 4.5 ng/min), this change just failed to reach levels of significance ($p = 0.056$) in the two tailed t test (Fig. 2).

The mean basal plasma epinephrine levels in aortic and coronary sinus blood were 0.083 and 0.054 ng/ml, respectively, showing a net extraction of epinephrine in the coronary vascular bed ($p < 0.001$). These levels did not change significantly during coupled pacing and the arteriovenous epinephrine difference was also unchanged.

The calculated influx and efflux rates increased significantly for both epinephrine ($p < 0.05$) and norepinephrine ($p < 0.001$) due to the enhanced coronary blood flow and the increase in plasma levels of norepinephrine and epinephrine (Fig. 2 and 3). The basal rate of epinephrine uptake was 2.23 ± 0.41 ng/min and this was unchanged during coupled pacing at 2.41 ± 0.055 ng/min (Fig. 3). Thus the percent uptake of epinephrine was reduced from 35 ± 1 to 26 ± 5%, but this was not significant. The calculated rate

Table 3. Group 2: Metabolic and Catecholamine Effects of Coupled Right Ventricular Pacing

							Lactate (mmol/liter)		Free Fatty Acids (μmol/liter)		Norepinephrine (ng/liter)		Epinephrine (ng/liter)	
Case	State	HR	Mean AoP	CBF	A-CSO_2	$M\dot{V}O_2$	A	CS	A	CS	A	CS	A	CS
16	C	70	103	152	13.0	19.8	1.25	2.4			336	543	41	10
	CP	41	100	175	13.2	23.1	1.25	1.65			440	584	153	120
17	C	90	95	190	9.9	18.8	1.7	1.7			473	564	79	72
	CP	50	75	273	11.4	31.1	1.5	1.65			941	1,058	122	113
18	C	62	83	121	9.5	11.5	0.9	0.85			564	906	71	70*
	CP	43	73	152	9.6	14.6	1.4	1.35			610	944	65	52
19	C	90	86	263	13.2	34.7			504	403	342	366	69	41
	CP	43	64	328	14.6	47.9			787	638	515	654	100	70
20	C	61	94	105	10.4	10.9			596	585	479	485	79	62
	CP	35	82	112	10.4	11.6			563	526	546	610	70	66
21	C	70	97	124	10.1	12.5			912	843	319	431	111	49
	CP	41	76	226	10.7	24.2			812	619	524	1,184	125	99
22	C	64	99	103	13.1	13.5	0.9	0.9			343	593	40	21
	CP	40	89	148	12.7	18.8	0.85	0.9			441	801	52	51
23	C	65	107	178	11.8	21	0.9	0.8	1,005	879	534	883	105	77
	CP	43	93	213	13.5	28.8	0.8	0.9	1,406	1,148	718	876	86	84
24	C	80	84	122	12.1	14.8	0.90	0.85	386	319	296	465	105	67
	CP	46	76	148	12.7	18.8	0.90	0.80	596	316	403	699	108	57
25	C	83	83	146	11.8	17.2	1.40	1.35			253	571	61	46
	CP	44	73	169	13	22	2.30	2.0			399	621	65	52
26	C	68	107	101	12	12.1	1.20	1.0	566	554	445	732	169	106
	CP	44	93	137	12.5	17.2	0.93	0.80	605	479	655	951	157	79
27	C	75	80	126	6.4	8.6	0.90	0.95	409	319	384	436	162	129
	CP	40	76	134	9	11.3	1.05	1.50	661	484	744	802	133	78
28	C	70	95	102	13.7	14.0	0.85	0.90	1,378	1,327	365	528	82	0
	CP	41	80	110	15.8	17.4	1.10	1.35	1,151	1,005	380	792	64	30
29	C	80	79	161	10.0	16.0	0.75	1.05	663	627	566	790	28	24
	CP	42	69	175	12.5	12.9	0.75	1.20	930	717	643	889	21	18
30	C	75	80	141	14.8	20.9	0.85	0.90	1,313	938	586	870	45	38
	CP	42	72	152	15.3	23.3	1.10	1.10	1,290	1,067	681	971	35	34
Mean control		73.5	91.5	142.3	11.5	16.4	1.04	1.14	779	679	421	611	83	54
± SEM		2.4	2.6	11	0.5	1.6	0.10	0.12	115	100	27	46	11	9
Mean coupled		42.3†	79.4†	176.8†	12.5*	21.5†	1.16	1.27	880	700	576†	836†	90	66
pacing ± SEM		0.8	2.6	15	0.5	2.4	0.11	0.11	96	89	41	46	11	8

*$p < 0.01$ versus control; †$p < 0.001$ versus control. A = aorta; A-CSO_2 = aortic coronary sinus oxygen ratio (ml/min); C = control; CBF = coronary blood flow; CP = coupled right ventricular pacing; CS = coronary sinus; $M\dot{V}O_2$ = myocardial oxygen consumption (ml/min).

of norepinephrine release within the myocardium was 25.6 ± 2.8 ng/min in the control state; this increased significantly during coupled pacing to 39.7 ± 5.2 ng/min ($p < 0.05$) (Fig. 2).

Lactate concentrations were unchanged during coupled pacing, but the rate of myocardial free fatty acid uptake increased threefold (8.34 ± 1.7 to 18.65 ± 3.6 μmol/min; $p < 0.001$).

None of the patients experienced subjective discomfort during the study protocol, nor were any changes in their clinical condition noted.

Discussion

Mechanical effect of postextrasystolic potentiation. The phenomenon of postextrasystolic potentiation of cardiac contractility is a fundamental property of both normal and despressed mammalian myocardium (1). Although first de-

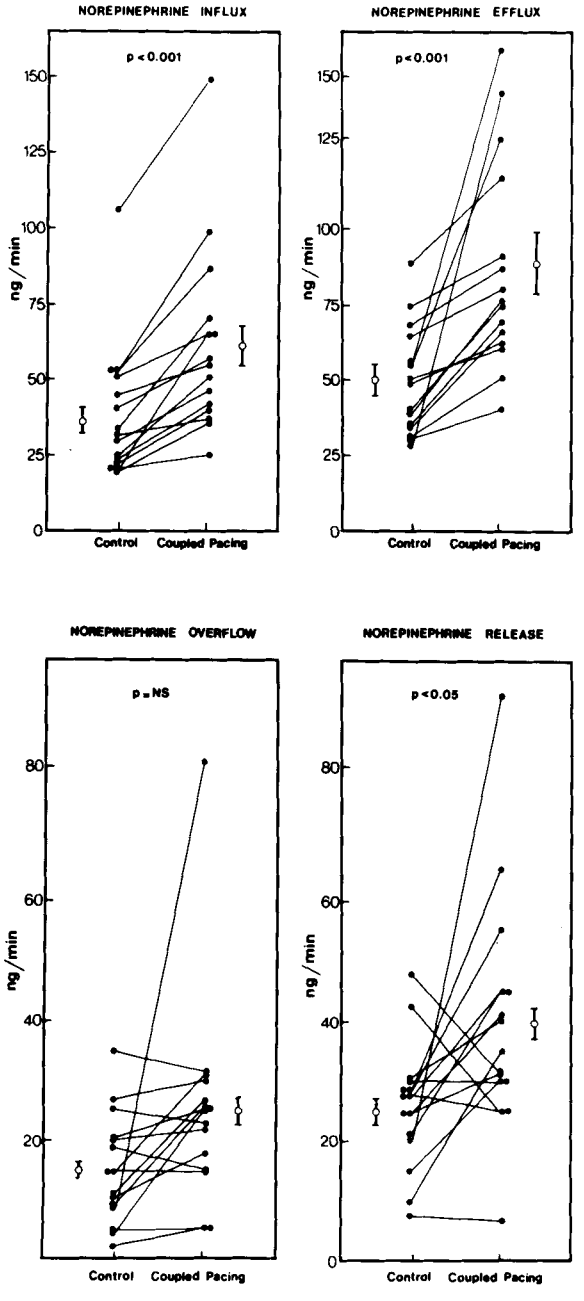

Figure 2. Individual and mean (± SEM) changes in norepinephrine turnover (influx, efflux and overflow) during coupled pacing.

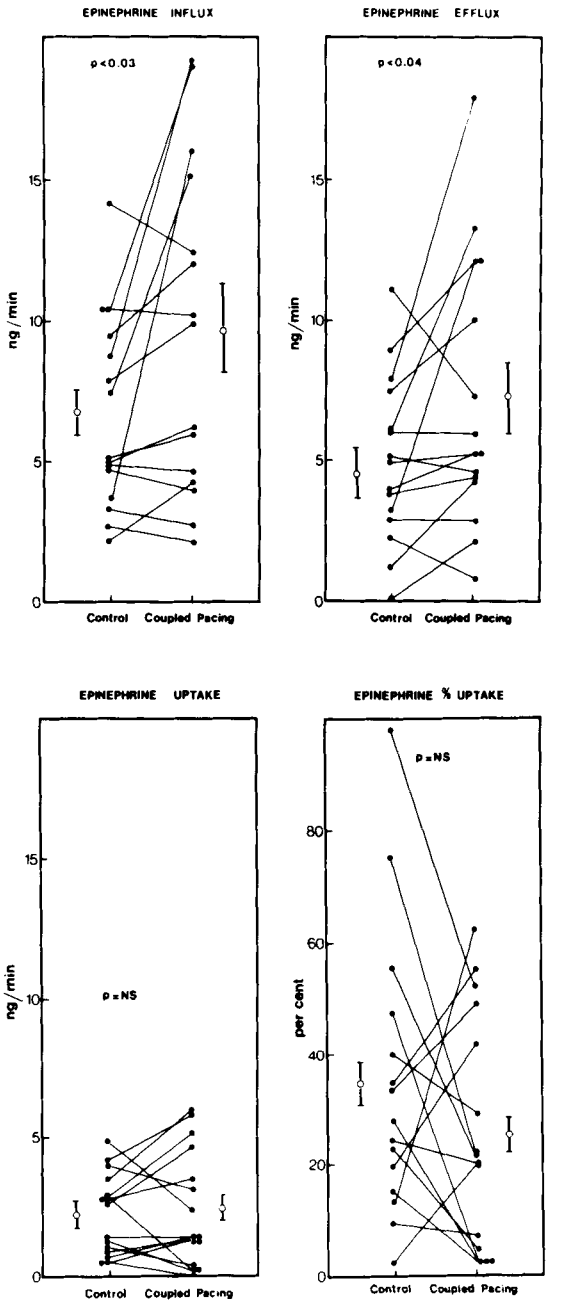

Figure 3. Individual and mean (± SEM) changes in epinephrine turnover (influx, efflux and uptake) during coupled pacing.

scribed by Langendorff in 1885, the mechanism of the inotropic effect is still not fully understood. Studies performed both in vitro on isometric cardiac muscle and isovolumetric heart preparations and in vivo in human subjects and intact animals suggest that three types of mechanism may participate. First, in vitro preparations demonstrated that postextrasystolic potentiation is associated with a primary augmentation of cardiac contractility which may be related to increased intracellular calcium availability and which occurs regardless of changes in preload and afterload (13–16). In addition, studies in intact animals (13) suggest that the decrease in aortic impedance during the compensatory pause may also enhance contractility, although the magnitude of this contribution is uncertain. Finally, increased ventricular filling during the compensatory pause may also contribute to postextrasystolic potentiation, although a recent study (4) showed enhanced left ventricular function in the absence of increased left ventricular end-diastolic volume, and cast doubt on the importance of the Frank-Starling mechanism in this context.

In this study, postextrasystolic potentiation was induced by sustained coupled ventricular pacing using the shortest coupling interval to minimize the mechanical effects of the extrasystoles and maximize the effects of potentiated beats. Although for ethical reasons it was decided not to subject our patients to a demanding and complex protocol in order to obtain simultaneous hemodynamic, angiographic and metabolic data, this difficulty was partially overcome by using two similar groups of patients "in parallel," a technique which albeit less compelling, can still yield useful data.

Our results in group 1 patients show that sustained coupled pacing markedly enhanced left ventricular function in all patients. Although it is impossible in vivo to consider the pumping function of the heart in isolation, the increase in left ventricular peak dP/dt, an isovolumic index relatively independent of afterload (18), suggests that cardiac contractility was augmented. The use of each patient as his or her own control showed that the increase in contractility was remarkably uniform among all group 1 patients, regardless of the type of cardiac diseases, and this agrees well with findings from previous reports (1,4,19–22). Taking into account the similarity of left ventricular function between the two groups as judged by ejection fraction and clinical state, it is reasonable to assume that a similar increase in contractility occurred in the patients in group 2, since both the technique of coupled pacing and the coupling interval were identical for group 1. Thus, although it was not directly assessed, the mechanical effect of sustained coupled pacing could be expected to be similar to that obtained in group 1 patients.

Role of catecholamines. The inotropic effects of catecholamines are known to be mediated by changes in calcium influx (5), but the role of endogenous catecholamines in postextrasystolic potentiation has not been previously investigated. We have now demonstrated that sustained coupled right ventricular pacing is also accompanied by significant increases in both plasma norepinephrine concentration and rate of release of norepinephrine from the myocardium. However, in determining the relation between these changes and the augmentation of contractility induced by coupled pacing, it is useful to consider the origin of the elevated circulating norepinephrine.

It is highly unlikely that the increase in plasma norepinephrine resulted solely from increased overflow from the heart. Tachycardia induced by "regular" pacing is not associated with elevation of plasma norepinephrine, although the overflow of norepinephrine from the heart may increase up to fivefold (23). Furthermore, in our patients, norepinephrine overflow increased from 15.2 ± 2.5 to 25.5 ± 4.5 ng/min with coupled pacing; at the same time, the plasma norepinephrine level increased by 155 ng/liter. Norepinephrine infusion studies (24,25) suggest that this increase in plasma norepinephrine would be achieved by a circulatory input of norepinephrine at a rate of approximately 3 to 5 ng/kg per min. Thus, the 10.3 ng/min increase in norepinephrine overflow in our patients could not itself have accounted for more than 5% of the increase in plasma norepinephrine.

In contrast, maneuvers such as dynamic (26) and isometric (27) exercise, which are known to stimulate sympathetic nervous activity (28), produce simultaneous increases in peripheral and coronary sinus norepinephrine plasma levels. The similarity between those findings and the results reported in this study confirm that coupled right ventricular pacing was associated with a generalized increase in sympathetic activity which led to the release of norepinephrine from sympathetic neurons in the heart and peripheral blood vessels. It is clear, however, that the small increase in circulating norepinephrine from 421 to 576 ng/liter is unlikely to have increased cardiac contractility. Studies (24,25) of infused norepinephrine indicate that a plasma concentration of between 1,000 and 1,800 ng/liter would be the minimal level required to produce detectable hemodynamic or metabolic effects.

Changes in norepinephrine turnover within the myocardium are less easily determined because although the overflow of norepinephrine from the heart can be derived from direct measurements, it is uncertain how closely it reflects cardiac sympathetic activity, being the net result of two opposing processes, namely, uptake and release. Theoretically more accurate is the use of the arteriovenous epinephrine difference as a marker for norepinephrine uptake since this allows the indirect assessment of myocardial norepinephrine release. The validity of this method depends principally on the percent uptake of norepinephrine and epinephrine being similar. Brown et al. (10) recently showed in normal subjects and patients with pheochromocytoma that there was no significant difference between the percent uptake of norepinephrine and epinephrine over a wide range of plasma concentrations and in a number of organs including the heart.

Our estimates suggest that the mean rate of release of norepinephrine within the myocardium increased markedly from 25.6 ± 2.8 ng/min under basal conditions to 39.7 ± 5.2 ng/min during coupled pacing (+ 55%). As this represents norepinephrine spillover from the synaptic cleft and reflects changes in neuronal release, it is likely that stimulation of myocardial beta-adrenoceptors was markedly increased and that this led to significant enhancement of cardiac contractility (29). Pacing-induced cardiac depolarization itself causes the release of norepinephrine regardless of the prevailing sympathetic tone (23), but in this study the total number of depolarizations (sinus plus paced) increased by only 11%. This is unlikely to have been the sole cause of the 55% increase in myocardial norepinephrine release. Thus, the release of norepinephrine in excess of what might be excepted as a result of pacing alone strengthens the argument

for enhancement of sympathetic activity within the heart as a contributory mechanism in postextrasystolic potentiation.

However, since it occurs in isolated hearts, postextrasystolic potentiation mainly acts by an intropic effect that is thought to be due to increased intracellular availability of calcium. The extent of the contributory role of catecholamines in the enhancement of myocardial contractility was not assessed because the effects of coupled pacing were not studied during administration of $beta_2$-adrenoceptor blocking agents or reserpine.

Catecholamines and myocardial metabolism. The enhancement of sympathetic activity within the heart is also supported by the marked increase in myocardial oxygen consumption during coupled pacing, which is in agreement with the findings reported by others (30,31). The increase in myocardial oxygen consumption occurred despite nearly a 50% reduction in the number of effective (that is, potentiated) contractions, and the total number of contractions (potentiated plus extrasystolic) increased by only 11%. A possible explanation would be that myocardial oxygen consumption increased as a result of the energy demands associated with the inotropic effect of sympathetic stimulation. This would be in keeping with the observation of Boerth et al. (32) that for a given increase in inotropic state, myocardial energy requirements were greater when the increase was caused by norepinephrine than when it was caused by increased heart rate. This is largely due to increased free fatty acid metabolism which is also augmented by catecholamine stimulation, again in excess of changes induced by pacing alone. Thus, our finding of a large increase in free fatty acid uptake despite a substantial decrease in effective heart rate is consistent with an underlying mechanism of accelerated release of norepinephrine within the myocardium.

Role of baroreceptors. The observation that regular cardiac pacing does not itself directly stimulate peripheral sympathetic activity (23) suggests that the mechanism involved in coupled pacing postextrasystolic potentiation may be reflex in origin. During the compensatory pause that precedes a potentiated beat, aortic blood pressure declines rapidly. Thus, during sustained coupled pacing the mean aortic pressure decreased abruptly by 12 mm Hg within one compensatory pause (Fig. 1). Baroreceptors are known to respond to changes in mean blood pressure and it is likely that this would lead rapidly by means of vagal disinhibition or sympathetic activation, or both, to increased release of norepinephrine. However, the influence of decreased average aortic pressure may be offset by the increased rate of pressure increase that occurs during coupled pacing. Animal studies (33) have shown that reflex changes in heart rate elicited by common carotid occlusion are mediated principally by the parasympathetic division of the autonomic nervous system which, in contrast to the relatively slow reaction time of the sympathetic division (measured in seconds), allows immediate adjustment of heart rate with time constants as short as 200 ms. It is also clear that changes in vagal activity may modulate myocardial norepinephrine release (34). This raises the possibility that beat to beat changes in cardiac automatic activity may be capable, at least theoretically, of influencing postextrasystolic potentiation after isolated spontaneous extrasystoles.

An autonomic nervous system role in postextrasystolic potentiation is compatible with interpretation of myocardial interval strength relations based on intracellular calcium flux (35). Studies in animals and human subjects have led to the concept of an intracellular calcium store whose contents are discharged to activate contractile proteins on each depolarization. Calcium influx may be accelerated by adrenergic stimulation, which would enhance filling of calcium stores during a compensatory pause.

Regarding the relation between cardiac sympathetic activity and coronary sinus norepinephrine levels, it has been observed by others (10) that the overflow of norepinephrine from an organ does not always correlate well with the density of its sympathetic innervation. In the dog heart, the tracer studies of Cousineau et al. (36) suggest that at the level of the coronary capillary endothelium, there is a barrier to the inward and outward diffusion of norepinephrine. In the context of our data, the two important implications of such a barrier would be: 1) amplification of the effects of locally released norepinephrine; and 2) attenuation of the outward diffusion of locally released norepinephrine into coronary capillary blood. Consequently, estimates of norepinephrine turnover based on coronary sinus norepinephrine concentrations will tend to underestimate the true figure.

Furthermore, if changes in the rate of myocardial norepinephrine uptake mask increases in release, it is possible that cardiac sympathetic activity may vary without necessarily being reflected by equivalent changes in norepinephrine overflow. The reduced effectiveness of coupled pacing in cardiac failure may be due at least in part to decreased myocardial sensitivity to catecholamines in this condition (37). In view of the growing interest in myocardial sympathetic function in cardiac failure, further work on techniques for stimulation and quantification of cardiac sympathetic responses in patients is required.

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