Propranolol Decreases Sympathetic Nervous Activity Reflected by Plasma Catecholamines during Evolution of Myocardial Infarction in Man

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ABSTRACT Plasma l-norepinephrine and epinephrine contents were strikingly elevated in 70 patients during evolution of myocardial infarction. Propranolol or placebo, 0.1 mg/kg i.v., was administered randomly an average of 10 h after infarction and continued orally for 3 d. Propranolol, but not placebo, acutely decreased l-norepinephrine contents from 2.24 ± 1.33 (mean$\pm$SD) to 1.31 ± 0.74 μg/liter, $P < 0.001$, and epinephrine contents from 0.97 ± 0.42 to 0.74 ± 0.42 μg/liter, $P < 0.02$. Decreases in l-norepinephrine contents were related to the initial plasma concentrations, $r = -0.85$, $P < 0.001$. A similar, but less strong relationship was observed between the initial epinephrine contents and propranolol-induced changes, $r = -0.51$, $P < 0.01$. Propranolol reduced plasma-free fatty acid contents from $1,121 \pm 315$ to 943 ± 274 μmol/liter, $P < 0.001$. Decreases in plasma contents of free fatty acids were related to decreases in epinephrine, $r = 0.66$, $P < 0.001$. Propranolol did not cause significant additional changes in plasma catecholamine contents during the subsequent 3 d. In the placebo group l-norepinephrine contents had decreased 24 h after infarction from 1.92 ± 0.99 to 1.37 ± 0.93 μg/liter, $P < 0.02$. Plasma epinephrine contents did not change. Heart rate remained below the control values during the entire study period in the propranolol, but increased in the placebo group. The data indicate that sympathetic hyperactivity, indirectly reflected by plasma catecholamine contents, is acutely reduced by propranolol during evolution of myocardial infarction.

INTRODUCTION

Plasma catecholamine contents are strikingly increased during evolution and early phase of myocardial infarction. Raab (1) as early as 1943 reported an increase in epinephrine and l-norepinephrine contents during exercise in patients with angina pectoris. Subsequent studies revealed high plasma catecholamine concentrations in myocardial infarction (2, 3) and release of catecholamines locally from ischemic myocardium (4). Serial determinations of plasma catecholamines during early myocardial infarction in man demonstrated that high catecholamine contents correlated with clinical status (5) and hemodynamic findings (6).

Although release of catecholamines initially represents a purposeful response to stress, excess release increases myocardial oxygen consumption and endangers viability of ischemic myocardium. Therefore, beta adrenergic blockade has gained increasing interest as therapeutic intervention in the acute state of myocardial infarction. Propranolol has been shown to be beneficial in experimental coronary occlusion (7) and in human myocardial infarction for a selected patient group (8–10). Recent studies have demonstrated, however, that propranolol increased plasma catecholamine contents in several clinical conditions (11–13), and thus caused concern about its use in acute myocardial infarction. We therefore evaluated the response of plasma catecholamines to propranolol in 35 patients with acute myocardial infarction and compared the results with those obtained after placebo drug. The study demonstrates that in the specific setting of evolving myocardial infarction propranolol acutely decreases plasma catecholamine contents. The complexity of a clinical study does not permit conclusions about mechanisms of action. The almost immediate effect of propranolol could be related to a reduction of afferent sympathetic traffic from ischemic myocardium, or to a direct effect on the central nervous system or on the peripheral sympathetic nerve terminal.

METHODS

Patients admitted to the coronary care unit were considered for the study when the following criteria were met: (*a*) suspected or definite acute myocardial infarction, as evidenced

by a characteristic history, acute ischemic changes in the electrocardiogram, and, if possible, by plasma creatine kinase MB (CK_{MB}) elevations; (b) no electrocardiographic evidence of an old transmural myocardial infarction (Q-waves); (c) functional (Killip) (14) classes I and II; (d) systolic blood pressure ≥ 95 mm Hg; (e) heart rate ≥ 55 beats/min; (f) absence of acute bundle branch block, of acute or old second- or third-degree atrioventricular block; (g) absence of insulin-dependent diabetes (>20 U/d); (h) absence of spastic lung disease; (i) age ≤ 75 yr. Informed consent, indicating the randomized, double-blind character of the study, was signed by all patients. The randomization schedule was provided by Ayerst Laboratories, New York.

Experimental procedures. A no. 7 Swan-Ganz thermodilution catheter (Edwards Laboratories, Division of American Supply Corp., Santa Ana, Calif.) was placed into the pulmonary artery. Cardiac output was obtained in triplicate determinations by the thermodilution technique (15). Intravascular and intracardiac pressures were measured with P23d Statham strain gauges (Statham Instruments, Inc., Oxnard, Calif.) and recorded on a multichannel oscilloscope (IM4, Electronics for Medicine, Pleasantville, N. Y.). Blood pressure was obtained by sphygmomanometer.

Each study included measurement of cardiac output, pulmonary artery and capillary wedge pressures, blood pressure, heart rate, substrate analysis of pulmonary artery blood and analysis of oxygen and carbon dioxide tensions and pH of pulmonary artery and arterial blood. After base-line evaluation, 0.1 mg/kg study drug was injected intravenously in three divided doses within 10 min. 20 min after initiation of intravenous injection all measurements were repeated. 40 min after intravenous injection, 40 mg of the study drug was continued per os, increased q6h in 20-mg increments up to 80 mg. Follow-up studies were performed in the fasting state between 6:30 and 8:00 a.m. on the three mornings after admission. These studies were obtained an average of 24, 48, and 72 h after infarction.

Methods of analysis. Plasma epinephrine and l-norepinephrine contents were measured by a modified method of Häggendal (16). The catecholamines were extracted into alumina by batch instead of column adsorption (17), resulting in consistent and increased recovery of 80±6% (SD), n = 12, and in minimal oxidation. Dithiothreitol instead of dimercaptopropanol was used as stabilizer, increasing the lutine fluorescence by 57.6% for epinephrine and 50.7% for l-norepinephrine, n = 10 (unpublished data). Milli Q2 Millipore water (Millipore Corp., Bedford, Mass.), free from fluorescent impurities was used. The minimum amount detectable with this method is 40 pg for epinephrine and 60 pg for l-norepinephrine. These limits are set by the sensitivity of the spectrophotofluorometer. The precision of the method was evaluated for epinephrine in the range of 0.093–4.34 μg/liter, coefficient of variability (CV),[1] 9.15%, for l-norepinephrine in the range of 0.140–4.24 μg/liter, CV, 9.66%, n = 28. Plasma contents, obtained from 10 fasting normal volunteers, 20 min after placement of an intravascular catheter and relaxation in the supine position, averaged 0.146±0.031 (SD) μg/liter (epinephrine) and 0.308±0.071 μg/liter (l-norepinephrine). To evaluate whether propranolol interferes with the analytic method, 100 ng of propranolol hydrochloride (Ayerst Laboratories) was added to 1 ml of plasma obtained from patients in the coronary care unit, but not necessarily with an acute myocardial infarction, n = 16. Plasma epinephrine contents averaged 0.703±0.666 μg/liter before, and 0.712±0.671 μg/liter after addition of propranolol,

CV, 8.10%; l-norepinephrine contents averaged 1.299±1.121 and 1.292±1.171 μg/liter, respectively, CV, 8.69%. Plasma propranolol contents were determined by a modified method of Shand (18), CV, 3.10%, n = 20. Details about determinations of blood concentrations of free fatty acids, of plasma pH, oxygen and carbon dioxide tensions were previously published (8).

The Student's paired *t* test was used for comparisons between adjacent sampling periods. Initial control values were compared to both study periods, 10 min and 3 d after propranolol/placebo administration. All other comparisons were obtained between one sampling period and the period immediately following it (Table I). The *t* test for unpaired data was used to compare results between patients with different infarct locations (Table II).

RESULTS

70 patients with acute myocardial infarction were studied, 35 received propranolol and 35 placebo. Six patients in the propranolol and five in the placebo group were female. The age averaged 57 (41–75) and 56 (39–70) yr in propranolol and placebo groups, respectively. The site of infarction was the anterior or anterior/lateral wall in 15 and 12 patients in the propranolol and placebo groups, the inferior or inferior/ posterior wall in 19 and 22 patients, and undetermined in one of each group, respectively. Subendocardial infarctions were observed in two and three instances in each group. Infarct size for the entire patient group averaged 48±33 (SD) CK_{MB}-g-eq (amount of infarcted myocardium liberating CK_{MB} into the circulation equivalent to the amount released from 1 g of homogenously necrotic myocardium). 0.1 mg/kg of study drug was administered intravenously in three divided doses within 10 min, propranolol an average of 10.0 (5.3–13.0) h and placebo an average of 9.6 (4.2–13.2) h after onset of infarction. The study drug was continued per os with an average dose of propranolol of 182±76 (SD) mg during the 1st d of infarction, of 217±111 mg during the 2nd d, and of 214±121 mg during the 3rd d. The corresponding doses for placebo per os averaged 249±33, 304±57, and 293±72 mg, respectively. The plasma propranolol contents immediately after intravenous injection averaged 89±33 (SD) ng/ ml, at 24 h after infarction 53±56 ng/ml, at 48 h 162±148 ng/ml, and at 72 h 154±133 ng/ml. There were two in-hospital cardiac deaths in the propranolol group (sudden arrhythmias) and one death in the placebo group (cardiac rupture, verified by autopsy).

Acute study. Plasma l-norepinephrine and epinephrine contents before drug administration were elevated more than fivefold, averaging for l-norepinephrine 2.24 and 1.86 μg/liter in the propranolol and placebo groups and for epinephrine 0.97 and 0.90 μg/liter, respectively (Table I). The plasma l-norepinephrine contents of the individual patients before and 20 min after initiation of intravenous drug administration are shown in Fig. 1. After propranolol

TABLE I
Plasma Catecholamine and Substrate Contents and Hemodynamics in Acute Myocardial Infarction

Average hours p̄ acute myocardial infarction	10		10		24		48		72	
Prop* / Plac	Initial control 35		10 min p̄ intravenous drug 35		34		34		34	
Measurement		*P*			Mean±SD					*P*
1-NE,* µg/liter										
Propranolol	2.24±1.33	<0.001†	1.31±0.74	NS	1.39±0.87	NS	1.40±0.98	NS	1.37±0.90	<0.02
Placebo	1.86±0.87	NS	1.92±0.99	<0.02	1.37±0.93	NS	1.37±1.12	NS	1.61±1.02	NS
EPI, µg/liter										
Propranolol	0.97±0.42	<0.02	0.74±0.42	NS	0.65±0.40	NS	0.67±0.49	NS	0.63±0.44	<0.05
Placebo	0.90±0.53	NS	0.88±0.56	NS	0.80±0.67	NS	0.78±0.76	NS	0.81±0.65	NS
FFA, µmol/liter										
Propranolol	1,121±315	<0.001	943±274	NS	933±288	NS	842±268	NS	766±233	<0.001
Placebo	1,087±262	NS	1,046±244	NS	1,035±252	<0.01	870±254	NS	838±213	<0.001
HR, beats/min										
Propranolol	77±16.21	<0.001	67±11.23	NS	66±9.95	<0.05	70±11.79	NS	71±10.89	<0.001
Placebo	73±16.17	NS	74±14.97	NS	78±12.81	<0.01	85±16.32	<0.05	80±16.21	<0.05
AP$_S$, mm Hg										
Propranolol	132±19.52	<0.05	126±20.25	<0.001	111±16.11	NS	107±13.11	NS	108±14.49	<0.001
Placebo	126±18.59	NS	125±18.53	<0.01	117±16.23	NS	115±13.97	<0.02	110±15.17	<0.001
AP$_D$, mm Hg										
Propranolol	88±11.58	NS	86±14.33	<0.001	74±11.35	NS	70±10.32	NS	72±10.34	<0.001
Placebo	84±11.76	NS	85±11.89	<0.001	77±11.19	<0.05	73±10.05	NS	73±10.33	<0.001

Prop	29		29		28		27		27	
Plac	34		34		33		32		32	

Measurement					Mean±SD					
CI, liters/min/m²										
Propranolol	2.64±0.60	<0.001	2.06±0.46	<0.02	2.28±0.45	<0.01	2.54±0.51	NS	2.59±0.45	NS
Placebo	2.61±0.57	NS	2.56±0.58	NS	2.54±0.51	<0.001	2.83±0.47	NS	2.87±0.56	<0.01
SVR, dyn-s-cm⁻⁵										
Propranolol	1,479±359	<0.001	1,752±384	<0.001	1,567±458	<0.02	1,362±464	NS	1,254±297	<0.001
Placebo	1,486±292	NS	1,502±332	NS	1,425±353	<0.001	1,265±237	NS	1,234±266	<0.001
PAP$_D$, mm Hg										
Propranolol	11.27±4.32	NS	12.42±5.50	NS	10.70±4.77	NS	9.33±4.29	NS	10.23±3.52	NS
Placebo	11.27±5.61	NS	10.54±5.63	NS	9.37±5.11	NS	8.79±4.32	NS	8.27±3.75	<0.01

* Prop, propranolol group; Plac, placebo group; 1-NE, 1-norepinephrine; EPI, epinephrine; FFA, free fatty acids; HR, heart rate; AP$_S$, systolic arterial pressure; AP$_D$, diastolic arterial pressure; CI, cardiac index; SVR, systemic vascular resistance; PAP$_D$, diastolic pulmonary artery pressure.

† P values are for paired t test. Comparisons were obtained between one sampling period and the period immediately following it. Control values were compared with both study periods, 10 min and 3 d after propranolol/placebo administration.

1-norepinephrine contents decreased in 28 of 35 patients, remained essentially unchanged in four, and increased in three patients. The mean value decreased from 2.24 to 1.31 µg/liter ($P < 0.001$). In contrast, placebo drug did not significantly change the mean value. 1-Norepinephrine contents increased in 12 patients, probably related to stress of the procedures, and fell in 7. The propranolol-induced changes in plasma epinephrine contents were less marked but were statistically significant. They decreased in 25 patients and remained essentially unchanged or increased in 10. The mean value fell from 0.97 to 0.74 µg/liter ($P < 0.02$). Plasma epinephrine contents did not change after placebo administration. Decreases in plasma 1-norepinephrine contents were related to plasma concentrations (Fig. 2). The higher the initial 1-norepinephrine contents, the greater the decreases after propranolol, $r = -0.85$, $P < 0.001$. A similar, but less strong relationship was also observed between the initial plasma epinephrine contents and the propranolol-induced changes, $r = -0.51$, $P < 0.01$.

Plasma-free fatty acid contents were elevated in both patient groups before interventions, averaging 1,121 µmol/liter in the propranolol and 1,087 µmol/liter in the placebo groups, respectively (Table I). Propranolol-induced decreases in free fatty acids correlated with decreases in plasma epinephrine contents, $r = 0.66$, $P < 0.001$. None of the correlations described for the propranolol group was observed in the placebo group.

Mean values of hemodynamic data are shown in Table I. Heart rate and cardiac index significantly decreased after propranolol, but not after placebo ad-
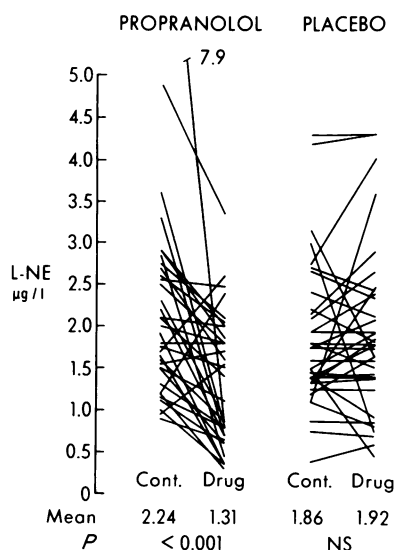
FIGURE 1 Plasma 1-norepinephrine contents of the individual patients before and after intravenous drug administration. After propranolol, 1-norepinephrine contents decreased in 28 patients, remained unchanged in 4 and increased in 3. In contrast, after placebo 1-norepinephrine contents increased in 12 patients, probably a result of the stress of the procedure, and fell in 7.

ministration. Diastolic pulmonary artery pressure remained essentially unchanged in both groups. Systemic vascular resistance significantly increased after intravenous propranolol and remained unchanged after placebo administration. Pulmonary artery oxygen saturation decreased from 72 ± 5.61 to $66\pm7.03\%$ ($P < 0.001$) in the propranolol and remained unchanged
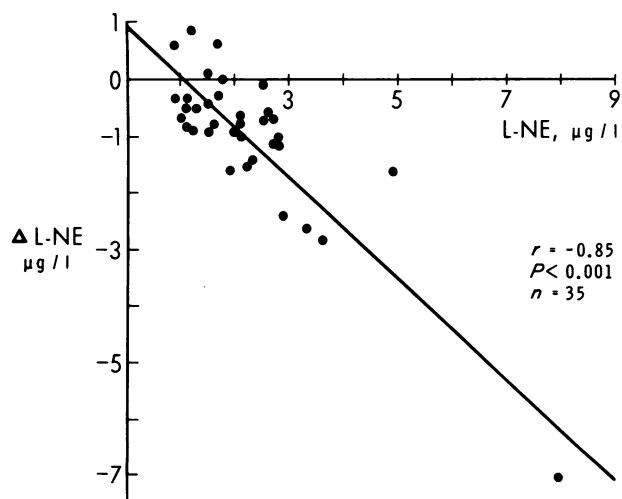

FIGURE 2 Correlation between initial plasma 1-norepinephrine contents and propranolol-induced changes. The higher the initial 1-norepinephrine contents, the greater the decreases after propranolol, $r = -0.85$, $P < 0.001$. 1-NE, 1-norepinephrine.

in the placebo group, 71 ± 5.53 and $72\pm5.29\%$, respectively.

Sequential studies. Mean values of plasma catecholamine contents and hemodynamic measurements for propranolol and placebo groups are shown in Table I and Fig. 3. The data were obtained an average of 24, 48, and 72 h after onset of infarction. After the acute reduction of plasma 1-norepinephrine and epinephrine contents following intravenous propranolol, there was no significant additional change during the remaining study period. In contrast, intravenous placebo had no acute effect on 1-norepinephrine contents. They decreased during the 1st d from 1.92 (acute study) to 1.37 μg/liter (24 h after infarction). Mean epinephrine contents did not change during the entire study period after placebo injection. The response of plasma-free fatty acids to propranolol was similar to that observed for the catecholamines. After the acute reduction following intravenous propranolol, plasma-free fatty acids remained essentially unchanged during days 1 and 2 and showed a second decrease on day 3; this change was significant when compared with the results of day 1 ($P < 0.01$). In the placebo group plasma-free fatty acids remained elevated at least during the 1st d of infarction. They decreased during the 2nd d, the mean value decreased from an average of 1,035 (24 h) to 870 μmol/liter (48 h), $P < 0.01$.

Mean values of heart rate and cardiac index—acutely reduced after intravenous propranolol administration—increased during the 3-d study period. Although heart rate remained below the control values for the entire 72 h, cardiac index had returned close to the initial control measurements at 48 h. In contrast, in the placebo group, heart rate and cardiac index increased during the 3 d of observation and were above the control values at day 3. The trends in systolic and diastolic arterial pressures were similar in both patient groups. All pressure measurements were significantly lower on day 3, compared with the control study. Systemic vascular resistance increased acutely after intravenous propranolol from an average of 1,479 to 1,752 dyn-s-cm^{-5}; the resistance decreased during day 1 and fell below control values at the 72-h study period. In the placebo group, systemic vascular resistance remained essentially unchanged during day 1, and significantly decreased during day 2. There was no significant difference between the systemic vascular resistance of the propranolol and placebo groups during days 2 and 3.

Separation of initial studies according to infarct location. Six patients with inferior/posterior infarctions, who had electrocardiographic evidence of anterior wall subendocardial ischemia, and two patients with undetermined site of infarction were excluded.
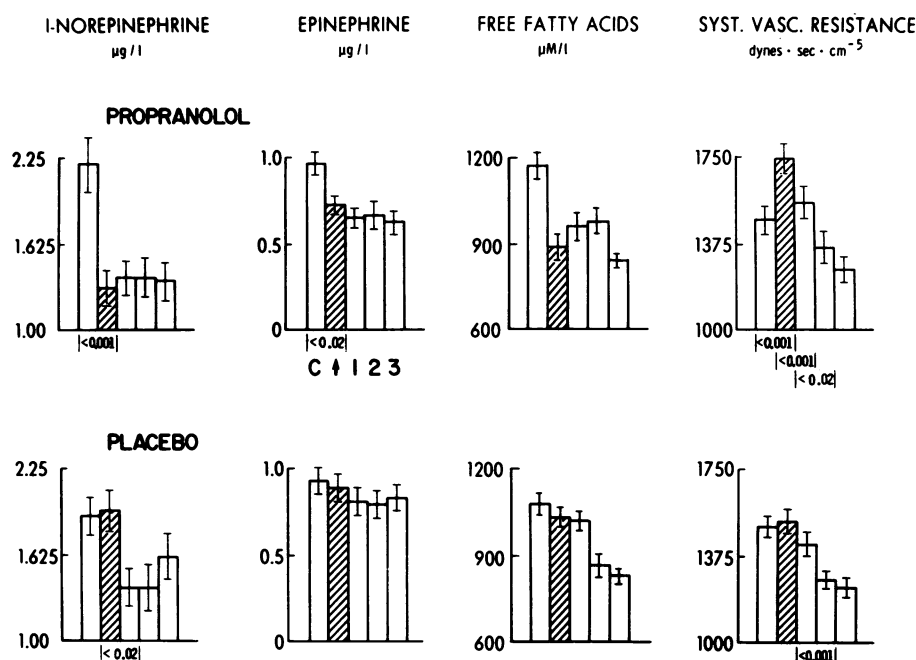
FIGURE 3 Sequential observations of plasma catecholamine and free fatty acid contents and of systemic vascular resistance in propranolol and placebo groups, mean±SE. Propranolol acutely decreased plasma catecholamines and free fatty acids. The effect on systemic vascular resistance was biphasic. In the placebo group, these changes occurred more slowly. Plasma epinephrine did not decrease. C, control; ↑, intravenous drug administration; 1, 2, and 3, days of study after infarction.

Separation of the control data of all study patients before drug administration according to anterior/lateral and inferior/posterior myocardial infarction did not show significant differences between plasma contents of 1-norepinephrine, epinephrine and free fatty acids, or between hemodynamic measurements, except for heart rate and pulmonary artery diastolic pressure (Table II). The measurements averaged 84±17 and 69±10 beats/min ($P < 0.001$), and 12±4.15 and 10±4.06 mm Hg ($P < 0.05$), respectively. Grouping of the initial control data according to infarct location separately for propranolol and placebo patients revealed similar results. Changes, induced acutely by intravenous propranolol, did not significantly differ between anterior/lateral and inferior/posterior infarctions, except for the following measurements: heart rate (mean of difference), −15±11 and −7.13±8.75 beats/min ($P < 0.05$); diastolic arterial pressure, −6.13±12 and +2.07±8.34 mm Hg ($P < 0.05$); and cardiac index, −0.72±0.39 and −0.40 ±0.30 liters/min per m² ($P < 0.05$), respectively.

DISCUSSION

The increased plasma catecholamine concentrations reported in this and other studies (1–6) reflect increased sympathetic nervous activity, although factors

TABLE II

Initial Plasma Catecholamine and Substrate Contents and Hemodynamics in Acute Myocardial Infarction

Infarct location	Anterior/lateral myocardial infarction	Inferior/posterior myocardial infarction	
Measurement	Mean±SD		P
	n = 27	n = 35	
1-NE,* µg/liter	1.95±1.39	2.02±0.86	NS
EPI, µg/liter	0.91±0.33	0.91±0.51	NS
FFA, µmol/liter	1,133±323	1,091±293	NS
HR, beats/min	84±17.12	69±9.78	<0.001
AP$_S$, mm Hg	130±19.26	128±19.17	NS
AP$_D$, mm Hg	89±10.29	85±11.97	NS
	n = 25	n = 30	
CI, liters/min/m²	2.58±0.55	2.66±0.56	NS
SVR, dyn-s-cm⁻⁵	1,462±428	1,450±321	NS
PAP$_D$, mm Hg	12±4.15	10±4.06	<0.05

* Abbreviations: 1-NE, 1-norepinephrine; EPI, epinephrine; FFA, free fatty acids; HR, heart rate; AP$_S$, systolic arterial pressure; AP$_D$, diastolic arterial pressure; CI, cardiac index; SVR, systemic vascular resistance; PAP$_D$, diastolic pulmonary artery pressure.

such as axonal re-uptake, local metabolism within the synaptic cleft, turnover, and binding to receptor sites (19, 20), alter the relationship between neural activity and plasma contents. Sympathetic nervous activity in acute myocardial infarction is influenced by hypotension-mediated baroreceptor reflexes, decreased peripheral perfusion with impaired tissue metabolism (13), cardio-cardiac reflexes (21), anxiety and activation of cardiac vagal afferent fibers (22). The almost immediate decrease of plasma catecholamine contents after administration of propranolol observed in our patients may be the result of a net decrease in afferent sympathetic impulses or a direct effect on the central nervous system or on peripheral sympathetic nerve terminals.

Considerable evidence exists that the release of neurotransmitter from the sympathetic nerve terminal is regulated by a presynaptic feedback system. Stimulation of presynaptic alpha receptors causes negative feedback, decreasing 1-norepinephrine release (23–26). Recent studies suggest that positive feedback through stimulation of presynaptic beta receptors also exists that is diminished or abolished by beta adrenergic blockade. Propranolol, but not the dextro isomer, in doses of 0.1 mg/kg, decreased the vasoconstrictor response of the cat hind limb to low-frequency sympathetic nerve stimulation, whereas the response to injected 1-norepinephrine was unchanged (27). Propranolol produced similar reductions of constrictor responses to sympathetic nerve stimulation in the guinea pig vas deferens (28), atria (29), oviduct (30), and in human peripheral arteries and veins (25, 31). Isoproterenol increased the overflow of tritiated 1-norepinephrine during low-frequency stimulation in the perfused cat spleen; this response was diminished by propranolol, and the reduction was greatest in those experiments with the highest output of neurotransmitter (32, 33). Yamaguchi et al. (26) demonstrated a positive presynaptic feedback control in the open chest dog. Isoproterenol caused a fourfold increase in 1-norepinephrine release into the coronary sinus during cardioaccelerator nerve stimulation; this effect was almost abolished by sotalol. Because heart rate, left ventricular dP/dt, and coronary blood flow showed congruent changes after isoproterenol and sotalol administration, the studies suggest that presynaptic beta receptors might play a physiological role in the control of neurotransmitter release.

The experiments, discussed above, indicate that presynaptic beta receptors are sensitive to sympathetic nerve stimulation in the frequency range of 1–10 Hz. Whether these stimulation frequencies are similar to those required for the more than fivefold elevation of 1-norepinephrine contents found in our study remains speculative. Observations in man during surgical procedures on the neck (34) have shown that the response of adrenergic-innervated structures is near maximal at 8–10 Hz. Stimulation-effector response curves obtained by Yamaguchi et al. (26, 35) in the dog indicate that the catecholamine concentrations, observed in our patients, are compatible with sympathetic nerve impulses in that range. Consequently, it is possible that the almost immediate decrease in plasma 1-norepinephrine contents after intravenous administration of propranolol is related to presynaptic beta adrenergic blockade.

Blockade of central beta adrenergic receptors could also produce a decrease in plasma catecholamine contents. The pressor effect of an intracerebroventricular injection of isoproterenol was blocked by a similarly administered dose of propranolol (36). A biphasic effect was observed when propranolol was injected into the cerebral ventricles; an initial hypertensive response was followed by a reduction in blood pressure within 20–30 min (37). These effects could not be demonstrated with the dextro isomer of propranolol which has little beta blocking activity. Intravenous propranolol decreased sympathetic activity recorded from a preganglionic peripheral sympathetic nerve (38).

Because propranolol has been shown to improve myocardial metabolism within 20 min in human myocardial infarction (8), another explanation for the observed effect on plasma catecholamines might be reduction of afferent impulses that initiated and maintained sympathetic hyperactivity. In contrast to our findings, Hansen et al. (12) observed in individuals with stable ischemic heart disease that intravenous propranolol increased plasma 1-norepinephrine contents at rest and during exercise. Afferent sympathetic activity arising from altered tissue metabolism appeared to be more important than baroreceptor mechanisms, because venous oxygen saturation was a much better predictor of 1-norepinephrine concentrations than blood pressure. In our patients, propranolol produced changes in hemodynamics and mixed venous oxygen saturation similar to those in Hansen's study at rest, but decreased plasma catecholamine contents, suggesting that some additional factors, related to acute myocardial infarction, were influenced by beta adrenergic blockade, thus overcoming peripheral sympathetic afferent signals.

Brown et al. (39) demonstrated in the vagotomized cat an increase in cardiac afferent sympathetic impulses during left coronary artery occlusion. A similar procedure in the cat enhanced preganglionic activity, demonstrating a cardio-cardiac sympathetic reflex (21). Plasma concentrations of 1-norepinephrine were increased after left coronary artery ligation; a series of surgical and pharmacologic interventions indicated that the effect was a result of afferent

impulses arising from the infarcted area (40). The possibility that propranolol in our patients decreased afferent sympathetic stimulation from the infarcted myocardium is supported by observations of Uchida and Murao (41). Intravenous injection of 0.5 and 1.0 mg/kg propranolol before coronary ligation in the dog reduced afferent sympathetic activity from the heart. In consequence, our data are compatible with the hypothesis that sympathetic hyperactivity after acute myocardial infarction in man is related to stimulation of cardiac sympathetic afferent fibers.

Activation of cardiac vagal afferents, however, may modify factors leading to increased sympathetic activity. In patients seen within 30 min of acute myocardial infarction, parasympathetic hyperactivity dominated in inferior/posterior, but was also present in anterior/lateral wall infarctions, whereas sympathetic hyperactivity dominated in the latter group (42). Occlusion of the circumflex, to a lesser degree of the left descending coronary artery in the aorto-sinus denervated dog, activated receptors producing bradycardia, hypotension, and a decrease in renal sympathetic nerve activity (43). The importance of vagal over sympathetic afferent control in the early minutes after coronary occlusion was supported by a relatively small increase in cardiac sympathetic nerve activity in spite of a depressor response (44). The fact that our initial control data do not show significant differences in plasma catecholamines and in most hemodynamic measurements between patients with anterior/lateral and inferior/posterior infarctions suggests that initial autonomic responses are substantially modified by hemodynamic, metabolic, and emotional stimuli later in the course. The greater response of heart rate to intravenous propranolol in anterior/lateral infarctions probably implies that sympathetic tone was higher in this group.

It is unlikely that the acute decrease in plasma 1-norepinephrine contents was produced by a membrane-stabilizing action of propranolol on the neuron that would impede depolarization. Nies and Shand (45) have estimated that plasma concentrations two or three times higher than the usual range of therapeutic concentrations, 80–100 ng/ml, would be necessary to produce a membrane-stabilizing effect. Studies in man have confirmed these differences between concentrations necessary to produce beta adrenergic blockade or membrane stabilization (46), indicating that the average level of 89±33 (SD) ng/ml in our patients was not high enough to directly interfere with depolarization.

The initial increases in peripheral vascular resistance in our patients receiving propranolol is a result, in part, of the decrease in cardiac function, but may also be a result of adrenergic dysbalance at the postsynaptic receptors, resulting in relative increase in alpha adrenergic tone. The impact of alpha adrenergic activity on coronary vascular resistance has been demonstrated in experimental myocardial infarction (47–49) and recently in a clinical study. In patients with stable ischemic heart disease, increase in coronary vascular resistance and chest pain, provoked by cold pressure test, were abolished by alpha adrenergic blockade (50). Although the decrease in catecholamine concentrations demonstrated in our study does reduce the amount of alpha adrenergic stimulation, the plasma levels are still several times greater than normal, and the withdrawal of opposing beta adrenergic activity could produce a net constrictor effect.

The binding of propranolol to several beta adrenergic receptors probably explains the previously reported beneficial effects of the agent in acute ischemic heart disease (7–10) and the differences between propranolol- and placebo-treated patients in this study. The sequential observations shown in Table I and Fig. 3 demonstrate that plasma contents of catecholamines and free fatty acids decline more slowly in the placebo group; heart rate and cardiac index became greater than on admission. Propranolol, in contrast, produces a rapid decrease in plasma catecholamine and free fatty acid concentrations, a biphasic effect on peripheral resistance, and a decrease in heart rate and cardiac index. The effect on plasma catecholamine contents appears to be related to the high initial concentrations encountered in these patients, emphasizing that the net effect of a drug is frequently dependent upon the specific clinical situation selected for evaluation.

ACKNOWLEDGMENTS

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