Haemodynamic effects of acebutolol¹

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We studied the haemodynamic effects of acebutolol, administered in intravenous doses of 0.5 mg/kg and 1.0 mg/kg body weight, in 7 patients who had undergone coronary artery bypass surgery and in 4 patients who had cardiac transplants. Myocardial contractility and ventricular volumes were assessed by computerised fluoroscopic analysis of the motion of surgically implanted left ventricular intramyocardial markers. In both groups of patients, acebutolol reduced all 4 measured indices of contractility. The end-diastolic and end-systolic volumes were increased by 13 per cent and 16 per cent, respectively. There was a mean reduction of 8 per cent in cardiac output. The mean heart rate fell by 12 per cent. Blood pressure and stroke volume were not significantly affected. Considered separately, the surgical patients with normal cardiac innervation and the transplant patients with denervated hearts showed the same direction and magnitude of change in all haemodynamic measurements except cardiac output, which fell only in the bypass patients. These results suggest that, while acebutolol exerts a mild cardiac depressant effect, it can be administered safely to patients with normal cardiac function in intravenous doses of at least 1.0 mg/kg body weight resulting in peak serum levels of over 2000 ng/ml. Furthermore, cardiac autonomic nervous reflexes do not appear to alter the haemodynamic effects of acebutolol in man.

Acebutolol is a new beta-adrenoreceptor blocking agent which is effective in the management of angina pectoris as well as hypertension (Lewis *et al.*, 1973a). As a beta-antagonist, it is approximately one-eighth as potent as propranolol. Acebutolol exerts a membrane stabilising effect similar to that of propranolol, but has somewhat greater cardio-selectivity (Kumana *et al.*, 1975). In a previous study we showed that acebutolol is well tolerated orally and is effective in reducing the frequency of premature ventricular contractions in patients with drug-resistant ventricular arrhythmias (Gradman *et al.*, 1975). The haemodynamic effects of acebutolol in man were the subject of a previous study in which a small dose of 30 mg was used (Lewis *et al.*, 1973b). In the present study we examined the haemodynamic effects in man of acebutolol in a dose of 1.0 mg/kg body weight, because this larger dose yields plasma concentrations in the therapeutic range (Gradman *et al.*, 1975). We investigated left ventricular dynamics by a new method in which the motion of surgically implanted myocardial markers is recorded fluoroscopically and the

information stored for subsequent computer analysis. In addition, we compared the effects of acebutolol in cardiac allograft recipients who have denervated hearts, with its effects in patients with normal cardiac innervation, in order to assess the contribution of cardiac autonomic reflexes to the overall haemodynamic action of acebutolol.

Subjects and methods

Seven patients without previous myocardial infarction or congestive heart failure, who had undergone coronary artery saphenous vein bypass grafting for angina pectoris, were selected for study on the basis of normal preoperative ventricular function, uncomplicated postoperative courses, and normal postoperative ventricular function as assessed by the myocardial marker method described below. An additional 4 cardiac allograft recipients were studied at a time when there were no signs of cardiac rejection or extracardiac disease. All patients were in New York Heart Association Functional Class I.

At the time of coronary bypass graft surgery or cardiac transplantation, 7 1.0 × 1.5 mm tantalum markers were inserted into the midwall of the left ventricle to lie in a single horizontal plane, so as to

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Table 1 Haemodynamic changes after acebutolol

	Coronary bypass patients		% change	P value	Transplant patients		% change	P value
	Control	Acebutolol			Control	Acebutolol		
HR (l/min)	73.0 ± 2.9	62.6 ± 2.7	-14	< 0.001	110.3 ± 4.7	100.0 ± 3.5	-9	NS
CO (l/min)	4.84 ± 0.58	4.14 ± 0.40	-12	NS (0.08)	5.93 ± 0.42	5.88 ± 0.56	0	NS
BP (mmHg)	95.6 ± 4.2	96.3 ± 4.1	+1	NS	93.1 ± 3.7	89.8 ± 4.0	-3	NS
EDV (ml)	124.8 ± 10.9	137.5 ± 11.9	+10	NS (0.07)	90.8 ± 8.6	105.4 ± 8.7	+17	< 0.01
ESV (ml)	59.6 ± 6.9	71.9 ± 8.4	+21	< 0.01	36.8 ± 7.2	46.2 ± 8.4	+27	< 0.01
SV (ml)	65.2 ± 5.9	65.6 ± 4.7	+3	NS	54.1 ± 4.0	59.2 ± 6.2	+9	NS
V (circ/s)	0.76 ± 0.05	0.58 ± 0.03	-23	< 0.001	1.10 ± 0.09	0.84 ± 0.07	-22	NS
VVSI	59.1 ± 4.7	39.4 ± 4.2	-33	< 0.001	79.8 ± 6.1	65.2 ± 5.3	-17	NS
S (%)	20.4 ± 1.4	19.0 ± 0.8	-5	NS	23.4 ± 1.2	21.5 ± 1.2	-8	NS
EF (%)	52.6 ± 3.2	48.4 ± 2.6	-8	< 0.02	57.9 ± 4.8	56.7 ± 5.5	-2	NS

HR, heart rate; CO, cardiac output; BP, mean blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume, V, mean circumferential velocity; VVSI, ventricular velocity/asynchrony index; S, mean segmental shortening; EF, ejection fraction; NS, not significant.

outline a profile of the left ventricle with the patient in a 30° right anterior oblique position (Ingels *et al.*, 1975). The motion of these markers was recorded by fluoroscopy on a video disc at 30 frames per second. The horizontal and vertical co-ordinates of the positions of the markers through 3 cardiac cycles were digitised and transmitted to a CDC-6700 digital computer for analysis of ventricular dynamics. Four indices of myocardial contractile state were derived: mean circumferential velocity, ventricular velocity/asynchrony index (Ingels *et al.*, 1975, 1976), mean segmental shortening, and ejection fraction. Accuracy and reproducibility of this method have been previously assessed (Ingels *et al.*, 1975).

Acebutolol (1 mg/kg body weight) was administered intravenously over a 10-minute period to 8 of the 11 subjects. Three transplant patients received an initial dose of 0.5 mg/kg followed 60 minutes later by a second dose of 1.0 mg/kg. In these 3 patients, results obtained after the first dose were used for data analysis, though the haemodynamic effects of the two doses were indistinguishable. Myocardial marker motion and blood pressure were recorded immediately before and 15 minutes after completion of the acebutolol infusion. Before acebutolol administration, isoprenaline was infused at a rate of 2 µg/min to determine the dose required to increase the heart rate to 25 per cent above the resting level. At the completion of the study, adequate beta-blockade was documented in all 11 patients by the absence of a heart rate response to this predetermined dose of isoprenaline.

All patients gave informed consent preoperatively for placement of the midwall left ventricular markers, and at a later date for the infusion of acebutolol and haemodynamic study. Procedures involving surgical marker placement and the acebutolol study were reviewed and approved by the Stanford University Committee on the Use of Human Subjects for Research. No complications of

marker implantation or drug infusion occurred.

Plasma concentrations of acebutolol were measured by a technique developed in our laboratory, using selective solvent extraction and gas chromatography (Meffin *et al.*, 1976). In the 3 patients who received an initial dose of 0.5 mg/kg and a second dose of 1.0 mg/kg, blood samples were obtained 25 minutes after initiation of each drug infusion. In 4 of the 8 patients who received a single dose of 1.0 mg/kg, blood samples were also obtained 25 minutes after the infusion was started; in 1 patient, blood sampling was not performed, and in the 3 remaining patients, plasma concentrations were measured immediately after termination of the 10-minute infusion.

Haemodynamic values before and after drug administration were compared by the two-tailed Student's *t* test for paired data.

Results

Table 1 shows the change in haemodynamic values after acebutolol administration for all patients, and for coronary surgery patients and transplant patients considered separately. The directions and magnitudes of change were similar for the coronary artery bypass surgery and transplant groups, and for both groups combined. Most of the haemodynamic changes in the transplant group did not achieve statistical significance, because of their small number.

HEART RATE, CARDIAC OUTPUT, AND BLOOD PRESSURE

A moderately large, statistically significant fall in heart rate was observed in both groups of patients after acebutolol administration (Fig. 1). The cardiac output fell modestly only in the bypass group (Fig. 2), while the calculated mean blood pressure showed minimal change after acebutolol administration (+1% for the entire group).

Both groups			
Control	Acebutolol	% change	P value
86.6 ± 6.1	76.2 ± 6.1	-12	< 0.005
5.24 ± 0.42	4.77 ± 0.41	-8	NS
94.1 ± 3.3	92.9 ± 3.5	-1	NS
112.5 ± 9.0	125.7 ± 9.3	+13	< 0.01
54.0 ± 5.2	62.5 ± 7.1	+16	< 0.05
		+5	NS
0.88 ± 0.07	0.68 ± 0.05	-23	< 0.001
66.7 ± 4.8	48.8 ± 5.0	-27	< 0.001
21.5 ± 1.1	19.1 ± 1.2	-10	NS (0.06)
54.5 ± 2.7	51.4 ± 2.7	-2	NS (0.06)

Fig. 1 Effect of acebutolol on heart rate. The resting heart rate fell in both groups of patients by 10 beats per minute; this change was statistically significant in the coronary bypass surgery patients. Standard errors of the means and P values are indicated in this and subsequent figures.

VENTRICULAR VOLUMES

End-diastolic, end-systolic, and stroke volumes were increased after acebutolol administration in both groups (Fig. 3), though the small mean change in stroke volume was not statistically significant. The transplant patients had significantly lower end-diastolic volumes than the bypass patients, because of their more rapid resting heart rates, but all volume values were within the normal range.

INDICES OF MYOCARDIAL CONTRACTILITY

In both groups of patients, acebutolol reduced all 4 indices of myocardial contractile state (Fig. 4). The predrug values for these indices were in the normal range in all the patients. Reductions in mean circumferential velocity and ventricular velocity/asynergy index were of the greatest magnitude and were statistically significant in the coronary artery bypass patients.

PLASMA CONCENTRATIONS

Plasma concentrations of acebutolol are shown in Table 2. The dose of 1.0 mg/kg acebutolol resulted in a mean plasma concentration of 719 ± 64 (SEM) ng/ml, which was 69 per cent greater than the level

Fig. 2 Effect of acebutolol on cardiac output. The reduction in cardiac output in the coronary bypass surgery patients was of borderline statistical significance ($P < 0.08$). Mean cardiac output was unaffected by acebutolol in the transplant patients. The 2 transplant recipients in whom there was an increase in cardiac output were the same 2 patients whose heart rates did not decrease.

Fig. 3 Effect of acebutolol on ventricular volumes. The mean end-diastolic volume is marked by the upper border of each vertical bar and the end-systolic volume by the lower border; the stroke volume is shown by the difference between these. End-diastolic and end-systolic volumes were increased in both groups by acebutolol, while the stroke volume did not change. Ventricular volumes in the transplant patients were lower than those of the coronary bypass surgery patients because of the resting tachycardia in the former group.

Fig. 4 Effect of acebutolol on indices of myocardial contractility. All 4 measures of the contractile state of the myocardium were reduced by acebutolol. In top left panel, the mean circumferential velocity of left ventricular wall motion was significantly reduced in the coronary bypass surgery patients. A fall of similar magnitude in the transplant patients did not reach statistical significance. The lower left panel shows that there was a fall in the ventricular velocity/asynergy index in both groups. The top right panel shows that mean segmental diameter shortening fell in both groups, but only slightly. The lower right panel shows that ejection fraction fell significantly in the coronary surgery patients but only slightly in the transplant patients.

attained with the smaller dose of 0.5 mg/kg body weight. In the 2 patients who received both dose levels of acebutolol and had blood sampling after both doses, the higher dose resulted in a plasma

concentration 40 per cent greater than that after the lower dose. All these blood samples were obtained 25 minutes after initiation of acebutolol infusion. The mean peak plasma concentrations, measured immediately after termination of the infusion in 3 patients, was 2179 ± 440 ng/ml. No patient reported side effects during or after acebutolol infusion.

Table 2 Plasma concentrations of acebutolol

Dose (mg/kg)	Time after initiation of infusion (min)	Plasma concentration (ng/ml)	Mean concentration $\pm$ SEM (ng/ml)
0.5*	25	529	426 $\pm$ 55
		407	
		341	
1.0	25	868	719 $\pm$ 64
		777	
		642	
1.0	10	588	2179 $\pm$ 440
		2886	
		2275	
		1371	

*Of the 3 patients who received this dose, 2 were given a 1.0 mg/kg dose 60 minutes later and attained plasma concentrations of 597 ng/ml and 452 ng/ml 25 minutes after the second dose.

Discussion

We have examined the haemodynamic effect of intravenously administered acebutolol in 11 patients who had miniature tantalum coils implanted in their left ventricular midwalls during open heart surgery. Fluoroscopic visualisation and subsequent computer analysis of the motion of these markers by a previously validated method allowed us to assess contractility and volume changes noninvasively. As would be expected of a beta-blocking agent,

acebutolol significantly reduced the resting heart rate, and promoted a slight fall in cardiac output. Acebutolol had no effect upon blood pressure in this group of patients. The end-diastolic and end-systolic volumes were increased, probably because of increased diastolic filling resulting from the fall in heart rate. The stroke volume increased slightly, but insufficiently to maintain cardiac output at the reduced heart rate. This failure to augment stroke volume appropriately is best explained by the depressant effect of acebutolol upon contractility. We found that acebutolol diminished all 4 measured indices of myocardial contractility; the decreases in mean circumferential velocity and ventricular velocity/asynchrony index (Ingels *et al.*, 1976) were statistically significant, though the decreases in mean segmental shortening and ejection fraction were not. The only previous study of the haemodynamic effects of acebutolol in man was reported by Lewis and his associates (1973b). However, they gave a total intravenous dose of only 30 mg to each of their subjects, in successive doses of 10 mg and 20 mg. They did not state the period of time which elapsed between doses and they did not monitor plasma concentrations. They observed a moderate reduction in heart rate and contractility. While they did not determine ventricular volumes, they reported a slight fall in stroke index and a 10 to 20 per cent diminution in cardiac index. Their findings are qualitatively and quantitatively similar to ours, despite the difference in dose.

We used a larger dose of acebutolol (1.0 mg/kg). In previous studies and in the present one, we have found that this dose yields plasma concentrations 25 minutes after initiation of infusion that are within the therapeutic range for oral treatment. Though steady-state plasma and tissue drug concentrations could not have been achieved in this study, the plasma concentration serves as a rough guide to judge the intravenous dose of acebutolol. Our results suggest that an intravenous dose of 1.0 mg/kg of acebutolol is well tolerated and should be appropriate for clinical use.

The haemodynamic effects of acebutolol are comparable with those of propranolol. Most investigators (Sowton and Hamer, 1966; Parker *et al.*, 1968) except for Wolfson *et al.* (1966), have reported a reduction in contractility, heart rate, blood pressure, and cardiac output, with concomitant increases in ventricular volumes and filling pressure after propranolol administration both in normal subjects and in patients with coronary artery disease. Though blood pressure was not significantly changed in this study, we have found in other studies that intravenous acebutolol reduces the blood pressure to a degree comparable with that of prop-

ranolol.¹ Thus, the haemodynamic effects of acebutolol do not appear to differ from those of other beta-adrenergic blocking agents.

Because of the possibility that reflex adjustments in cardiac autonomic tone could compensate for the myocardial depressant effect of acebutolol, we studied its action in cardiac allograft recipients in whom, because of anatomical cardiac denervation, there can be no reflex effects on myocardial function. Patients with cardiac disease, especially those with congestive heart failure, also have defective cardiac sympathetic and parasympathetic function (Covell *et al.*, 1966; Beiser *et al.*, 1968; Eckberg *et al.*, 1971), and in this respect are similar to transplant recipients. The direction and magnitude of change of each of the haemodynamic variables studied, except for the cardiac output, were similar in the two groups of patients. The mean cardiac output fell by 8 per cent after acebutolol in the coronary bypass surgery group, but did not change in the transplant recipients. The major points of difference between the two groups were the initially higher heart rate and contractility indices and the lower ventricular volumes observed in the allograft recipients. (The increase in heart rate in this group is a result of cardiac denervation, and the increased contractility and reduced volumes are primarily a result of tachycardia.) Though we studied only 4 transplant patients, their behaviour after acebutolol does not differ from that of patients with normal cardiac innervation. It appears, then, that changes in cardiac autonomic tone do not mask the haemodynamic effects of beta-blockade by acebutolol, and that patients with impaired autonomic responsiveness can be expected to show similar haemodynamic changes to those occurring in patients with normal autonomic function at rest.

In summary, we have found that acebutolol can be safely administered intravenously in doses of 0.5 mg/kg and 1.0 mg/kg to patients with normal myocardial function, with or without normal cardiac autonomic innervation. Acebutolol reduced resting myocardial contractility, heart rate, and cardiac output, and increased ventricular volumes. These changes are similar to those reported for propranolol. Finally, the similarity of the results in coronary bypass and in transplant patients suggests that autonomic reflexes do not counteract the haemodynamic effects of acebutolol in man.

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¹Unpublished data from our laboratory.

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