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Important Differences Between Short- and Long-Term Hemodynamic Effects of Amiodarone in Patients With Chronic Ischemic Heart Disease at Rest and During Ischemia-Induced Left Ventricular Dysfunction

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To assess and compare the hemodynamic profile of short- and long-term amiodarone administration in the same set of patients and to investigate hemodynamic mechanisms responsible for the antianginal effect of this drug, 10 patients with documented coronary artery disease and stable angina pectoris were studied. Simultaneous right heart catheterization and equilibrium radionuclide angiocardiography were performed at rest and during exercise before therapy (control), after a 5 minute intravenous infusion of 7.5 mg/kg of amiodarone and after 21.0 ± 4.3 days of peroral therapy (10 days 800 mg/day, 7 days 400 mg/day and then 200 mg/day). After acute drug administration, ejection fraction, stroke index and systolic blood pressure decreased, whereas heart rate, left and right ventricular filling pressures and systemic vascular resistance increased. These effects were reversed after long-term therapy; all measured values returned to control levels except for heart rate, which decreased below the control value, and right atrial pressure, which remained slightly elevated. Amiodarone drug levels decreased from 4.8 ± 1.8 after intravenous infusion to 1.2 ± 0.6 mg/liter after long-term therapy. After adjustment for hemodynamic changes at rest, there were still significant reductions in heart rate, mean arterial pressure and rate-pressure product during exercise.

It is concluded that the marked negative inotropic effect of amiodarone administered acutely in the dose applied calls for cautious use of this drug when administered intravenously. In contrast, long-term oral amiodarone therapy seems hemodynamically safe, even in patients with moderately depressed left ventricular function. Amiodarone also exerts a mild but significant antiischemic effect, mainly through afterload reduction and improvement in myocardial oxygen consumption.

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Amiodarone has been shown to be an effective antiarrhythmic agent in many supraventricular and ventricular rhythm disorders (1–10). Whereas this effectiveness is virtually undisputed with long-term amiodarone therapy (4–9), there remains some controversy over its acute antiarrhythmic action as reflected by a disparity between clinical and electrophysiologic effects (6,11–14). This phenomenon has been explained partly by the pharmacokinetic properties of amiodarone, which differ markedly from those of other antiarrhythmic drugs (15–19) but may also have a hemodynamic basis or parallel. The hemodynamic action of amiodarone has been studied (20–22) after acute administration of the drug demonstrating negative inotropic and afterload-reducing effects. In a recent study (23), the acute cardiodepression seemed to disappear over a 24 hour observation period of continuous amiodarone infusion. There is, however, little information on the long-term hemodynamic effects of this drug, and an intraindividual comparison between short- and long-term hemodynamic effects is lacking. Moreover, although amiodarone was introduced for the treatment of angina pectoris (24–26), there are almost no data on hemodynamic mechanisms responsible for its antianginal property.

The aim of the present investigation, therefore, was twofold: 1) to assess and compare the hemodynamic profile of short-term intravenous and long-term peroral amiodarone administration at rest in the same set of patients, and 2) to

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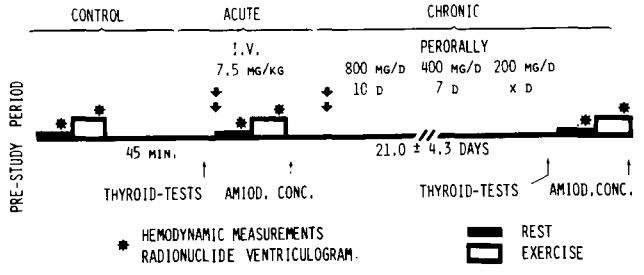
study hemodynamic changes during exercise in patients with chronic ischemic heart disease presenting with stable angina pectoris.

Methods

Patients. Ten male patients aged 54.1 ± 5.1 years (range 42 to 60) referred for evaluation of stable angina pectoris (New York Heart Association functional classes II and III despite medical therapy) were studied after informed consent had been obtained (study protocol approved by this institution's Ethics Committee on June 18, 1982). Included were only patients in whom all antianginal drugs could be withdrawn at least 48 hours (nitrates: 24 hours) before study and who had neither a left ventricular ejection fraction of less than 0.35, mitral incompetence, lung disease or thyroid dysfunction. Three patients had a documented myocardial infarction more than 3 months before this investigation. Three patients had one vessel disease and 7 had three vessel disease, as documented in all 10 patients by coronary angiography. In addition, exercise-induced ischemia was demonstrated by distinct reversible perfusion defects during thallium-201 scintigraphy (all 10 patients) and significant ST segment depression (5 patients) at a symptom-limited maximal work load of 108.0 ± 29.4 watts.

Study protocol (Fig. 1). All patients had simultaneous hemodynamic measurements and equilibrium radionuclide angiocardiography at rest and during exercise before medication (control period), immediately after 7.5 mg/kg of amiodarone infused intravenously over 5 minutes (short-term study) and after an average of 21.0 ± 4.3 days of oral amiodarone treatment (long-term study; one patient refused the second right heart catheterization, but had all other measurements performed). For oral treatment, patients initially received 800 mg/day of amiodarone over 10 days, followed by 400 mg/day over 7 days and 200 mg/day thereafter up to the long-term study. Amiodarone drug levels were measured immediately after the short- and long-term hemodynamic measurements (drug level determinations by high pressure liquid chromatography performed at the Clin-Midy Research Center, Montpellier, France). Intravenous thyrotropin-releasing hormone tests to assess variables of thyroid function (free thyroxin index, free triiodothyronine index, d-thyrotropin) were performed before any amiodarone administration and during long-term amiodarone therapy.

Figure 1. Study protocol showing the prestudy period (with discontinuation of antianginal therapy, clinical examination, exercise electrocardiogram, thallium-201 scintigraphy, coronary angiography and contrast ventriculography), as well as the three study periods, namely, control, acute and chronic, with corresponding dosages of amiodarone (AMIOD). CONC = concentration; I.V. = intravenously.



Hemodynamic measurements. For standard hemodynamic measurements and determination of cardiac output according to the Fick method, a flow-guided balloon catheter was placed in the pulmonary artery. Oxygen consumption for calculation of cardiac output was determined by a Hellige oximeter. Because all patients had normal arterial oxygen saturation at left heart catheterization, this measurement was assumed to remain unchanged for all further calculations (27). Pressures were recorded using Hewlett-Packard 1280 transducers with midchest as reference. All variables were analyzed by a dedicated Hewlett-Packard catheter computer system. Peripheral blood pressure was measured using a standard mercury sphygmomanometer; mean pressure was approximated as diastolic pressure plus one-third of the pulse pressure.

Equilibrium radionuclide data were accumulated at rest and continuously during exercise for calculation of left ventricular ejection fraction as previously described (28). Equilibrium radionuclide angiocardiography was performed after in-vivo red cell labeling with 25 mCi of technetium-99m. Imaging was accomplished in the modified left anterior oblique projection with a conventional scintillation camera equipped with a high sensitivity collimator. Global left ventricular ejection fraction was computed from composite time-activity curves from a 2 minute acquisition period at rest and at peak exercise using a special computer algorithm (MUGE, Medtronic MDS-A^2 computer system). Ejection fraction values determined by this technique have previously been shown to correlate well with those of biplane cineangiography and to be reproducible (28,29). End-diastolic volume was calculated by dividing hemodynamic stroke volume by radionuclide ejection fraction.

Exercise studies. All patients underwent supine bicycle exercise on an electronically braked Elema-Schönander ergometer (type EM 350), which maintained a constant work load for each patient during the entire exercise period over a pedal range of 45 to 70 rpm. The exercise level previously determined to produce anginal pain was used for all tests in each patient. The exercise electrocardiogram was not analyzed since only one lead was recorded for arrhythmia monitoring and to serve as a trigger signal for the gated radionuclide studies. We have previously shown that a similar protocol provided reproducible results (30,31).

Statistical analysis. All data are presented as mean values ± 1 standard deviation. Comparison of each treatment period with corresponding control measurements was per-

formed using the two-tailed *t* test for paired samples. For comparison of the three measurements at rest (control, short- and long-term), an analysis of variance was applied. Subgroups of patients with moderately depressed left ventricular function at rest as defined by an ejection fraction of less than 0.50 (three patients) or a cardiac index of less than 2.6 (five patients) were separately analyzed and compared with values in the remaining patients with normal left ventricular function. Finally, analysis of covariance was used for comparison of the three exercise periods after adjustment for changes at rest. A p value of less than 0.05 was considered statistically significant.

Results

Hemodynamic effects of amiodarone at rest. *Short-term effects. (Table 1, Fig. 2).* After intravenous administration of amiodarone, ejection fraction, stroke index and systolic blood pressure decreased, whereas heart rate, left and right ventricular filling pressures and systemic vascular resistance increased. This resulted in no significant changes in cardiac index, and end-diastolic volume index also remained virtually unchanged. Thus, a marked negative inotropic effect was noted acutely.

Long-term effects. These short-term changes were reversed after 3 weeks of amiodarone treatment. All measured values returned to control levels, except for heart rate which had decreased below and right atrial pressure which was still higher than values before treatment. The difference between short- and long-term hemodynamic effects as compared with control measurements is shown in Figure 3, indicating that the acute cardiodepression caused by amiodarone was almost completely reversed after chronic therapy.

A comparison of hemodynamic changes in subgroups of patients with normal versus moderately abnormal left ventricular function at rest revealed no statistically different

Table 1. Hemodynamic Results Before (control) and After Short- and Long-Term Amiodarone Therapy

		Short-Term Therapy		Long-Term Therapy		
	Control	Value	p Versus Control	Value	p Versus Short-Term	p Versus Control
HR (min^{-1})						
Rest	72.2 ± 11.0	77.9 ± 10.2	<0.01	66.7 ± 12.8	<0.01	<0.05
Ex	115.7 ± 18.8	113.5 ± 14.3	NS	104.9 ± 13.5	<0.01	<0.01
SBP (mm Hg)						
Rest	133.0 ± 14.4	127.5 ± 16.4	<0.05	137.5 ± 15.1	NS	NS
Ex	182.5 ± 23.4	170.5 ± 24.4	<0.01	181.5 ± 24.4	<0.05	NS
DBP (mm Hg)						
Rest	86.5 ± 7.5	89.5 ± 10.1	NS	88.0 ± 12.9	NS	NS
Ex	103.5 ± 5.8	95.5 ± 9.6	<0.05	94.5 ± 10.9	NS	<0.05
CI (liters/min·m^2)						
Rest	2.9 ± 0.6	2.5 ± 0.9	NS	3.0 ± 0.4	NS	NS
Ex	4.6 ± 0.9	4.2 ± 1.4	NS	4.9 ± 0.6	NS	NS
SI (ml/m^2)						
Rest	40.9 ± 11.2	33.2 ± 13.3	<0.01	47.3 ± 8.4	<0.05	NS
Ex	40.4 ± 10.1	38.0 ± 16.7	NS	47.7 ± 7.7	NS	<0.05
EF (%)						
Rest	54.1 ± 11.2	44.3 ± 10.3	<0.001	56.4 ± 13.4	<0.001	NS
Ex	44.2 ± 10.7	42.7 ± 11.6	NS	48.3 ± 12.9	<0.01	NS
SVR (dynes·s·cm^{-5})						
Rest	1,461 ± 343	1,704 ± 519	<0.05	1,373 ± 281	NS	NS
Ex	1,137 ± 210	1,194 ± 333	NS	974 ± 203	NS	<0.05
PCW (mm Hg)						
Rest	10.3 ± 2.8	13.9 ± 2.9	<0.001	12.1 ± 2.4	<0.05	NS
Ex	24.2 ± 6.8	27.7 ± 5.5	<0.05	26.7 ± 5.8	NS	NS
RAP (mm Hg)						
Rest	5.3 ± 1.6	7.5 ± 1.7	<0.001	7.0 ± 1.7	NS	<0.01
Ex	8.6 ± 2.4	9.6 ± 2.5	NS	11.0 ± 2.6	NS	<0.01
EDVI (ml/m^2)						
Rest	80.6 ± 33.8	81.8 ± 48.4	NS	88.3 ± 31.2	NS	NS
Ex	99.9 ± 48.5	101.0 ± 68.1	NS	109.0 ± 46.7	NS	NS

CI = cardiac index; DBP = diastolic blood pressure; EDVI = end-diastolic volume index; EF = ejection fraction; Ex = exercise; HR = heart rate; p = significance; PCW = pulmonary capillary wedge pressure; RAP = right atrial pressure; SBP = systolic blood pressure; SI = stroke index; SVR = systemic vascular resistance.

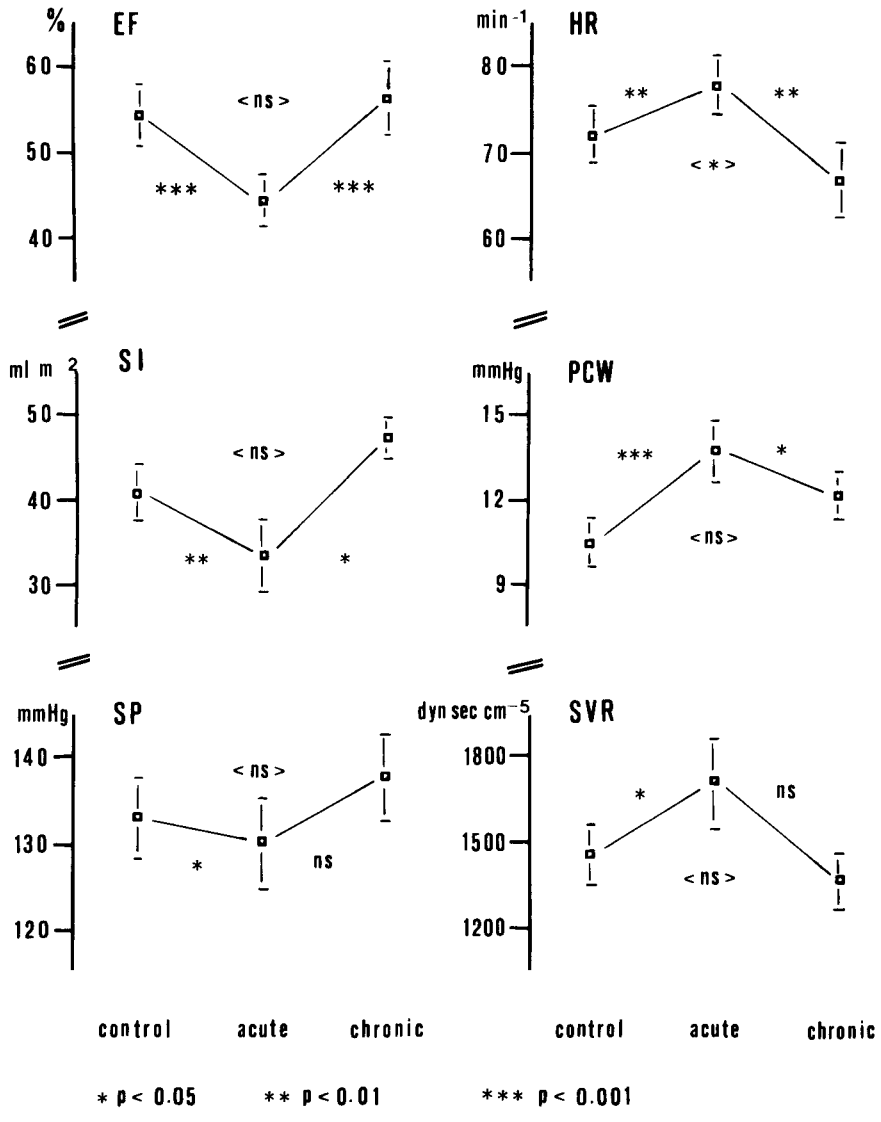


Figure 2. Hemodynamic effects of acute and chronic amiodarone administration at rest. EF = ejection fraction; HR = heart rate; PCW = pulmonary capillary wedge pressure; SI = stroke index; SP = systolic blood pressure; SVR = systemic vascular resistance.

behavior; that is, acute cardiodepressant effects and their reversion after long-term amiodarone therapy were similar in both subgroups. At the same time, amiodarone drug levels decreased from 4.8 ± 1.8 after intravenous infusion to 1.2 ± 0.6 mg/liter after long-term therapy ($p < 0.001$), whereas desethylamiodarone, the main metabolite, increased from a nondetectable level after infusion to 0.64 ± 0.17 mg/liter after long-term therapy in 9 of the 10 patients.

Hemodynamic effects of amiodarone during exercise. The directional changes induced by amiodarone on hemodynamic variables during exercise were similar to those observed at rest, but in general they were smaller (Table 1). After adjustment for these changes at rest, however, there was still a significant reduction in heart rate and mean systemic blood pressure (Fig. 4). Therefore, the rate-pressure product as an index of myocardial oxygen consumption improved significantly. It is important to note that after intravenous amiodarone infusion ischemia-induced left ventricular dysfunction, as indicated by decreased ejection fraction and increased left ventricular filling pressure, showed no further deterioration. After long-term therapy, exercise stroke index increased and vascular resistance decreased relative to control values.

Clinical and side effects. Amiodarone was well tolerated in all patients, although 6 of the 10 experienced a transient flush phenomenon of varying intensity during initial drug infusion. No rhythm disturbances were recorded. None of these patients with medically refractory angina became symptom-free after acute or chronic amiodarone therapy. Five patients reported an increased need for nitrates during the study period as compared with their previous drug regimen (mostly beta-receptor blocking drugs or calcium-channel antagonists, or both), although anginal pain was less severe subjectively in 8 of the 10 patients during the short-term exercise versus control study. Thyroid function remained normal in seven patients, whereas free thy-

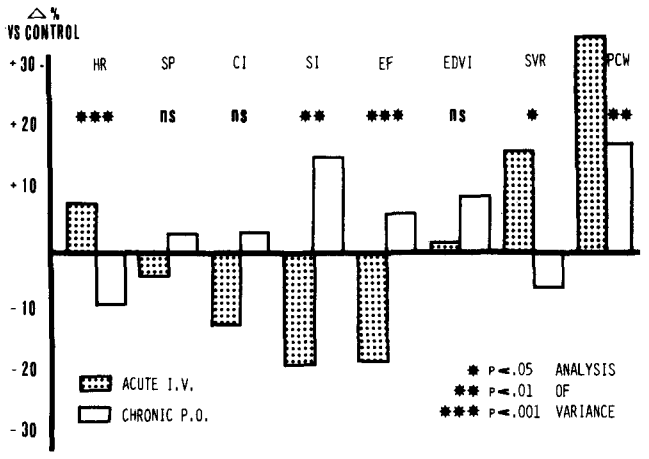


Figure 3. Hemodynamic effects of acute and chronic amiodarone therapy at rest compared with control values. Percent changes from control values (Δ%) are shown on the ordinate. CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; HR = heart rate; I.V. = intravenous; PCW = pulmonary capillary wedge pressure; P.O. = oral; SI = stroke index; SP = systolic blood pressure; SVR = systemic vascular resistance. Significance according to analysis of variance.

roxin index values increased to the borderline hyperthyroid range in three patients with normal intravenous triiodothyronine indexes (no hyperthyroidism).

Discussion

In this study, the hemodynamic profiles of amiodarone infused intravenously and administered orally over 3 weeks differed substantially in the same set of patients with chronic ischemic heart disease. Significant cardiodepression was the predominant mechanism in the short-term study, whereas negative chronotropic effects and afterload reduction prevailed with long-term treatment. These latter two mechanisms could also be shown to play a major role in the antianginal mode of action of amiodarone.

Acute hemodynamic effects of amiodarone. In previous short-term hemodynamic studies using a dose of 5 mg/kg, Ourback (20) and Bellotti (23) and their coworkers noted a similar decrease in cardiac index with an increase in systemic vascular resistance and left ventricular filling pressure. In contrast, Sicart (21) and Côté (22) and their coworkers observed an increase in heart rate and cardiac index and a decrease in systemic vascular resistance. Although these differing hemodynamic patterns during the initial minutes after bolus injection have been explained in part by the effects of the solvent (Tween 80), Sicart et al. (21) reported that the action of the solvent characterized by a decrease in aortic pressure and vascular resistance and an increase in heart rate lasted only up to 4 minutes after intravenous injection. Bellotti et al. (23), infusing amiodarone not dissolved in Tween 80, had results similar to ours when infusing amiodarone over 5 minutes. The negative inotropic effect was even more pronounced in our study, most likely because the higher dose (7.5 mg/kg) used probably masked any solvent effects. Such high doses are used clinically today (10), even though experimentally the reduction in contractility is hardly perceptible at doses up to 5 mg/kg but becomes significant at 10 mg/kg (21). The marked acute cardiodepressant effects most likely were responsible for the observed acute (reflex) increases in systemic vascular resistance and heart rate.

Figure 4. Effect of amiodarone (acute/chronic) on exercise-induced changes of hemodynamic variables vs. control after adjustment for drug-induced changes at rest (analysis of covariance). EX = exercise; MP = mean arterial pressure; other abbreviations as in Figure 2.

	HR	SP	MP	HR x SP	CI	SI	EF	EDVI	SVR	PCW
Δ REST-EX	↓	↓	↓	↓	=	=	=	=	=	=
VS CONTROL	*	*	***	***	NS	NS	NS	NS	NS	NS

* P < .05
*** P < .001
ANALYSIS OF COVARIANCE

It has recently been shown (32) that the negative inotropic effect of short-term amiodarone administration seems to be even more pronounced in patients with a severely depressed left ventricular ejection fraction (< 0.30). Even after slow drug infusions of 5 mg/kg over 20 minutes, overt heart failure and profound hypotension occurred in two of nine patients (32), and similar deleterious effects were observed by Benaim et al. (33). Therefore, such patients were not included in the present investigation. Analysis of subgroups of patients with moderately depressed left ventricular function in our study revealed similar cardiodepressant effects when compared with patients with normal ventricular function. Although well established standard hemodynamic methods have been used, minor methodologic limitations of this study may result from indirect measurement of systemic arterial pressure by inflatable cuff.

Chronic hemodynamic effects of amiodarone. After 24 hours of amiodarone infusion in patients with Chagas' disease, vascular resistance decreased relative to short-term measurements, and cardiac index returned to normal due to peripheral vasodilatory effects (23). These results are very similar to those observed after 3 weeks of oral amiodarone in our patients with ischemic heart disease. In addition, there was a decrease in heart rate at this time in both studies, probably as a result of sinus node depression (11,34,35). All other hemodynamic variables returned to control levels except for persistently elevated right ventricular filling pressures, suggesting a persistent minimal negative inotropic effect. This improvement in cardiac function was paralleled by a significant decrease in amiodarone drug levels, which remained well in the range accepted for chronic antiarrhythmic effectiveness (18,19,36), even though drug levels

of amiodarone and its metabolites may not truly reflect active tissue concentrations of this drug.

Effects of amiodarone on exercise-induced ischemia. During exercise-induced ischemia, amiodarone exerted its antianginal effects by significant reductions in heart rate and systolic blood pressure; that is, myocardial oxygen consumption improved as demonstrated by a slight increase in stroke index. In addition, previous studies have reported increases in coronary blood flow (22) and spasmolytic effects (37). Still, the improvement in ischemia-induced left ventricular dysfunction after amiodarone was not very impressive (either hemodynamically or clinically) and seemed smaller than that observed in similar studies with nitroglycerin, beta-adrenergic blocking drugs or nifedipine (30,31).

Side effects of amiodarone. Amiodarone was well tolerated except for an initial transient flush of variable intensity in a majority of patients. Side effects on thyroid function were not significant during the short observation period of this study. More severe side effects have been described (38–42) after longer amiodarone administration and with higher doses.

Implications. In view of the marked negative inotropic effect observed after a 5 minute intravenous infusion of 7.5 mg/kg of amiodarone, this study calls for cautious use of intravenous amiodarone, especially in patients with depressed left ventricular function. There is some evidence that this cardiodepressant action may be less important with smaller doses and at slower rates of infusion. In contrast, long-term use of amiodarone seems to be hemodynamically safe even in patients with moderately depressed left ventricular function. Besides its antiarrhythmic properties, amiodarone exerts a mild but significant antiischemic effect mainly by afterload reduction and improvement in myocardial oxygen consumption and may, therefore, be especially suitable for patients with chronic ischemic heart disease.

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