

Original Research

Amiodarone Attenuates the Proarrhythmic Effects of Dobutamine in Patients with Advanced Congestive Heart Failure

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Introduction: The long-term use of positive inotropic pharmaceuticals in patients suffering from end-stage congestive heart failure (CHF) has been associated with increased mortality, presumed to be due to proarrhythmia. Oral amiodarone combined with intermittent dobutamine infusions (IDI), on the other hand, has been shown to increase survival. This study evaluated the effects of oral amiodarone on the arrhythmias caused by dobutamine in patients with advanced CHF.

Methods: Thirty patients with CHF, in New York Heart Association functional class III or IV despite optimal medical therapy, were treated with weekly 8-h infusions of dobutamine 10 µg/kg/min. All patients were treated for ≥1 month with oral amiodarone, 400 mg/day, before initiation of IDI. A 24-h ambulatory electrocardiogram was recorded on the day before dobutamine infusion and repeated the next day, starting with the onset of infusion.

Results: The average heart rate on the 24-h ambulatory electrocardiogram was 72 ± 14 beats/min before vs. 72 ± 12 beats/min during IDI (p=1.000). Likewise, dobutamine did not increase the frequency of premature ventricular complexes (23 ± 32 per h before vs. 42 ± 69 per h during infusion, p=0.131), ventricular couplets (18 ± 36 per 24 h vs. 17 ± 28 per 24 h, p=0.859), or the incidence of non-sustained ventricular tachycardia (27% vs. 40%, p=0.383). No patient developed ventricular fibrillation or sustained ventricular tachycardia during or after IDI.

Conclusions: Chronic low-dose oral amiodarone attenuates the proarrhythmic effects of dobutamine, increasing the safety of ambulatory IDI.

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The attribution of congestive heart failure (CHF) to a primary defect of cardiac contractility has prompted the evaluation of positive inotropic agents to enhance myocardial performance. However, clinical experience with these agents has been disappointing with respect to long-term survival. When administered in the long term, inotropic therapy improved the clinical status of patients with CHF refractory to standard medical treatment, including angiotensin converting enzyme inhibitors, diuretics, digitalis and aldosterone,¹⁻⁴ though at the cost of a higher av-

erage mortality.⁵⁻⁸ Proarrhythmia has been held as an important contributor to this adverse effect. Increases in mortality observed with milrinone, flosequinan, vesnarinone, xamoterol and enoximone have been specifically attributed to a higher incidence of sudden death, presumed to be arrhythmic.^{6,7,9-11}

The proarrhythmic effects of dobutamine are supported by several observations. It increases the dispersion of action-potential duration in adjacent areas of ischemic and non-ischemic myocardium,¹² facilitates the induction of ventricular tachy-

cardia in experimental animals,¹³ and increases the incidence of ventricular arrhythmias (VT) in patients.¹⁴⁻¹⁹ We hypothesized that if amiodarone, a potent antiarrhythmic agent²⁰ with anti-adrenergic properties and minimal negative inotropic effects,²¹⁻²³ was added to dobutamine, it would attenuate the latter's proarrhythmic effects. A significant survival benefit conferred by intermittent dobutamine infusions (IDI) combined with oral amiodarone was observed in two previous controlled studies.^{24,25}

The aim of this study was to evaluate the effects of long-term oral amiodarone therapy on the arrhythmias induced by intravenous dobutamine in patients with advanced CHF.

Methods

Study population

The study population consisted of 30 consecutive patients with CHF refractory to optimal drug therapy, including digoxin, enalapril, spironolactone, and diuretics, who were successfully weaned from an initial 72-h infusion of dobutamine. All patients were either intolerant of treatment with metoprolol, 6.25 mg twice daily, or carvedilol, 3.125 mg twice daily, or beta-adrenergic blockade had been permanently discontinued at the time of the most recent episode of cardiac decompensation. The patients, who had not previously been treated with amiodarone, were placed on an oral regimen of 400 mg/day; recipients of implantable cardioverter-defibrillators received 800 mg/day. When hemodynamically stabilized, all patients underwent baseline clinical and laboratory evaluations, including echocardiography, radionuclide ventriculography, right heart catheterization and biochemical tests. They were then readmitted to the hospital for weekly 8-h IDI at a rate of 10 µg/kg/min. The first infusion began 2 to 4 weeks after the initial stabilization and continued for at least 6 months, regardless of the degree of clinical improvement, before weaning from inotropic therapy was attempted. In case of CHF exacerbation at any time during follow-up, episodes of paroxysmal nocturnal dyspnea in particular, the interval between IDI was shortened to <4 days, as necessary, until cardiac transplantation, if the patient was a candidate, or until death occurred.

Ambulatory monitoring

A 24-h ambulatory electrocardiogram (ECG) was recorded on the day before the first infusion of dobuta-

mine, and on the next day, starting at the onset of dobutamine infusion and continuing for 15 h past the completion of infusion.

All 24-h ambulatory ECG recordings were processed by a core laboratory unaware of the treatment. Leads V₁, V₅, and aVF were analyzed on a Zymed model 2010 scanner (Zymed Medical Instruments, Camarillo, CA, USA). Computer-assisted rate measurements and arrhythmia analyses were performed with verification and editing by a technician. Noise and artifacts were deleted, and cardiac arrhythmias were quantified. A physician reviewed all final analyses.

Non-sustained (NS) VT was defined as ≥3 consecutive premature ventricular complexes (PVC) terminating spontaneously within 30 s. VT was defined as sustained if lasting >30 s, or requiring earlier termination because of hemodynamic collapse. Ventricular fibrillation (VF) was defined as a disorganized rhythm without a distinct QRS complex. We measured the changes from baseline in 1) maximum, minimum and average heart rates; 2) mean number of PVC per hour; and 3) numbers of ventricular couplets and episodes of VT/VF per 24 h.

The Cardiac Arrhythmia Pilot Study (CAPS) criteria were applied to determine whether individual increases in the density of ventricular arrhythmias between baseline and treatment with dobutamine were proarrhythmic.²⁶ They included a ≥10-fold increase in PVC when baseline ectopy was 10 to 50 PVC/h, a ≥5-fold increase in PVC when ectopy at baseline was 51 to 100 PVC/h, a 4-fold increase in PVC when ectopy at baseline was 100 to 300 PVC/h, and a 3-fold increase in PVC when ectopy at baseline was ≥300 PVC/h. A ≥10-fold increase in runs of NSVT was also defined as proarrhythmic, regardless of the baseline frequency of episodes.

The Ethics Review Board of our institution approved this study, and all patients gave their informed consent to participate.

Statistical analyses

Categorical variables are presented as counts and percentages and continuous variables as mean ± standard deviation (SD). Student's paired t-test was used to examine changes among individual patients. P-values <0.05 were considered statistically significant.

Results

The study included 30 patients with advanced CHF despite optimal medical therapy. Their baseline demo-

graphic, clinical and hemodynamic characteristics are given in Table 1.

Ambulatory electrocardiogram analysis

Dobutamine had no apparent proarrhythmic effects, neither during infusion nor during the 16 h following its completion (Table 2). There was no significant difference in average, minimum and maximum heart rates between baseline and the infusion period. PVC were recorded at baseline in all patients, ranging in number between 1 /24 h and 136 /h. On the day of dobutamine infusion, 28 of the 30 patients (93%) had PVC, ranging in number between 8 /24 h and 607 /h. There was no significant difference in the average rate of PVC between the two recordings. Ventricular couplets were recorded in 21 of 30 patients at baseline (70%), ranging in number between 1 and 172 /24 h. On the day of dobutamine infusion, 18 of the 30 patients (60%) had ventricular couplets ranging in numbers between 1 /24 h and 95 /24 h. There was no significant difference in the

average rate of ventricular couplets between the two recordings. No patient developed sustained VT or VF. Of the 8 patients (27%) with episodes of NSVT observed on the baseline 24-h ambulatory ECG recording, 4 had NSVT on the 24-h ambulatory ECG that included the dobutamine infusion. Eight patients (27%) with no episodes of NSVT at baseline developed between 1 and 18 episodes of NSVT on the day of dobutamine infusion. There was no significant difference in the average rate of NSVT between the two recordings.

Using the CAPS criteria to define the clinically most significant ventricular arrhythmias, dobutamine was proarrhythmic in 4 patients (13%).

Patients with ischemic versus non-ischemic heart disease

When the 24-h ambulatory ECG recordings were analyzed according to the underlying heart disease, the dobutamine infusion did not change the heart rate or the frequency of ventricular arrhythmias either in patients with ischemic or in those with non-ischemic heart disease (Table 3). All patients who developed proarrhythmic effects according to the CAPS criteria suffered from idiopathic dilated cardiomyopathy.

Infusion versus post-infusion period

In a subgroup of 14 patients, the 24-h ambulatory ECG recordings were analyzed separately for the first 8 h, corresponding to the period of dobutamine infusion, and the next 16 h, corresponding to the post-infusion period. The average heart rate and the frequency of ventricular arrhythmias did not change from baseline either during dobutamine infusion or during the post-infusion period (Table 4).

Discussion

The present study used 24-h ambulatory ECG recordings to examine the effects of dobutamine on the heart rate and ventricular arrhythmias in patients with advanced CHF treated with long-term oral amiodarone. Dobutamine did not increase the heart rate or the frequency of ventricular arrhythmias, either during its infusion or in the post-infusion period.

Dobutamine is an inotropic pharmaceutical that improves the hemodynamic and clinical status of patients suffering from CHF refractory to standard treatment,¹⁻⁴ though at the cost of an adverse effect on survival.^{4,5,8} Proarrhythmia is considered to be an impor-

Table 1. Baseline demographic, clinical and hemodynamic characteristics of the 30 patients included in the study.

Characteristics	
Age, y	57 ± 13
Men/women, n	27/3
Ischemic/non-ischemic heart disease, n	15/15
Systolic blood pressure, mmHg	100 ± 15
Heart rate, beats/min	75 ± 20
Left ventricular end-diastolic diameter, mm	71 ± 6.9
Left ventricular end-systolic diameter, mm	58 ± 8.4
Left ventricular ejection fraction, %	22 ± 6
Mean right atrial pressure, mmHg	13 ± 6
Right ventricular systolic pressure, mmHg	58 ± 15
Mean pulmonary arterial pressure, mmHg	45 ± 10
Pulmonary capillary wedge pressure, mmHg	31 ± 6.4
Cardiac index, L/m ² /min	2.2 ± 0.6
Pulmonary vascular resistance, Wood units	3.7 ± 2.6
New York Heart Association functional class	3.8 ± 0.4
Serum creatinine	1.8 ± 1.1
Serum sodium	137 ± 6.9
Drug therapy, n (%) of patients:	
Enalapril	20 (66)
Spironolactone	11 (36)
Digoxin	12 (40)
Amiodarone	30 (100)
Furosemide, mg/day	340 ± 180

Unless otherwise indicated, values are expressed as mean ± SD.

Table 2. Results from 24-h ambulatory ECG at baseline and during dobutamine infusion.

	Baseline	Dobutamine infusion	p
Heart rate, beats/min:			
Maximum	99 ± 22	98 ± 20	0.852
Minimum	58 ± 12	57 ± 11	0.785
Average	72 ± 14	72 ± 12	1.000
Premature ventricular complexes per h, n	23 ± 32	42 ± 69	0.131
Ventricular couplets per 24 h, n	18 ± 36	17 ± 28	0.859
Non-sustained ventricular tachycardia per 24 h, n	0.8 ± 2	1.1 ± 3.3	0.656
Sustained ventricular tachycardia, n	0	0	1.000
Ventricular fibrillation, n	0	0	1.000

Values are mean ± SD.

Table 3. Results of 24-h ambulatory ECG at baseline and during dobutamine infusion in 15 patients with ischemic and 15 patients with non-ischemic heart disease.

	Ischemic disease (n=15)			Non-ischemic disease (n=15)		
	Baseline	Dobutamine	p	Baseline	Dobutamine	p
Heart rate, beats/min:						
Maximum	92 ± 19	93 ± 16	0.861	105 ± 26	103 ± 23	0.720
Minimum	54 ± 10	55 ± 9	0.522	61 ± 13	59 ± 12	0.506
Average	66 ± 10	67 ± 9	0.429	77 ± 14	75 ± 13	0.568
Premature ventricular complexes per h, n	20 ± 38	30 ± 49	0.253	26 ± 27	52 ± 83	0.241
Ventricular couplets per 24 h, n	21 ± 46	16 ± 26	0.680	15 ± 26	17 ± 30	0.721
Non-sustained ventricular tachycardia per 24 h, n	1.0 ± 2.7	0.07 ± 0.3	0.230	0.6 ± 1.2	2.0 ± 4.4	0.244

Values are mean ± SD.

Table 4. Ambulatory ECG findings from the day before dobutamine administration (Baseline) and the day of dobutamine administration (Dobutamine) in a subgroup of 14 patients. Results from the dobutamine administration period (0-8 hours) and the post-infusion period (9-24 hours) on the dobutamine day are compared with the corresponding time intervals on the baseline ECG.

	0-8 hours			9-24 hours		
	Baseline	Dobutamine	p	Baseline	Dobutamine	p
Average heart rate, beats/min	77 ± 14	77 ± 18	0.930	74 ± 16	64 ± 20	0.096
Premature ventricular complexes per h, n	23 ± 30	33.7 ± 37	0.288	35 ± 54	33 ± 62	0.952
Ventricular couplets per 24 h, n	12 ± 30	9.5 ± 20	0.809	1 ± 2	9 ± 19	0.156
Non-sustained VT per 24 h, n	0.8 ± 2	0.38 ± 0.9	0.475	1.5 ± 3	1.4 ± 4.1	0.961

VT – ventricular tachycardia.

tant contributor to this detrimental effect. Animal studies¹² and clinical trials¹³⁻²⁰ have suggested that dobutamine has a considerable proarrhythmic potential. The intravenous infusion of dobutamine in dogs with anterior myocardial infarction caused an increase in the inducibility of ventricular arrhythmias by programmed ventricular stimulation.¹² Furthermore, the ventricular refractory period was longer in dogs with inducible than in those without inducible arrhythmias.¹² In another

animal study dobutamine caused either lengthening or shortening of the action potential duration in the non-ischemic myocardial zones, and a homogeneous and significant shortening of the action potential duration in ischemic zones, resulting in significant dispersion of repolarization.¹³

These pre-clinical observations were confirmed in several studies of patients with CHF who received dobutamine, either in a chronic, intermittent manner,

or acutely for CHF decompensation. Vecchia et al reported a patient with chronic, severe CHF secondary to dilated cardiomyopathy, who developed QT prolongation and *torsades de pointes* VT during one cycle of intermittent low-dose dobutamine.¹⁶ David et al described 2 patients with refractory CHF, in whom low-dose dobutamine increased the density of complex ventricular arrhythmias significantly, including multifocal PVC and VT.¹⁴ Antiarrhythmic therapy suppressed the ventricular ectopy to baseline levels. An increased frequency of ventricular arrhythmias on 24-h ambulatory ECG by dobutamine, in patients with end stage CHF treated with IDI, was also reported by Tarján et al.¹⁸ The proarrhythmic effects of dobutamine subsided on the day after the infusion. Finally, Burger et al reported that dobutamine uniformly increased all forms of ventricular ectopy, compared to nesiritide, in patients with ischemic and non-ischemic heart disease and acutely decompensated CHF.¹⁹

We found, in a previous non-randomized study, that the addition of oral amiodarone to IDI increased the survival of patients with refractory CHF, compared with patients who did not receive amiodarone.²⁴ This observation was confirmed in a randomized double-blind placebo-controlled trial of 30 patients, where patients treated with dobutamine and amiodarone had a 60% reduction in the risk of death compared to the group treated with placebo and amiodarone.²⁵

In this study, all patients were treated with ≥ 400 mg/day of oral amiodarone for at least 1 month before the initiation of IDI. The 8-h dobutamine infusion did not cause significant changes in the 24-h ambulatory ECG measurements. The average heart rate remained unchanged during the infusion and the post-infusion period. This might be important, since heart rate is a major determinant of myocardial oxygen demand, and an increase in the latter in the context of advanced CHF, particularly in the presence of ischemic heart disease, can worsen the clinical status. The frequency of PVC, couplets and NSVT was also unchanged. The development of, or an increase in, ventricular ectopy and VT might also decrease stroke volume significantly, causing decompensation of CHF, and increase the likelihood of VF and death. Amiodarone attenuated the expected aggravation of ventricular arrhythmias by dobutamine, creating a safer environment for the administration of the inotrope.

The protective effects of amiodarone were expressed similarly in patients with ischemic and non-ischemic heart disease. This is particularly important, since inotropic therapy has been shown to be more harmful in

patients with ischemic disease;²⁷ antiarrhythmic protection might be particularly relevant for this subgroup of patients.

Despite our encouraging results, it is noteworthy that 4 patients met the CAPS criteria for proarrhythmia. While none of them developed sustained VT or VF, these patients might remain at risk of life-threatening arrhythmias during further dobutamine infusions. Meticulous avoidance of other factors that might also precipitate arrhythmias, such as electrolyte imbalance, probably in combination with higher amiodarone doses, might further increase the safety of dobutamine for these patients.

The precise mechanisms by which dobutamine increases the risk of arrhythmias are not clear, although prolongation of the ventricular refractory period^{13,16} and inhomogeneous repolarization¹² have been suggested. Amiodarone, by homogeneously increasing repolarization,²⁸ might attenuate the increase in dispersion of repolarization caused by dobutamine,¹² decreasing the likelihood of reentrant tachycardia. Furthermore, the prevention of rate acceleration by the antiadrenergic activity²⁹ and intrinsic sympatholytic activity³⁰ of amiodarone might prevent potential adverse effects on myocardial oxygen balance and consequent electrical instability, particularly in patients presenting with ischemic heart disease.³¹

Limitations of the study

The most important limitation of the present study is its uncontrolled design. This, along with the spontaneous variability of ventricular ectopy³² in the setting of end stage CHF might have introduced biases. However, the patients served as their own controls, and several reports have already documented the proarrhythmic effects of dobutamine in patients suffering from CHF who are not treated with amiodarone.

In conclusion, our observations suggest that the addition of oral amiodarone to the infusion of dobutamine in patients presenting with CHF refractory to standard treatment attenuates the proarrhythmic effects of dobutamine.

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