# Dobutamine effects on spontaneous variability of ventricular arrhythmias in patients with severe chronic heart failure: the Italian Multicenter Study

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*Key words:*
**Arrhythmias, ventricular; Chronic heart failure; Dobutamine.**

*Background.* **Dobutamina Studio Italiano Multicentrico (Do.S.I.M.) is a prospective, randomized, multicenter interuniversity Italian study aimed at assessing the effects of dobutamine on spontaneous variability of ventricular arrhythmias in sinus rhythm NYHA class III-IV patients with congestive heart failure (CHF).**

*Methods.* **Out of 74 *pre-hoc* estimated CHF patients, 68 (92%) were randomized electively to either being washed out of all active drugs except diuretics (group A) or to continue with the standard regimen including digitalis, diuretics and ACE-inhibitors (group B, standard therapy). In 63 patients, complete Holter data were obtained and are reported here. After 72 hours, in both groups, 48-hour Holter monitoring (Holter 1) was performed. The spontaneous variability of ventricular arrhythmias was assessed by calculating the natural logarithm of the sum of hourly incidences (during 48 consecutive hours) of index events such as the mean heart rate or the various forms of total and either sustained or non-sustained ventricular arrhythmias. The results were then grouped for the first and second 24-hour Holter periods. All patients were submitted to 10 µg/kg/min infusion of dobutamine for 72 hours and 48-hour Holter monitoring (Holter 2) was repeated 24 hours before the end of dobutamine infusion. The incidence of arrhythmia and the distribution of laboratory and echocardiographic variables was also studied in group A and B patients. The data of the two groups along with the intrapatient ± 95% confidence intervals were pooled, both on and off dobutamine.**

*Results.* **There was no significant difference between Holter 1 and Holter 2 in the rates of index events in 63 patients with regard to pro-arrhythmic effects. Pro-arrhythmic effects were seen during dobutamine infusion in 21% of cases, an effect which subsided (to 5%) when dobutamine was discontinued. Interestingly, the positive inotropic effects of dobutamine (based on ejection fraction changes) were parallel (22%) to the pro-arrhythmic changes, although they persisted long after dobutamine discontinuation (18%). The pro-arrhythmic effects of dobutamine, both during (5%) as well as after (1%) drug infusion, were unrelated to heart rate changes. The prevalence and incidence of non-sustained ventricular tachycardia due to dobutamine were 47 and 29% respectively.**

*Conclusions.* **In sinus rhythm patients with severe CHF, dobutamine had chronotropic effects and increased a depressed ejection fraction without significantly increasing arrhythmogenicity.**

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## Introduction

The depression of contractile function in established congestive heart failure (CHF) has been documented in various studies[1-3]. Therefore, especially patients with severe CHF often become dependent on intravenous inotropic agents such as dobutamine, necessitating prolonged intensive care unit stay[4]. Dobutamine is a synthetic catecholamine that possesses predominantly $\beta_1$-receptor agonist properties and has a very short half-life (2 min)[5]. Although dobutamine is used as inotropic therapy for CHF, it has been shown that it also causes arrhythmias and tachycardia and increases the risk of ischemia[6-11]. These conclusions were valid in the mid 90's when data on the effectiveness of ACE-inhibitors were accumulating and before the advantages offered by β-receptor antagonists were proved in patients with CHF[4].

The aim of this study was to assess the effects of dobutamine on the spontaneous variability of various forms of ventricular arrhythmias in sinus rhythm NYHA class III-IV patients with CHF. A second aim was to estimate the incidence of arrhythmia in these patients, as this has rarely been per-

formed with appropriate and precise methods[12]. The study lasted between October 1990 and September 1992 and 6 Italian University Centers participated. Preliminary results were presented in abstract form in September 1993[13]. Yet, formal submission of the study results was never performed as the investigators and the Coordinating Center felt that the study had been stopped, on consensus, when its power was such that the accepted β error might have been seen as high. Since during the following decade, no further data on the specific study aims have been presented, we felt that the accumulated evidence may still be of interest and decided to publish this article. In fact, inotropic therapy, despite several negative results in long-term studies, remains the only option for an increasing number of acute patients and dobutamine has to be compared, even on a cost-effectiveness basis, with the new active drugs that have been developed in the last years[14,15].

## Methods

**Patients.** Out of 74 *pre-hoc* literature-estimated patients (see later for sample size calculation and its consequences) with sinus rhythm and NYHA class III-IV CHF, 68 (92%) (basal two-dimensional echocardiographic ejection fraction 27 ± 10%) were electively randomized (using unidentified envelopes previously sent from the Coordinating Center and sorted on the basis of a balanced randomization scheme) to either being washed out of all active drugs except diuretics (group A) or to continue with a standard regimen with digitalis, diuretics and ACE-inhibitors (group B, standard therapy). In each Center, the dosages of the active drugs were the responsibility of the treating physicians. No patient was treated with amiodarone or β-receptor antagonists.

In 63 patients (93% of the included and 85% of the *pre-hoc* estimated patients respectively), complete 96-hour Holter data were obtained and are reported here. There were 28 patients with dilated cardiomyopathy, 30 with ischemic cardiomyopathy (4 of whom with previous myocardial infarction), 3 patients with hypertensive cardiomyopathy (with mitral insufficiency), 1 patient with cardiomyopathy of uncertain origin, and 1 patient with aortic insufficiency. The etiology distribution did not differ between the patients randomized in group A and B. Among the participating Centers, 6 randomized more than 9 patients and 2 more than 14 patients. The overall inclusion adherence (randomized/randomizable patients) was met in 67% of the participating Centers. The total inclusion time of the randomized patients was 23 months.

**Holter monitoring.** In both groups, 48-hour Holter monitoring (Holter 1-$H_1$) was performed 72 hours following randomization (Fig. 1). The spontaneous variability of ventricular arrhythmias was assessed by calculating[12] the natural logarithm of the sum of hourly incidences (during 48 consecutive hours) of index events such as the mean heart rate or the various forms of total and either sustained or non-sustained ventricular arrhythmias. The results were then grouped for the first and second 24-hour Holter periods ($H1_A$ vs $H1_B$). The resulting values were treated as continuous variables (conventional t statistics), plotted for each patient and were used to assess the ± 95% confidence intervals. The natural logarithm of index events per hour, to allude just to the case of premature ventricular contractions (PVCs) is obtained using the formula: ln (PVCs/hr + 1). By this transformation the variability among patients is reduced, and the skewness in the distribution of PVCs per hour both among and within patients is eliminated. One is added to the PVC rate so

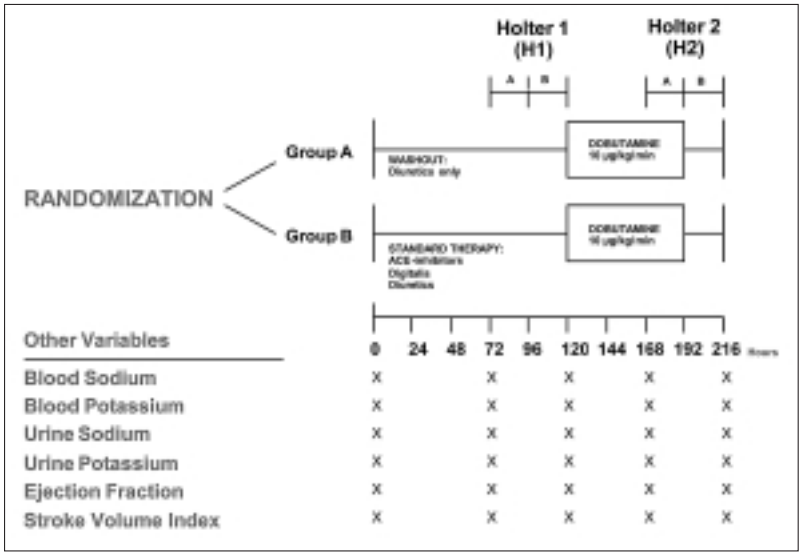


**Figure 1.** *Study protocol.*

that the logarithm is defined even in the event of a "zero" response rate. These transformations were made for all index events, including the laboratory and echocardiographic variables.

**Dobutamine infusion.** All patients were submitted to 10 μg/kg/min infusion of dobutamine for 72 hours and 48-hour Holter monitoring (Holter 2-$H_2$) was repeated 24 hours before the end of dobutamine infusion. The hourly incidences of arrhythmias ($H_{2A}$ vs $H_{2B}$) were assessed, as described above, on and off dobutamine. In spite of the fact that the patients had advanced CHF, the dose of dobutamine was selected bearing in mind that the aim of the study was to investigate arrhythmogenicity. It was felt that < 5 μg/kg/min was a low dose and that > 20 μg/kg/min was a very high dose[5]. The short half-life of the drug was estimated to enable representation of the off-dobutamine status during the $H_{2B}$ period.

**Other variables measured.** Figure 1 shows that at 0, 72, 120, 168, and 216 hours after randomization, both blood and urine sodium and potassium levels were measured. At the same times, ejection fraction and stroke volume index were measured at two-dimensional echocardiography. Hemodynamic variables were monitored as part of the routine clinical assessment of the patients but the data were not analyzed.

**Statistical analysis.** *Sample size.* The study size was calculated on the basis of the literature prevalence (20-48%) data of non-sustained ventricular tachycardia[16-19]. This arrhythmia was diagnosed on the Holter records as a run of > 3 and < 10 successive ventricular extrasystoles at a rate of ≥ 130 b/min. For sample size calculations, the conservative figure of a 20% prevalence of non-sustained ventricular tachycardia was selected. This means that at baseline it was estimated that 20 out of 100 NYHA class III-IV sinus rhythm patients with CHF may present with non-sustained ventricular tachycardia.

*Hypothesis.* The null hypothesis of dobutamine-increased arrhythmogenicity was based on a 30% (absolute) incidence of non-sustained ventricular tachycardia. This means that in the present investigation the arrhythmogenicity of dobutamine may have been concluded after at least 50 out of 100 patients were found to have non-sustained ventricular tachycardia while on the drug. It is necessary to point out that at the time of the protocol design there were no data published on this important aspect. Therefore, a "guess" was obtained by the consensus of the study investigators.

*Statistical considerations.* Using the above-mentioned figures for the prevalence (20%) and incidence (30%) of non-sustained ventricular tachycardia (the target to decide on drug-induced arrhythmogenicity), at a conventional 5% α-error (z = 1.96) and 10% β-error (z = 1.28), 37 patients per group (therefore n = 74) were required to test the hypothesis with a high power (1-β). Accordingly, the investigators accepted to run the study and to schedule up to 74 patients in this trial.

To further refine the analysis of the incidence of arrhythmia and the distribution of other laboratory and echocardiographic variables on the basis of intrapatient confidence intervals which take into account the spontaneous variability of the incidence of arrhythmia, we also adopted the resulting rates of the ± 95% confidence interval to judge either the anti- or the pro-arrhythmic effects of dobutamine. The SAS forecasting interval method was used to assess the intrapatient distribution of the observed (based on $H_2$) vs the expected spontaneous variability of both heart rate and ventricular arrhythmias (based on $H_1$), both on and off dobutamine. This method is based on linear regression and on the 95% confidence interval and assesses how much the observed incidence deviates from the expected incidence of index events in each patient. Among several other theoretical advantages, this method also includes multiple comparisons performed intraindividually while positioning deviations in the fluctuation of confidence. This method, however, requires complete data and it may therefore be applied on a smaller group (n = 63) than the one (n = 67) where classical t tests were performed on continuous variables. Statistical differences were considered as significant at the level of $p < 0.05$.

## Results

The clinical characteristics and absolute basal values of the study variables of all the patients enrolled and having analyzable data (n = 67) are shown in table I. There were no differences between group A and B patients in these parameters.

In table II, one-sample t-test statistics are shown on the absolute variable-differences subdivided according to the presence of dobutamine and patient groups. This table presents the core evidence of the study in 67 patients. All index variables (based on Holter monitoring and on laboratory and echocardiographic data) were assessed by hourly incidences and treated as natural logarithms. The grouped data are reported as the absolute differences between the Holter periods (first period minus second period) first at baseline, thus assessing spontaneous variability (absent-absent: $H_{1A}$-$H_{1B}$), second evaluating the presence of dobutamine (absent-on: $H_{1A}$-$H_{2A}$); and third the off-dobutamine status (absent-off: $H_{1A}$-$H_{2B}$). This analysis was undertaken separately between groups A and B and then with the two groups pooled. Whereas t statistics denote each variable's significance according to the period difference considered, T denotes between-group differences.

There was a wide overlap of significant differences between periods in both groups A and B. This is reflect-

**Table I.** Clinical characteristics and absolute basal values of the study variables. None are statistically different.

| | Group A (n=33) | Group B (n=34) |
|---|---|---|
| Clinical characteristics | | |
| Age (years) | 64 ± 9 | 63 ± 10 |
| Sex (M/F) | 24/9 | 18/16 |
| NYHA class | 3.55 ± 0.51 | 3.44 ± 0.50 |
| Total of liquid infused during 72 hours (ml) | 983 ± 639 | 876 ± 422 |
| Clinical tolerance of dobutamine infusion (%) | 88 | 94 |
| Dosage modification (%) | 21 | 29 |
| Holter monitoring variables (Holter 1) (ln [Σ hour-incidences]) | | |
| Heart rate | 6.14 ± 1.60 | 6.06 ± 1.62 |
| Total ventricular arrhythmias | 6.15 ± 2.02 | 6.14 ± 2.27 |
| Non-sustained ventricular tachycardia | 0.67 ± 1.03 | 0.98 ± 1.37 |
| Sustained ventricular tachycardia | 0.10 ± 0.44 | 0.24 ± 0.79 |
| Coupled ventricular arrhythmias | 2.59 ± 1.87 | 2.57 ± 2.50 |
| Single ventricular arrhythmias | 6.29 ± 1.83 | 6.08 ± 2.21 |
| Laboratory variables (mEq/l) | | |
| Blood sodium | 138 ± 5 | 140 ± 4 |
| Urine sodium | 81 ± 62 | 96 ± 54 |
| Blood potassium | 4.29 ± 0.58 | 4.43 ± 0.56 |
| Urine potassium | 33 ± 17 | 34 ± 16 |
| Echocardiographic variables | | |
| Ejection fraction (%) | 29 ± 10 | 27 ± 10 |
| Stroke volume index (ml/m$^2$) | 103 ± 50 | 108 ± 48 |

ed by significant t values in the pooled groups, meaning that the specific index variable had a different incidence in the considered periods. However, when taking into account t statistics between groups A and B, only non-sustained ventricular tachycardia (respectively absent-on and absent-off) and urine sodium (absent-off) were significantly different. These data may be interpreted as showing a significant group difference (A vs B) with non-sustained ventricular tachycardia increasing significantly during dobutamine infusion in group A vs a relative decrease in group B, a difference that was maintained even when dobutamine was off. In the latter period there also was an increase of urine sodium in group A which instead was decreased in group B, a difference which is statistically significant. On the other hand, the pooled data show that when dobutamine was on, the total, coupled and single ventricular arrhythmias did increase as did ejection fraction and heart rate, but arrhythmogenicity (as judged by the design on non-sustained ventricular tachycardia) did not significantly vary.

Table III shows the global ($H_2$ vs $H_1$) rates (%) of index events in 63 patients in whom complete Holter monitoring data were obtained divided according to either a) no change (remaining inside the intrapatient confidence intervals of spontaneous variability); b) showing a downward deviation from the 95% confidence interval, meaning that an antiarrhythmic effect was achieved; and c) showing an upward deviation from the 95% confidence interval, meaning that a pro-arrhythmic effect was observed. When the analysis is applied to heart rate or ejection fraction, the interpretation relates to chronotropism and inotropism respectively. Since these data represent a complete 96-hour Holter assessment they are particularly important as a statistical response to the study question. At univariate analysis, there was no difference between group A and B patients in the rates of the index events considered (data not shown). Therefore, logistic regression was used to further define, in the overall population of 63 patients, the predictive covariates of either the positive inotropic or chronotropic effects of dobutamine but none were significantly related. In particular, the covariate defining groups (A vs B) was unrelated to any index event considered in the present investigation (results not shown). Interestingly, when dobutamine was on, there was a parallel increase in non-sustained ventricular tachycardia and ejection fraction (Table III, column C) whereas when dobutamine was discontinued the rate of non-sustained ventricular tachycardia fell down much more than that of ejection fraction (Table III, column C).

Table IV shows the results of classical analysis of data based on the predicted and observed rates of the index event non-sustained ventricular tachycardia, comparing the estimation based on the literature data at the time of the protocol design, and the observed rates in the present study. It is evident that the prevalence was much higher than estimated *pre-hoc*, thus implicating that a larger number of patients per group had to be included (62 vs 37) if the β-error had to be 10%. However, the investigators believed it was unethical to continue patient inclusion for a period of at least another 24 months, as calculated on the basis of the trial experience at *interim* analysis (n = 68). They also

**Table II.** One-sample t-test statistics on absolute variable differences divided according to dobutamine presence and patient groups.

| | Group A | | | T | Group B | | | Pooled groups | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | DF | t | | Mean ± SD | DF | t | Mean ± SD | DF | t |
| Holter monitoring variables (ln [Σ hour-incidences]) | | | | | | | | | | |
| Heart rate | | | | | | | | | | |
| Absent-absent | -0.07 ± 0.29 | 32 | -1.39 | -1.30 | -0.003 ± 0.06 | 33 | -0.30 | -0.04 ± 0.21 | 66 | -1.41 |
| Absent-on | -0.12 ± 0.12 | 28 | -5.48 | 0.84 | -0.16 ± 0.25 | 31 | -3.65 | -0.14 ± 0.20 | 60 | -5.58 |
| Absent-off | -0.16 ± 0.60 | 28 | -1.49 | -1.47 | 0.11 ± 0.85 | 31 | 0.72 | -0.02 ± 0.74 | 60 | -0.23 |
| Total ventricular arrhythmias | | | | | | | | | | |
| Absent-absent | -0.09 ± 0.90 | 32 | -0.60 | -1.19 | 0.14 ± 0.71 | 33 | 1.16 | 0.03 ± 0.81 | 66 | 0.26 |
| Absent-on | -0.73 ± 1.41 | 29 | -2.83 | -0.93 | -0.42 ± 1.16 | 31 | -2.05 | -0.57 ± 1.28 | 61 | -3.49 |
| Absent-off | -0.33 ± 1.67 | 29 | -1.10 | -1.66 | 0.26 ± 1.05 | 31 | 1.39 | -0.03 ± 1.40 | 61 | -0.16 |
| Non-sustained ventricular tachycardia | | | | | | | | | | |
| Absent-absent | -0.02 ± 0.41 | 32 | -0.29 | -0.05 | -0.01 ± 0.88 | 33 | -0.08 | -0.02 ± 0.69 | 66 | -0.20 |
| Absent-on | -0.68 ± 1.55 | 29 | -2.40 | -1.98 | 0.06 ± 1.36 | 31 | 0.23 | -0.30 ± 1.49 | 61 | -1.59 |
| Absent-off | -0.20 ± 0.91 | 29 | -1.18 | -2.24 | 0.37 ± 1.08 | 31 | 1.95 | 0.10 ± 1.03 | 61 | 0.74 |
| Sustained ventricular tachycardia | | | | | | | | | | |
| Absent-absent | -0.03 ± 0.28 | 32 | -0.60 | -1.52 | 0.06 ± 0.18 | 33 | 1.91 | 0.02 ± 0.24 | 66 | 0.52 |
| Absent-on | 0.06 ± 0.47 | 29 | 0.69 | 0.51 | -0.008 ± 0.57 | 31 | -0.08 | 0.02 ± 0.52 | 61 | 0.37 |
| Absent-off | 0.01 ± 0.51 | 29 | 0.15 | -0.02 | 0.02 ± 0.43 | 31 | 0.22 | 0.02 ± 0.47 | 61 | 0.26 |
| Coupled ventricular arrhythmias | | | | | | | | | | |
| Absent-absent | -0.16 ± 1.69 | 32 | -0.53 | -0.38 | -0.005 ± 1.56 | 33 | -0.02 | -0.08 ± 1.62 | 66 | -0.41 |
| Absent-on | -0.76 ± 1.62 | 29 | -2.57 | -0.91 | -0.44 ± 1.08 | 31 | -2.30 | -0.60 ± 1.37 | 61 | -3.43 |
| Absent-off | -0.13 ± 2.02 | 29 | -0.35 | -0.96 | 0.29 ± 1.38 | 31 | 1.21 | 0.09 ± 1.72 | 61 | 0.41 |
| Single ventricular arrhythmias | | | | | | | | | | |
| Absent-absent | 0.10 ± 1.53 | 32 | 0.37 | -0.50 | 0.24 ± 0.68 | 33 | 2.08 | 0.17 ± 1.17 | 66 | 1.19 |
| Absent-on | -0.47 ± 1.98 | 29 | -1.30 | -0.23 | -0.37 ± 1.19 | 31 | -1.78 | -0.42 ± 1.61 | 61 | -2.06 |
| Absent-off | -0.12 ± 2.17 | 29 | -0.29 | -0.95 | 0.34 ± 1.58 | 31 | 1.23 | 0.12 ± 1.88 | 61 | 0.51 |
| Laboratory variables (mEq/l) | | | | | | | | | | |
| Blood sodium | | | | | | | | | | |
| Absent-absent | 1.39 ± 3.86 | 32 | 2.08 | -0.38 | 0.09 ± 3.09 | 33 | 0.17 | -0.09 ± 3.84 | 66 | -0.19 |
| Absent-on | -1.53 ± 5.39 | 29 | -1.56 | -1.63 | 0.33 ± 3.35 | 32 | 0.57 | -0.56 ± 4.50 | 62 | -0.98 |
| Absent-off | -1.17 ± 5.59 | 29 | -1.14 | -1.87 | 1.06 ± 3.53 | 32 | 1.73 | 0.000 ± 4.72 | 62 | 0.00 |
| Urine sodium | | | | | | | | | | |
| Absent-absent | -5.12 ± 19.30 | 32 | -1.52 | -0.89 | 9.97 ± 29.05 | 33 | 2.00 | 6.12 ± 35.54 | 66 | 1.41 |
| Absent-on | -10.87 ± 51.27 | 29 | -1.16 | -1.31 | 4.79 ± 42.70 | 32 | 0.64 | -2.67 ± 47.26 | 62 | -0.45 |
| Absent-off | -5.57 ± 49.28 | 29 | -0.64 | -2.00 | 16.58 ± 38.25 | 32 | 2.49 | 5.94 ± 44.92 | 62 | 1.05 |
| Blood potassium | | | | | | | | | | |
| Absent-absent | 0.003 ± 0.43 | 32 | 0.04 | 0.43 | -0.04 ± 0.47 | 33 | -0.55 | -0.02 ± 0.45 | 66 | -0.38 |
| Absent-on | 0.07 ± 0.57 | 29 | 0.64 | -0.35 | 0.12 ± 0.52 | 32 | 1.28 | 0.09 ± 0.54 | 62 | 1.35 |
| Absent-off | 0.04 ± 0.66 | 29 | 0.30 | 1.09 | -0.14 ± 0.59 | 32 | -1.32 | -0.05 ± 0.63 | 62 | -0.68 |

(*continues Table II*)

(*continued Table II*)

| | Group A | | | T | Group B | | | Pooled groups | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | DF | t | | Mean ± SD | DF | t | Mean ± SD | DF | t |
| Urine potassium | | | | | | | | | | |
| Absent-absent | -1.36 ± 16.13 | 32 | -0.49 | -0.51 | 0.41 ± 11.87 | 33 | 0.20 | -0.46 ± 14.05 | 66 | -0.27 |
| Absent-on | -2.67 ± 17.08 | 29 | -0.86 | -1.19 | 2.42 ± 16.78 | 32 | -1.19 | 0.000 ± 19.98 | 62 | 0.00 |
| Absent-off | -6.07 ± 17.13 | 29 | -1.94 | -0.62 | -3.06 ± 21.38 | 32 | -0.82 | -4.49 ± 1.38 | 62 | -1.84 |
| Echocardiographic variables | | | | | | | | | | |
| Ejection fraction (%) | | | | | | | | | | |
| Absent-absent | 0.12 ± 4.75 | 32 | 0.15 | 1.59 | -2.26 ± 5.07 | 33 | -2.61 | -1.19 ± 5.65 | 66 | -1.73 |
| Absent-on | -4.14 ± 8.82 | 28 | -2.53 | 0.59 | -5.30 ± 6.25 | 32 | -4.88 | -4.76 ± 7.52 | 61 | -4.98 |
| Absent-off | -2.03 ± 6.44 | 29 | -1.73 | 0.81 | -3.18 ± 4.61 | 32 | -3.97 | -2.63 ± 5.54 | 62 | -3.78 |
| Stroke volume index (ml/m$^2$) | | | | | | | | | | |
| Absent-absent | 4.18 ± 15.14 | 32 | 1.59 | 0.17 | 3.62 ± 11.58 | 33 | 1.82 | 3.90 ± 13.35 | 66 | 2.39 |
| Absent-on | 13.97 ± 20.62 | 28 | 3.65 | 1.75 | 5.70 ± 15.86 | 32 | 2.06 | 9.56 ± 18.56 | 61 | 4.06 |
| Absent-off | 18.84 ± 3.44 | 29 | 1.21 | 0.20 | 3.39 ± 10.59 | 32 | 1.84 | 3.76 ± 14.97 | 62 | 1.99 |

DF = degrees of freedom; T = between-group t statistics (separate variance). Subgrouping of the variables referring to dobutamine (first Holter period minus second Holter period): Absent-absent ($H1_A$-$H1_B$); Absent-on ($H1_A$-$H2_A$); Absent-off ($H1_A$-$H2_B$); $t > |1.98|$ $p < 0.05$.

considered the slightly lower than expected incidence of non-sustained ventricular tachycardia during the trial and they carefully evaluated the possibility (based on the figures shown in table IV) of accepting a larger (33%) β-error *post-hoc*. It was in fact felt that the analysis based on the spontaneous variability of arrhythmias as illustrated in tables II and III, was in line with that position.

## Discussion

Growing evidence suggests that secondary neurohumoral changes characterized by activation of the adrenergic and renin-angiotensin-aldosterone systems have a key role in the progression and perpetuation of heart failure[18]. Regardless of the cellular and biochemical mechanisms of the decreased inotropic state, decreased contractility is associated with an impaired left ventricular pump function and hemodynamic abnormalities of heart failure. The rationale for inotropic therapy is to improve pump function by increasing contractility[19]. Activation of the sympathetic nervous system increases cardiac output through activation of β- and α-adrenoceptors. Human myocardium is known to express both subtypes of β-adrenoceptors ($\beta_1$ and $\beta_2$) which both couple to the adenylate cyclase pathway to increase contractility[20].

Although the clinical utility of short-term intravenous positive inotropic therapy, including dobutamine, in the management of acute heart failure is well established, its benefits may be offset by the risk of new or worsened ventricular arrhythmias[21-24]. Dobutamine has marked $\beta_1$-receptor agonist, modest $\beta_2$-receptor agonist and weak α-receptor agonist activities[5]. The main mechanism by which dobutamine increases inotropism is by activation of $\beta_1$-receptors. Dobutamine also has systemic vascular effects but these effects are small compared to those of norepinephrine, isoprenaline and dopamine[25]. In patients with heart failure, dobutamine[5] improves systemic hemodynamics through various mechanisms, including a decreased left ventricular afterload and ventriculo-arterial coupling. The mean arterial pressure generally remains unchanged. However, long-term dobutamine therapy is limited by the development of tolerance, manifesting as soon as 3 days after the beginning of infusion[26]. For this reason, dobutamine should be administered intermittently[27,28]. Moreover, with larger doses (> 20 μg/kg/min) of dobutamine, tachycardia may also develop and myocardial oxygen demand may increase due to increased heart rate and contractility[5]. Packer[29] reported that therapy with β-adrenergic agonists is a double-edged sword: long-term therapy with β-receptor agonists may produce clinical benefits by improving left ventricular systolic and diastolic function but may also provoke ventricular arrhythmias by a direct effect on the heart or by inducing hypokalemia.

**Table III.** The global (Holter 2 vs Holter 1) rates (%) of index events in 63 patients in whom complete Holter monitoring data were obtained divided according to either a) no change (remaining inside the intrapatient confidence interval of spontaneous variability), b) showing a downward deviation from the 95% confidence interval, and c) showing an upward deviation from the 95% confidence interval.

| | Dobutamine on | | | Dobutamine off | | |
|---|---|---|---|---|---|---|
| | a | b | c | a | b | c |
| Heart rate | 3 | 92 | 5 | 5 | 94 | 1 |
| Total ventricular arrhythmias | 2 | 84 | 14 | 8 | 83 | 9 |
| Non-sustained ventricular tachycardia | 6 | 73 | 21 | 6 | 89 | 5 |
| Ejection fraction | 5 | 73 | 22 | 3 | 79 | 18 |

See "Statistical considerations" section for details of interpretation.

**Table IV.** The results of classical analysis of data based on the predicted and observed rates of the interest event non-sustained ventricular tachycardia, comparing the estimation based on the literature data at the time of the protocol design and the observed rates in the Do.S.I.M. study.

| | Literature-based | Observed in Do.S.I.M. |
|---|---|---|
| Prevalence | 20/100 (20%) | 32/68 (47%) |
| Incidence | 30/100 (30%) | 10/34 (29%) |
| α-error | 5% (z=1.96) | 5% (z=1.96) - 5% (z=1.96) |
| β-error | 10% (z=1.28) | 10% (z=1.28) - 33% (z=0.44) |
| No. per study group | 37 | 62 - 34 |

In some studies, it has been shown that dobutamine has a potential arrhythmogenic activity[30,31]. However, in NYHA class III-IV CHF patients few serious arrhythmias were seen with dobutamine doses in the range of 2.5-15 μg/kg/min in comparison with milrinone[30] and it appears that *de novo* arrhythmias were observed with higher doses (> 10 μg/kg/min)[31]. We found that dobutamine at a dose of 10 μg/kg/min increases inotropism in both group A and B sinus rhythm patients with CHF in NYHA class III-IV, without significantly increasing arrhythmogenicity as judged by the target event of the present investigation (non-sustained ventricular tachycardia), although several forms of ventricular arrhythmias had a higher incidence. Pro-arrhythmic effects were seen during dobutamine infusion in 21% of cases, effects which subsided (5%) when dobutamine was discontinued. Interestingly, the positive inotropic effects of dobutamine (based on ejection fraction changes) paralleled (22%) the pro-arrhythmic changes, although they lasted long after dobutamine discontinuation (18%). The pro-arrhythmic effects of dobutamine were unrelated to heart rate changes, both during (5%) as well as after (1%) drug infusion (Table III).

In a study including 22 patients, Nanas et al.[32] reported that long-term intermittent dobutamine infusion (10 μg/kg/min) combined with oral amiodarone improves the survival of patients with severe CHF. This result was more recently confirmed in a prospective, randomized, double-blind, placebo-controlled clinical trial of 30 patients with end-stage CHF refractory to standard medical treatment. In this study, a 60% reduction in the risk of death due to any cause was observed in the group treated with the combination of dobutamine and amiodarone, compared with the group treated with placebo and amiodarone[33]. There was also an improvement in functional class at 6 months in survivors[33]. These data thus clearly reinforce the potential clinical benefit of pulsed β-stimulant therapy in advanced CHF, a potential consequence of pharmacological conditioning[34]. In our study no patient was treated with amiodarone.

Our results show that the observed prevalence of non-sustained ventricular tachycardia (47%), as crude rate, was in the highest part of the interval estimated on the basis of the literature data at the time of protocol design (20 to 48%)[16-19], and very similar to that reported (48%) by Anastasiou-Nana et al.[12] in only 23 CHF patients in NYHA class II-III from the placebo arm of the Western Enoximone Study. However, in this study the conservative figure of a 20% prevalence of non-sustained ventricular tachycardia was selected for sample size calculation due to the fact that the trial included only patients in sinus rhythm. We thought that such patients have a lower prevalence of this form of arrhythmia. Since the incidence of non-sustained ventricular tachycardia was slightly lower than expected (29 vs 30%), it is possible to refute the null hypothesis of the present investigation with the actual sample size (n = 68), only accepting a β-error of 33% (Table IV).

It is advisable to conduct investigations of positive inotropic agents in CHF to determine whether pro-arrhythmic effects occur when using repeated long-dura-

tion Holter monitoring, as in this study, and the technique of forecasting confidence intervals, since spontaneous variability of arrhythmias makes it difficult to draw any definite conclusion on the basis of crude incidence rates alone. Since the prevalence of non-sustained ventricular tachycardia (as a target event) is rather high, large cohorts need to be evaluated. This is feasible only in multicenter studies. This may be particularly important as new agents such as levosimendan which presents with hemodynamic and survival advantages over dobutamine have been recently introduced into clinical practice[14].

On the basis of the rate results, it may be concluded that our study is relatively underpowered (Table IV); however, the impressive quantity of data on 96-hour Holter monitoring in 63 patients sophisticatedly analyzed[12] and the continuous data shown in table II enable a collective conclusion which may have a clinical impact. In fact, between group A and B patients there is an important (and statistically significant) difference when dobutamine is on: an increased pro-arrhythmic effect (incidence of non-sustained ventricular tachycardia) in the former vs the latter group. However, when the two groups are pooled, ejection fraction increases as does the incidence of total, coupled and single ventricular arrhythmias, although arrhythmogenicity (as judged by the design on non-sustained ventricular tachycardia) does not increase significantly (Table II). Ejection fraction, on the other hand, increases in both groups in a similar manner. On the other hand, the chronotropic and batmotropic effects appear to be in the confidence of spontaneous variability (Table III) which certainly deserves further study for any clear-cut conclusions.

Our study applies only to patients in sinus rhythm, in whom neither amiodarone nor β-receptor antagonists were used. On the other hand, levosimendan has recently been demonstrated to be significantly more effective than placebo or dobutamine in terms of the overall hemodynamic response rate (in acute CHF), with clear benefits also seen for mortality and for the combined risk of worsening heart failure or death for up to 180 days (in chronic CHF). Unfortunately, no real advantage over dobutamine was observed for dyspnea and fatigue[14,35]. If this new drug is to achieve widespread clinical use it will be essential to reduce the total incremental cost per life-year saved for levosimendan relative to dobutamine, from the median € 3205,00 calculated in the year 2000[14,15].

## Appendix

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