Acute reduction of ventricular volume decreases QT interval dispersion in elderly subjects with and without heart failure

Francine C. de Carvalho, Fernanda M. Consolin-Colombo, Carlos Alberto Pastore, Marcelo C. Rubira, José Claudio Meneguetti, Eduardo Moacyr Krieger, and Mauricio Wajngarten

Heart Institute (InCor), Medical School, University of São Paulo, São Paulo, Brazil

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Heart failure (HF) is a highly prevalent and important cause of morbidity and mortality in the elderly population (20). Although improvements in HF therapy have lowered mortality caused by disease progression, nearly half of the patients with HF experience sudden death (22, 34). Some studies (4, 7, 12, 14, 39) have suggested that QT interval dispersion (QTd) could be associated with a higher risk of sudden death. Indeed, some investigators (16, 44) have correlated structural alterations observed in HF with increased QTd and a worse prognosis. Thus a better prognosis due to the use of drugs that attenuate ventricular remodeling [e.g., angiotensin-converting enzyme (ACE) inhibitors] seems to be associated with a more homogeneous repolarization, which leads to a decrease in QTd (3).

As a result, research to detect a possible relationship between QTd behavior and factors known to influence the prognosis of HF [e.g., ventricular dysfunction, ventricular volume (VV), and neurohormonal activation] can be very useful (1, 35). Among such factors, VV is the least complex variable to study. One model that induces acute reductions in VV consists of the application of lower body negative pressure (LBNP), whereby cardiac preload is decreased because of a reduction in venous return (10). This method has not been used to evaluate the influence of acute alterations in VV on QTd. We evaluated QTd modulation in response to acute LBNP-induced decreases in VV in elderly subjects with and without HF.

METHODS

Study population. Fourteen elderly (mean age, 74.5 ± 1.6 yr) male patients with HF selected from the InCor Cardiogeriatrics Outpatient Service were studied. They had a New York Heart Association (NYHA) function class II or III dilated cardiomyopathy of idiopathic or ischemic etiology and a left ventricular (LV) ejection fraction (LVEF) of < 40% as assessed by Doppler echocardiogram. Patients were excluded when they presented with conditions that could potentially interfere with the study such as right bundle branch block, atrial fibrillation, metabolic or electrolyte disturbance, implanted pacemaker, severe valvopathy, recent (<3 mo) infection or cerebrovascular accident, consumptive disease, or use of β-blockers or antirhythmic drugs. Patients were on standard medications for HF (ACE inhibitors and diuretics, spironolactone) and, when indicated, nitrates, aspirin, and a statin.

Eleven healthy elderly men (mean age, 68.0 ± 1.9 yr) were studied as a control group. These subjects were considered healthy if there were no abnormalities detected during an extensive evaluation including medical history, physical examination, laboratory tests, 12-lead ECG, chest radiograph, and two-dimensional echocardiography (normal LVEF > 60%). Also, all of the control subjects underwent stress testing or dipyridamole-sestaMIBI (99mTc hexakis 2-methoxy-2-isobutyl isonitrile) test to exclude silent myocardial ischemic disease.

The University of São Paulo Medical Ethics Committee approved the study protocol, and informed consent was obtained from all subjects before the study was initiated.

Experimental protocol. Patients were asked to refrain from eating for 4 h before the study was started. Their usual medications where not interrupted with an exception made for diuretics, which were held for that day, and digitalis, which was stopped 1 wk before the study.

The subjects were placed in a supine position with their legs and pelvis enclosed in a negative-pressure chamber [Bioengineering Department, Heart Institute (InCor), University of São Paulo], which was sealed with adhesive tape. The tests were performed in a quiet room.
with dimmed lights and 22°C temperature. The subjects rested for 30 min before recording of data was started. The subjects’ hemodynamic variables were constantly monitored during the three study phases (baseline and −15 and −40 mmHg LBNP) with an Ohmeda 230 monitor (Finapres Monitoring Systems; Englewood, CO). Arterial blood pressure, heart rate, and systolic, diastolic, and mean arterial blood pressures were continuously displayed on a screen and recorded on a Gateway 2000 computer (4DX2-66V) using a computer-operated data-acquisition software system.

Both LBNPs (−15 and −40 mmHg) were applied for 15 min, which is the amount of time needed for image acquisition by a radioisotope scintigraphy device (a moveable ADAC Transcam gamma camera). The equilibrium ventriculography technique was employed to process the images, which were obtained from the left anterior oblique position perpendicular to the interventricular septum, thus allowing assessment of both ventricles. The radioactive counts proportional to chamber volumes during maximum diastole and systole were obtained over ventricular regions of interest. Ejection fractions were calculated from background-corrected counts and time-activity curves using a commercially available program and the following equation:

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ejection\space\text{fraction} = \frac{CMD - CMS \times 100}{CMD}
\]

where CMD and CMS are the blood cell counts at maximal diastole and systole, respectively.

Systolic volume values were obtained by determining the difference between the end-systolic and end-diastolic volumes (ESV and EDV, respectively).

An 87-lead, body surface potential mapping device (HPM 7100; Fukuda Denshi; Tokyo, Japan) was used to record the ECG signals. During the 15-min baseline period as well as during LBNP application, QT interval recordings were obtained at 5, 10, and 15 min. The QT interval used to calculate QTd (the difference between the longest and shortest QT intervals) was the mean of these three values. The Campbell method was used to define the end of the T wave (11). Furthermore, two independent observers who were unaware of the study groups and the tests analyzed the QTd to account for the reproducibility of the method.

After 10 min of baseline recording and after 10 min of LBNP application at both −15 and −40 mmHg, venous blood samples were obtained for determination of plasma norepinephrine (Nor) levels by high-performance liquid chromatography (HPLC) with electrochemical detection.

**Statistical analysis.** Values are presented as means ± SE. The χ² or Fisher exact test was used to compare proportions between the two groups. QTd values determined by the two observers were compared using Pearson correlation, and the reproducibility of these measures was tested using the Bland-Altman method. ANOVA with repeated measures was used to compare the two groups with regard to variations in VV and QTd. A P value of <0.05 was considered statistically significant.

**RESULTS**

Table 1 summarizes the demographic and clinical characteristics of the two groups. Patients with HF had a significantly higher mean age than control subjects. The etiology of the HF was ischemic in eight patients and unknown (idiopathic cardiomyopathy) in six. Nine patients were in NYHA function class II and five were in function class III. As expected, the ejection fraction determined by echocardiography was significantly lower in the HF group (33 ± 1.3%) than in the control group (72 ± 0.6%). LV mass was significantly higher in the HF group (188 ± 9 g/m²) compared with the control group (87 ± 9.8 g/m²). Although three patients were diabetic, blood glucose levels were normal in all of them. The body mass index and laboratory test results did not differ between groups (Table 1).

Table 2 summarizes values of the different intervals obtained by the 12-lead ECG. Compared with the control subjects, the patients with HF had a significantly higher baseline heart rate (65.5 ± 2.9 vs. 75.5 ± 3.5 beats/min; P < 0.05), QRS duration (51.8 ± 4 vs. 100.7 ± 16 ms; P < 0.05), and QT interval corrected for heart rate (QTc; 414.7 ± 6 vs. 468.6 ± 16 ms; P < 0.05). Although QTd did not differ significantly between the groups, there was a trend toward higher QTd values in the HF group compared with the control group (67.8 ± 6.8 vs. 57.2 ± 3.8 ms; P = 0.05). To identify the possible influence of left bundle branch block (LBBB) on the QTd, patients with HF and LBBB (50% of the HF group) were analyzed as a subgroup; the mean QTd values found in this subgroup were similar to those in the HF patients without LBBB at baseline and during different phases of the study.

**Effects of LBNP application on right and left ventricular count, volume, and hemodynamics.** At baseline, the right ventricular (RV) volumes determined by radioisotope ventriculography [EDV, stroke volume (SV), and ESV] in the HF group were similar to those in the control group (Fig. 1). The RV ejection fraction (RVEF) values were also similar in both groups (49 ± 3.5 vs. 57 ± 4% in the HF and control groups, respectively). Both groups had a similar and significant decrease in all RV volumes in response to application of −15 mmHg LBNP. When −40 mmHg LBNP was used, no additional decrease was observed. There was no change in the RVEF during application of either stimuli (Fig. 1).

As expected, the HF group had significantly higher LV volumes (EDV, SV, and ESV) and a significantly lower LVEF at baseline compared with the control group (35 ± 5 vs. 61 ± 8%, respectively; Fig. 2). Application of −15 mmHg LBNP...
significantly decreased EDV and SV in both groups with no difference in the absolute or relative percentile values between them. Application of −40 mmHg LBNP caused no additional decrease in LV volume. There was no change in LVEF in either group during application of both stimuli (Fig. 2).

Regarding other hemodynamic variables, blood pressure remained nearly the same with no significant alterations observed during the stimuli. Although application of −15 mmHg LBNP did not alter the heart rate, −40 mmHg LBNP significantly increased heart rate in both the HF and control groups (75.1 ± 14.5 to 77.1 ± 12.9 and 62.0 ± 7.03 to 68.4 ± 10.3 beats/min; Fig. 3).

At baseline, plasma Nor levels seemed higher in the HF group than in the control group but did not significantly differ (Fig. 4). Application of −15 mmHg LBNP significantly increased plasma Nor levels in both groups (from 286.7 ± 31.5 to 388.8 ± 41.2 pg/ml in the control group and from 405.8 ± 56.4 to 477.6 ± 47.4 pg/ml in the HF group). In response to application of −40 mmHg LBNP, Nor levels increased even more to a level significantly higher than observed at −15 mmHg LBNP (475.5 ± 33.8 pg/ml in the control group and 586.5 ± 55.9 pg/ml in the HF group).

**Effects of LBNP application on QTd.** When the QTd measurements recorded during the stimuli were analyzed, the same trend in behavior was found in both groups (Fig. 5). At −15 mmHg LBNP, both groups experienced a similar and significant reduction in QTd (from 57.2 ± 3.8 to 49.1 ± 3.4 ms in the control group and from 67.8 ± 6 to 63.7 ± 5.9 ms in the HF group). However, no additional alterations in QTd were observed in either group when −40 mmHg LBNP was applied.

A significant positive agreement was found between QTd measurements obtained by the two independent observers during the three study phases, with $R^2$ values of 0.795, 0.845, and 0.843 corresponding to baseline, −15 mmHg LBNP, and −40 mmHg LBNP, respectively.

**DISCUSSION**

The main finding of this study was that acute LBNP-induced reductions in VV decreased the QTd measured in elderly subjects both with and without HF. Under a low pressure stimulus (LBNP of −15 mmHg), decreases in VV and QTd associated with a significant increase in plasma Nor levels were observed in both groups. Although the Nor levels further increased in response to application of −40 mmHg LBNP, which indicates progressive activation of peripheral sympathetic nerve activity, both VV and QTd did not experience additional change. This suggests that QTd changes were primarily due to changes in the intracardiac blood volume and not to autonomic nervous system activation.
The similar behavior of the QTd values in elderly men with and without HF further supports this proposal. That is, the similarity in volume modulation by LBNP in the HF group despite the potentially higher levels of sympathetic activity suggests that intracardiac blood volumes more strongly influenced the QTd values. Indeed, compared with the control subjects, the patients with HF were older and had higher basal heart rates and significantly higher Nor levels as well (as expected) diminished ejection fractions. It also is possible that more pronounced sympathetic activity was not detected in these patients because they were receiving medications that could not be withdrawn because of ethical reasons.

Acute reduction in venous return primarily caused reduction in SV and stimulation of autonomic responses. As happens with QTd, both phenomena seem to influence the prognosis of patients with congestive HF. Although multiple and complex factors have been shown to influence QTd (5, 6, 16, 29, 41, 42, 44, 47), this study showed for the first time that LBNP decreases VV, and, therefore, a possible relationship exists between reductions in VV and QTd.

A significant decrease in VV was observed in both groups under −15 mmHg LBNP, but no significant further reduction occurred under −40 mmHg LBNP. This finding does not support reports of other investigators (2, 30, 33), who found that a decrease in VV only occurs with the higher stimulus. However, those studies were performed on young subjects, and it is well known that in elderly individuals exposed to LBNP, venous return is smaller because of the decreased venous compliance of the lower legs (17, 18, 36, 45). The more intense (−40 mmHg) LBNP was unable to provoke, despite the additional negative pressure, an increase in blood pooling in the lower legs. Besides this, it can also be assumed that −40 mmHg LBNP was ineffective in activation of baroreflex. However, the significant increase in heart rate and plasma Nor levels observed during exposure to −40 mmHg LBNP supports the hypothesis of the existence of an autonomic response (27).

The baseline mean QTd values in the HF group were similar to those found in a series of studies that involved >1,000 patients (26). Although the subjects in our HF group had dilated cardiomyopathy, their mean QTd values showed only a tendency toward higher values than those of the control subjects. Others have reported similar findings (1a, 26), which points toward a more complex relationship between QTd and chronically increased VV. Because QTd responsiveness to both LBNP stimuli was similar in both groups, the changes in QTd may have been physiological responses.

Other investigators have also found that cardiac volumes do influence QTd. Reiter et al. (38) observed increased dispersion of ventricular refractoriness after acute dilatation of the heart in a rabbit model. When assessing the influence of various autonomic stimuli over QTd, Haapalahti et al. (19) found that QTd decreased only during the tachycardial phase of the Valsalva maneuver, which also modulates VV. The effect of ventricular filling on ventricular repolarization has been characterized as contraction-excitation feedback (24). In the present study, the observed increases in heart rate and Nor level show a progressive increase in sympathetic activity from baseline toward the application of −15 mmHg and then −40 mmHg LBNP. The decrease in QTd associated with the increase in sympathetic tone induced by the less intense stimulus is in contradiction with several other studies, because these showed an increase in QTd with sympathetic stimulation (21, 23, 46) that was reduced with the use of β-blockers (6, 28, 37). Considering that the reduction of VV and adrenergic activation have opposite effects on QTd, it is possible that the reduction of VV in our study prevailed over the autonomic activation and led to a decrease in QTd. It should be emphasized that sympathetic autonomic responses in the elderly are diminished (9, 13, 48). Indeed, in contrast with our findings, a decrease in QTd was observed in young healthy individuals during the tilt test; similar to our model, the tilt test reduces venous return and activates adrenergic responses (31).

Study limitations. This study has some limitations that need to be analyzed.

First, determination of the end of the T wave on ECG tracings is difficult and might influence QTd measurements.
We tried to minimize this problem by choosing leads in which the T wave could be clearly visualized; furthermore, two independent observers who were unaware of the groups and the tests analyzed the QTd, and both the reproducibility of and correlation between these measurements were statistically acceptable. The lack of standardization of methods used to evaluate QTd (26) precludes comparison of our results with those obtained from other studies.

Second, we did not adjust LV mass for age, but the similar ages of the individuals in the groups likely reduces the possibility of age-related changes in LV mass contributing to observed differences due to heart failure.

Third, HF patients were under ACE inhibitor therapy, which could interfere with the results. Aside from the acute and chronic effects that ACE inhibitors have on hemodynamic parameters, they also potentially modulate the sympathetic nervous system.

The study was started 3–4 h after captopril ingestion (when patients were experiencing the steady-state effects of the drug) and therefore avoided vigorous hemodynamic effects that could interfere with the volume modulation related to LBNP application. Indeed, the captopril hemodynamic peak effects almost always occur between 60 and 90 min after its administration and reach a plateau after 2 h (27, 44) even in patients who are already using the drug chronically (9). Furthermore, patients were not exposed to the potential risk of having an increase in sympathetic activity promoted by ACE withdrawal, which also could interfere with the interpretation of the results. Cessation of captopril administration has been demonstrated (34) to elicit abrupt increases in circulating ANG II levels, arterial pressure, pulse rate, and plasma Nor levels, and these findings are consistently associated with activation of the sympathetic system.

Finally, regarding the long-term ACE inhibitor treatment effects, Dibner-Dunlap et al. (15) demonstrated that captopril administration causes a decrease in sympathetic activity in HF patients by improving cardiovascular reflex control elicited during volume modulation. To avoid this influence, ACE inhibitors should be withdrawn several days before the test, which is not an ethical procedure. Although our group of HF patients was using ACE inhibitors, their baseline Nor levels were still higher (405.8 ± 56 pg/ml) than the control group (286.7 ± 32 pg/ml), which suggests that the sympathetic nervous system was not completely depressed by ACE inhibitors. The fact that during application of LBNP stimuli, Nor levels increased similarly in both the HF and the control groups indicates that the reflex control elicited by volume modulation was not compromised in the HF patients. These data favor the interpretation that in our clinically stable patients who were under medication, QTd changes primarily followed changes in intracardiac blood volume and not autonomic nervous system activation. We cannot rule out the possibility of a different sympathetic nervous system behavior, evaluated by Nor levels, if patients were not using ACE inhibitors.

We conclude that application of −15 mmHg LBNP was associated with significant reductions in VV and QTd and discrete autonomic stimulation, and, whereas −40 LBNP enhanced autonomic stimulation, no additional reductions of VV or QTd were observed. Together, these data suggest that alterations in QTd are more related to changes in volume than changes in autonomic nervous system activity. This is additionally supported by the similar QTd behavior observed in elderly men with and without HF despite the trend of the former to have increased sympathetic activity.

Other studies should be conducted to assess the influences of these factors on the risk of sudden death, in other populations, and in patients with subacute and chronic conditions.

REFERENCES


