Left ventricular diastolic function and cardiac disease
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Circadian rhythm in left ventricular relaxation of patients with congestive heart failure: diagnostic and therapeutic implications

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Summary

Background: Since afterload is an important determinant of left ventricular (LV) relaxation, the physiological circadian variation of arterial blood pressure may induce diurnal variability of LV filling parameters in patients with congestive heart failure (CHF).

Methods: In 15 patients with chronic stable CHF (NYHA class II or III) and reduced LV ejection fraction (<40%) due to previous myocardial infarction, treated with either a calcium channel blocker or placebo, radionuclide angiography was performed at 10 AM and at 1 PM to assess whether or not LV filling indices follow a diurnal rhythm. Blood pressure was measured simultaneously. This procedure was repeated after one week.

Results: At 10 AM compared to 1 PM a higher systolic blood pressure (SBP, 138 ± 16 vs 131 ± 15 mmHg, P<0.01) and diastolic blood pressure (DBP, 75 ± 10 vs 71 ± 11 mmHg, P<0.01), a lower peak filling rate (PFR, 0.88 ± 0.30 vs 1.02 ± 0.29 end diastolic volume/second, P<0.01), and a longer time to peak filling rate (TPFR, 598 ± 74 vs 574 ± 61 millisecond, P<0.05) were found. Using repeated measures analysis of variance, the changes of PFR were related to the daily changes of SBP and DBP (each P<0.05).

Conclusion: These data suggest that LV relaxation as measured by PFR and TPFR is inversely correlated with a circadian fall in blood pressure in patients with CHF. This could have the important diagnostic implication that the timing should be taken into account when assessing diastolic LV function in patients with CHF, as well as the therapeutic implication that treatment regimens should account for an increased risk of pulmonary edema in these patients early in the morning.

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A circadian rhythm exists in physiological mechanisms such as blood pressure, vagal and sympathetic action, and heart rate,\textsuperscript{1,2,3,4} and has been associated with the circadian occurrence of cardiac events such as myocardial infarction,\textsuperscript{5,6,7} transient myocardial ischemia,\textsuperscript{8,9} and sudden cardiac death.\textsuperscript{10} Recently, a circadian variation of left ventricular (LV) performance as measured by diastolic function in healthy voluntary subjects has been observed.\textsuperscript{11} The existence of a diurnal variation of LV performance in patients with congestive heart failure (CHF) could have important implications for the appropriate timing of diagnostic assessments. In addition, it may have therapeutic consequences for patients with imminent pulmonary edema due to cardiac failure. However, no such data are available to date. Accordingly, the aim of the present study was to investigate the presence of such a diurnal variation of LV filling in patients with stable CHF. For that purpose we analyzed the data of a radionuclide angiography (RNA) study in patients with stable cardiac failure treated with either placebo or incremental dosages of calcium channel blocker. The results of this study on the effects of calcium channel blockade on diastolic function compared to placebo have been published,\textsuperscript{12} and did not reveal important differences. For the purpose of the current paper the data of the two groups were taken together and analyzed for circadian differences in diastolic function as measured by radionuclide angiography. Since arterial blood pressure is an important determinant of LV relaxation,\textsuperscript{13} and in addition, the load dependence of relaxation in heart failure is increased,\textsuperscript{14} we emphasized the relation between the levels of blood pressures and LV filling.

**METHODS**

**Patients.** Fifteen patients with chronic CHF, NYHA class II or III, were included in the study. Baseline demographic characteristics of the study population are previously published.\textsuperscript{12} All patients had sustained a myocardial infarction > 3 months prior to the investigation. The LV ejection fraction (EF) was \( \leq 40\% \). Exclusion criteria were unstable angina pectoris, clinically significant valvular disease including mitral regurgitation, hypertrophic obstructive or dilated cardiomyopathy, moderate or uncontrolled hypertension, clinically significant arrhythmia's including atrial fibrillation, bradycardia, and atrioventricular block of any degree. All calcium channel blockers and \( \beta \)-blocking agents, were withdrawn at least 5 half-life's before the start of trial. All other oral medication was continued.

**Study design.** The patients underwent RNA at approximately 10 AM and 1 PM. During RNA resting brachial artery cuff systolic and diastolic blood pressure (SBP and DBP respectively) were measured and mean arterial pressure (MAP) was calculated. Heart rates and heart rate pressure products were also determined. After the first RNA, five of the patients were treated with placebo and ten of them with mibefradil in doses ranging from 6.25 to 100 mg once daily for one week. All of the patients were measured again
at the completion of the week of treatment.

**Radionuclide Angiography.** To evaluate LV systolic and diastolic function rest supine multigated RNA images were obtained according to the protocol we described in our previous work.\(^{12}\) Shortly, the studies were made with forward gating and a 5% cycle-length-window. After 150,000 counts per 20 ms frame acquisition was completed. Using five Fourier harmonics temporal smoothing was achieved.

**Analysis of data.** From the LV time-activity curve and the first derivative of this curve we derived the parameters of systolic and diastolic function (Figure 5.1). EF was defined as the ratio of stroke volume (SV) and end diastolic volume (EDV). Atrial contribution (AC) was expressed as a fraction of SV. The first derivative of the volume curve was depicted as a flow curve. In this, peak filling rate (PFR) was defined the maximum instantaneous flow during early rapid filling, and peak ejection rate (PER) as the maximum flow during LV emptying. Time to peak filling rate (TPFR) was measured from the beginning of emptying, and was divided into two parts: time to end of systole (TES), and time from end of systole to peak filling rate (TPFR\(^{\prime}\)).

**FIGURE 5.1.** Redrawn time-activity curves of the left ventricle obtained from one of the study patients (top) and their first derivatives (bottom) at 10 AM (left) and at 1 PM (right). Left and right time axis and vertical axis are identical. AC indicates atrial contribution to diastolic filling; EDV, end diastolic volume; PER, peak ejection rate; PFR, peak filling rate; sec, seconds; SV, stroke volume; TES, time to end of systole; TPFR, time to peak filling rate measured from the beginning of emptying; TPFR\(^{\prime}\) time from end of systole to peak filling rate. At 1 PM compared to 10 AM left ventricular filling is enhanced as shown by increased PFR and decreased TPFR, despite unchanged left ventricular ejection fraction (SV/EDV).
Statistical analysis. Since the same variable was obtained on several occasions statistical analysis was performed using repeated measures analysis of variance. Circadian rhythm of a parameter with similar changes on both study days was tested with a cubic trend. With this trend similarly directed variability is tested on repeated occasions. To test whether the change patterns of the parameters equaled the variation of blood pressure we added mean blood pressure as a co-variate to the repeated measures model. Because of the use of co-variation of differences we tested in this situation with a quadratic trend. In a sequence of three differences between following measurements this trend tests opposite parameter directions. Also, the measurements of 10 AM from both study days, and those of 1 PM were taken together. Differences were tested by paired $t$ tests. For the correlations between the changes between 10 AM and 1 PM the Pearson correlation was used ($r$). All of the data were expressed as mean ± 1 SD unless otherwise stated. A P value <0.05 was considered as statistically significant. Values of 0.05 to 0.10 were also stated, since they may indicate a trend of the measured variable.

RESULTS
Of the fifteen patients who entered the study mean EF was low (25 ± 7%). As there were no significant differences between the effects of mibefradil and placebo on blood pressure or LV function, the data of the two groups were analyzed both separately and together (Table 5.1).

Radionuclide angiographic variables. The repeated measures analysis of the

| TABLE 5.1. Hemodynamic and radionuclide angiographic measurements in 15 patients with heart failure. The measurements at study start on 10 AM and those on 1 PM were taken together with the measurements after one week of treatment with placebo (n=5) or a calcium channel blocker (n=10). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | placebo         | mibefradil      | all measurements |
|                 | 10 AM           | 1 PM            | 10 AM           | 1 PM            | 10 AM           | 1 PM            |
| SBP (mmHg)      | 130 ± 12        | 124 ± 11        | 141 ± 16        | 135 ± 15        | 138 ± 16        | 131 ± 15**      |
| DBP (mmHg)      | 76 ± 8          | 71 ± 6**        | 75 ± 11         | 71 ± 12         | 75 ± 10         | 71 ± 11**       |
| MAP (mmHg)      | 94 ± 8          | 89 ± 7**        | 97 ± 10         | 92 ± 10         | 96 ± 10         | 91 ± 9**        |
| HR (beats/min)  | 71 ± 7          | 75 ± 5*         | 70 ± 14         | 72 ± 13         | 70 ± 12         | 73 ± 11*        |
| RPP (mmHg,bpm/1000) | 9.3 ± 1.5    | 9.3 ± 1.3       | 10.0 ± 2.3      | 9.7 ± 1.8       | 9.7 ± 2.1       | 9.5 ± 1.7       |
| EF (%EDV)       | 27 ± 13         | 27 ± 12         | 30 ± 7          | 31 ± 6          | 29 ± 9          | 30 ± 8          |
| PER (EDV/s)     | -1.2 ± 0.5      | -1.3 ± 0.5      | -1.4 ± 0.3      | -1.5 ± 0.3      | -1.3 ± 0.4      | -1.5 ± 0.4**    |
| PFR (EDV/s)     | 0.79 ± 0.32     | 1.03 ± 0.33     | 0.92 ± 0.28     | 1.01 ± 0.27     | 0.88 ± 0.30     | 1.02 ± 0.29**   |
| TPFR (ms)       | 589 ± 29       | 570 ± 53       | 602 ± 88       | 576 ± 64       | 598 ± 74       | 574 ± 61*       |
| TES (ms)        | 422 ± 55       | 379 ± 69*      | 387 ± 55       | 385 ± 58       | 399 ± 57       | 383 ± 62        |
| TPFR' (ms)      | 167 ± 41       | 192 ± 31       | 215 ± 86       | 191 ± 60       | 199 ± 78       | 191 ± 52        |
| AC (%SV)        | 40 ± 17        | 40 ± 19        | 42 ± 13        | 43 ± 15        | 41 ± 15        | 42 ± 17         |

p<0.05 vs. 10 AM; ** p< 0.01 vs. 10 AM
AC = atrial contribution; bpm = beats per minute; DBP = diastolic blood pressure; EDV = end diastolic volume; EF = ejection fraction; HR = heart rate; MAP = mean arterial pressure; PER = peak ejection rate; PFR = peak filling rate; RPP = heart rate pressure product; SBP = systolic blood pressure; SV = stroke volume; TES = time to end of systole; TPFR = time to peak filling rate measured from the beginning of emptying; TPFR' = TPFR measured from the beginning of filling.
radionuclide angiographic data showed no diurnal change of EF. In contrast, a statistically significant cubic trend of the mean value of PER was demonstrated ($P<0.01$), indicating an equal variation of this parameters on both study days. For the PFR ($P<0.06$) and TPFR ($P<0.08$) a tendency towards a cubic trend was obtained. The diurnal change of these variables was consistently and equally present on both study days. However, there was no diurnal variation present in the TES, TPFR', and AC. The measurements of both study days were then evaluated together. At 10 AM compared to 1 PM a clear difference was showed with respect to PER, PFR and TPFR (Table 5.1). At 10 AM PER and PFR were lower, and TPFR was longer. There were no differences between 10 AM and 1 PM with respect to EF, TES, TPFR', and AC.

**Blood pressure, heart rate, and heart rate pressure product.** The repeated measures analysis revealed a statistically significant cubic trend for the means of the values of SBP ($P<0.05$), DBP ($P<0.05$), MAP ($P<0.05$), and heart rate ($P<0.05$). The change of value of these variables was equally directed on both study days, but predominated on the first day. At 10 AM compared to 1 PM SBP, DBP, and MAP were higher, and heart rate was slightly but statistically significant lower. Heart rate pressure product did not show a diurnal variation because of opposite variations of heart rate and blood pressure.

**Blood pressure and heart rate vs RNA.** The relation between variations of blood pressure values and variations of PER and PFR was examined by adding mean values of SBP, DBP, and MAP as co-variates to the model of repeated measures of variance. In the change pattern of PFR, SBP and DBP were recognized as co-variates (both: $P<0.05$). Also MAP was recognized for co-variation ($P<0.01$). In the change pattern of PER no co-variation for this parameters was demonstrated (all parameters: $P>0.10$). Weak but statistically significant correlations were found between the change from 10 AM to 1 PM of the mean PFR, and the change of the mean DBP ($r=-0.44$, $P<0.05$), MAP ($r=-0.38$, $P<0.05$), and heart rate ($r=0.37$, $P<0.05$), but not with SBP ($r=-0.169$, $P>0.10$).

**DISCUSSION**

The aim of the present study was to investigate the possible existence of a day-time variability of LV filling in patients with CHF. For this purpose we used RNA which is a reliable noninvasive technique of measuring LV filling and may be used to serially follow diastolic LV function. The parameters of early diastolic filling, PFR and TPFR', are correlates of left ventricular relaxation, i.e. of early diastolic LV function. In many clinical conditions of LV diastolic failure, prolonged contraction and impaired relaxation are, although conceptually different, difficult to distinct, and may lead to prolongation of the contraction-relaxation cycle. In the present study TPFR is used to measure this. The analysis of the data resulted in the observation of a diurnal variation of LV filling
parameters. The observed changes in PFR and TPFR suggest the presence of a
decreased LV relaxation in the morning when compared with early afternoon. Also
diurnal fluctuations of blood pressure and heart rate, but not of heart rate pressure
product, were found. The diurnal changes of LV filling and the diurnal changes of blood
pressure and heart rate were interrelated.

To our knowledge no previous studies on diurnal physiological variations of
diastolic cardiac function have been performed in patients with CHF. In healthy
volunteers, however, a recent study showed diurnal changes of LV relaxation suggestive
of a circadian rhythm. The proposed underlying mechanism might have been the day-
night cycle in sympathoadrenal activity. The circadian changes in blood pressure in
these volunteers were too small to explain the diurnal variation of LV filling. Although
earlier investigators have reported a significant decrease in LV relaxation due to an
increase in afterload, early LV filling results in variable responses to blood pressure
elevations in subjects with normal LV systolic function without mitral regurgitation. In
heart failure, however, the load dependence of relaxation may be enhanced. Because
patients with heart failure without mitral regurgitation were concerned in our
study, the variations of blood pressure may have had a direct effect on the diastolic
cardiac function parameters. The variations in PFR were not only related to blood
pressure but to heart rate as well. Earlier reports on a correlation between heart rate
and PFR were based on observations made during exercise in patients with heart rates
above 90 beats per minute. In these high heart rate patients, loss of diastasis makes the measurement of PFR more sensitive to heart rate changes. In our study no
exercise testing was performed. So, the heart rates were well below 90 beats per
minute, and every time-activity curve showed clear signs of diastasis. Because of these
methodological limitations in our material, our results do not allow to indicate the nature
of the relation between heart rate and PFR. Besides the interrelation of heart rate and
PFR, associations of high heart rate and low PFR with increased AC are often
described. In the present study however AC was not associated with heart rate or
PFR because these parameters lead to opposite effects on AC. The day-time
fluctuations of blood pressure and heart rate as demonstrated studies of healthy
subjects, are probably related to a circadian variation in vagal and sympathetic cardiac
control, and are modified by physiological actions, such as exercise and food intake. Compared to healthy volunteers, patients with heart failure due to coronary artery
disease may be subject to attenuation of circadian variability of blood pressure and
heart rate. Nevertheless, the present data show a diurnal variation of blood pressure
and heart rate and a trend towards diurnal variability in LV filling in patients with severely
impaired LV function. During \( \beta \)-adrenergic stimulation in human subjects LV early
diastolic pressure is reduced by changes in contractility and LV relaxation, causing an
increased left atrial-ventricular pressure gradient. This in turn augments the rate and
magnitude of early diastolic filling. Augmentation of LV filling parameters, like PFR
and TPFR’ at 1 PM in the present study, are therefore expected in the presence of \( \beta \)-
adrenergic stimulation. Because $\beta$-adrenergic stimulation also enhances contractility, the entire contraction-relaxation cycle may be shortened,\(^{17}\) thereby decreasing TPFR in the present study as well. Circadian variability of sympathoadrenal activity, although not measured, may be directly responsible for the observed changes in LV filling. The increased PFR and shortened TPFR of 1 PM however were associated with and correlated to decreased blood pressure. Therefore the decreased PFR and TPFR at 10 AM compared to 1 PM may indicate the presence of diastolic failure with systolic compensation in response to an increased afterload, instead of a direct sympathoadrenal effect on diastolic LV relaxation. In this situation increased end-diastolic LV pressure increases risk of pulmonary edema.\(^{17}\) The absence of a circadian rhythm in TPFR\(^{1}\) in the present population may be of methodological nature. Because in patients with coronary artery disease increased regional systolic asynchrony is associated with prolonged isovolumic relaxation\(^{27}\) or early segmental relaxation,\(^{24}\) this condition may increase the inaccuracy of estimation of TES. Although the present global assessment of LV filling does not allow conclusions on regional asynchrony, the higher standard deviation of TES compared to the standard deviation of TES in a normal population measured in the same laboratory,\(^{15}\) may indicate the presence of prolonged isovolumic relaxation time.

The occurrence of transient myocardial ischemia also shows a circadian variation which may be related to variations in LV filling.\(^{28,29,30}\) Although in our population no patients complained of chest pain or other symptoms of myocardial ischemia during the follow-up period, transient myocardial ischemia may remain unnoticed. In earlier studies a circadian variation in the onset of silent and symptomatic ischemia was described with peaks between 8 and 10 AM, and 4 and 5 PM.\(^{28}\) Myocardial ischemia decreases relaxation causing a reduction of PFR and an increase of TPFR,\(^{29,30}\) thereby giving a possible explanation for our findings. However, no changes of rate pressure product, which is a measure of myocardial oxygen demand, were found between 10 AM and 1 PM. In addition, if the observed variability of blood pressure and LV filling parameters was due to silent myocardial ischemia, the administration of mibebradil, a potent anti-ischemic calcium channel blocker with a significant effect on silent myocardial ischemia,\(^{31}\) would have resulted in differences of PFR and TPFR between placebo and drug treated patients.

Although it cannot be completely excluded that small variations of blood pressure, heart rate, and LV function may be related to the administration of the study drug, the influence of this mechanism is probably negligible. The slight reduction of heart rate during mibebradil ($p<0.05$), can definitely not explain all of the circadian changes observed in our material. The fact that the differences between the various dose groups and placebo with regard to blood pressure and RNA data were small and insignificant,\(^{12}\) suggests that the measured variations are at least partly due to effects on the measured parameters in patients with mibebradil coinciding with parallel effects in the placebo group (Table 5.1). Although all other calcium channel blockers and $\beta$-
blocking agents were withdrawn before the start of the trial, other administered drugs, including angiotensin-converting enzyme inhibitors, diuretics, long-acting nitrates, and digoxin, might have had a confounding influence on the study result. In view of the fact that both type of medication and moment of intake were diverse, effects on blood pressure, heart rate and left ventricular filling were probably heterogeneous. This, in fact, supports that the variation of blood pressure and LV filling was a circadian phenomenon rather than a drug associated effect. We therefore assume that a circadian fall of blood pressure and a rise of diastolic performance reflect a true circadian phenomenon rather than an epiphenomenon of drug treatment.

The conclusions of the present study regarding circadian variability were based on observations on diastolic LV filling and blood pressure and heart rate on 2 different occasions each study day. The detailed assessment of circadian variability of LV diastolic function in patients with stable congestive heart failure however requires more frequent measurements at regular intervals on 1 study day, and not only during day-time. To confirm the findings of the present study, future studies of circadian rhythm in patients with congestive heart failure should meet this criteria. A greater number of patients entering the study would possibly increase the statistical power.

**Conclusions.** In the present study we found a circadian rhythm of RNA parameters of LV filling in patients with CHF due to previous myocardial infarction. This is probably caused by a physiological diurnal variation of blood pressure, as demonstrated in our patients, producing an increased afterload for the LV early in the morning. This may have the important implication that the timing should be taken into account when assessing diastolic LV function in patients with CHF. Also, it may have the therapeutic consequence that treatment regimens should account for an increased risk of pulmonary edema in these patients early in the morning.

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