Baroreflex sensitivity and cardiovascular mortality in patients with mild to moderate heart failure

Karl Josef Osterziel, Dankward Hänlein, Roland Willenbrock, Christina Eichhorn, Friedrich Luft, Rainer Dietz

Abstract

Objective—To assess the influence of both sympathetic (plasma noradrenaline concentrations) and parasympathetic (baroreflex activation) tone on survival in patients with congestive heart failure.

Design—Invasive study with determination of parasympathetic activity and follow up for at least 4-5 years.

Subjects—35 patients with sinus rhythm and mild to moderate heart failure (New York Heart Association grades II-III) (mean age 53 (SD 3)).

Results—20 patients whose hearts survived were compared with 15 patients whose hearts did not (12 died and three received transplants). The two groups differed significantly in terms of mean arterial blood pressure (98 (3) v 90 (3) mm Hg), heart rate (82 (2) v 93 (4) beats/min), and mean pulmonary artery pressure (24 (3) v 35 (2) mm Hg) (all P < 0.05), while cardiac index, stroke volume index, and right atrial pressures were not different. The survivors had significantly lower plasma renin activities (3-6 (0-8) v 9-0 (3-6) angiotensin I/mlh; P < 0.05) and tended to have lower noradrenaline values than non-survivors (170 (23) v 286 (74) pg/ml) at baseline. Baroreflex sensitivity was significantly lower in non-survivors than in survivors (1·3 (0·2) v 2·3 (0·3) ms/mm/Hg; P < 0·02). As the time of cardiac transplantation is dependent on complex logistical factors the three patients who received a transplant were excluded from the analysis of survival time. The risk of death in relation to baroreflex sensitivity at the median sensitivity of 1·48 ms/mm Hg was calculated. Survival was significantly different (P < 0·04) between the resulting two groups; three of the 16 subjects with high baroreflex sensitivity died compared with nine of the 16 with a baroreflex sensitivity <1·48 ms/mm Hg. When systemic blood pressure, pulmonary artery pressure, stroke volume index, plasma noradrenaline concentrations, and baroreflex sensitivity were entered into a Cox proportional hazards regression, only systolic blood pressure and plasma noradrenaline values predicted survival (P < 0·001).

Conclusions—Low vagal tone is correlated with a poor prognosis in patients with heart failure. Sympathetic tone measured as plasma noradrenaline concentration also contributed to survival. An additional contribution of vagal tone to survival could not be shown when sympathetic tone was considered simultaneously. This may be due to the inverse relation of sympathetic and parasympathetic tone and to the insensitivity of the multiple regression method to identify additional risk factors in small numbers of patients.

Keywords: renin-angiotensin system; parasympathetic nervous system; prognosis; heart failure

Ejection fraction and plasma noradrenaline concentration are important variables predicting survival in patients with congestive heart failure. Cohn and colleagues showed that noradrenaline concentration as a measure of sympathetic tone was inversely correlated with survival. Patients with congestive heart failure have not only increased sympathetic activation but also decreased vagal (parasympathetic) tone. Baroreceptor activation reflects parasympathetic tone in that an increase in baroreceptor sensitivity indicates a greater decrease in heart rate when the baroreceptor is activated. Conversely, a decrease in baroreflex sensitivity is associated with a lesser decrease in heart rate with baroreceptor activation. Recent data showing that sudden death increased when baroreflex sensitivity was decreased in patients with myocardial infarction who did not have congestive heart failure underscore an important role for parasympathetic tone. We examined parasympathetic tone in patients with symptomatic heart failure. Our hypothesis was that parasympathetic tone itself would be an indicator of survival.

Patients and methods

We identified 35 patients with mild to moderate congestive heart failure (New York Heart Association grades II-III), and sinus rhythm. Heart failure was caused by idiopathic dilated cardiomyopathy in 28 patients and coronary artery disease in seven patients as certified by cardiac catheterisation. All patients were limited by symptoms and signs of heart failure and not by angina. Concomitant treatment with β blockers was not allowed. The low proportion of patients with coronary artery disease and sinus rhythm was due to the fact that...
many patients were limited by angina and often treated with β blockers at the time of evaluation and had to be excluded. At entry into the study the patients were investigated haemodynamically and their baroreflex sensitivity was determined. Twenty eight patients were taking diuretics and 26 patients were receiving maintenance treatment with digoxin. Four patients received quinidine, one in combination with verapamil, and one patient received mecalazine. All patients were given an angiotensin converting enzyme inhibitor on discharge from the hospital after having been studied.

We used a modification of the technique described by Ludbrook et al., to measure baroreflex sensitivity. Briefly, a tightly fitting chamber was placed around the neck of the patients, which permitted rapid (<0-1 s) suction to 40 mm Hg negative pressure. The time course of the reflex response allowed the increase in parasympathetic nerve activity to be determined. The negative transmural pressure at the carotid sinus baroreceptors stimulated the baroreceptor reflex by simulating an increase in systemic blood pressure. The reflex response was determined as the decrease in heart rate expressed per cardiac cycle length. Neck suction was applied in random order twice at 0, −10, −20, −30, and −40 mm Hg for 30s. We calculated one regression line and its slope from these values of neck suction and the according increases in cardiac cycle length for each patient. For the calculation of maximal baroreflex sensitivity, the maximal cycle length was subtracted from the average of five cycle lengths before the suction was applied. In addition, baroreflex sensitivity was determined from the increase in cycle length from the two cardiac cycles immediately before and after neck suction, according to the method of Ebert et al. The two results were termed the maximal and the immediate baroreflex sensitivity respectively. Although not tested in this study, the reproducibility of the baroreflex determination is good: there was no change in the slope of baroreflex sensitivity after administration of placebo in another study.

Haemodynamic variables were measured by a Swan-Ganz catheter placed in the pulmonary artery. Cardiac output was measured by thermodilution. The mean of three determinations with a variation of <10% was taken as the cardiac output. Plasma renin activity and adrenaline and noradrenaline concentrations were measured by radioimmunoassay and radioenzymatic assay respectively. Serum sodium and creatinine concentrations were measured by an automated method.

STATISTICAL ANALYSIS

Groups were compared by the non-parametric Wilcoxon-Mann-Whitney test. The survival distribution function was determined by the Kaplan-Meier method. Differences between groups were examined by the Mantel-Cox, Tarone-Ware, Breslow, and Peto-Prentice tests. Multivariate regression analysis was performed using the Cox proportional hazards model. Only covariates which contributed significantly to an improvement in the prediction of survival were entered into the model. Fiducial limits are expressed as means (SD). A probability of P < 0.05 was accepted as significant.

Results

The patients were followed up for a minimum of 56 months. By this time 12 patients had died and three had undergone cardiac transplantation because of refractory heart failure. These 15 patients (non-survivors) were compared with the 20 patients whose hearts had survived the 56 months. As outlined in table 1, the groups did not differ in terms of aetiology of heart failure, age, and height but were marginally different in body weight. At the time of the baroreflex determination survivors had a slightly greater systolic, diastolic, and mean systemic pressure; lower heart rate; and lower pulmonary artery pressure than the non-survivors (figure 1). Cardiac index, right atrial pressure, and systemic vascular resistance, however, did not differ. Serum sodium concentration was lower and the serum creatinine concentration slightly higher in non-survivors than in survivors. Plasma renin activity was higher in non-survivors than in survivors; however, adrenaline and noradrenaline values were not different. As shown in figure 2, both the maximal and the immediate baroreflex sensitivity were significantly lower in non-survivors than in survivors.

The patients who died were classified according to whether their death fitted the clinical classification of cardiac death. We next compared all the above variables in the six patients within the non-survivors who died suddenly and the nine patients who died of progressive congestive heart failure or received a transplanted heart. None of the variables examined were significantly different between those who died suddenly and those

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**Table 1** Comparison of patients still living after 56 months (survivors) with those who died (n = 12) or received transplants (n = 3) (non-survivors). Values are means (SD) unless stated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 20)</th>
<th>Non-survivors (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>15</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (2)</td>
<td>55 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (2)</td>
<td>174 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (3)</td>
<td>71 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>98 (3)</td>
<td>90 (3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 (2)</td>
<td>93 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.2 (0.1)</td>
<td>2.9 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>39 (2)</td>
<td>33 (2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>24 (3)</td>
<td>35 (2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>7 (1)</td>
<td>9 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/s/cm²)</td>
<td>1268 (77)</td>
<td>1255 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma adrenaline (pg/nl)</td>
<td>66 (19)</td>
<td>66 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma noradrenaline (pg/ml)</td>
<td>170 (23)</td>
<td>286 (74)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng angiotensin I/ml/h)</td>
<td>3.6 (0.8)</td>
<td>9.0 (7.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>140 (1)</td>
<td>137 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>3.9 (0.1)</td>
<td>3.8 (0.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/100 ml)</td>
<td>1.4 (0)</td>
<td>1.4 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Baroreflex sensitivity (ms/mm Hg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>2.3 (0.3)</td>
<td>1.3 (0.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Immediate</td>
<td>2.1 (0.4)</td>
<td>1.1 (0.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Survival time (months)</td>
<td>&gt; 56</td>
<td>26 (4)</td>
<td></td>
</tr>
</tbody>
</table>
Baroreflex sensitivity and cardiovascular mortality in patients with mild to moderate heart failure

who died of congestive heart failure or received transplants (table 2). Because the timing of cardiac transplantation is dependent on complex logistical factors the three patients who developed terminal heart failure and received a transplant were excluded from the following analysis on survival. To calculate the risk of mortality in relation to the baroreflex sensitivity we arbitrarily used the median in the remaining 32 patients as a cut off point (median of the maximal baroreflex sensitivity = 1.48 ms/mm Hg). After 56 months (figure 3), the mortality

Figure 1 Comparison of haemodynamic variables at baseline between survivors and non-survivors (those who died or received heart transplants for refractory heart failure).

Figure 2 Maximal and immediate baroreflex sensitivity in survivors and non-survivors.

Figure 3 Survival in the 32 patients with mild to moderate heart failure when the patients with a maximal baroreflex sensitivity of the median value and above were compared with those with a baroreflex sensitivity below the median. The three patients receiving transplants were excluded from analysis.
curves showed that three of 16 subjects (19%) with a baroreflex sensitivity of 1-48 ms/mm Hg or above had died, compared with nine of 16 patients (56%) with a sensitivity below the median. When other variables thought to be related to prognosis were analyzed by dividing the patients into two groups according to the median systolic blood pressure and systolic pulmonary artery pressure, those patients with a poor prognosis could be distinguished from those with a good prognosis (figure 4). Dividing the patients into two groups according to noradrenaline concentration and stroke volume did not allow such differentiation.

When the patients who received transplants were excluded five variables showed a univariate significant regression coefficient in terms of survival—namely, stroke volume index, the inverse of systolic blood pressure, pulmonary artery pressure, plasma noradrenaline concentration, and maximal baroreceptor sensitivity. The selection of the variables considered in a stepwise procedure was derived from the significance level of the univariate analysis. Only two of these variables entered the multiple regression model (P < 0.001).

These variables were systolic blood pressure and plasma noradrenaline concentration. The relation was defined by the Cox hazards model equation: S(tz) = (S(t)) exp(zg) where S(tz) = survival function at time t and covariate variable z, S(t) = baseline survival function corresponding to survival at z = 0, and f(z) = 0.0364 × systolic blood pressure + 0.0039 × plasma noradrenaline concentration.

Similar results were obtained when the three patients who received transplants were included in the analysis.

Discussion

Two variables are closely associated with prognosis in patients with congestive heart failure—namely, left ventricular function and activation of the sympathetic nervous system.14-19 Our data suggest that diminished baroreflex sensitivity representing low vagal tone is also a prognostic indicator in patients with congestive heart failure. Moreover, determining vagal tone may be useful not only in patients after myocardial infarction10-12 but also in patients with symptomatic heart failure. To confirm the influence of vagal tone on prognosis, however, further studies are required in patients with heart failure. In a clinical setting this could be achieved by analyzing heart rate variability, which is another way to measure vagal tone.

We used the baroreceptor reflex to determine the level of parasympathetic tone. We believe that this conclusion is justified because of earlier studies showing that the early reflex bradycardia elicited by neck suction is dependent only on reflex parasympathetic activation and is not influenced by the withdrawal of sympathetic tone.13 Thus, patients who show only a slight decrease in heart rate on neck suction show low parasympathetic activity. These patients have a poorer prognosis than patients with a brisk response.

Vagal tone may alter prognosis by its influence on malignant arrhythmias. This is supported by several studies. Dogs with myocardial infarction induced by having a ligature around one coronary artery were more likely than dogs whose vagal tone remained normal to develop ventricular fibrillation if their vagal tone was decreased.22,23 Patients

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Table 2  Comparison of patients who died of progressive heart failure (n = 6) or received transplant (n = 3) with those dying from sudden cardiac death. Values are means (SD) unless stated otherwise.

<table>
<thead>
<tr>
<th>No of patients with:</th>
<th>Died of progressive heart failure or received transplant (n = 9)</th>
<th>Sudden cardiac death (n = 6)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>8 / 5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 / 1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 (5) / 57 (12)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (3) / 175 (3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 (6) / 73 (5)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>89 (3) / 91 (7)</td>
<td>&lt;0.007</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 (5) / 99 (8)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.0 (0.2) / 2.8 (0.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>34 (3) / 30 (4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>35 (2) / 35 (5)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>9 (2) / 9 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes/cm²)</td>
<td>1262 (112) / 1243 (47)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasma adrenaline (pg/ml)</td>
<td>67 (22) / 95 (6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasma noradrenaline (pg/ml)</td>
<td>242 (73) / 385 (189)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity (ng angiotensin l/ml/h)</td>
<td>10.6 (5.1) / 5.2 (1.6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>138 (1) / 136 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.2 (0.1) / 3.8 (0.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/100 ml)</td>
<td>1.4 (0.2) / 1.5 (0.1)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Baroreflex sensitivity (mm/s/mm Hg):</td>
<td>1.3 (0.3) / 1.3 (0.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>1.2 (0.4) / 0.8 (0.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>26 (4.9) / 32 (7.9)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
after myocardial infarction but without conges-
tive heart failure had a significantly higher
risk of sudden cardiac death when the vagal
tone was low.²⁴ We did not, however, find a
greater risk of sudden death in our patients
with diminished vagal tone, even though the
immediate baroreceptor response tended to
be lower in the subjects who died suddenly
than in those who did not. Deterioration of
left ventricular function is associated with a
decrease in parasympathetic tone.⁶ ¹² ²⁰ Vagal
tone therefore identifies not only a subgroup
at high risk of sudden cardiac death but also a
subgroup at high risk of pump failure. Both
parameters are closely related to prognosis in
left heart failure; therefore indices of vagal tone
are associated with both sudden cardiac death
and terminal myocardial dysfunction, as we
found in this study.

The sympathetic and parasympathetic ner-
vous systems are regulated as an inverse servo
mechanism: when sympathetic tone increases,
parasympathetic tone decreases. Thus, sym-
pathetic tone may have been greater in the
patients who died than in those who had a
better prognosis. The variability of plasma
noradrenaline values precluded our showing a
difference in the sympathetic tone of these
two groups or a significantly different survival
in the two groups on dividing the patients
according to median noradrenaline concen-
trations. However, the multiple regression
analysis we performed accepted only systolic
blood pressure and plasma noradrenaline val-
ues. Since sympathetic and parasympathetic
tone are highly inversely correlated, it is not
surprising that the model accepted only one of
these variables.

We did not determine left ventricular ejec-
tion fraction, which is a prognostic indicator
in patients with congestive heart failure,³¹ but
we found that other variables reflecting a poor
left ventricular function were related to prog-
osis. When the median of systolic blood
pressure or systolic pulmonary artery pressure
was used to define two groups a significantly
worse prognosis was found in patients with
low systolic blood pressure or high pulmonary
artery pressure. The multivariate Thoracol
analysis, however, considers the study variables in
their order of importance. We believe that systolic
blood pressure reflected poor left ventricular
function in our patients as blood pressure is
determined in patients with depressed left
ventricular function by the heart’s ability to
adequately supply the tissues at the required
afterload. Schwartz et al reported similar find-
ings, in that they were also able to show an
independent contribution of systolic left ven-
tricular pressure on prognosis.³²

Clinical studies have shown the importance
of reduced vagal tone on the prognosis of
congestive heart failure. ⁵ ²⁶ ²⁸ In addition, clinical intervention trials have shown that by
decreasing the activity of the renin-angio-
tensin system and the sympathetic nervous
system, the prognosis of patients with conges-
tive heart failure may be improved.²⁹ ³⁰ ³¹ Angiotensin converting enzyme inhibitors
would be expected to increase parasympa-
thetic tone by two mechanisms. The lower
angiotensin II concentrations could influence
vagal tone centrally by acting at the area
postrema, an area of the brain where the
blood–brain barrier is particularly sensitive
to the influences of circulating concentrations
of angiotensin II.³³ Furthermore, global haemo-
dynamic improvements evoked by angiotensin
converting enzyme inhibitors would be ex-
pected to improve parasympathetic tone. Thus,
parasympathetic tone may extend beyond heart rate responses. For instance, in
patients with severe mitral insufficiency an
increase in vagal tone was associated with
improved haemodynamics.³⁴ Finally, we
recently showed an increase in cardiac vagal
activity after angiotensin converting enzyme
inhibition.¹² This was confirmed by Binkley et al,
who found an augmentation of vagal tone
after treatment with converting enzyme
inhibitors in patients with heart failure. The
effects of converting enzyme inhibitors may be
partly mediated in this way. For instance,
studies in humans suggest that the anti-
arrhythmic action of converting enzyme
inhibitors may be related to the suppression of
foci triggered by ischaemia²² ²³ or the suppres-
sion of ventricular tachycardia.³ This conclu-
sion is supported by the results of the second
vasodilator heart failure trial, in which the
incidence of sudden death was reduced with
enalapril compared with hydralazine-
isosorbide dinitrate in patients with mild heart
failure.²⁸ ³⁶

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