Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation

Andrea Mortara, Maria Teresa La Rovere, Maria Gabriella Signorini, Paolo Pantaleo, Gianni Pinna, Luigi Martinelli, Claudio Ceconi, Sergio Cerutti, Luigi Tavazzi

Abstract

Background and objectives—Autonomic dysfunction seems to be involved in the progression and prognosis of severe congestive heart failure. Parasympathetic activity can still be abnormal 4–8 weeks after haemodynamic improvement by heart transplantation. To identify patients in heart failure with a more pronounced neural derangement and to analyse the changes in sympathetic and parasympathetic activity soon after heart transplantation, spectral indices of heart rate variability were assessed in 30 patients in severe heart failure and in 13 patients after heart transplantation; a group of 15 age-matched subjects served as controls.

Methods and results—Heart rate variability was assessed by standard electrocardiography (ECG) in patients in heart failure and by oesophageal ECG in patients after heart transplantation. Compared with controls, the mean RR interval and total power were reduced in heart failure. The 30 patients showed two different patterns of heart rate variability: in 14 no power was detected in the low frequency band (0.03–0.15 Hz) (LF) and total power was mainly concentrated in the high frequency band (0.15–0.45 Hz) (HF), whereas in the remaining 16 patients power in the LF band was increased and power in HF band was reduced compared with the controls. Patients with undetectable LF had a lower mean RR interval and total power (745(25) v 864(36) ms, $p < 0.05$; 118(16) v 902(202) ms², $p < 0.001$), higher concentration of plasma noradrenaline (635(75) v 329(54) pg/ml, $p < 0.05$), and worse clinical status and prognosis (4 deaths v no deaths at 6 month follow up) than patients with a dominant LF band. In the post-transplant patients both the mean PP interval of the remnant atrium and total power resembled results in the patients with heart failure; in 7 of the 13 post-transplant patients no power was detectable in the LF band: when both HF and LF power were present the results resembled those in the 16 patients in heart failure.

Conclusions—These data suggest that in more advanced stages of congestive heart failure, power spectral analysis of heart rate variability allows identification of a subgroup of patients with higher sympathetic activation and poorer clinical status who are at major risk of adverse events. In the short term after cardiac transplantation the spectral profile of the rhythm variability of the remnant atrium was not improved, suggesting that parasympathetic withdrawal and sympathetic hyperactivity persist, despite the restoration of ventricular function.

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Divisione di
Cardiologia and
Bioingegneria Centro
Medico di
Montescano,
Fondazione Clinica
del Lavoro, IRCCS,
Pavia, Italy
A Mortara
M T La Rovere
P Pantaleo
G Pinna
L Tavazzi

Dipartimento di
Bioingegneria
Politecnico di Milano,
Milano, Italy
M G Signorini
S Cerutti

Divisione di
Cardiochirurgia,
Policlinico San
Matteo, IRCCS,
Pavia, Italy
L Martinelli

Centro di
Fisiopatologia
Cardiovascolare,
Centro Medico di
Gussago, Fondazione
Clinica del Lavoro,
IRCCS, Pavia, Italy
C Ceconi

Correspondence to:
Dr Andrea Mortara,
Divisione di Cardiologia,
Centro Medico di
Montescano 27040
Montescano (Pavia), Italy.
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Heart failure in both experimental and clinical settings is associated with considerable neurohumoral excitation, resulting in abnormal autonomic control of cardiovascular function. Increased sympathetic activity and plasma concentrations of noradrenaline,^{1,2} parasympathetic withdrawal,^{3–5} and impaired baroreflex gain^{6–8} have been reported. This excessive neurohumoral activation is involved in progression of heart failure and in prognosis.

Analysis of heart rate variability is regarded a valid technique to assess non-invasively the sympathovagal balance of the heart. Frequency domain analysis of heart rate fluctuations identifies the relative influence of the two neural limbs that regulate heart rhythm.^{9–11} When this technique was used to study patients in congestive heart failure the results did not accord, perhaps because methods and patient selection differed.^{4,5}

Parasympathetic activity assessed by time domain analysis of the variability of the sinus rhythm in the remnant remained subnormal 4–8 weeks after cardiac transplantation despite restoration of normal left ventricular function.¹² There are no data on frequency domain measurements of recipient sinus rhythm variability. Such analysis might give better discrimination of the role of sympathetic activity in the recovery of autonomic function.

In our present study we tested the hypothesis that power spectrum analysis of heart rate variability in congestive heart failure may identify patients with a more pronounced

sympathovagal imbalance and who, as a consequence, could be at major risk of the disease worsening and have a poorer prognosis. We also used power spectral estimates of recipient sinus rhythm fluctuations to assess the sympathetic and parasympathetic modulation of the heart after haemodynamic function had been improved by heart transplantation.

Patients and methods

PATIENTS

We studied three groups of patients.

Group 1—Thirty patients (mean (SE) age 54(3)) with severe congestive heart failure secondary to ischaemic ($n = 19$) or idiopathic ($n = 11$) cardiomyopathy who were already on the waiting list for cardiac transplantation. The mean (SE) duration of symptoms was 24(4) months. All patients were being treated with diuretics and vasodilators; 18 were receiving digoxin and 11 amiodarone. All were in a stable condition with no change in signs and symptoms within two weeks of the measurement of heart rate variability. None had had an acute myocardial infarction or had undergone cardiac surgery during the previous three months. We excluded patients with more than 10/min supraventricular and/or ventricular extrasystoles.

Group 2—We studied 20 patients who were referred to the Montescano Medical Centre after orthotopic cardiac transplantation (mean (SE) age 45(4) yr) between January 1991 and December 1991. All heart transplantations were performed at the Policlinico S. Matteo, Pavia by a standard surgical technique.^{13 14} During the operation the recipient ventricles and portions of the atria were removed while the great vein-atrial junctions and recipient sinus node remained in situ. Heart transplantation was completed by suturing the donor ventricles and portions of the donor atria to the recipient atrial remnants, which remained normally innervated. Heart rate variability was measured 40(5) days (range 15–68 days) after the operation when there was minimal or no rejection according to cardiac biopsy performed within 5 days of the study. Before heart transplantation eight patients had coronary artery disease and 12 had idiopathic cardiomyopathy: the mean duration of heart failure symptoms was 18(3) months. All 20 transplant recipients were treated with cyclosporin, azathioprine, and prednisone immunosuppression and 15 were also treated with diuretics. None was treated with vasodilators, digitalis, or β blockers. We excluded patients in whom hypertension developed (diastolic pressure > 100 mm Hg or systolic pressure > 160 mm Hg) and those who had diabetes. Thirteen transplant recipients completed the study: four patients were excluded because of hypertension, an oesophageal recording could not be obtained in two, and in one the remnant atrium showed atrial fibrillation.

In the heart failure and post-transplant groups we measured serum electrolyte concentrations and arterial blood gases and performed renal function studies within 24 hours

of the study; no patient had hypoxaemia, hypercapnia, or acidaemia.

Group 3—The control group comprised 15 (mean age 57(3) yr) with ischaemic heart disease with no signs or symptoms of ventricular dysfunction (ejection fraction $> 50\%$, NYHA class 0 or 1) and no ischaemia during effort tests, Holter monitoring, or thallium-201 scintigraphy. Patients with a history of hypertension and diabetes were excluded. None had had myocardial infarction or had undergone coronary angioplasty, or bypass grafting in the preceding 6 months.

All patients gave their informed consent and the study protocol was approved by the local ethics committee.

RECORDINGS

Studies were carried out in the morning with the subjects in a supine position and fasting. In all groups a standard ECG lead and respiratory signal (via an endonasal thermistor) were recorded and analysed off line. In post-transplant patients the PP interval recordings were obtained from the recipient atrium by an oesophageal ECG lead that transmitted both donor and remnant atrial activity; electrical activities were then separated by digital filtering and averaging techniques (see data processing). After 30 min of supine rest, which allowed for stabilisation, recordings were performed for at least 30 min, while the patient was breathing spontaneously.

DATA PROCESSING

The signal processing was performed at the Departments of Biomedical Engineering in the Medical Centre of Montescano (Pavia) and in the Polytechnic University of Milan.

Signal acquisition—All 30 min recordings were split into segments of at least 512 beats; segments containing artefacts and fast transients were excluded. Final data are the mean of at least three good quality recording segments for each patient. Signals were digitised off line by a 12 bit, analogue to digital converter board, amplitude ± 5 V (Metabyte Das-8, Texas, USA) at a sampling rate of 300 Hz. Associated RR and PP intervals were measured from the zero-crossing point of the interpolated first derivative of the signal. This increased the time resolution by up to 1 ms. For each RR and PP interval we took a sample of the respiratory signal that corresponded with the R/P wave to obtain the reference value of the respiratory frequency. The beat-to-beat series of respiratory values is called a respirogram.¹⁵ Premature extrasystoles were identified and corrected by linear interpolation with the previous and following beats. Possible artefacts and noise were also excluded. We singled out the activity of the recipient atrium by using a procedure of weighed averaging on a beat-to-beat basis on the oesophageal lead trace (fig 1A) that was synchronised with the maxima of QRS peaks of the donor heart activity previously acquired from the surface ECG (fig 1B). In this way we obtained an averaged QRS complex of donor rhythm (template) with a temporal window of

Figure 1 (A) Signal from oesophageal lead showing both donor heart (D) and remnant atrium (R) rhythms. Two different and unrelated rhythms are clearly detectable (B) Example of a surface ECG signal of the donor heart (D). (C) Example of remnant atrium electrical activity obtained after separation of donor heart ECG by the averaging procedure reported in the text.

200 ms before and 450 ms after the R peak. We subtracted this template from the original oesophageal signal after synchronisation with donor QRS maxima and using an adaptive gain that depended on the QRS amplitude.¹⁶ From the resulting signal (fig 1C), which represents the electrical activity of the recipient atrium, and from the donor heart signal, we calculated a time discrete series of successive PP and RR intervals (tachograms, see fig 2).

Signal processing—The time series of the RR and PP intervals were analysed on a personal computer and the power spectral density was calculated according to an autoregressive model estimation. The autoregressive technique calculates the model for the data generation mechanisms by a least squares minimisation of the prediction error. Such a model also allows for the entire spectrum to be divided into single spectral components (one for each degree of freedom of the model itself). The optimum order of autoregressive model identification was chosen by minimisation of the Akaike Information Criteria figure of merit, starting from a minimum of 8. The reliability of the identification (and hence the fitting of the model to the generated data) was tested by applying the Anderson test (whiteness test) to the prediction error. Records of data that did not fall within 95% confidence intervals for this test were excluded from the analysis.¹⁷ For each sequence, the main spectral components were identified automatically

and their power and central frequency were computed according to the method proposed by Zetterberg.¹⁸ The following variables were analysed: (a) average value of the sequence (mean RR or mean PP); (b) total power (total variance of mean RR or PP variability); (c) low frequency power (0.03–0.15 Hz) in power spectral density, which reflects modulation by both sympathetic and parasympathetic cardiac efferent activity^{9–11 19–22}; (d) high frequency power (0.15–0.45 Hz) in power spectral density, which reflects modulation by parasympathetic activity synchronous with respiration^{9–11 19 23 24}; (e) low frequency power/high frequency power ratio, which reflects the balance between the sympathetic and parasympathetic limbs.¹¹ The power spectrum of the respirogram (see above, signal acquisition) was used to detect correctly the high frequency peak on RR and PP signals to establish whether occasional slow respiration rates produced a spurious oscillation in the low frequency band. The very low frequency (VLF) power (0–0.03 Hz) component was not analysed. This power, though it may contain clinical information,⁴ is erratic when it is measured over a few minutes because it is affected by baseline wandering and other sources of slow frequency noise. VLF components are currently investigated on longer variability series by non-linear modelling of deterministic chaos, in an attempt to evaluate the complex dynamics of long-term regulation

Figure 2 Beat-to-beat variability signals (tachograms) after heart transplantation. (A) Series of RR intervals of the donor denervated heart, (B) series of PP intervals of the remnant atrium extracted from the oesophageal ECG, (C) series of respiratory values corresponding with the occurrence of R peak. AU, arbitrary units.

mechanisms that are believed not to be fixed at a certain frequency or frequency band.

Each spectral component is presented in its absolute value (ms²) and in normalised units (nu) obtained by dividing the absolute power of the component by the total power minus the VLF component (if present), and multiplying by 100. Only components making up >5% of the total power were considered for the study.

Measurement of plasma noradrenaline
Noradrenaline was assayed in 6 ml samples of blood drawn from the forearm vein and col-

lected into chilled tubes containing 1 mg/ml EDTA for immediate storage at -70°C. Plasma noradrenaline was measured by high performance liquid chromatography with electrochemical detection as described elsewhere.²⁵ In our laboratory the mean value of normal subjects is 275(34) pg/ml.

STATISTICAL ANALYSIS
All results are reported as mean (SEM). Groups were compared by a general linear model one way analysis of variance and variables were compared by linear regression analysis. Before statistical analysis we log transformed the power spectral variables to produce distributions that were nearly normal. Differences with a p value of < 0.05 were regarded as statistically significant.

Results
Table 1 summarises the general characteristics of the patients with heart failure and the post-transplant patients. There was no difference in mean age between the two groups though the post-transplant recipients tended to be younger than those with heart failure. The patients with congestive heart failure and the transplant patients (before the operation), had similar ejection fractions, haemodynamic variables, and NYHA class distribution.

HEART PERIOD VARIABILITY
Table 2 lists the indices of power spectrum estimate.

Group 1—As expected, patients with heart failure had a reduced mean RR interval and total power than the control group (803(24) v

Table 1 Patients' characteristics (mean (SEM))

Characteristic	CHF (n = 30)	CT (n = 13)	
		Pre	Post
Age (y)	54 (3)	45 (4)	
NYHA class (%)			
III	22 (73)	5 (38)	0 (0)
IV	8 (26)	8 (62)	0 (0)
EF (%)	19.5 (1.1)	17.9 (0.9)	55.4 (2.5)
CI (l/min/m ²)	2.04 (0.1)	2.06 (0.2)	3.35 (0.2)
PCP (mm Hg)	21.1 (1.8)	22.9 (3.4)	10.4 (1.9)
RAP (mm Hg)	6.8 (1.5)	9.5 (1.2)	2.0 (0.3)
PAR (mm Hg/l/min)	2.6 (0.7)	2.7 (0.7)	1.1 (0.2)
Symptoms (mnth)	24 (4)	18 (3)	—
Na ⁺ (mEq/dl)	137 (1)	136 (2)	139 (0.7)
Po ₂ (mm Hg)	77 (2.5)	N/A	87 (2.8)
Pco ₂ (mm Hg)	36 (1.5)	N/A	34 (1.0)
Days from CT	—	—	40 (5)
Cyclosporin (ng/dl)	—	—	267 (21)
Medication (%)			
Diuretic	30 (100)	13 (100)	11 (85)
Digitalis	18 (60)	7 (54)	0 (0)
ACE inhibitors	27 (90)	13 (100)	0 (0)
Nitrates	12 (40)	6 (46)	0 (0)
Amiodarone	11 (37)	4 (31)	0 (0)
Immunosuppression	—	—	13 (100)

N/A, not available; CHF, congestive heart failure; CT, cardiac transplantation; EF, ejection fraction; CI, cardiac index; PCP, pulmonary capillary pressure; RAP, right atrial pressure; PAR, pulmonary arteriolar resistance; Po₂, partial pressure of oxygen in blood; Pco₂, partial pressure of carbon dioxide in blood.

Table 2 Indices of heart rate variability (mean (SEM))

	Mean RR (ms)	Total Power (ms ²)	LF (ms ²)	LF (nu)	HF (ms ²)	HF (nu)	LF/HF (ratio nu)
CHF:							
Total group (n = 30)	803 (24)*	496 (121)†					
With LF (n = 16)	864 (36)§	902 (202)‡	203 (55)	67 (6)*	78 (23)	26 (5)*	3.31 (0.8)*
Without LF (n = 14)	745 (25)§	118 (16)‡			82 (28)	69 (4)	—
CT (rec):							
Total group (n = 13)	809 (44)*§	324 (91)†‡					
With LF (n = 6)	816 (58)§	527 (33)‡§	209 (57)	72 (8)*	53 (29)	14 (3)*	5.21 (1.5)*
Without LF (n = 7)	803 (70)§	150 (46)‡§			72 (32)	62 (9)	—
CT (don):							
Total group (n = 13)	755 (27)§	12 (3)‡					
With LF (n = 5)	772 (28)	12 (8)	1.5 (1)	24 (3)	5.8 (2)	63 (4)	0.46 (1.6)
Without LF (n = 8)	744 (59)	11 (6)			4.4 (1)	57 (8)	—
Controls (n = 15)	921 (37)	1821 (325)	354 (87)	49 (3)	223 (55)	38 (3)	1.6 (0.6)

CHF, chronic heart failure; CT (rec), recipient atrium rhythm; CT (don), donor heart rhythm; LF, low frequency power; HF, high frequency power

* $p < 0.05$ v controls; † $p < 0.002$ v controls; ‡ $p < 0.005$; § $p < 0.05$.

921(37) ms ($p < 0.05$) and 496(121) v 1821(325) ms², ($p < 0.002$) respectively). Spectral analysis did not show any LF component (specifically any discrete peak in the 0.03–0.15 Hz band) in 14 of the 30 patients studied, whereas in the remaining subjects

the LF component predominated over the HF component (LF = 203(55) ms², HF = 78(23) ms²) fig 3A). The finding was the same when the LF and HF components were expressed as normalised units: both LF and the LF/HF ratio were significantly higher and HF was significantly lower in patients with heart failure than in the controls (LF 67(6) v 49(3) nu, $p < 0.05$; HF 26(5) v 38(3) nu, $p < 0.05$; LF/HF ratio 3.31(0.8) v 1.6(0.6), $p < 0.05$). Mean RR and total power were lower in patients without a detectable LF component than in those with an LF component (RR 745(25) v 864(36) ms, $p < 0.05$; TP 118(16) v 902(202) ms², $p < 0.005$). Moreover ventricular function (ejection fraction 17.7(1) v 21.4(1)%, $p < 0.05$) and functional class (8 class IV plus 6 class III v 16 class III) were worse in those patients without detectable LF than in those with a detectable LF component.

Plasma noradrenaline was measured in the last 14 patients examined (mean 461(60) pg/ml). Concentrations were significantly higher in patients with undetectable LF than in those with detectable LF (635(75) v 329(54) pg/ml, $p < 0.05$).

Post-transplant group—We analysed the heart rate variability of the RR interval sequences of the donor heart and the PP interval sequences of the recipient atrium, which is normally innervated and can reflect the changes in the sympathovagal activity of the heart after the restoration of the cardiac function. The mean RR interval of the donor heart was 755(27) ms; there was little fluctuation around the mean and the total power was 12(3) ms². In all donor recordings a high frequency component was evident, whereas no power in the low frequency band was detectable in eight of the 13 patients. Five had a well defined low frequency peak though it was of a very low amplitude (1.5(1) ms², 24(3) nu, 0.09(0.02) Hz) (fig 3B). Compared with the donor rhythm, the recipient atrium showed a significantly different mean PP interval (809(44) ms, $p < 0.05$), and a greater total power (324(91) ms², $p < 0.005$). Spectral components of PP variability were detected at the same frequency bands as the donor heart fluctuations (LF 0.091(0.01) v 0.088(0.02) Hz, NS; HF 0.30(0.03) v 0.30(0.02) Hz, NS). The LF component was

Figure 3 Examples of decomposition of the entire spectrum into the single spectral components from a patient with heart failure (A), a donor heart (B), and a native atrium (C). In all the groups on the left the low frequency power was undetectable and the small amount of total variability was concentrated in the high frequency band; the prevalence of low frequency power is shown on the right hand side. PSD, power spectral density.

Figure 4 Relation between total power (ms^2) and interval since cardiac transplantation (CT).

still not detectable in seven of the 13 patients (example fig 3C). The LF component (when present), and HF component were both of significantly greater amplitude than the donor rhythm components (LF 209(57) *v* 1.5(1) ms^2 ; HF 63(21) *v* 5.1(1) ms^2). Like the patients with heart failure, post-transplant patients with a detectable LF component had a larger total power than those without LF (527(33) *v* 150(46) ms^2 , $p < 0.05$); also the interval between operation and assessment of heart period variability was significantly longer in those with LF (respectively 51(5) *v* 29(6) days, $p < 0.05$).

COMPARISON BETWEEN PATIENTS WITH HEART FAILURE AND POST-TRANSPLANT PATIENTS

There were no significant differences between

the spectral indices of PP variability of the post-transplant remnant atrium and the RR variability of patients with heart failure. The two groups showed a similar mean PP and RR interval (809(44) *v* 803(24) ms, $p = 0.76$) and no significant difference in total power (324(91) *v* 496(121) ms^2 , $p = 0.49$). In addition the percentages of patients with an undetectable LF component (54% *v* 47%) and both LF (when present), and HF powers were not significantly different in the two groups.

CORRELATION WITH CLINICAL VARIABLES

In both groups (heart failure and post-transplant) there was no significant correlation between the duration of heart failure symptoms and the mean PP or RR interval and total power. Blood sodium concentration and blood gas partial pressures were not related to the indices of heart period variability. In post-transplant patients plasma cyclosporin concentrations were unrelated to the rhythm variability of the recipient atrium ($r = 0.40$, $p = 0.17$) whereas the total power of the mean PP interval was significantly related to the interval since heart transplantation ($r = 0.68$, $p < 0.01$) (fig 4).

Discussion

Our data showed that in the more advanced stages of heart failure, heart rate variability was so reduced that neural modulation of cardiac rate seemed almost lost. Power spectral analysis of heart rate variability may allow identification of a subgroup of patients—with undetectable power in the low frequency band—who show increased sympathetic activation as assessed by plasma noradrenaline blood concentrations, more severe clinical status, and a worse prognosis. The spectral profile of the variability of the recipient sinus node soon after cardiac transplantation showed that sympathetic overactivity and parasympathetic withdrawal persisted despite restoration of ventricular function.

HEART PERIOD VARIABILITY IN CONGESTIVE HEART FAILURE

Like others we found that heart period variability was reduced in patients with congestive heart failure.^{4 5 26 27} We identified two different spectral patterns. The first was characterised by a predominant LF component and a reduced HF component, suggesting sympathetic predominance and parasympathetic withdrawal. In the second we found a major reduction in total power, an undetectable LF component and a low amplitude HF peak. Patients with undetectable LF were more severely affected, with depressed left ventricular function and a higher degree of sympathoexcitation, reflected by the higher plasma noradrenaline concentrations. The apparent paradox of more pronounced sympathetic hyperactivity associated with an undetectable LF component (considered by some to be a marker of sympathetic activity^{9 11 19 22} is explained by the concept that in the more severe stages of the disease the neurohormonal excitation reduces reflex

Figure 5 Examples of spectral decomposition of donor heart (A) and native atrium (B) tachograms, systogram (systolic arterial pressure time series) (C) and respirogram (D) in the same recording segment. In panel A there is a defined peak in the low frequency band, synchronous (coherence = $K2 > 0.5$) with the systogram and tachogram of the native atrium, suggesting a possible influence of systolic pressure fluctuations on donor heart rhythm variability.

modulation of heart rate to a such extent that above 0.03 Hz, only small fluctuations that are synchronous with breathing activity are detectable.²⁴⁻²⁸ Interestingly the progressive reduction in the LF power that is seen during exercise-induced sympathetic hyperactivation seems to confirm that this part of the spectrum is markedly affected by overstimulation of the sympathetic system.²⁹ Hence, in our population, patients with undetectable LF and much reduced total power may be regarded as the far end of a range of sympathoexcitation which can be assessed by heart rate variability. Recent data showing a close and negative correlation between the amount of heart rate variability and plasma noradrenaline concentrations or muscle sympathetic activity are consistent with this idea.²⁷ On the other hand we cannot exclude the possibility that abnormalities or "saturation" of the response of the sinus node to changes in efferent traffic can conceal the sympathetic overactivity on heart rate fluctuations.

Our data accord with studies by Saul *et al*⁴ even though they used a different processing method; they reported no power component between 0.04 and 0.15 Hz and a small but discernible peak in the HF band. Saul *et al* detected a consistent power in the VLF band (below 0.04 Hz) but this was less effective in distinguishing between heart failure patients and controls than distribution of the power above 0.04 Hz. Though the power in the VLF band may be of clinical relevance (despite the absence of experimental data), we focused our attention on the two bands (LF and HF) that at experimental and clinical levels have been more extensively related to the sympathovagal activity that modulates the heart rhythm.^{9-11, 22}

It has been suggested that parasympathetic activity is inversely related and that sympathetic activity and noradrenaline concentrations are directly related to the severity of heart failure and prognosis.^{1, 3, 30, 31} Though we studied only a small number of patients, within a follow up of six months there were four deaths (two of them due to arrhythmia and two preceded by symptoms of worsening pump failure) in the patients with undetectable LF and no deaths in the group in which the LF component predominated over the HF component. These findings raise the possibility that in patients with heart failure the extent of autonomic abnormalities gives information on the prognosis, just as reduced heart rate variability and depressed baroreflex sensitivity do after myocardial infarction.^{32, 33} Specifically a pattern of low total power and an undetectable LF component may be useful in identifying heart failure patients with a more pronounced sympathoexcitation.

HEART PERIOD VARIABILITY AFTER HEART TRANSPLANTATION

Denervated heart

As in other studies³⁴⁻³⁶ the heart rate variability of the denervated heart was markedly reduced by the interruption of the sympathetic and parasympathetic fibres. There is controversy over whether any power spectral components

are recognisable after spectral decomposition. In all patients we detected a high frequency peak that was synchronous with respiration. In the denervated heart the high frequency component was interpreted as being caused by an intrinsic mechanism (mechanically induced) of the heart muscle independent of neural regulation.²⁴ In a few patients we also observed a well defined peak in the low frequency band that cannot simply be due to sympathetic or baroreflex activity (as it is in the intact heart). This observation is consistent with previous reports,^{35, 36} and it is not accounted for by the results presented in this paper. However, when we examined our preliminary data on polyparametric spectral analysis of different signals in post-transplant patients (donor heart rate, recipient atrium rate, respiratory signal, and systolic blood pressure), we found that the low frequency peaks of the donor heart and remnant atrium and systolic blood pressure variability, if present, were all in the same frequency band (0.08–0.1 Hz) and significantly coherent ($K2 > 0.5$), occurring at a frequency not related to breathing activity (fig 5). If confirmed, these data indicate a possible influence of systolic pressure fluctuations on the variability of the donor heart rhythm.

Recipient remnant atrium

During heart transplantation a portion of the recipient atrium, including the sinus node, is left in situ and remains normally innervated. Thus the analysis of the sinus node variability of the remnant atrium gives an opportunity of studying the sympathovagal influences on the heart after normal haemodynamic function is restored. In heart failure patients the time domain indices of heart rate variability remained subnormal after cardiac transplantation.¹² We attempted to distinguish between the contributions of vagal and sympathetic activity by using frequency domain measurements. In our study the total spectral variability of the PP interval was significantly larger than the donor rhythm variability, confirming that there is neural modulation of the recipient sinus node. We also found in these sequences that breathing activity regulates the heart rate fluctuations in the high frequency band and that the low frequency component is detectable only in subjects with larger variability. Our comparison of power spectrum findings in post-transplant and heart failure patients showed that 4–6 weeks after transplantation all the spectral indices of heart period variability of the innervated recipient atrium were still impaired. In our population total power was reduced in all patients and the low frequency component was not detectable in seven out of 13 patients. Table 2 shows that neither the high frequency nor low frequency components, when present, had a significantly different power compared with the heart failure group, thus suggesting that sympathetic overactivity and parasympathetic withdrawal had not returned to normal. These observations suggest that nerve traffic to the heart is not restored by haemodynamic

improvement soon after heart transplantation, and tends to normalise later. This time-dependent resumption was reported by others^{7,12} and there is evidence for it in our study in the significant correlation between total power and the interval since heart transplantation. These observations of a delayed resumption of variability of the remnant sinus node despite normalisation in left ventricular function indicate that remnant atrium variability is unlikely to be a reliable marker of sympathovagal balance after heart transplantation. Nevertheless, despite removal of its normal blood supply the recipient sinus node usually remained viable and responded appropriately to physiological stimuli.^{14,37}

MECHANISMS OF SYMPATHETIC OVERACTIVITY AFTER SHORT-TERM HEART TRANSPLANTATION
Though restoration of the balance of sympathovagal influence on the heart after transplantation is time dependent, our data showed that 4–6 weeks after the operation both parasympathetic withdrawal and sympathetic overactivity persisted. Evidence of sympathetic overactivity was reported by Mohanty *et al*³⁸ who found that forearm vasoconstriction and plasma noradrenaline responses to the application of lower body negative pressure were also impaired after orthotopic heart transplantation despite the normalisation of resting noradrenaline concentrations. Moreover, muscle sympathetic nerve overactivity was detected in post-transplant patients when plasma noradrenaline concentrations were much lower than in congestive heart failure but still in the upper limit of the normal range.³⁹ These findings suggest only a weak correlation between noradrenaline concentrations and sympathetic nerve traffic in post-transplant patients.

The sympathovagal imbalance we found 4–6 weeks after cardiac transplantation may be related to a delayed recovery though other factors contributing to sympathetic overactivity itself cannot be excluded. Among these factors is cardiac surgery which was shown to increase sympathetic outflow to the heart and increase its rate.⁴⁰ Several features of cardiac surgery may be involved. These include the ischaemia time of the donor heart, the anaemia that follows heart transplantation, and manipulation of the pericardium, which in the intact heart regulates sympathetic tone through prostaglandin secretion.⁴¹ In addition ventricular deafferentation of the donor ventricles may impair the tonic inhibitory influence on the sympathetic outflow that originates from sensory receptors in the cardiopulmonary region.³⁸ Cyclosporin treatment too may be involved in sympathetic activation.³⁹ Though the influence of cyclosporin cannot be excluded in our study, it seems unlikely, because patients with hypertension were excluded and no relation was found between the blood concentration of cyclosporin and the total heart rate variability. Moreover normotensive patients with kidney transplants treated with similar doses of immunosuppressant therapy did not show any

signs of sympathetic cardiac overactivity.³⁸ Normal right atrial pressure in our patients (table 1) seems to exclude the possibility of volume overload that could have induced mechanical stretch of the remnant atrium.

POTENTIAL LIMITATIONS

A possible limitation of our study is that we compared different groups of patients before and after heart transplantation. However, as table 1 shows, the haemodynamic and clinical states of transplant patients before operation resembled the heart failure group. Ventricular function was impaired and the NYHA functional class, indicated a similar imbalance in the autonomic nervous system in all patients. Furthermore we excluded post-transplant patients in whom hypertension developed because this affects the restoration of sympathovagal balance.^{7,12}

Pharmacological agents are among the factors that might have influenced our data. Post-transplant patients were treated mainly with diuretics and none was treated with β blockers or calcium antagonists. So this group of patients was influenced solely by immunosuppressive therapy. In the heart failure group a pharmacological influence on sympathovagal balance cannot be excluded, particularly in those patients treated with angiotensin converting enzyme inhibitors or digoxin.^{42,43} None the less, the clinical state of our patients would only allow changes or withdrawal of drug therapy at the expense of losing the "steady condition".

In conclusion, in our study, which because of its limited size should be regarded as a pilot study, power spectrum analysis of heart rate variability seemed to be a valid technique to identify non-invasively those patients with severe heart failure who show more pronounced sympathetic activation. If neural derangement is involved in the progression and worsening of heart failure, this subgroup of patients may be at higher risk of adverse events: our limited follow-up data are consistent with this suggestion. In the short-term after heart transplantation the spectral profile of heart rate variability does not seem to improve, suggesting the persistence not only of parasympathetic withdrawal but also of sympathetic hyperactivity. Continuing follow up of such patients will probably clarify the natural course of the recovery and whether a full recovery can be attained.

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