Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function

J Nolan, A D Flapan, S Capewell, T M MacDonald, J M M Neilson, D J Ewing

Abstract

Background—Activation of the sympathetic nervous system has been extensively studied in patients with chronic heart failure, but the parasympathetic nervous system has received relatively little attention. The objective in this study was to investigate cardiac parasympathetic activity in chronic heart failure and to explore its relation to left ventricular function.

Methods—Heart rate variability was measured from 24 hour ambulatory electrocardiograms by counting the number of times each RR interval exceeded the preceding RR interval by more than 50 ms (counts). This method provided a sensitive index of cardiac parasympathetic activity.

Results—Mean (range) of counts were: waking 48 (1–275)/h, sleeping 62 (0–360)/h, and total 1310 (31–7278)/24 h. These were lower than expected, and in 26 (60%) of the 43 patients counts fell below the lower 95% confidence intervals (95% CI) for RR counts in normal subjects. A significant correlation between total 24 hour RR counts and left ventricular ejection fraction was present ($r = 0.49$, $p < 0.05$).

Conclusions—These results indicate that most patients with chronic heart failure have reduced heart rate variability and therefore reduced cardiac parasympathetic activity. The degree of parasympathetic dysfunction is related to the severity of left ventricular dysfunction. This may be relevant to the high incidence of ventricular arrhythmias and poor prognosis of patients with chronic heart failure.

Unlike most other diseases of the cardiovascular system, the incidence and prevalence of chronic heart failure is rising in the Western world.^{1,2} Chronic heart failure is therefore an increasing cause of disability and death in the community.

Autonomic control of the cardiovascular system is deranged in chronic heart failure and contributes to the pathophysiology of the syndrome.³ The sympathetic nervous system has been widely studied and its activity is enhanced in chronic heart failure.⁴ The

amount of sympathetic activation is linked to symptoms⁵ and haemodynamic indices of impaired left ventricular function.^{6,7} Although the sympathetic nervous system is activated in chronic heart failure, reflex changes in autonomic activity during stress are impaired.^{8,9} Increasing sympathetic activation is associated with a progressive rise in afterload leading to a deterioration in myocardial pump function^{7,10,11} and has an inverse relation with survival.¹² Although abnormal parasympathetic function has also been found in chronic heart failure, this has not been extensively studied.^{13,14}

Analysis of variability of heart rate has been developed over the last decade as a useful non-invasive way of measuring activity of the autonomic nervous system. We have developed a method, with 24 hour electrocardiograms, that is a reliable and a specific index of cardiac parasympathetic function,¹⁵ and is valid even in the presence of frequent ventricular extrasystoles.¹⁶

Our aims in this study were to determine whether abnormal cardiac parasympathetic activity is present in patients with chronic heart failure and to examine the relation between resting left ventricular function and cardiac parasympathetic function.

Patients and methods

PATIENTS WITH CHRONIC HEART FAILURE

Sixty ambulatory patients (42 men) with chronic heart failure due to ischaemic heart disease were studied. Their mean age was 61 (range 36–72), and all had moderate limitation of their daily activities, categorised as grade II or III of the New York Heart Association (NYHA) classification. Resting left ventricular function was impaired in all patients. This was assessed by a standard radionuclide technique for calculation of ejection fraction.¹⁷ The mean (range) ejection fraction of patients was 17.8 (5–35)%. All patients were in sinus rhythm.

Patients were receiving only diuretics to control their chronic heart failure, with a mean (range) frusemide dose of 102 (40–160) mg. No patient had diabetes or renal failure and their clinical state had been stable for at least three months before the study. No patient had any history or clinical evidence of autonomic neuropathy. Because a recent myocardial infarction may affect cardiac parasympathetic activity, we excluded all patients with a

University
Departments of
Medicine, Medical
Physics, and
Engineering and
Department of
Cardiology, Royal
Infirmary, Edinburgh

J Nolan
A D Flapan
S Capewell
T M MacDonald
J M M Neilson
D J Ewing

Correspondence to:
Dr J Nolan,
Department of Medicine,
Royal Infirmary,
Edinburgh EH3 9YW.

Accepted for publication
30 October 1991

documented myocardial infarction during the previous six months.

Tapes from 17 patients were excluded from analysis because of the presence of frequent supraventricular extrasystoles or technical problems with tape quality. There were no significant differences in baseline characteristics between the 43 patients (30 men, 13 women) included and the 17 patients (12 men, five women) excluded from further study.

METHODS

Electrocardiograms were obtained with a miniature tape recorder (Tracker, Reynolds Medical Limited) for 24 hours from all patients during normal ambulant out of hospital activities. Times of going to bed and getting up were noted by the patients.

Tapes were replayed through a Pathfinder arrhythmia analyser (Reynolds Medical Limited) at 120 times the original recording speed. Heart rate variability was then assessed by the count based time domain method we have previously described.^{15 16} Briefly, each RR interval was measured and successive beat by beat RR interval differences calculated. Each time an RR interval exceeded the preceding interval by more than 50 milliseconds a count was registered. Counts were accumulated and the results presented as total 24 hour RR counts, mean hourly waking RR counts, mean hourly sleeping RR counts, and mean waking and sleeping heart rates.

Segments of tape in which changes in RR intervals occurred due to the presence of ventricular extrasystoles were excluded from analysis by the Pathfinder arrhythmia analyser, which detected ventricular extrasystoles due to the difference in their morphology and timing.^{16 18} As the Pathfinder arrhythmia analyser is unable to detect atrial arrhythmias, the signal was also closely monitored by the operator and tapes in which atrial arrhythmias occurred were discarded. Where less than 24 hours of recording were available for analysis, the results were normalised to the equivalent of 24 hours. Recordings shorter than 18 hours or with less than 40% of the tape suitable for analysis were rejected.

We have already defined normal age related 95% confidence intervals (95% CI) for counts with the same equipment and technique.¹⁹ Values obtained from patients with chronic heart failure have been compared with this normal range.

We have discussed the reasons why our technique provides a measure of cardiac parasympathetic activity.^{15 20} Abrupt changes in RR interval that occur at the start of muscular exercise, standing up, or lying down, are mediated by the vagus nerve.²¹⁻²³ Variation in RR interval is abolished in animals by cutting the vagus nerve²⁴ and in humans by parasympathetic blockade with atropine,²⁰ but is unaffected by β adrenoreceptor blockade.¹⁵ Patients with transplanted hearts and diabetic patients with cardiovascular reflex evidence of vagal damage have very little variability in RR interval as measured by our technique.¹⁵ Also, animal studies suggest that the degree of

respiratory sinus arrhythmia is directly related to vagal efferent activity.²⁵⁻²⁷

Our method also correlates well with the high frequency (>0.15 Hz) band of the power spectrum,²⁸ which is thought to be mediated by cardiac parasympathetic pathways.^{29 30} Our method is probably more specific as a measure of cardiac parasympathetic activity than other commonly used time domain methods.²⁸ RR interval counts that fall below the normal lower 95% CI therefore represent reduced cardiac parasympathetic activity.

STATISTICAL ANALYSIS

Because the RR counts are not normally distributed data were log transformed before analysis. A simple linear regression was used to investigate the relation between total 24 hour RR counts and ejection fraction. Counts are expressed as geometric mean (range). Heart rates are expressed as arithmetic mean (SD).

Results

HEART RATE VARIABILITY

Group mean (range) counts of RR interval changes were; waking 48 (1-275)/h sleeping 62 (0-360)/h, and total 1310 (31-7278)/24 h. Counts were lower than the predicted mean values for normal subjects of the same mean age of 61 years (waking 72, sleeping 122, and total 2512). Figure 1 depicts total 24 hour RR counts plotted against age. Twenty six of the 43 patients fell below the lower 95% CI for normal subjects. Mean waking (85 (14) beats per min) and sleeping (77 (15) beats per min) were normal.

Figure 1 Total 24 hour counts of RR interval changes plotted against age. Solid lines represent 95% confidence intervals (95% CI) for counts in normal subjects. Twenty six of the 43 patients with chronic heart failure had values below the lower 95% CI.

Figure 2 Total 24 hour counts of RR interval changes plotted against radionuclide ejection fraction. A significant relation exists, with the lowest counts obtained in those patients with the most severe impairment of left ventricular function.

RELATION BETWEEN HEART RATE VARIABILITY AND LEFT VENTRICULAR FUNCTION

Figure 2 shows the relation between total 24 hour RR counts and left ventricular ejection fraction. A significant linear correlation was found with the lowest counts obtained in the patients with the greatest impairment of left ventricular function ($r = 0.49$, $p < 0.05$).

Discussion

We have shown in our study that most of our patients with chronic heart failure due to ischaemic heart disease have reduced heart rate variability and by inference, therefore, reduced cardiac parasympathetic activity. Also, we have shown that a significant relation exists between the severity of left ventricular dysfunction and the extent of parasympathetic impairment. These findings have a number of potential implications.

Previous studies have shown that sympathetic activation occurs in chronic heart failure,⁴ initially as a compensatory mechanism to maintain adequate central blood pressure.³¹ The role of the parasympathetic nervous system in the pathophysiology and prognosis of chronic heart failure has not been studied in depth. Two previous studies of heart rate variability in chronic heart failure, one using power spectral analysis,³² and the other a standard deviation method of analysis,³³ show a similar pattern of reduced heart rate variability but suffer from certain drawbacks. Standard deviation methods do not clearly differentiate between sympathetic and parasympathetic influences. Power spectral analysis, unlike our method, is rendered unreliable in the presence of ventricular extrasystoles, which occur frequently in patients with chronic heart failure. Our method is specific as a measure of parasympathetic function and clearly shows that impaired cardiac parasympathetic activity occurs throughout the 24 hour period.^{15 16 19 20 28}

Both resting left ventricular function and the amount of sympathetic activation are linked to prognosis in patients with chronic heart failure.^{12 34 35} Patients with severe impairment of left ventricular function have maximal

activation of the sympathetic system. We have shown that a similar relation exists for impaired parasympathetic function.

There are several potential mechanisms to explain the abnormalities we found. The renin angiotensin system is activated in patients with symptomatic chronic heart failure of NYHA grade II and greater treated with diuretics,^{4 36 37} and there is evidence that the amount of this activation is proportional to the clinical severity of the heart failure.³⁸ Angiotensin II is known to interact both centrally and peripherally with the autonomic nervous system to enhance sympathetic^{39 40} and inhibit parasympathetic activity.^{41 42} Increasing neuroendocrine activation in patients with chronic heart failure may therefore explain the presence of parasympathetic impairment and its relation to impaired left ventricular function. An alternative or additional mechanism in patients with ischaemic heart disease could be direct injury to intracardiac nerves and receptors, leading to disruption of autonomic reflexes. We have previously shown that parasympathetic impairment occurs early in the course of anterior myocardial infarction.²⁰ As chronic heart failure is more likely to occur after anterior than inferior infarction, this lends support to direct damage as a possible mechanism for original parasympathetic impairment in these patients, with increasing neuroendocrine activation contributing to progressive changes in those patients whose left ventricular function declines with time.

Sudden death occurs in almost 50% of patients with chronic heart failure.^{2 43} Autonomic imbalance is known to be linked to the production of ventricular arrhythmias that are thought to be the cause of sudden death in most patients with chronic heart failure.^{44 46} The reduction of parasympathetic activity that we have shown to occur in the presence of sympathetic overactivity, may therefore provide suitable conditions for the production of ventricular arrhythmias. We have already investigated the role of the angiotensin converting enzyme inhibitor captopril in regulating parasympathetic activity in chronic heart failure.⁴⁷ Captopril is known to have a beneficial effect on the incidence of ventricular arrhythmias⁴⁸ and sudden death in chronic heart failure.⁴⁹ The increase in parasympathetic activity that we demonstrated along with the reduction in sympathetic activity that is known to occur with captopril treatment, may be relevant to these effects.

We have also studied the effect of class I and class III antiarrhythmic drugs, commonly used in the treatment of ventricular arrhythmias in patients with chronic heart failure.¹⁶ Some class I agents reduce cardiac parasympathetic activity and this may be an important factor in the adverse effect on prognosis that can occur when class I agents are used to treat ventricular arrhythmias in patients with impaired ventricular function.⁵⁰ By contrast, the class III agent amiodarone does not reduce cardiac parasympathetic activity. This may explain why this agent does not have an adverse effect⁵¹ and may improve survival⁵² when used to treat

ventricular arrhythmias in chronic heart failure.

In conclusion, we have shown that cardiac parasympathetic activity is reduced in most patients with chronic heart failure and that the magnitude of this reduction is correlated with the severity of left ventricular impairment. Reduced heart rate variability is a powerful independent risk factor for sudden death in survivors of myocardial infarction.⁵³ Long term follow up studies of patients with chronic heart failure are now needed to find out whether reduced heart rate variability will have a similar predictive value in these patients.

- 1 Ghali JK, Cooper R, Ford E. Trends in hospitalization rates for heart failure in the United States 1973–1986: evidence for increasing population prevalence. *Arch Intern Med* 1990;150:769–73.
- 2 McFate Smith W. Epidemiology of congestive heart failure. *Am J Cardiol* 1985;55:3A–8.
- 3 Thomas P, Sheridan DJ. Pathophysiology of autonomic dysregulation in heart failure. In: Bannister R, ed. *Autonomic Failure. A textbook of disorders of the autonomic nervous system*. 2nd ed. Oxford: Oxford University Press, 1988:97–112.
- 4 Mancica G. Neurohormonal activation in congestive heart failure. *Am Heart J* 1990;120:1532–7.
- 5 Thomas AJ, Marks BH. Plasma norepinephrine in congestive cardiac failure. *Am J Cardiol* 1978;41:233–43.
- 6 Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to haemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659–66.
- 7 Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 1982;104:725–31.
- 8 Levine TB, Francis GS, Goldsmith SR, Cohn JN. The neurohumeral and haemodynamic response to orthostatic tilt in patients with congestive heart failure. *Circulation* 1983;67:1070–5.
- 9 Cody RJ, Franklin KW, Kluger J, Laragh JH. Mechanisms governing the postural response and baroreceptor abnormalities in chronic congestive heart failure: effects of acute and long term converting enzyme inhibition. *Circulation* 1982;66:135–42.
- 10 Dzau VJ, Hollenberg NK, Williams GH. Neurohormonal mechanisms in heart failure: role in pathogenesis, therapy, and drug tolerance. *Federation Proceedings* 1983;42:3162–9.
- 11 Francis GW, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to haemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659–66.
- 12 Cohn JN, Levine TB, Olivari MT, Carberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:119–23.
- 13 Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877–83.
- 14 Goldstein RE, Beiser GD, Stampfer M, Epstein SE. Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. *Circ Res* 1975;36:571–8.
- 15 Ewing DJ, Neilson JMM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. *Br Heart J* 1984;52:396–402.
- 16 Zuanetti G, Latini R, Neilson JMM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with cardiac arrhythmias: effect of antiarrhythmic drugs. *J Am Coll Cardiol* 1991;17:604–12.
- 17 Wathen CG, Muir AL, Hannan WJ. Radionuclide studies of left ventricular function in normal subjects. *Nucl Med Commun* 1990;11:607–15.
- 18 Neilson JMM. Computer detection of ventricular ectopic beats: On line and off. In: *Computers in cardiology*. Los Alamitos: IEEE Computer Society Press, 1975:33–5.
- 19 Ewing DJ, Neilson JMM, Shapiro CM, Steward JA, Reid W. 24 hour heart rate variability: effects of posture, sleep and time of day in normal subjects and comparison with bedside autonomic function tests in diabetic patients. *Br Heart J* 1991;65:239–44.
- 20 McAreavey D, Neilson JMM, Ewing DJ, Russell DC. Cardiac parasympathetic activity during the early hours of acute myocardial infarction. *Br Heart J* 1989;62:165–70.
- 21 Fagraeus L, Linnarsson D. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. *J Appl Physiol* 1976;40:679–82.
- 22 Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. *J Appl Physiol* 1980;49:809–14.
- 23 Bellavere F, Ewing DJ. Autonomic control of the immediate heart rate response to lying down. *Clin Sci* 1982;62:57–64.
- 24 Samaan A. The antagonistic cardiac nerves and heart rate. *J Physiol* 1935;83:332–40.
- 25 Katona PG, Tih F. Respiratory sinus arrhythmias: non-invasive measure of parasympathetic cardiac control. *J Appl Physiol* 1975;39:801–5.
- 26 Eckberg DL. Human sinus arrhythmias as an index of vagal cardiac outflow. *J Appl Physiol* 1983;54:961–6.
- 27 Eckberg DL. Parasympathetic cardiovascular control in human disease: a review of methods and results. *Am J Physiol* 1980;239:H581–93.
- 28 Myers GA, Martin GJ, Magid NM, Barnett PS, Schaad JW, Weis JS, Lesch M, Singer DH. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *Trans Biomed Eng* 1986;33:1149–56.
- 29 Askelrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213:220–3.
- 30 Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;248:H151–3.
- 31 Zelis R, Mason DT. Compensatory mechanisms in congestive heart failure — the role of the peripheral resistance vessels. *N Engl J Med* 1970;282:962–4.
- 32 Saul JP, Yutaka A, Berger RD, Lilly LS, Collucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol* 1988;61:1292–9.
- 33 Casolo G, Balli E, Taddei T, Amuhaji J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. *Am J Cardiol* 1989;64:1162–7.
- 34 Unverferth DV, Magorien DR, Moeschberger ML, Baker PB, Fettes JK, Leier CV. Factors influencing the one year mortality of dilated cardiomyopathy. *Am J Cardiol* 1984;54:147–52.
- 35 Schwarz F, Mall G, Zebe H, Schmitzer E, Martley J, Scheurien H, Kubler W. Determinants of survival in patients with congestive cardiomyopathy: quantitative morphological findings and left ventricular haemodynamics. *Circulation* 1984;70:923–8.
- 36 Genest J, Granger P, De Champlain J, Boucher R. Endocrine factors in congestive heart failure. *Am J Cardiol* 1968;22:35–42.
- 37 Laragh JH. Endocrine mechanisms in congestive heart failure. Renin, aldosterone and atrial natriuretic hormone. *Drugs* 1986;32(suppl 5):1–12.
- 38 Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin aldosterone system to clinical state in congestive heart failure. *Circulation* 1981;63:645–51.
- 39 De Jonge A, Knappe JTA, Van Meel JCA, et al. Effect of captopril on the sympathetic neurotransmission in pithed normotensive rats. *Eur J Pharmacol* 1983;88:231–5.
- 40 Zimmerman BG. Adrenergic facilitation by angiotensin: does it serve a physiological purpose. *Clin Sci* 1981;60:343–4.
- 41 Potter EK. Angiotensin inhibits the action of the vagus nerve at the heart. *Br J Pharmacol* 1982;75:9–11.
- 42 Lumbers ER, McCluskey DI, Potter EK. Inhibition by angiotensin II of baroreceptor evoked activity in cardiac vagal efferent nerves. *J Physiol* 1979;294:69–80.
- 43 Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;72:681–5.
- 44 Schwartz PJ. Sympathetic imbalance and cardiac arrhythmias. In: Randall WC (ed). *Nervous Control of Cardiovascular Function*. Oxford: Oxford University Press 1984:225–52.
- 45 Verrier RL, Lown B. Sympathetic parasympathetic interactions and ventricular electrical stability. In: Schwartz PJ, Brown AM, Malliani A, Zanchetti A, eds. *Neural Mechanisms in Cardiac Arrhythmias*. New York: Raven Press, 1977:75–86.
- 46 McAreavey D, Neilson JMM, Russell DC. Evidence for reduced vagal tone preceding ventricular fibrillation in man. *Eur J Clin Invest* 1986;16:A5.
- 47 Flapan AD, Nolan J, Neilson JMM, Ewing DJ. Captopril therapy increases parasympathetic activity in patients with congestive cardiac failure. *Circulation* 1990;82(suppl III):382.
- 48 Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, et al. Captopril in heart failure—a double blind controlled trial. *Br Heart J* 1984;52:530–5.
- 49 Newman TJ, Maskin CS, Dennick LG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *Am J Med* 1988;84:140–44.
- 50 The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report. Effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. *New Engl J Med* 1989;321:406–12.
- 51 Stewart RA, McKenna WJ, Poloniecki JD, Michelson JK, Das SK, Morady F, et al. Prospective randomised double blind placebo controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular extra systoles. *Br Heart J* 1989;61(S):459–60.
- 52 Cleland JGF, Dargie HJ, Findlay IN, Wilson JT. Clinical haemodynamic and anti arrhythmic effects of long term treatment with amiodarone of patients in heart failure. *Br Heart J* 1987;57:436–45.
- 53 Kleiger RE, Miller JP, Bigger JT, Moss AJ. Multicentre post infection research group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–62.