REVIEW

Heart rate variability in left ventricular dysfunction and heart failure: effects and implications of drug treatment

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Abstract

Objective—To review the importance of heart rate variability analysis in left ventricular dysfunction and heart failure and to assess the effects of drug treatment. In patients with left ventricular dysfunction or heart failure, a low heart rate variability is a strong predictor of a low probability of survival. Because drug treatment in these patients has rapidly changed over the past two decades, the effect of these drugs on heart rate variability needs special attention.

Design—A study of published reports to give an overview of heart rate variability in patients with left ventricular dysfunction or heart failure and how it is affected by drug treatment.

Results—Analysis of heart rate variability provides an easily obtained early marker for progression of disease. It seems to be more closely related to the degree of neurohumoral activation than to haemodynamic variables. Cardiovascular drugs may either stimulate or inhibit the degree of neurohumoral activation, and the effects of pharmacological intervention can be closely monitored with this method.

Conclusions—The analysis of heart rate variability, including spectral analysis, is a novel non-invasive way to obtain potentially useful clinical information in patients with reduced left ventricular function. The effects of drug treatment on heart rate variability are in general consistent with their long-term effects in left ventricular dysfunction and heart failure.

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Therefore, the autonomic changes found in patients with LV dysfunction and chronic heart failure can set the stage for sudden cardiac death.

Measurement of HR variability provides a non-invasive method to obtain reliable and reproducible information on autonomic modulation of HR⁸ and has become an important tool for risk assessment. As the incidence of sudden death is disproportionately high in patients with mild heart failure but a relatively preserved LV function,⁹ it is very important to identify these patients. Obviously, in this group of patients sudden death is particularly devastating.¹⁰

Measurement of HR variability may also be used to evaluate the effects of drug treatment in these patients. In this review, we discuss the current data on HR variability in LV dysfunction and heart failure. Furthermore, the effects of drug interventions on HR variability are considered and implications for clinical use of analysis of HR variability are suggested.

Heart rate variability in left ventricular dysfunction and heart failure

Under physiological conditions, there are periodic fluctuations of HR due to respiration, baroreflexes, and slow variations—for example, temperature regulation.¹¹ For measurement of HR variability, basically two methods are used: time domain and frequency domain analysis.^{8 12 13}

Early HR variability studies in heart disease¹⁴ focused on patients with acute myocardial infarction. Variability in HR was shown to be reduced within a few days,^{15 16} and this correlated with a poor prognosis.^{15 17 18} It was hypothesised, that impairment of HR variability might be related to the development of heart failure, as 44% of patients with a low HR variability (SD of RR intervals <50 ms) were shown to have signs of heart failure, compared with only 8% of patients with a high HR variability.¹⁷ Furthermore, neurohumoral activation in the first days after acute myocardial infarction was more pronounced in those with an impaired LV function compared with those with a normal function.¹⁹

As part of the captopril and thrombolysis study,²⁰ we recently showed, that HR variability early after myocardial infarction may

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Heart rate (HR) and blood pressure are under continuous autonomic control.¹ In patients with left ventricular (LV) dysfunction and heart failure, changes in autonomic control are often found.² Sympathetic activation, either isolated or during exercise³ is associated with the occurrence of ventricular arrhythmias⁴ and reduces the threshold for ventricular fibrillation.⁵ Furthermore, reduced vagal activity has been associated with the occurrence of ventricular fibrillation.^{6 7}

Figure 1 Absolute changes in measures of HR variability variables SD, rMSSD, and pNN50 between the period before discharge and three months after a first anterior myocardial infarction in 53 patients no dilatation (n = 25, and dilatation n = 28). rMSSD, root mean square of successive difference; pNN50, the proportion of adjacent RR intervals >50 ms different from its preceding interval.

predict subsequent LV dilatation.²¹ Before discharge from hospital, at a time when LV volume was still normal, patients with a low HR variability index had a significantly higher risk for subsequent dilatation compared with those with a high index.²¹ Furthermore, patients who developed an increase in LV end systolic volume after three months showed hardly any improvement in HR variability, whereas in those without LV dilatation HR variability had clearly improved after three months follow up (fig 1).²²

Among the first to study HR variability in chronic heart failure were Saul *et al*,²³ who showed that patients with advanced heart failure had a considerably reduced HR variability. Casolo and coworkers were able to confirm these findings.²⁴ Binkley *et al* showed that parasympathetic withdrawal is an important component of autonomic imbalance in

Figure 2 Circadian relation between the four quartiles of plasma noradrenaline concentrations and HR variability, measured as coefficient of variation. High plasma noradrenaline concentrations correlate with low circadian HR variability and vice versa.²⁷

chronic heart failure, as sympathetic stimulation alone (by isoprenaline) did not result in the typical pattern of HR variability found in heart failure.²⁵ Therefore, probably both sympathetic and parasympathetic components of autonomic control are abnormal in chronic heart failure, and both affect the variability pattern.

To provide information about neurohumoral maladaptation in heart failure it was suggested that impairment of HR variability should be examined.²⁶ We recently studied the relation between neurohumoral activation and HR variability in a large group of patients with chronic heart failure.²⁷ A negative correlation was found between plasma noradrenaline concentrations and relatively slow fluctuations in HR variability ($r = -0.30$ to -0.34 , $P < 0.01$; fig 2). Furthermore, a significant positive correlation was found between ejection fraction and more rapidly fluctuating HR variability parameters ($r = 0.30$; $P < 0.05$).²⁷ Also, we recently discovered that short-term improvement of haemodynamics improved HR variability in patients with severe chronic heart failure,²⁸ which underlines the relation between haemodynamic and autonomic function.

Only two studies have so far investigated the predictive value of HR variability in chronic heart failure.^{29, 30} Binder *et al* showed that HR variability was the most powerful predictor of an increased risk of cardiac death in patients on a waiting list for heart transplantation,²⁹ and Woo *et al* found that a reduced HR variability indicated an increased likelihood of sudden death.³⁰

Effects of drug treatment on heart rate variability

Neurohumoral activation plays an important part in chronic heart failure, and may not be just a marker for the severity of chronic heart failure, but may actually contribute to the progression of disease.³¹ As a consequence, neurohumoral inhibiting agents, particularly angiotensin converting enzyme (ACE) inhibitors³² and β blockers,³³ but possibly also digoxin and dopamine agonists,³⁴ might have a favourable long-term effect in chronic heart failure. By contrast, drugs that increase neurohumoral activation, such as calcium channel blockers,³⁵ inotropic agents,³⁶ and probably also some antiarrhythmic drugs, particularly those of class I,³⁷ could be expected to have adverse effects on prognosis.³⁸ Whether or not these drugs also adversely affect HR variability would therefore be of interest (table). As HR is inversely proportional to HR variability, the most interesting agents would be those that do affect HR variability without effects on HR.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The ACE inhibitors have become a cornerstone in the treatment of chronic heart failure. Recent data suggest that the neurohumoral effects may be one of their

Effects of cardiovascular drugs on neurohumoral activation
HR variability, and survival in patients with left
ventricular dysfunction or chronic heart failure

	Neurohumoral activation	HR variability	Survival
β Blockers	↓	↑	↑
ACE inhibitors	↓	↑	?
Digoxin	↓	↑	?
Dopamine agonists	↓	↑	?
Calcium antagonists	↓/—	—	↓?
Diuretics	↑	?	?
Inotrops	↑	?	↓
Class I AAD	?	—	?
Class III AAD	?	—	?

AAD, antiarrhythmic drug; ↑, increase; ↓, decrease; —, unchanged; ?, unknown.

most important properties.³⁹ The favourable effect on survival was most pronounced in patients with the highest degree of neurohumoral activation.⁴⁰ Both captopril⁴¹ and zofenopril⁴² were found to affect HR variability through an increase in parasympathetic activity in patients with chronic heart failure. By contrast, in normal subjects, ACE inhibition did not affect HR variability.⁴³ This effect of ACE inhibitors on HR variability therefore parallels their neurohumoral modulating effects in chronic heart failure as well as their beneficial effect on prognosis.

β BLOCKING AGENTS

β Blocking agents may be beneficial in patients with chronic heart failure and their ability to reduce sympathetic activity possibly leads to a favourable long-term effect.^{38 44} After myocardial infarction, these drugs increased the vagal component of HR variability.⁴⁵ In patients with chronic heart failure, β blockers were reported to restore the autonomic imbalance, as shown by normalisation of HR variability.⁴⁶ The degree by which β blockers may influence autonomic control has been suggested to depend on whether these drugs are lipophilic or hydrophilic.⁶ The clinical relevance of these findings, however, remains to be elucidated.

DIGOXIN

Digoxin has been a controversial drug in many ways.⁴⁷ Recent studies, however, indicate that the drug has a place in the treatment of heart failure.^{48–50} Digoxin increased baroreceptor sensitivity and reduced neurohumoral activation by enhancing vagal activity.^{34 51 52} In patients with chronic heart failure, we have recently shown that digoxin increased vagal activity.⁵³ Also, digoxin partly restored the disturbed circadian pattern of HR variability. Even in healthy people, treatment with digoxin notably increased the vagal component of HR variability without effects on the mean RR interval: a 51% increase in the high frequency component was reported.⁴³

DOPAMINERGIC AGENTS

One of the newer neurohumoral modulators is ibopamine, an orally active dopamine agonist. Its haemodynamic effects are primarily due to peripheral vasodilation by activating dopamine receptors.⁵⁴ Also, this drug has neurohumoral inhibiting effects, as it reduces

plasma noradrenaline, and to a lesser extent, plasma aldosterone and renin.^{34 55} In a recent placebo controlled study in patients with chronic heart failure, ibopamine partly prevented the deterioration of HR variability found in the placebo group. This paralleled the mild neurohumoral effects of ibopamine.⁵³

By contrast with drugs that inhibit neurohumoral activation in heart failure, as discussed earlier, other drugs do not affect or even enhance neurohumoral activation, including calcium channel blockers, diuretics, positive inotropic agents and antiarrhythmic drugs.

CALCIUM CHANNEL BLOCKERS

The use of calcium channel blockers in LV dysfunction and chronic heart failure is still controversial. Apart from small reports in patients with primarily diastolic dysfunction,⁵⁶ so far there are no long-term studies that show positive results. Negative findings have been primarily attributed to the negative inotropic effects of calcium channel blockers and their ability to increase or at least not inhibit neurohumoral activation.⁵⁷ Cook *et al* could not show any effect of diltiazem on HR variability in normal subjects.⁵⁸ After myocardial infarction, however, diltiazem was found to reduce low frequency power.⁵⁹ To our knowledge, there are no long-term data on the effects of calcium channel blockers on HR variability in patients with heart failure.

DIURETICS

Diuretics are effective in the treatment of acute heart failure, by reducing volume overload. Paradoxically in this condition, diuretics may be able to inhibit neurohumoral activation.⁶⁰ In chronic heart failure, however, neurohumoral activity is less pronounced, and diuretics may in fact further stimulate neurohumoral activity, particularly the renin-angiotensin system.⁶¹ Whether this also leads to untoward effects on HR variability during chronic treatment has not been reported so far.

POSITIVE INOTROPIC AGENTS

Positive inotropic agents such as β adrenergic agonists and phosphodiesterase inhibitors without calcium sensitising properties, improved haemodynamics in heart failure, but were disappointing in long-term treatment.⁶² This may be related to an aggravation of arrhythmias, but also to other factors—for example, increasing neurohumoral activation.³⁶ Effects of these drugs on HR variability have not been published so far.

ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs (class I and III) have generally been found to be of limited value in patients with LV dysfunction and heart failure. Whereas the aim of treatment is to prevent arrhythmic events, proarrhythmic effects are often found in patients with a reduced LV function, partly because of their negative inotropic effects. Effects of antiarrhythmic

drugs on HR variability may not only be the result of the effects on the autonomic nervous system, but also of a direct effect on sinus node function. The effects of amiodarone (class III)⁶³ and some class I agents on HR variability have been studied.^{63,64} Zuanetti *et al* reported that amiodarone did not affect vagal activity, whereas both flecainide and propafenone caused significant decreases (−56% and −64% respectively).

Summary

Measures of heart rate variability correlate with the degree of neurohumoral activation in patients with LV dysfunction or heart failure. Because a significant correlation is present, analysis of HR variability also provides information on prognosis of these patients. Furthermore, HR variability may be used to predict LV dilatation after myocardial infarction, which is a strong independent risk factor. This indicates that before adverse haemodynamic changes have developed, changes in HR variability are already present. Variability in HR is indeed more closely correlated with neurohumoral activation than with haemodynamic variables, and as neurohumoral activation is disturbed earlier than the haemodynamic variables in heart failure, HR variability may be an early marker of progression of disease or loss of effect of treatment.

An important issue is the finding that drugs that inhibit neurohumoral activation in general seem to improve HR variability. By contrast, drugs that stimulate neurohumoral activation seem to have an adverse effect on HR variability. Interestingly, this division into two groups also seems to be consistent with the long-term value of drugs in chronic heart failure. The relations between drug induced neurohumoral modulation, changes in HR variability, and prognosis in patients with LV dysfunction or heart failure need more attention. Restoration of the modulating properties of the autonomic nervous system in patients with chronic heart failure should be an important aim of treatment, which may contribute to improved survival.

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