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Autonomic Effects of Spironolactone and MR Blockers in Heart Failure

Justine I. Davies, MRCP,[1] Miles D. Witham, MRCP[2] and Allan D. Struthers, FRCP[1]

[1]Department of Clinical Pharmacology, Division of Medicine and [2]Department of Ageing and Health, Ninewells Hospital and Medical School, Dundee, Scotland, DD1 9SY

Abstract. **Neurohormonal dysfunction is an important and potentially modifiable part of the disease process of heart failure. In this review we will discuss the ways in which the autonomic system is deranged in congestive cardiac failure and the different ways we have of monitoring these abnormalities i.e.: heart rate variability, plasma norephinephrine activity, MIBG scanning, heart rate turbulence, baroreceptor function and briefly, microneurographic techniques and QT interval analysis. We will then discuss the direct effects of aldosterone and of aldosterone blockade on some of these parameters. We conclude that neurohormonal dysfunction is an important component of chronic heart failure, which is affected by aldosterone and can be modified by the use of aldosterone receptor blockade.**

Key Words. **heart failure, autonomic, spironolactone, aldosterone**

Introduction

One of the key insights into the pathophysiology of heart failure over the past twenty years has been the understanding that neurohormonal dysfunction is an important and modifiable aspect of the disease process. Derangements of autonomic function, affecting the sympathetic and parasympathetic systems, are a common and important subtype of this neurohormonal dysfunction in patients with heart failure [1–4]. Several markers of autonomic dysfunction have been shown to be powerful independent prognostic markers in patients with heart failure [5–8].

Autonomic dysfunction is not just a manifestation of the disease process; it also appears to influence progression of the disease process by worsening ventricular function and by increasing the likelihood of malignant ventricular arrhythmias. Evidence for this is provided by the fact that therapies that improve autonomic balance result in an improved prognosis in heart failure. Modification of sympathetic function via beta blockers leads to important improvements in symptoms, mortality and hospitalisation [9–11], and exercise training, which is known to increase parasympathetic tone and reduce sympathetic tone, also reduces mortality and hospitalisation [12].

The autonomic system does not act in isolation. It is intimately linked with other neuroendocrine systems, especially the Renin-Angiotensin-Aldosterone system (RAAS). Two large multicentre randomised controlled trials—RALES [13] and EPHESUS [14], show that aldosterone receptor blockade similarly reduces death, including sudden cardiac death, in patients with left ventricular systolic dysfunction. This article reviews the evidence for the influence of aldosterone receptor blockade on autonomic function in heart failure. We first discuss methods of assessing autonomic function and describe the derangements of autonomic indices seen in heart failure, then discuss the effect of aldosterone and aldosterone blockade on these parameters.

Derangements of the Autonomic System in Heart Failure

There are two main changes seen in autonomic function in heart failure—increased sympathetic activity and reduced parasympathetic activity. Of the two, the sympathetic system has been better studied. In order to explore the impact of aldosterone blockade on the autonomic system, it is necessary to measure the activity of the sympathetic and parasympathetic systems. This can be done by a variety of different methods. The main methods for studying the activities of the parasympathetic and sympathetic nervous systems and their abnormalities in patients with CHF are discussed below.

Heart Rate Variability

The quantification of fluctuations in heart rate over time is termed heart rate variability. Changes in heart rate occur on a wide variety

Address for correspondence: Justine Davies, MRCP, Department of Clinical Pharmacology Division of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, DD1 9SY. E-mail: j.i.davies@dundee.ac.uk

of timescales—from a few seconds to many hours [15]. It is possible to assess heart rate variability in both time and frequency domains. Broadly speaking time domain parameters can be divided into those that are long or short term. The standard deviation of all R-R intervals (SDNN) and the standard deviation of mean R-R intervals every 5 minute (SDANN) reflect longer term heart rate variability. The standard deviations of R-R intervals within each 5 minute time period (SDNNI) reflect short term heart rate variability. The root mean square of differences of successive R-R intervals (RMSSD) and percentage of R-R (N-N) intervals differing by more than 50 ms (pNN50) reflect very short term variability in heart rate. SDNNI has been correlated with sympathovagal balance, whereas RMSSD and pNN50 have been correlated with parasympathetic activity [15]. In the frequency domain tracings can be analysed for low frequency (LF) and high frequency (HF) elements; the ratio between LF and HF elements can also be calculated. A full understanding of all the mechanisms underlying these variations has proven elusive as yet, but it is clear that the parasympathetic system is a key influence on high frequency HRV (0.15–0.4 Hz). High frequency HRV can be abolished by administration of the parasympathetic blocker, atropine [16].

The effect of sympathetic activity on heart rate variability is more complex. It was initially thought that the LF element was attributable to sympathetic nervous system activity, but further research has shown that no single measurement of HRV appears to correlate well with sympathetic activity. However, the ratio of high frequency to low frequency (0.04 to 0.15 Hz) variability does seem to be influenced by the balance between sympathetic and parasympathetic activity [15]. In addition, sympathetic activity may have an influence on overall heart rate variability—plasma norepinephrine levels correlate with overall HRV power as well as with low-frequency power [1]. This is important, as overall HRV power is a powerful prognostic marker [5].

HRV undergoes diurnal variation in normal subjects with an increase in heart rate and LF elements on wakening. During the night time hours HF elements increase associated with a decrease in LF [17].

In subjects with heart failure heart rate variability is reduced, and although the circadian rhythm is preserved, overall heart rate variability is diminished [5,17,18].

Plasma Norepinephrine Activity

This is a very simple measure of sympathetic activity. It is influenced by the rate of sympathetic nerve discharge and the rate of clearance of norepinephrine, but unfortunately tells us nothing about the *effect* of a given amount of norepinephrine. Furthermore, a single sample cannot reflect the differential activity of the sympathetic nervous system between different organs. Like heart rate variability plasma norepinephrine activity undergoes diurnal variation, with peak concentrations in the morning and levels falling during the night-time hours [19].

Despite the potential problems mentioned above regarding the usefulness of plasma norepinephrine activity it is known to be elevated in patients with heart failure [2], and levels correlate strongly and independently with prognosis [6,7]. It is thought that this elevation of plasma norepinephrine activity in patients with CHF is mainly due to spillover (see below) from the heart and kidneys [2], however, reduced clearance also plays a role.

Norepinephrine Spillover

Analysis of norepinephrine spillover partially circumvents the problem of localisation of sympathetic activity seen with a single plasma norepinephrine sample, by analysing the gradient of norepinephrine production ('spillover') across organs. This technique demonstrates that in heart failure patients, the heart and kidneys, but not the lungs, are major sources of norepinephrine production [2]. This increased spillover may be due to either increased sympathetic activity within these organs, or to a decrease in reuptake [2]. Although Hasking et al. found neuronal uptake to be normal in heart failure patients other authors have found this to be decreased [20,21].

Metaiodobenzylguanidine (MIBG) Scanning

Radiolabelled MIBG scanning allows us to assess the capacity of the heart to take in and destroy epinephrine and norepinephrine ("re-uptake"), preventing them from exerting deleterious actions locally on the heart. Neuronal uptake of the radioactive tracer^{123} I-MIBG is reduced in cardiac failure, and reduced uptake is also a powerful prognostic marker in heart failure patients [8].

Heart Rate Turbulence (HRT)

HRT is a novel marker of autonomic function which describes the response of the heart rate to the fall in blood pressure that follows a premature ventricular ectopic beat. This response is under vagal control, as evidenced by the ability of atropine to severely curtail the phenomenon [22]. In patients with cardiac failure HRT is markedly reduced, and heart rate turbulence correlates strongly with baroceptor reflex sensitivity (see below) [23,24]. Like measures of autonomic function discussed previously in this review disturbed HRT

is an independent prognostic marker in heart failure as well as in coronary artery disease [25–27].

Baroceptor Function

In normal circumstances a rise or fall in blood pressure will produce a reciprocal fall or rise in heart rate to allow maintenance of cardiac output. This baroreceptor function can be measured in the laboratory by infusing either pressor or vasodilator substances and measuring the change in heart rate that results. Infusion of phenylephrine causes an increase in systemic blood pressure. This increase in blood pressure is sensed by baroceptors, which lead to a reduction in heart rate and consequent reduction in cardiac output. This homeostatic mechanism is mediated mainly by parasympathetic outflow, and the degree of bradycardia thus acts as an index of parasympathetic activity. In normal humans, vagal tone appears to be the predominant mediator of the baroreflex response to phenlyephrine, as the response is virtually abolished by atropine [4].

Similarly, reduction in blood pressure using vasodilators such as sodium nitroprusside, leads to a compensatory tachycardia—an index of sympathetic function.

The baroceptor response to phenylephrine is markedly reduced in patients with heart failure [3,4], as is the response to vasodilators. The bradycardic response to phenylephrine correlates with low frequency heart rate variability, but not with high frequency HRV [1].This suggests that the balance between sympathetic and parasympathetic responses (as denoted by low frequency HRV) may be more important than blunted vagal drive alone in explaining the reduced response to phenylephrine.

Microneurographic Techniques

Direct measurement of sympathetic nerve firing activity by microneurographic techniques gives further evidence for sympathetic overactivity when compared to healthy controls [28]. Sympathetic nerves exhibit increased activity in muscle, but not in skin [29] in patients with heart failure; overactivity as measured by microneurography correlates with reduced high frequency HRV, but most closely with reduced low-frequency HRV [30]. This is consistent with the hypothesis that increased sympathetic drive tilts sympathovagal balance to one extreme, reducing the room available for heart rate to vary.

QT Interval Analysis

There are several different ways of analysing the QT interval. It is possible to measure QT interval duration, QT interval interlead variability (dispersion), maximum heart rate corrected QT interval (QTc max) and QT peak. Prolongation of the QT interval assessed by these different methods is known to predict death in several disease states [31,32]. The QT interval is not a pure indicator of the state of the autonomic system as several other factors contribute to this parameter, for example electrolyte balance [33], however the autonomic system is certainly a strong contributor to the QT interval. Importantly QT dispersion and QTc max are predictive of death in heart failure patients [31,34].

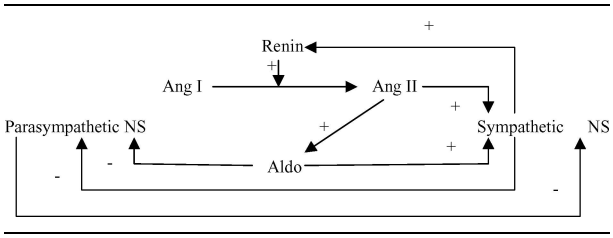

Fig. 1. *The interaction between the autonomic and the renin-angiotensin-aldosterone systems.*

The Effects of Aldosterone on Autonomic Function

The interaction between the RAAS and the autonomic system is complex (Fig. 1) and although some studies have looked directly at the effect of aldosterone on autonomic function in humans most of these studies have involved the study of baroreceptor function. Many of the rest of the studies conducted in this area have implied the involvement of aldosterone in the autonomic system by studying the effects of aldosterone blockade on autonomic parameters. The fact that both aldosterone and the autonomic nervous system undergo diurnal variation with early morning peaks in both aldosterone and sympathovagal balance is consistent with the idea that the two systems are linked [17]. In fact there is probably a causal relationship between the two since aldosterone blockade reduces the early morning rise in heart rate that is seen in non β-blocked patients [35].

Effects on the Baroceptor Reflex

Aldosterone infusion produces rapid effects on the baroceptor reflex—too rapid to be explained by the effects of sodium retention. In healthy male volunteers, aldosterone impairs the bradycardic response to phenylephrine infusion as compared to phenylephrine infusion alone (Fig. 2), suggesting impairment of the parasympathetic response to the increase in blood pressure caused by phenylephrine [36]. Aldosterone has similar effects on the bradycardic response to a noradrenaline infusion [37]. Interestingly, aldosterone has no effect

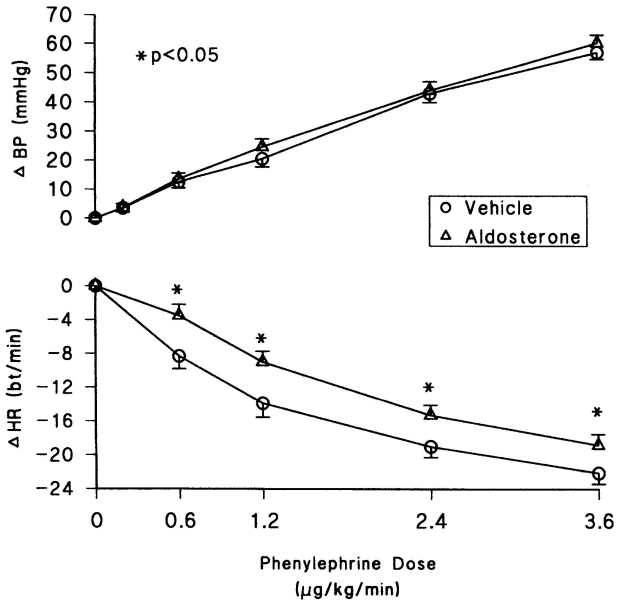

Fig. 2. Heart rate response to increasing BP with phenylephrine during aldosterone or placebo infusion [36].

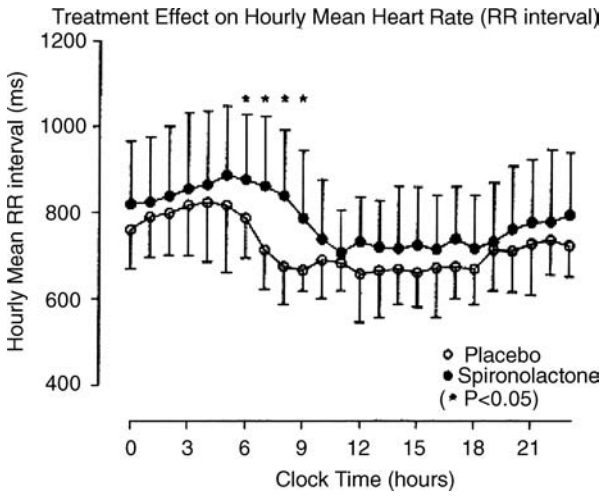

Fig. 3. Effects of placebo or spironolactone therapy on hourly mean RR interval at the end of 8 weeks of therapy [35].

on the tachycardic response to sodium nitroprusside induced hypotension. These results suggest that aldosterone decreases the parasympathetic contribution to baroreceptor function whilst leaving that of the sympathetic nervous system intact.

It has been suggested that the effect of aldosterone on the baroreceptor response is mediated via Na/K/ATPase stimulation. Aldosterone is known to act on this enzyme, and blockade of Na/K/ATPase with digoxin improves baroreceptor sensitivity [38].

Effects on QT Interval

In a small study of hypertensive patients the combination of fludrocortisone and salt produced an increase in QT dispersion. Unfortunately in this study it is difficult to tease out how much of the effect on QT dispersion was due to fludrocortisone and how much was due to the disturbances in sodium and potassium that were seen [39].

The Effects of Spironolactone on Indices of Autonomic Function

Heart Rate Variability

In heart failure patients, spironolactone improves both time and frequency domain parameters of heart rate variability. It improves SDNN, SDANN, SDNNi, triangular index and pNN50 [35,40]. In the frequency domain spironolactone improves high frequency power, suggesting improvement in parasympathetic function as well as decreasing the ratio of low to high frequency power, consistent with improvement in the balance of sympathetic and parasympathetic tone [17].

Interestingly, in CHF patients spironolactone appears to blunt the increase in heart rate that occurs in the early hours of the morning (Fig. 3), suggesting that it may reduce the sympathetic drive seen at this time of day [35]. This is of great importance given that the early hours of the morning (6–9 am) are also the peak time for myocardial infarction and arrhythmic death in patients with cardiac disease [41,42]. Spironolactone also increases high frequency HRV power and improves LF/HF balance between 6 and 10 am [17]. Amiloride has no effect on HRV parameters which suggests that spironolactone doesn't produce beneficial HRV effects simply by altering electrolyes [43].

These results imply that aldosterone blockade leads to an increase in parasympathetic and perhaps a decrease in sympathetic tone. The fact that aldosterone blockade seems to decrease sympathetic tone when heart rate variability is studied would seem to infer that it acts more on the parasympathetic than the sympathetic nervous system.

More recent studies conducted on heart failure patients already on beta blockers fail to show improvements in HRV parameters with spironolactone treatment, including during the early morning period [44]. This suggests that the beneficial effects of spironolactone on heart rate variability are at least in part mediated by modulation of sympathetic tone as in patients already on beta blockers this pathway has been blocked already.

Plasma Norepinephrine Levels

One small study showed that 16 weeks of spironolactone therapy in heart failure patients led to an increase in both resting norepinephrine levels and norepinephrine levels after exercise. Levels returned towards baseline on discontinuation of spironolactone [45]. Another study showed that spironolactone did not affect noradrenaline levels, noradrenaline spillover, or diurnal variation in noradrenaline levels [17]. Although this may appear paradoxical, given the other beneficial effects that spironolactone has on indices of autonomic function, it suggests that spironolactone blunts the *effect* of norepinephrine. Increased uptake and disposal of norepinephrine by the myocardium may be one explanation (see below); further evidence is provided by a study of patients with end-stage renal failure on haemodialysis. In these patients, spironolactone blunted the pressor effect of noradrenaline infusions, and exhibited a dose-response effect [46]. The effect was seen after only three days of spironolactone therapy.

MIBG Uptake

In a small placebo controlled study, spironolactone significantly increased myocardial uptake of ^{123}I-MIBG [47]. This effect was accompanied by a reduction in the frequency of ventricular ectopics, although some of this effect on reduction in ventricular ectopics may have been due to increased plasma potassium and magnesium levels in the spironolactone treated group. The MIBG findings of this study have been confirmed in a larger study with longer follow up where increased MIBG uptake was paralleled by reductions in LV end-diastolic volume on spironolactone [48].

QT Interval

Spironolactone reduces QT parameters in patients with heart failure [17,49], and interestingly has maximum effect on these parameters in the morning when both aldosterone and sympathetic activity are rising. Unfortunately it is difficult to discern how much of the benefit of spironolactone is due to the alterations in electrolytes that it produces [43]. Indeed it is likely that much of the QT shortening effect is due to potassium and magnesium retention since amiloride has the same QT shortening effect in heart failure [43].

In Summary

Aldosterone contributes markedly to the autonomic system derangements seen in heart failure and blockade of aldosterone partially reverses these autonomic disturbances, presumably helping to contribute to the decrease in sudden cardiac death seen in both the RALES and EPHESUS trials.

It remains to be seen whether aldosterone withdrawal will be beneficial in other disease states where autonomic derangements are present for example in hypertension, diabetes mellitus and coronary artery disease. However, a cautionary note is necessary, as it has recently been shown that spironolactone worsens short-term indices of heart rate variability in normotensive type II diabetics who did not suffer from heart failure [50]. Further studies are required to delineate which patient groups benefit from the autonomic modulating effects of aldosterone blockade.

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