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Congestive Heart Failure: the Case for Decreased Variability as a Unifying Theme

R. M. Peters

Many parameters of normal cardiovascular function suggest that variability is an intrinsic property of a healthy cardiovascular system and gives it the necessary flexibility to adapt to various stressors. In the congestive heart failure syndrome, this variability is significantly decreased, reducing the ability to adapt to stressors and increasing the risk for adverse events. Reduced variability is a useful unifying concept in understanding the many interactive aspects of the congestive heart failure syndrome. *J Clin Basic Cardiol 2000; 111–3.*

Key words: congestive heart failure, variability

O ver the past two decades an explosion of research has greatly increased our understanding of the congestive heart failure syndrome. With so much information about the various yet interrelated aspects of this complex syndrome, it would be useful to our conceptualization of this entity if much of this knowledge could be tied together under one unifying concept. This paper makes the case that decreased variability is an underlying theme that can be useful in our understanding of congestive heart failure.

Variability is defined simply as the range of any measured physiologic or laboratory value, coupled with the degree of fluctuation of this value with various physiologic at states over time. For example, the ability to change the heart rate from a value of 52 beats per minute during sleep to 168 beats per minute during exercise later in the day would indicate greater variability than a patient in whom the lowest recorded heart rate over a 24 hour period was 76 beats per minute, and in whom the heart rate only increased to 114 beats per minute with exercise. Figure 1 contrasts heart rate variability in a normal patient with a congestive heart failure patient. Although tools to measure vari-

ability have been used in other fields such as statistics and finance, their application to medical data is relatively recent and not well studied. Hence many of the examples of decreased variability discussed in this paper will not be formally quantitative in nature.

Traditional statistical calculations of variance and standard deviation can be useful. Spectral analysis of time-domain and frequency-domain measures have been used in many studies [1, 2] to look at the decreased heart rate variability seen in cardiac disease. New recently described methods of heart rate variability analysis derived from nonlinear dynamics (chaos theory and fractal analysis) may be more useful in variability analysis than traditional measures [3].

Each of the following sections examines a major aspect of the con-

gestive heart failure syndrome and attempts to show that decreased variability repeatedly pervades as an underlying recurring theme.

Decreased haemodynamic variability

A normal patient is capable of greatly increasing cardiac output from resting levels to very high levels as seen in exercise, while patients with heart failure cannot do this [4]. Normals are able to vary their cardiac output as they move along the Frank-Starling curve-increasing output as preload increases [4, 5]. Heart failure patients operate on a flat Frank-Starling curve, so they cannot vary their cardiac output with changes in preload [5]. Normals can also vary regional systolic wall motion and function – with exercise they can increase regional contractility with wall thickening and decreased left ventricular size at end-systole [6]. Heart failure patients often cannot augment regional wall motion with exercise, and with ischaemic cardiomyopathy may actually show impairment of regional and global systolic function [6].



Figure 1. Twenty-four hour heart rate recordings in a young healthy subject (normal variability) contrasted with a congestive heart failure patient (decreased variability)

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Regarding diastolic function, the normal heart is able to vary its ability to handle increased venous return by increasing myocardial relaxation and elastic recoil thus increasing left ventricular distensibility [7]. In heart failure, diastolic dysfunction is often seen. The left ventricle cannot vary its distensibility due to increased myocardial stiffness, thus cannot vary its response to increased venous return [7]. Thus decreased variability is seen in both systolic and diastolic aspects of congestive heart failure.

Decreased neurohormonal variability

In normal patients, there is a daily wide range of variability in the degree of activation/deactivation of the sympathetic and parasympathetic nervous systems during the course of daily activities [8]. This is often reflected in the wide range of heart rates seen over the course of a day (see later section). Similarly, in response to various activities, as well as volume and salt factors, there is variability in the level of activation of the renin-angiotensin system, the level of various peptides such as atrial natriuretic peptide, and the secretion of arginine vasopressin [8]. This variability is part of normal physiological processes in the setting of a normal cardiac output.

In congestive heart failure, decreased cardiac output and the resulting perceived decrease in effective circulatory volume (arterial underfilling) results in a generalized activation of these neurohormonal mechanisms [9]. Many studies [10–12] show increased activation of the sympathetic nervous system associated with elevated plasma norepinephrine levels, vasoconstriction, and elevated heart rates. Parasympathetic tone is greatly reduced as the normal variability is lost [13].

Likewise, there is generalized activation of the renin-angiotensin system with its circulatory and renal effects (see later sections) [14–16]. Loss of normal variability is also seen with elevated levels of vasopressin [17], atrial natriuretic peptide [18], brain natriuretic peptide [19], and adrenomedullin [19]. Recent work also suggests elevated levels and changes in the natural variability of circulating cytokines such as tumor necrosis factor, a myocardial depressant [20, 21]. Thus generalized neurohormonal activation results in a decrease in the usual variability seen with these mechanisms.

Decreased renal variability

Normal kidneys are capable of great variability in their regulation of salt and water balance. Depending on the physiological state, they can excrete large salt and water loads, maximally dilute the urine, retain salt and water avidly, or maximally concentrate the urine. Because of the activation of neurohormonal mechanisms in heart failure with the perceived arterial underfilling of the kidneys with associated renal vasoconstriction, there is constant avid salt and water retention by the kidneys, often despite an increase in intravascular volume [22]. In an attempt to improve renal perfusion, renal vasodilator prostaglandins remain at high levels, losing their usual variability [23]. Although the kidneys are in a sense innocent bystanders as their functional variability can return to normal after cardiac transplantation [22], they are another example of the decreased variability found in the congestive heart failure syndrome.

Decreased peripheral circulatory variability

Normal patients can show variability in vascular tone, changing between constriction and dilatation depending on the physiologic circumstances. Normal patients can also shunt blood flow to where it is needed – increasing splanchnic flow after a meal or increasing limb flow to exercising muscles. Baroreceptor function is normal with normal reflex responses in pulse rate and blood pressure to adrenergic activity.

In heart failure there is again loss of this variability. The generalized neurohormonal activation mentioned above results in generalized vasoconstriction with increased peripheral vascular resistance and impaired vasodilator responses to exercise or hormonal stimuli [24]. Increased levels of endothelin, a potent vasoconstrictor, and decreased activity of the vasodilating L-arginine-NO metabolic pathway [25], contribute to this loss of variability. The cardiac output is redistributed in heart failure with shunting of blood away from the splanchnic, renal, and limb vessels [26].

Abnormal baroreceptor activity is also seen in heart failure with blunted reflex responses of heart rate, arterial pressure, and vascular resistance [27, 28]. During upright tilt there is a blunting of the normal increases in plasma norepinephrine and forearm vascular resistance [29]. Heart failure patients may have a blunted baroreceptor response to orthostasis [30]. Thus again decreased variability is seen compared to normal physiology.

Decreased heart rate variability

Normal patients can have a wide variability in heart rate with periods of sinus bradycardia when parasympathetic tone predominates (sleep) to periods of sinus tachycardia up to 100 % predicted maximum heart rate for age when sympathetic tone predominates (exercise) associated with various fluctuations in heart rate with daily activities. Many studies have shown a decrease in heart rate variability in congestive heart failure [31– 33]. Using time and frequency domain analysis of 24 hour recordings, these studies show a predominance of sympathetic tone, however, heart failure patients show less increase in their heart rates with adrenergic stimulation [34]. This chronotropic incompetence is one factor leading to decreased heart rate variability.

Decreased exercise and pulmonary variability

Patients with heart failure have a reduced exercise capacity [35] compared to normals. Besides reductions in stroke volume and heart rate with exercise, several other factors such as decreased peripheral vascular response due to vasoconstriction, abnormalities of skeletal muscle including impaired function and altered metabolism, and muscle atrophy due to deconditioning also contribute to the decreased variability in exercise capacity [36].

There is decreased pulmonary capacity in congestive heart failure. With lung congestion there is decreased pulmonary compliance, reductions in vital capacity and total lung capacity, and decrease in the maximum total oxygen uptake with exercise [37]. These pulmonary factors contribute to the decreased exercise variability seen in congestive heart failure.

Discussion

The normal cardiovascular system is characterized by a high degree of variability. The cardiac output can be increased dramatically before returning to resting levels. The heart rate may at times double from resting rates, while at other times sinus bradycardia may be present. Powerful neurohormonal mechanisms can be activated to cause vasoconstriction, renal sodium and volume retention, increased sympathetic nervous system activity, and shunting of cardiac output to various organs. At other times there can be activation of mechanisms to cause vasodilatation, renal sodium and volume excretion, or increased parasympathetic tone. This intrinsic variability gives the healthy cardiovascular system the necessary flexibility-adaptability to handle the various exigencies of an unpredictable and changing environment. These may be routine stressors such as exercise, changes in posture, changes in ambient temperature, volume expansion or contraction, salt increase or deprivation, or digesting large meals. They may also be non-routine stressors such as infection, surgery, trauma, or major blood loss. High intrinsic variability and its associated high flexibility-adaptability are characteristic of good cardiovascular health.

In the syndrome of congestive heart failure, this intrinsic variability is greatly reduced. Cardiac output is relatively fixed or can increase little from resting levels. Heart rates show much less variation than normally and the ability to increase heart rate is blunted. Sympathetic and vasoconstrictive sodium and volume retaining mechanisms predominate. This reduction in variability translates into less flexibility-adaptability in dealing with stressors. Thus infection, arrhythmias, environmental or emotional excesses, salt or volume loads, or other illnesses may cause adverse consequences in the low variability congestive heart failure patient.

In conclusion, decreased variability appears to be an underlying theme in the congestive heart failure syndrome. Further research into this area, including whether medical treatment can partially improve decreased variability, would be of considerable interest. For example, in one study of patients with chronic congestive heart failure, treatment with captopril was associated with an increase in parasympathetic activity [38].

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