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Mini Review

How Abnormal Sympatho-Activation Can Potentially Develop Heart Failure: A Mini Review

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ABSTRACT

Cardiac sympathetic afferent that signal the sensation of cardiac pain, ostensibly, has more underlying mechanisms than what scientists have ever been led to believe. Cardiac sympathetic afferent reflex, also known as (CSAR), has been shown to be responsive to a variety of stimuli. Many of which scientists observed in increased levels during ischemia hydrogen ion, oxygen radicals, potassium, lactate, ATP, prostaglandins bradykinin, substance p and, finally and most importantly, endogenous substances (neurohormones) such as *norepinephrine* (NE). In the outset of chronic heart failure (HF), it has been known for a long time, that there are abnormalities in arterial baroreceptor input which depress its sensitivity, and arterial chemoreceptors seem augmented. Therefore, they tend to not only initiate sympathetic outflow but also to sensitise cardiac afferents which are appearing to do the same thing where there are abnormalities in vagus mechano-reflexes as well. Some of these receptors are in the spinal reticulate tract and interestingly these a third pathways give off neurons to the brainstem some in the hypothalamus and trance translate through the thalamus and then ultimately up into the cortex where we have sensation of pain. Here in this essay, we aim to discuss important aspects of cardiac failure in relation to abnormal sympatho-activators through evaluation of different available studies and animal models.

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Introduction

I History

Not so long ago, Peter Schwartz participated in a study in which they simply looked at in rhythmic genesis following a coronary artery occlusion in dogs [1]. During coronary occlusion there are a variety of arrhythmias that were induced both premature ventricular contractions (PVCs) and tachycardia. However, the interesting part is after dorsal rhizotomy, much of these of these arrhythmias were reduced and this finding rose the idea that there are chemicals go through the dorsal roots that may participate in modulation of sympathetic outflow to the myocardium as a pro arrhythmogenic pathway. This investigation has been reproduced many times by other investigators in a variety of different models.

II Renin-Angiotensin System

The renin-angiotensin testosterone system is a classic endocrine system that helps to regulate long term blood pressure at extracellular volume of the body [2]. The system begins with the release of angiotensinogen into circulation by the liver. This maybe in response to low blood pressure and adverse changes in sodium concentrations. An enzyme, renin, is secreted which cleaves angiotensinogen to convert to inactive form, angiotensin I. Further transformation of angiotensin is carried out by angiotensin converted enzyme (ACE).

This enzyme is predominantly found in pulmonary circulation. Despite this, ACE is also produced in the vascular endothelium of many tissues including the kidney, adrenal gland and heart. ACE enzyme converts the inactive precursor angiotensin I into the vasoactive peptide angiotensin II [3]. In addition, alternative pathways exist that do not rely on neither renin nor ACE. In non-renin pathways, enzymes like Tonin and cathepsin D, release angiotensin I from angiotensinogen and tissue plasminogen activator (tPA) which can make angiotensin II directly from angiotensinogen I. This can bypass the midway production of angiotensin I. Enzymes like kinase forms angiotensin II from angiotensin I via an ACE independent pathway. ACE also degrades Bradykinin which is required for synthesis of major vasodilator such as

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nitric oxide (NO) [4]. Angiotensin II binds angiotensin type 1 receptor (AT_1) receptors expressed on the surface of vascular endothelium and impairs nitric oxide synthesis. Reduced bioavailability of nitric oxide combines with the stimulation of AT_1 receptors on the smooth muscle cells which then causes vasoconstriction. In addition to vasoconstriction effect, stimulation of AT_1 receptors causes the adrenal glands release aldosterone (hormone) which results in sodium retention [5]. Combining of vasoconstriction and sodium retention results in increase in blood pressure.

Angiotensin II type 2 receptors (AT_2) can be find in low levels and mainly in heart and central nerves system and kidney. The counteractive behaviour of AT_2 receptors to AT_1 is widely studied in heart failure pathological mechanisms to which that changes in the number of these receptors (receptor polymorphism) can affect upregulation and down regulation of fibrosis process in an event of heart failure [5]. For a long time in heart failure, there is autonomic imbalance which is characterized by increased sympathetic activity or parasympathetic activity autonomic imbalance. RAS activation is associated with progression of heart failure. By blocking sympathetic nervous system and the RAS activity, it appears to be a remarkable improvement in the outcome of patients with heart failure [5].

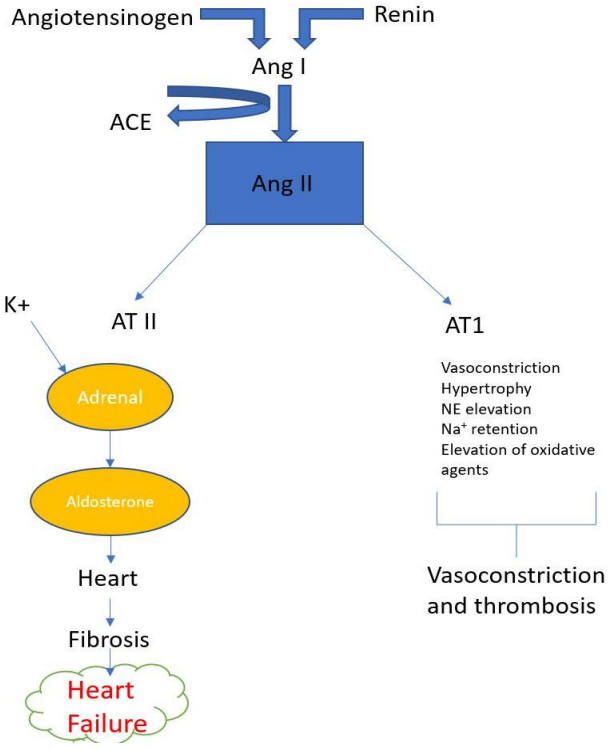

Figure 1: Schematic representation of RAAS system (sketched by Microsoft PowerPoint ™, accessed:2018).

III Sympathetic Inflammatory Response as A Risk to Develop Heart Failure

Trip receptors, primarily TrpV1 receptors, a form of *capsaicin* receptor, are located on the endings of peptidogenic nociceptors (a type of pain receptor which contain specialized form of neuropeptides such as substance P). Capsaicin has high potential as an activator of TrpV1 than most potent substance that have ever been studied. Activation of capsaicin receptors depolarizes the neurons largely by opening a calcium channel and we can get the SNS activation through neuropeptide release of a variety of other set of neurons located in the dorsal root ganglion and the spinal cord. This pathway probably mediates most of the sympathetic excitation that impacts neuropeptides where tend to both be raised or vanished later and change membrane permeability. They act on endothelial cells and once they are in the cell, substance P activates the NK 1 receptor, causing plasma extravasation which mediates neurogenic inflammation (an inflammatory mechanism which can awake in presence of endogenous neuropeptides such as endothelin 1). These series of activations have a role, both in augmenting sympathetic outflow and in modulating localized inflammation. There are other important exogenous molecules such as resineferitoxin (RTX) that activates TrpV1receptors on sensory afferents especially those attached to group C (a bundle of postganglionic nerves which delivers sensory information, particularly damage and pain). nociceptors in the myocardium [6].

Discussion

Fortunately, there are at least three animal models that have tested the hypothesis that increasing vagal tone, by directly stimulating the vagal system, have had improved outcomes in patients suffering from HF. The first model is the rat myocardial infract (MI) model which first was described by Li and his colleagues (2004) [7]. They used the post MI rats to create a heart failure and then divided rats into two groups. They wiggle nerve stimulation in one group for six weeks after 14 days of post using 20Hz stimulation whereas they kept the other post MI group as a control group. They found that although the vagal nerve stimulation did not have any effect on the infarct side, but it did significantly improve remotely and had a remarkable effect of decreasing norepinephrine and plasma brain natriuretic peptide (BNP). Remarkably, this was accompanied by a considerable reduction in mortality in the group given vagus nerve stimulation (VNS) at seventy-three percent relative risk reduction in all-cause mortality [7].

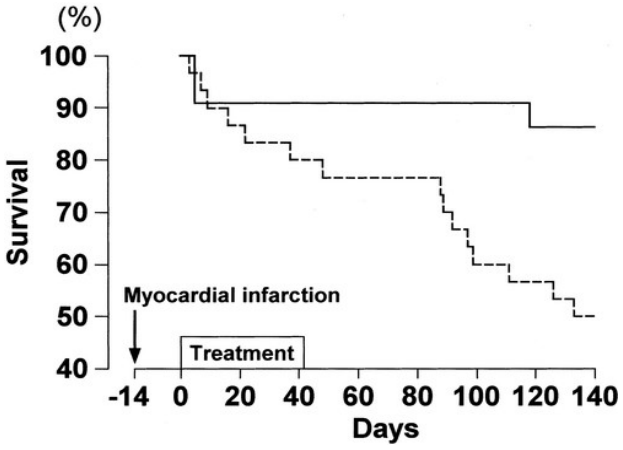

Figure 2: The broken line indicates the survival rate of post MI rats control group, where the solid line indicates post MI rats' group after 14 days of treatment with VNS [7].

The second model was Zheng pacing induced heart failure dogs' model [8]. There were 15 mongrel dogs where they produced heart failure by passing them at a rate of 200 beats per minute for four weeks. After 4 weeks, they then reduced at 180 beats per minute to maintain heart failure. Half the animals were then given implanted with the cyberonic

VNS system. The right VNS nerve continuously stimulated at a duty cycle of 14s "on" and 12s "off".

They found that there was a very nice improvement in remodeling attenuation of the left ventricular end-diastolic and systolic volume. In addition, there was an improvement in ejection fraction in the animals treated with VNS compared to animals in control groups. The improvement in highly sensitive c-reaction protein (CRP) as well as reduction in norepinephrine and angiotensin 2 were also identified as the main outcomes of this model. The third model was to Sabah's model (2011) of micro embolization in induced heart failure. Sabah's group investigated vegal nerve stimulation using Bio Controls Cardio-Fit System ™ [9].

The model stimulated right vagal nerve and synchronous with the cardiac cycle in order to reduce the heartbeat by approximately ten percent on average. The reduction in heartbeat in their experiments was approximately ten beats per minute but the range was wide from one to twenty-eight beats minute. By looking at data at baseline (Figure 3), after three months follow up, there is a great enough stimulation which had a remarkable effect on rates and in fact reversing remodeling both in systole and lastly for LV end diastolic. Also, for the systolic volumes and a significant rise in ejection fraction, they also found that they were the attenuated inflammatory cytokines in these animals. Reduction in tumour necrosis factor alpha and interleukin-6 were also noticeable. Furthermore, by taking the histology of their animals, they found that there was a reduction in the interstitial fibrosis in the VNS treated animals. In addition, there was a significant increase in the capillary density in the end of myocardium [9].

One the basis of studies above, the group in Italy led by Peter schwartz, they set up an experiment for stimulation of vagal nerve in patients with heart failure started off with eight patients and then enlarged the scope of their study to a multi-centre European study with 32 patients. Their patients were selected from NYHA (New York Heart Association) class II to IV, predominately. For class II to III, there were 23 patients with left ventricle ejection fraction less than 35 percent. All their patients were in silence rhythm. They were medically treated with all the heart failure drugs, including, beta blockers.

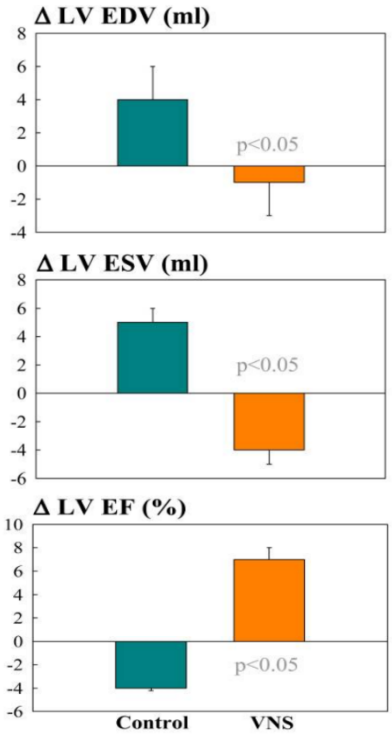

Figure 3: Representation of changes in LV end diastolic volume, LV end systolic volume and LV ejection fraction between VNS treated and control group animals.

Some years ago, in a dog pacing model of heart failure chronic, also known as tachycardia model of heart failure, scientist showed that if one puts Bradykinin onto the surface of the heart epicardium, there was an augmented response in animal with heart failure [10].

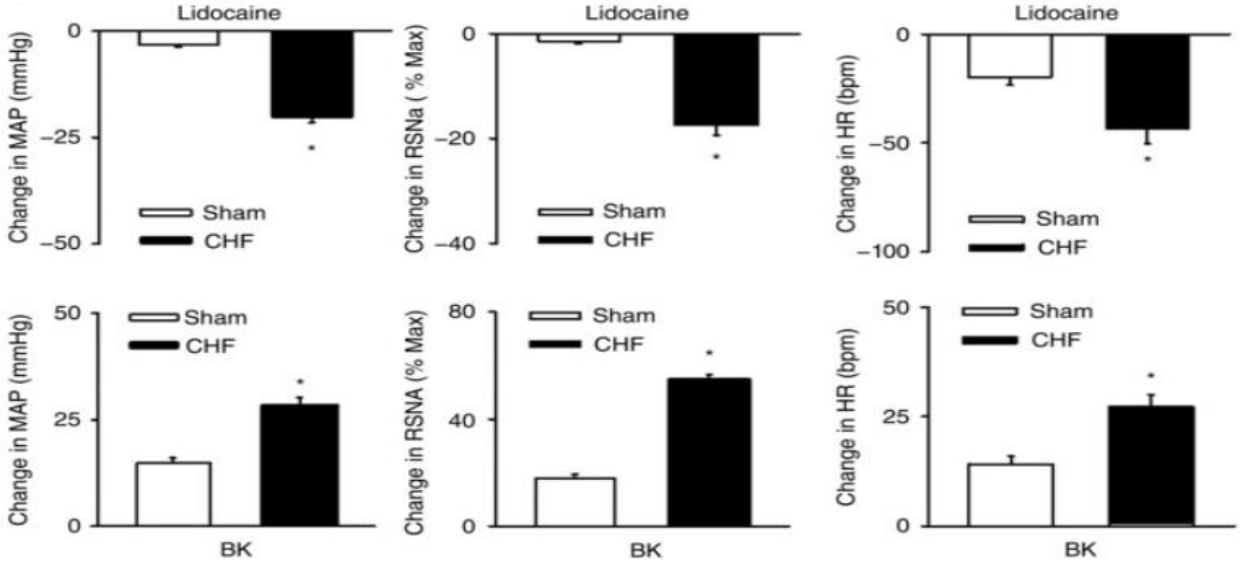

Figure 4: The effects of lidocaine (first row) and bradykinin (second row) on the epicardium surface of CHF dogs. As it shows, unlike, bradykinin rises three important characteristics of the heart, lidocaine falls in these activities by comparing the changes in both groups of control and CHF. [11].

In a comparative analytical study between the HF and non-HF animal groups, the renal sympathetic nerve activity exhibits augmented response and proportionately direct correlation with the cohort of animals suffering from the HF [11]. As shows in (Figure 4) the same outcomes for capsaicin. Therefore, in heart failure animal group, the response in terms of sympathetic nerve activity is increased with capsaicin. More importantly, if one takes and simply puts lidocaine onto the surface of the heart of the vagotomised (partial or complete removal of vagus nerve) dogs, then there is a reduction in basal sympathetic nerve activity. This simply can be explained and since these animals were vagotomised, the assumption is that by blocking a cardiac- sympathetic afferents which tend to be distributed towards the surface of the myocardium. In response to capsaicin or bradykinin, there is an increase in discharge in heart failure animals compared to sham controls [12].

Lat but not least, one of the strategies that believe to impact spinothalamic tract (CNS critical pain receptors cells) is whether the intervention at the nerve ending leads to reduce input from cardiac sympathetic afferents and as the result to develop a form of heart failure [12]. From previous studies, nerve innervation is augmented in the setting of chronic heart failure. The sympathectomy for reducing a cardiac pain is not a new technique but removal of the t1 to t4 sympathetic ganglion chain was pretty efficacious management and it actually reduced the pain and arrhythmogenesis. Although the technique was abandoned for many years but probably employ only in the most severe resistant cases of arrhythmias and invasive ischaemic heart failure.

One of the areas that picked up interest, in an event of cardiac failure, is haemodynamic. In a different study from Han Wang's group (2014), the left ventricular end diastolic pressure (LVEDP) values in CHF rats that were treated with RTX was relatively low compared to sham animals [13]. In spite of the fact that infarct size was about the same in both groups (Figure 3- highlighted area), but the diastolic pressures were low. Interestingly, the negative dp/dt rate (the maximum rate of LVED pressure) seem to be improved, however, positive diastolic arterial pressure (DAP) was not much improved. One reason can explain this is that in heart failure animals with high levels of cardiac sympathetic nerve activity, where their epidural was treated with RTX, it reduced DAP even more if a significant reduction occurs in cardiac sympathetic nerve activity and renal sympathetic nerve activity which explained at the beginning of the discussion [13].

Table 1: The table above represents mean values for 17 different variables which were considered as major characteristics of measuring the size of haemodynamic in sham and hear failure rats after treated with RTX [13].

Parameters	Sham+Vehicle (n=21)	Sham + RTX (n=20)	CHF+Vehicle (n=23)	CHF + RTX (n=25)
Body weight, g	429 ± 7	430 ± 7	452 ±8	440 ± 8
Heart weight, mg	1438±28	1430 ± 30	2239± 61*	1650± 49*†
HW/BW, mg/g	3.4± 0.1	3.3 ± 0.1	5.0 ± 0.1*	3.8 ± 0.1*†
WLW/BW, mg/g	4.4± 0.1	4.5 ± 0.1	8.7 ± 0.3*	5.1 ± 0.2*†
SAP, mmHg	127.9 ± 2.2	128.8 ± 2.8	115.3± 2.0*	120.8 ± 2.3*
MAP, mmHg	103.5 ± 2.4	105.0 ± 3.1	96.7 ± 2.0*	101.3 ± 2.1
DAP, mmHg	91.6 ± 2.5	92.8 ± 3.2	87.3 ± 2.2	90.8 ± 2.2
LVEDP mmHg	5.0± 0.4	4.8± 0.4	21.3± 1.0*	8.3± 0.7*†
HR, bpm	357.3 ± 6.1	362.0 ±6.8	368.9 ± 5.1	348.3± 5.5f
dp/dt_{max}	9108±324	8601±224	5137± 180*	5446±173*
dp/dt_{min}	-8458±235	-8088±196	-3452±113*	-4643±149*†
Infarct size, %	0	0	42.5± 1.4*	39.1 ± 1.2*

Concluding Remarks

In summary, cardiac sympathetic activities can be targets for further research directions and not the exclusion of other aspects that we have already heard about and we will hear about, but we can impact both the sympathetic as well as the cardiac remodelling during cardiac heart failure. some of the inflammatory happened following myocardial infarction and probably other forms of heart failure as well.

The primary endpoint of the Peter Schwartz study was about safety and side effects. The secondary endpoints were efficacious endpoints which by considering at objective endpoints such as; LV remodelling, LV ejection fraction, diastolic end-systolic volume. They also considered subjective output of improvement in symptoms caused by heart failure by monitoring their patient's quality of life, using Minnesota Life Heart Failure Questionnaire (MLHFQ). Capsaicin substance p seems to have gained lot of interest in relation to the heart failure. It is not all solely about substance p but the concrete fact that is rather important in some of the HF inflammatory mechanisms. In other words, activation of SNS leads to activation and release of immune peptides that are in the ischemic area it leads to the cardiac sympathetic activation.

In last several years, researches are more interested in denervation as a modulatory mechanism for variety of disorders including hypertension, diabetes and heart failure, there is various stimulation for heart failure and controlling arrhythmias. Heart failure is readily recognised at the bedside or in clinic but is difficult to define and it has a highly variable course. It is a heterogenous mix of a number of clinical syndromes. For future directions and studies, carotid body denervation has been introduced as a potential way of reducing sympathetic outflow and impacting not only the heart failure state but hypertension as well. However, there has been less work done on the cardiac sympathetic afferent reflex as it seems very hard to denervate and examine the size of ischaemia in an event of preparing the autopsy from a necrotic heart sample.

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