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Review

Cardiac sympathoexcitation in heart failure

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ABSTRACT

Heart failure (HF) is a serious debilitating condition with poor survival rates and an increasing level of prevalence. The excessive sympatho-excitation that is a hallmark of heart failure has long-term effects that contribute to disease progression. The mechanisms causing the increase in renal sympathetic nerve activity (RSNA) have been extensively investigated in experimental models of heart failure, but there is less information on the factors causing the increase in cardiac SNA (CSNA). This review focuses on our recent investigations of the mechanisms driving the increased CSNA in an ovine rapid ventricular pacing model of HF. In conscious sheep with mild heart failure (ejection fraction 35–40%) the arterial baroreflex control of CSNA was normal. In contrast, the normal inhibition of CSNA with volume expansion was abolished in HF, indicating desensitisation of the cardiopulmonary mechano-reflex. Antagonism of central angiotensin AT1 receptors with losartan substantially reduced CSNA, demonstrating a critical role for the central renin–angiotensin system. Investigation of the role of the paraventricular nucleus of the hypothalamus (PVN), which plays a critical role in setting the increased RSNA in HF, demonstrated that the PVN did not maintain the increased CSNA in HF or the resting level of CSNA in normal animals. Furthermore, inhibition of the PVN in normal animals reversed the reduction in RSNA, but not CSNA, induced by volume expansion. These studies emphasise that the mechanisms controlling CSNA in the normal state, and causing the increase in HF, are different to those controlling sympathetic activity to the kidney.

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1. Introduction

Heart failure (HF) is a major public health epidemic and is one of the few health conditions with increasing prevalence in developed countries. It is a major burden on society because of the poor quality

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of life and premature death of affected individuals, and the high costs of medical care with HF being the main cause of hospital admission for those over 65 years of age. An estimated 5.7 million Americans have heart failure, and it is predicted that a further 3 million will have heart failure by 2030 (Roger et al., 2012). Despite advances in therapies, the mortality and morbidity of HF remains at unacceptably high levels. The five year mortality rates for subjects with HF in the Framingham Heart Study were 59% for men and 45% for women (Levy et al., 2002), this rate being worse than for most cancers (Stewart et al., 2001). The increased frequency of HF is due to ageing of the population and a decrease in fatality associated with improved treatment of acute coronary syndromes.

A hallmark of HF is activation of many neurohumoral systems in response to decreased cardiac output and subsequent under-perfusion of tissues. Although these compensatory mechanisms help maintain homeostasis in the short term, chronically the increased activity of these systems leads to further deterioration and progression of HF, and a worse prognosis. Thus inhibition of the effects of the sympathetic nervous system and renin–angiotensin system (RAS) is a major focus of current therapy (CIBIS Investigators, 1994; Swedberg and Kjekshus, 1988; Pfeffer et al., 1992). It is important to note that activation of the sympathetic nervous system occurs not only in classical HF with reduced systolic ejection fraction, but also in HF with preserved ejection fraction (Kitzman et al., 2002), which is estimated to encompass 50% of the patients with clinical features of HF.

2. Consequences of increased SNA in HF

The sustained and excessive level of sympathetic nerve activity (SNA) has serious adverse consequences that contribute to the progression of HF. The importance of increases in SNA to the heart and kidney in HF is emphasised by the finding that these organs account for 62% of the increase in total plasma noradrenaline spillover in HF patients (Hasking et al., 1986). These increases in sympathetic drive to the heart and kidney are especially detrimental, and are associated with reduced survival (Kaye et al., 1995; Petersson et al., 2005).

The high level of noradrenaline release at the heart in HF causes down-regulation of cardiac β-adrenoceptors, and has toxic effects on sympathetic nerve terminals mediated by the formation of noradrenaline derived free radicals (Liang et al., 2000); both these effects act to reduce the inotropic and chronotropic actions of noradrenaline. Excess noradrenaline release also induces left ventricular fibrosis and hypertrophy (Briest et al., 2001), and promotes the development of arrhythmias and sudden death (Kaye et al., 1995). Noradrenaline also acts to cause coronary vasoconstriction, as does the co-released peptide neuropeptide Y, which is released in greater amounts in HF (Kaye et al., 1994). Underscoring the detrimental effect of the increased sympathetic drive to the heart in HF is the effectiveness of treatment with β-blockers (Woodley et al. 1991; CIBIS Investigators, 1994) together with the finding that cardiac norepinephrine spillover is the strongest prognostic marker in HF patients (Kaye et al., 1995). In HF, the increased renal SNA (RSNA) leads to renal vasoconstriction and a fall in renal blood flow, excessive stimulation of renin secretion and inappropriate salt and water retention, which increase the work of the heart by promoting sodium retention and ventricular overfilling. Renal denervation has been shown to prevent the reduction in renal blood flow and also the increase in renal AT1 receptor expression and decrease in renal AT2 receptor expression that occurred in rabbits with pacing-induced HF (Clayton et al., 2011).

This review will focus on the mechanisms contributing to the increase in cardiac sympathetic nerve activity (CSNA) in HF, with less emphasis on sympathetic outflow to the kidney, which has been discussed in many comprehensive reviews (Felder et al., 2001; Patel, 2000; Zucker et al., 2012). Studies from our and other laboratories indicate major differences in the control of sympathetic outflow to the heart compared with that to other organs. For example, in conscious cats anaesthesia caused greater depression of CSNA than RSNA (Matsukawa et al., 1993), and behavioural stimuli induced differential changes in these two sympathetic outflows (Ninomiya et al., 1988). In conscious sheep we found that central administration of angiotensin or hypertonic saline stimulates CSNA, but inhibits RSNA (May and McAllen, 1997; Watson et al., 2004), the resting levels of CSNA and RSNA are different (Ramchandra et al., 2009a), and resuscitation from haemorrhage with intravenous hypertonic saline stimulates CSNA but not RSNA (Frithiof et al., 2011). Furthermore, clinical studies of noradrenaline spillover in HF indicate that the size and time course of the increase in CSNA are different to the changes in spillover to other organs (Hasking et al., 1986; Rundqvist et al., 1997). These studies indicate that the physiological and pathophysiological mechanisms controlling CSNA are not identical to those controlling SNA to other organs.

3. Resting levels of sympathetic nerve activity in heart failure

An indication that sympathetic activity is increased in HF first came from studies showing elevated plasma levels of noradrenaline in HF patients (Chidsey et al., 1962; Thomas and Marks, 1978). The development of the noradrenaline spillover technique allowed organ specific noradrenaline release to be determined, and this demonstrated large differences between the levels of noradrenaline released from individual organs in HF. In patients with severe HF the rate of cardiac noradrenaline spillover was elevated up to 50 fold, whereas that from the kidney was only increased 3 fold, and that from the lungs, gut and liver was unchanged (Hasking et al., 1986). These seminal findings indicated that there are distinct mechanisms inducing the increased SNA to individual organs in HF. A further important finding was that the elevation in cardiac spillover occurred before that to other organs (Rundqvist et al., 1997), indicating that the heart is not only exposed to higher levels of noradrenaline release than other organs, but for longer. It is important to note that it was the cardiac noradrenaline spillover technique that confirmed that the heart was not denervated in HF, as had been proposed, and was in fact releasing increased amounts of noradrenaline. This led to the first trial demonstrating the life saving properties of a β-adrenergic blocker in heart failure (Packer et al., 1996), leading to the current widespread use of β-blockers as a primary therapy in HF.

There is evidence that the increased cardiac noradrenaline spillover in HF may be partly accounted for by impaired neuronal noradrenaline uptake (Rundqvist et al., 1997), although this is not supported by all studies (Meredith et al., 1993). Using direct recordings of CSNA, in an ovine rapid ventricular pacing model of HF, we have confirmed that there is indeed a large increase in CSNA in HF. The animal model of pacing-induced HF has been used extensively and shows the symptoms of HF seen clinically, including decreased ventricular function and intense neurohumoral activation (Liu et al., 1999; Yarbrough and Spinale, 2003). Sheep with pacing-induced HF had a lower mean arterial pressure (76 ± 3 vs. 87 ± 2 mm Hg; $P<0.05$), ejection fraction (37 ± 2 vs. 81 ± 2 %; $P<0.001$) and fractional shortening (17 ± 1 vs. 48 ± 2%; $P<0.001$), together with ventricular dilatation (end diastolic diameter: 4.4 ± 0.2 vs. 3.5 ± 0.1 cm; $P=0.015$ and end systolic diameter: 3.5 ± 0.2 vs. 1.9 ± 0.1 cm; $P=0.001$), and decreased heart rate variability (32.8 ± 7.3 vs. 57.4 ± 7.5 ms; $P<0.01$) (Ramchandra et al., 2008; Watson et al., 2007).

In this model of HF there was a striking 3 to 4 fold increase in CSNA burst incidence (bursts of pulse related activity/100 heart beats) from about 30% to over 90% (Fig. 1) (Watson et al., 2007). We extended these findings to simultaneously record CSNA and RSNA in conscious normal and HF sheep. Interestingly, in normal healthy animals the resting level of CSNA was set much lower than that of RSNA, indicating differential central control of these sympathetic outflows (Fig. 1) (Ramchandra et al., 2009a). In sheep with HF, there was a large increase in CSNA with little change in the level of RSNA (Fig. 2). These findings provide an explanation for the