CROSSTALK

CrossTalk proposal: The late sodium current is an important player in the development of diastolic heart failure (heart failure with a preserved ejection fraction)

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Introduction

Approximately half of all patients with heart failure have an ejection fraction greater than 40–50% and may be diagnosed as having Heart Failure with preserved Ejection Fraction (HFpEF). Diastolic dysfunction is central to the pathophysiology of HFpEF (Borlaug & Paulus, 2011), and describes the slowing of ventricular relaxation and increased diastolic stiffness which ultimately impairs ventricular filling. The mechanistic basis of this impairment is complex and not yet well understood. Structural remodelling undoubtedly plays an important role in increasing left ventricular stiffness. However, the acute worsening of diastolic dysfunction during stress or exercise characteristic of HFpEF suggests an important contribution from dynamic changes in left ventricular (LV) functional properties. Frequency-dependent elevation of diastolic tension and intracellular Ca^{2+} ($[Ca^{2+}]_i$) has been observed in cardiac muscle strips from patients with left ventricular hypertrophy and diastolic dysfunction, or heart failure (Sossalla *et al.* 2008; Selby *et al.* 2011), implying that dysregulation of $[Ca^{2+}]_i$ homeostasis of the cardiomyocyte contributes to diastolic dysfunction.

Intracellular Ca^{2+} regulation is closely linked to intracellular Na^+ homeostasis, through the Na^+–Ca^{2+} exchanger (NCX). Intracellular Na^+ of cardiomyocytes from failing hearts is increased and associated with elevated diastolic tension (Pieske *et al.* 2002). An important mechanism underlying this observation may be an increase in the late sodium current ($I_{Na,L}$). The Na^+ conductance responsible for rapid depolarization of cardiomyocytes does not completely inactivate during the action potential. (Noble & Noble, 2006; Maier, 2012) Some channels continue to conduct, or even reactivate at relatively positive membrane potentials during the plateau and repolarization phases. This is $I_{Na,L}$ (Zaza *et al.* 2008). Consequently, about half of the myocyte Na^+ entry occurs during the initial 2–3 ms, and about half during the remainder of the action potential (Makielski & Farley, 2006). At the molecular level, $I_{Na,L}$ results from channel reopening during sustained depolarization by two different modes of gating: burst openings and late scattered openings (Maltsev & Undrovinas, 2008).

As outlined in Fig. 1, increased Na^+ entry through $I_{Na,L}$ increases intracellular Na^+ ($[Na^+]_i$), which reduces the driving force for extrusion of Ca^{2+} and favours Ca^{2+} influx via the Na^+–Ca^{2+} exchanger (NCX). This leads to increased $[Ca^{2+}]_i$. Elevated $[Ca^{2+}]_i$ eventually increases actin–myosin filament interaction during diastole and thus increases diastolic tension. This mechanism of Ca^{2+} overload has been demonstrated in numerous animal studies, and in strips of ventricular muscle or myocytes isolated from patients with failing hearts (Valdivia *et al.* 2005; Makielski & Farley, 2006; Maltsev & Undrovinas, 2008; Sossalla *et al.* 2008; Selby *et al.* 2011; Coppini *et al.* 2013). Further, specific augmentation of $I_{Na,L}$ with the sea anemone toxin ATXII in isolated myocytes and perfused hearts results in Na^+ and Ca^{2+} overload (Fraser *et al.* 2006; Sossalla *et al.* 2008) and impaired diastolic function. Diastolic dysfunction with preserved systolic function has also been described in LQT syndrome type 3 patients, where $I_{Na,L}$ is enhanced due to a Na^+ channel mutation (Moss *et al.* 2008; Hummel *et al.* 2013).

We propose that a pathological increase in Na^+ influx through cardiac Na^+ channels, specifically due to enhanced $I_{Na,L}$ is a major contributor to Ca^{2+} overload and diastolic dysfunction in HFpEF. Key evidence to support this hypothesis is outlined below.

In pathological conditions with diastolic dysfunction, cardiomyocyte $I_{Na,L}$ is enhanced up to 5-fold

This has been characterized in cardiomyocytes isolated from patients with hypertrophic cardiomyopathy (Coppini *et al.* 2013), from human (Maltsev *et al.* 2007; Sossalla *et al.* 2008) and dog failing hearts (Maltsev *et al.* 2007), in rat (Xi *et al.* 2009; Aistrup *et al.* 2013) and mouse (Toischer *et al.* 2013) models of

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pressure overload and in numerous species following hypoxia, ischaemia or metabolic stress (Shryock *et al.* 2013); all factors of relevance to the genesis of diastolic dysfunction in heart failure. Elucidation of the underlying mechanisms whereby $I_{Na,L}$ is enhanced is incomplete. Single channel studies on myocytes isolated from failing human hearts suggest that functional changes such as slowing of the two modes of gating comprising $I_{Na,L}$ (late scattered and bursting modes) contribute to enhanced $I_{Na,L}$ (Maltsev & Undrovinas, 2008). Evidence has also been gathered that Na^+ channel isoform expression (Xi *et al.* 2009) and functional regulation (Zaza *et al.* 2008) differs in diastolic dysfunction. There is considerable evidence that under pathological conditions $I_{Na,L}$ can, in a rate-dependent manner, induce Ca^{2+} overload and consequently ventricular dysfunction and arrhythmogenesis (Valdivia *et al.* 2005; Maltsev & Undrovinas, 2008; Zaza *et al.* 2008; Shryock *et al.* 2013).

Inhibiting $I_{Na,L}$ in isolated cardiac tissue improves relaxation and diminishes Ca^{2+} accumulation

One pivotal early study demonstrated that the $I_{Na,L}$ inhibitor ranolazine effectively prevented the frequency-dependent increase in diastolic tension in tissue strips from failing human hearts (Sossalla *et al.* 2008). This observation is key in understanding the role of $I_{Na,L}$ in HFpEF, characterized by exercise intolerance in part due to the worsening of diastolic function at elevated heart rates. Similar observations were made in myocytes isolated from dog failing hearts and from patients with hypertrophic cardiomyopathy. Diastolic Ca^{2+} became elevated at high pacing rates compared to healthy cells, and this effect could be diminished by ranolazine (Undrovinas *et al.* 2010; Coppini *et al.* 2013). Although selective for $I_{Na,L}$ over peak I_{Na}, ranolazine has multiple pharmacological targets of potential relevance to diastolic dysfunction. However, similar to ranolazine, other $I_{Na,L}$ inhibitors including the specific Na^+ channel inhibitor tetrodotoxin (TTX) attenuate $I_{Na,L}$ induced-Na^+-dependent Ca^{2+} overload in failing ventricular myocytes, and in myocytes exposed to H_2O_2 or ATXII (Undrovinas *et al.* 2010; Qian *et al.* 2012; Belardinelli *et al.* 2013). Although Na^+ channel knockout mice studies have shed light on mechanisms of arrhythmia, they did not specifically investigate the role of $I_{Na,L}$ on relaxation and diastolic calcium (Derangeon *et al.* 2012; Yang *et al.* 2012).

Inhibiting $I_{Na,L}$ improves diastolic function in experimental heart failure

Early insights into the potential contribution of $I_{Na,L}$ to diastolic dysfunction were gained from studies that examined the effects of $I_{Na,L}$ inhibition in heart failure. In 2002, the effect of ranolazine to acutely improve heart function was examined in dogs with chronic heart failure. Whereas ranolazine had no significant effects in normal dogs, ranolazine both decreased end-diastolic pressure and improved systolic functional parameters in dogs with heart failure (Sabbah *et al.* 2002). In a follow-up experiment, 3 months' treatment with ranolazine decreased end-diastolic pressure and circumferential wall stress whether alone, or combined with beta blockade or ACE inhibition in dogs with heart failure (Rastogi *et al.* 2008). Interestingly, all treatment regimens also diminished the pathological LV remodelling that occurred relative to placebo.

With increased recognition of the unique pathology of HFpEF relative to heart failure with a reduced ejection fraction, studies are being performed in models that more specifically reproduce the phenotype of diastolic dysfunction (Doi *et al.* 2000; LeGrice *et al.* 2012). In a recent study Aistrup *et al.* (2013) demonstrated that $I_{Na,L}$ is elevated in the spontaneously hypertensive rat and that 3 months' treatment with ranolazine prevented progression of LV hypertrophy, disruption of t-tubule architecture, and improved intracellular Ca^{2+} cycling. Combined, these data suggest that sustained inhibition of enhanced $I_{Na,L}$ and subsequent Ca^{2+} overload may improve diastolic function not only by improving dynamic Ca^{2+} regulation, but also interrupting the aberrant structural remodelling characteristic of diastolic heart failure.

The $I_{Na,L}$ inhibitor ranolazine improves diastolic function in patients

When ranolazine was administered acutely to 15 patients with ischaemic heart disease the regional peak filling rate and wall lengthening increased in ischaemic regions and the diastolic pressure volume relation was shifted downward, suggesting improvement of diastolic function (Hayashida *et al.* 1994). In a cohort of 22 patients with angina, ranolazine treatment for a mean of 65 days improved both systolic and diastolic parameters assessed by echocardiography (Figueredo *et al.* 2011). Systolic and diastolic left ventricular wall synchrony was also increased by 4 weeks' ranolazine treatment in patients with coronary artery disease (Venkataraman *et al.* 2012). While ranolazine has multiple mechanisms of action, in long QT syndrome type 3 patients with a specific enhancement of $I_{Na,L}$, acute infusion of ranolazine improved parameters of relaxation (Moss *et al.* 2008). In the recent RALI-DHF trial studying HFpEF patients,

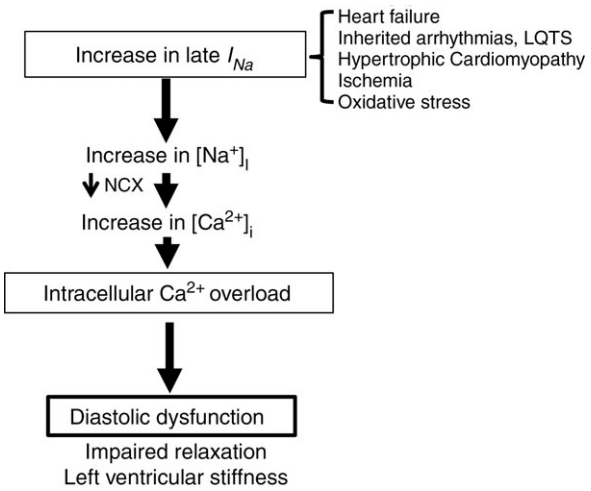

Figure 1. A pathological enhanced $I_{Na,L}$ contributes to Na^+-dependent Ca^{2+} overload, diastolic dysfunction

acute intravenous ranolazine was found to improve measures of haemodynamics including LV end-diastolic pressure and pulmonary artery pressure, but did not alter the LV relaxation rate. Oral treatment was extended for a further 13 days. Although no improvements in diastolic function were apparent by echocardiography at this time, this clinical study was underpowered to address this hypothesis (Maier *et al.* 2013).

Conclusion

Taken together, experimental data suggest that $I_{Na,L}$ is enhanced in many conditions and is an important contributor to Ca^{2+} overload and diastolic dysfunction.

Call for comments

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Additional information

Competing interests

LB is an employee of Gilead Sciences, Inc. (owner of ranolazine).