Antiarrhythmic effects of Sacubitrilat (LBQ657) on Ca2+ homeostasis in ventricular cardiomyocytes

Authors:
J Eiringhaus¹, C Wuensche², J Herting², G Hasenfuss², S Sossalla³, T Fischer¹, ¹Hannover Medical School, Dept. of Cardiology and Angiology - Hannover - Germany, ²University clinic, Dept. of Cardiology & Pneumology - Goettingen - Germany, ³University Hospital Regensburg, Dept. of Cardiology - Regensburg - Germany,

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Background and Objectives – Simultaneous inhibition of neprilysin and angiotensin II receptors by sacubitril/valsartan was shown to significantly reduce morbidity and mortality in heart failure patients compared to sole interference with the renin angiotensin system. Beneficial effects of increased levels of natriuretic peptides following neprilysin inhibition have been suggested, whereas direct effects of sacubitrilat on myocardial Ca2+ cycling properties remain elusive.

Methods and Results – Under basal conditions the combination of active neprilysin-inhibitor sacubitrilat (LBQ657) and angiotensin II receptor inhibitor valsartan did not influence diastolic Ca2+ spark frequency (CaSpF) nor arrhythmogenic SR Ca2+ leak in murine ventricular cardiomyocytes (confocal microscopy, n CMs/hearts=80/7 vs. 100/7, P=0.91/0.99). In contrast, sacubitrilat/valsartan treatment significantly reduced CaSpF by 35±9 % and SR Ca2+ leak by 45±9 % in CMs that had been put under catecholaminergic stress (isoproterenol 10nM, n=81/7 vs. 62/7, P<0.001 both). This effect could be clearly be attributed to the neprilysin inhibitor sacubitrilat as sole sacubitrilat treatment also reduced both parameters by similar degrees (reduction of CaSpF by 57±7 % and SR Ca2+ leak by 76±5 %; n=101/4 vs. 108/4, P<0.01 both) whereas sole valsartan treatment did not affect diastolic SR Ca2+ leak. Of note, systolic Ca2+ release, SR Ca2+ load and Ca2+ transient kinetics of murine CMs were not compromised upon treatment with sacubitrilat (epifluorescence microscopy, n=41/6 vs. 39/6). Importantly, sacubitrilat/valsartan in combination as well as sacubitrilat alone also reduced diastolic CaSpF and SR Ca2+ leak by 40-74 % in human left-ventricular CMs from patients with end-stage heart failure (n=71/8 vs. 78/8, P<0.05).

Conclusion – This study demonstrates that neprilysin-inhibition directly exerts beneficial effects on Ca2+ homeostasis in human heart failure. We can show for the first time that neprilysin-inhibition by sacubitrilat yields a strong reduction of arrhythmogenic SR Ca2+ leak without affecting systolic Ca2+ release. These effects might contribute to the mortality benefit of sacubitril/valsartan treatment in the PARADIGM Study.