KLF2 mediates enhanced chemoreflex sensitivity, disordered breathing and autonomic dysregulation in heart failure

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Key points: Enhanced carotid body chemoreflex activity contributes to development of disordered breathing patterns, autonomic dysregulation and increases in incidence of arrhythmia in animal models of reduced ejection fraction heart failure. Chronic reductions in carotid artery blood flow are associated with increased carotid body chemoreceptor activity. Krüppel-like Factor 2 (KLF2) is a shear stress-sensitive transcription factor that regulates the expression of enzymes which have previously been shown to play a role in increased chemoreflex sensitivity. We investigated the impact of restoring carotid body KLF2 expression on chemoreflex control of ventilation, sympathetic nerve activity, cardiac sympatho-vagal balance and arrhythmia incidence in an animal model of heart failure. The results indicate that restoring carotid body KLF2 in chronic heart failure reduces sympathetic nerve activity and arrhythmia incidence, and improves cardiac sympatho-vagal balance and breathing stability. Therapeutic approaches that increase KLF2 in the carotid bodies may be efficacious in the treatment of respiratory and autonomic dysfunction in heart failure. Abstract: Oscillatory breathing and increased sympathetic nerve activity (SNA) are associated with increased arrhythmia incidence and contribute to mortality in chronic heart failure (CHF). Increased carotid body chemoreflex (CBC) sensitivity plays a role in this process and can be precipitated by chronic blood flow reduction. We hypothesized that downregulation of a shear stress-sensitive transcription factor, Krüppel-like Factor 2 (KLF2), mediates increased CBC sensitivity in CHF and contributes to associated autonomic, respiratory and cardiac sequelae. Ventilation (Ve), renal SNA (RSNA) and ECG were measured at rest and during CBC activation in sham and CHF rabbits. Oscillatory breathing was quantified as the apnoea?hypopnoea index (AHI) and respiratory rate variability index (RRVI). AHI (control  $6 \pm 1/h$ , CHF  $25 \pm 1/h$ ), RRVI (control  $9 \pm 3/h$ , CHF  $29 \pm 3/h$ ), RSNA (control  $22 \pm 2\%$  max, CHF  $43 \pm 5\%$  max) and arrhythmia incidence (control  $50 \pm 10/h$ , CHF  $300 \pm 100/h$ ) were increased in CHF at rest (FIO2 21%), as were CBC responses (Ve, RSNA) to 10% FIO2 (all P &It; 0.05 vs. control). In vivo adenoviral transfection of KLF2 to the carotid bodies in CHF rabbits restored KLF2 expression, and reduced AHI ( $7 \pm 2/h$ ), RSNA ( $18 \pm 2\%$  max) and arrhythmia incidence ( $46 \pm 13/h$ ) as well as CBC responses to hypoxia (all P &It; 0.05 vs. CHF empty virus). Conversely, lentiviral KLF2 siRNA in the carotid body decreased KLF2 expression, increased chemoreflex sensitivity, and increased AHI ( $6 \pm 2/h$  vs.  $14 \pm 3/h$ ), RRVI ( $5 \pm 3/h$  vs.  $20 \pm 3/h$ ) and RSNA ( $24 \pm 4\%$  max vs.  $34 \pm 5\%$  max) relative to scrambled-siRNA rabbits. In conclusion, down-regulation of KLF2 in the carotid body increases CBC sensitivity, oscillatory breathing, RSNA and arrhythmia incidence during CHF. © 2017 The Authors. The Journal of Physiology © 2017 The Physiological Society

apnoea

arrhythmia

carotid body

heart failure

Krüppel-like Factor 2

oscillatory breathing

sympathetic nerve activity

angiotensin converting enzyme 1

endothelial nitric oxide synthase

kruppel like factor 2

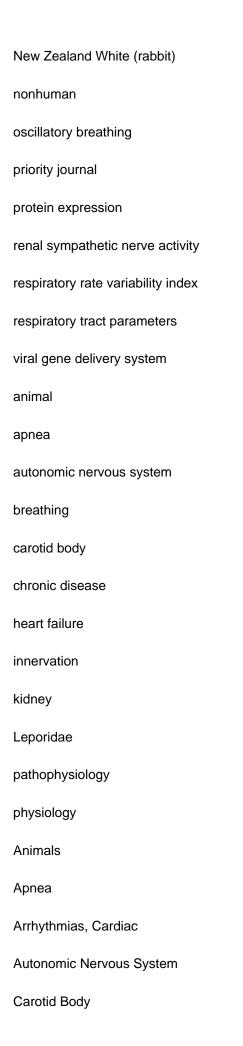
peptide hydrolase

small interfering RNA

unclassified drug

kruppel like factor

adult
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breathing disorder
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heart arrhythmia
heart ejection fraction
heart failure
heart rate variability
hypoxia
in vivo study
left ventricular diastolic volume
left ventricular systolic volume
lung minute volume
male
nerve conduction



Chronic Disease
Heart Failure
Kidney
Kruppel-Like Transcription Factors
Male
Rabbits
Respiration