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 ± 1/h, CHF 25 ± 1/h), RRVI (control 9 ± 3/h, CHF 29 ± 3/h), RSNA (control 22 ± 2% max, CHF 43 ± 5% max) and arrhythmia incidence (control 50 ± 10/h, CHF 300 ± 100/h) were increased in CHF at rest (FIO2 21%), as were CBC responses (Ve, RSNA) to 10% FIO2 (all P < 0.05 vs. control). In vivo adenoviral transfection of KLF2 to the carotid bodies in CHF rabbits restored KLF2 expression, and reduced AHI (7 ± 2/h), RSNA (18 ± 2% max) and arrhythmia incidence (46 ± 13/h) as well as CBC responses to hypoxia (all P < 0.05 vs. CHF empty virus). Conversely, lentiviral KLF2 siRNA in the carotid body decreased KLF2 expression, increased chemoreflex sensitivity, and increased AHI (6 ± 2/h vs. 14 ± 3/h), RRVI (5 ± 3/h vs. 20 ± 3/h) and RSNA (24 ± 4% max vs. 34 ± 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.

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

animal cell

animal experiment

animal model

animal tissue

apnea hypopnea index

Article

autonomic dysfunction

breathing disorder

cardiovascular parameters

carotid body

chemoreceptor reflex

controlled study

down regulation

fractional shortening

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

New Zealand White (rabbit)

nonhuman

oscillatory breathing

priority journal

protein expression

renal sympathetic nerve activity

respiratory rate variability index

respiratory tract parameters

viral gene delivery system

animal

apnea

autonomic nervous system

breathing

carotid body

chronic disease

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Leporidae

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Animals

Apnea

Arrhythmias, Cardiac

Autonomic Nervous System

Carotid Body

Chronic Disease

Heart Failure

Kidney

Kruppel-Like Transcription Factors

Male

Rabbits

Respiration