and that PPARα is an essential regulator of metabolism in hypoxia. PPARα−/− mice (n=18) and wild-type (wt) controls (n=20) were exposed to 3 weeks of normobaric hypoxia. Control activated receptor alpha−/− (n=17) and wt mice (n=21) were housed in normoxic conditions within the same room. Oxygen content was reduced incrementally in the first week of housing, followed by 2 weeks at 11% oxygen. In-vivo cardiac function was measured using multislice cardiac magnetic resonance imaging. Hearts were perfused in the Langendorff mode to measure palmitate oxidation and glycolysis using 3H-labelled substrates. Cardiac output was unchanged in hypoxic wt and normoxic PPARα−/− mice, but was reduced by 31% by hypoxia in PPARα−/− mice (p<0.02). Late-stage ventricular filling was 46% lower in hypoxic PPARα−/− mice (p<0.001). Hypoxia reduced palmitate oxidation by 27% in mouse wt hearts, but did not affect PPARα−/− hearts. Hypoxia increased net lactate efflux 2.4-fold in hearts from wt animals (p<0.01), but lactate efflux from PPARα−/− hearts was unchanged with hypoxia. Hypoxia increased basal glycolytic flux 2.4-fold in wt hearts but did not alter lacticoyl flux in PPARα−/− mouse hearts (p>0.01), which was already 5.7-fold greater than wt hearts. Thus PPARα−/− hearts lack the metabolic flexibility essential for adaptation to chronic hypoxia, and their inability to upregulate glycolysis probably impairs cardiac function.

Conclusions

Nox2−/− BMM display marked abnormalities in morphological and migratory behaviour that may contribute significantly to the ability of the monocyte to differentiate and migrate in vivo in response to pathological stimuli. This phenotype could underlie the protection against fibrosis observed in vivo in Nox2−/− mice.

006 NORMOBARIC HYPOXIA IMPAIRS CARDIAC ENERGETICS IN NORMAL HUMAN VOLUNTEERS

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Background

In the first few days of hypoxic exposure, left ventricular dysfunction is consistently observed in the human heart, yet the cellular mechanisms underlying the dysfunction are poorly understood.

Objective

Our hypothesis was that normobaric hypoxia impairs cardiac energetics, leading to cardiac dysfunction in healthy subjects.

Methods

Normal healthy volunteers underwent 20 h of normobaric hypoxia in purpose-built hypoxia chambers. The partial pressure of oxygen during end tidal expiration (PETO2) was kept between 50 and 60 mm Hg, while keeping peripheral oxygen saturation (SpO2) above 80%. Cardiac function was measured using magnetic resonance imaging and echocardiography. High-energy phosphate metabolism was measured as the ratio of phosphocreatine to ATP (PCr/ATP) by 31P phosphorus magnetic resonance spectroscopy before and after 20 h of hypoxia. Healthy men (n=12, aged 24±2 years) were recruited from the University of Oxford.

Results

During hypoxia, PETO2 and SpO2 averaged 55±1 mm Hg and 83±6±0.4%, respectively. There was a 15% reduction in cardiac PCr/ATP, from 2.0±0.1 to 1.7±0.1 after hypoxia (p<0.01) and reduced diastolic function, measured as E/E′, from 6.1±0.4 to 7.5±0.7, p<0.01.

Conclusion

Short-term normobaric hypoxia led to rapid changes in cardiac metabolism and alterations in diastolic function in normal human hearts. Impaired high-energy phosphate metabolism may explain the cardiac dysfunction observed after hypoxic exposure, whether in health or disease.