Assessing myocardial microvascular reactivity with a novel MRI imaging approach as an early biomarker of diabetic heart failure

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Introduction: Microvascular dysfunction (mvD), and more specifically coronary microvascular disease (CMD), has been implicated as the primary hallmark of diabetic cardiomyopathy and HFpEF, afflicting millions of people worldwide. The onset and progression of microvascular disease is driven by vascular inflammation and is characterized by vascular smooth muscle cell thickening and impaired vasomodulation, both of which ultimately reduce perfusion and damage tissue. To meet metabolic demands, the body recruits additional assistance from our microvascular reserve, which is diminished during stress, thus resulting in a dampened vasomodulatory response to stimuli. Diagnosing mvD in the myocardium, therefore, requires a non-invasive method to measure vasomodulation or, more precisely, changes in microvascular blood volume.

Purpose: Current clinical imaging platforms lack the ability to detect vasomodulation in a sensitive and specific manner. Because of this shortcoming, there is also no literature sex comparison of cardiac microvascular reactivity in response to stress in diabetics. This work aims to address this technology and knowledge gap by developing and demonstrating a novel MRI technique for the specific assessment of vasomodulation without confounding influences from changes in blood oxygen saturation, hematocrit, or flow.

Methods: Elevated CO2 is a safe and reliable vasodilatory stimulus and is effective in differentiating healthy from diseased vasculature. 10% CO2 was mixed with 21% oxygen and directed into an intubated rat. A blood-pool T1 contrast agent (Ablavar) was injected intravenously as a bolus (0.3mmol/kg) followed by a saline flush, to saturate the blood volume fraction, eliminating sensitivity to molecular oxygen and producing changes in T1 dominated by the blood volume fraction. The extended residency time of Ablavar, which stems from protein binding, allows a prolonged period of stable T1 signal enhancement (approx. 40 minutes).

Results: Exposure to 10% CO2, a known cardiac vasodilator, elicited conflicting results when compared across sexes. Young female rats demonstrated a strong vasodilatory response within 10 minutes of hypercapnic exposure, quantified through the drastic reduction in T1, while their male counterparts exhibited little to no change. When reverting to room air following 10 minutes of CO2, both male and female animals exhibited strong vasoconstriction. Young pre-diabetic female rats exhibited a blunted response when exposed to 10% CO2, losing their ability to vasodilate and constrict.

Conclusion: This work described a novel MRI diagnostic tool for highly specific assessment of microvascular vasomodulation and demonstrated a greater vasodilatory response to hypercapnic stimuli in healthy female rats compared to male, along with blunted response in diabetic females. This non-invasive technology will be valuable for early diagnosis of cardiac disease in patients predisposed to developing mvD.

T1 myocardial microvascular reactivity
Blunted pre-diabetic female stress-CMR