Maintained cGMP-PDE5 signaling in coronary microvascular of swine with multiple co-morbidities

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Background: Coronary microvascular dysfunction is thought to play a key role in perturbations in myocardial perfusion, thereby contributing to myocardial dysfunction. Multiple comorbidities, including diabetes mellitus (DM), hypercholesterolemia (HC) and chronic kidney disease (CKD) have been associated with coronary microvascular endothelial dysfunction through a reduction in nitric oxide (NO) bioavailability and/or signaling. Here we investigated if phosphodiesterase 5 (PDE5) signaling is altered in the coronary microvasculature of swine with multiple comorbidities (DM+CKD+HC).

Methods: In seven female swine, DM (streptozotocin, 3x50 mg/kg), CKD (renal artery embolization) and HC (high fat diet) were induced. Six months later, animals were chronically instrumented with fluid filled catheters for hemodynamic measurements and oximetry. Eight healthy, age matched female swine were used as control (CON). Myocardial sensitivity to NO was assessed by measuring coronary vascular conductance (CVC), during infusion of cumulative doses of the NO donor sodium nitroprusside (SNP). The influence of blockade of PDE5 on myocardial perfusion was assessed in vivo during treadmill exercise, by infusion of the PDE5 inhibitor sildenafil (10mg iv). Myocardial PDE5 activity was assessed in vitro.

Results: Hyperglycemia(19±1.4 in DM+CKD+HC vs 8.9±1.5 mmol/l in CON, P<0.001), CKD (glomerular filtration rate: 132±14 vs 191±9 ml/min, P<0.01) and hypercholesterolemia (8.2±1 vs 1.7±0.1 mmol/l, P<0.001) were successfully induced. Myocardial oxygen delivery was impaired in DM+CKD+HC swine both at rest and during exercise (P<0.05), forcing the myocardium to increase its oxygen extraction, resulting in reduced coronary venous oxygen content compared to CON (both P<0.05) suggestive of impaired NO bioavailability. However, the response to SNP was increased in the DM+CKD+HC swine (*P=0.043, figure), indicating an increased NO sensitivity. PDE5 inhibition resulted in a mild decrease in myocardial oxygen extraction (CON P=0.14, DM+CKD+HC †P=0.01, figure) that was similar in DM+CKD+HC and CON swine (P=0.92). This was supported by a similar PDE5 activity in myocardial tissue of both groups (P=0.26).

Conclusions: Impaired NO bioavailability in coronary microvasculature of swine with multiple comorbidities seems to be compensated by a higher sensitivity to NO and maintained PDE5 signaling.
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