Abstract: P550

Loss of nitric oxide contributes to perturbations in myocardial oxygen balance in exercising swine with multiple comorbidities

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Introduction: Multiple comorbidities, including diabetes mellitus (DM), hypercholesterolemia, hypertension (HT) and chronic kidney disease (CKD) are thought to cause a pro-inflammatory state, which leads to coronary microvascular dysfunction and impaired myocardial perfusion. In the present study, we investigated the effects of DM, CKD and high fat diet (HFD) on microvascular function and myocardial blood flow regulation in swine, with a particular focus on the role of NO.

Methods: DM and CKD were induced in 5 female swine that were subsequently fed HFD (DM+HFD+CKD), while 6 female healthy swine on normal pig chow served as controls (CON). At 6 months follow-up coronary flow regulation was studied at rest and during treadmill exercise in the absence and presence of the eNOS inhibitor, nitro-L-arginine after chronic instrumentation. At sacrifice, small epicardial coronary arteries (250-300 μm) were isolated and studied in vitro in Mulvany wire myographs. The endothelium-dependent vasodilation to bradykinin (BK) was studied in the absence and presence of eNOS blockade. Myocardial levels of NO metabolites NO2- and NO3- were measured using a Griess reaction colorimetric assay. TNF-α plasma levels were determined by ELISA.

Results: DM+HFD+CKD animals had hyperglycaemia (glucose: 18.7±1.9 vs 7.5±0.6 mmol/L), renal dysfunction (glomerular filtration rate: 123±12 vs 202±8 ml/min), hypercholesterolemia (total cholesterol: 7.3±0.7 vs 1.7±0.1 mmol/l) which were associated with a pro-inflammatory state (TNF-α: 52±5 vs 25±5 pg/ml, all P<0.05). DM+HFD+CKD swine showed impaired myocardial oxygen delivery both at rest and during exercise, forcing the myocardium to increase its oxygen extraction (MO2ex) (Figure) and resulting in reduced coronary venous oxygen content compared to CON (all P<0.05). eNOS-inhibition resulted in coronary microvascular constriction in CON, reflected in an increased MO2ex (P<0.05), while it had no effect in DM+HFD+CKD, suggesting that loss of NO was principally responsible for the perturbation in myocardial oxygen delivery in DM+HFD+CKD (Figure). This was supported by lower myocardial levels of NO2-+NO3- in DM+HFD+CKD compared to CON (0.20±0.02 vs 0.34±0.06 μmol/mg protein, P<0.05). Isolated vessels of DM+HFD+CKD swine showed decreased endothelial dependent vasodilation to BK, mediated via a complete abolishment of the NO-dependent vasodilator pathway, consistent with the in vivo observations.

Conclusion: Prolonged exposure to DM, HFD and CKD results in a pro-inflammatory state associated with impaired coronary microvascular NO production, thereby altering coronary microvascular dilation and hampering myocardial perfusion.
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