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**Altered myocardial function and perfusion in a swine model of diastolic dysfunction with multiple co-morbidities**

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**Introduction and Purpose:** Patients with diastolic dysfunction often have associated co-morbidities such as diabetes mellitus (DM), hypercholesterolemia (HC) and chronic kidney disease (CKD). The hypothesis of the present study is that the co-morbidities produce systemic inflammation and microvascular dysfunction resulting in impaired myocardial perfusion and alterations in myocardial structure and function in swine.

**Methods:** We induced DM (streptozotocin, 150mg/kg i.v.), HC (high fat diet) and CKD (renal artery embolization), (DM+HC+CKD) for 6 months in 16 female swine, while 15 female healthy swine on normal diet served as controls (CON). Myocardial function, structure and vascular tone-control were studied during anesthesia, as well as awake, at rest and during graded treadmill exercise. Results: The DM+HC+CKD group showed high plasma glucose (22.7±0.9mmol/l vs 6.1±0.7mmol/l in CON) and cholesterol (16.9±3.4 vs 2.2±0.1mmol/l), and impaired kidney function (glomerular filtration rate: 139±19 vs 197±10 ml/min, all P<0.05), associated with increased inflammation and impaired coronary small artery endothelial function. A subgroup of animals studied during exercise, showed reduced cardiac index (CI, P<0.05), higher levels of left atrial pressure required for similar CI, reduced stroke volume index and impaired myocardial efficiency (Figure, all P<0.05 vs CON). Furthermore, the animals with the three co-morbidities demonstrated perturbations in myocardial perfusion, requiring an increased myocardial oxygen extraction (Figure), during exercise, which resulted in lower coronary venous oxygen content levels. These functional alterations were accompanied by increased myocardial collagen content, reduced capillary/fiber ratio and elevated passive cardiomyocyte stiffness associated with a shift towards the stiff titin isoform (N2BA/N2B ratio: 1.29±0.07 vs 1.65±0.10, P<0.05), resulting in increased left ventricular end-diastolic stiffness (end-diastolic elastance at sacrifice: 0.15±0.02 vs 0.07±0.01 mmHg/ml, P<0.05), while ejection fraction was maintained (45±4 vs 54±3%, P=NS). Conclusion – Diabetes mellitus, hypercholesterolemia and chronic kidney disease lead to systemic inflammation, coronary microvascular dysfunction, which associate with impaired vascular tone control, myocardial stiffening and LV diastolic dysfunction with preserved ejection fraction.
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Conclusion – Diabetes mellitus, hypercholesterolemia and chronic kidney disease lead to systemic inflammation, coronary microvascular dysfunction, which associate with impaired vascular tone control, myocardial stiffening and LV diastolic dysfunction with preserved ejection fraction.