Regional and temporal variation in the expression of metalloproteinases and their inhibitors in the venous wall of arteriovenous shunt in an experimental model

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Objective: Vascular access graft failure is primarily related to the intimal hyperplastic response in the venous outflow of arteriovenous shunts (AVS) used for hemodialysis. Metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) assume key roles in extracellular matrix degradation and development of intimal hyperplasia. Our study determined the time-course and regional heterogeneity of *MMP2*, *MMP9*, *TIMP1*, and *TIMP2* expression in the venous wall of AVS in an animal model.
Methods: 24 healthy male Landrace pigs underwent AVS creation between the carotid artery and ipsilateral jugular vein via ePTFE graft. Animals were allocated into three groups, sacrificed 2, 4, and 12 weeks postoperatively. The shunted and contralateral veins were excised and divided into three parts, according to topography (proximal, central, and distal). Subsequent to isolation of total RNA from tissue and synthesis of cDNA, mRNA expression of *MMP2, MMP9, TIMP1,* and *TIMP2* genes was studied with quantitative real-time PCR.
Results: Increased expression of all genes was found in shunted than contralateral veins. At 2 weeks, a marked rise of *MMP2* (5.98±0.70 (fold differences vs.control ($2^{-\Delta\Delta CT}$)) vs. 3.91±0.34 vs. 1.94±0.12, $p<0.05$) and *MMP9* (2.38±0.30 vs. 1.26±0.20 vs. 1.00±0.14, $p<0.05$), and a smaller one of *TIMP1* (4.80±0.82 vs. 8.17±0.06 vs. 10.59±1.33, $p<0.05$) and *TIMP2* (5.69±0.70 vs. 9.46±1.24 vs.11.08±1.83, $p<0.05$) levels was noted in central than proximal and distal regions, aggravated over time.
Conclusions: AVS creation via ePTFE graft elicited extracellular matrix degradation, especially in the central region. Our findings, pertaining to regional and temporal variations in expression of metalloproteinases and their inhibitors, may enhance our understanding of the pathophysiology of graft access complications.

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