

Evidence of liver tolerance in a model of hyperacute rejection after discordant xenotransplantation.

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INTRODUCTION

Multivisceral transplantation (MT) is currently a clinical reality worldwide. Xenotransplantation is a potential solution for organs shortage, mainly for MT. There is a lack of models to study MT. In this pioneer study we portray multivisceral xenotransplantation and describe the features of hyperacute rejection (HR) using three species combination.

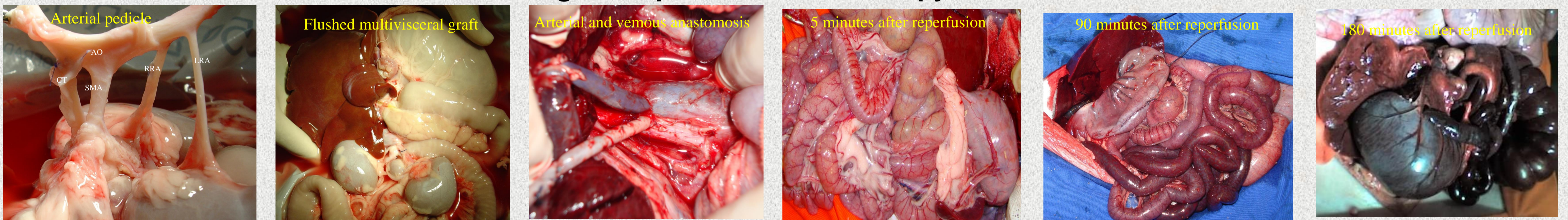
METHOD

Multivisceral grafts containing esophagus, stomach, small intestine, colon, liver, pancreas, spleen and kidneys were implanted heterotopically using 3 different combinations: dog-to-pig (n=5); pig-to-dog (n=5) and rabbit-to-pig (n=15). Multivisceral allotransplantation using pigs (n=5), dogs (n=4) and rabbits (n=5) composed the negative control group of HR. During three hours after graft reperfusion we performed serial endoscopy of stomach and bowels and collected samples from all graft organs for histology and IgG fixation assessment by immunofluorescence. HR were graded as 0 = normal tissue; I = mild HR (edema, vascular congestion, and clumping of platelets in the microcirculation), II = moderate HR (diffuse edema, presence of some fibrin thrombi, intense vascular congestion, epithelial dysplasia, and foci of hemorrhage), and III = severe HR (presence of fibrin thrombi in all vessels, extensive interstitial edema, diffuse interstitial hemorrhage, and confluent necrosis).

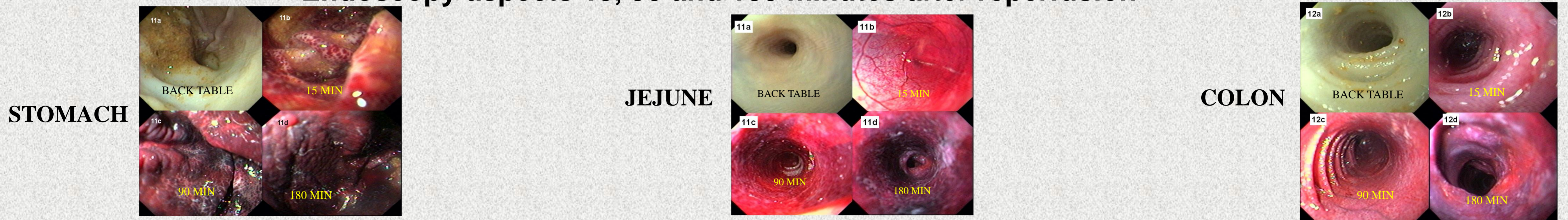
RESULT

All animals survived until the end of the experiment. HR was macroscopically noted in xenograft around 15 minutes after reperfusion. HR were observed by microscopy in all organs from multivisceral xenograft. Features of HR was similar in the three different species combination appraised (Graphs 1, 2 and 3). HR was less aggressive in liver (tolerance?). IgG fixation was strong in xenografts in the sites of HR (histopathological pictures below) . The occurrence of HR was macroscopically absent in allograft up to experimental end point. Autopsy of allografts reveled normal appearance or mild reperfusion injury in all organs and absence of IgG fixation by immunofluorescence. Endoscopy observed the progression of HA in stomach, jejunum and right colon (histological pictures below)

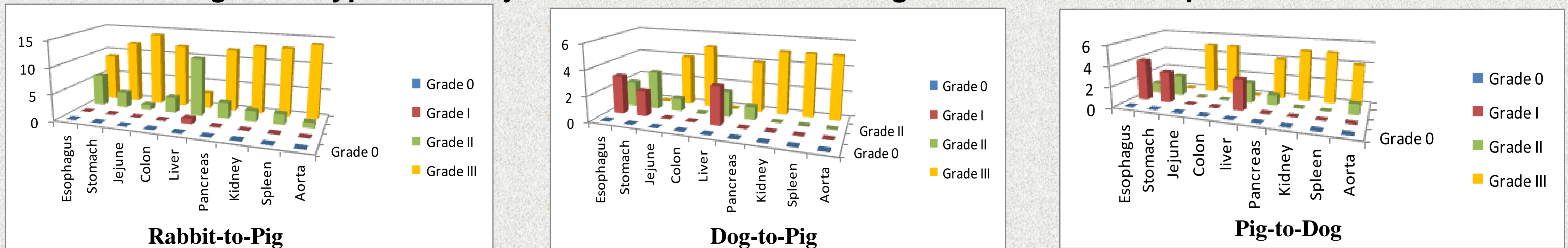
Surgical aspects and macroscopy



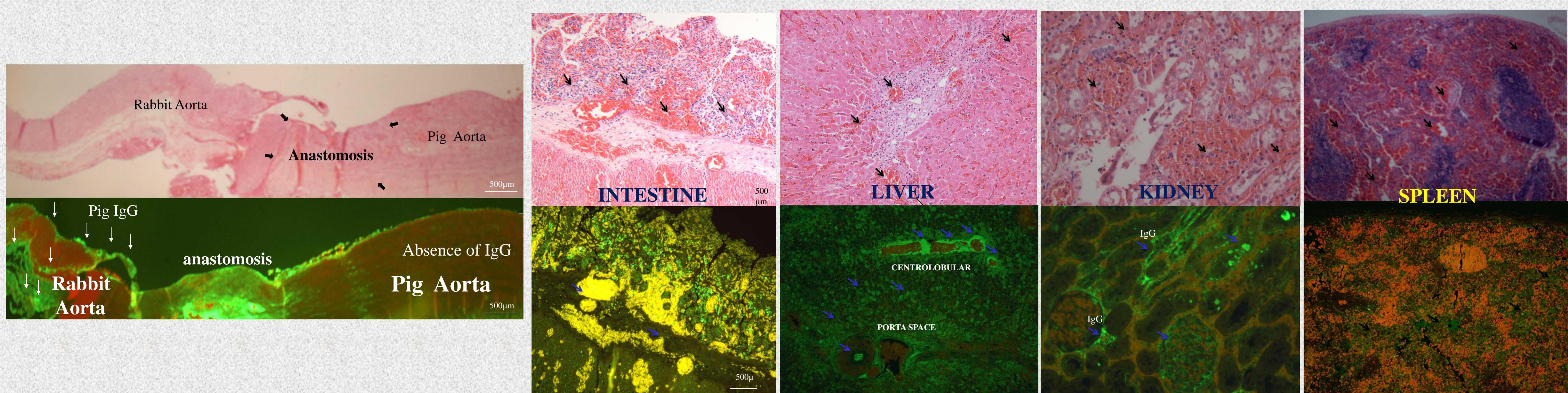
Endoscopy aspects 15, 90 and 180 minutes after reperfusion



Degree of hyperacute rejection in multivisceral xenograft 180 min. after reperfusion



Features of hyperacute rejection by hematoxylin-eosin (up) and IgG immunostaining in green color (down)



CONCLUSION

This research introduces multivisceral xenotransplantation as a viable method for the future. Features of HR were similar in the three different species combinations appraised. HR was less aggressive in liver (tolerance?), while it was severe in intestine, pancreas, spleen, and kidneys. IgG fixation was strong in the sites of HR. Allografts revealed normal appearance and absence of IgG fixation.