

Endothelin receptor distribution in pulmonary endarterectomy specimens from patients with Chronic thromboembolic pulmonary hypertension

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Introduction: Pulmonary endarterectomy (PEA) is the treatment of choice for patients with chronic thromboembolic pulmonary hypertension (CTEPH). In excised PEA specimens there are often focal areas of re-canalisation containing endothelialised channels surrounded by smooth muscle cells (SMCs). Endothelin-1 (ET) is a potent vasoconstrictor and promotes endothelial and smooth muscle cell proliferation. Although, ET levels are elevated in patients with CTEPH and fall post-PEA and the off-label use of ET receptor antagonists is of benefit in some CTEPH patients, little is known regarding ET receptor distribution in CTEPH and PEA specimens.

Methods: PEA specimens (n=19 patients) comprising a proportion of the pulmonary artery intima and all intraluminal material was obtained from patients undergoing PEA for CTEPH at our centre. Representative samples of distal and proximal PEA were snap-frozen in liquid nitrogen and crysectioned for either immunohistochemical or autoradiographical studies. Autoradiography for ET receptors was performed using [¹²⁵I]-ET (Total binding) and to ET_A or ET_B sub-types by selective inhibition of the radioligand. ET receptor expression was then co-localised to specific cell lineages or tissue structures using anti-SMA (smooth muscle cells) or anti-CD31 (endothelial cells) immunohistochemical markers and confocal microscopy.

Results: Specimens were categorised, based on morphology as fresh thrombus, partially organized thrombus or highly organized thrombus. Fresh thrombus showed no ET receptor binding. Partially organized thrombi consisted of abundant fibromyxoid granulation tissue with admixed SMCs predominantly of a morphologically secretory phenotype (short, stellate cells) with occasional dispersed contractile SMCs and no recanalised channels. Partially organized thrombi showed ET binding in the fibromyxoid thrombus core but this did not localise with the SMCs which were largely negative for ET binding. Highly organized thrombi contained frequent recanalised channels each recapitulating the histological architecture of an artery with a distinct endothelial cell layer (CD31 positive) surrounded by arranged contractile (fusiform) SMCs. ET binding (mostly ET_A) was strongly associated with the recanalised vessels, being present in medial (contractile) SMCs.

Conclusions: Our results indicate that ET receptors are present on contractile SMCs observed surrounding recanalised channels in fully organised thrombus but not in the secretory SMCs of partially organized thrombus. The abundance of ET receptors within PEA specimens may provide a rationale for the use of endothelin receptor antagonists in the treatment of selected cases with CTEPH.