Increased vascular endothelial growth factor signalling following loss of endothelial endoglin leads to peripheral arteriovenous shunting and high output heart failure.

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Background: Endoglin is a co-receptor for TGFbeta/BMP9/10 signalling and ENG mutations lead to the vascular disorder hereditary haemorrhagic telangiectasia type I (HHT). Endoglin is also required for normal vascular development and angiogenesis, but little is known about endoglin’s role in quiescent adult vascular endothelium.

Purpose: The goal of this present study is to determine how endoglin maintains vessel calibre in adult life to prevent AVM formation and thereby protect heart function.

Methods: To investigate this role, tamoxifen was administered to adult Cdh5(PAC)-CreERT2;Engfl/fl mice to generate endothelial-specific depletion of endoglin (Eng-iKOe). Cardiac magnetic resonance imaging, myography, vascular casting, microsphere injection, immunohistology, qPCR and aortic telemetry were used to evaluate cardiovascular changes after endoglin knockdown.

Results: Endothelial-specific loss of endoglin leads to an enlarged heart and cardiomyocyte hypertrophy within 5 weeks, progressing to high output heart failure (HOHF). In vivo aortic telemetry revealed significant loss of aortic pressure within a few days of endoglin depletion. Increased cardiac size and reduced cardiac afterload were confirmed by ventricular pressure loop analysis. As HOHF could result from arteriovenous malformations (AVMs), and these are found primarily in mucocutaneous and pulmonary tissues in HHT, we systematically screened for AVMs using microspheres and vascular casting. Although AVMs were absent in the majority of tissues, they were observed in the pelvic region and may account for the rapid increase in cardiac output. The pelvic cartilaginous symphysis is a noncapsulated cartilage with a naturally high endogenous expression of vascular endothelial growth factor (VEGF). Development of pelvic AVMs in this region of high VEGF expression occurred because loss of endoglin in endothelial cells leads to increased sensitivity to VEGF and a hyper-proliferative response. Finally, we found that inhibition of VEGFR2 was protective against AVMs development, enlargement of the heart and dilatation of the ventricles.

Conclusion: Our results showed the essential role of endoglin in the maintenance of adult cardio-vasculature through crosstalk with the VEGF signalling pathway.