Besides the control of vasomotor tone and the regulation of tissue blood flow, vasoactive peptides
exert numerous functions. They act as growth factors and are able to remodel the vascular wall, they
modulate hormonal and cytokine production, they exert neuronal effects. In addition, several of
these peptides possess an \textit{in vitro} and \textit{in vivo} pro- or anti-angiogenic effect. For example,
angiotensin II, adrenomedullin, bradykinin are proangiogenic compounds. Endothelin, a potent
vasoconstrictor, when produced in recombinant cells, exhibits a marked angiogenesis in the chick
chorio-allantoic membrane (CAM) assay. This proangiogenic effect can be suppressed by bosentan,
a mixed endothelin receptor antagonist. This effect is likely mediated by VEGF since a VEGF
tyrosine-kinase inhibitor abolishes totally the endothelin proangiogenic properties. Endothelin can
participate to tumoral angiogenesis in cases like malignant pheochromocytomas where there is a
strong expression of endothelin and of its receptor ET\textsubscript{A}. The development of endothelin receptor
antagonists in clinic will permit to assess the role of endothelin in pathological angiogenesis.

Angiotensin II, at least at pharmacological doses, is proangiogenic. However, angiotensinogen, the
angiotensin precursor, is anti-angiogenic. Indeed, angiotensinogen shares with other members of the
serin protease inhibitor (serpins) family \textit{in vitro} and \textit{in vivo} anti-angiogenic properties.
Angiotensinogen inhibits endothelial cell proliferation and migration, and is anti-angiogenic \textit{in ovo}
in the CAM assay.

Angiotensinogen affects vascular wall remodeling \textit{in vivo}. In a model of overexpression of human
angiotensinogen in male transgenic mice, the vessel wall thickness of kidney arterioles was thinner
than in control animals. There is a relationship between the effect of angiotensinogen on arterial
wall thickness and the local expression of angiotensinogen. Because human angiotensinogen is not
cleaved to a significant extent by mouse renin, the reduction in kidney arterial wall thickness is due
to angiotensinogen itself and not to angiotensin II. The anti-angiogenic property of angiotensinogen
has been further explored in several models of tumoral angiogenesis. A recombinant adenovirus
carrying the human angiotensinogen gene under the control of the cytomegalovirus promoter
(AdAGT) has been constructed. AdAGT selectively inhibits endothelial cell proliferation. \textit{In vivo}
jinfections of AdAGT into pre-established human mammary carcinomas in nude mice inhibited
tumor growth by 70 \% compared to controls. This effect was associated with the suppression of
intratumoral vascularization and marked necrosis. Furthermore, \textit{in vitro} AdAGT infection of
mammary carcinoma cells and murine melanoma cells strongly blocked their \textit{in vivo}
tumorigenicity. Finally, in a mouse model of genetically-induced hepatocellular carcinoma, human
angiotensinogen inhibits angiogenesis, tumor growth and delays significantly animal death.
Therefore, angiotensinogen is a very potent anti-angiogenic factor \textit{in vivo}, independently of
angiotensin II generation. Its delivery by gene transfer may represent a new strategy to block
primary tumor growth and to present metastasis.
Altogether, these data show that a vasoactive peptide such as angiotensin II exerts, at least at pharmacological doses, a pro-angiogenic effect. However, angiotensinogen, the proteic precursor of angiotensin II, clearly inhibits vascular wall remodeling at high doses, and can inhibit tumoral angiogenesis, independently of angiotensin II production. The overall effect of the renin-angiotensin system in the control of angiogenesis and in vascular wall remodeling must take into account these opposing effects of two components of this system. This is particularly relevant because of the wide use of blockers of the renin angiotensin system in clinic. Their net effects on angiogenesis deserve further investigation.