Pathological cardiac hypertrophy emerges in the mammalian heart during chronically increased workload (e.g., arterial hypertension or aortic stenosis). Although it might in the short term help to compensate cardiac function, it predisposes to the development of heart failure in the long term. It is characterized by an increase in cardiomyocyte size and profound changes in gene expression and is accompanied by fibrosis and contractile dysfunction.1 Myocardial hypertrophy was previously thought to be mainly a disease of cardiomyocytes, but research in recent years revealed important contributions by other cell types. Myocardial endothelial cells are found in the endocardium, in cardiac conductance vessels, and as main component of capillaries. As an organ mainly dependent on oxidative energy production, the capillary density in the heart is high, and each cardiomyocyte is supplied roughly by one capillary. Capillary endothelial cells are closely associated with cardiomyocytes in an ideal diffusion range for capillary-derived nutrients and oxygen, but also for reciprocal paracrine signals between these cells. It has been demonstrated that cardiomyocytes regulate the formation and adaptation of the myocardial capillary network. For example, about 70% of the VEGF-A within the heart is produced by cardiac myocytes.2 Cardiomyocyte specific deletion of VEGF-A, consequently, leads to myocardial capillary rarefaction and dilated cardiomyopathy.2 Upstream cardiomyocyte signaling molecules that induce VEGF-A production are, for example, the transcription factors HIF1α and GATA4 and the protein kinase B/Akt.3–5 GATA4 and Akt are activated by myocardial overload and are themselves capable of inducing cardiomyocyte growth.1 Indeed, during pathological cardiac hypertrophy an increased abundance of myocardial capillaries has been demonstrated.3–5 However, as pathological hypertrophy progresses to heart failure, capillary rarefaction emerges.6

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What is the consequence of a reduction in capillary density in the stressed heart? Use of angiogenesis inhibitors like TNP-470 or a VEGF trap reduces the development of pathological cardiac hypertrophy and also diminishes cardiac function in mice.4,5,7 In turn, overexpression of proangiogenic molecules (angiopoietin-1 and VEGF-A) rescues angiogenesis and improves cardiac function during cardiac pressure overload.3,4 With regard to cardiac growth, it has been suggested that induction of angiogenesis alone (by the angiogenic factor PR39) is sufficient to drive the development of myocardial hypertrophy, although in other models capillary density is not positively correlated with cardiomyocyte growth.3,8,9 Therefore, rather than the pure quantity of endothelial cells, their quality (i.e., their state of activation, association with pericytes, permeability, and the kind of paracrine/juxtacrine signals they release) might be more important. It is often difficult to discern whether an effect of capillaries on cardiomyocyte hypertrophy or function can be explained by differences in cardiac perfusion (and therefore the supply of nutrients and oxygen) or whether specific signals from endothelial cells might be involved. In order to resolve this important issue, a reductionist approach could be used, in which endothelial cells are cocultured with cardiomyocytes. It was demonstrated in such a model that endothelial cells reduce cardiomyocyte death, trigger the spatial organization of myocytes, and also promote their synchronized contraction.10 As another (complementary) approach, genetic elimination of suspected paracrine factors from endothelial cells in vivo can reveal important signals. In this manner, it was demonstrated that endothelial derived neuregulin-1 supports cardiomyocyte survival and upholds cardiac function by acting through ErbB2/ErbB4 receptors on cardiomyocytes.11 Similarly, apelin from myocardial endothelial cells has a strong positive inotropic effect on cardiomyocytes.12 Which endothelial cell signals might regulate cardiac hypertrophy? Peptide growth factors like endothelin-1 and neuregulin-1 are derived from endothelial cells and are potent inducers of cardiomyocyte growth, whereas the free radical gas nitric oxide that is produced by the endothelial nitric oxide synthase (eNOS) mainly in endothelial cells (but also in cardiomyocytes) is known to inhibit hypertrophy. In line with this, eNOS knock-out (KO) mice exert cardiac hypertrophy under baseline conditions.13 However, pressure overload leads to “uncoupling” of the eNOS enzyme.14 In the uncoupled state eNOS produces large amounts of superoxide anions (O2•−) that can be converted by extracellular superoxide dismutase (ecSOD) to hydrogen peroxide, which is a strong inducer of cardiomyocyte hypertrophy. In line with this, eNOS KO mice are protected from pathological myocardial hypertrophy during pressure overload.14 Therefore, in dependence of the circumstances, the very same endothelial protein (eNOS) can either inhibit or induce cardiomyocyte growth.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Higashikuni et al add important information regard-
ing the protective role of cardiac endothelial cells against reactive oxygen species dependent stress and endothelial regulatory mechanisms of cardiomyocyte growth in pressure overload. They demonstrate that the ATP-binding cassette transporter ABCG2 is mainly expressed in endothelial cells, transports glutathione out of endothelial cells and thereby enriches the extracellular space with this important antioxidant. The reduced form of glutathione is a substrate of the glutathione peroxidase, an enzyme that is also present in the extracellular space and that converts hydrogen peroxide to water by oxidizing glutathione. Consequently, the reduction of hydrogen peroxide levels in the extracellular space eliminates a trigger for hypertrophy. Accordingly, Higashikumi et al show in their elegant study that mice lacking the ABCG2 transporter have an exaggerated form of cardiac hypertrophy in response to experimental transverse aortic constriction (TAC), which is associated with reduced plasma and myocardial abundance of glutathione and increased lipid and protein oxidation as a consequence of reduced antioxidative capacity in these mice. In support of the authors’ conclusion that the increased reactive oxygen species are the main culprit in this case, “antioxidative therapy” with the SOD and catalase mimetic MnTBAP (efficiently protecting cells from hydrogen peroxide) reduces hypertrophy and the associated mortality in ABCG2 KO mice after TAC and brings it back to the level of wild-type mice. Importantly, the authors also use a reductionist approach to demonstrate that these antihypertrophic endothelial cell properties are not dependent on perfusion: Transfer of cell culture supernatant from human cardiac endothelial cells (stimulated to extrude glutathione) to cultured cardiomyocytes inhibits hydrogen peroxide triggered cardiomyocyte hypertrophy. In turn, blocking ABCG2 in endothelial cells abolishes the antihypertrophic effects of the supernatant. Despite increased hypertrophy, Higashikumi et al observed a reduced myocardial capillary density after TAC in the ABCG2 KO mice. First, this demonstrates that capillary abundance alone is not a major determinant of cardiac growth. Second, this observation is in agreement with a previous study by the same group that demonstrated reduced capillary density in the border zone of myocardial infarction due to decreased endothelial cell survival and angiogenic function. This was attributed to accumulation of protoporphyrin IX within endothelial cells due to defective transport in the absence of ABCG2. Third, the reduced capillary density is not improved by MnTBAP similar to the reduced cardiac function after TAC, which is only partially rescued and stayed lower when compared to wild-type. This on the one hand supports the notion of separated molecular mechanisms of hypertrophy and capillary rarefaction in this model; on the other hand it may again draw a close connection between capillary density and cardiac function. In the light of the previous studies mentioned above, it is likely that cardiac function would have been completely rescued by bringing myocardial vascularity back to normal levels, but it is still unknown whether these effects are dependent on one or multiple paracrine endothelial factors, on enhanced perfusion or a combination of both.

As many good studies do, this work raises new questions. For example, the authors demonstrate a marked increase in myocardial macrophage content after TAC that is even exaggerated in ABCG2 KO mice but is reduced back to wild-type levels by MnTBAP. Because macrophages can be potent producers of cytokines and growth factors, their role in modifying the myocardial micromilieu and regulating cardiomyocyte growth needs to be better defined in the future. In addition, the authors show that ablation of ABCG2 does not affect endothelial cells in the limb after ischemia, because perfusion after hind-limb ischemia is not different between wild-type and KO mice. Is expression of ABCG2 a unique feature of cardiac endothelial cells? Related to this, does ABCG2 in cardiac endothelial cells also possess a more physiological function for example during embryonic or postnatal growth of the heart? The normal phenotype of the ABCG2 KO mice does not preclude this possibility, because compensatory mechanisms might be in place during chronic ABCG2 deficiency. Timely targeted endothelial cell-specific deletion of ABCG2 could resolve these issues.

In conclusion, we still need to gain a better understanding of endothelial-cardiomyocyte communication and identify more proteins that serve this purpose. Especially the factors from endothelial cells might help us in the treatment of heart failure in human patients and, in this manner, neuregulin-1 and apelin are already on their way into the clinic (Figure). Acknowledgments

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Disclosures

None.
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Joerg Heineke

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