In this thesis we investigated if and how AMPK in the endothelium (ecAMPK) regulates insulin-induced microvascular recruitment (IMVR) in skeletal muscle and myocardium. Also, we investigated the functional relevance of IMVR in skeletal muscle and myocardium by both inhibiting IMVR in murine knockout models and increasing IMVR in human by infusion of prostacyclin analogues and physical activity.

We showed that insulin decreases microvascular blood volume in the myocardium of type 2 diabetes patients and in western diet fed mice. We found subsequently that a forced exercise program increases IMVR in type 2 diabetes patients (DM2) and that IMVR is higher in physically active individuals. We found that ecAMPK regulates IMVR in the myocardium, but not in skeletal muscle. Furthermore, we found that ecAMPK in the myocardium is a regulator of the positive effects of physical activity on IMVR and that ecAMPK regulates left ventricular contractility probably via expression of MYH1, 4 and 11 and others.

Increasing IMVR in skeletal muscle by infusion of prostacyclin analog or decreasing IMVR by endothelium-specific knockout of the insulin receptor did not respectively increase or decrease whole-body insulin sensitivity. Thus, the data in this thesis shows that skeletal muscle IMVR is not always a determinant of whole-body insulin sensitivity. In the myocardium, however, blunting of IMVR by endothelium-specific knockout of the insulin receptor decreased left ventricular function.

In conclusion we show in this thesis that IMVR in the myocardium is a relevant physiological phenomenon that is regulated by ecAMPK, decreased in DM2 and after western diet feeding, is recovered by prostacyclin analogue and exercise, and is a determinant of left ventricular function. Myocardial IMVR and ecAMPK are thus promising therapeutic targets in the treatment of disorders in which myocardial IMVR is decreased such as DM2 and maybe the coronary microvascular dysfunction syndrome.