Small artery tone under control of the endothelium
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Summary

Small artery tone is a major determinant of organ tissue blood flow and of total peripheral resistance. Pathophysiological alterations in small artery function towards a more constrictive state ("small artery dysfunction") restricts the organ’s blood supply, and increases peripheral vascular resistance, and hence blood pressure. The endothelium plays an important role in the control of small artery tone by releasing dilative mediators, i.e. nitric oxide (NO), prostaglandins (PGs), and endothelium-derived hyperpolarizing factor (EDHF), which act in balance to mediate endothelium-dependent dilation. An impaired dilative function of the endothelium ("endothelial dysfunction") has been demonstrated to underlie the highly constrictive state of small arteries in many forms of cardiovascular and renal disease, which could play a role in disease progression and/or disease induction. However, cause-effect relations between small artery dysfunction and disease progression are not well explored. For a long time the impairment of the NO system has been the focus of attention regarding endothelial dysfunction in cardiovascular and renal disease. Recently, an important role of endothelium-derived hyperpolarizing factor (EDHF), and the importance of differences between endothelium-derived mediators in arteries of different vascular beds, and in arteries with different vessel size has been proposed. Therefore, the first important aim of this thesis was to investigate disease-related endothelial alterations in more detail, with emphasis on EDHF and the underlying mechanisms of its impairment, and with respect to differences in arteries derived from different vascular beds.

The results presented in this thesis to treat this aim indicate an important role of an impairment of the arterial EDHF response in different animal models of renal and cardiovascular disease. More specifically, the data show that renal organ dysfunction (in the MWF rat strain) gives rise to localized rather than generalized EDHF impairment preferentially in small coronary arteries, as to (partly) explain the relatively high incidence of cardiovascular complications in renal disease (Chapter 2). Furthermore, the extent of organ damage, i.e. infarct size in the experimental rat model of chronic heart failure (CHF), determined the extent of arterial EDHF impairment (Chapter 3). Overall, the results emphasize the differences in the contribution of EDHF to mediate endothelium-dependent dilation between different vascular beds in healthy rats (Chapter 2, 3, 5, 6, 7, 8), and a differentially pronounced disease-related impairment in the EDHF response in different artery types, obviously affecting "NO-dependent" artery types such as the coronary artery more than artery types in which the endothelium-dependent dilation is rather independent of NO such as the mesenteric artery (Chapter 2).

Importantly, the data provide indications on the underlying mechanisms of EDHF impairment, namely the interrelation of attenuated EDHF-mediated dilation with increased myogenic constriction (Chapter 5). This may generally fit with the observation that the myogenic response is increased in different forms of cardiovascular and renal disease, and we could confirm this also for the experimental model of CHF in Chapter 4. Investigating the underlying mechanisms of the relation between the myogenic response and EDHF, and the potentially involved ion channels, we found that the K\textsubscript{Ca} channel opener NS1619 profoundly increased EDHF-mediated dilation in coronary arteries (Chapter 5). Such a potentiating effect on the EDHF response has not been demonstrated before, and may have important (clinical) implications. The vascular bed specific effect of the K\textsubscript{Ca} channel opener may provide the advantage of dilating coronary arteries, while avoiding a general hypotensive response due to general vasodilation of peripheral resistance arteries such as the mesenteric artery. As the
EDHF pathway is believed to be an important compensating dilative pathway when NO is impaired, K$_{Ca}$ channel openers may have the ability to protect "NO-dependent" artery types in presence of risk factors known to impair NO activity. Although K$_{Ca}$ channel openers are not yet available for clinical use, a large progress has been made in characterizing the channel (subunits), and to develop suitable substances with (tissue specific) agonist activity.

In the second part of this thesis we focussed on the endothelial mediator balance in healthy rats, and on its variability among individuals, as to define endothelial characteristics of small intra-organ arteries potentially predisposing for development of disease in this organ. In Chapter 6 we found that individual renal endothelial dilator function, measured as the dilative response to acetylcholine, could predict the severity of renal disease progression induced by 5/6 nephrectomy. This implicates that out of a group of healthy rats individuals with high risk for renal impairment could be identified. The prognostic value was determined by the individual endothelial mediator balance, i.e. with high NO and PG mediated dilation being related to less severe renal damage after 5/6 nephrectomy. It can not be determined from this study whether there is a direct protective effect of NO and PG mediated dilation on renal function, or whether this may rather be a reflection (i.e., a marker) for other protective properties. Nevertheless, when this finding can be confirmed also for other forms of renal disease, and especially for the human situation, this may open important directions towards individual risk assessment. Bearing in mind a potential protective action of the individual endothelial mediator balance, in Chapter 7 and 8 we investigated different strategies of chronic in vivo treatment to modulate the endothelial mediator balance in healthy rats. We found that low sodium diet as well as chronic ACE inhibitor therapy (under control diet) indeed altered the balance among endothelial mediators, and to a different extent in different artery types, while leaving the total endothelium-dependent dilation intact. These results provide important directions for future studies to evaluate treatment strategies of early intervention to prevent renal disease development by modulation of endothelial mediator balance.