Kidney oxygenation under pressure
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CHAPTER 7
Discussion and perspectives
DISCUSSION

Although not yet fully understood at the time, the conceptual framework introduced at the beginning of this thesis served as the pathophysiological basis for the development of catheter based renal sympathetic denervation (RDN) in the first decade of the two thousands \(^1\)\(^2\). This technique aimed to interrupt the kidneys’ sympathetic innervation by severing the sympathetic nerves located along the vascular wall of the renal arteries using radiofrequency ablation, thereby taking away the sympathetic signal arising from the kidneys. Resulting in a decreased sympathetic tone, reduced renin/angiotensin activity, lowered blood pressure and potentially improved kidney oxygenation. This made RDN ideally suited for the treatment of therapy resistant hypertension, rapidly generating interest from clinicians who previously had been without adequate further treatment options such patients.

However, after initial enthusiasm aroused by two open label trials that indicated therapeutic benefit, the sham controlled Symplicity HTN-3 trial failed to show treatment efficacy of RDN on the blood pressure goals \(^3\)\(^4\). Now much controversy surrounds the use of the technique and the basis on which it was founded \(^5\)\(^7\). Proposed reasons for the failure of RDN are much varied, from technique failure, the large Hawthorne effects, increased drug adherence and patient selection, to a flawed pathophysiologic rationale \(^6\)\(^-11\). This thesis investigates several mechanisms related to (nephrogenic) hypertension. Some of their results question the pathophysiological rationale for RDN in humans, starting with a study into the relations between the sympatho-vagal balance and cardiovascular risk in the general population and an expanded repeat of one of the studies that founded the rationale for RDN \(^12\).

The sympathetic nervous system is not uniquely affected in CKD

The study by Hering et al. suggested an altered renal chemoreflex response in CKD patients during oxygen supplementation, attenuating sympathetic activity and blood pressure during systemic hyperoxia. With this in mind, one would expect increased sympatho-vagal impairment with renal function decline compared to other cardio-metabolic risk factors. However, we found no such relation in baroreflex sensitivity analysis among almost 6,000 participants of the HELIUS study described in Chapter 2. Furthermore, we were unable to repeat the results of these experiments in a group of 19 CKD patients in Chapter 3. In our hands, oxygen supplementation causes a dose-dependent blood pressure increase in these patients, which was caused by an increase in systemic vascular resistance, likely as the result of hyperoxic vasoconstriction independent of baroreflex function in patients with an insufficient nitric oxide mediated vasodilatory response. Although, oxygen supplementation may alleviate peripheral sympathetic activity \(^12\), it presents a major cardiovascular stressor to CKD patients. The central hemodynamic effects overshadows any beneficial renal effect, if at all present. Whether sympathetic dysregulation in patients is cause or consequence of cardio-metabolic
disease cannot yet be determined based on the studies so far, upcoming prospective data will provide the opportunity to make the distinction.

**Kidney BOLD MRI associates most with the kidneys’ filtration fraction, not with GFR**

According to the conceptual framework the two determinants of tubular oxygen demand, kidney perfusion and thus oxygenation are sympathetic nerve and renin/angiotensin activity. However, the effect of sympathetic activity on kidney oxygenation has only been investigated in animal models. Non-invasive assessment of kidney oxygenation in humans using blood oxygen level dependent (BOLD) MRI has rapidly developed over the past years. By comparing the effects of angiotensin II on kidney perfusion and oxygenation to gold standard GFR and effective renal plasma flow we were able to gather that kidney BOLD MRI associates most with the kidneys’ filtration fraction and not with GFR. As the FF is the product of both the GFR and renal plasma flow, we therefore conclude that simultaneous renal blood flow measurements are indispensable for the correct interpretation of renal BOLD (Chapter 4). In the meantime, another group has substantiated this in CKD patients.

**Sympathetic activation decreases kidney perfusion without a reduction in oxygenation**

With these insights we moved on to investigate the effects of sympathetic activation on kidney hemodynamics and oxygenation using lower body negative pressure (LBNP), in Chapter 5. Using LBNP as a selective sympathetic stimulant we found that it substantially increased renal vascular resistance and reduced kidney perfusion, similar to that achieved by angiotensin II infusion. However, this was not accompanied by a reduction in kidney oxygenation, not in the cortex nor in the medulla. These exploratory data question the physiological concept that sympathetic hyperactivity per se decreases kidney oxygenation. In contrast to the conceptual framework, this implies that systemic sympathetic activation decreases kidney perfusion without a parallel reduction in oxygenation, at least in healthy humans. Conversely in patients, pre-existent metabolic dysregulation in the kidneys may cause hypoxia during increased sympathetic activity. This has yet to be investigated.

**Improving MRI based functional assessment of the kidneys**

Current functional MRI of the kidneys is not yet capable to fully evaluate the complex rheological attributes of the kidneys. On the one hand this can be overcome using innovative post processing techniques, and the implementation of new advanced MRI modalities on the other. Innovative post processing can for instance be used to visualize and quantify the oxygenation gradient within the kidneys, as shown in Chapter 4. Adoption of other MRI modalities to quantify and map kidney perfusion could prove valuable in the future as the currently used phase contrast method only provides global kidney perfusion quantification.
without mapping. Using arterial spin labeling \(^{18,19}\) or intravoxel incoherent motion (IVIM) analysis of diffusion weighted imaging \(^{20}\). Both techniques provide spatially differentiated perfusion data, however only IVIM analysis can potentially differentiate between blood and urine perfusion within the kidney. In Chapter 6, we used a kidney specific tri-exponential approach to IVIM analysis to show its capability to track changes renal perfusion and GFR. Its further development might provide new opportunities for a non-invasive, spatially differentiated assessment of kidney perfusion and filter function in kidney disease.

**IMPLICATIONS AND PERSPECTIVES**

**For the clinic**
The role of kidney hypoxia in the pathophysiology and progression of chronic kidney disease and its relation to systemic sympathetic hyperactivity may not be as simple as previously thought \(^{7,21}\). Consequently, this could partially explain the ineffectivity of RDN. Therefore, intervention in this pathway is not as appealing anymore.

None the less, kidney hypoxia remains an attractive factor and potential therapeutic target to prevent CKD progression \(^{7}\). For example, new compounds that intervene in the hypoxia inducible factor (HIF) pathways are becoming available in the near future. Although these compound have been developed as alternatives to erythropoietin, these are expected to have reno-protective effects as well. HIF stabilization may directly influence the metabolic efficiency of cells, thereby lowering oxygen consumption, alleviating tissue hypoxia and potentially reducing or halting the nephrosclerotic process. Several clinical trials in non-dialysis and dialysis CKD patients have reported positive outcomes \(^{22-26}\).

As therapeutic options targeting kidney hypoxia are underway, reliable methods for future therapy and patient evaluation will become indispensable for research and clinic. Multimodal MRI seems ideally suited for such applications. To fully elaborate on the role of hypoxia in CKD in humans, further studies should focus on the effects of hypoxia reduction on CKD progression. Using the developed MRI techniques, patients’ current drug therapy may already be optimized to reduce the kidney metabolic demand and improve filtration fraction.

**For research**
The advent and eventual failure of RDN as an antihypertensive therapy may have been in part be a consequence of inappropriate human extrapolation of data obtained from animal studies. Our studies underlines the essential role of human studies to translate animal data to human (patho)physiology. Although such human studies may be intensive and/or use
physically strenuous interventions, these will deliver true insight into human physiology and therefore will remain indispensable.

Conducting human research relies heavily on the availability, development and application of safe, technically advanced and minimally invasive measurements. Therefore, the integration of technology and clinic or physics and physiology becomes ever more important. This thesis is proof that the Technical Physician is very much at home in such an environment and can be a valuable asset to a multidisciplinary team of clinicians and engineers.
REFERENCES


