Left atrial vascular and metabolic remodeling in pig models of atrial fibrillation

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CHAPTER 7

OPPORTUNITIES FOR VALORIZATION

Relevance to healthcare
Atrial fibrillation (AF) is the most common sustained tachyarrhythmia in clinical practice\(^1\). The prevalence of AF in the developed countries ranges between 1 to 2% of the general population\(^2\). In the Netherlands, an estimated 300,000 people have AF. The risk of developing AF strongly increases with age. In the Rotterdam study, performed on a large population of Dutch people aged 55 years and above, the overall AF prevalence was 5.5%, with 0.7% prevalence in the 55-59 years to 17.8% in those aged 85 years and above\(^3\). With the ageing of the general population in the western world, AF prevalence and the associated health care costs are expected to rise substantially over the next 50 years\(^4\).

Because AF leads to the formation of emboli, particularly in the left atrium, AF increases the risk of stroke: in 1 out of every 5 strokes AF is the underlying cause\(^5\). This is the most important reason that AF is also associated with increased mortality\(^6,7\). As a consequence, AF represents a large, and growing burden on our healthcare system\(^8,9\).

Current AF therapy is still unsatisfactory. In the patients in whom sinus rhythm can be restored by electrical or pharmacological cardioversion, AF very often recurs. The risk of stroke can be reduced by anti-coagulation therapy, but with potentially harmful side-effects such as uncontrolled bleeding, including cerebral hemorrhage. The efficacy of ablation therapy is limited in patients with (longstanding) persistent AF.

In many patients, AF gradually becomes harder to treat as a result of a slow process of structural remodeling. This process includes i.e. fibrosis, cellular hypertrophy and fatty infiltration\(^10,11\) that increase the complexity of fibrillatory conduction and thereby the stability of AF. Despite extensive research, the exact mechanisms responsible for structural remodeling are still poorly understood. Treatment options that inhibit structural remodeling could halt AF progression in patients.

Novelty of the concept
Because of their obvious relevance in diseases such as ischemic heart disease and heart failure, (left) ventricular metabolism and blood supply have been investigated in great detail for decades. By comparison, we know very little about atrial metabolism and tissue perfusion, how they are affected by risk factors for AF, and the way in which they contribute to the pathogenesis of AF.

In this thesis, we have characterized some aspects of atrial metabolic and vascular remodeling as a result of atrial fibrillation (AF) and congestive heart failure (CHF), a major risk factor for AF. Understanding the pathophysiological processes occurring in the atria would help in identifying new therapeutic targets/approaches that could...
improve the treatment AF.

AF is characterized by fast and irregular atrial activation. The rapid rates of electrical activity and contraction during AF must present an enormous challenge to the energy balance of atrial myocytes. This challenge can be met by scaling back energy demand and by increasing energy supply, and there are several indications in the literature that both phenomena occur as a result of AF. Still, there is also ample evidence that these adaptations fall short of redressing this disbalance, that may represent a driving force for atrial electrical as well as structural remodeling.

Road to product
The data in this thesis strongly support the existence of metabolic and vascular remodeling. We have observed striking changes in vascular regulation and mitochondrial physiology after one week of AF. Despite the activation of angiogenic signalling, capillary rarefaction had occurred after 5 weeks of AF. In the model of CHF, vascular remodeling coincided with profound atrial contractile dysfunction that is likely to accelerate the development of heart failure.

We show that AF and CHF have a substantial impact on the atrial metabolism and vasculature, but our knowledge on these effects is still quite limited. On the whole, our data are consistent with supply/ demand ischemia and consequent metabolic and vascular remodeling in the important early phase of AF progression. However, our present data represent only snapshots of the pathogenesis of AF, and other time-points, both earlier and later, will have to be studied in a similar way to fully characterize these processes. This should include characterization of metabolic and vascular remodeling in a model of paroxysmal AF, where each AF episode may represent a renewed ischemic insult to the atrial myocardium, leading to an accumulation of (structural) damage.

At present, evidence that metabolic and vascular remodeling play a causative role in electrical and structural remodeling are largely circumstantial. Evidence for causation would be strengthened using large animal models of AF by testing intervention strategies that selectively target determinants of the atrial supply/ demand balance. A possible approach is stimulation of atrial angiogenesis and/ or stabilization of newly formed capillaries to increase atrial perfusion in fibrillating atria. Alternatively, a treatment strategy could be targetted at ‘improving’ atrial metabolism12 to enhance oxygen efficiency and preserve atrial function. If successful in large animal models, such interventions could lead to new treatment options in AF patients. This would eventually lead to highly desirable ‘upstream therapy’ to prevent the progression of AF in patients.