Supply-demand balance in the atrium

APPENDIX

OPPORTUNITIES FOR VALORIZATION

The aim of this chapter is to identify opportunities to valorize the research findings of this thesis. Knowledge valorization refers to the "process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use, and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities" (adapted definition based on the National Valorization Committee 2011:8). According to this definition, scientific research is valued by its direct socio-economic impact. Although the socio-economic impact of basic research is difficult to quantify, increasing knowledge of complex (patho)physiolocial processes is pivotal to future innovations.

1. Societal conditions

As described in CHAPTER 1 of this thesis, atrial fibrillation (AF) is the most common arrhythmia in clinical practice and the prevalence of AF increases with age [1-3]. AF significantly increases the risk for all cause mortality, cardiovascular mortality, stroke and congestive heart failure [3]. In the Netherlands, an estimated 300.000 people suffer from AF. With the ageing of the population, this number is expected to increase to 1.000.000 in 2050. Thus, AF represents a significant socio-economic burden. Current AF treatment involves maintaining patients with paroxysmal and persistent AF in sinus rhythm (rhythm control) or controlling the ventricular rate (rate control). In addition, patients are treated with anti-coagulation therapy to decrease the risk of stroke [4]. However, anti-coagulation therapy has potentially harmful side effects, such as an increased risk of bleeding, and therefore needs to be carefully controlled. Except for anti-coagulation therapy, so far there is no treatment available that substantially improves the prognosis of AF patients [5]. In AF patients, the arrhythmia is often progressive, with a gradual increase in the duration of AF episodes. AF causes structural remodeling of the atrial myocardium, and it is generally accepted that this process is responsible for AF progression. By causing structural remodeling that increases the stability of the arrhythmia, AF is self-perpetuating. Although various aspects of structural remodeling, e.g. fibrosis, myocyte hypertrophy and hibernati-

on, have been characterized extensively, the factors leading to structural remodeling are still poorly understood. Insight into these pathogenic factors is essential for the development of successful upstream therapy, i.e. therapy preventing structural remodeling and thereby inhibiting AF progression.

2. Novelty of the concept

Several potentially important pathogenic factors have been proposed in AF progression, e.g. atrial dilatation/ stretch, calcium overload, oxidative stress, inflammation and altered neurohumoral signaling. Although atrial ischemia has been mentioned as a possible contributor [6-12], its occurrence and role has not been investigated systematically. Nevertheless, it is likely that the rapid rates occurring during AF represent a substantial increase in atrial energy expenditure. If this increase cannot be met by an increase in atrial coronary supply, a state of supply-demand ischemia will develop. In this thesis, we have investigated the structure of the atrial vasculature (CHAPTER 3), the regulation of atrial coronary blood flow (CHAPTER 5) and the occurrence of supply-demand ischemia (CHAPTER 4 and 6). Several remodeling processes observed in AF (e.g. myocyte hibernation) can be viewed as energy saving mechanisms to restore the supply-demand balance. To our knowledge, this is the first study to show atrial supply-demand ischemia induced by acute AF (CHAPTER 4). We have also shown that after a few weeks of AF, atrial supply-demand balance is restored, although accompanied by potentially detrimental vascular remodeling (CHAPTER 6).

3. Road to product

A logical next step to evaluate the role of atrial ischemia as a pathogenic factor leading to structural remodeling is to test interventions that would reduce supply-demand ischemia. Both inventions that affect atrial metabolism (leading to conservation of energy) and the atrial vasculature (leading to improvement of supply) would be suitable candidates for upstream therapy. These would first have to be tested in a suitable large animal model of AF. If such a therapy would prove successful in inhibiting structural remodeling and AF progression in an animal model, they

could be considered a treatment option for patients with AF or patients at risk for developing AF. Targeting supply-demand ischemia may prove particularly suitable in patients with paroxysmal AF, where episodes of AF and sinus rhythm alternate, and where each AF paroxysm may represent an ischemic insult that leads to an accumulation of damage to the atrial myocardium.

4. Conclusions

On the short term, the research findings in this thesis about supply-demand balance in the atrium will be of value to researchers in directly related fields. In addition, knowledge about the atrial vascular anatomy may be relevant in cardiac surgery and the development of new ablation strategies, as described in CHAPTER 3 of this thesis in the paragraph "atrial ischemia in ablation strategies and myocardial infarction". On the long term, these findings may lead to the development of new strategies for upstream treatment of AF. If atrial supply-demand ischemia indeed proves to be an important pathogenic factor in the development of a substrate for AF, then it is likely that vascular or metabolic interventions can inhibit the progression of AF.

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