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## The dilated left ventricle. Sympathetic activation and effect on $\beta$ -blockade

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

1999

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Antonio, R. L. (1999). *The dilated left ventricle. Sympathetic activation and effect on  $\beta$ -blockade*. s.n.

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## Summary

### Introduction

Left ventricular dilation is the prerequisite of heart failure, and is accompanied by autonomic dysfunction and neurohormonal activation. Heart failure research of the University of Groningen (both at the Institute of Clinical Pharmacology and at the University Hospital) has initially focused on measurement of plasma neurohormones. More recently, other parameters of autonomic dysfunction have been evaluated. In this thesis different autonomic mechanisms in the development of clinical and experimental models of heart failure have been investigated, and these are described in **Part 1**. In addition, since the beginning of the 1990's, the place of  $\beta$ -blockade has rapidly increased. Potential mechanisms which may explain their benefit, and clinical use will be discussed in **Part 2**.

### Part 1:

In **chapter 2** a new model of heart failure in the rat is described, which is a combination of systolic dysfunction (myocardial infarction), and diastolic dysfunction (~ systemic hypertension), leading to augmented left ventricular dilation. This combined model consists of the rat myocardial infarction model, with an additional increased afterload by abdominal aortic banding. Together with this combined model, the separate models are studied. In myocardial infarction rats, baseline values of contractile function were decreased, but not after inotropic stimulation. In aortic banding rats, contractile parameters were not significantly impaired, compared with controls. Both myocardial infarction and the combined myocardial infarction/aortic banding animals, but not aortic banding rats, had a significantly increased heart weight and increased left ventricular cavity volume compared to control animals. It is concluded that myocardial infarction/aortic banding provides a new experimental model, which may yield important information. Furthermore, it provides insight into the pathophysiology allowing evaluation of changes that may mimic clinical myocardial infarction with additional increased after load as observed in clinical (concomitant) hypertension.

$\beta$ -adrenoceptor density or  $B_{\max}$  may also reflect autonomic tone, and is altered in various cardiac diseases. It can be measured by invasive techniques using endomyocardial biopsy material, and non-invasively using positron emission tomography (PET). **Chapter 3** gives a brief overview of several experimental models and pathophysiologic circumstances, in which  $\beta$ -adrenoceptor density is changed. Furthermore, in this chapter the first results of clinical  $\beta$ -adrenoceptor measurements using PET in humans are discussed. Using (S)-[ $^{11}\text{C}$ ]-CGP12177 PET and standardized reorientation to ten short

axis slices, changes in  $\beta$ -receptor distribution, e.g. due to myocardial infarction and ischemia may be better identified and characterized. Additionally, because its non-invasive character, PET also provides the possibility of serial measurements, and may elucidate the effects of different treatment strategies in several heart diseases on cardiac  $\beta$ -adrenergic receptors. In **chapter 4** changes in  $\beta$ -adrenoceptor density in myocardial infarction model in rats are described. Twelve weeks after myocardial infarction, a decreased  $\beta_1$ -adrenoceptor density was found in the infarcted myocardium, compared with non-infarcted myocardium. This indicates that the surviving myocardial cells in the infarcted myocardium have a decreased  $B_{\max}$  due to a decreased  $\beta_1$ -adrenoceptor density.

Decreased heart rate variability (HRV) is another autonomic parameter, and carries prognostic value in heart failure. In **chapter 5**, the accuracy and feasibility of analysis of HRV using radio telemetry to assess autonomic function in (freely moving) healthy rats, is described. With radio telemetry, electrocardiograms were obtained during autonomic blockade and Langendorff perfusion. Hereafter, Fourier Transform was performed on RR interval times. The study showed, that this technique is feasible, and may thus be used as an experimental model to investigate autonomic function.

## Part 2:

While ACE inhibitor treatment is currently the cornerstone of treatment in heart failure, recent large-scale trials indicate that  $\beta$ -blockers have significant additive value in this patient population. In **chapter 6** the mechanisms involved in left ventricular dilation after myocardial infarction, and the individual place of ACE inhibitors and  $\beta$ -blockers, and combination, are discussed. Included are the effects in the acute phase after myocardial infarction and in the chronic phase of heart failure, and mechanisms regarding remodeling are discussed. Based on the beneficial effects of ACE-inhibition and  $\beta$ -blockade in acute myocardial infarction and in chronic heart failure, in this chapter a treatment strategy is proposed in which both ACE-inhibition and  $\beta$ -blockade are started early after myocardial infarction.

Despite the risk associated with initiation and up-titration of  $\beta$ -blockade in heart failure, these drugs are increasingly gaining attention as beneficial treatment in heart failure. **Chapter 7** describes the feasibility of out of hospital dose titration in patients with idiopathic dilated cardiomyopathy. To predict which patient will show a prolonged titration time and will not reach the target dose or needs adjustment of concomitant treatment, patients were extensively studied. Interestingly, failure of dose titration was only associated with low systolic blood pressure, and not with parameters of severity of heart failure.

In the CIBIS I trial, bisoprolol was shown to be more beneficial in patients with heart failure due to idiopathic dilated cardiomyopathy than in those with heart failure due to ischemic dilated cardiomyopathy. **Chapter 8** describes a 24-hour heart rate sub-study of the CIBIS I trial. In patients with idiopathic dilated cardiomyopathy, bisoprolol caused a significant decrease in morning heart rate, but in patients with ischemic heart failure (“ischemic dilated cardiomyopathy”) there was no significant treatment effect. It was concluded that the observed differential effect on morning heart rate, possible as reflection of reduced sympathetic activation, may possibly be the explanation for a different clinical effect. It cannot be excluded however, that a higher dose of bisoprolol might also be beneficial in patients with ischemic dilated cardiomyopathy.

While the beneficial effects of ACE-inhibitors on endothelial function are well-known, the additive effects of add-on  $\beta$ -blockade on this parameter are unclear. Given the favorable effects of add-on  $\beta$ -blockade in recent large-scale trials (and the reduction in ischemic events), the effects of add-on  $\beta$  blockade on endothelial function were investigated in **chapter 9**. In this chapter, the effect of ACE-inhibition and combined ACE-inhibition +  $\beta$ -blockade are investigated in rats with experimental myocardial infarction, where we looked at endothelial function in relation to left ventricular dilation,  $\beta$ -receptor density and neurohumoral activation. Twelve weeks after myocardial infarction, infarct size was comparable in all infarct groups. Endothelium dependent relaxation to acetylcholine, however, was significantly decreased in the untreated group and was similarly preserved by captopril and combined captopril metoprolol. These results do not support the concept, that the observed beneficial effects of add-on  $\beta$ -blockade in heart failure are related to an effect on endothelial function.

### **Conclusive remarks**

In part 1, the rat model of heart failure is successfully used to measure autonomic activity, as reflected by  $\beta$ -receptor density and heart rate variability. In addition, these techniques can be used to assess drug-induced changes. In contrast, at this moment measuring Bmax with PET is not yet available. While initial studies in healthy volunteers were feasible, further research showed that this technique was not (yet) applicable in patients with heart failure.

In part 2, the (add-on) effects of  $\beta$ -blockade in heart failure are investigated, as well as mechanisms involved. The results suggest, that heart rate and its variability are potential surrogate endpoints, since it correlated with clinical endpoints. Effects of endothelial function, however, are less clear. (Up)titration of  $\beta$ -blockers in patients with heart failure appears to be related to baseline blood pressure, and surprisingly, not to other parameters of severity of heart failure.