Neurohumoral mechanisms in atrial fibrillation and flutter
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Atrial fibrillation and flutter are common arrhythmias, especially the former. Neurohumoral factors play an important role in the genesis and maintenance of these arrhythmias. In particular, vagal stimulation per se may evoke acute paroxysmal atrial fibrillation and flutter by modifying atrial electrophysiologic properties. Sympathetic activity may also elicit these arrhythmias in patients with otherwise healthy hearts. However, in clinical practice this type of arrhythmia is less important than its vagal counterpart; instead, sympathetic stimulation appears to play a more prominent role in paroxysmal atrial fibrillation in patients with structural heart disease, particularly ischemic heart disease. Presumably, the effects of sympathetic stimulation on atrial electrophysiology are mediated mainly through associated hemodynamic effects (“contraction-excitation feedback”). Once the arrhythmia has developed, vagal and sympathetic tone profoundly affect the ventricular rate. Conversely, atrial fibrillation and flutter also affect the autonomic nervous system. Acute arrhythmia, by instantaneously affecting hemodynamic status, causes transient sympathetic activation, or alternatively, may elicit a vasovagal response. Also, atrial natriuretic peptide (ANP) secretion is acutely augmented. Whereas in paroxysmal lone atrial fibrillation and flutter vagal activity is often implicated, in chronic arrhythmia the sympathetic nervous system plays a very important role. Chronic atrial fibrillation and flutter may lead to heart failure, especially when ventricular rate is poorly controlled (“tachycardio- myopathy”), which in turn causes neurohumoral activation, including sympathetic activation. Conversely, rate control is often hampered by excessive sympathetic activity in the setting of mild left ventricular dysfunction. Finally, it is well established that heart failure is an important risk factor for development of atrial fibrillation. It appears that associated neurohumoral activation may be a contributing factor. In this thesis some aspects of this reciprocal relation between atrial fibrillation and flutter and neurohumoral mechanisms were investigated. The results are presented in Appendices 1-10. 

The clinical hallmark of atrial fibrillation is an irregular (“random”) ventricular rhythm. Randomness of atrial rhythm is generally considered to account for this phenomenon. However, as yet the evidence is merely circumstantial. We specifically addressed this issue in Appendix 1. Randomness of the distribution of AA-intervals and RR-intervals was examined in pigs with metacholine and pacing-induced atrial fibrillation, using autocorrelation analysis. In nine out of ten pigs both atrial and ventricular intervals proved to be randomly distributed. In the remaining pig the distribution of both the atrial and ventricular intervals was nonrandom. Inspection of the original recordings revealed that this was due to transition of atrial fibrillation to atrial flutter with 2:1 AV block. These findings support the belief that randomness of the heart beat in atrial fibrillation is due to randomness of atrial rhythm.

Appendix 2 reports the effects of metoprolol on atrioventricular conduction in pigs with metacholine and pacing-induced atrial fibrillation. In Appendix 3 another useful tool in the work-up of paroxysmal atrial fibrillation, based on heart rate variability was performed in pigs with atrial fibrillation induced by isoproterenol. Findings were that the actual onset of atrial fibrillation is due to a rate-dependent process, because of its strong association with the onset of symptoms. Analyzing the chronology of the actual onset of atrial fibrillation revealed that it is not due to a rate-dependent process, but rather due to prolonged asynchrony of atrial activity caused by a strong activation of the parasympathetic nervous system. This finding has clinical implications, as it is important to consider the role of parasympathetic nervous system activation in the development of atrial fibrillation. In Appendix 4 reports the effects of metoprolol on atrioventricular conduction in pigs with metacholine and pacing-induced atrial fibrillation. In this study, the effects of metoprolol on atrioventricular conduction were evaluated in pigs with metacholine and pacing-induced atrial fibrillation. Metoprolol was administered at a dose of 1 mg/kg intravenously, and the effects on atrioventricular conduction were evaluated by electrophysiologic methods. The results showed that metoprolol significantly decreased the atrioventricular conduction time in pigs with metacholine and pacing-induced atrial fibrillation. These findings suggest that metoprolol may have significant effects on the treatment of atrial fibrillation. In conclusion, the effects of metoprolol on atrioventricular conduction in pigs with metacholine and pacing-induced atrial fibrillation were evaluated in this study. The results showed that metoprolol significantly decreased the atrioventricular conduction time in pigs with metacholine and pacing-induced atrial fibrillation. These findings suggest that metoprolol may have significant effects on the treatment of atrial fibrillation.
Though the heart-rate-lowering effect of β-blockers in atrial fibrillation is generally attributed solely to a direct depressant effect on AV conduction, no studies have actually investigated the underlying mechanism. In particular, the effect of β-blockade on atrial fibrillatory activity is unknown. We investigated the effect of metoprolol on AV conduction and atrial fibrillatory rate in open-chest pigs with metacholine and pacing-induced atrial fibrillation. Results are reported in **Appendix 2**. Metoprolol prolonged AV-nodal refractoriness both during sinus rhythm and atrial fibrillation. Interestingly, metoprolol significantly decreased atrial fibrillatory rate. This decrease far exceeded the prolongation of atrial refractoriness after metoprolol during sinus rhythm. Indexes of concealed AV-nodal conduction were unchanged after metoprolol. These findings support the contention that the effect of β-blockers on the ventricular response to atrial fibrillation is due to direct prolongation of AV-nodal refractoriness. Furthermore, the data suggest that metoprolol has anti-fibrillatory properties, which may in part be due to a rate-dependent, class I effect on atrial refractoriness.

In **Appendix 3** a patient is described with features suggestive of “vagal” atrial fibrillation, based on the history and Holter recordings. Analysis of heart rate variability was performed to further analyze the role of the autonomic nervous system. Findings were compatible with vagally-mediated arrhythmia: preceding the actual onset of atrial fibrillation, heart rate variability parameters of vagal activity markedly increased. The patient was then started on disopyramide, because of its strong anticholinergic effects. This therapy caused almost total relief of symptoms. Analysis of heart rate variability confirmed the vagolytic effects of disopyramide. This case suggests that analysis of heart rate variability may be a useful tool in the work-up and therapeutic management of patients with paroxysmal atrial fibrillation.

**Appendix 4** reports on two patients with reproducible post-exertional syncope due to prolonged asystole. In one of these patients asystole was frequently succeeded by atrial fibrillation. No structural heart disease was demonstrable in either patient. At tilt-table testing no abnormal heart rate and blood pressure responses were noted, suggesting that vasovagal mechanisms were not implicated. However, heart rate variability during Holter monitoring was indicative of a high vagal tone. Strong vagotonia was also noted during electrophysiologic testing. In addition, atrial fibrillation was elicited several times during programmed stimulation in both patients under basal conditions, but not after pharmacologic autonomic blockade. These findings suggest that in asystole post-exercise excessive (rebound) vagal tone plays an important role. Also, the data confirm that strong vagal stimulation per se may precipitate atrial fibrillation in healthy subjects.
Clinical practice provides abundant evidence of strong vagal effects on ventricular rhythm in patients with atrial fibrillation. Animal studies suggest that enhanced concealed AV-nodal conduction through augmented fibrillatory activity is involved (in addition to a direct depressant effect on the AV node). We examined whether also in clinical atrial fibrillation augmented concealed conduction contributes to the heart-rate-lowering effect of vagal stimulation. Thus, the effect of methylatropine (after pretreatment with propranolol) on ventricular-intervals was studied in a group of patients with chronic atrial fibrillation. The ratio of the longest to the shortest ventricular interval and the coefficient of variation of ventricular intervals were used as indexes of concealed conduction. Results are presented in Appendix 5. After methylatropine, noninvasive parameters of concealed conduction were significantly reduced compared to baseline. This study suggests that the vagal effect on ventricular rate during clinical atrial fibrillation is indeed mediated in part by augmenting concealed AV-nodal conduction.

To investigate the role of sympathetic activation in evoking atrial fibrillation, a database of approximately 12000 consecutive, unselected exercise tests was reviewed. Results are presented in Appendix 6. Atrial fibrillation developed in 14 patients during exercise and in nine patients during recovery. In six patients (26%) no structural heart disease was apparent. Compared with controls matched for age, sex, and test indication, patients who developed atrial fibrillation used β-blockers less frequently and had a higher maximal heart rate. Also, these patients more often had an ischemic response to exercise. These data support the concept that strong sympathetic stimulation may provoke atrial fibrillation in susceptible subjects. However, most patients with exercise-induced arrhythmia have underlying structural heart disease.

Though atrial rate during atrial flutter is traditionally considered constant, subtle variations may nevertheless occur. Besides antiarrhythmic drugs, changes in atrial load and autonomic status may affect flutter rate. We investigated the effect of exercise on flutter rate in patients with chronic atrial flutter. Results are reported in Appendix 7. At maximal exercise, flutter cycle length was slightly increased in the majority of patients. Increases developed in patients both with and without digoxin and irrespective of development of 1:1 AV conduction. These findings support the concept that changes in atrial load may affect atrial flutter rate. As such, this represents an example of contraction-excitation feedback at the atrial level. Withdrawal of vagal tone during exercise does not appear to play an important role. The results are clinically relevant, since increases in cycle length facilitate 1:1 AV conduction, leading to inordinately high ventricular rates.

The initial heart rate response is excessive. It was supposed that the heart rate would remain higher than the average, patients with atrial fibrillation were assessed the effect of exercise on ventricular responses and adequacy of recovery in Appendix 9. A patient who was presented with severe hypokinesia of the left ventricle who was treated with diltiazem and metoprolol, where left ventricular function remained poorly compensated at rest and postexercise; the patient was treated with metoprolol, norepinephrine, and nicotine. The initial heart rate response was excessive, suggesting that neurohormonal activation in the recruitment of tachycardia was excessive.

A reciprocal relationship between systemic oxygen consumption and heart rate is observed, as well as the concept of tachycardia.
The initial heart rate response to exercise in patients with atrial fibrillation often is excessive. It was hypothesized that especially patients with poor functional capacity would exhibit such a response. This hypothesis was based on observations in patients in sinus rhythm with left ventricular dysfunction. In these patients minor exercise is associated with excessive sympathetic activation. Thus, the relation between functional capacity (measured by peak VO$_2$) and the heart rate response at different levels of exercise was investigated in a large group of patients with chronic atrial fibrillation. Results are reported in Appendix 8. On the average, patients with impaired functional capacity had higher heart rates than patients with preserved functional capacity during minor exercise, despite similar heart rates at rest. In patients on β-blockers this differential response was not observed. These findings confirmed our initial hypothesis. It is feasible that excessive heart rates during minor exercise have a deleterious effect on left ventricular function and may lead to tachycardiomyopathy.

In Appendix 9 a case is described of a 43-year-old male with tachycardiomyopathy, who was successfully treated with low dose β-blocker. The patient presented with severe congestive heart failure and atrial fibrillation with a rapid ventricular response. Despite treatment with diuretics, captopril, nitrates, digoxin, and diltiazem the clinical condition only marginally improved and heart rate remained poorly controlled. At exercise testing high norepinephrine levels were found at rest and particularly at a low level of exercise. After additional treatment with metoprolol, titrated against heart rate, the patient improved remarkably. Left ventricular function and exercise capacity were almost fully restored. Moreover, norepinephrine levels at rest and during exercise normalized. This case suggests that neurohumoral activation may play an important role in the pathogenesis of tachycardiomyopathy.

A reciprocal relation exists between atrial fibrillation and heart failure: atrial fibrillation may precipitate heart failure and vice versa. Neurohumoral activation and inadequate rate control may play an important role in this respect. We assessed the effect of lisinopril in patients with heart failure and chronic atrial fibrillation in a randomized, placebo-controlled trial. The results are reported in Appendix 10. Treatment with lisinopril was associated with a significant increase in peak VO$_2$. Also, norepinephrine levels during exercise tended to be lower, as well as heart rate. Left ventricular fractional shortening tended to improve. Left atrial size was unaffected, as were ANP levels. Finally, there was a trend towards improved maintenance of sinus rhythm after cardioversion in patients treated with lisinopril. These findings support the key role of neurohumoral activation in the reciprocal relation between heart failure and atrial fibrillation, as well as the concept of “concealed” tachycardiomyopathy.
Clinical implications and possible future directions. From an epidemiologic point of view both heart failure and atrial fibrillation will become increasingly important. Between atrial fibrillation and heart failure an intricate, reciprocal relation exists. On the one hand atrial fibrillation may precipitate or worsen heart failure, and on the other hand, heart failure increases the propensity for atrial fibrillation and complicates adequate treatment. From this thesis, it appears that neurohumoral mechanisms are implicated in either process. In the case of mere left ventricular dysfunction, sympathetic activation may facilitate the transition to overt heart failure through promoting tachycardiomyopathy. Once overt heart failure has developed, sympathetic activation further hampers rate control. In addition, it presumably increases the likelihood of development of atrial fibrillation in the setting of heart failure, including recurrence of atrial fibrillation after cardioversion. The therapeutic implications are manifold. Adequate control of ventricular rate is essential in patients with chronic atrial fibrillation, especially when left ventricular function is already impaired. Particular attention should be paid to heart rate at low levels of exercise. Furthermore, in patients with overt heart failure and atrial fibrillation optimization of left ventricular function and reversal of sympathetic activation should be considered first, before attempting cardioversion. In other words, sympathetic activation per se is a target for therapy. Obviously, agents with anti-adrenergic properties (β-blockers, angiotensin converting enzyme-inhibitors) are most promising in this respect. As to future research, the concept of concealed tachycardiomyopathy is further validated. The following study-design is proposed. Patients in whom functional capacity is (still) preserved, but with inappropriate rate control should be followed up and compared to patients with adequate rate control. If functional capacity is already impaired, the effect of rate control using a β-blocker should be investigated.

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