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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 ("tachycardiomyopathy"), which in turn causes neurohumoral activation, including sympathetic activation. Conversely, rate control is often hampered by excessive sympathetic activation 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.

Though the heart is generally attributed to have actually involved β -blockade on atrial metoprolol on AV metacholine and p **pendix 2**. Metoprolol rhythm and atrial fibrillation refractoriness after nodal conduction contentions that the conduction is due to direct data suggest that may be due to a rate-dep

In **Appendix 3** a pig with atrial fibrillation, based on variability was performed system. Findings were the actual onset of activity markedly increased cause of its strong arrhythmia of symptoms. Analysis of disopyramide. This is a useful tool in the treatment of paroxysmal atrial fibrillation.

Appendix 4 reports on a pig with atrial fibrillation due to prolonged asystole preceded by atrial fibrillation in another patient. At tilt-table responses were noted, however, heart rate was increased by vagal tone. Strong vagal tone in addition, atrial fibrillation in both patients was abolished by vagal blockade. The (rebound) vagal tone was increased by vagal stimulation per

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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 reponse 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 is excessive. It would be expected that stroke volume capacity would be increased in patients with atrial fibrillation. In patients with atrial fibrillation, minor exercise increases the relation between heart rate and stroke volume. The rate response at maximal exercise in patients with chronic atrial fibrillation is, on the average, similar to that in patients with normal hearts. The relation between heart rate and stroke volume is similar in patients with atrial fibrillation and in patients with normal hearts. The excessive heart rate is not observed. The excessive heart rate is a result of impaired ventricular function.

In **Appendix 9** a patient with atrial fibrillation and left bundle branch block, who was suffering from heart failure, is presented with severe symptoms. The patient was treated with several antiarrhythmic drugs, including digoxin, and diltiazem. The patient remained poorly responsive to treatment. The patient was found at rest and pulseless. The patient was treated with metoprolol, but the patient remained pulseless. Left ventricular function was severely impaired. However, norepinephrine improved the patient. This suggests that neurohumoral activation is the cause of the genesis of tachycardia.

A reciprocal relation exists between atrial fibrillation and stroke volume. Atrial fibrillation may produce a decrease in stroke volume and inadequate stroke volume may be assessed by the effect of treatment. The effect of treatment on atrial fibrillation in a randomized trial is presented in **Appendix 10**. Treatment with digoxin increases peak $\dot{V}O_2$ and stroke volume, as well as heart rate. The effect of treatment on stroke volume is not proven. Left atrial size is increased. The trend towards improvement in stroke volume in patients treated with digoxin is not proven. The activation in the recipient of the treatment, as well as the concept

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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 therapeutical 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 in particular needs further validation. 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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