Part C. Clinical illustrations and observations on the intractability of atrial fibrillation
Appendix 5

Heart failure and atrial fibrillation: current concepts and controversies

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SUMMARY

Heart failure and atrial fibrillation are very common, particularly in the elderly. Owing to common risk factors both disorders are often present in the same patient. In addition, there is increasing evidence of a complex, reciprocal relation between heart failure and atrial fibrillation. Thus heart failure may cause atrial fibrillation, with electromechanical feedback and neurohumoral activation playing an important mediating role. On the other hand, atrial fibrillation may promote heart failure; in particular, when there is an uncontrolled ventricular rate tachycardiomyopathy may develop and thereby heart failure. Eventually, a vicious circle between heart failure and atrial fibrillation may form, in which neurohumoral activation and subtle derangement of rate control are involved. Treatment should aim at unloading of the heart, adequate control of ventricular rate and correction of neurohumoral activation. Angiotensin converting enzyme inhibitors may help to achieve these goals. Treatment should also include an attempt to restore sinus rhythm through electrical cardioversion, though appropriate timing of cardioversion is difficult. His bundle ablation may be used to achieve adequate rate control in drug-refractory cases.

BACKGROUND

Congestive heart failure is a large epidemiologic problem, particularly in the elderly. The same holds for atrial fibrillation, another very common disorder especially affecting elderly subjects. The two disorders profoundly limit life-expectancy. Another important epidemiologic feature is that both are often present in the same patient. This is partly due to the fact that heart failure and atrial fibrillation share important risk factors. On the other hand, a causal, reciprocal relation exists between heart failure and atrial fibrillation. In this review relevant epidemiologic aspects as well as pathophysiologic and clinical aspects of this interplay between heart failure and atrial fibrillation will be discussed.
The Framingham Study estimated the mean prevalence of heart failure to be approximately 1% of its local population. The prevalence of heart failure rose sharply with age; it doubled every decade, exceeding 10% above the age of 80 years. Importantly, based on the number of hospitalizations, the prevalence of heart failure would appear to increase over time. The epidemiologic significance of heart failure is also reflected by its profound adverse effect on prognosis, especially in severe cases. In the Framingham Study, one-year mortality was 43% and 5-year mortality 75%.

The Framingham Study has also provided insight into the epidemiology of atrial fibrillation; the overall chance that subjects 30 to 62 years old in the Framingham population would develop atrial fibrillation during 22 years of follow-up was 2%. However, the incidence was strikingly age-dependent, older age age (>55 years) conferring a chance >3% of developing atrial fibrillation. Unfortunately, there are as yet no reliable data as to whether the epidemiology of atrial fibrillation is changing, i.e. whether atrial fibrillation is becoming more common, though this would seem likely, given the fact that elderly are increasing in number. The prognostic implications of atrial fibrillation are grave. In the Framingham Study, development of atrial fibrillation was associated with a relative risk of 1.8 for overall mortality and 2.7 for cardiovascular mortality, compared to subjects with sinus rhythm. The average time to death was 6 years.

**Heart failure and atrial fibrillation** From an epidemiologic point of view, a strong association exists between heart failure and atrial fibrillation. Whereas atrial fibrillation is relatively rare in mild heart failure, it is a common concomitant disorder in patients with more advanced disease (table 1). In one smaller study, as many as 35% of the patients with heart failure were reported to have concomitant atrial fibrillation. The impact of atrial fibrillation on mortality in patients with heart failure is controversial. In the largest study, combining data from the V-HeFT I and II Studies, no effect of atrial fibrillation on mortality was demonstrable. Conversely, heart failure is a common finding in patients with atrial fibrillation, and one which adversely affects their prognosis (as could be expected, given the grim prognosis of heart failure per se).
Appendix 5

PATHOPHYSIOLOGICAL ASPECTS

The similarity of the epidemiologic profile of heart failure and atrial fibrillation and their frequent coexistence can readily be explained by considering the risk factors of either disorder. Heart failure and atrial fibrillation share to a considerable extent the same risk factors, i.e. predisposing conditions. The importance of old age has already been mentioned, and the significance of ischemic heart disease, hypertension and valve disease is well established. Finally, specific factors such as diabetes mellitus and left ventricular hypertrophy on the electrocardiogram also prognosticate the development of both heart failure and atrial fibrillation. There is, however, also evidence of a causal relation between the two disorders.

Heart failure as a cause of atrial fibrillation Heart failure is an established predisposing condition for development of atrial fibrillation. In fact, in the Framingham Study heart failure was the most powerful independent precursor of atrial fibrillation, with a relative risk of approximately sixfold. Interestingly, in another report from the Framingham Study even asymptomatic left ventricular dysfunction was found to be predictive of atrial fibrillation. Data from cardioversion studies provide another line of evidence substantiating the importance of heart failure in the development of atrial fibrillation. Thus, it has been shown that heart failure increases the likelihood of recurrence of atrial fibrillation after electrical cardioversion to sinus rhythm.

Whereas the empirical evidence that heart failure may cause atrial fibrillation is irrefutable, the underlying pathophysiologic mechanism is only partly

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of patients</th>
<th>Mean LVEF (%)</th>
<th>AF (%)</th>
<th>Impact on mortality</th>
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<tr>
<td>Likoff et al</td>
<td>201</td>
<td>20</td>
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<td>Keogh et al</td>
<td>232</td>
<td>16</td>
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<td>Carson et al</td>
<td>1427</td>
<td>30</td>
<td>14</td>
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</table>

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; NA, not available.
understood. “Mechano-electrical feedback” at the atrial level presumably plays an important role. As a result of increased cardiac loading due to heart failure, the atria stretch, which in the experimental setting has been shown to produce profibrillatory changes in atrial conduction and refractoriness.\textsuperscript{12,13} In particular, the dispersion in atrial refractoriness increased secondarily to acute atrial loading, which was associated with enhanced inducibility of atrial fibrillation. These findings in animals have been confirmed in humans, acute changes in atrial load similarly affecting atrial electrophysiologic properties.\textsuperscript{14} In addition to these acute, transient effects of atrial loading, it may be surmised that sustained atrial overload in the setting of chronic heart failure causes structural atrial enlargement, which in turn would strongly facilitate atrial fibrillation. Supporting this possibility, we found that left atrial volume in a group of atrial fibrillation patients with overt heart failure was larger than in randomly selected atrial fibrillation patients, other factors known to affect left atrial volume being comparable; mean left atrial volume was 86 ml and 74 ml respectively.\textsuperscript{15,16}

Secondly, it may be hypothesized that atrial fibrillation in the setting of heart failure is also promoted by associated neurohumoral activation. In particular, activation of the sympathetic nervous system might facilitate the onset of atrial fibrillation by directly modifying atrial electrophysiologic

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total no. of patients</th>
<th>No. of patients with EF &lt;50% or FS &lt;27%</th>
<th>LV function before His bundle ablation (%)</th>
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<td>29</td>
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<td>EF:32</td>
<td>EF:45</td>
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*The data pertain only to the subgroup of patients with the depressed left ventricular function prior to His bundle ablation (except the study of Twidale et al in which the effect was not specified according to the two subgroups); no significant changes were observed after His bundle ablation in the subgroup of patients with preserved left ventricular function. EF, ejection fraction; FS, fractional shortening; LV, left ventricular.
properties, thereby promoting atrial ectopy necessary for initiation of atrial fibrillation.\textsuperscript{17,18} Furthermore, elevated catecholamine and angiotensine II levels produce structural changes in the myocardium (myocyte hypertrophy, collagen accumulation, fibrosis), which in turn may promote arrhythmias,\textsuperscript{19} presumably including atrial fibrillation. Underscoring the importance of sympathetic activation, Borzak et al. have demonstrated in a dog model of heart failure that the propensity for development of atrial fibrillation was strongly related to the level of plasma norepinephrine.\textsuperscript{20} In fact, in that study development of atrial fibrillation was not predicted by any measure of left ventricular performance, but exclusively by plasma norepinephrine. Finally, in a recent study we found that plasma norepinephrine prior to electrical cardioversion tended to be higher in heart failure patients with subsequent recurrence of atrial fibrillation (after cardioversion) than in patients who maintained sinus rhythm.\textsuperscript{15}

**Atrial fibrillation as a cause of heart failure** Besides the fact that heart failure can cause atrial fibrillation, atrial fibrillation may also cause heart failure. Among clinicians it is common knowledge that acute atrial fibrillation may precipitate overt heart failure in the setting of asymptomatic left ventricular dysfunction. Impaired diastolic filling secondary to loss of atrial systolic function and to rapid, irregular ventricular rhythm plays a crucial role in this connection. However, if ventricular rate is inadequately controlled, atrial fibrillation may also depress systolic function, which may eventually result in severe heart failure, even without prior structural heart disease.\textsuperscript{21-27} This phenomenon has been termed “tachycardiomyopathy”. The clinical evidence for this type of cardiomyopathy stems from the observation that left ventricular function often markedly improves after alleviation of high ventricular rate per se. Radiofrequency ablation of the His bundle may be used to this end (table 2). Numerous animal studies support the concept of tachycardiomyopathy; in fact, rapid cardiac pacing was already an established means of producing experimental heart failure long before appreciation of the concept by clinicians became widespread.

In addition to the aforementioned (sub)acute effects of atrial fibrillation, there is also evidence of a more subtle, insidious long-term deleterious effect of atrial fibrillation on left ventricular function. Unlike straightforward
tachycardiacardiomyopathy this would affect many patients with atrial fibrillation, even when ventricular rate is adequately controlled, i.e. according to clinical practice. Thus, in the V-HeFT II Study, patients with atrial fibrillation showed a significant decline in peak oxygen consumption compared to patients with sinus rhythm starting after 2 years of follow-up (Figure 1). Recently, we observed a comparable phenomenon in a 2-year follow-up study after electrical cardioversion: despite similar clinical characteristics at baseline, patients who maintained sinus rhythm showed a gradual, sustained increase in peak oxygen consumption, whereas patients with recurrence of atrial fibrillation demonstrated a clear decrease after 2 years. Furthermore, it was shown that electrical cardioversion of atrial fibrillation is associated with a discrepancy in the time course of recovery of atrial systole and ventricular function: while the atrial contribution to ventricular filling normalized within one week after cardioversion, left ventricular ejection fraction continued to increase beyond that time frame, reaching peak values after one month. It was noteworthy that the increase in peak oxygen consumption was parallel to the increase in ejection fraction.

Taken together, these observations suggest the presence of a subtle form of cardiomyopathy, inherent to chronic atrial fibrillation. The underlying
Figure 2. Relation between stage of exercise and heart rate comparing 21 patients with chronic atrial fibrillation with peak oxygen consumption $\leq 20\text{ ml/min/kg}$ (open circles) and 24 patients with peak oxygen consumption $>20\text{ ml/min/kg}$ (closed circles). All patients were on digoxin and/or calcium antagonists for control of ventricular rate; no patients used antiadrenergic agents, including angiotensin converting enzyme inhibitors or beta-blockers. Patients with preserved functional capacity (peak oxygen consumption $>20\text{ ml/min/kg}$) showed a gradual increase in heart rate as a function of exercise. In contrast, though heart rate at rest was reasonably well controlled, in patients with impaired functional capacity (peak oxygen consumption $=20\text{ ml/min/kg}$) a marked heart rate increase was observed at low levels of exercise compared to patients with preserved functional capacity. In addition, maximal heart rate was attenuated. (Reproduced with permission from Van Den Berg et al., Chronotropic response to exercise in patients with atrial fibrillation: relation to functional state. Br Heart J 1993;70:150-153. Copyright 1993 BMJ Publishing Group.)

mechanism is as yet unknown. However, two factors might be involved, the first of which is “concealed” tachycardiomyopathy; though ventricular rate at rest may be well controlled (<100 beats/min), patients with atrial fibrillation often exhibit disproportionately high rates (>120 beats/min) during minor exercise, corresponding with normal daily activities. Particularly patients in whom the left ventricular function is already impaired exhibit such responses, due to excessive sympathetic activation early during exercise (Figure 2). It is conceivable that in the long run this has a deleterious effect on left ventricular systolic function, considering the fact that tachycardiomyopathy may develop in patients with paroxysmal atrial fibrillation and with ventricular rates as “low” as 120 beats/min or even lower.

Second, depletion of atrial natriuretic peptide may play a role. Whereas in the acute stage atrial fibrillatory activity per se (i.e. irrespective of concomitant hemodynamic changes) may enhance atrial natriuretic peptide secretion, long-standing atrial fibrillation is associated with atrial natriuretic peptide depletion; as a result of extensive atrophy and fibrosis of the atria, the production of atrial natriuretic peptide gradually diminishes in long-standing atrial
fibrillation, which may result in complete “endocrinologic silence”. Recently, we found that this phenomenon may also be operative in patients with concomitant heart failure by observing the presence of an inverse relation between plasma atrial natriuretic peptide and the duration of atrial fibrillation in these patients (unpublished results). Though diminished atrial natriuretic peptide production does not directly affect left ventricular systolic function, it may contribute to eventual hemodynamic deterioration, i.e. heart failure.

CLINICAL MANAGEMENT

Traditionally, many clinicians rely on cardioversion (either chemical or electrical) as a first therapeutic measure in patients with atrial fibrillation, irrespective of concomitant heart failure. This approach is supported by the very consistent finding that the duration of atrial fibrillation is a prime determinant of the likelihood of maintenance of sinus rhythm after cardioversion: the longer the duration of atrial fibrillation the higher the risk of relapse of atrial fibrillation. However, irrespective of the duration of atrial fibrillation, it is important that untreated hypertension, myocardial ischemia, thyrotoxicosis or heart failure should be treated before attempting cardioversion. In addition, it should be realized that the prophylactic use of antiarrhythmic drugs is hazardous in cases of heart failure; while the efficacy in maintaining sinus rhythm after cardioversion is low, these agents may actually increase mortality, due to negative inotropic and proarrhythmic effects. Hence, unless in cases of emergency (hemodynamic shock) in which cardioversion may prove beneficial, cardioversion is generally not suited as a first measure in patients presenting with heart failure and atrial fibrillation; treatment should instead focus on heart failure.

We have shown recently that treatment with an angiotensin converting enzyme inhibitor is useful to this end. Also, adequate control of ventricular rate is crucial. Though classically digoxin is widely used, it is often necessary to add another (intravenous) agent, the options being a beta-blocker or a calcium-antagonist. Diltiazem has been shown to be generally safe in the setting of acute heart failure and atrial fibrillation, and to rapidly and effectively control ventricular rate. Alternatively, a case can be made for the betablocker esmolol. Due to its ultrashort half-life (9 minutes) this agent is theoretically
well suited for the critical care setting, including acute heart failure and atrial fibrillation. Rate control with digoxin as monotherapy is often also insufficient beyond the acute stage; though by virtue of its vagomimetic effect it may control ventricular rate reasonably well at rest, rate control during exercise, including low levels of exercise, is usually inadequate. Hence, like in the acute stage, it is often necessary to add another agent. The efficacy of calcium antagonists and beta-blockers in this connection is unknown; previous studies have included mainly atrial fibrillation patients with (near) normal cardiac function, and have focussed on heart rate at maximal exercise rather than heart rate at lower levels of exercise. Furthermore, the duration of treatment in most studies was relatively short (2-3 weeks). These considerations, together with those mentioned before, provide a rationale for adding a beta-blocker to digoxin rather than a calcium-antagonist. The dose will probably have to be relatively low to allow for a sufficient rise in heart rate during heavy exercise, and treatment should presumably be continued for a long time before a beneficial effect can be expected. However, anecdotal experience suggests that patients may indeed benefit. Finally, when the patient proves drug-refractory despite the use of a combination of negative dromotropic agents, His bundle ablation is an option.

Acronyms: V-HeFT: Vasodilator Heart Failure Trial

References
8. Van Gelder IC, Crijns HJ GM, Tieleman RG, Hilleghe HJ, Gosselink ATM, Lie KL. Mortality in patients with atrial fibrillation is related to the severity of the underlying disease and not to the arrhythmia (abstract). Circulation 1994;90(suppl I):541.


