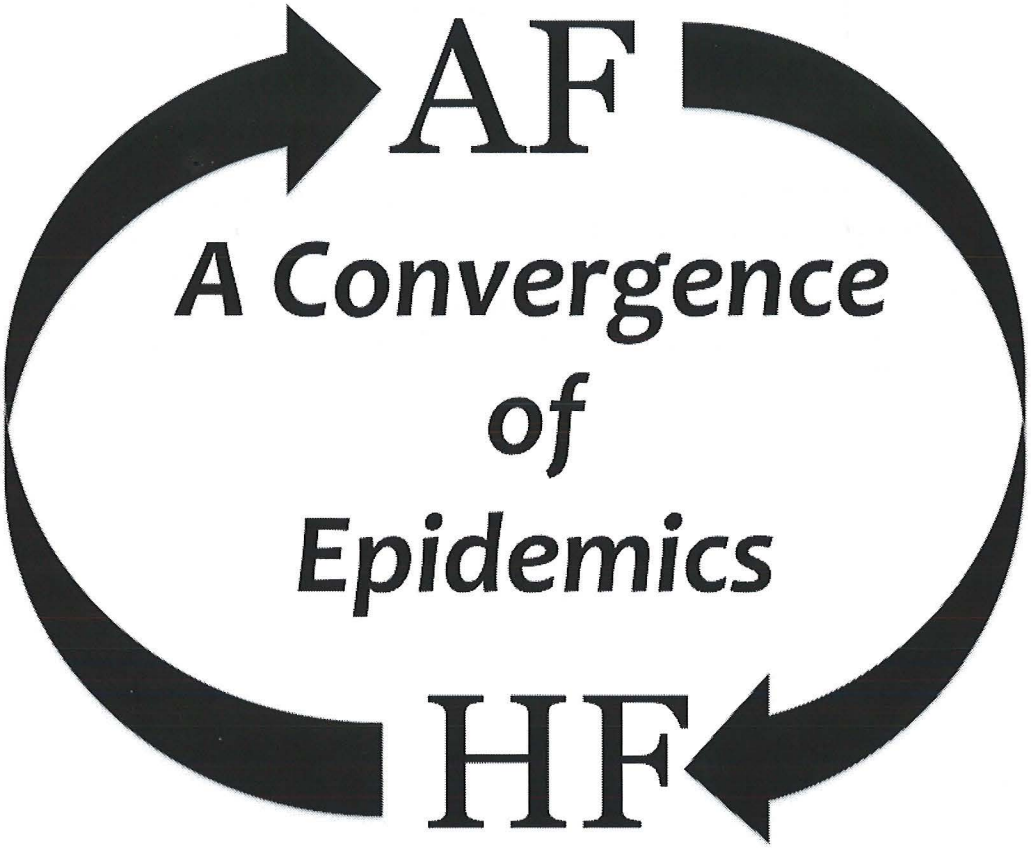

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Internal Medicine Grand Rounds
UT Southwestern Medical Center
April 8, 2011

This is to acknowledge that Owen A. Obel M.D. has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Obel will not be discussing off-label uses in his/her presentation

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Introduction

Heart failure (HF) and atrial fibrillation (AF) are both major public health problems. Both conditions are najor causes of morbidity and mortality and are occurring in epidemic proportions. The two conditions share many risk factors and frequently coexist in the same patient. AF often significantly aggravates the clinical course of HF, and may even be the sole cause of HF in some cases. Similarly HF may make AF more resistant to cure, and can also aggravate its own clinical course by increasing the ventricular rate during AF. This paper will briefly describe the current epidemiological status of these 2 conditions and their risk factors. Following this, I will discuss how these conditions affect each other's pathogenesis and clinical course. This will be followed by a discussion on the clinical techniques that are used to reverse this vicious cycle.

Epidemiology

Heart failure (HF) is the leading cause of morbidity and mortality in the United States affecting close to 5 million patients with 500 000 new cases being identified annually (Figure 2).[1,2,3] HF contributes to 2 million hospitalizations annually and as such is the leading cause of hospitalizations in patients aged 65 years and older. HF is the single largest Medicare expenditure accounting for approximately $4 billion annually, accounting for an estimated 2-3% of the annual health care budget.[1,3] Most estimates suggest that the incidence of HF is increasing and will continue to do so well into the 21st century.

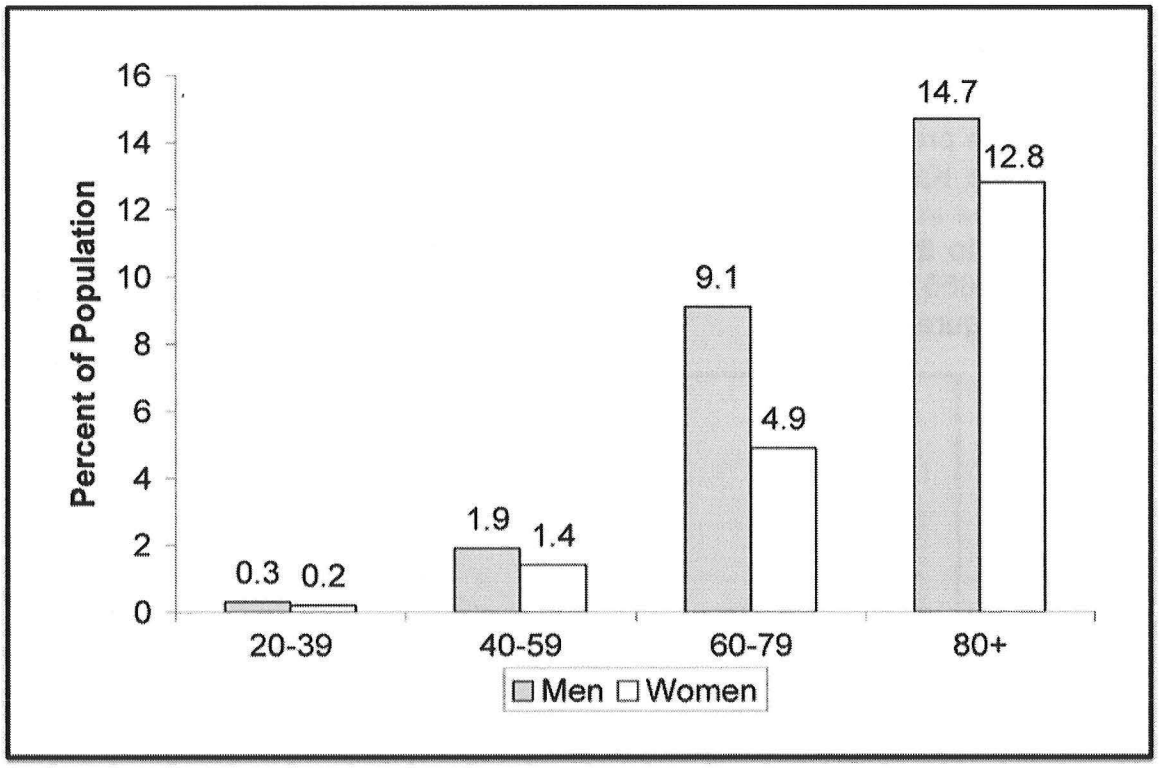

Figure 1: Prevalence of HF by sex and age (NHANES: 2003–2006). Source: NCHS and NHLBI.

Atrial fibrillation (AF) is similarly a major public health problem affecting approximately 2.2 million people in the United States.[4] The overall prevalence of AF is 0.5%-1% and rises to over 10% in individuals aged over 80.[5] In Framingham Study, which initially recruited 5209 men and women, approximately 7.2% of subjects developed AF when followed biennially for 30 years.[6] The prevalence of AF is rising rapidly.[7] In industrialized countries, the number of affected individuals is projected to

more than double over the next 50 years. There has been a doubling in the past 20 years of the rate of AF-related hospital admissions (Figure 2).[8-10]

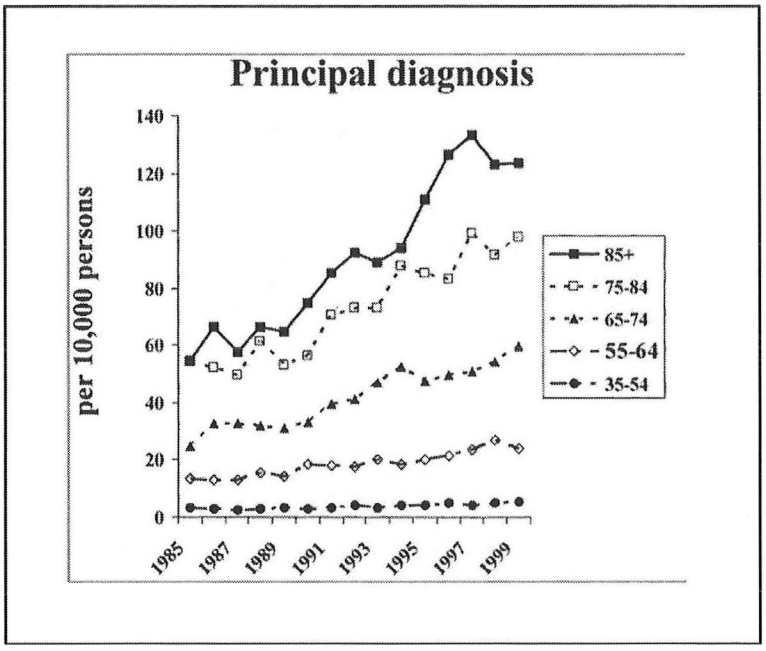

Figure 2: Incidence of AF as a principle hospital diagnosis is increasing with the majority of cases occurring in elderly populations[10]

Aiming to estimate the prevalence of AF in 2050, Go and colleagues performed a census of almost . million patients in the Kaiser Permanente heath system. They found the overall and age-specific prevalence of AF to be in keeping with current estimates outlined above. By combining this age and gender specific data to the estimates of population growth and demographics, they found that the prevalence of AF in 2050 is likely to be almost triple current levels with the majority of patients being aged 80 and older (Figure 3).[11]

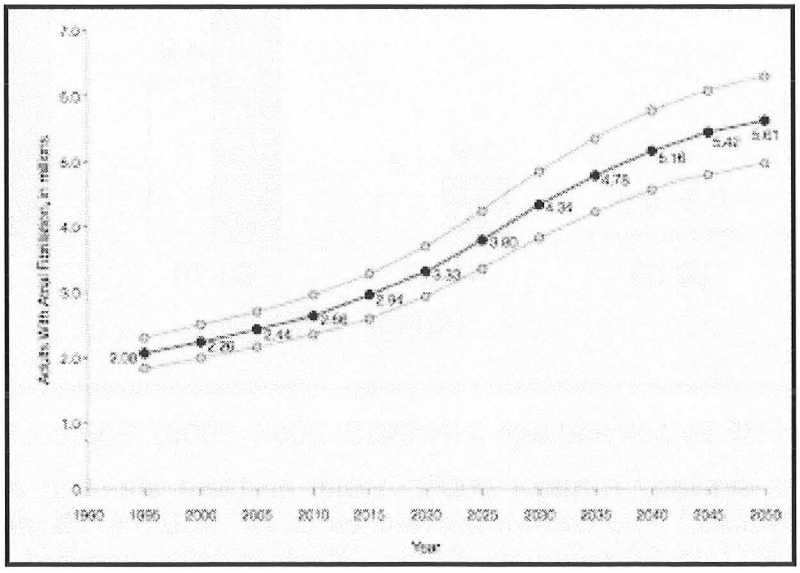

Figure 3: Projected number of adults with atrial fibrillation between 1990 and 2050[11]

THE PREVALENCE OF AF IN HEART FAILURE

The prevalence of AF increases as the severity of HF increases. Patients with mild HF symptoms have a prevalence of AF of ≤5%, whilst those with the most severe degree of symptomatic HF have a prevalence of AF of almost 50%.[12,13] The incidence of AF in patients with HF is 2-5% depending on the severity of HF. Many predisposing clinical factors are shared between AF and HF including hypertension (HT), increased alcohol consumption, diabetes mellitus (DM), and coronary artery disease (CAD). Several of the echocardiographic hallmarks of HF are major risk factors for AF including reduced LV systolic function, LV wall hypertrophy, and left atrial (LA) enlargement. Most studies examining the effect of AF on outcomes in HF suggest that the presence of AF is associated with a worsening of prognosis in HF. The SOLVD trial, a major HF trial, included 419 patients with AF. In this study, patients in AF had a higher all-cause mortality than those in SR. Similarly, the DIG trial that enrolled 7788 patients found that the development of AF resulted in an increase in mortality (relative risk - RR = 2.45) and increased HF hospitalization rate (RR = 3) relative to SR.[14]

RISK FACTORS FOR AF AND HEART FAILURE

HF and AF share several risk factors, many of which are occurring in epidemic proportions in the Western world. Hypertension (HT) is known to be a major risk factor for both the development of AF and HF. Diabetes mellitus (DM) is a risk factor for coronary artery disease (CAD) and as such is a risk factor for the development of both AF and HF. Furthermore, both DM and HT are risk factors for stroke in AF.[15] Obstructive sleep apnea (OSA) is a risk factor for the occurrence of both AF and HF and patients with OSA have less freedom from AF recurrence after catheter ablation. OSA is steadily increasing in incidence.[16]

It is notable that obesity is a major risk factor for all of the above conditions and hence has the effect of being the major underlying risk factor for the development of both AF and HF. Levels of obesity in many societies are steadily increasing. It is estimated that by 2030, over 50% of the American population will be obese.[17] Excessive alcohol consumption is a recognized cause of dilated cardiomyopathy (CMO) and is also a major risk factor for the development of AF.

Finally, and most importantly, AF is a risk factor for HF. Likewise, HF is a risk factor for AF. Therefore these two conditions often perpetuate each other. The inter-relationship of AF and HF can potentially result in a number of clinical syndromes and effects, which can significantly impair cardiac function.

The Effects of Atrial Fibrillation on Heart Failure

AF results in a 15-25% reduction in CO. The reasons for this are multi-factorial and include disturbance of ventricular rate, irregularity of ventricular rhythm, induction of a cardiomyopathy (CMO), and loss of coordinated atrial contribution to cardiac filling.

RAPID VENTRICULAR RESPONSE

AF is associated with atrial rates of 300 - 600 beats per minute (bpm). Ventricular rate (VR) is one of the main determinants of the effect of AF in HF and is dependant on AV nodal, His-Purkinje, and ventricular tissue conduction properties.

A rapid ventricular response (RVR) can result in significant ventricular dysfunction through 2 mechanisms: 1) Patients with pre-existing left ventricular dysfunction (systolic and/or diastolic) may be compensated at baseline, however when exposed to a rapid ventricular rate may experience a significant de-compensation in heart failure; 2) Chronic exposure to an elevated VR can result in a tachycardia-induced CMO (TIC), see below.[18]

Tachycardia-Induced cardiomyopathy

TIC can be an isolated diagnosis in which cure or control of the tachycardia can be expected to result in complete reversal of the CMO and therefore HF. Conversely, TIC may be one element of a multi-

factorial process, in which case cure or control of tachycardia will result in partial reversal of HF.[18] The importance of considering TIC is critical since there are several treatment options, which offer highly effective means of curing or controlling various forms of tachycardia. TIC is one of the few forms of CMO that can be completely reversed.

TIC has been reported to arise as a result of a variety of arrhythmias including AF, atrial flutter, other SVTs, and even frequent ventricular premature beats. Moderately rapid (e.g. 100-120 bpm) arrhythmias are more likely to result in TIC than very rapid arrhythmias because: 1) slower tachycardia may cause minimal symptoms of palpitation, thus patients may not notice tachycardia or seek help and it may remain untreated for months or years; 2) from an electrophysiologic perspective, slower tachycardia is more liable to stabilize and to become sustained for longer periods than more rapid tachycardia. Despite ample evidence that a RVR can result in precipitation of and even cause HF, the exact rates at which these effects become manifest are difficult to define. This is because individuals' heart rates often vary widely, and in the case of paroxysmal AF, duration of episodes may vary widely therefore the time-at-rate needs to be taken into account, and this may not be known. In order for TIC to develop as a direct result of AF, chronic exposure to a resting VR consistently >100 bpm, and/or a VR of consistently >150bpm during mild exercise might be expected to produce this effect.

TIC may occur as a completely isolated phenomenon, or may exacerbate a preexisting CMO (see below). The severity of TIC appears to be related to the speed VR itself, the length of exposure to the elevated VR, and the presence (if any), and type of underlying heart disease. For example, AF associated with a RVR in a patient with hypertensive heart disease may result in a greater degree of TIC than in a patient who does not have underlying heart disease.

There are significant gaps in our current understanding of the various factors predisposing to TIC. First, the degree of loss of VR control required for TIC to develop in the setting of AF is unknown Second, the mechanism of the interaction of tachycardia with preexisting CMO or other heart disease is not fully understood. Preexisting CMO (due to any cause) or other underlying heart diseases may interact with TIC in 2 possible ways: 1) by predisposing to the development of TIC; 2) TIC may result in frank clinical HF as a result of the additional disturbance of cardiac function in a patient with previously subclinical CMO.

A number of mechanisms for the pathophysiology of TIC have been proposed.[18] Myocardial energy stores (high energy phosphates) are depleted by chronic tachyarrhythmia.[18] Evidence of impaired coronary flow reserve and reduced subendocardial–to-subepicardial flow in TIC suggest that myocardial ischemia may play a role in its pathogenesis.[19] Abnormal calcium (Ca^{++}) handling can result in decreased Ca^{++} sensitivity and abnormal excitation-contraction coupling and has been demonstrated in models of TIC (Figure 4).[20] In addition, structural abnormalities have been noted in the mitachondria, myocytes, and the basement membrane-myocyte interface, and may affect myocardial performance in TIC.[19]

After cure or effective control of tachycardia, TIC can be expected to resolve within approximately 3 months.[21] Resolution of TIC is manifested echocardiographically by an increase in ejection fraction (EF), and a reduction in cardiac volume. Interestingly, end-systolic volume is reduced more promptly that end-diastolic volume, which can remain, elevated for some time after improvement in EF and amelioration of HF.[22]

There is no specific diagnostic test for TIC. The diagnosis of TIC can only be reached retrospectively after substantial or complete reversal of CMO occurs once tachycardia is effectively cured or controlled. Thus the gold standard for the diagnosis of TIC is the improvement or cure of CMO and HF after elimination of tachycardia.

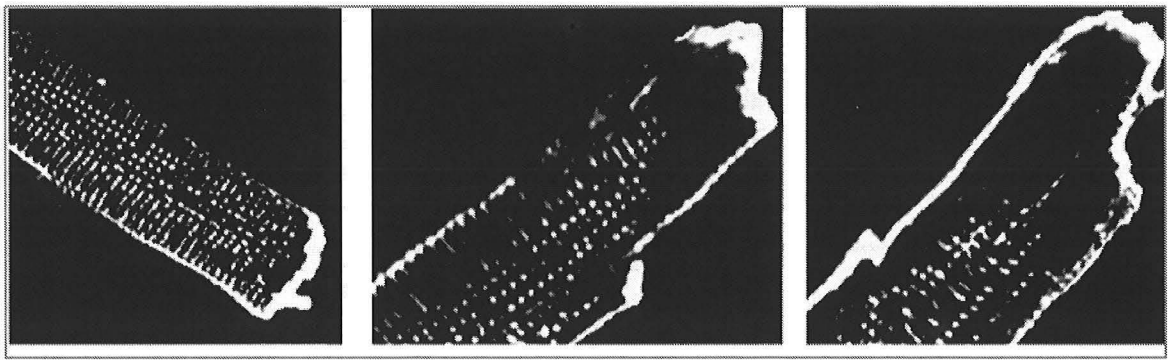

Figure 4: Failing canine ventricular myocytes exhibit prominent depletion of T-tubules and changes in the density of a variety of proteins in both surface and T-tubular sarcolemma [20]

Techniques for Monitoring Ventricular Rate During AF

There are various techniques for monitoring VR, these include: 1) ambulatory monitoring through externally applied devices such as a standard Holter or another variation of external ambulatory monitor; 2) Implantable loop recorders (ILRs). These were initially designed and indicated for the investigation of syncope, however such newer devices are designed to asses the occurrence of AF episodes and record details such as VR, duration, and patterns of occurrence (Figure 5); 3) Pacemakers (PPM) and implantable-cardioverter defibrillators (ICD) systems can provide extensive details regarding AF occurrences particularly if an atrial lead is part of the system. PPMs and ICDs are not implanted primarily for the purposes of monitoring such parameters as AF burden, however many patients for whom these devices are implanted have AF, and such information can be very valuable.

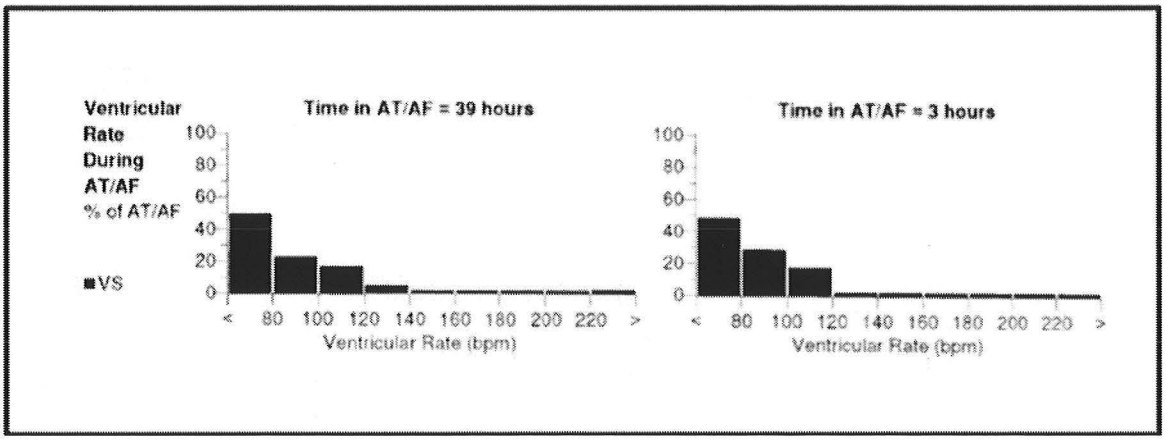

Figure 5: Report from a Reveal XT™ implantable loop recorder showing a profile of ventricular rate during AF

IRREGULAR VENTRICULAR RATE

AF is associated with a ventricular response that is irregularly irregular. There is strong evidence that like elevated VR, chronic irregularity of ventricular rhythm can also profoundly adversely affect ventricular function. The reasons for the negative effects of irregularity of rhythm on ventricular function on are manifold and only partially understood.

In studies performed in patients undergoing AV node ablation during which heart rate can be entirely controlled by ventricular pacing, it is possible to make measurements during both regular and irregular ventricular sequences (Figure 6).[23,24] In both these studies an irregular ventricular rhythm resulted in a reduced cardiac output (CO) and an increased pulmonary capillary wedge pressure. An irregular ventricular sequence may result in significant autonomic disturbance. Wasmund et al demonstrated increased sympathetic nerve activity (SNA) after induction of AF in part due to the

irregularity associated with AF.[25] Further studies independently studying the effect of rate and regularity revealed that for every 1% in irregularity there was a 6% increase in SNA.[26] Increased sympathetic activity is highly undesirable in HF since it can have the effects of promoting ventricular arrhythmia, perpetuating AF, and worsening the clinical course of HF through toxic effects on th cardiomyocyte.[27] Ventricular irregularity may also result in valvular dysfunction particularly the mitra valve.

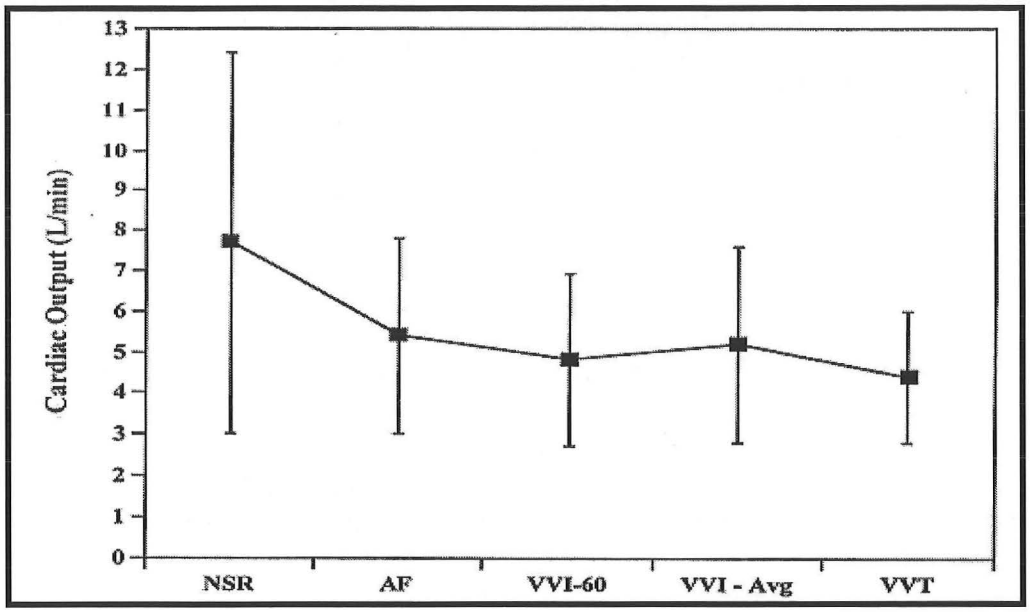

Figure 6: The effect of ventricular irregularity on cardiac output. Note that pacing at an irregular rhythm (VVT) but at the same rate results in a drop in cardiac output.[23]

LOSS OF ATRIAL CONTRIBUTION TO CARDIAC OUTPUT

The atria function as reservoirs, conduits, and as boosters of CO. AF results in a loss of coordinated atrial mechanical function meaning that atrial contribution to CO is lost. In general, it is accepted that atrial contribution to CO is approximately 10-15% in normal individuals.[28] In an open-chest study on dogs with induced complete heart block, ventricular rate and rhythm as well as atrial rhythm could be independently adjusted. AF resulted in a reduction of CO of approximately 20% during both regular as well as irregular ventricular pacing.[29] The degree to which atrial contribution contributes to the overall CO varies amongst patients with different cardiac disease states and also depends on individual volume status. As will be discussed, patients with diastolic LV dysfunction are particularly dependant on atrial contribution to LV filling and such patients who are in borderline HF during sinus rhythm (SR), may develop frank HF with the occurrence of AF.

THE EFFECTS OF AF ON PROGNOSIS IN HEART FAILURE

AF has a significant negative impact on the outcome of HF. In a study on 390 patients with severe HF (EF 20%) and followed for approximately on year, Middlekauf et al. demonstrated a survival of 52% in the presence of AF and 71% when SR was present.[30] Similarly in mild/moderate HF, AF imparts a negative prognosis. In patients with either symptomatic or asymptomatic HF in the SOLVD trials, AF was associated with an increased all-cause mortality.[14]

The temporal effects of the association between AF and HF was reported by Wang et al. who studied approximately 1400 patients from the Framingham study, the design of which allowed for analysis of the chronology of developing either condition. In this study the effect of the development of AF on prognosis in patients who had HF and vice-versa was examined. Of 931 patients diagnosed with HF, 24% had previous or concurrent AF, and 17% developed AF subsequently. In those subjects with HF who were free of AF at enrollment, the development of AF resulted in an adjusted hazard ratio of 1.6 in men and 2.7 in women indicating that the development of AF in patients with existing HF results in

a worsening of prognosis. In a meta-analysis involving over 50 000 patients from 16 studies, it was demonstrated that the presence of AF was associated with a worsening of mortality in patients with HF associated with both depressed EF and with preserved systolic function.[31]

AF AND DIASTOLIC HEART FAILURE

The development of AF in patients with diastolic dysfunction often results in a worsening of symptoms, a longer 6-minute walk time, a reduced quality of life, and can result in a worsened mortality.[32] This is in part to irregularity of ventricular rhythm since short R-R intervals result in diminished relaxation capacity and patients with diastolic HF are dependant on a long diastolic interval.[33] Similarly, rapid ventricular rates also worsen the clinical course in patients with diastolic dysfunction and may precipitate acute HF and flash pulmonary edema. In addition, atrial contribution to cardiac output is of particular importance in the setting of diastolic dysfunction, with a greater proportion of CO being attributed to atrial systole. Loss of atrial systole can result in a clinically significant worsening of HF in the setting of significant diastolic dysfunction. Patients with hypertrophic cardiomyopathy tolerate AF poorly for the same reason, and development of AF in this patient group often heralds a marked worsening of their clinical course.[34,35]

THE EFFECTS OF AF IN CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT) is a highly effective therapy for patients with HF and electromechanical dysynchrony as identified by a broad QRS complex on the 12-lead EKG.[36] CRT is achieved by placing pacing leads in the endocardial right ventricle (RV) and on the epicardial left ventricle (LV) via tributaries of the coronary sinus. In addition, an atrial lead is incorporated in the system to impart atrio-biventricular synchrony. This system is known as a biventricular (BiV) pacing system and is usually combined with an implantable cardioverter defibrillator (ICD). CRT has been shown to significantly improve cardiac efficiency (at a decreased oxygen demand), HF symptoms, exercise capacity, quality of life, and mortality. Although this therapy is highly effective, and in some cases the response is dramatic, approximately 30% of patients fail to respond to CRT.

Patient selection is important in this differential response: 1) patients with LBBB are more likely to respond that those with RBBB;[37, 38] 2) patients with nonischemic dilated cardiomyopathy (DCM) are more likely to respond than those with ischemic cardiomyopathy (ICM);[39] 3) the broader the baseline QRS, the better the response;[40] and 4) the presence of AF results in a diminished response to CRT. It is estimated that approximately 20% of CRT recipients are in persistent AF. In a study on nearly 1200 patients undergoing CRT, Santini et al. reported that even a relatively small burden of AF resulted in a significant reduction in CRT benefit.[41] In a recent meta-analysis on 23 observational studies following a total of 7495 CRT recipients, AF was associated with an increased risk of non-response to CRT and all-cause mortality.[42]

In order for CRT to be effective, it is imperative that native conduction through the AV node is completely preempted since it will result in dysynchronous conduction to the ventricles as a result of bundle-branch-block. Instead, the ventricles must be exclusively activated the BiV pacing system. Even fusion between native and paced conduction is undesirable; exclusive biventricular pacing has the best chance of resulting in synchronized left ventricular contraction and relaxation. In patients undergoing CRT who are in AF, a significant proportion of AF beats will conduct faster to the ventricles than the BiV pacing can preempt. In these beats, native or fused (combination of native and paced) conduction occurs and the effect of CRT is lost. In addition, the disruptive effects of rapid VR, irregular rhythm and loss of atrial contribution to cardiac output all still apply.

It is estimated that for CRT to be effective in the presence of AF that anything less than 90% BiV pacing (>10% native conduction of AF) will result in a poor response to CRT.[43] The best response has been shown when >92% BiV pacing has been achieved.[44] The percentage of BiV pacing that is occurring can be retrieved by interrogation of the device. However, one needs to apply significant caution when using this percentage since a significant number of the 'paced' beats are in fact fused or pseudo-fused (pacing impulse is present but all conduction is native) and even more may be

triggered by algorithms that have been developed in an attempt to deal with this problem. In a study utilizing Holter monitoring in patients with AF undergoing CRT in whom the device had reported >90% pacing, it was shown that only 47% of patients were in fact effectively BiV pacing (>90% true paced events). The remainder were having a significant number of fused or pseudo-fused events.[45] Thus in patients with AF undergoing BiV pacing, AV node blockade must be completely effective to allow CRT to occur. Very often, medication in the form of AV nodal blocking agents such as beta-blockers or calcium channel blockers is simply not effective enough to achieve this. In such patients, AV nodal ablation resulting in complete heart block is required, and our threshold for performing this procedure in such patients should be low. Indeed, AV node ablation has been directly shown to predict a successful outcome in patients with AF undergoing CRT (Figure 7).[46, 47]

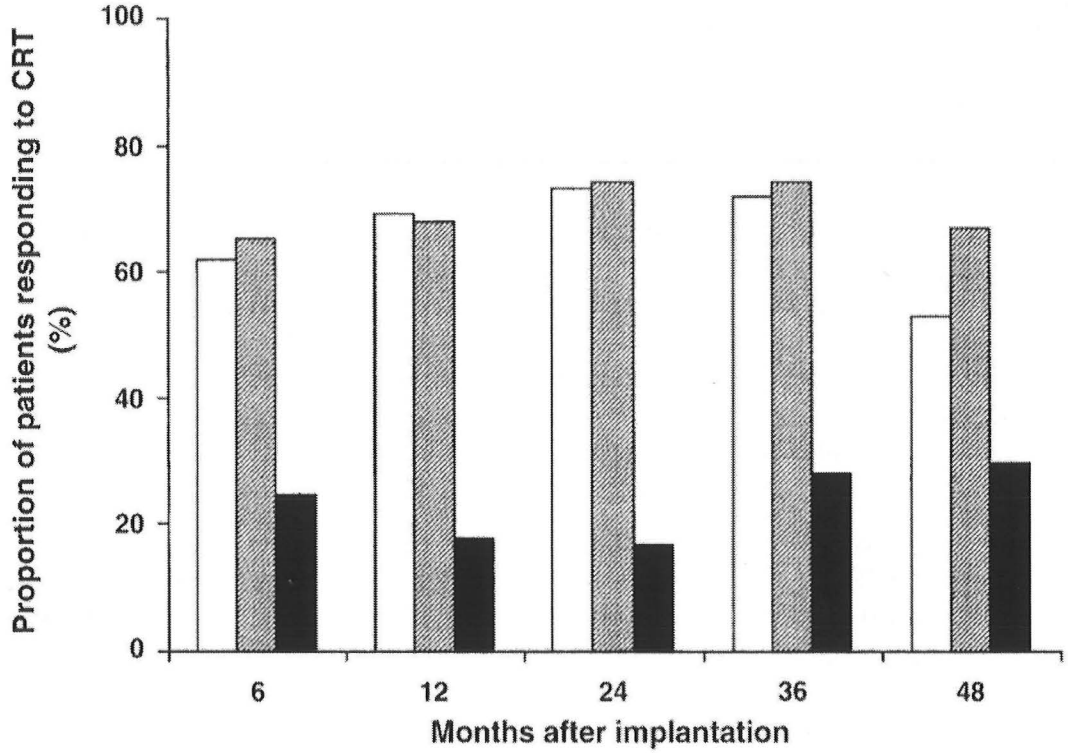

Figure 7: Percentage responders to CRT over time according to cardiac rhythm. Open bars = sinus rhythm; grey bars = AF patients who underwent AV node ablation; black bars = AF patients with native AV conduction[46]

The Effects of Heart Failure on Atrial Fibrillation

HEART FAILURE AS AN INITIATING AND PERPETUATING FACTOR IN ATRIAL FIBRILLATION

The complete pathophysiology by which HF promotes AF has been not yet been fully defined. The initiation AF and perpetuation of AF requires a trigger acting on a vulnerable substrate. Thus risk factors may induce, and/or encourage, and/or perpetuate AF. Indirect evidence for the effect of HF in AF comes from trials on pharmacologic treatments such as ACE inhibitors and Angiotensin II blockers which are used in the treatment of HF and are associated with a reduction in the incidence of AF indicating that successful treatment of HF may promote resolution of AF.[48] Similarly, CRT has been shown to encourage the emergence of sinus rhythm even after years of persistent AF. In a report on 46 patients with persistent AF undergoing CRT, Hauck and colleagues reported that 7 patients regained sinus rhythm, in 6 the conversion was spontaneous.[49] This effect appears to be linked to CRT response. Lellouche et al. report that responders to CRT are more likely to exhibit a reduction in atrial dimension (major factor in AF occurrence) and a reduction in the incidence and duration of episodes of AF.[50] We have demonstrated unexpected reversion to SR in patients undergoing AV

nodal ablation and BiV pacing for patients with previously recalcitrant AF associated with a rapid VR and HF undergoing AV node ablation and BiV pacing.[51]

The mechanisms by which HF worsens AF are diverse: 1) It is known that in scenarios such as HF and post-operative AF which are associated with raised sympathetic tone can be a potent trigger for AF.[52] 2) HF is frequently associated with hypoxia, and electrolyte shifts which can also promote AF. 3) Myocardial fibrosis causes slowing and uncoupling of electrical conduction and therefore electrical re-entry, and is a common substrate for AF. Both HF and AF are associated with profibrotic conditions including age, HT, DM, valvular heart disease (VHD), CAD, and various causes of CMO including alcoholic and hypertensive CMO. 4) LV failure results in raised LA pressure, which results in atrial stretch, atrial enlargement and fibrosis, and electrophysiological dysfunction.

Atrial enlargement can promote AF by increasing the available area for AF wavelets to circulate without self-extinguishing. Atrial enlargement is a recognized risk factor for AF to occur and to be resistant to attempts at maintenance of sinus rhythm. Atrial enlargement results in atrial stretch and raised atrial pressure. Several investigators have studied the effects of atrial stretch/raised pressure on atrial electrophysiology in animals.[53,54,55] Atrial stretch/raised pressure has been shown to result in a reduction and an increased dispersion of atrial electrical refractoriness, an effect that strongly favors the development and maintenance of AF.[54] Others have reported an increased dispersion of conduction velocities in atrial tissue in response to stretch. In a canine model of HF-induced AF, a significant increase in atrial scarring was noted and found to be related to the development of AF.[55] Thus the increased atrial pressure and stretch associated with HF can both act as an initiating factor for AF, and as a substrate for the perpetuation of AF. HF therefore may participate substantially in the formation of a substrate for AF to develop and sustain.

HEART FAILURE PROMOTES POOR RATE CONTROL IN ATRIAL FIBRILLATION

HF is associated with a significantly raised sympathetic tone and reduced parasympathetic tone.[56,57,58] In addition to significantly reducing the likelihood of restoration and maintenance of sinus rhythm, the raised sympathetic and reduced parasympathetic tone greatly encourage rapid AV nodal conduction of AF. This results in a significant increase in ventricular rate and all its negative effects which have been described above.

Atrial Fibrillation and Heart failure are Mutually Causative

It can be seen that patients with AF and HF are often in situation where a vicious cycle between these conditions exists resulting in a major disruption of cardiac function with severe consequences. The two conditions share many common risk factors. In addition, each acts a major risk factor for the other. AF results in a worse outcome in HF patients through a variety of mechanisms. In turn, HF encourages the initiation and perpetuation of AF and encourages a rapid ventricular rate, which in turn has a powerful negative impact on the pathophysiology of HF and can even act as an additional cause of cardiomyopathy in patients who already have severe heart disease (Figure 8).

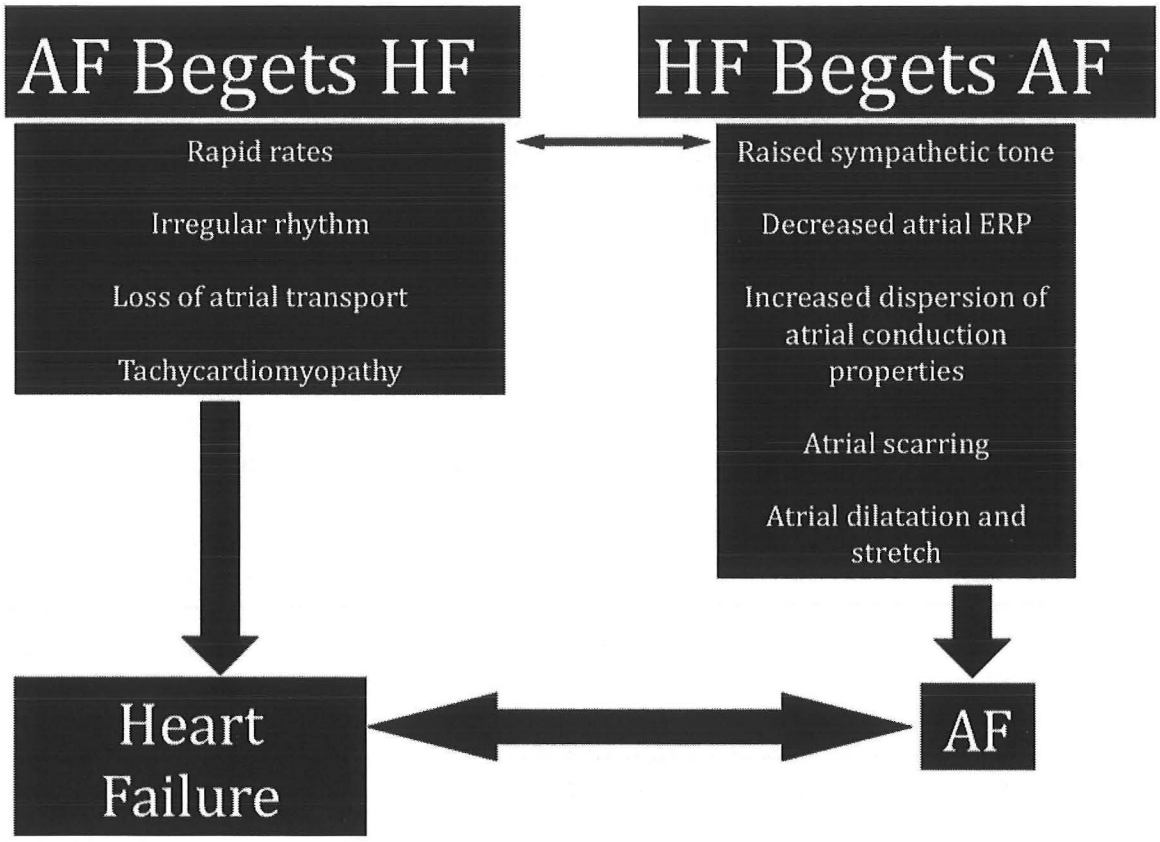

Figure 8: The vicious cycle between atrial fibrillation and heart failure

Management of Patients With Atrial Fibrillation and Heart Failure

Since AF and HF are causative in each others progression, it is sometimes not possible to ascertain: 1) Whether HF or AF started first; 2) the relative contribution of each condition to the others progression; and 3) to what degree HF status will respond to effective control of AF (either by restoration and maintenance of sinus rhythm or by effective ventricular rate control). Nevertheless, the vast majority of patients with AF and HF will respond to a significant degree to effective AF management.

When approaching a patient with AF and HF, it is clear that HF should be managed aggressively with diuretics, ACE inhibitors, beta-blockers, and aldosterone antagonists. This may have a beneficial effect on AF. Management of AF is more controversial. The first decision in the management of AF is whether to pursue a rhythm or a rate control strategy.

Rhythm Versus Rate Control

The strategy of 'rhythm control' is that in which one or more attempts are made at restoring and maintaining SR, effectively aiming to cure AF. As will be outlined below, AF in general and particularly when associated with HF, is a challenging arrhythmia to cure. Since many of the negative effects of AF in HF arise as a result of rapid ventricular rate, a valid strategy is to leave patients in AF and simply control the ventricular rate either by pharmacologic or invasive methods. This is known as a 'rate control' strategy. Studies comparing these 2 strategies have shown little difference in terms of survival in patients both with normal and those with impaired LV function and HF.[59,60,61]

In the AF/CHF trial, 1376 patients with HF and a history of AF were randomized to either a rhythm control strategy (in which cardioversion whilst the patient was taking an anti-arrhythmic drug and repeated if necessary), or a rate control strategy (either pharmacologic or AV node ablation + permanent pacing). The groups were well-matched with an average age of 67 years with 82% being

male. After a mean follow-up of approximately 3 years the primary outcome of death from cardiovascular causes was equivalent between groups (27% in the rhythm control and 25% in the rate control group). Secondary endpoints were death from any cause, hospitalizations for HF, quality of life, cost of therapy, and stroke. These were equivalent between groups however the proportion of patients who required hospitalization was higher in the rhythm control group as was the proportion of patients who required therapy for bradycardia. Importantly, ablation of AF was not performed as part of the rhythm control strategy and this will be discussed below.[61]

Rhythm control: Pharmacologic

Anti-arrhythmic drugs (AADs) have modest efficacy in the cure of AF. Class 1C AADs, specifically Flecainide and Propafenone have good efficacy in the prevention of paroxysmal AF in patients without significant heart disease. Unfortunately these drugs are contraindicated in patients with HF since they predispose to lethal ventricular arrhythmias in this population. Class III AADs such as Sotalol and Dofetilide have modest efficacy in the maintenance of long-term SR. Through their effect on QT interval prolongation they can cause torsades des pointes, a potentially fatal proarrhythmic side effect that is more likely in the presence of renal failure, electrolyte disturbances, and HF. They are relatively useful drugs in this scenario, however they must be used with caution. Sotalol has significant beta-blocking action, and therefore must be used skillfully in HF. Both drugs are contraindicated in the presence of anything more than mild LV hypertrophy.

Dronedarone is a new antiarrhythmic agent related to Amiodarone and has very modest efficacy in AF however it is contraindicated in HF of anything other than the mildest degree. Amiodarone is easily the most effective AAD for the treatment of AF with approximately 40% success rate in maintenance of SR.[62] It is safe in HF, CAD, and in patients with renal dysfunction; however, it is a potentially toxic drug, particularly with long-term use. Amiodarone can cause thyroid, pulmonary, hepatic, skin, eye, and nerve damage. Thus although it is a very useful drug, it has a limited risk-benefit profile for long-term use in AF. Anti-arrhythmic drugs in general have increased mortality in HF patients[63,64] and this combined with their limited efficacy mean that they provide a satisfactory solution to this clinical problem in a limited number of patients. A trial of anti-arrhythmic drugs is often combined with one or more attempts at DC cardioversion.

Rhythm control: Electrical cardioversion

Direct-current cardioversion (DCC) is a technique whereby pads attached to an external defibrillator are applied to the patients chest. The patient is placed under light anesthesia for a short time (5 minutes). One or more shocks, synchronized to the R wave of the cardiac cycle, are delivered with the intent of restoring sinus rhythm. If AF fails to respond or recurs, many physicians will try DCC at a separate session after the patient has been loaded on an AAD. Broadly speaking, ± 70% of patients undergoing DCC for AF are restored to SR, of these 50% will maintain SR giving an overall long-term success rate of long-term maintenance of SR 35% in all patients. These success rates are likely to be significantly lower in patients in HF.

Rhythm control: Ablation of Atrial Fibrillation

Ablation of AF which aims to cure the patient of AF, came into clinical use in the late 1990s and has seen an exponential rise in its use.[65,66] AF ablation is complex, carries small but significant risk of major complications, and is highly operator-dependant. Success rates for ablation of paroxysmal AF are higher (70-90%) than those with persistent and permanent AF (30-60%). Furthermore, at least 30-40% of patients with persistent AF require 2 or more procedures. Each AF ablation procedure is associated with a 5% risk of major complications including stroke, cardiac perforation, esophageal, phrenic nerve damage, and others.[67] For these reasons, few operators perform AF ablation in patients aged >75 years. Patients who are in HF are probably at higher risk of complications from this procedure and frequently have LA dilatation which significantly reduces the likelihood of success. In summary, patients with permanent AF, significant atrial dilatation, HF, and who are aged >75 years

are at high risk for complications form catheter-based AF ablation. This is the demographic of many patients with AF and HF for whom therefore AF ablation is precluded.

Nevertheless, ablation of AF in patients with HF has been shown to improve the clinical course and echocardiographic changes associated with HF and may be a vey reasonable alternative in relative younger patients. Hsu and colleagues studied 58 patients with AF, HF and an EF of <45% undergoing ablation of AF.[68] 50% of patients in both groups underwent 2 procedures and after one year of follow-up approximately 80% of patients in each group were in sinus rhythm. The group with HF had significant improvement in NYHA class, exercise time, quality of life and ejection fraction. Maintenance of sinus rhythm was the only predictor of improvement in these outcomes. Interestingly, even those patients in whom rate control was adequate had an improvement in these outcomes although the improvement was less marked than those with poor rate control. This is further evidence for the disruptive effects of irregularity and loss of active atrial contraction on cardiac function.

Rate control: Pharmacologic

Since many of the adverse manifestations that AF imposes on patients with HF arise as a result of the rapid ventricular rate, a 'rate control' strategy is often used in patients in permanent AF in whom curative measures are unlikely to succeed and/or are associated with too much risk. Pharmacologic agents including beta-blockers, calcium channel blockers, and digoxin, sometimes in combination, have only moderate efficacy in the rate control of AF. Patients with both HF and AF are particularly difficult to rate control, since as discussed, these patients have chronically raised sympathetic tone which increases AVN conduction. Furthermore, these rate controlling agents do not regularize the ventricular rhythm which itself contributes to the development of LV dysfunction and a reduced CO. Nevertheless if rate control is chosen as a strategy, initial attempts will invariably be pharmacologic. A beta-blocker/ digoxin combination is the ideal first choice not only because this combination has been shown to be most effective in rate control[69] but also because both of these medications (particularly beta-blockers) are of benefit in HF independent of the presence of AF.

Rate control: AV Node Ablation and Biventricular Pacing Device Implantation

In many cases of AF and HF in whom a rate control strategy is chosen (either initially or when a rhythm control strategy fails), pharmacologic AV nodal blockade is not effective enough to significantly reverse the downward clinical spiral. In such cases, AV node ablation followed by permanent pacing can be a highly effective option.

First performed in the 1908s, AV node ablation was in fact the first cardiac ablation ever performed, and initially employed DC energy as a modality.[70] By creating complete heart block, both the rapid ventricular rate and irregularity of the ventricular response are completely ameliorated. Permanent pacemaker implantation is necessary following the procedure. Randomized studies comparing this strategy to medical AV nodal blockade have confirmed improvements in palpitations, effort dyspnea, and exercise tolerance; however previously failed to consistently demonstrate an improvement in LV function.[65] This arose as a result of the deleterious effects of chronic right ventricular (RV) pacing which results in iatrogenic left bundle branch block and hence dysynchonous ventricular function. This issue has been addressed by the recently published PAVE study which compared RV pacing to biventricular pacing after AV node ablation and found that the latter resulted in improved LV ejection fraction, and 6-minute walk distance, particularly when the ejection fraction is less than 45%.[71,72]

Since conventional right ventricular (RV) permanent pacing can result in mechanical dysynchrony of ventricular function and therefore HF, pacing after AVN ablation for permanent AF in the setting of HF is achieved by BiV pacing which maintains ventricular synchrony.[71] By virtue of depressed ventricular function, most of these patients fulfill standard criteria for implantation of an implantable cardioverter-defibrillator (ICD) for the prevention of sudden cardiac death (SCD). Therefore the BiV PPM is combined with an ICD resulting in a BiV ICD which is the most common device implanted after AVN ablation for permanent AF in HF patients. This procedure is highly efficacious in a substantial number of subjects and has been shown to reduce HF hospitalizations, improve symptoms, and exercise

tolerance. In some, the improvement in ejection fraction (EF) is dramatic. The procedure is sometimes performed during 2 separate sessions (particularly if patients are frail) with BiV ICD implantation followed by AVN ablation one month later. The disadvantage of AVN ablation/BiV ICD implantation is that CHB is created, and the patient is dependant on the pacing device to a degree ('dependence' is not complete). Thus the procedure is generally reserved for patients aged over 70 years, however if circumstances are severe, and AF is incurable, AVN ablation and BiV ICD implantation is sometimes performed in younger patients too.

We have recently concluded a retrospective study in which we have compared the outcome after AVN ablation/BiV ICD implantation for HF and AF in patients with nonischemic versus ischemic cardiomyopathy. A total of 55 patients were included from a 4-year period. In this retrospective analysis, we showed a striking difference in outcome between the 2 groups. The outcome variables we studied were LVEF (pre- and post-procedure), hospitalizations for HF following the procedure, and the occurrence of ventricular arrhythmias following the procedure. In this study, patients with nonischemic had a significantly greater improvement in LVEF, less hospitalizations for HF, and less ventricular arrhythmia following the procedure than those with ischemic cardiomyopathy. The results of this study likely reflect the higher burden of confluent scar in patients with ischemic cardiomyopathy. This scar renders tissue nonviable. Furthermore our results suggest that TIC may play a greater role in patients with nonischemic cardiomyopathy, AF and HF than in ischemic patients (Figures 9 and 10).[73]

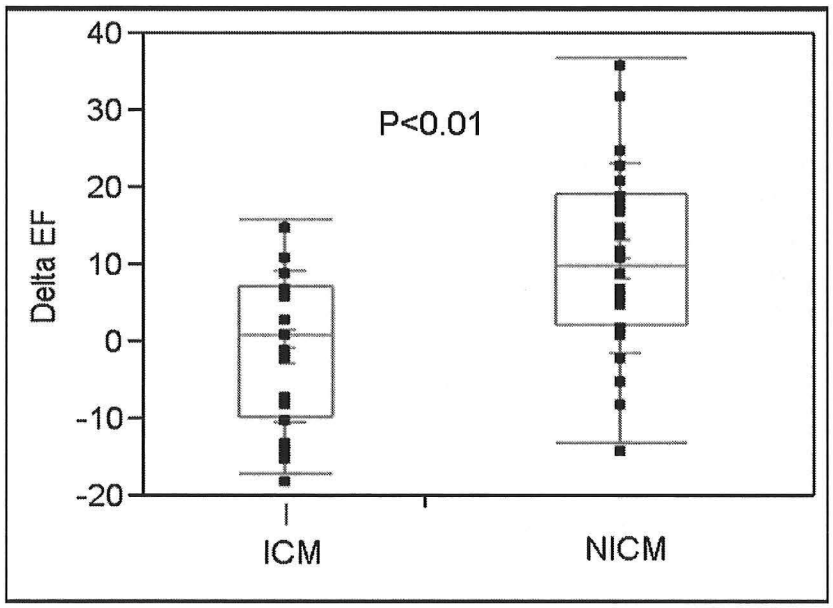

Figure 9: Comparison of ΔEF pre- and (>6 months) post-AVN ablation/BiV ICD implantation between patients with ICM and NICM. The red boxes represent one standard deviation the lines through the boxes represent the median ΔEF. Patients with NICM had a significantly greater improvement in EF than patients with ICM.

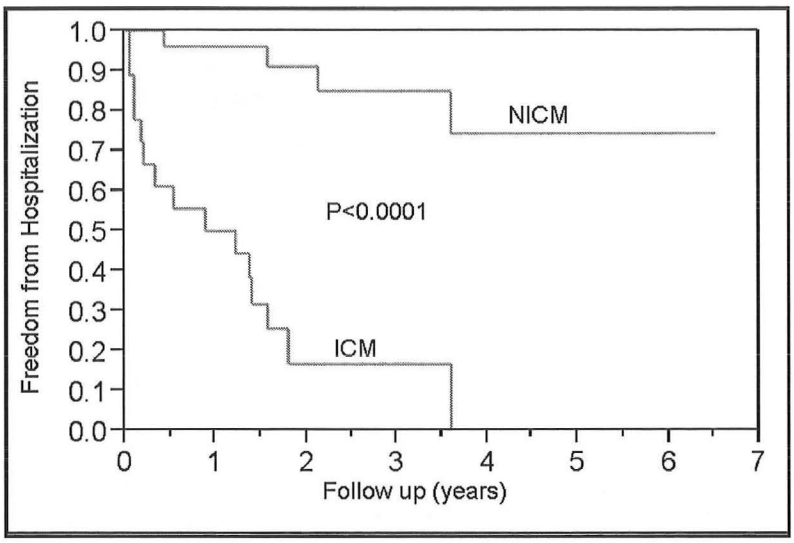

Figure 10: Comparison of hospitalizations between patients with ICM and NICM for worsening HF following AVN ablation/BiV ICD implantation. Patients with NICM had significantly less hospitalizations for HF than ICM following the procedure.

The recently reported PABA CHF study compared a strategy of ablation of AF versus AV node ablation and BiV pacing in patients with drug-resistant AF, HF and an EF of <40%.[74] The study found that those undergoing AF ablation farted better in terms of quality-of-life, 6-minute walk test, and improvement of EF. Approximately 70% of the patients in the ablation group were in sinus rhythm at 6 months. Before the results of this study can be generalized, a few points should be borne in mind. First, the mean age of patients in this study was 60 years. This is younger than the average age of patients with AF and HF in many practices. The complications of AF ablation are more pronounce with advanced age. Furthermore, follow-up was short in this study. It is known that recurrence of AF following ablation is high and continues to increase in incidence well beyond 5 years following the procedure.[75]

REVERSAL OF LONG-STANDING AF AFTER AV NODE ABLATION AND BIVENTRICULAR PACING

We have recently observed a cohort of patients undergoing AV node ablation and BiV pacing for what was previously completely irreversible AF who either spontaneously or after a shock (as part of ICD testing or for VT) who regain and maintain sinus rhythm.[51] This is of considerable interest when considering the pathophysiology of this syndrome, and also can result in clinical benefit since these patients now not only have amelioration of rapid ventricular rate and restoration of a regular rhythm, but active atrial contraction and its contribution to cardiac output is restored. We are currently performing a prospective study in this area (Figure 11).

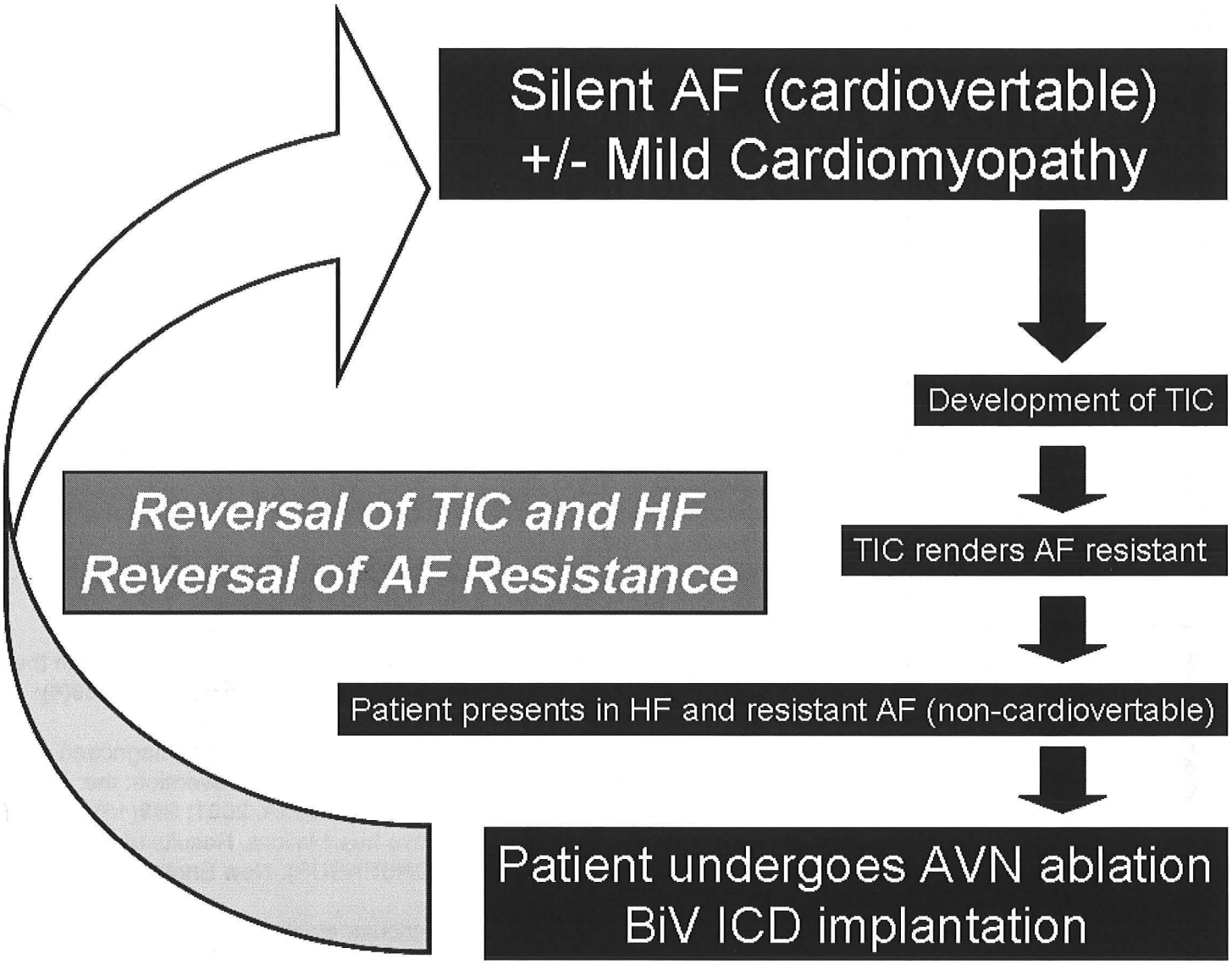

Figure 11: Proposed potential mechanism for reversal of the pathophysiology of AF and HF progression by AVN ablation/BiV ICD implantation.

Conclusions

Atrial fibrillation and heart failure are major public health concerns. They are both significantly increasing in incidence and share many common risk factors. Furthermore they are both risk factors for each others' development and maintenance, worsening each others outcome, and resulting in a clinical syndrome of highly disordered cardiac function with a severe impact on quality of life and a high hospitalization rate and mortality. Aggressive treatment of HF can somewhat improve AF outcome, and treatment of AF can significantly improve HF outcome. Advances in the ablation of AF are likely to positively impact this syndrome for many patients, however the average age of patients who are presenting with this syndrome is likely increasing and AF ablation may not be suitable for many. In such cases, and where AF ablation is not successful, AV node ablation and BiV pacing offers a highly effective therapeutic strategy for many patients.

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