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W. Arthur, G. C. Kaye

Cardiac arrhythmias are a frequent finding in those with congestive heart failure regardless of aetiology. Atrial fibrillation is common in the natural history of heart failure and is associated with considerable morbidity. The likelihood of potentially lethal ventricular tachyarrhythmias is highest in those with a substrate for arrhythmia propagation and potential trigger factors for initiation. Those with poor left ventricular function secondary to myocardial ischaemia are particularly at risk. The severity of heart failure, both in terms of functional capacity and ejection fraction, has been uniformly found to be a strong independent predictor of mortality. Clinical trials show that pharmacological suppression of arrhythmias in heart failure is associated with disappointing long term results that highlight the potential of proarrhythmia. Non-pharmacological management strategies improve morbidity and mortality. Implantable cardioverter defibrillators have a pivotal role in the treatment of ventricular tachycardia and ventricular fibrillation in this setting. *J Clin Basic Cardiol* 2001; 4: 115–122.

Key words: heart failure, arrhythmias, proarrhythmia, mortality, implantable cardioverter defibrillator

The diagnosis of congestive heart failure (CHF) infers a poor prognosis. Atrial fibrillation (AF) and ventricular tachyarrhythmias are the most important rhythm disturbances found in ventricular dysfunction both in terms of the number of patients affected and the associated mortality and morbidity. The purposes of this article are to describe briefly the epidemiology of these important arrhythmias, the associated prognosis, and to review the detrimental and successful modes of therapy administered to those with compromised ventricular function. With the exception of AF little data exists between the association of supraventricular tachycardias and heart failure. The mechanism of atrioventricular and atrioventricular nodal re-entrant tachycardias makes their prevalence in heart failure unlikely to be greater than that found in the general population. Atrial flutter and atrial tachycardia can adversely influence ventricular function therefore specific therapy to treat these arrhythmias is included.

Evidence for the proposed treatment of arrhythmias in heart failure is based on studies that have demonstrated both the disadvantage and benefit of varying pharmacological agents. In some cases non-pharmacological therapy, developed throughout the 1990's, offers improved mortality and morbidity in those with heart failure and associated arrhythmias.

Epidemiology

Heart failure and ventricular dysfunction

From echocardiographic studies ventricular dysfunction is apparent in around 4–6 % of those over the age of 65. The prevalence of those with symptomatic heart failure in the same age group is believed to be 2–5 % [1]. The increasing proportion of the population over the age of 65 coupled with the improved treatment of coronary artery disease and CHF is likely to cause an increase in the prevalence and the absolute number affected. The number of patients with heart failure complicated by arrhythmias is similarly expected to rise and so attention to this problem is essential.

Atrial fibrillation

Atrial fibrillation is arguably the most important arrhythmia with regards to patient morbidity. The prevalence of AF in patients referred for management of heart failure is around 15–20 % [2]. The Framingham study showed that heart failure is the most frequent precursor of AF. The relative risk of

developing AF with pre-existing heart failure was 4.5 and 5.9 in men and women, respectively (Table 1) [3]. The risk factors for AF are the same as for ischaemic heart disease and so it is not surprising to find that those with pre-existing AF are more likely to develop CHF than matched controls [4].

Ventricular tachyarrhythmias

Ambulatory electrocardiograph recordings in patients who have died suddenly have revealed that ventricular tachycardia (VT) or ventricular fibrillation (VF) are the most common terminal events [5]. Complex ventricular arrhythmias are recorded in as many as 80 % of patients with heart failure, with nonsustained ventricular tachycardia (NSVT) occurring in 40 %. Almost all patients with CHF are found to have premature ventricular complexes on 24 hour Holter recordings [6, 7]. The majority of these arrhythmias are asymptomatic.

The Prognostic Importance of Arrhythmias in Those With Heart Failure

Despite advances in the treatment of CHF the mortality rate continues to be high. Close to 50 % of deaths in heart failure are thought to occur suddenly [8]. The principal cause of sudden death in CHF is not clear but the presence of cardiac arrhythmias in those with heart failure suggests a poor prognosis.

Atrial fibrillation

The prognostic significance of AF in heart failure remains controversial with conflicting results from published studies. Data collated retrospectively from 419 patients in the Studies

Table 1. Risk of developing atrial fibrillation associated with cardiovascular variables: 38-year follow-up of Framingham study subjects. Adapted with permission from JAMA [3]

Cardiovascular variable	Risk factor-adjusted Odds Ratio	
	Men	Women
ECG – LVH	1.4	1.3
Hypertension	1.5 [†]	1.4 [§]
Myocardial infarction	1.4 [§]	1.2
Heart failure	4.5[†]	5.9[†]
Valve disease	1.8 [†]	3.4 [†]

[§]P ≤ 0.05; [†]P ≤ 0.01; [‡]P ≤ 0.001

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of Left Ventricular Dysfunction (SOLVD) trials found the presence of AF in those with left ventricular systolic dysfunction (symptomatic or asymptomatic) is associated with an increased risk of all-cause mortality, primarily associated with pump failure [9]. No significant association between AF and arrhythmic death was found. These results differ from previous studies that have examined the significance of AF in heart failure with respect to mortality. Retrospective data from 206 patients with AF from the Vasodilator-Heart Failure (V-HeFT) I and II trials revealed that in mild to moderate heart failure AF was not associated with all cause mortality or sudden death [2]. Middlekauff et al. demonstrated an increase in mortality in those with AF due to an increased risk of sudden unexpected death [10]. The patients in this prospective study comprised of a greater proportion of patients with severe (New York Heart Association (NYHA) class IV) heart failure compared to the SOLVD trials. In addition a high proportion of patients in the analysis from Middlekauff et al. were taking Vaughan Williams class I antiarrhythmic drugs which in themselves may have increased sudden death mortality by proarrhythmic mechanisms. More recently a prospective study by Mahoney et al. found that in patients with severe heart failure referred for cardiac transplantation the presence of AF did not adversely influence event free survival [11].

The unifying message from studies of patient survival is that the worse the left ventricular dysfunction, the poorer the prognosis. Both the symptomatic status of the patient as described by the NYHA class and the left ventricular ejection fraction (LVEF) are well recognised as important predictors of patient survival [12]. The results of the survival studies of AF may appear conflicting and the matter is further complicated if the relative contributions of uncontrolled ventricular rate, variations in ventricular cycle length, and the absence of atrioventricular synchrony to the loss of left ventricular function are taken into consideration.

Perhaps of greater significance is the irrefutable evidence that AF is a major independent risk factor for stroke, producing a 3- to 5-fold increased risk. The coexistence of AF and cardiac failure imposes a further 2-fold increase in the risk of a cerebrovascular event [13].

Ventricular tachyarrhythmias

The prognostic significance of ventricular arrhythmias in the patient with depressed left ventricular function has been examined in a number of studies with conflicting conclusions. Studies have examined two distinct patient groups with differing substrates capable of supporting ventricular arrhythmias; those with left ventricular dysfunction following myocardial infarction and those with chronic CHF.

Following myocardial infarction the presence and frequency of asymptomatic ventricular ectopy detected by pre-discharge Holter monitoring predicts mortality [14]. Bigger et al. found that a reduced LVEF and frequent ventricular ectopic beats were both independent risk factors. A low LVEF has a much stronger effect on mortality than ventricular ectopy. The probability of dying in patients with LVEF < 30 % and frequent premature ventricular beats was found to be almost seven times greater than in patients without any risk factors in the two years following the index event [15]. Data from the GISSI-2 study, examining 8676 post myocardial infarction patients, showed that ventricular arrhythmias were more frequent when signs or symptoms of left ventricular damage were present. The presence of frequent premature ventricular beats was found to be an independent risk factor for total mortality and sudden death at 6 months [16].

The significance of NSVT following myocardial infarction is controversial. The GISSI-2 data suggests that NSVT is

not an independent risk factor of mortality despite being associated with a higher mortality risk in the univariate analysis [16]. Bigger et al., on the other hand, found that NSVT had a strong and statistically significant association with all-cause and arrhythmic mortality independent of other risk variables that were associated with ventricular tachycardia. Adjusted for other risk indicators, NSVT nearly doubled the risk of dying during an average follow-up of 31 months. Patients with NSVT were more likely to have an ejection fraction < 30 % and signs of left ventricular failure [17]. In this study patients with longer runs of NSVT tended to have a higher mortality rate.

In studies of patients with chronic CHF attributable to ischaemic heart disease and idiopathic dilated cardiomyopathy frequent ventricular extrasystoles were found to be related to mortality [18, 19]. Whether or not NSVT in those with chronic CHF is an independent risk of mortality above and beyond the associated ventricular dysfunction has been the subject of many studies. Analysis by Singh et al. of data from 674 patients in CHF-STAT found that, after adjusting for other variables, especially LVEF, NSVT could not independently predict all cause mortality or sudden death. This was true regardless of the rate or length of the NSVT runs; only LVEF could predict sudden cardiac death [20]. The GESICA study, which randomised 516 patients, came to the opposite conclusion that NSVT is an independent marker of increased mortality and sudden death in those with CHF [21]. Szabo et al. examined 211 patients with left ventricular dysfunction and found that low LVEF and presence of VT after adjustment had statistically prognostic value in predicting sudden death [22]. More recently analysis of data from the PROMISE study, including 1080 patients with NYHA class III/IV symptoms and a LVEF < 35 %, showed that ambulatory asymptomatic ventricular arrhythmias do not specifically predict an increased risk of sudden death despite being independent predictors of overall mortality. Of the several measures of ventricular ectopy that were predictors of overall mortality, the frequency of NSVT was the most powerful [23].

The discrepancies between studies may be related to their different sample sizes, classifications of death and variations in the severity of ventricular dysfunction. Overall, the data suggests that following myocardial infarction frequent premature ventricular beats are predictive of mortality and more likely to occur in the presence of ventricular dysfunction. Given the conflicting information, no definite conclusion can be reached as to the true prognostic relevance of NSVT in post MI patients and those with chronic CHF. The larger studies would seem to suggest that in patients with heart failure NSVT is a marker for a severely compromised ventricle that in turn is primarily responsible for haemodynamic and clinical instability.

Ambulatory ECG evidence exists that implicate VF or VT at the time of sudden death [5]. In patients with terminal VF or VT the mechanism by which the devastating arrhythmia occurs may not be primarily electrical. Controversy surrounding this concept exists and the role of vascular events in the mode of sudden cardiac death in those with CHF awaits further investigation [24].

Prognostic Importance of Heart Failure in Those With Ventricular Arrhythmias

The severity of heart failure in those having experienced a ventricular tachyarrhythmia is the strongest independent predictor of mortality regardless of the underlying aetiology [25, 26]. Patients with idiopathic VT with normal right and left ventricular function have a benign arrhythmia with a

good prognosis. The development of arrhythmogenic right ventricular cardiomyopathy in those previously thought to have idiopathic right ventricular outflow tract (RVOT) VT is more serious, having a yearly mortality rate of 2 % per year [27]. In patients who experience symptomatic ventricular tachyarrhythmia > 48 hrs after a myocardial infarction, clinical variables predictive of mortality can be identified. Willems et al. found that the presence of compromised inotropic function, expressed by the dyspnoea functional class, is the most important predictor of mortality. The presence of multiple previous myocardial infarctions (also a measure of pump function) and cardiac arrest during the index arrhythmia are also important independent predictors of total mortality [28].

Predictors of Arrhythmia in Those With Ventricular Dysfunction and Heart Failure

Atrial fibrillation

Subjects in the Framingham Heart Study were routinely evaluated with M-mode echocardiography; from these data echocardiographic predictors of AF could be defined. The population at risk comprised of 1924 subjects, ranging in age from 59 to 90 years. Persons who developed AF had larger left atrial and left ventricular end-diastolic and end-systolic dimensions. Left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular fractional shortening were predictive of risk for non-rheumatic AF [29].

Ventricular tachyarrhythmias

Left ventricular dysfunction is commonly manifest by symptomatic heart failure and arrhythmia. Analysis of data from the SOLVD trial has demonstrated that these clinical features are sometimes absent despite severely compromised ventricular systolic function. Patients included in the SOLVD trial all had ejection fractions < 35 %; some had overt heart failure whilst others were symptom free [30]. Evidence of impaired diastolic function, along with larger and more spherical ventricles were particularly common in those with overt heart failure. Examination of symptomatic and asymptomatic subjects revealed that ventricular premature beats and episodes of NSVT were found more often in those with greater left ventricular end-diastolic volumes. There was no correlation with indexes of LV systolic function such as wall stress, ejection fraction, or regional wall motion index [31]. Alternative studies, focusing on systolic function, have shown that the propensity for ventricular ectopy appears to correlate with a reduced ejection fraction [15, 32]. The SOLVD trials would suggest that once systolic function has deteriorated to the point of an ejection fraction of < 35 % the primary correlate of ventricular arrhythmia is LV size.

The ability to induce sustained VT at electrophysiological study can be used in those with heart failure to stratify those at greatest risk of sudden cardiac death. Those with ventricular dysfunction, coronary artery disease and a history of NSVT who are not inducible do significantly better than patients who are inducible [33].

Proarrhythmia

Proarrhythmia is defined as the provocation of a new arrhythmia or the aggravation of a pre-existing arrhythmia that occurs during therapy with a drug at doses or plasma concentrations below that considered to be toxic [34]. Practical criteria for determining the presence of proarrhythmia has been suggested by Friedman and Stevenson (Table 2). Proarrhythmia may become evident because of the interplay between the electrophysiological effects of a drug and extrane-

ous factors. Such factors may occur in those with no evidence of structural heart disease but are particularly common in those with CHF; this may be as a consequence of the use of other drugs used to treat CHF or simply due to the disease state. Heart failure is frequently associated with reduced renal perfusion, be it due to intrinsic pump failure, drug induced hypovolaemia or neurohormonal changes. The resultant alteration of antiarrhythmic drug metabolism and excretion may unexpectedly provoke arrhythmia. A further example is illustrated in the Cardiac Arrhythmia Suppression Trial where ongoing myocardial ischaemia was believed to be responsible for the excess mortality found in the active treatment arm [35, 36].

Torsade de pointes

One of the clearest examples of proarrhythmia due to an antiarrhythmic drug is that of torsade de pointes. This arrhythmia is closely associated with the presence of a prolonged QT interval. Virtually all antiarrhythmic drugs have been implicated as a cause of this arrhythmia although the evidence is strongest with class IA or class III drugs. Factors favouring QT prolongation include hypokalaemia and hypomagnesaemia, both of which are more common in those with CHF [37].

Ventricular fibrillation and ventricular tachycardia

Ventricular fibrillation may occur as a manifestation of proarrhythmia in the absence of QT prolongation [38]. Class IA and IC drugs have been studied most intensely although all antiarrhythmic agents have been implicated. The most important factor increasing the risk of VF and VT is the presence of left ventricular dysfunction [38, 39]. The risk of changing NSVT to sustained VT or precipitating new, unheralded sustained VT is greatest with drugs such as class IC antiarrhythmics that slow conduction velocity. Simplistically, if a drug slows conduction velocity to a greater extent than prolonging the refractory period of a re-entrant circuit, propagation of an arrhythmia is likely. Patients treated for supraventricular arrhythmias with well preserved ventricular function only rarely suffer this complication [40].

Proarrhythmia in the context of treating atrial fibrillation and flutter

The use of class IA and IC antiarrhythmics to suppress ventricular arrhythmias in those with symptomatic ventricular dysfunction has become less popular. The treatment of paroxysmal atrial fibrillation and flutter continues to include the use of these drugs. In those with AF and NYHA class I/II CHF, the incidence of serious proarrhythmia at the time of introduction of class IC drugs is around 10 % [41]. In those at risk drug administration should occur in the hospital setting with ECG monitoring facilities. In patients with overt heart failure with paroxysmal atrial fibrillation class IA and IC

Table 2. Suggested criteria for determining proarrhythmia. Reprinted from Am J Cardiol [34] Copyright (1998) with permission from Excerpta Medica Inc.

- New appearance of sustained arrhythmia
 - Torsade de pointes, QT interval prolongation
 - Polymorphic ventricular tachycardia, normal QT interval
 - Ventricular fibrillation
 - Sustained monomorphic ventricular tachycardia, intermittent
 - Sustained monomorphic ventricular tachycardia, incessant
 - Atrial flutter with 1 : 1 conduction
- Conversion of nonsustained to sustained arrhythmia
- Acceleration of tachycardia rate
- New appearance of bradyarrhythmia conduction defect

drugs have been shown to increase the sudden death rate more than 3-fold [42]. Symptomatic ventricular dysfunction may not be apparent in patients with AF. In the SOLVD study 40 % of patients with AF were in the asymptomatic prevention arm of the study [9]. This factor, coupled with the knowledge that ventricular dysfunction detected by transthoracic echocardiography independently predicts the risk of stroke in those with persistent AF [43], should encourage the routine use of this investigation in all patients with AF.

The proarrhythmic effect of drugs used to treat atrial fibrillation and flutter in those with ventricular dysfunction may be directed primarily towards the ventricle producing the ventricular arrhythmias described previously. Alternatively, drugs that slow atrial conduction velocity and reduce the atrial rate may theoretically accelerate AV nodal conduction and produce a rapid 1:1 ventricular response [44]. Drugs with anticholinergic properties may also result in 1:1 AV conduction. The combination of ventricular dysfunction and such a fast ventricular rate may have lethal consequences. Digoxin is frequently prescribed to those with AF with evidence of CHF. Although not strictly a proarrhythmic effect, digoxin overdose may lead to a variety of arrhythmias. Digoxin induced VT occurs due to triggered activity due to delayed after-depolarisation [45], an arrhythmic mechanism which may be promoted by myocardial stretch.

Treatment of Arrhythmias in Patients With Heart Failure

Atrial fibrillation and atrial flutter

Atrial fibrillation is thought to promote its own propagation and bring about new or additional ventricular dysfunction. Chronic atrial stretch and dilatation is probably the most important factor, this slows conduction velocity and increases the dispersion of refractoriness facilitating re-entrant circuits [46]. Multiple wavelets with short wavelengths are thought to be required for atrial fibrillation to be sustained. Increased atrial size permits the coexistence of multiple re-entrant circuits with differing wavelengths [47]. Once AF is induced, 'electrical remodelling' characterised by shortening of refractoriness occurs, further stabilising the dysrhythmia [48]. The loss of atrial transport compromises cardiac output, further reducing renal perfusion and exacerbating the neurohormonal imbalance leading to sodium and water retention. Increased sympathetic drive promotes atrioventricular conduction so reducing ventricular filling time and stroke volume (Figure 1). The vicious circle that ensues is an attractive explanation for the concept of "tachycardiomyopathy". This phenomenon is characterised by heart failure in the absence of structural heart disease that results from chronic AF and an inadequately controlled ventricular rate [49].

Type 1 or 'common' atrial flutter results from a single re-entrant circuit in the right atrium [50]. The factors which self propagate AF are common to atrial flutter and progression from flutter to fibrillation often occurs.

Pharmacological therapy

The complex reciprocal relationship between AF and heart failure creates a circle that has to be broken for optimal management to occur. Angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with heart failure [51]. The rationale behind using ACE inhibitors in patients with heart failure holds true for those with coexisting AF. Oral anti-coagulation, in the absence of contraindications, should be used routinely in those with heart failure and AF to reduce the high rate of thromboembolic complications [52].

Control of ventricular rate is of paramount importance in atrial fibrillation and flutter to avoid further progression of left ventricular dysfunction. Impaired function may be found at rates as low as 100 beats/min [53]. Digoxin may control heart rate at rest but is ineffective in controlling exercise heart rate driven by activation of the sympathetic nervous system. The mortality benefits found using beta-blockers in heart failure make this mode of ventricular rate control in atrial fibrillation and atrial flutter more attractive and capable of controlling inordinate exercise heart rates.

Non-pharmacological therapy

Cardioversion is the best option in terms of restoring physiological rate control. Left ventricular systolic function may improve dramatically after restoration of sinus rhythm [53, 54]. Cardioversion should be performed within 48 hours of arrhythmia onset or, as is more frequently the case, after adequate anticoagulation has been adhered to for 6 to 8 weeks. Early cardioversion is supported by the consistent finding that the duration of AF is a prime determinant of the likelihood of maintenance of sinus rhythm after cardioversion: the longer the duration of AF the higher the risk of relapse [55]. In the presence of left ventricular dysfunction amiodarone appears the most effective therapy for maintaining sinus rhythm post-cardioversion [56]. Unfortunately late recurrence of AF following restoration of sinus rhythm is a common event in those with heart failure [57]. The options available in this scenario are essentially 2-fold; accept AF with a tightly controlled ventricular rate or attempt repeat cardioversions. The results of randomised studies comparing these two treatment strategies are awaited [58, 59].

Many patients with heart failure and AF may endure multiple, unsuccessful cardioversions or experience ventricular rates that are refractory to pharmacological control. This group

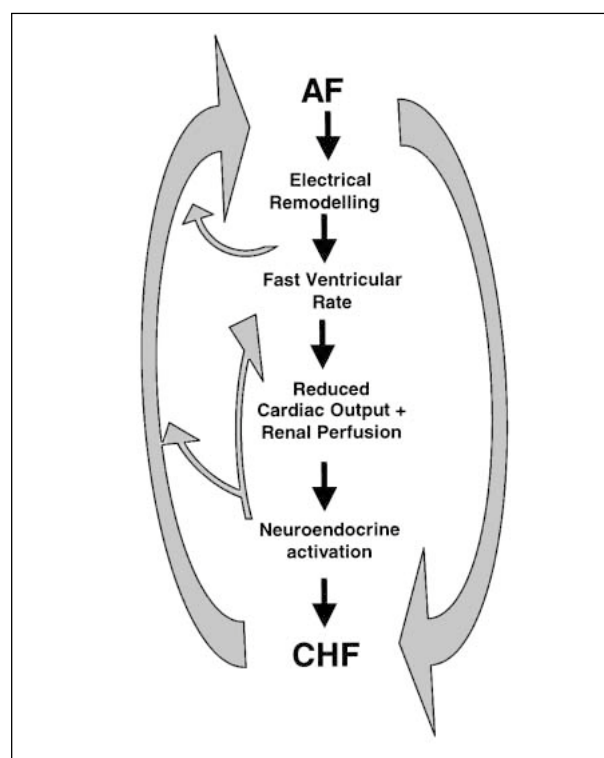


Figure 1. The self-propagating interaction between atrial fibrillation and congestive heart failure. AF = atrial fibrillation; CHF = congestive heart failure

of patients is at greatest risk of further deterioration of ventricular function that may progress to severe congestive heart failure. Atrioventricular nodal ablation and pacemaker implantation is an alternative form of therapy that has been shown to improve ventricular function and quality of life in patients with AF and coexistent ventricular dysfunction [60]. A meta-analysis of studies examining the outcome of 1181 patients confirmed that ablation and pacing therapy improved clinical outcomes and demonstrated low one year mortality rates comparable with medical therapy [61]. In patients with chronic AF, a VVIR is inserted. For those with severely symptomatic episodes of paroxysmal atrial fibrillation, DDDR mode-switching devices are more appropriate. The deleterious haemodynamic effect of right ventricular apical pacing is presumably outweighed by ventricular rate control that breaks the vicious circle of AF. In a study by Mera et al. right ventricular septal pacing was found to improve LVEF compared to right ventricular apical pacing in patients with left ventricular dysfunction who underwent His-bundle ablation for chronic AF [62]. Left ventricular free wall or multisite pacing may improve haemodynamic function further, particularly in those with evidence of intraventricular conduction delay [63].

The single circuit re-entrant mechanism of atrial flutter makes this arrhythmia amenable to catheter ablation with a high success rate associated with few complications [50, 64]. This is in contrast to ablation of chronic atrial fibrillation which is arduous and has a relatively low success rate [65]. Atrial flutter and other atrial tachycardias with focal origins may be amenable to ablation therefore resolving or preventing progression to cardiomyopathy [66, 67].

Ventricular arrhythmias

The exact mechanism of ventricular arrhythmias in heart failure is difficult to clarify in individual cases. Attempted control and suppression of arrhythmias with antiarrhythmic medication is impeded by the potential risk of proarrhythmia and sudden death. Strategies to modulate the factors promoting arrhythmias in heart failure might be more effective than primary antiarrhythmic drug therapy that focuses on distinct arrhythmia mechanisms.

Pharmacological therapy

In patients treated with ACE inhibitors following myocardial infarction the risk of sudden cardiac death is reduced as well as overall mortality [68]. By slowing down the progression of heart failure, mortality due to sudden cardiac death is reduced [69]. ACE inhibitors reduce ventricular stretch and preserve left ventricular function [70]. They also lower plasma norepinephrine levels [71]. The extent to which modification of these factors might contribute to reductions in sudden cardiac death was demonstrated in the V-HeFT II study. The reduced risk of sudden death in this study was accompanied by a reduction in the prevalence of VT [72].

Beta-blockers reduce the mortality rate in patients with chronic heart failure [73–75]. Attempts to extricate the anti-ischaemic and antiarrhythmic mechanisms of how beta-blockers produce this effect in CHF are almost unattainable. It may be argued that the anti-ischaemic efficacy of beta-blockade alone precludes the occurrence of ischaemia induced arrhythmias and that no other significant mechanisms exist. Whatever the mechanism the treatment effects of beta-blockers have been shown to be independent of the cause of heart failure [74].

Apart from beta-blockers, the class III antiarrhythmic drug, amiodarone is the only pharmacological antiarrhythmic agent that has been shown to reduce all cause mortality in patients

with CHF in a randomised controlled trial [76]. The largest trial to examine the effects of amiodarone in patients with ventricular dysfunction following myocardial infarction, found a reduction from arrhythmic death in those treated with amiodarone, but no overall survival benefit in this group [77]. A meta-analysis examining 13 randomised trials investigating the prophylactic use of amiodarone following myocardial infarction and in congestive heart failure demonstrated an overall reduction of 13 % in total mortality. Interestingly, the survival benefit from the GESICA study was in the subset of patients who had a fast baseline heart rate, within this group both sudden death and progressive heart failure death were reduced [78]. Amiodarone's inherent beta-blocker properties may be the reason for this, and supplementary beta-blockers may confer additional benefit to the efficacy of amiodarone [79]. Long term maintenance with effective amiodarone therapy is problematic and in many cases patient compliance is poor or withdrawal of therapy is indicated. Following administration of amiodarone the most serious adverse effect, that of pulmonary toxicity, may occur in up to 7 % at one year [80].

Patients successfully resuscitated from cardiac arrest who have a low ejection fraction (< 40 %) continue to exhibit high arrhythmia recurrence and sudden death rates despite empiric therapy with amiodarone [81]. This finding, together with the questionable efficacy of antiarrhythmic agents in the primary prevention of ventricular arrhythmias in CHF, has promoted the development of alternative therapies.

Non-pharmacological therapy

The implantable cardioverter defibrillator (ICD) has been shown to reduce overall mortality in patients at high risk of ventricular arrhythmias [33, 82]. In the MADIT study all patients had a LVEF < 0.35; a history of prior myocardial infarction; NSVT and nonsuppressible ventricular tachyarrhythmia on electrophysiological testing. Therapy with ICD was found to be superior to conventional medical therapy, including amiodarone [82]. The MUSTT study, although not a specific ICD trial for primary prevention of sudden cardiac death, revealed that only with ICD back-up can a significant reduction in arrhythmic death be achieved. In MUSTT the benefit of electrophysiologically guided therapy against no therapy, in high risk coronary artery disease with a LVEF < 0.4 and NSVT, was assessed (Figure 2). Electrophysiologically guided therapy with ICDs, but not with antiarrhythmic drugs, reduced the risk of sudden death and total mortality (Figure 3) [33]. About 20 % of patients awaiting heart transplantation because of severe left ventricular dysfunction die whilst waiting for a suitable donor organ. ICD therapy in these patients has been demonstrated to reduce sudden death rates [83]. The overall mortality in this population however is not influenced by ICD therapy suggesting that those with very severe ventricular function will die of heart failure regardless of effective arrhythmia treatment. Recent data, in small patient numbers, suggest that biventricular pacing may have the potential to improve the functional status of those with severe heart failure [84]. A biventricular pacemaker with defibrillation capabilities may prove ideal for patients with advanced CHF.

In patients who have been successfully resuscitated following a cardiac arrest, treatment with an ICD reduces sudden death and overall mortality in comparison to antiarrhythmic therapy [85, 86]. Over 55 % of the patients included in the AVID study had a history of congestive heart failure and 10 % of the total population had idiopathic dilated cardiomyopathy. Those with idiopathic dilated cardiomyopathy showed survival benefits with ICD therapy rather than empiric amiodarone therapy similar to the entire study cohort [86].

Success in radiofrequency catheter ablation (RFCA) of the Bundle of His, accessory bypass tracts and AV nodal slow pathways has encouraged attempts to ablate the sources of recurrent monomorphic VT. To be amenable to RFCA, the clinically occurring VT has to be reproducibly inducible, well

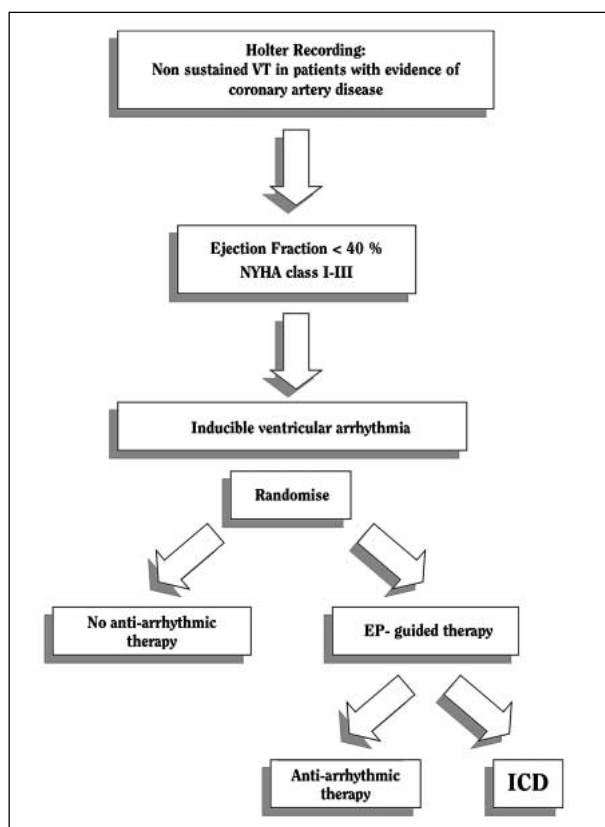


Figure 2. Schematic representation of the Multicenter Unsustained Tachycardia Trial (MUSTT)

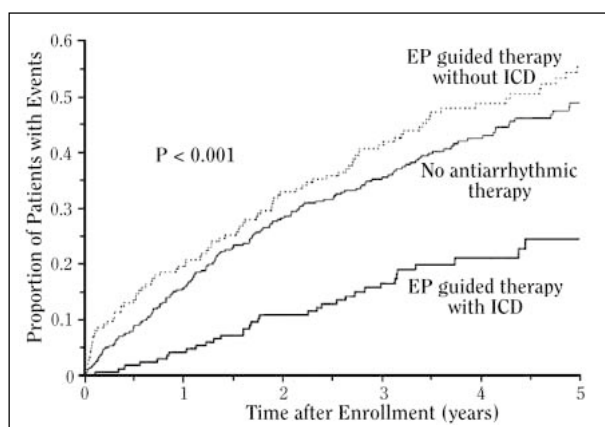


Figure 3. Kaplan-Meier estimates of the rates of overall mortality in the MUSTT study according to whether patients received treatment with an implantable cardioverter defibrillator (ICD). The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically (EP) guided therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy. Reproduced with permission from NEJM [33]. Copyright © 1999 Massachusetts Medical Society. All rights reserved.

tolerated, and should be morphologically distinct. Because of the limited area of necrosis induced by radiofrequency energy, ablation of closely defined areas of electrical conduction delivers the most rewards. Catheter ablation is very effective in macro re-entrant VTs involving the bundle branches [87]. Ablation of the right bundle branch by RFCA in those with the predominant left bundle branch block VT morphology effectively eliminates recurrent tachycardia. Dilated cardiomyopathy is present in over 90 % of those with bundle branch re-entry VT; follow up of those successfully ablated demonstrates that CHF is a common cause of death in this population [87, 88]. In non bundle branch block VT, found in dilated cardiomyopathy, RFCA is more complex and less successful [89]. Increasing the therapeutic impact of RFCA in VT requires improving its results in patients having a post MI scar as an arrhythmogenic substrate. Unfortunately in those with significant LV dysfunction VT is frequently poorly tolerated and may not be reproducibly induced. In addition reentrant circuits based on epicardial or deep intramural substrates and wide intra scar pathways requiring successive RF applications reduces the success rate of RFCA. Successful ablation of the clinical VT may unveil VTs of differing morphology that may be clinically significant. Patients with benign RVOT ventricular tachycardia associated with good ventricular function have excellent curative results from RFCA [90]. In those with cardiomyopathy associated non-bundle branch block VT or post-MI VT, catheter ablation is more an adjunctive than a curative therapy [91].

Antiarrhythmic drugs, RFCA and implantable devices in the control of arrhythmias cannot be considered in isolation. Whilst trial results demonstrate the superiority of ICD therapy over and above that of antiarrhythmic drugs, combination therapy is frequently used and may improve quality of life by reducing arrhythmia recurrence and the need for shock therapy.

Conclusion

Subclinical left ventricular dysfunction and CHF are common conditions that are associated with increased levels of mortality. The progression of ventricular dysfunction and dilatation parallels that of the tendency for arrhythmia; conversely the most important determinant of arrhythmia mortality is the degree and nature of ventricular dysfunction.

Treatment of the factors predisposing to arrhythmias should be instituted early in the course of the natural history of heart failure. The older strategies designed to suppress arrhythmias have delivered disappointing and often disastrous proarrhythmic results. The recognition of proarrhythmia has discouraged the use of class I drugs in heart failure and encouraged interventions designed to alter the loading conditions of the myocardium and the neurohormonal responses found with the failing heart.

Atrial fibrillation requires special attention in those with evidence of ventricular dysfunction. It is a common problem associated with much suffering. Much of the morbidity in those with atrial fibrillation is avoidable if patients are treated early, and with either rate limiting, or rhythm modulating therapy. The results of large-scale trials should help to decide which are the optimum treatment modalities.

Large randomised trials have provided the evidence demonstrating the efficacy of non-pharmacological treatment of arrhythmias associated with heart failure. Catheter ablation of the AV junction in patients with refractory, poorly tolerated AF is now a routinely performed option. The improvements in sudden death and overall mortality found using ICD therapy, both in primary and secondary prevention,

should be improved upon with the introduction of multisite pacing. Patients with the most severe heart failure may benefit the most from this development. Future studies may demonstrate an optimal combination of device therapy and pharmacological agents to reduce mortality and improve morbidity.

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