Sudden cardiac death (SCD) accounts for approximately one-third of all deaths in patients with heart failure. It is primarily caused by ventricular tachycardia (VT) and/or ventricular fibrillation (VF): an analysis of 157 documented cases of SCD showed that 83% were caused by VT progressing to VF, or to primary VF. Therefore, prevention of VT/VF is a key issue in the treatment of heart failure patients. There are mutual interactions between heart failure and arrhythmia; heart failure predisposes to arrhythmia and arrhythmias aggravate heart failure. In addition, certain therapies for heart failure are undesirable for arrhythmia, and certain therapies for arrhythmia can exacerbate heart failure.

Mechanisms of VT/VF in Heart Failure

Ventricular Remodeling and Arrhythmogenic Substrates
Development and progression of heart failure is associated with structural and functional remodeling of the ventricles, including spatially heterogeneous fibrosis, hypertrophy, necrosis, ischemia, apoptosis, and disruption of intercellular communication via the cell membrane and the gap junction. These changes result in depolarization abnormalities and repolarization dispersion of cardiomyocytes.

The action potential duration (APD) in ventricular muscle has been shown to be prolonged in failing hearts through a decrease of outward currents and/or an increase of inward currents. As to the changes in outward currents, reductions in the Ca\(^{2+}\)-independent transient outward current (I_{to}), inward rectifier K\(^+\) current (I_{Kr}) and delayed rectifier K\(^+\) currents (I_{Ks}, I_{K1}) have been reported for the inward currents, the Na\(^{+}/Ca^{2+}\) exchange current (I_{Na/Ca}) is increased, whereas the L-type Ca\(^{2+}\) current (I_{Ca,L}) is unaffected. Upregulation of the hyperpolarization-activated inward current (I_{h}) and an increase of the stretch-activated nonselective cation channel current (I_{SAC}) have been also reported.

Gap junction remodeling in the failing heart, in concert with interstitial fibrosis, may produce substrates for reentrant arrhythmias through the creation of a spatially heterogeneous conduction disturbance. Downregulation of connexin (Cx) 43, an altered phosphorylation state of Cx43, and upregulation of Cx40 and Cx45 have been reported. Altered Ca\(^{2+}\) handling in the ventricular myocytes plays an important role in the development of ventricular tachyarrhythmias in the failing heart. A reduction of Ca\(^{2+}\) uptake into the sarcoplasmic reticulum (causing intracellular Ca\(^{2+}\) overload), an increase in spontaneous Ca\(^{2+}\) leakage from the sarcoplasmic reticulum Ca\(^{2+}\)-release channels (ryanodine receptors), and an increase in I_{Na/Ca} have been recognized in animal models of heart failure, and in part in human patients with extensive heart failure. A combination of these events sets the stage for triggered activities resulting from oscillation of membrane potentials characterized by early afterdepolarization or delayed afterdepolarization. Activation of I_{h} or I_{SAC} may contribute to enhanced automaticity (Fig 1).

Modifiers

Elevated sympathetic activity in the failing heart may enhance the intracellular Ca\(^{2+}\) overload through ß-receptor-mediated increase of I_{Ca,L}, favoring the occurrence of triggered activity and reentry, and causing VT/VF. A recent large-scale clinical study showed that ß-blockers improved the prognosis of chronic heart failure by reducing the incidence of SCD.

Activation of the renin–angiotensin–aldosterone system...
in heart failure facilitates myocardial fibrosis causing arrhythmic substrates. A meta-analysis of large-scale clinical studies found that angiotensin-converting enzyme inhibitors (ACEIs) reduced the incidence of SCD in post-myocardial infarction patients. Myocardial ischemia, acidosis, free radicals, and extracellular electrolyte abnormalities (eg, hyperkalemia, hypokalemia, and hypomagnesemia) are involved in the onset of arrhythmia (Fig 1).

Drug therapy for heart failure (eg, diuretics, ACEIs, and aldosterone antagonists) can be arrhythmogenic through modification of the renin–angiotensin system and by electrolyte imbalances. Clinical studies of phosphodiesterase inhibitors done in the 1990s showed that inotropic agents in heart failure facilitate myocardial fibrosis, causing arrhythmic substrates. A meta-analysis of large-scale clinical studies found that angiotensin-converting enzyme inhibitors (ACEIs) reduced the incidence of SCD in post-myocardial infarction patients. Myocardial ischemia, acidosis, free radicals, and extracellular electrolyte abnormalities (eg, hyperkalemia, hypokalemia, and hypomagnesemia) are involved in the onset of arrhythmia (Fig 1).

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**Drug Therapy to Terminate VT/VF**

Immediate defibrillation by DC shocks is mandatory for the treatment of VT/VF associated with serious hemodynamic deterioration. Defibrillation by DC shocks is usually carried out with 200 J of biphasic or 360 J of monophasic pulses, and if this is ineffective the shocks are repeated after intravenously injecting epinephrine or vasopressin. The main emphasis is on life-saving, rather than on treating the arrhythmia; the primary therapeutic focus is on maintaining organ blood flow. If the arrhythmia persists after several DC shocks, lidocaine, procainamide, amiodarone, or nifekalant is given intravenously. A placebo-controlled, randomized, comparative study (ARREST study) examined intravenous amiodarone in patients with VF or pulseless VT who had an out-of-hospital cardiac arrest and did not respond to at least 3 DC shocks. The ratio of successful resuscitation was significantly higher in patients treated with amiodarone than in those treated with lidocaine (22.8% and 12.0%, respectively, p=0.009). Several nonrandomized clinical studies in Japan have suggested the usefulness of nifekalant for resuscitating patients who develop out-of-hospital cardiopulmonary arrest resistant to DC shocks. A post-marketing study of nifekalant documented that 13 of 26 patients with VF (50%) were successfully defibrillated by nifekalant alone and 15 of 30 patients who had VF resistant to DC shocks were successfully defibrillated by repeat DC shock following intravenous injection of nifekalant.

In sustained VT with stable hemodynamics, either intravenous lidocaine or nifekalant is indicated. Although intravenous procainamide is indicated for mild heart failure, its use can exacerbate heart failure, as well as leading to hypotension and prolonged QRS.

**Drug Therapy to Prevent VT/VF**

**Beta-Blockers**

In heart failure patients, the level of norepinephrine in the myocardium is elevated, and there are ion current abnormalities. At the cardiomyocyte level, stimulation of ß-adrenergic receptors alters the activity of a number of ion channels and transporters. In the nonfailing human heart, approximately 80% of adrenergic receptors are ß1-receptors and 20% are ß2-receptors. Stimulation of these receptors leads to activation of adenyl cyclase and formation of cyclic AMP through the activated stimulatory G-protein (Gs). In the failing human heart, however, there is selective downregulation of ß1-receptors and relative upregulation of ß2-receptors to approximately 40%. ß-receptors not only link to the Gs, but also to inhibitory G-protein (Gi), which hypothetically may ameliorate the harm of excessive adrenergic stimulation.

Beta-blockers have multiple antiarrhythmic mechanisms, and should be particularly effective in arrhythmia caused by increased sympathetic drive in heart failure. They also suppress structural remodeling of the heart induced by sympathetic stimulation through modification of cell growth, apoptosis and extracellular matrix composition. Metoprolol is a selective ß1-adrenergic antagonist; it changes action potentials and alters membrane currents by suppressing various ion channels. An experimental study showed that metoprolol shortened the APD and inhibited I_{K1}, I_{Ca}, and I_{O}}
in isolated feline ventricular myocytes. Carvedilol blocks not only β1- but also β2- and β1-adrenergic receptors. In addition, carvedilol has an antioxidant effect. In experiments on rabbit ventricular myocytes, carvedilol was shown to have direct inhibitory effects on a variety of ionic currents, especially on Iks, Ito, Ica1. and, to a lesser extent, Ikr. The APD of ventricular muscle is prolonged moderately by carvedilol through a reduction of IKr, but the QT interval on ECG is virtually unaffected, probably because of a concomitant reduction of Ica1.26-28

Table 1 summarizes the large-scale clinical studies on β-blockers in heart failure patients. In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study, carvedilol showed a 76% reduction in the incidence of malignant ventricular arrhythmia (VT, VF or ventricular flutter) compared with placebo in post-myocardial infarction patients, and that they may partially affect the onset of arrhythmia in heart failure. The Vasodilator-Heart Failure Trial II (V-HeFT-II) compared enalapril and hydralazine combined with isosorbide in chronic heart failure patients with LVEF <45%, and found that enalapril slightly reduced the incidence of SCD.42 The Cooperative North Scandinavian Enalapril Survival Trial (CONSENSUS)43 and Studies of Left Ventricular Dysfunction (SOLVD)44 in severe heart failure patients showed that enalapril reduced total mortality, but had no significant affect on SCD. ARBs are expected to have similar beneficial effects to ACEIs on the survival of heart failure patients, most likely through prevention of ventricular structural remodeling. However, large-scale clinical trials will be required to substantiate this speculation.

### Aldosterone Antagonists

In the Randomized Aldactone Evaluation Study (RALES), severe heart failure patients with LVEF ≤35% and NYHA functional class III/IV were randomly assigned to receive spironolactone (an aldosterone antagonist) or standard agents, such as ACEIs and loop diuretics. The results showed that spironolactone significantly reduced total mortality (relative mortality risk 0.70, p<0.001) and SCD (relative mortality risk 0.71, p=0.02).45 In the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) involving acute myocardial infarction patients, eplerenone (an aldosterone antagonist) significantly lowered total mortality (relative mortality risk 0.85, p=0.008) and SCD (relative mortality risk 0.79, p=0.03).46 The exact

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**Table 1 Mortality Reduction in Heart Failure Trials of β-Blockers**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Population</th>
<th>Mean follow-up (months)</th>
<th>All-cause Mortality</th>
<th>All-cause Risk reduction</th>
<th>Sudden death Mortality</th>
<th>Sudden death Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol 1999</td>
<td>Carvedilol vs Placebo</td>
<td>LVEF ≤35%, NYHA II-IV ischemic 52%</td>
<td>6.5</td>
<td>3.2% vs 7.8%</td>
<td>65% (p&lt;0.001)</td>
<td>1.7% vs 3.8%</td>
<td>55% NA</td>
</tr>
<tr>
<td>COPERNICUS 2001</td>
<td>Carvedilol vs Placebo</td>
<td>LVEF &lt;25%, NYHA III-IV ischemic 67%</td>
<td>10.4</td>
<td>12.8%/y vs 19.7%/y</td>
<td>35% (p=0.0014)</td>
<td>3.9% vs 6.1%</td>
<td>36% (p=0.016)</td>
</tr>
<tr>
<td>ANZ 1997</td>
<td>Carvedilol vs Placebo</td>
<td>LVEF &lt;45%, NYHA I-III ischemic 100%</td>
<td>19</td>
<td>9.6% vs 12.6%</td>
<td>24% (NS)</td>
<td>4.8% vs 5.3%</td>
<td>10% (NS)</td>
</tr>
<tr>
<td>CIBIS 1994</td>
<td>Bisoprolol vs Placebo</td>
<td>LVEF &lt;40%, NYHA III, IV ischemic 50%</td>
<td>22.8</td>
<td>16.6% vs 20.9%</td>
<td>20% (NS)</td>
<td>5.9% vs 7.5%</td>
<td>21% (NS)</td>
</tr>
<tr>
<td>CIBIS II 1999</td>
<td>Bisoprolol vs Placebo</td>
<td>LVEF ≤35%, NYHA III, IV ischemic 50%</td>
<td>15.6</td>
<td>11.8% vs 17.3%</td>
<td>34% (p&lt;0.001)</td>
<td>3.6% vs 6.3%</td>
<td>44% (p=0.0011)</td>
</tr>
<tr>
<td>MDC 1999</td>
<td>Metoprolol vs Placebo</td>
<td>LVEF &lt;40%, NYHA I-IV ischemic 0%</td>
<td>12</td>
<td>11.9% vs 10.1%</td>
<td>(NS)</td>
<td>9.3% vs 6.3%</td>
<td>(NS)</td>
</tr>
<tr>
<td>MERIT-HF 1999</td>
<td>Metoprolol CR/XL vs Placebo</td>
<td>LVEF ≤40%, NYHA II-IV ischemic 65%</td>
<td>12</td>
<td>7.2%/y vs 11.0%/y</td>
<td>34% (p=0.0062)</td>
<td>4.0% vs 6.6%</td>
<td>41% (p=0.0002)</td>
</tr>
<tr>
<td>COMET 2003</td>
<td>Carvedilol vs Metoprolol</td>
<td>LVEF ≤35%, NYHA II-IV ischemic 53%</td>
<td>58</td>
<td>34% vs 40%</td>
<td>34% (p=0.0017)</td>
<td>14.4% vs 17.2%</td>
<td>19% (p=0.02)</td>
</tr>
</tbody>
</table>

**ACEIs/Angiotensin Receptor Blockers (ARBs)**

A meta-analysis of large-scale clinical studies indicated that ACEIs lowered the incidence of SCD in post-myocardial infarction patients13 and that they may partially affect the onset of arrhythmia in heart failure. The Vasodilator-Heart Failure Trial II (V-HeFT-II) compared enalapril and hydralazine combined with isosorbide in chronic heart failure patients with LVEF <45%, and found that enalapril slightly reduced the incidence of SCD.42 The Cooperative North Scandinavian Enalapril Survival Trial (CONSENSUS)43 and Studies of Left Ventricular Dysfunction (SOLVD)44 in severe heart failure patients showed that enalapril reduced total mortality, but had no significant affect on SCD. ARBs are expected to have similar beneficial effects to ACEIs on the survival of heart failure patients, most likely through prevention of ventricular structural remodeling. However, large-scale clinical trials will be required to substantiate this speculation.
mechanisms of the reduction of mortality by aldosterone antagonists remain to be elucidated.

Amiodarone

Amiodarone affects a variety of inward and outward ion channel currents, suppresses sympathetic activities, and modifies thyroid function. Like lidocaine, it blocks the Na+ channel current (INa) through a high affinity for the inactivated state and relatively fast binding/unbinding kinetics. Amiodarone blocks both voltage-gated and ligand-gated K+ channel currents; the former include IKr and Ito, and the latter, acetylcholine-sensitive K+ currents (IK,ACh) and ATP-sensitive K+ currents (IK,ATP). The pharmacological actions of amiodarone can be divided into acute and chronic. The major acute electrophysiological effect of amiodarone on the heart is a moderate suppression of excitability and conductivity through blockade of ICa,L and INa. The major chronic electrophysiological effect is a moderate prolongation of APD by reducing IK (especially IKs) and Ito.47

The Cardiac Arrhythmia Suppression Trial (CAST) revealed that treatment of ventricular arrhythmias with potent INa blockers (Class I antiarrhythmic drugs) in post-myocardial infarction patients results in increased mortality and SCD48 Subsequently, many clinical trials to evaluate the potential benefit of Class III antiarrhythmic drugs and amiodarone for the prevention of SCD have been conducted. A meta-analysis of 13 randomized trials showed that amiodarone significantly reduced overall mortality by 13%, and arrhythmic mortality and SCD by 29%.49

Two large-scale randomized trials have assessed amiodarone as a primary prevention for SCD in heart failure patients. The Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) in heart failure patients (>10 premature ventricular beats per hour and LVEF <40%) found no reduction in overall mortality and no SCD benefit from amiodarone, although there was a trend toward reduced overall mortality among patients with nonischemic cardiomyopathy (p=0.07) (Fig 2).50 In contrast, the use of amiodarone in the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial in patients with severe heart failure because of nonischemic (70%) or ischemic (30%) cardiomyopathy showed a 28% risk reduction in mortality, both SCD and heart failure death, independently of the presence of nonsustained VT (Fig 3).51

Although ICDs have been shown in several trials to be superior in preventing SCD among high-risk patients52 the Amiodarone Versus Implantable Cardioverter-Defibrillator:
Randomized Trial (AMIOVIRT) in nonischemic dilated cardiomyopathy patients with LVEF ≤35% and nonsustained VT found no reduction in overall mortality benefit from ICD treatment (Fig 4).51

In recent years, β-blocker therapy has been established as a treatment option for heart failure. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) and European Myocardial Infarct Amiodarone Trial (EMIAT) in myocardiac infarction patients with reduced LVEF showed that the interaction of amiodarone with a β-blocker was significant for preventing cardiac death (p=0.05) and arrhythmic death or resuscitated cardiac arrest (p=0.03).52 The Optimal Pharmacology Therapy in Cardioverter Defibrillator Patients (OPTIC) study also demonstrated a favorable interaction of amiodarone and β-blocker.53 Therefore, amiodarone may be useful as an adjunctive therapy in at least some heart failure patients, together with ACEIs, β-blockers and an ICD, and is potentially effective for preventing VT/VF, especially in high-risk patients with nonischemic heart failure.

Sotalol

Sotalol is a unique β-blocker that possesses substantial Class III activity. It is a racemic compound, but the Class II activity arises only from l-sotalol, although both isomers have Class III activity. The Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) trial showed that sotalol was better than 6 Class I antiarrhythmic drugs in patients with sustained VT/VF, although the study was not designed to compare the efficacy of antiarrhythmics.54 However, the pure Class III agent d-sotalol increased mortality in post-myocardial infarction patients with LVEF ≤40% in the Survival With ORal D-sotalol (SWoRD) study.55 Therefore, racemic sotalol (d,l-sotalol) is used clinically.

Sotalol can exacerbate heart failure in patients with low LVEF because of its negative inotropic effect. The β-blocking activity, but not the Class III activity, of sotalol is evident at low dosages.56 Sotalol has a different spectrum of adverse effects from amiodarone, and is less likely to cause extracardiac reactions. But, because sotalol prolongs the APD, it can cause torsades de pointes (TdP) accompanied with QT prolongation.

Pure Class III Agents

Since the CAST study, attention has shifted to Class III antiarrhythmic drugs, such as amiodarone, and pure Class III agents have been developed as new potential antiarrhythmics. However, most of the newly developed pure Class III agents have been discontinued because of undesirable side-effects, especially TdP with QT prolongation.

In Japan, the pure Class III agent, intravenous nifekalant, was approved for the treatment of the following types of lethal VT/VF: (1) recurrent sustained VT/VF with organic heart disease resistant to Class I agents, (2) incessant VT induced by Class I agents; (3) sustained VT where amiodarone is of limited value; and (4) VT resistant to DC shocks. Nifekalant is also useful in heart failure patients because of its positive inotropic effect. In Japan, post-marketing studies have shown that nifekalant prevented VT/VF recurrence in 60 of 99 patients (60.6%) in the emergency setting, and tended to improve the hemodynamic state after maintenance infusion.57 Nifekalant exerts its effect mainly by inhibition of Iks. It is likely to induce marked QT prolongation and TdP by bradycardia because of its reverse use-dependent effect. Therefore, it is important to closely monitor QT time, heart rate, and electrolytes, particularly the serum K level.

Conclusions

Preventing VT/VF resulting in SCD is a critical issue in the treatment of heart failure patients. Although ICDs reduce SCD, they are limited to preventing triggers for VT/VF or cardiac death in heart failure patients. Antiarrhythmic drugs with Class III activity have an important role in the treatment of ventricular tachyarrhythmia with heart failure. Optimal drug therapy, including β-blockers, ACEIs and aldosterone antagonists, improves survival and reduces the incidence of VT/VF or SCD in heart failure patients.

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