Sudden unexpected death in patients with congestive heart failure: a second frontier

Milton Packer, M.D.

For the last 200 years the management of patients with congestive heart failure has focused on the alleviation of symptoms of the disease that greatly limit the lifestyle of these individuals. For the last 30 years we have concentrated on elucidating the pathophysiologic mechanisms that underlie the hemodynamic abnormalities of the heart failure state and, consequently, we have been enormously successful in developing a variety of potent inotropic, diuretic, and vasodilator drugs that can produce clinical improvement in the vast majority of patients. In our enthusiasm to make our patients feel better, however, we have ignored the fact that the mortality of patients with congestive heart failure remains extremely high, and that no therapeutic intervention has yet been shown to improve long-term survival. We should not be surprised that our patients are dying from progression of their underlying heart disease, since the hemodynamic interventions available to us at the present time only incompletely alleviate the markedly abnormal loading conditions in the heart that likely contribute to the progression to terminal right and left ventricular dysfunction. What is surprising, however, is that many of our patients are dying suddenly, unexpectedly, without any evidence of hemodynamic or functional deterioration. As we continue to advance in our ability to pharmacologically improve pump performance, it is likely that sudden unexpected death will soon become the most frequent means of demise in patients with congestive heart failure.

The problem of sudden unexpected death in patients with congestive heart failure. We define sudden unexpected death as death from circulatory failure within 1 hour of onset of symptoms in a patient with advanced left ventricular dysfunction whose heart failure symptoms have remained stable or improved over the previous 2 to 4 weeks and in whom another cause for circulatory collapse cannot be identified clinically. We are thereby excluding patients whose death (albeit sudden) is the terminal event in a progressively worsening clinical picture, characterized by repeated hospitalizations for treatment and progressively shorter periods of clinical stability. We are also excluding the 10% to 15% of patients whose deaths follow the typical symptomatic presentation of an acute myocardial infarction or pulmonary embolism. So defined, sudden unexpected death comprises 35% to 45% of all deaths of patients with congestive heart failure and is equal in frequency to that of deaths secondary to progressive ventricular dysfunction (table 1). Available evidence suggests that the incidence of sudden unexpected death has not changed significantly over the last 10 to 15 years, is not related to the etiology or severity of congestive heart failure, and has not been altered by the advent of direct-acting vasodilator drugs.

Sudden unexpected death in patients with congestive heart failure is most likely the result of a terminal ventricular tachyarrhythmia, either ventricular tachycardia or ventricular fibrillation. Studies using 24 hour ambulatory monitoring indicate that 60% to 90% of patients with congestive heart failure have frequent or complex ventricular ectopy, and that 40% to 60% have nonsustained ventricular tachycardia (table 2). The presence of ventricular arrhythmias and left ventricular dysfunction appear to act synergically to determine the subsequent occurrence of sudden death. Hence, it is not surprising that the frequency of sudden unexpected death is greater in patients with congestive heart failure than in any other definable subset of patients in cardiovascular medicine. This risk of sudden death for patients with heart failure is substantially higher than that for patients during the first year after an acute myocardial infarction.
dial infarction, who have been traditionally viewed by cardiologists as being at greatest risk of unexpected circulatory collapse and have consequently become the focus of major rehabilitative and public health programs aimed at preventing the occurrence of fatal arrhythmias.

**Predisposing factors to sudden unexpected death in congestive heart failure.** What factors underlie the occurrence of malignant ventricular arrhythmias in patients with congestive heart failure? Although previous reports have validly emphasized the importance of structural and hemodynamic factors (such as myocardial fibrosis and ventricular wall stress) in predisposing to the reentry phenomena that are critical to the development of ventricular ectopic rhythms, recent evidence points to three potentially *reversible* arrhythmogenic factors in patients with congestive heart failure: (1) electrolyte deficits, (2) activation of neurohormonal mechanisms, and (3) drug therapy for heart failure (table 3).

**Electrolyte depletion.** Patients with congestive heart failure have marked deficits of total body and intracellular potassium, which may or may not be reflected by a measurable decrease in serum potassium concentration. The administration of diuretic drugs may further deplete body stores of potassium (as well as magnesium) by promoting the renal excretion of these predominantly intracellular cations, an effect potentiated by coexistent hyperaldosteronism and metabolic alkalosis. Furthermore, the high levels of circulating catecholamines in patients with heart failure may enhance the movement of potassium into cells by a $\beta_2$-receptor–mediated mechanism, thereby exacerbating the hypokalemic state and potentiating its arrhythmogenic effects. Recent studies indicate that malignant ventricular ectopic rhythms in some patients with congestive heart failure may be entirely the result of potassium and magnesium depletion; short- and long-term electrolyte repletion may abolish these arrhythmias and prevent the recurrence of sudden death without long-term antiarrhythmic drug therapy. As might be expected, potassium and magnesium deficits commonly coexist. Under such circumstances, repletion of magnesium appears to be critical to the success of treatment; therapy with potassium salts alone may fail to restore normal serum levels of potassium or normal sinus rhythm, whereas magnesium administration corrects not only the hypomagnesemia and the hypokalemia but abolishes the accompanying tachyarrhythmias as well.

**Activation of neurohormonal mechanisms.** The sympathetic nervous system and the renin-angiotensin system are activated in patients with congestive heart failure in an attempt to preserve circulatory homeostasis as cardiac output falls and serve to mediate the systemic vasoconstriction and salt and water retention that characterize patients with this disorder. These systems may be further activated by treatment with diuretic drugs, direct-acting vasodilators, or by the administration of potent inotropic agents. Circulating levels of catecholamines may be directly arrhythmogenic or may contribute to and potentiate the arrhythmogenic effects of hypokale-
TABLE 2
Relationship of ventricular ectopic activity to subsequent occurrence of sudden unexpected death in patients with congestive heart failure (studies ranked according to increasing mortality rates)

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>Relation of VT to SUD</th>
<th>Relation of VT to total mortality</th>
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<tbody>
<tr>
<td></td>
<td>average follow-up (%)</td>
<td>patients with VT (%)</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>35 11/34 60</td>
<td>No</td>
</tr>
<tr>
<td>Costanzo-Nordi et al.</td>
<td>55 16 40</td>
<td>No</td>
</tr>
<tr>
<td>Meieritz et al.</td>
<td>74 26/11 49</td>
<td>Yes</td>
</tr>
<tr>
<td>Unverferth et al.</td>
<td>69 35/12 41</td>
<td>Yes</td>
</tr>
<tr>
<td>Holmes et al.</td>
<td>31 45/14 39</td>
<td>Yes</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>77 65/12 51</td>
<td>Yes</td>
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</tbody>
</table>

In the first two studies the event rates were too low (< 20%) to show that ventricular arrhythmias were of prognostic significance. In all of the four remaining studies, the occurrence of ventricular tachycardia (> 3 beats) predicted total mortality but not sudden death, suggesting that such malignant ventricular ectopy reflected the severity of hemodynamic and functional abnormalities and was not an independent risk factor. The study by Meieritz et al. showed a relationship between sudden unexpected death and the frequency (but not the occurrence) of ventricular tachycardia, but the extremely high arrhythmia rate (≥ 20 episodes of ventricular tachycardia per 24 hr) proposed by these authors for the identification of high-risk patients is rarely observed in patients with congestive heart failure.

SUD = sudden unexpected death. VT = ventricular tachycardia.


Angiotensin II may exacerbate ventricular arrhythmias by promoting the renal losses of potassium and magnesium by the stimulation of aldosterone synthesis or by potentiating the central and peripheral effects of the sympathetic nervous system. Hence, both neurohormonal systems not only worsen ventricular loading conditions by systemic vasoconstriction, but may provoke life-threatening tachyarrhythmias by their direct and indirect actions on ventricular irritability. These combined effects may explain why plasma catecholamines and plasma renin activity are the most powerful predictors of long-term survival in patients with congestive heart failure. 4,5

The most compelling evidence that neurohormonal activation may play a critical role in the pathogenesis of sudden unexpected death in patients with congestive heart failure derives from studies of long-term treatment with neurohormonal antagonists. In a double-blind crossover trial in which captopril was compared with placebo therapy in 14 patients with severe chronic heart failure, 6 converting-enzyme inhibition not only ameliorated the symptoms of heart failure and prolonged exercise tolerance but also reduced the frequency of ventricular premature complexes and the number of episodes of nonsustained ventricular tachycardia during ambulatory monitoring. These antiarrhythmic effects were accompanied by both a reduction in circulating levels of angiotensin II and catecholamines and by an increase in serum and total body potassium. The ability of captopril to promote cation repletion and reduce circulating levels of potentially arrhythmogenic neurohormones may help explain the reduction in overall mortality seen in retrospective analysis of data from patients with heart failure treated with converting-enzyme inhibitors. 5, 7 Alternatively, direct antagonism of the proarrhythmic effects of catecholamines may be achieved by the administration of β-adrenergic–blocking agents. Recent data from the Beta-Blocker Heart Attack Trial (BHAT) indicate that treatment with β-blockers substantially reduces the incidence of sudden death in patients following an acute myocardial infarction that was complicated by congestive heart failure, 8 presumably through an antiarrhythmic mechanism. These observations support the findings of uncontrolled studies that long-term low-dose β-blockade may reduce mortality in patients with a congestive cardiomyopathy. 9

Therapy with drugs used to treat heart failure. Most of the drugs used to improve cardiac performance and clinical symptoms in patients with congestive heart failure can exacerbate ventricular tachyarrhythmias. Of all the available treatment modalities, diuretic drugs may prove to be the most arrhythmogenic. These agents activate both the sympathetic nervous and renin-angiotensin systems and promote the renal loss of potassium and magnesium, the serum levels of which may be further reduced by the concomitant elevation of circulating catecholamines and aldosterone. All of these factors, acting alone or in concert, may contribute sub-

TABLE 3
Factors predisposing to ventricular arrhythmias in patients with heart failure

<table>
<thead>
<tr>
<th>Structural factors</th>
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<tbody>
<tr>
<td>Hemodynamic factors</td>
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<tr>
<td>Electrolyte depletion</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Neurohormonal mechanisms</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
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<tr>
<td>Renin-angiotensin system</td>
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<tr>
<td>Heart failure therapy</td>
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<tr>
<td>Inotropic drugs</td>
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<tr>
<td>Diuretic agents</td>
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<td>Direct-acting vasodilators</td>
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stantially to the frequency and complexity of malignant ventricular rhythms in patients with congestive heart failure. A similar provocation of arrhythmic events has been postulated to occur during the administration of diuretics in hypertensive patients and may explain the failure of diuretic therapy to reduce overall cardiovascular mortality in these patients in large-scale trials.\textsuperscript{10}

Most disturbing is the arrhythmogenic potential of inotropic therapy in patients with congestive heart failure. A long-sought but incompletely realized goal of clinical cardiovascular pharmacologists has been the development of a drug for the treatment of left ventricular dysfunction that increases cardiac contractility without increasing cardiac irritability; unfortunately, most agents that have been developed to date have a narrow toxic-therapeutic ratio. Digitalis may produce serious ventricular tachyarrhythmias not only when its circulating levels are elevated, but also in therapeutic concentrations should potassium stores be depleted. Such malignant arrhythmias may contribute to the increased cardiovascular mortality noted in patients with heart failure and complex ventricular ectopy who receive long-term digitalis therapy after an acute myocardial infarction.\textsuperscript{11} Recently developed potent inotropic agents enhance cardiac contractility by increasing intramyocellular levels of cyclic AMP, either by promoting its synthesis (catecholamines) or by retarding its degradation (phosphodiesterase inhibition); both mechanisms are potentially arrhythmogenic. Although intravenously administered catecholamines can increase ventricular ectopy in patients with congestive heart failure, neither dopamine nor dobutamine appear to have increased the risk for sudden death, since these drugs are not generally administered over a long term. Unfortunately, orally active phosphodiesterase inhibitors (such as amrinone, milrinone, and enoximone) are being developed for long-term use and appear to have a similar arrhythmogenic potential, which may explain the high frequency of sudden death in patients with heart failure treated with these agents.\textsuperscript{12} Whether the proarrhythmic effects of digitalis and phosphodiesterase inhibitors can be antagonized by concomitant treatment with converting-enzyme inhibitors, \(\beta\)-blockers, or antiarrhythmic agents remains to be seen.

**Prevention of sudden unexpected death in patients with congestive heart failure.** In attempting to design a therapeutic approach to the prevention of sudden unexpected death in patients with congestive heart failure, two central questions need to be considered: (1) Which patients with congestive heart failure are at high risk of sudden death and should receive prophylactic therapy? (2) Are conventional antiarrhythmic drugs successful in preventing sudden death in these patients?

**Identification of patients with heart failure at high risk of sudden death.** There is general agreement that patients with symptomatic ventricular tachycardia or fibrillation should be treated to prevent future sudden cardiac death, but only a small fraction of patients with congestive heart failure who will die suddenly will experience premonitory symptoms. The clinical picture in most individuals is so dominated by dyspnea and fatigue that sudden death is usually the first manifestation of a clinically important arrhythmia problem. Unfortunately, there remains no clear means of identifying patients who are likely to die suddenly before the terminal event occurs. Some investigators have suggested that the finding of complex ventricular rhythm disturbances (especially nonsustained ventricular tachycardia) on ambulatory electrocardiographic monitoring predicts future fatal arrhythmias, but such malignant ventricular ectopy is usually a reflection of the severity of hemodynamic and functional abnormalities and therefore predicts total mortality rather than the occurrence of sudden unexpected death (table 2). Other observers have proposed that the finding of sustained ventricular tachycardia during programmed ventricular stimulation can identify a high-risk patient population, but the arrhythmias in patients with cardiomyopathies may be particularly resistant to electrical provocation,\textsuperscript{13} and ventricular tachyarrhythmias may be induced in many patients who are not at risk of future events. Still other investigators have suggested that the finding of late diastolic potentials on signal-averaged electrocardiograms can distinguish those patients with heart failure predisposed to potentially lethal arrhythmias\textsuperscript{14}; these findings need to be confirmed, but such abnormalities may prove to be more closely related to the severity of ventricular dysfunction than to ventricular irritability. I believe that there is as yet no validated means of identifying patients with congestive heart failure who are at high risk of sudden unexpected death. Furthermore, because the frequency of sudden death in the overall heart failure population is substantial (20\% annual event rate), I view all patients with congestive heart failure as being at high risk and would suggest that all such patients are candidates for long-term prophylactic treatment, were an effective and well-tolerated therapeutic approach available.

**Efficacy of conventional antiarrhythmic drugs in preventing sudden death.** Presently available antiarrhythmic agents are seriously flawed in their ability to suppress ventricular tachyarrhythmias in patients with congestive heart
failure. Although pharmacologic approaches to the treatment of ventricular ectopy are generally successful in patients with normal ventricular function, the efficacy of antiarrhythmic drugs markedly diminishes as left ventricular ejection fraction declines, such that only a small fraction of patients with heart failure and an ejection fraction less than 30% are responsive to antiarrhythmic drug therapy. The efficacy of these agents may be further reduced in patients with coexistent electrolyte deficiencies. Even the modest response in some patients can be outweighed by the proarrhythmic effects of these drugs in others. Furthermore, many antiarrhythmic agents have potent negative inotropic effects that may exacerbate the heart failure state (especially disopyramide) or interfere with the inotropic actions of digitalis (quinidine). These observations may explain why no antiarrhythmic drug has yet been shown to prevent sudden death in patients with congestive heart failure.

The most successful approaches to the control of arrhythmias in the future for patients with congestive heart failure may be endomyocardial resection of the reentry pathway (guided by electrophysiologic mapping) or the use of an automatic implantable defibrillator. Although use of such aggressive and expensive therapies can be rationalized for the patient with symptomatic ventricular tachyarrhythmias, they are not practical solutions to the problem of sudden death for most patients with heart failure.

In conclusion, with the advent of potent inotropic and vasodilator agents that can improve pump performance, sudden unexpected death from ventricular tachyarrhythmias may soon become the most common cause of death in patients with congestive heart failure. Recent evidence indicates that complex ventricular ectopy is nearly universally present in these patients and may be exacerbated by conventional heart failure therapy (digitalis and diuretics) that may lead to electrolyte deficits and activate neurohormonal mechanisms. On the other hand, therapeutic interventions that preserve intracellular cations or reduce circulating levels of vasopressor hormones (converting-enzyme inhibitors or β-blockers) may suppress ventricular ectopic activity and prevent sudden death. The empiric use of conventional antiarrhythmic drugs has generally proved to be an ineffective and potentially dangerous approach to control of arrhythmias in these individuals.

Our attention is slowly shifting from not only making patients with heart failure feel better (the first frontier) but also making patients with heart failure live longer (the second frontier). In doing so, it is imperative that we begin to understand why patients with heart failure die. What factors mediate the progression of left ventricular dysfunction in these patients and what factors predispose to the development of fatal ventricular arrhythmias? Until such information is forthcoming, present evidence suggests that electrolyte deficits and neurohormonal forces may be the most important treatable mechanisms of sudden death in patients with congestive heart failure. Prospective large-scale clinical trials are in order to evaluate if converting-enzyme inhibition or β-blockade can really prolong life in these severely ill patients.

References

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