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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Management of Ventricular Arrhythmias in Patients With Advanced Heart Failure

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ABSTRACT

Advanced heart failure (A-HF) is characterized by progressive symptoms of heart failure despite optimal therapy. In patients with A-HF, ventricular arrhythmias (VAs) are common. Clinical studies evaluating different therapies to prevent VAs had very limited representation of patients with A-HF. Among antiarrhythmic drugs, only amiodarone reduces VAs, although its use may be associated with increased mortality. Catheter ablation with substrate modification is effective to achieve VA suppression in patients with A-HF, including those with left ventricular assist devices. In high-risk cases, temporary mechanical hemodynamic support tailored to the individual patient on the basis of presentation and hemodynamic conditions may be beneficial. Advanced therapies for pump failure or refractory VAs, including heart transplantation and durable mechanical circulatory support, may be required in high-risk patients who are reasonable candidates for these surgical therapies. In this review, the authors discuss important management considerations in patients with VAs and A-HF. (J Am Coll Cardiol 2017;69:1842-60) © 2017 by the American College of Cardiology Foundation.

Congestive heart failure (HF) is a progressive affliction affecting more than 5.1 million patients, and accounting for a significant burden of hospitalizations and mortality (1). The basis of disease progression is poorly understood, but includes: 1) activation of maladaptive neurohormonal pathways; 2) myocardial adverse remodeling and fibrosis; and in more recent work, 3) disruption of metabolism and energy homeostasis (2,3). Despite substantial clinical progress with pharmacological and device therapies, the patients with refractory symptoms of HF with severe limitation of physical activity (American College of Cardiology/American Heart Association Stage D or advanced heart failure [A-HF]) represent a formidable challenge with an estimated 125,000 to 250,000 cases in the United States, and are associated with significant morbidity and mortality (4). One of the clinical challenges in this group of patients has been the management of ventricular arrhythmias (VAs), which are highly prevalent at this stage of HF (5). Although several landmark clinical trials have addressed the role of pharmacological and pacemaker/defibrillator therapy for patients with significantly reduced left ventricular ejection fraction (LVEF), no study to date has investigated the management of VAs in refractory, American College of Cardiology/American Heart Association Stage D HF (A-HF) (6,7). The objectives of this review are: 1) to identify the overlapping mechanisms that can explain the increasingly recognized risk of VAs as a component of disease progression in chronic HF; 2) to summarize the knowledge base of clinical management of VAs in patients with A-HF, including the growing number of patients who have transitioned to long-term mechanical circulatory support (MCS) with left ventricular assist

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device (LVAD) therapy (8); and 3) to identify the knowledge gaps for future studies, in an effort to further the evidence-based care of patients with A-HF challenged by VAs. Given the paucity of published data on this topic, our review will also reflect our institutional experience and approach to manage VAs in the setting of A-HF.

MECHANISMS: PUMP FAILURE AS A SUBSTRATE FOR VAs

In patients with A-HF, VAs are common, with a prevalence of up to 33% in chronic ambulatory patients with an increased mortality from HF (5,9–11), and up to 45% in patients supported with a LVAD who were noted to have pre-operative VAs (12). For the purpose of this review, we will use the term *VAs* to refer to VAs that warrant therapeutic interventions, such as sustained VAs, frequent nonsustained VAs, and frequent premature ventricular contractions. From a mechanistic standpoint, the structural changes that occur in patients with advanced stages of HF, including replacement fibrosis, regional ventricular hypertrophy, and changes in myocyte mechanical and electrical function, promote the development and maintenance of VAs (13,14). It is surprising that more patients with advancing cardiomyopathies do not develop VAs. The mechanisms that could explain the heterogeneity in the development of clinically important VAs are not well understood, but include the multifaceted process of adverse myocardial remodeling at the tissue, cellular, and subcellular levels, which can lead to myocardial scarring or areas of altered myocardial structure/function. They also include the multifaceted response to failure that is present in patients with various degrees of neurohormonal activation, metabolic adaptation, and response to neurohormonal blockade.

It is not surprising that indicators of more advanced HF, such as increased New York Heart Association (NYHA) functional class and decreased renal function, have been associated with appropriate implantable cardioverter-defibrillator (ICD) shocks and VAs (5,15,16). In a substudy of the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial that adjudicated the cause of mortality, the presence of a LVEF <20% or NYHA functional class IV were strongly associated with an increased risk of sudden cardiac death (5). The findings raise the question of whether the time-dependent progression of HF itself constitutes a substrate or triggering event for the incident occurrence of fatal VAs. More recent studies are identifying features of advanced cardiomyopathies associated with mechanical/bioenergetic inefficiency, such as regional mechanical dysfunction, as measured by tissue Doppler imaging (left ventricle [LV] mechanical dispersion), as predictors of VAs (17). Progressive myocardial fibrosis (resulting in large part from the activation of maladaptive neurohormonal pathways, such as the renin-angiotensin and aldosterone systems [RAAS]) not only results in a decline in myocardial function and reserve, but also forms the electrophysiological substrate that triggers and possibly sustains the VAs associated with a wide spectrum of ischemic and nonischemic cardiomyopathies. In patients with A-HF, studies have identified that the volume and distribution of scar, as measured by contrast-enhanced cardiac magnetic resonance (CMR), especially *nontransmural* scar, is associated with sustained VAs (18,19). By treating HF patients with neurohormonal blockade of the RAAS pathway, including angiotensin-converting enzyme inhibitors and mineralocorticoid-receptor antagonists, a reduction, not only in pump failure death, but also in VAs and sudden cardiac death, has been documented (20–23). Thus, successful treatment or possibly reversal of pump failure *with therapies that target specific pathways* can reduce the frequency and lethality of VAs. Interestingly, although cardiac resynchronization therapy has been proven to decrease fibrosis and improve myocardial remodeling (24), reversing HF and decreasing mortality from pump failure in a substantial subgroup of class III and class IV HF patients (6) do not reduce sustained VAs or the risk of sudden cardiac death (11,25). This is in contrast to a substudy from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trial, which included a "less sick" cohort of HF patients in NYHA functional classes I and II, and demonstrated that patients who achieved the most significant degree of reverse remodeling with cardiac resynchronization therapy had the lowest rate of ventricular tachycardia (VT) and ventricular fibrillation/flutter (VF) (26). In the case of the reversal of HF that is achieved early on with a LVAD (27–29), several studies have identified a very high prevalence of VAs after LVAD insertion, especially in patients with a pre-operative history of VT (30,31), despite the improvement in HF that can be achieved with this

ABBREVIATIONS AND ACRONYMS

A-HF = advanced heart failure
AAD = antiarrhythmic drug
AHD = acute hemodynamic decompensation
ARVC = arrhythmogenic right ventricular cardiomyopathy
CI = confidence interval
CMR = cardiac magnetic resonance
CSD = cardiac sympathetic denervation
ECMO = extracorporeal membrane oxygenation
HF = heart failure
ICD = implantable cardioverter-defibrillator
LV = left ventricle/ventricular
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
MCS = mechanical circulatory support
MHS = mechanical hemodynamic support
NYHA = New York Heart Association
OR = odds ratio
PCWP = pulmonary capillary wedge pressure
PET = positron emission tomography
RV = right ventricle/ventricular
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia