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The challenge of management of electrical storm and out-of-hospital cardiac arrest

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Electrical storm refers to a situation when rapid clustering of episodes of malignant ventricular tachyarrhythmias (VT) develops requiring repetitive attempts at cardioversion. This situation is seen in patients with acute coronary syndrome (ACS) as well as in some patients with the implantable cardioverter-defibrillator (ICD). A similar situation is encounterd in victims of out-of-hospital cardiac arrest in whom VT is the mechanism of out-of-hospital cardiac arrest. In this group of patients, besides management of hypoxia, electrolyte disturbances, acidosis, volume depletion, etc., drugs are administered to either assist direct current (DC) cardioversion and/or maintain a stable rhythm. The first line recommended anti-arrhythmic therapy these days is intravenous (IV) amiodarone and not lidocaine [1]. This change came around gradually in the last several years when head-to-head comparison of IV amiodarone and lidocaine showed the first drug to be unequivocally superior [2]. In fact lidocaine prophylaxis in ACS appears to be associated with increased mortality and this practice has largely been abandoned [3]. However, lidocaine is still being used by some for out-of-hospital cardiac arrest as a second tier drug. Other second-tier drug therapy in this situation also includes intravenous magnesium and procainamide.

Although IV amiodarone is available worldwide, its use is disallowed in Japan. However, luckily for the Japanese, one of their drug companies has introduced a new selective Ikr blocker [4] that has been in use since June 2000 in situations when IV amiodarone would be indicated, i.e., primarily in patients with electrical storm and out-of-hospital cardiac arrest [5–7]. Although the drug, Nifekalant, is a pure Ikr blocker and as such is reverse-use dependent specially in the presence of fast VT, yet it has proven effective. An efficacy rate approaching 75% has been reported both in patients with electrical storm and in out-of-hospital cardiac arrest. However, the drug as in the case of other pure Ikr blockers can result in significant QT prolongation and induce torsade de pointe VT. In other words, the drug can successfully terminate, for instance, VT in the setting of ACS and then induce a torsade de pointe type VT [7]. In this issue of Cardiology Journal, Dr. Amino and associates from Japan reported on the efficacy of the combination of Nifekalant with acute left stellate ganglion blockade (LSGB) in patients with intractable VT in out-of-hospital cardiac arrest [8]. As expected DC cardioversion and Nifekalant were effective in 40 of 55 patients (73%). In the remaining 15 patients, VT continued in spite of repeated doses of Nifekalant. In this group, acute LSGB was performed in 11 patients and resulted in a stable sinus rhythm in 7 (64%). The short-term mortality was 45% in the LSGB group and 100% in the 4 patients who comprised the non-LSGB group. The numbers are relatively small and the results are hardly impressive if we remember that only 2 patients out of the LSGB group seem to have survived long term. Never the less, the study is of interest because it re-focuses attention on a rarely utilized management modality in a very serious clinical situation.

The rationale for the use of acute LSGB as means of sympathetic blockade in the setup of electrical storm or out-of-hospital cardiac arrest is straight forward. A majority, if not all, of these patients will have an increased sympathetic drive. The latter, is universally accepted as arrhythmogenic

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especially in patients with ACS, patients with ischemic and non-ischemic cardiomyopathy, and patients with certain channelopathies. The exact electrophysiological mechanism(s) by which increased sympathetic drive to the heart can be arrhythmogenic in most of the above situations is not fully understood. However, innumerable experimental [9, 10] and clinical [11, 12] data have shown that blocking the increased sympathetic drive to the heart in both its acute and chronic versions can be significantly antiarrhythmic. Sympathetic blockade could be achieved by intravenous beta-blocking drugs like propanolol or esmolol or by acute LSGB. The authors argue in favor of LSGB by citing its specific blockade of sympathetic innervations to the left ventricle and the potentially negative inotropic and chronotropic effects of IV beta-blockade in these settings. Even though LSGB has an alpha-blocking effect in addition to beta-blocking effect, several studies have demonstrated that LSGB and beta-blockade are equally effective in treating post-myocardial infarction malignant VT [11, 13]. Few patients receiving beta-blocking agents for electrical storm can develop electromechanical dissociation [13]. However, a strong counter argument in favor of IV beta-blockade is its ease of use and ready availability compared to acute LSGB. The latter requires some degree of expertise, is not always successful, and is more difficult to implement when time is of the essence. Further, the effects of acute LSGB can dissipate resulting in recurrence of malignant VT [13]. The present report did not comment on this event and the strategy put in place to rectify the situation. In fact it may turn out that the best use of acute LSGB would be in hospitalized patients with electrical storm who are relatively more stable compared to out-of-hospital cardiac arrest patients.

Acute LSGB is just one attempt to address the challenge of current management of electrical storm and out-of-hospital cardiac arrest. Another management modality has been rescue VT ablation of drug refractory electrical storm in patients with acute coronary syndrome [14], with ischemic cardiomyopathy [15], or ICD [16].

The dramatic change in the last decade in the management of malignant VT is explained both by the development of effective nonpharmacologic therapies such as targeted ablation of the arrhythmogenic tissue and the ICD as well as the limited efficacy and proarrhythmic potential of current antiarrhythmic agents. The failure of development of a new antiarrhythmic drug particularly for electrical storm in the setting of acute coronary syndrome is not because of lack of trying on the part of the pharmaceutical industry. In fact different innovative approaches to antiarrhythmic drug therapy have been exploited [17]. To mention a few: 1) The adenosine-triphosphate sensitive (K_{ATP}) K^+ channel is a metabolic sensor that opens during myocardial ischemia [18] and has a key role in ischemic action potential duration shortening. K_{ATP} has a complex role, mediating cardiac protective as well as arrhythmogenic functions. These actions can be dissociated with cardioprotective function mediated largely by a mitochondrial K_{ATP} channel and electrical changes due to a sarcolemmal channel [19]. Certain compounds can selectively block the sarcolemmal K_{ATP} channels and prevent associated malignant VT [20]; 2) Cell-to-cell communications and their pharmacological manipulation has yielded new approaches to ischemia-associated uncoupling of gap junctions and its role in promoting malignant VT [21]. Several recent experimental studies have shown that drugs that enhance gap junction conductance like rotigaptide can be antiarrhythmic in the setting of acute ischemia [22]; 3) The identification of calstabin2 depleted ryanodine receptor (RyR_2) as a source of diastolic sarcoplasmic reticulum (SR) Ca^{2+} leak in catcholaminergic polymorphic ventricular tachycardia and in patients with heart failure susceptible to malignant VT has led to the hypothesis that increasing calstabin2 binding to RyR_2 could be a potential new target to treat triggered malignant VT [23]. Whether this approach is helpful in arrhythmias secondary to acute ischemia is not known.

There are at least 3 reasons why no new effective antiarrhythmic drug against ischemia-related malignant VT has made it to the clinical setting in the past several years: 1) The heterogeneity of the arrhythmogenic substrate during ischemia and in the post-infarction period is a daunting obstacle; 2) There is a plethora of experimental studies showing significant antiarrhythmic effect of one or another new drug but preciously little clinical data. It is indeed reasonable to question the validity of some of the experimental models currently in use for new antiarrhythmic drug development; 3) In view of this author, a main limitation for the development of a new clinically effective antiarrhythmic drug therapy for ischemia-related VT is simply our current incomplete understanding of the underlying electrophysiological mechanisms. One prominent example is the recent report showing that ischemia/ /reperfusion associated ventricular arrhythmias may be secondary to fast oscillatory intracellular Ca^{2+} responses that can trigger local ventricular depolarizations [24]. The latter, based on how these conduct to the surrounding myocardium can explain

both the sporadic ventricular premature beat as well as ventricular fibrillation.

In summary, the report of Amino and associates is important for focusing the attention on the challenge in management of electrical storm and out-of-hospital cardiac arrest and the need for continued search for new management modalities in these situations.

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