EVALUATION OF ANTIARRHYTHMIC DRUGS. SHOULD THE LOWN CLASSIFICATION BE USED AS A MEASURE OF EFFICACY?

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INTRODUCTION

Current methods of identifying and developing drugs have provided a wide range of therapies predominated by those with local anaesthetic activity. Clinical investigations have shown these drugs to be effective in the control of an individual patient's ventricular arrhythmias. Confirmation of anti-arrhythmic activity of these agents in patient populations has come predominantly from observations of reduced ventricular ectopic complex frequency with their use. Despite this undisputed efficacy, these drugs have performed poorly preventing apparently arrhythmic deaths in high risk patient populations. In the management of patients after the acute phase of myocardial infarction, prophylactic therapy with procainamide (1), diphenylhydantoin (2), mexiletine (3) and aprindine (4), has usually reduced ventricular ectopic frequency without affecting mortality. In similar studies, practolol (5) and alprenolol (6) significantly reduced mortality although neither drug would be considered as a powerful agent against ventricular arrhythmias.

In survivors of out-of-hospital ventricular fibrillation, a recent report has suggested reduced mortality with the use of local anaesthetic antiarrhythmic drugs despite a disappointing action on ventricular ectopic complex frequency (7). These apparent discrepancies may be explained in a variety of ways. For instance, ventricular arrhythmias may be markers of risk in some patients but death when it occurs is not arrhythmic. Most evidence is to the contrary. Any other explanation must question the capabilities of the drug to prevent fatal arrhythmias. In clinical practice it is rarely feasible to test antiarrhythmic drugs directly against arrhythmias such as ventricular fibrillation and we often rely upon their effect against lesser arrhythmias. What potential flaws can we identify in our methods of evaluating antiarrhythmic drugs? In clinical research of antiarrhythmic drugs the Lown Classification of ventricular arrhythmias is the most widely used system but it was not derived originally for this purpose. Introduced
in 1971 on the basis of ECG observations of patients following acute myocardial infarction it became the foundation of arrhythmia management in most coronary care units (8). Even in this context, the validity of the Classification is now being challenged. Data from analyses of continuous ECG recordings had suggested that its original premises do not hold true (9, 10, 11). Whether or not it has a role in the management of patients with acute myocardial infarction, it remains the only classification of ventricular arrhythmias in widespread use. Is it justifiable to use this system in the evaluation of antiarrhythmic therapy? The seductive simplicity and flexibility of the original classification ensured its survival, with modifications, to the present (12). These adaptations have improved the scope and precision of the Classification which can now be used to describe not only categories of ventricular arrhythmias but also their incidence and prevalence. Nonetheless, difficulties arise in the use of this Classification for the evaluation of antiarrhythmic therapy. The basic problems are the misuse of the Classification and the fundamental limitations of the Classification.

**MISUSE OF THE LOWN CLASSIFICATION**

**Category Grouping**

In many studies categories of the Lown Classification are grouped together. The most common arrangement is separation of simple ventricular arrhythmias (grades 0, 1 and 2) from "complex" or "malignant" ventricular arrhythmias (grades 3, 4, and 5). Reducing the categories of ventricular arrhythmias from six to two artificially increases the frequency of events within these two categories. There is no data to support this practice and indeed it is highly unlikely to be scientifically valid. For instance, it implies that abolition of multiform ventricular ectopic complexes (grade 3) has the same significance as abolition of ventricular tachycardia (grade 4). This is methodologically unsound for antiarrhythmic drug evaluation.

**Hierarchical Use with Single Grade Allocation**

A number of investigations have described patient's arrhythmias as the highest grade achieved in the Lown Classification. Drug effectiveness has been assessed by reduction of Lown Grades. Whilst acceptable for Lown Grades 2, 1 and 0 which form part of a continuous spectrum of frequency of single ventricular ectopic complexes, the practice is not