Dr. Gordon Moe and the Analysis of Sustained Irregularity of the Pulse

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Introduction

Dr. Moe probably would have been the first to recognize that the title of this article is the translation of the title of Hering's article (Hering, 1903), in which for the first time the clinical syndrome we call atrial fibrillation (AF) has been described.

Indeed, continuous irregularity of the heart was recognized and described well before the age of the electrocardiograph (Katz and Hellerstein, 1982), but physicians had no way of understanding what actually happened in the heart until 1911, when Lewis observed "fibrillation of the auricles" in an open-chested horse with "irregularity of the heart's action" (Lewis, 1911-1912). At that time, serendipity had not yet been introduced in medical literature, but Lewis certainly deserves the credit of showing serendipity for relating his observations in a slaughterhouse with what he called "complete irregularity of the human heart." Ever since then, mechanism(s) that cause "complete irregularity of the human heart" have remained an enigma and an intellectual challenge to clinician and physiologist alike. Since no intellectual challenge, where the electrical behavior of the heart is concerned, escaped Dr. Moe's attention, he studied cause and effect of fibrillating atria.

This paper is a short tribute to Gordon Moe and his contribution to our understanding of atrial fibrillation.

Ventricular Response in Atrial Fibrilation

Despite Lewis' far-reaching foresight in introducing the term "complete irregularity of the human heart," he did not and could not give a quantitative definition, let alone a mathematical analysis, of the irregularity of the heart (actually the ventricles) during AF. It had to wait until the computer era before an attempt could be made to analyze and describe in mathematical terms how irregular the heart is during AF (Horan and Kistler, 1961; Braunstein and Franke, 1961; Goldstein and Barnett, 1967).

After the introduction of sophisticated time-sequence analyzing techniques in the early fifties, the irregular ventricular rhythm in AF became the target of studies of several groups of investigators. The results were influenced by the choice of statistical technique, but also by the selection of patients, and the introduction of what was called "artificial AF," for the study of ventricular irregularity gave rise to confusion and even controversies (Urbach, 1984). In a study we published in 1970 (Bootsma, et al., 1970), employing serial autocorrelograms and histograms in patients with permanent AF before and during digitalis treatment, at rest, and during exercise, we finally came to the conclusion that the ventricular rhythm in patients with uncomplicated AF is random; we return to this concept later. Figure 1 shows the histogram and autocorrelogram of RR intervals of a patient with AF (A) before, and (B) during digitalis treatment. Despite a significant change in the shape of the histogram due to digitalis, the autocorrelogram was not affected by the treatment. We also found that in spite of its effect on ventricular rate, exercise did not change the random behavior of the ventricular rhythm.

These findings did not support the original theories developed by Moe and Abildskov in 1964 (Moe and Abildskov, 1964). They had found clustering of long and short RR intervals, and concluded that concealed conduction in and changes of the effective refractory period of the AV junction determined the irregular pattern of ventricular responses during AF. Moe and Abildskov, however, used dogs in which they had

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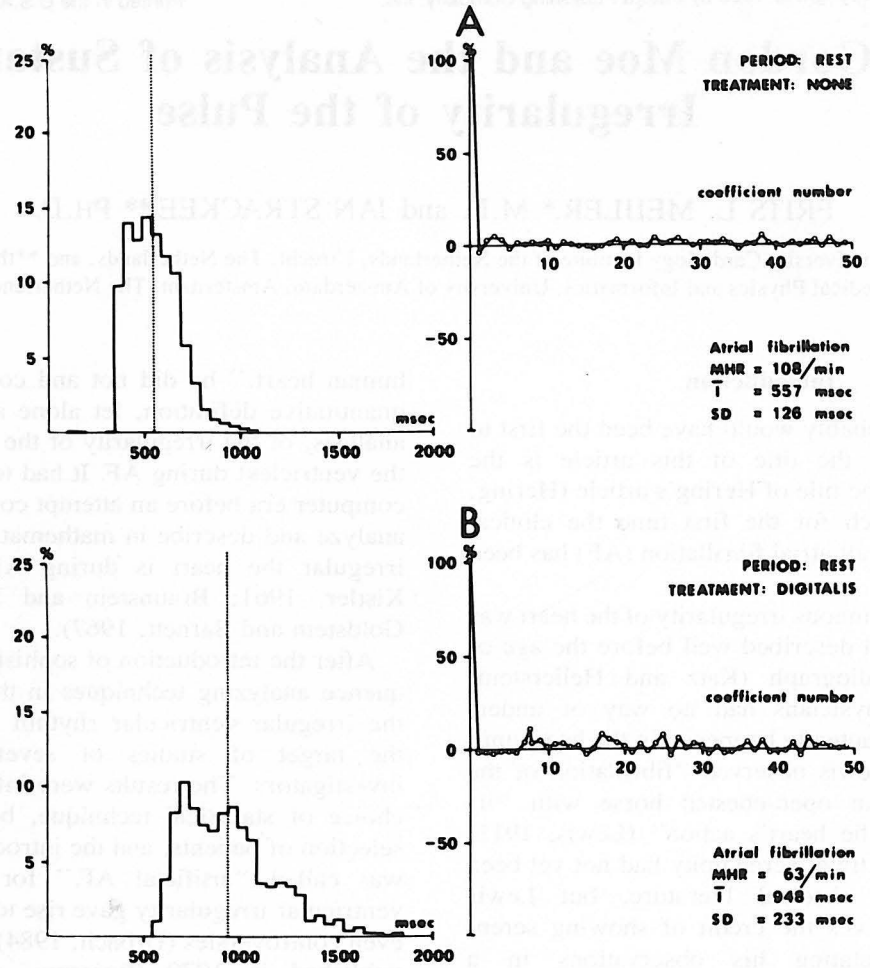

Figure 1. *Autocorrelogram and histogram of a patient with sustained AF before (A), and after (B) digitalis treatment. Despite the change in histogram, the autocorrelogram did not change, so the ventricular rhythm remained random. (Reprinted with permission from Bootsma, et al., Circulation 1970;41:783-794).*

introduced AF by rapid (regular) stimulation of the atria. Indeed, in this experimental setup the irregularly beating ventricles do not show a random rhythm (Strackee, et al., 1971). In 1978 a WHO/ISFC Task Force considered a random ventricular response a prerequisite for the existence of AF in human patients (Robles de Medina, et al., 1978).

When we accept that irrespective of the shape of the histogram, the ventricular rhythm has to be random for the diagnosis of AF to be made, it follows that the electrical characteristics of the fibrillating atria ultimately determine whether or not the ventricles will be depolarized in a random fashion. Only a random input into the atrioventricular (AV) junction will result in a random, if scaled-down random output (Meijler, 1983).

Definition of Randomness

The term "complete irregularity" of the human heart in atrial fibrillation, as first used by Lewis, provides no mathematical or statistical handgrip to distinquish between AF and other atrial arrhythmias like atrial flutter, which may result in irregular ventricular rhythms as well. One of Dr. Moe's major contributions to cardiac electrophysiology has been his design of quantitative and mathematically sound experiments for the explanation of the underlying mechanisms of arrhythmias in clinical cardiology. We therefore consider it appropriate to offer some mathematical background from which our original conclusion, that the ventricular rhythm in AF is random, has been derived.

To put Lewis' term "complete irregularity of the human heart" on a more mathematical basis, we considered the occurrence of heart beats as a point process. This is a process in which the duration of an event—here the R wave—is short compared with the interval time between the events. The best-known point process is the one formed by the emissions from a radioactive source. However, the action potentials of a nerve fiber, wars, and coal-mining disasters can and have been considered such a process (Cox and Isham, 1980).

A basic tool for the description of such time series is the histogram of the interval times. However, it is clear that when one scrambles the intervals, the histogram does not change, so one needs a second tool. For this we used the autocorrelogram, being a measure of how the intervals are mutually related (Bootsma, et al., 1970).

In the patients with AF we investigated, it turned out that the values of this measure always pointed to mutual independence between the RR intervals. We therefore defined the ventricular rhythm during AF as such, i.e., a time series having mutually independent intervals.

In a statistical sense, the RR intervals in AF form a renewal process. This is a point process without memory, meaning that after each event the process starts from scratch, totally disregarding its past. This simplifies matters, since the process is then completely covered by its histogram. For instance, a radioactive process has an exponential histogram, sometimes referred to as Poisson histogram (Cox and Lewis, 1966). Looking at the RR interval histograms during AF (Fig. 1), they seem to belong to the class of gamma densities. These densities can be produced by a radioactive source that generates intervals by selecting, for instance, every fifth or tenth emission. Accordingly, AF could be thought of as randomly-spaced impulses with an exponential histogram arriving at the AV node from random directions, and being divided by 5 or 10. This principle of dividing randomly-spaced impulses was formerly used to make a so-called uranium clock.

It did not seem very hard to explain the histograms and autocorrelograms of the RR intervals under our AF definition, and this is what we have been doing for the last 25 years. However, it now appears that we probably made a mistake in the interpretation of AV nodal function, because recent clinical findings (Wittkampf, et al., 1988 and 1989) do not seem to confirm our original ideas (Bootsma, et al. 1970), nor the experimental findings by others (Mazgalev, et al., 1982). This problem is currently under study.

What Causes the Atria to Fibrillate?

In a number of computer simulation studies, Moe and Abildskov were able to analyze and define the factors that cause the transition of a well-organized excitation pattern of the atria, for instance during sinus rhythm, into a self-sustaining electrical chaos during fibrillation (Moe and Abildskov, 1959; Moe, 1962; Moe, et al., 1964). Moe and his co-workers discovered that (1) the total number of cardiac cells involved, and (2) the (in)homogeneity of the electrical properties of those cells are the major prerequisites to cause the atria to fibrillate. One should take into consideration that cardiac muscle is composed of individual cells, which, in all mammals (from mouse to whale), are quite uniform in diameter (Sommer and Johnson, 1970 and 1979; Meijler, 1985). Since large mammals have large hearts, large atria, and many myocardial cells, atrial fibrillation is often seen in large animals, e.g., horses (Hilwig, 1977; Deem and Fregin, 1982; Meijler et al., 1984). The (in)homogeneity of the electrical properties of the atrial myocardial cells also have to be taken into account, however. For each given individual the ventricles contain more cells than the atria, but we must realize that ventricular electrical homogeneity is preserved by the presence of the His-Purkinje system, and the larger the heart, the more elaborately the Purkinje fibers are intertwined with the ventricular myocardial cells (Meyling and ter Borg, 1957). Only gross morphological and functional changes of the myocardium, e.g., myocardial infarction or myocarditis and short-circuiting of the AV node during AF in patients with a Wolff-Parkinson-White Syndrome (Wellens and Durrer, 1974), may cause the ventricles to fibrillate. Since the atria of the larger mammals do not contain Purkinje fibers, more subtle changes in the electrical properties of atrial myocardial cells may result in chaotic electrical behavior, and thus cause the atria to fibrillate. Whether this chaotic electrical behavior of the atria is related to chaotic motion, as introduced among others by Schuster (Schuster, 1988), is open for discussion. The combination of a sufficiently large atrium and myocardial changes that cause (sufficient) electrical inhomogeneity is

necessary to develop and sustain AF in humans and animals.

Spach (Spach, et al., 1988), and Allessie and co-workers (Allessie, et al., 1985) have further laid the basis for our understanding of the electrophysiology of atrial fibrillation. The fibrillation threshold is set by the number of cells and their electrical properties. It is therefore of considerable interest that when the link between spontaneously fibrillating auricles (Sir Thomas Lewis' term) and irregularity of the heart's action was definitely established for the first time, a horse was involved. The chances are slim that Lewis could have seen spontaneously fibrillating auricles in dogs, cats, or even smaller animals.

AF therefore is common in horses (Deem and Fregin, 1982), humans (Brill, 1937), and large dogs (Bohn et al., 1971), because their atria contain a large number of cells and their life span is long enough to develop atrial myocardial abnormalities, and thus inhomogeneity, through fibrous tissue or disease. Selzer (Selzer, 1982) and Godtfredsen (Godtfredsen, 1985) gave comprehensive reviews of the clinical syndromes that usually accompany or cause AF. The real-life picture of AF in human patients is a further confirmation of Gordon Moe's theory.

Conclusion

Our understanding of AF as a pathophysiological mechanism in clinical cardiology is based mainly upon Moe's experimental and computational work. AF is caused by a chaotic electrical behavior of the atria, which can be explained by Moe's multiple wavelet theory, and which results in a random ventricular response. The random ventricular rhythm is the basis of the clinical diagnosis of the arrhythmia. It is therefore not only to basic cardiac electrophysiology, but also to clinical cardiology that Dr. Moe has made an everlasting contribution.

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