Editorial

Recent Advances in Clarifying the Genesis of Cardiac Fibrillation

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The genesis of cardiac fibrillation has not been ultimately clarified in spite of intense efforts by many investigators for a long time. A number of theories advocated up to the present can be in essence classified into two varieties: re-entry theories and ectopic focus theories. The former includes theories of large circus movement, of micro re-entry, and of one and multiple re-entries. The latter includes single and multiple ectopic focus theories. Reviewing recent trends since the symposium in “Circulation,” it is found that, in addition to the time-honored dispute between the two varieties, many studies have been done on the ionic aspects of fibrillation. The reason seems to be as follows. A great variety of factors were mentioned as inducing fibrillation such as biochemical agents, hormonal and neural factors, physical environment, etc. But, since fibrillation is an abnormal electrical activity of the cell membrane, they may be ascribed to more essential factors such as changes of electrolytes outside and inside the cell and of various cell-membrane characters.

Reliability of Old Theories on Fibrillation

Long active controversies seem to give the impression that there must be ample evidence for each proponent. Actually, however, most of the evidence was obtained in experiments of flutter, and presumptions have been extended to the mechanism of fibrillation. Not a few experiments have been done on fibrillation, but these have given only questionable results. For instance the multiple direct lead electrocardiogram was used formerly to pursue the propagation of excitation in fibrillation. A short time after the onset of fibrillation it becomes extremely difficult to find any relationship between deflections of all the leads taken simultaneously. High speed cinematography gives only illusions. Furthermore, Sano et al.3) showed by microelectrodes that in the

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middle or terminal stage of fibrillation fractionation was so extreme that the electrocardiogram, even the direct close bipolar lead, could not show the electrical activity of one muscle group, because it took the electrical field of a number of myocardial fibers. How can we discuss the electrical activity of a group of cardiac muscle in fibrillation when even the direct close bipolar lead electrocardiogram takes electrical activities of several groups which activate differently? In order to use the electrocardiogram for analysis of the propagation pathway of fibrillation waves, appropriate stages must be selected when disintegration is not so marked. This is the reason why Sano and Scher\textsuperscript{3}) selected the initial stage and recovery stage in a study employing direct close bipolar leads. For analysis of other stages other methods should be devised.

**RE-ENTRY THEORIES**

Re-entry theories have gained more elaborate support recently, but this may be a kind of rebound from the tendency of 10 years ago when Scherf's\textsuperscript{4}) and Prinzmetal's\textsuperscript{5}) theories were so influential. Tenney and Wedd\textsuperscript{6}) exposed the isolated turtle auricle to aconitine and found a multiple response by single, properly-timed shocks. This multiple response occurred at a time when all spontaneous pacemakers of the heart showed a profound depression. Acetylcholine increased the rate and prolonged the rate of the multiple response. Furthermore, "the marked shortening of refractory period and slowing of conduction by aconitine together with the fact that the stimulus that evokes a multiple response must be placed in the relative refractory, a time of maximum tissue nonhomogeneity," led them to support the hypothesis of re-entry rather than of focal mechanism. On the contrary Goto and Tamai\textsuperscript{7}) supported rather focal mechanism because of their experiments by a similar method but with different results: they found that acetylcholine inhibited aconitine-induced fibrillation of the rabbit atrium and that atropine or adrenaline promoted it. Covino and D'Amato\textsuperscript{8}) studied the mechanism of ventricular fibrillation of mammals in hypothermia and supported the circus movement theory by finding a marked reduction in conduction velocity which was not counterbalanced by a proportional prolongation of the refractory period. Moe and associates\textsuperscript{9,10}) found that the refractory period of the dog atrium was not uniformly abbreviated by vagal stimulation and showed that a self-sustaining atrial fibrillation independent of focal discharge was possible in the presence of adequate cholinergic discharge. They\textsuperscript{11,12}) also found with the dog ventricle that temporal dispersion of recovery was increased after an early premature beat. It increased whether the average refractory period was reduced (sympathetic nerve stimulation, ouabain intoxication, ischemia),
or increased (chloroform, quinidine in high dosage, or hypothermia). They believe that such nonuniformity of cardiac excitability induces fibrillation by re-entrant mechanism. Employing the Starling heart-lung preparation of the dog, Burn and associates\textsuperscript{13)\textsuperscript{13))} reported that they could always induce atrial fibrillation by infusing acetylcholine with electrical stimulation. In contrast to the atrium they\textsuperscript{14)\textsuperscript{14)),\textsuperscript{15)\textsuperscript{15})} could induce ventricular fibrillation not by administration of carbamylcholine, but by low potassium solutions and high calcium solutions. Burn\textsuperscript{14)} pointed out also that oxygen lack, lack of glucose, and metabolic inhibitors such as dinitrophenol, sodium azide and sodium moniodoacetate induce ventricular fibrillation. Summarizing all of these factors, Burn\textsuperscript{14)} concluded that under the influence of factors decreasing the refractory period of myocardial fibers, factors which throw fibers out of phase cause fibrillation, supporting the re-entry theory.

In considering the genesis of fibrillation, its initiating cause and maintaining cause have not been separated sufficiently. As for its maintaining cause the re-entry mechanism probably cannot be denied: we\textsuperscript{3)\textsuperscript{3)} also showed

![Fig. 1. Tachysystole appearing near the stimulating electrodes at the onset of atrial fibrillation (An unpublished record, Sano and Scher, 1961).](image)

On the left side of the record sinus rhythm is seen. Electrical single shocks were repeatedly given to the right atrium of the dog in situ, which are seen by square wave artifacts in the record. Eventually tachysystole of about 2,000 per min. appeared in channels 4 and 5 recorded by electrodes inserted close to the stimulating electrodes. Every one or two of these deflections are seen to spread to the other leads. This was actually the onset of the atrial fibrillation.

Channels from 1 to 7 were close bipolar leads obtained at various sites of the atrium. Channel 8 was the standard bipolar limb lead 2. Time marks at the top and the bottom indicate 50-msec. time interval. See ref. 3 for details.
its possibility by observing the recovery phase of short-lasting fibrillation. But the possibility of re-entry as initiating cause needs more evidence.

Sano and Scher\textsuperscript{3}) found extreme tachysystole of about 2,000 per min. at the area very close to the stimulating electrodes and regarded this as the initiating cause of atrial fibrillation (Fig. 1). The ordinary type of fibrillation occurs with every one or two tachysystoles spreading to the whole atrium. This might be interpreted to mean that fibrillation was caused by an increase of excitability at one focus. Fibrillation seems to have started from one focus, but we really do not know whether there is increase of excitability or micro

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![Fig. 2. Straightening of the propagation pattern at the recovery phase of the atrial fibrillation. (An unpublished record, Sano and Scher, 1961)](image-url)

At the last beat of atrial fibrillation, which is denoted by a black arrow above the record, the deflection of each lead was seen lined up, namely the propagation pattern connecting time points of these deflections of this beat became shorter in duration than that of any other preceding beats during atrial fibrillation. Simultaneous records of the cathode ray oscilloscope and of the direct writing oscillograph were lined up by the time marks recorded at the top and the bottom of each record. The lowest channel was the standard bipolar limb lead 2 and the P wave and the QRS complex can be seen on this channel at the sinus beat after fibrillation which is seen on the right end of the record. All of the other channels were close bipolar leads placed various sites of both atria of a dog in situ. See ref. 3 for details.
re-entries in this small focus. The possibility of micro re-entry impressed us because at the recovery phase of the same short-lasting atrial fibrillation a strange phenomenon which we called straightening of the propagation pattern was occasionally observed (Fig. 2). Some of these seem to suggest a recovering mechanism of fibrillation in which a few separated groups of cardiac muscles fall into phase. This is a spontaneous defibrillation which is supposed to have a mechanism similar with that presumed for artificial defibrillation. The mechanism of artificial defibrillation is said to be simultaneous depolarization, and the fact that this is effective for defibrillation is said to support the re-entry theory. For as Scherf\textsuperscript{16} pointed out, if increase of excitability is the cause, how can it be stopped by an electrical shock? However, this line of thinking is not decisive at all. We have not any conclusive evidence as to whether our observation of tachysystole was due to increase of excitability or to micro re-entry.

**Ionic Factors and Those Which Change the Cell-Membrane Characters**

A number of factors causing fibrillation have been mentioned. Some are more essential than others. It is important to analyze the mechanism by which electrical stimulation or aconitine application induces fibrillation, since any agents may cause fibrillation eventually by a mechanism similar to this. It is important as well to find out factors which are more likely to cause fibrillation clinically. As such, oxygen lack, mechanical stretch, thyroid hormone, hypothermia, acidosis and so forth have been mentioned. From these factors might probably be deduced more essential factors. For example, Covino and Hegnauer\textsuperscript{17} considered acidosis and hypothermia as exerting their deleterious effect via a change in the electrolyte balance of the heart by finding that myocardial exchange between intracellular potassium and hydrogen ions and extracellular calcium ions was observed only in those hypothermic acidotic dogs which succumbed to ventricular fibrillation. Recently, the general tendency has been to regard ionic changes and changes of cell membrane characters as more essential factors than the above-mentioned stretching, temperature, oxygen, hormones and so forth. Many attempts have been made along this line for explaining fibrillation. It is rather surprising how confusing and even contradictory various results have been. First of all the role of potassium ion in fibrillation has been contradictory in appearance, since it has been said to induce as well as to abolish ventricular fibrillation. Harris and associates\textsuperscript{18} suggested that the potassium released from the ischemic myocardium might act as an excitatory factor at the boundary of the infarction.
and establish ectopic foci. They advocated this by evidence that injection of cardiac tissue extract or of potassium solution into the coronary stream elicits extrasystoles and anoxic cells liberate potassium. However, other investigators presented evidence that low potassium induces fibrillation and high potassium defibrillates. For instance, Armitage et al. showed that the proportion of heart in which ventricular fibrillation persisted after electric stimulation could be raised from none to include all hearts by decreasing the potassium concentration in the perfusing fluid from twice the normal content to one quarter. And when potassium alone was not sufficiently effective in reversing ventricular fibrillation, the addition of glucose with or without insulin was frequently successful by inducing potassium into the cell. Infusion of insulin-glucose or of sodium bicarbonate acted probably in the same way. When potassium induces fibrillation, it occurs probably in more complicated situations, such as when Grumbach showed that injections of KCl after administration of epinephrine initiate an accelerating ventricular tachycardia ending in fibrillation. He explained that such KCl causes A-V block enabling epinephrine to cause a paroxysmal ventricular tachycardia, and secondly, that it causes the paroxysmal ventricular tachycardia to accelerate by delaying the recovery of excitability so that at least one premature systole can fall into the recovery phase of a preceding impulse, initiating a self-sustaining tachycardia ending in fibrillation.

As for the mechanism by which low potassium causes fibrillation, no clear conclusion can be drawn. In the case of atrial fibrillation, Burn and associates found that the fibrillation induced by acetylcholine can be restored to normal rhythm by the infusion of KCl and attributed the maintenance of atrial fibrillation to the maintenance by acetylcholine of an increased permeability of the cell membrane to K+ ions. As for ventricular fibrillation, they found that adenosine triphosphate arrested fibrillation and dinitrophenol prolonged it and presumed that dinitrophenol depresses the action of the sodium pump to which may be linked the potassium pump for driving potassium back into the cell. It prevents the energy provided by oxidative processes from being used to replenish the cells' own store of adenosine triphosphate. They imagined that ATP arrested fibrillation by providing more energy for forcing back the potassium between the contractions. However, Holland and Tinsley found that dinitrophenol, NaCN and ATP had little or no effect on the incidence of the fibrillatory process. It is probable because ATP is not believed able to enter the cell and when present externally, cannot supply the energy. The infrequent reversals of fibrillation by ATP might be due only to the calcium chelating properties of this substance.

Calcium effects are also confusing. Armitage et al. found that the cal-
The role of sodium has also given rise to conflicting opinions. Armitage et al.15) and Karki26) showed that reduction of the extracellular sodium concentration also increased the incidence of fibrillation similar to reducing the extracellular potassium concentration. Nahas and associates27) reported that the administration of 1.5 M NaCl during CO₂ washout with 100% oxygen after a period of severe hypercapnic acidosis in dogs prevented ventricular fibrillation. In contrast Grumbach28) found that low sodium solutions could stop ventricular fibrillation and regarded this as support for the hypothesis that antifibrillatory drugs and excess potassium chloride defibrillate by interfering the entrance of sodium ions in the rising phase of the action potential. The situation has been largely clarified by several reports by Holland and his associates.21),29)-33) They found that the initiation of both atrial and ventricular fibrillation was associated with an increased K efflux, decreased K influx and marked increase of Na influx. After finding that the high firing rate alone was not entirely responsible for the changes noted, they interpreted the data to suggest that both atrial and ventricular fibrillation are initiated by the same basic mechanism: that is an increase in Na entry above a critical value (K leaving the tissue in exchange). They reported also a difference in atrial fibrillation induced by acetylcholine and Ca in isolated rabbit heart. In both types of arrhythmia an increased sodium influx initiates fibrillation. If the arrhythmia is to continue there must be inactivation of this inward sodium movement. In ACh-induced fibrillation potassium appeared to make the predominant contributions to Na inactivation initially. In Ca-induced
fibrillation Cl influx played a more important role in Na inactivation. Cl movement was found to be extremely important in initiating and especially in maintaining both arrhythmias.

**The Relation Between Ionic Factors and Old Theories**

Ionic aspects of fibrillation should be eventually related with the old theories of either re-entry or ectopic focus. Overall aspects of the problem cannot be revealed until both sides are more clarified. Some attempts were already mentioned. Here only one of our recent observations related to this aspect will be described in brief, the details of which will be reported elsewhere. Among various conditions in the perfusing fluid potassium decrease with or without calcium increase was most liable to cause fibrillation in the isolated rabbit atrial muscle strip according to our results. Under these circumstances the right atrial muscle strip including the sinus node showed fibrillation much more frequently than the left atrial muscle strip, when no electrical stimulation was given. Inserting microelectrodes into the sinus node and other atrial portions together with taking direct atrial electrograms, single impulses of the sinus node were frequently found to induce tachysystole from 600 to 1,200 per min. in several parts of the atrium in the right atrial muscle strip, which developed into fibrillation. The difference of rate of occurrence of fibrillation between the right atrial strip and the left atrial strip seemed to be that the former received the sinus impulse whereas the latter did not. Therefore, a single electrical shock was given to the left atrial strip under the same circumstances. Not only did the rate of occurrence of fibrillation actually approach that of the right atrial strip, but also similar tachysystole was observed in several portions of the left atrial strip. These observations are interesting because the stimulus was not given during the vulnerable period: the sinus node impulses reached the atrium long after the preceding vulnerable period was over in the right atrial strip, and a single electrical shock was given in the quiescent stage in the left atrial strip. They are interesting also because tachysystole similar to that induced artificially by electrical stimulation in our previous experiments was actually found to be induced spontaneously by sinus node impulses in external decrease of potassium with or without increase of calcium. The tachysystole appeared to be a kind of oscillatory potential. But again the possibility of re-entry could not be excluded.

**References**