Electrophysiological Concept of Ventricular Defibrillation Mechanism

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Sudden cardiac death is a major health problem in most industrialized countries around the world including Thailand. It is mainly caused by ventricular fibrillation (VF). Currently, defibrillation is the only effective clinical treatment of this fatal arrhythmia. Although defibrillation mechanism has been investigated extensively for many decades, its definite mechanism is still debated. It is known that understanding the basic mechanism of defibrillation is essential to develop better treatment of VF. In the present article, seven hypotheses commonly proposed as the mechanism of ventricular defibrillation are reviewed. Since research in the field of defibrillation mechanism is dynamic, the present review is to update the information to clinicians and basic investigators on the mechanism of defibrillation available to date.

Keywords : *Defibrillation, Fibrillation, Mechanism*

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Sudden cardiac death is a major health problem in many industrialized countries including Thailand. It is mainly caused by a lethal cardiac arrhythmia known as ventricular fibrillation (VF)[1,2] VF has been characterized as a rapid, disorganized, and asynchronous contraction of the ventricular muscle[3,4], which causes the failure of the pumping function of the heart leading to vital organ failure and causing death within minutes[5]. The most common underlying abnormality for the development of VF is coronary artery disease[6-9]. However, approximately 40% of the victims have no history of heart disease[10]. Although VF has been known for over a century, there is only one effective treatment for this fatal arrhythmia. It is known as electrical defibrillation[11,12].

A large number of researches have been performed to investigate how VF generates[13-25], and how an electrical shock terminates it[26-32]. Despite the extreme efforts to overcome this fatal arrhythmia, it was not until several decades ago that information obtained from these studies helped to invent the first medical device known to terminate VF as well as to prevent sudden cardiac death in patients, the implantable cardioverter defibrillator (ICD). The idea of developing the automatic ICD came from Mirowski[33] and Schuder[34], who independently reported their work on the implantable device to terminate VF in dogs. Subsequently, the idea was tirelessly tested in animal studies[35-40] for more than 10 years before it was first implanted in a human in 1980[41]. The basic concept for this device is the ability to detect the arrhythmia and deliver an electric shock to defibrillate the heart and bring it back to sinus rhythm as soon as possible without false detection and false delivery of the shock.

After a decade of improvement, the ICD has been referred to as the "gold standard" of anti-arrhythmic therapy[42]. However, the current ICD still needs much improvement. This is due in part to our vague understanding of the mechanism of ventricular defibrillation and how VF occurs. This article is deliberately written to highlight some commonly proposed hypotheses that explain mechanisms of ventricular defibrillation.

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The Probabilistic Nature of Ventricular Defibrillation

Ventricular defibrillation has been known to be complicated. This is partly due to a distinct charac-

teristic of defibrillation in that it is probabilistic in nature. There is no discrete value for the shock strength (i.e. defibrillation threshold) to indicate that the shock strength at or above the defibrillation threshold will always successfully defibrillate. In fact, the relationship between the shock strength and the successful defibrillation outcome is a sigmoid shape, meaning that greater shock strengths are associated with greater percentages of success[43]. Many studies of defibrillation have been done in the past decades by using various shock strengths delivered at different timing to understand the basic mechanism behind this probabilistic nature. These data have helped investigators to hypothesize on the possible effects of the shock on cardiac tissues and the relationship of these effects to the shock outcome.

Mechanisms of Ventricular Defibrillation

The mechanism of ventricular defibrillation has been extensively investigated for many decades. However, the definite mechanism of defibrillation is still unclear. Although many hypotheses have been proposed, seven hypotheses on ventricular defibrillation are highlighted in the present review. Four of those are most commonly proposed as the mechanism for defibrillation at present. Interestingly, these four hypotheses are also related to the VF induction hypotheses. A concept of each hypothesis will be discussed briefly and whether it is a possible mechanism or not, according to current research, will be emphasized.

The total extinction hypothesis

The total extinction hypothesis was proposed by Wiggers in 1940[44]. This hypothesis, which focused on the termination of VF activation fronts by the shock, stated that the shock must depolarize all excitable tissues and stop *all* activation fronts present on the entire ventricles during fibrillation in order to obtain a successful outcome. It also implied that, after a failed defibrillation, ventricular fibrillation is reinitiated by any remaining activation front which was not halted by the shock. However, the total extinction hypothesis was later rejected by data from Zipes et al in 1975, who demonstrated that not all tissues need to be depolarized to get a successful defibrillation[45].

The electrical paralysis hypothesis

In 1968, Dudel observed the absence of cardiac electrical signals for seconds to minutes after strong shocks were delivered that successfully defibrillated[46]. Based on this observation, he hypothesized that the basic mechanism for successful defibrillation was that shocks must be strong enough to inactivate or *paralyze* cells for several seconds so that they were not excitable within that period. This hypothesis is sometimes called the "prolonged depolarization" hypothesis because it was believed that the shock must prolong the time until the first post-shock activation occurs[47].

Later reports that activation is usually observed less than a second after a defibrillation shock[18,48] allowed the rejection of this hypothesis. The prolonged depolarization after strong shocks observed by Dudel may be caused by an electroporation, i.e. a rupture of cardiac cell membrane, created by the shocks which then altered ionic concentrations inside the cells[49-51]. Jones et al[49,52] confirmed this concept when they found that the shocks created "holes" in the cell membranes of cultured chick embryo myocytes at a potential gradient of 200 V/cm. According to this finding, electrical paralysis may impede success in defibrillation because it can decrease myocyte contractile function and may possibly induce arrhythmias resulting from electroporation[51,53].

The critical mass hypothesis

The importance of a critical mass of the cardiac tissue for maintaining fibrillation was first reported by Garrey in 1914[54]. He found that a fibrillating heart would no longer fibrillate when the myocardial mass of the heart was serially decreased into smaller pieces. In the mid 1970s, studies on defibrillation showed that successful defibrillation could occur when low-energy shocks were delivered through transvenous catheters [35,39,40]. which suggested that the shock may need to defibrillate only a critical mass of the ventricles to get a successful outcome. These results challenged the total extinction hypothesis for defibrillation but corroborated Garrey's early findings.

In 1975, Zipes et al provided further validation for this idea with their study[45] and proposed that the shock does not need to stop all activation fronts on the entire heart in order to successfully defibrillate, but only those occurring in the *critical mass* of the ventricles. Activation fronts not terminated by the shock in the remaining mass are not sufficient to maintain fibrillation and soon die out. This hypothesis is known as the critical mass hypothesis. Failed defibrillation occurs because the shock failed to depolarize the critical amount of cardiac cells, allowing the remaining undisturbed cells to continue fibrillating, leading the whole ventricles back into VF. Early studies reported

that approximately 75% of the ventricular mass must be depolarized by the shock to get a successful outcome in dogs[45,54], but in a recent report, this critical mass value was reported to be $\geq$ 90%[55].

The upper limit of vulnerability hypothesis for defibrillation

Since the implementation of multi-channel electrical cardiac mapping systems, the understanding of the defibrillation mechanism has advanced. New findings obtained from these studies are not explained by the critical mass hypothesis. Chen et al and Shibata et al have demonstrated that the patterns of activation fronts following defibrillation shocks were always different from those before the shock in both successful and failed defibrillation[48,56-58]. These findings countered the critical mass hypothesis because it suggested that post-shock activations were not the unaltered activations continuing from pre-shock activations. This led to a new explanation for the defibrillation mechanism, the upper limit of vulnerability (ULV) hypothesis for defibrillation.

The ULV hypothesis for defibrillation states that, in order to successfully defibrillate, a defibrillation shock must have two of the following affects on the entire ventricles. First, the shock must stop all activation fronts present at the time the shock is delivered by either directly activating the myocardium or by prolonging refractoriness of myocardium just ahead of these activation fronts[59,60]. Second, the shock must not give rise to new activation fronts which could propagate away from the border of the directly excited region and reinitiate fibrillation[61]. It also postulates that a shock that is slightly weaker than the strength required to defibrillate terminates all activation fronts during VF, but also creates new activation fronts by stimulating myocardium in some regions during their vulnerable period, causing re-initiation of VF. The ULV hypothesis for defibrillation is opposite from the critical mass hypothesis because it suggests that all activations must be terminated by the shock and that activations which arise after the shock induce VF by the same mechanism as induction of VF by delivery of a premature stimulus during the vulnerable period[57].

Although many cardiac mapping studies support the ULV hypothesis for defibrillation[48,55,62], there are several conflicting studies[63,64]. The studies from Ideker's group demonstrated that the earliest activation, which appears in the weakest shock potential gradient region of the ventricle, has a different activation pattern than those appearing before the shock[48,56-58]. If the earliest activation was an unaltered continuation of a pre-shock activation, as the critical mass hypothesis predicts, the activation pathway would not be altered after the shock. They found that the time interval between the last activation before the shock and the earliest activation after the shock at the earliest site is also significantly longer than the cycle length of VF[48,56].

However, Witkowski et al[63] later indicated statistically that the cycle length of activation during VF at any recording site can vary within a $\pm$ 2 standard deviation of the mean measured VF cycle length at that site. Their data showed that the time intervals between the last activation before the shock and the earliest activation after the shock at the earliest site were always within a $\pm$ 2 standard deviation following failed defibrillation, suggesting that the post-shock activation was the continuation of activation before the shock. Chen et al[57], however, have theoretically shown that a new activation front arising after the shock with a different activation pattern could also be within that same range.

The most striking feature of the ULV hypothesis is that it combines the mechanism of defibrillation and VF induction into one concept. It suggests that failed defibrillation has the same underlying mechanism as successful VF induction[18,61]. One possible explanation to support this concept is the formation of a critical point, leading to reentry and VF in both cases[47,60]. However, the ULV hypothesis does not limit itself solely to the critical point hypothesis because there are several observations which the critical point hypothesis cannot explain. For example, the existence of a focal activation pattern following failed defibrillation[48,58] or successful VF induction[65] and type B successful defibrillation[18] (ie, nonsustained repetitive responses following shocks prior to a sinus beat) are good examples of observations which cannot be explained by the critical point hypothesis[47].

The refractory period extension hypothesis

It is known that the refractory period can be prolonged when a strong stimulus is delivered to relatively excitable cardiac cells[66,67]. This finding is true for a shock that is delivered during both pacing cycles and fibrillation[68-70]. The finding that the refractory period extension is greater in successful defibrillation than in failed defibrillation leads to the proposed basic defibrillation mechanism known as the refractory period extension hypothesis[11,66]: This

hypothesis states that a successful defibrillation shock extends the refractory period of action potentials in relative excitable myocardium and terminates VF wavefronts by blocking their propagation throughout the ventricles[11,63,69].

This hypothesis is likely to be the fundamental concept for both the critical mass and the ULV hypothesis because blocking the propagation of all activation fronts appearing throughout the ventricles is important in successful defibrillation. One possible way to block those activation fronts is to insure that the shock prolongs the refractory period of the action potential of the myocardium around the directly excited region throughout the ventricles. This, therefore, will prevent propagation of a new activation front. The shock strength plays an important role in this case because only a sufficiently strong shock producing optimal potential gradient will prolong the refractoriness of the myocardium. Therefore, to successfully defibrillate, the shock must create an optimal potential-gradient in the weak-potential gradient region which is far away from the defibrillation electrodes, in order to successfully prolong the refractoriness of action potentials in the low gradient areas. Several studies [18,56,58] reported that a longer post-shock response duration (an isoelectric window) has a higher success rate of defibrillation, which is consistent with this hypothesis.

Nonuniform dispersion of refractoriness on the myocardium, proposed to be a mechanism for VF induction, can also be a factor that may contribute to failed defibrillation after the shock[71,72]. Since different strength shocks create different potential gradients in high and low intensity regions, and a stronger shock can prolong the refractoriness more than a weaker shock, each shock strength may create a different degree of refractory period extension at different regions throughout the ventricles. A successful defibrillation shock, therefore, causes a more uniform refractory period extension, decreasing dispersion of refractoriness, throughout the ventricles[72,73].

The synchronized repolarization hypothesis

Synchronized repolarization or constant repolarization time after the shock has been proposed as another cellular response in successful defibrillation[74]. The finding indicated that shocks could create an additional phase of depolarization throughout all phases, from just after completion of the upstroke (phase 0) to a nearly maximal repolarization time (late phase 3), of the fibrillating action potentials. This hypothesis states that the shocks cause the myocardium to repolarize at a constant time after the shock regardless of its fibrillating electrical activity prior to the shock. This constant repolarization time after the shock creates a uniformly prolonged post-shock response duration (an isoelectric window) as well as a reduction in dispersion of refractoriness in successful defibrillation. So far, this hypothesis is supported by only one study in an isolated perfused rabbit heart[74]. A recent defibrillation study in pigs has demonstrated that synchronized repolarization was observed following both successful and failed shocks of near defibrillation threshold in strength[75].

The virtual electrode polarization hypothesis

The latest mechanism of defibrillation is proposed by Efimov and is known as the virtual electrode polarization hypothesis[76]. This is due to the findings that defibrillation shocks delivered to cardiac tissues can produce both depolarization and hyperpolarization in cardiac tissues adjacent to each other simultaneously[76,77]. Therefore, if the optimal transmembrane potential gradient between the depolarized and hyperpolarized regions is met, activation fronts in the depolarized region can propagate into the hyperpolarized region, leading to reentry and eventually VF. Currently, the virtual electrode hypothesis and the ULV hypothesis for defibrillation are the most debated hypotheses.

Pros and Cons on defibrillation mechanisms

Most mechanisms of defibrillation presented in the present review propose that reentry is the post-shock activation pattern responsible for failed defibrillation. However, recent electrical and optical mapping studies have demonstrated otherwise. Following shocks of strength near the defibrillation threshold (DFT), recent electrical[78-80] and optical mapping studies[75] have consistently demonstrated that the first few post-shock cycles always arise in one region where the weakest shock field is located. These early sites give rise to activation fronts that propagate focally across the entire epicardium in an organized, cohesive cycle. For transvenous defibrillation with electrodes in the right ventricle and superior vena cava, these early sites are at the left ventricular apex[75]. These early sites give rise to rapid activations which either last for 5 or more cycles before degenerating into VF in failed defibrillation or spontaneously terminate after 1 or more cycles in successful defibrillation. In both cases, the characteristics of the first post-shock activation are not different. However, successive cycles arise

from the early sites faster and propagate slower in failed defibrillation, whereas, they arise slower from the early site and propagate faster across the ventricles in successful defibrillation[78-80]. No reentry was present on the epicardium during the first 5 cycles. A recent three-dimensional mapping study has demonstrated similar results, suggesting that transmural or endocardial reentry was not present following near DFT shocks[81].

It has been postulated that these first few rapid repetitive post-shock activations observed after the shock could be caused by afterdepolarizations or triggered activity[82,83]. During VF, heart rate is greatly elevated. Following a defibrillation shock, additional factors such as increased sympathetic tone, myocardial stretch, tissue damage, and reperfusion may be involved. These factors alone or in an additive fashion help promote delayed afterdepolarizations (DADs) [84,85]. In addition, recent optical mapping studies have demonstrated that following near-DFT shocks, complete repolarization is observed followed by a 40-60 ms quiescent period after which repetitive focal activations appear on the epicardium and later degenerate into VF[75]. This finding indicates that the first ectopic cycle arises after complete repolarization is achieved after the shock, suggesting that DADs are a possible mechanism of the rapid repetitive post-shock activity. Recently, defibrillation efficacy has been tested using a DAD blocker which is shown to be able to significantly decrease the DFT[86].

Conclusion

Defibrillation is very complicated. Despite enormous research on the mechanisms of defibrillation, the definite mechanism is still controversial. It is possible that all proposed hypotheses for defibrillation are true but for different circumstances[87]. Furthermore, most information regarding these hypotheses has been acquired from animal studies. They have yet to be validated in the clinical setting since the ultimate goal of research in this field is to understand the mechanism of defibrillation and to improve the treatment of VF in humans. Understanding the mechanisms of defibrillation will assure a development of better strategies to treat patients suffering from lethal arrhythmias.

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Summary of Abbreviations

DADs = Delayed afterdepolarizations
DFT = Defibrillation threshold
ICD = Implantable cardioverter defibrillator
ULV = Upper limit of vulnerability
VF = Ventricular fibrillation

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สรีรวิทยาทางไฟฟ้าของการเกิดดีฟีบริเลชั่นในหัวใจทางคลินิก

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การเสียชีวิตอย่างเฉียบพลันจากโรคหัวใจ เป็นปัญหาทางสุขภาพที่สำคัญในกลุ่มประเทศทางอุตสาหกรรม รวมถึงประเทศไทยเองด้วย สาเหตุหลักของการเสียชีวิตชนิดนี้มักมาจาก การที่หัวใจห้องล่างเต้นผิดจังหวะชนิดร้ายแรง ที่เรียกว่า Ventricular Fibrillation (VF) ในปัจจุบันนี้ การรักษา VF มีอยู่เพียงวิธีเดียวคือ การปล่อยไฟฟ้าแรงสูงเข้าไป ทำการช๊อคหัวใจ ที่เรียกว่า ดีฟีบริเลชั่น (Difibrillation) ถึงแม้ว่าการค้นคว้าวิจัยในกลไกการเกิด ดีฟีบริเลชั่น ได้ทำมานานแล้ว ความเข้าใจในกลไกนี้ยังไม่ชัดเจน ในบทความนี้ เจ็ดสมมุติฐานของกลไกการเกิด ดีฟีบริเลชั่น ได้ถูกนำมาเสนอ ทั้งนี้เพื่อจะได้เป็นข้อมูลในการช่วยให้เกิดความเข้าใจในเรื่องของกลไกการเกิด ดีฟีบริเลชั่น แก่แพทย์และนักวิจัยต่อไป