Experimental Study of the Effects of Multi-site Sequential Ventricular Pacing on the Prophylaxis of Ventricular Fibrillation

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SUMMARY

Previous studies report a significant prophylactic effect on the occurrence of atrial fibrillation by simultaneous multi-site atrial pacing. We investigated the effects of multi-site sequential ventricular pacing (MSVP), which may be preferable to simultaneous multi-site pacing in terms of the prophylaxis of the occurrence of ventricular fibrillation (VF).

Needle electrodes were inserted at ten different epicardial sites on both ventricles for MSVP in 12 adult beagle dogs. Four premature ventricular extrastimuli (PVE) were introduced to provoke VF reproducibly from a separate electrode in the left ventricle. The 4 PVE were applied to try to provoke VF during MSVP in a comparable fashion to the activation sequence during sinus rhythm. We compared the prophylactic effects of MSVP on the inducibility of VF by changing the number of stimulation sites to either 1, 3, 5, or 10 epicardial sites.

We performed a total of 363 trials of induction and suppression of VF. The occurrence rates of VF by the 4 PVE for the various number of epicardial stimulation sites of MSVP, i.e., at 1, 3, 5, and 10 sites, were 0.8263, 0.4286, 0.4450, and 0.2857, respectively ($p < 0.05$). There was a significant prophylactic effect of MSVP on the inducibility of VF, and this effect became stronger as the number of MSVP sites was increased from 3 to 10. The hemodynamic state was relatively stable during MSVP.

MSVP seems to be a promising method with which to reduce the occurrence of VF, and a larger number of stimulation sites would be more...
VENTRICULAR fibrillation (VF) is potentially lethal and the most common arrhythmia documented at the time of sudden cardiac death.\textsuperscript{1,2} Despite considerable research efforts, the mechanism that sustains this arrhythmia remains disputed. There are several therapeutic modalities to treat VF. Antiarrhythmic agents,\textsuperscript{3,4} catheter or surgical ablation,\textsuperscript{5,6} and implantable defibrillation devices\textsuperscript{7,8} are options available for the treatment for this lethal ventricular dysrhythmia. However, there are no reliable methods to predict or prevent its occurrence, not only because of the apparent random and chaotic nature of fibrillation, but also because the precise mechanisms of its initiation, maintenance, and termination are unknown. Recently, multi-site atrial pacing has been proven to be effective for prophylaxis of paroxysmal atrial fibrillation. Therefore, multi-site ventricular pacing may potentially be prophylactic against the occurrence of ventricular fibrillation. In the present study, we investigated the effects of multi-site sequential ventricular pacing, which may be more physiological than simultaneous ventricular pacing, on the prophylaxis of VF.

**METHODS**

Twelve adult beagle dogs weighing 10 to 15 kg (11 ± 0.7 kg) were anesthetized with a bolus of intravenous sodium pentobarbital (30 mg / kg) and maintained on a constant-drip infusion of 2 mg / min throughout the study. Ventilation was maintained via a cuffed endotracheal tube and a Harvard respirator at room air. A median sternotomy was performed and the heart suspended in a pericardial cradle. The femoral arterial pressure was monitored continuously with a fluid-filled catheter using the cut-down procedure. The animals were perfused with saline at flow rates of 2.0 to 2.5 ml / min / kg and the mean femoral arterial pressure was maintained at 80 to 100 mmHg throughout the study. All data were obtained on the beating heart.

Two limb leads of the standard electrogram were monitored continuously. Specially designed epicardial needle electrodes, consisting of groups of four conductive needles of 5 mm in length and 0.5 mm in diameter spaced 2 mm apart from each other, and of which one pair of electrodes was utilized for recording and the other for bipolar stimulation, were inserted at ten separate points equally distanced from each other on the epicardial surface of both ventricles avoiding the location of the coronary arteries (Figure 1A). The needle electrodes were inserted 3 to 4 centimeters apart. An additional needle electrode was inserted on the
Panel A: The needle electrodes consist of four conductive needles, one pair of electrodes used for recording the ventricular excitation and the other pair for stimulating the ventricle in a bipolar fashion. Panel B: These needle electrodes were inserted at ten separate points equally distanced from each other on the epicardial surface of both ventricles, and each pair of electrodes was connected either to the MSVP stimulator or recorder. D-C: direct current defibrillator, EP: electrophysiologic study equipment.

A specially designed cardiac stimulator (OM model stimulator, HERZ Co., Ltd, Tokyo) was utilized, which could deliver a total of ten stimuli sequentially with the coupling interval of each stimuli adjustable to be adjusted by 1 msec increments. A pair of epicardial defibrillation patches were placed on the right and left epicardial surfaces and connected to a defibrillation device (Cardiac-Defibrillator Model 2815, Guidant-CPI, Santa Clara, CA, USA) to deliver a monophasic truncated exponential shock to the ventricle to terminate the VF and restore sinus rhythm (Figure 1B).

**Experimental protocol:** During sinus rhythm, the ventricular excitation sequence was mapped using the electrograms recorded through the needle electrodes inserted in both ventricles. We programmed each coupling interval of the multi-site stimulator in order to pace both ventricles in a fashion almost comparable to that of the physiological ventricular excitation pattern during sinus rhythm determined from the mapping data of the ventricular activation sequence obtained through the needle electrodes in the epicardial myocardium. We then delivered electrical impulses of 2.0 msec in duration at a constant current of 2 times the diastolic threshold through the epicardial needle electrodes at the following number of sites chosen at random; one, three, five, and ten epicardial surface of the left ventricle and was used for the induction of VF. All electrograms were filtered with a high band-pass filter of 40 Hz and a low band-pass filter of 400 Hz, and all the physiologic signals were recorded continuously on an optical disc (EP Lab System, Quinton, Seattle, WA, USA).
sites, with a cycle length 20–30 msec shorter than that of sinus rhythm in a sequential fashion according to the activation sequence obtained from the ventricular mapping during sinus rhythm. The number of the ventricular pacing sites was determined in a random order by drawing cards with the numbers 1, 3, 5 or 10 written on them. We examined whether all the ventricular pacing sites were activated by the electrical stimulation by checking the local ventricular electrograms recorded from the needle electrodes.

During sinus rhythm, premature ventricular extrastimuli (PVE) of 2.0 msec in duration at a current of 2 to 3 times the diastolic threshold ranging from single (S1) to four (S4) extrastimuli were introduced from the needle electrode placed on the left ventricular apex to provoke VF. S1 was inserted 350 msec after the last sinus QRS complex and moved progressively closer to the last sinus beat, by 10 msec decrements, until the ventricular effective refractory period (ERP) was reached. If VF was not induced, S1 was set at 10 to 20 msec outside the ERP and the second PVE (S2) was introduced and moved progressively closer to S1, by 10 msec decrements, until ventricular refractoriness was reached, starting at a coupling interval between S1 and S2 of 300 msec. The S2 was set at 10 to 20 msec outside the point of refractoriness and the third PVE (S3) was then inserted and moved in by 10 msec decrements. If VF was not provoked, diastole was scanned with a fourth PVE (S4). The reproducibility of VF was ascertained in order to be able to repeat the same pacing protocol from the same site at least twice. Once VF was induced by the PVE, direct current (D-C) was delivered through the epicardial patches to terminate the VF as soon as possible. VF induction trials were repeated after recovery of the hemodynamic status to the control state. The exact same pacing protocol that induced VF was repeated during multi-site simultaneous ventricular pacing, at a rate 20~30 msec faster than sinus rhythm. Sequential ventricular pacing (MSVP) was then performed in an identical fashion. S1 was inserted 350 msec after the last driven QRS complex and moved progressively closer to the last sinus beat, by 10 msec decrements, until the ventricular effective refractory period (ERP) was reached. Multiple PVE by MSVP were added, if necessary to induce VF, in an identical fashion to that during sinus rhythm as described above. PVE were delivered during MSVP after the hemodynamic status became stable. The ventricular drive of the MSVP was instituted at a cycle length shorter than that of sinus rhythm by 20 to 30 msec and the first stimulus of the PVE (S1) was inserted 350 msec after the last driven complex. We compared the inducibility of VF by PVE against the results obtained during sinus rhythm and 1, 3, 5 and 10 site MSVP. The frequency of VF or VT was calculated by dividing the occurrence time of VF or VT by the total trial to induce VF or VT.

During MSVP, the blood pressure was simultaneously monitored through
the infusion catheter inserted into the femoral artery. We examined the difference in the hemodynamic effects of MSVP during the various number of ventricular pacing sites and sinus rhythm.

**Statistical analysis:** Values are presented as mean ± SEM. The response to multi-site sequential pacing for the prophylaxis of VF was analyzed using multivariate analysis. A *p* value of < 0.05 was considered statistically significant. When *p* was < 0.05 but was greater than the adjusted value, the findings were considered to be of borderline statistical significance.

**RESULTS**

**Hemodynamic effects:** Systolic as well as diastolic blood pressure dropped significantly just after the onset of MSVP compared to that during sinus rhythm, and later returned to its control value. When the number of ventricular pacing sites was smaller than five, both the systolic and diastolic blood pressure significantly decreased (from 123 ± 79 to 102 ± 57, and from 78 ± 52 to 53 ± 18 mmHg, respectively, *p* < 0.05), and it took a minute for these hemodynamic parameters to return to their pre-pacing values (Figure 2A). However, the blood pressure returned to its control value in approximately ten seconds during 5 and 10 site sequential ventricular pacing and was comparable to that during sinus rhythm (Figure 2B). There was however no statistical difference regarding the degree of the drop in blood pressure just after the onset of ventricular pacing.

**Figure 2.** Panel A: The blood pressure initially decreased from approximately 120 mmHg to 80 mmHg for the systolic pressure and from 80 mmHg to 50 mmHg for the diastolic pressure, and then returned to the baseline value within one minute during pacing from a smaller number of pacing sites than five. The paper speed was 10 mm / sec. Panel B: The blood pressure initially decreased to the same extent as during pacing with a smaller number of pacing sites, however, it returned to the control value in ten seconds. Tracings from top to bottom are the electrocardiographic leads II, aVF, and the intracardiac electrograms from left ventricle (LV) and right ventricle (RV).
Electrophysiological effects: In all the trials four PVE (S1-S4) were required to reproducibly and reliably provoke VF. In the beginning part of the experiment, VF induction was performed approximately 30 times during simultaneous multi-site ventricular pacing from a various number of sites, and VF was provoked in all the trials with this pacing method. Therefore, the aim of this experiment was focused on examining the effects of sequential instead of simultaneous multi-site ventricular pacing on the prophylaxis of VF. A total of 461 trials for inducing VF during MSVP were performed. When VF was provoked by the PVE and D-C cardioversion was applied through the epicardial patches as soon as possible, VF was immediately terminated and sinus rhythm restored in all cases. Further, the blood pressure also returned to its control value within a few minutes. The final number of trials at the 1, 3, 5, and 10 pacing sites was 86, 34, 139, and 202, respectively.

Not only VF, but also nonsustained polymorphic ventricular tachycardia (VT) was provoked by the 4 PVE during sinus rhythm and MSVP. The electrograms obtained during the MSVP showed that all the needle electrode insertion sites of the ventricular myocardium were activated by the artificial multisite stimulator in all the cases. During the induction of VF by PVE, non-stimulated ventricular activation provoked by multiple PVE failed to sustain when the ventricle was excited by the stimuli of MSVP at a timing earlier than the non-stimulated ventricular activation (Figure 3A). This phenomenon occurred in 43 % of multi-site sequential pacing attempts when the pacing site number was less than 5 and in which VF could not be provoked by the multiple PVE, and in 39 % of those with 10 ventricular pacing sites in which VF could not be induced by the multiple PVE. In other cases, neither multiple PVE nor the stimuli of the MSVP were able to excite the entire myocardium of both ventricles. In these cases, the nonstimulated beats provoked by the multiple PVE seem to have collided with the ventricular excitation created by the MSVP and then disappeared (Figure 3B). This phenomenon occurred in 57 % of multi-site pacing attempts in which the pacing site number was less than 5 sites and in which VF was not induced by the multiple PVE, and in 61 % of those with 10 pacing sites. There were no significant differences noted.

The occurrence rate of nonsustained polymorphic VT for 1, 3, 5, and 10 different stimulation sites in the ventricles was 0.233 (20 / 86), 0.147 (5 / 34), 0.179 (25 / 139), and 0.113 (23 / 202), respectively, as shown in Figure 4. Ten site MSVP could significantly suppress the inducibility of nonsustained polymorphic VT in comparison to that of the other numbers of MSVP sites and sinus rhythm ($p < 0.05$). As the pacing sites increased from 1 to 10, the occurrence rate of VF also significantly changed. The occurrence of VF was
Figure 3. Panel A: In this trace the ventricular activation provoked by the S4 stimulus of the 4 PVE (S1–S4) captured the entire part of the ventricle, and the last beat of the following nonstimulated ventricular beat failed to capture the entire ventricular tissue because the ventricle was excited by the next stimulation of the MSVP or collision of the pulses occurred between the stimulation of the MSVP and nonstimulated beat by S4. This was suggested by the subtle difference in the last QRS complex configuration compared with that of the fully captured MSVP (S) beats (indicated by the open arrow). The paper speed was 200 mm/sec. Panel B: The last beat of the nonstimulated beats induced by the 4 PVE (S1–S4) collided with the ventricular excitation from the MSVP (S), resulting in the disappearance of repetitive ventricular responses followed by the next sinus rhythm (SR), and which was indicated by the fusion beat between the last nonstimulated beat by the 4 PVE and the beat stimulated by the MSVP (indicated by the open arrows). This is also indicated by the distinct double potentials observed in several of the intracardiac recording traces (indicated by the closed arrows).

Figure 4. The induction rate of nonsustained polymorphic VT by the 4 PVE during MSVP at each of the various number of stimulation sites was significantly lower during ventricular pacing with the 10 site MSVP.
The occurrence rate of VF by the 4 PVE during MSVP at each of the various number of stimulation sites was significantly lower during ventricular pacing with the 10 site MSVP.

Figure 5. The occurrence rate of VF by the 4 PVE during MSVP at each of the various number of stimulation sites was significantly lower during ventricular pacing with the 10 site MSVP. Ten site MSVP could also significantly suppress the inducibility of VF in comparison to that of the other numbers of MSVP sites and sinus rhythm (p < 0.05).

DISCUSSION

Sustained monomorphic ventricular tachycardia (VT), unassociated with organic heart disease, is amenable to catheter ablation. Furthermore, implantable defibrillators as well as antiarrhythmic agents have limited efficacy in suppressing or managing VF. Although spontaneous reversion of VF has been reported,9) in the majority of the cases this lethal arrhythmia usually leads to cardiac arrest.10,11) In some clinical cases, the administration of antiarrhythmic agents may be contraindicated, therefore, a nonpharmacological prophylactic method for VF would be preferable.

Hemodynamic effect of MSVP: The exact mechanism involved in the change of the hemodynamic parameters observed during MSVP remains unknown in the present study. Saxon, et al. recently demonstrated that simultaneous right and
left ventricular apical pacing resulted in acute improvement in the global ventricular performance in patients with depressed ventricular function.\(^{12}\) The phase data in their study showed that simultaneous electrical activation of the ventricles markedly alters the segmental left ventricular and interventricular septal contractile sequence in patients with depressed left ventricular function. They suggested that the resequencing of segmental ventricular wall motion observed with this pacing mode and the resulting pacing-induced global coordination through recruitment of left and right ventricular apical and septal segments critical to effective ventricular contraction contributes to the acute improvement in the global ventricular performance.

Moreover, an asynchrony of the ventricular excitation observed during pacing from an implanted pacemaker may cause impairment of the ventricular function.\(^{13}\) The MSVP stimulator was designed to try and excite the entire ventricle in a physiological fashion to settle this issue. This effect of multi-site sequential pacing might have contributed to the favorable results obtained in the present study.

**Mechanism of the efficacy of multi-site sequential ventricular pacing:** Multi-site pacing methods for arrhythmia suppression have been applied to ventricular arrhythmias with limited success.\(^ {14}\) Saksena, *et al.* clinically demonstrated that two site right atrial simultaneous pacing prolonged arrhythmia-free intervals in patients with drug-refractory paroxysmal atrial fibrillation.\(^ {15}\) The mechanism which they suggested is that biatrial pacing can eliminate the dispersion of atrial refractoriness, abbreviate the right and left atria activation, and eliminate, reduce or modify the area of delayed activation.\(^ {16}\) Previous reports have demonstrated that a critically timed second stimulus or a train of stimuli could prevent the induction of VF by an earlier stimulus or by a train of stimuli delivered during the vulnerable period of the normal rhythm.\(^ {17,18}\)

One explanation which we would like to propose is that a relatively large area of the ventricular myocardium was mandatorily depolarized by the stimulation introduced through the needle electrodes from multiple epicardial sites by MSVP, which then rendered the myocardium refractory to the induced stimulated or nonstimulated beats from the 4 PVE as shown in Figure 3A. Further, this stimulation may be able to improve the dispersion of the ventricular refractoriness resulting in a lesser chance of provoking VF.

The second explanation is that the ventricular excitation elicited by the stimulation through the epicardial needle electrodes collided with the stimulated or nonstimulated beats of the PVE and then failed to continue activating the ventricular myocardium to provoke reentry as shown in Figure 3B. Recently, Friedman, *et al.* experimentally demonstrated that the lengthening of the basic cycle length in the atrium increased the atrial fibrillation vulnerability.\(^ {19}\) In the
present study, ventricular pacing at a slightly faster rate than sinus rhythm also contributed to a decreased incidence of VF.

The third explanation is that depending on the time of the electrical stimulation relative to the reentrant activation of VF, a stimulus might result in termination of the reentrant wavefronts of VF suggested by Bonometti, et al. In this case, PVE might excite the ventricular myocardium during the cycle phase of the excitable gap. Moreover, a strong stimulus occurring before complete recovery may prolong the action potential duration and refractoriness. When the leading edge of the reentrant wavefront of VF returns to this refractory area, it can not reenter, resulting in termination of VF. In the present study, the strength of the MSVP was relatively high, therefore, this also might explain the suppressive effects of MSVP on VF occurrence.

The hemodynamic status was more stable than that of pacing from a lesser number of sites than ten. This may contribute to the prophylactic effect of ten site MSVP.

Mechanisms of insufficient effects of multi-site sequential ventricular pacing: In some instances of VF induction by the PVE, we failed to suppress the occurrence of VF during MSVP, and this even occurred in approximately 30% of the 10 site MSVP trials and approximately 50–80% of the trials with a smaller number of MSVP sites than ten. We speculate that the reason for these results is that the premature ventricular contraction resulting from the PVE that was able to propagate through the ventricle and find excitable tissue, may have stimulated repetitive ventricular firing or initiated intraventricular reentry which was electrically inclined to induce VF. Further, the excitation wavefronts of the MSVP from multiple ventricular sites, capable of traveling in a radial fashion in the ventricle, might induce new patterns of ventricular activation caused by the collision with the PVE, culminating in the induction of VF.

Clinical implications: Previous reports have demonstrated that lethal ventricular dysrhythmias, which require immediate treatment such as direct current cardioversion or which need prophylactic administration of antiarrhythmic agents to prevent recurrences, are apt to occur during the acute phase of a myocardial infarction. There is a risk of injuring the myocardium by delivering a high density of direct current. Furthermore, some antiarrhythmic agents are not preferable for cases whose hemodynamic status is unstable. In these cases, other prophylactic methods besides D-C cardioversion or antiarrhythmic agents will be required to suppress the spontaneous occurrence of these lethal arrhythmias during the acute phase of myocardial infarction. Multiple electrode catheters could be inserted in the left and right ventricles through the vein and artery to be used to pace multiple endocardial sites throughout the ventricles, and may be effective in suppressing spontaneous occurrences of serious ventricular tac-
hyarrhythmias in this state.

**Limitations:** In the present study, we attempted to induce VF in the intact canine heart with very high current stimulation from the left ventricle. The simulation mode in this experiment might have been more realistic if we had used dogs that had myocardial infarction elicited by ligation of the coronary arteries.\(^\text{23}\) In this case, the density of the current used for the induction of VF might be much less than that of the value adopted in the present study. The results of the present study might have been different, because a higher current density is arrhythogenic and can induce fibrillation.\(^\text{24}\) Further, there might be a more significant difference in terms of the suppression of the occurrence of VF from the 4 PVE during MSVP among the various numbers of MSVP pacing sites, because the high current density of the 4 PVE might act to minimize the prophylactic effect of MSVP on VF. Therefore, we failed to propose a minimum number of pacing sites which would effectively prevent the occurrence of VF. Moreover, we provoked VF by electrical stimulation, therefore, the results of the present study might not entirely be applicable to VF in the setting of myocardial ischemia such as acute myocardial infarction.

Even single site ventricular pacing was able to suppress the occurrence of VF by approximately 18% as compared to the control (4PVE during sinus rhythm). The reproducibility of VF in the control state might have fluctuated which could have influenced the results of this study, even though we repeated the induction mode of VF to make sure of the reproducibility. However, we would like to think that the larger number of sites for the multi-site ventricular pacing exerted a significant supressive effect on VF as compared to single site ventricular pacing, considering the lack of a stable reproducibility of VF.

**Conclusions:** Multisite sequential ventricular pacing at a slightly faster rate than sinus rhythm could suppress the occurrence of VF by the 4 PVE. The hemodynamic effect of this pacing mode is relatively stable.

**REFERENCES**

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