Experimental Studies

Effect of Cervical Vagal Nerve Stimulation on Defibrillation Energy
A possible adjunct to efficient defibrillation

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SUMMARY
The efficacy of electrical defibrillation is considered to be related to the autonomic status. In search of a possible adjunct to enhance the therapeutic performance of an implantable cardioverter-defibrillator, we investigated whether parasympathetic manipulation by cervical vagal nerve stimulation (VNS) increases defibrillation efficacy. The effects of VNS on transcardiac defibrillation threshold (DFT) were assessed in 55 anesthetized dogs. In neurally intact dogs, right and left unilateral VNS at 10 mA for 7 seconds significantly decreased the DFT after 10 seconds of ventricular fibrillation (control: 3.1±0.9 J, right: 2.1±0.9 J [Δ-35±12%, P<0.0001], left: 2.2±0.8 J [Δ-31±11%, P<0.0005]), while bilateral VNS did not (2.8±1.0 J). In dogs with decentralized vagus nerves, both unilateral and bilateral VNS decreased the DFT. The extent of the VNS-induced decrease in DFT was dependent on the current and the duration of stimulation. We conclude that unilateral VNS decreases the DFT, while bilateral VNS paradoxically has no effect on the DFT unless the vagi are decentralized. (Jpn Heart J 2003; 44: 91-100)

Key words: Defibrillation, Defibrillation threshold, Autonomic nerve system, Implantable cardioverter-defibrillator

The effect of autonomic modulation on defibrillation efficacy has been mainly studied in animal experiments.1-7 Among these studies, Morillo, et al demonstrated a decrease in the defibrillation threshold (DFT) during treatment with muscarinic drugs.5 Recently, intermittent electrical stimulation of the cervical vagus nerve by an implanted stimulator has been used to treat medically intractable epilepsy.8,9 Based on these reports that discussed the tolerability of chronic implantation of electrodes around the human vagus nerve, we speculated that acute cervical vagal nerve stimulation (VNS) could be used to enhance the therapeutic performance of the implantable cardioverter-defibrillator. In the present...
study, we examined if VNS after the onset of ventricular fibrillation (VF) could
decrease the energy requirement for defibrillation.

METHODS

General preparation: All experiments were performed in accordance with the
“Guide for Animal Experimentation” of the Faculty of Medicine of the University
of Tokyo.

Fifty-five mongrel dogs weighing 9-17 kg were used. Dogs used in protocol
1-4 were anesthetized with an intravenous bolus of sodium pentobarbital (30 mg/
kg: \( n=49 \)), while those for protocol 5 were anesthetized with \( \alpha \)-chloralose (75
mg/kg: \( n=6 \)). Dogs were intubated with a cuffed endotracheal tube and ventilated
with a mixture of room air and 100% oxygen using a Harvard respirator. A silicon
cannula (7F) was introduced into the femoral artery and the aortic pressure was
monitored through a Statham pressure transducer (Amplifier AP621G, Nihon
Kohden, Tokyo). Cannulas were also inserted into the femoral vein and the
remaining femoral artery for the administration of fluid or for blood sampling.
Arterial blood gases and electrolytes were periodically determined by a portable
clinical analyzer (i-STAT 200A, i-STAT Corporation, Princeton, New Jersey),
and abnormal pH, \( P_O_2 \), \( P_C_O_2 \), and \( K^+ \) values were appropriately corrected.

The heart was exposed by a midsternal incision. A pair of square titanium
defibrillation electrodes with a 4-cm\(^2\) surface area were sutured to the pericar-
dium over the right and left ventricles. Defibrillation shocks were supplied by a
programmable two-channel unit (165 \( \mu F \times 2 \)) that could deliver truncated expo-
nential pulses at preset voltages up to 800 V (DPS-1200D, Diamedical, Tokyo).
The delivered currents were displayed on a digital storage oscilloscope using a
voltage divider and a 0.1 \( \Omega \) resistor in series with the defibrillator output (Digital
oscilloscope 5020A, Kikusui Electronics, Tokyo).

Bipolar electrodes were sutured to the right ventricular surface and the left
lateral ventricular surface for recording of the local electrograms. In addition, a
unipolar electrode was sutured to the right ventricular outflow tract to induce VF.

VNS: The bilateral cervical vagus nerves were isolated in dogs assigned to pro-
tocol 1, while only the left cervical vagus nerve was isolated in dogs used for pro-
tocols 2-5. VNS was performed using a multi-channel stimulator (Electronic
Stimulator SEN7203, Isolator SS-103J, Nihon Kohden) and a pair of epoxy-
coated hook-shaped electrodes (3/4 circumference of a 4-mm circle in diameter,
with an interelectrode distance of 6 mm) tied around each cervical vagus nerve.
Two isolators were used for bilateral VNS.

To confirm that VNS was able to modify vagal activity, the threshold caus-
ing marked prolongation of the sinus cycle length (600 ms) or advanced atrioven-
tricular block was determined as the vagal threshold.

**Electrophysiologic monitoring:** Bipolar epicardial ventricular electrograms (50 Hz-1 kHz) as well as two surface ECGs were recorded on an ink-jet recorder (RIJ-2108, Nihon Kohden) together with the aortic blood pressure. The sinus cycle length and peak-to-peak interval of VF (VF interval) were measured. The VF interval was defined as the mean of 10 consecutive peak-to-peak intervals in surface ECGs and ventricular electrograms preceding the defibrillation shock. The VF interval was measured in three fibrillation-defibrillation sequences, and was averaged to represent the baseline status or each type of VNS.

**Measurement of DFT:** VF was induced by a 2-second train of 4-ms pulses (33 Hz) delivered to the right ventricle (BC-02A Cardiac Stimulator, Fukuda Denshi, Tokyo). After 10 seconds of VF, a biphasic shock (6 ms/4 ms) with a peak voltage of 200 V or 260 V was applied. The voltage of phase two was adjusted so that the leading current was equal to the tailing current of phase one, but had opposite polarity. If the test shock was unsuccessful, the dogs were defibrillated by one or more rescue shocks. Then an iterative increment-decrement protocol was used, with the steps being approximately 10% of the preset voltage. Fibrillation/defibrillation sequences were separated by at least 3 minutes. We defined DFT as the energy of the successful shock, when the next lower setting failed to defibrillate the heart in the preceding or subsequent attempt. By repeating a step up-step down protocol, triplicate DFT values were determined through three reversals as part of a continuous trial. The mean of the triplicate values was calculated as the baseline DFT or the DFT for each type of VNS.

**Experimental protocol:**

**Protocol 1 (n=17): Comparison among three different methods of VNS:** A diagram of the experimental protocol is shown in Figure 1. Three methods of VNS were tested, ie, unilateral right VNS, unilateral left VNS, and bilateral VNS. VNS was started three seconds after the end of train stimulation for the induction of VF and lasted for 7 seconds, ie, it was terminated simultaneously with a defibrillation shock. A train of 4-ms pulses (20 Hz) at a current of 10 mA was used for VNS. In each dog, four DFT values (including control measurements without VNS) were determined in a random order. In 10 of the 17 dogs, data were obtained without decentralization of the vagus nerve (neurally intact dogs). In the remaining seven dogs, the cervical vagi were cut and decentralized.

**Protocol 2 (n=17). Beta-adrenergic blockade and VNS:** To obtain an insight into the mechanisms of VNS-induced changes in DFT, the effect of left VNS on DFT was assessed in the presence of pharmacological blockade of beta-adrenergic activity (Figure 1). The temporal profile of VNS was the same as in protocol 1. After measurement of the DFT in the baseline state and with left VNS, propranolol (0.5 mg/kg) was given intravenously as a bolus, followed by a maintenance
infusion at 0.01 mg/kg/min. The DFT was again determined in the presence and absence of left VNS. The order of the DFT measurements with and without VNS was randomized. Data were collected in nine neurally intact dogs and in eight dogs with the left vagus nerve cut and decentralized.

Protocol 3 (n=8). Current-dependency of VNS: The current-dependency of the effect of VNS on DFT was investigated. The onset and end of VNS was the same as for left VNS in protocol 1, while the stimulation current was varied (0 mA, 1 mA, 3 mA, 6 mA, or 10 mA). Five DFT values for different VNS currents, including 0 mA as a control, were randomly determined in each dog.

Protocol 4 (n=7). Time-dependency of VNS: The time-dependency of the effect of VNS on DFT was studied using 10-mA left VNS. VNS was started 2, 4, or 8 seconds prior to the defibrillation shock and was terminated simultaneously with the shock. In each dog, four DFTs, including a control value without VNS, were randomly determined.

Protocol 5 (n=6). Effect of anesthetic agents: Anesthetic agents are known to affect autonomic nerve activity and myocardial electrophysiologic properties. To test whether the effect of VNS on defibrillation was dependent on anesthetic agents, DFT was determined in neurally-intact α-cloralose anesthetized dogs.
using unilateral left-VNS. The temporal profile of VNS was the same as in protocol 1 (ie, 10 mA and 7 seconds in duration).

**Statistics:** The results are expressed as the mean±SD. The significance of differences between values was tested by the paired or unpaired *t* test. DFTs obtained under different conditions were compared by two-way analysis of variance (ANOVA). When a significant *F* value was obtained, further comparisons between pairs of groups were conducted using the Bonferroni method. Probability values less than 0.05 were considered to indicate significance.

**RESULTS**

**Protocol 1:** In 10 neurally intact dogs, the thresholds of the right and left cervical vagi were 0.56±0.42 mA and 0.60±0.37 mA, respectively. Bilateral VNS at a current equal to the unilateral vagal threshold also caused a marked bradycardic response. The control DFT in these dogs was 3.1±0.9 J. As shown in Figure 2A, unilateral right and left VNS, respectively, reduced the DFT to 2.1±0.9 J (*P*<0.0001 by ANOVA, *P*<0.0001 vs control [Δ-35±12%]) and to 2.2±0.8 J (*P*<0.0005 vs control [Δ-31±11%]). However, bilateral VNS failed to cause a marked change in DFT (2.8±1.0 J, *P* = not significant [NS] vs control, *P*<0.0001 vs right VNS, and *P*<0.01 vs left VNS). The VF interval of the surface ECG was 102±14 ms in the control state. None of the three different modes of VNS influenced the surface VF interval (right VNS: 101±16 ms, left VNS: 99±16 ms, bilat-

![Figure 2.](image-url)

*Figure 2.* A: Comparison of control DFT and DFTs obtained with different modes of VNS in neurally intact dogs (mean±SD, *P*<0.0001 by ANOVA). Unilateral right and left VNS decreased DFT, while bilateral VNS did not significantly affect it. B: Comparison of control DFT and DFTs obtained with different modes of VNS in dogs after vagal decentralization (*P*<0.002 by ANOVA). Both unilateral VNS and bilateral VNS tended to decrease DFT. C=control; R=right VNS; L=left VNS; Bi=bilateral VNS.
eral VNS: 101±14 ms). Similarly, the VF interval on the ventricular electrograms remained unchanged during any mode of VNS (right ventricular electrogram, control: 103±15 ms, right VNS: 104±14 ms, left VNS: 103±14 ms, bilateral VNS: 102±16 ms).

DFT data obtained from seven dogs after decentralization are shown in Figure 2B. The right and left vagal thresholds were 0.53±0.72 mA and 0.71±0.45 mA, respectively. Thus, cutting the vagi did not significantly affect the threshold. Right VNS decreased DFT to 1.7±0.7 J from the control value of 2.4±0.9 J (P<0.002 by ANOVA, P<0.05 vs control [Δ-29±12%]). Although the change was not significant, both left VNS and bilateral VNS caused a reduction of DFT (left VNS: 1.7±0.9 J [Δ-34±26%], bilateral VNS: 1.9±0.6 J [Δ-22±12%]). The VF interval was also not affected by VNS in this experiment.

**Protocol 2:** In dogs with intact vagi, propranolol prolonged the sinus cycle length from 405±42 ms to 531±70 ms and decreased the systolic blood pressure from 132±20 mmHg to 111±14 mmHg. As shown in Figure 3A, both left VNS and propranolol decreased DFT to a comparable extent (P<0.0001 by ANOVA, control DFT 3.0±0.9 J, left VNS 2.3±0.8 J [P<0.005 vs control, Δ-23±16%], propranolol 2.0±0.9 J [P<0.02 vs control, Δ-32±18%]). The combination of left VNS and propranolol did not cause a further decrease in DFT (Δ-4±22% vs propranolol alone). In dogs after decentralization, similar sinus cycle length and blood pressure responses were observed as in dogs with intact vagi (sinus cycle length: from 423±33 ms to 553±58 ms, systolic blood pressure: from 144±17 mmHg to 126±17 mmHg). The DFT profiles were also comparable to those observed in dogs without decentralization (Figure 3B, P<0.002 by ANOVA).

![Figure 3](image-url)

**Figure 3.** A: Comparison of effects of left VNS, propranolol, and propranolol plus left VNS in neurally intact dogs (mean±SD, P<0.0001 by ANOVA). Both left VNS (L) and propranolol (P) markedly decreased DFT. Left VNS failed to cause a further reduction of DFT in the presence of propranolol (L+Pro). B: Comparison of effects of left VNS, propranolol, and propranolol plus left VNS in dogs after vagal decentralization (P<0.002 by ANOVA). Similar results to those found in neurally intact dogs were obtained.
Protocol 3: The results of this protocol are shown in Figure 4A. The control DFT was 2.7±0.9 J and there was a current-dependent change in DFT \((P<0.0001\) by ANOVA) and the difference from the control value was significant with 10-mA stimulation. VNS at a strength of 1 mA or 3 mA scarcely affected DFT. Although 6-mA VNS tended to decrease DFT \((2.4±0.9 J [\Delta-14\pm13\%])\), the difference from the control was not statistically significant. Finally, 10-mA VNS caused a marked reduction of DFT \((1.9±0.9 J, P<0.005 vs control [\Delta-33\pm14\%])\).

Protocol 4: Figure 4B summarizes the results. Baseline DFT was 2.9±1.3 J and DFT tended to decline in proportion to the duration of VNS \((P<0.05 by ANOVA)\). However, a significant decrease in DFT was only achieved by 8-s VNS \((2.0±1.1 J, P<0.05 vs control [\Delta-29\pm20\%])\).

Protocol 5: The threshold of the left cervical vagus to show a marked negative chronotropic effect was 0.43±0.25 mA, and was not different from that determined in the pentobarbital-anesthetized dogs in protocol 1. In the baseline state, DFT was 3.2±0.9 J. Left VNS at a strength of 10 mA significantly decreased the DFT to 2.4±1.0 J \((\Delta-26\pm14\%, P<0.01)\). The degree of VNS-related decrease in DFT was comparable to that observed in the pentobarbital-anesthetized dogs in protocol 1.

**DISCUSSION**

The major findings of the present study are as follows: 1) Both right and left unilateral VNS decreased DFT, while bilateral VNS did not markedly affect DFT unless the cervical vagi were cut and decentralized; 2) the effect of VNS on DFT was dependent on the duration and strength of electrical stimulation; and 3) VNS did not significantly modify the DFT during treatment with propranolol.
Earlier studies on the autonomic modulation of electrical defibrillation efficacy:
To determine the association between autonomic tone and defibrillation, the
effects of pharmacological autonomic agonists and antagonists on defibrillation
efficacy have been investigated.\(^1\)\(^-\)\(^7\) Ruffy, \textit{et al} studied the effects of adrenergic
activity on defibrillation in unanesthetized closed-chest dogs. In their study, iso-
proterenol decreased DFT, while propranolol not only reversed the effect of iso-
proterenol but also increased DFT.\(^2\) They also obtained similar findings in
anesthetized dogs.\(^1\) On the contrary, isoproterenol significantly increased the
energy requirement for defibrillation in another study,\(^4\) and it was also reported
to have little influence on DFT.\(^6\) In humans, the effect of epinephrine on the effi-
cacy of internal defibrillation has been studied by Sousa, \textit{et al}.\(^7\) Shocks that suc-
cessfully terminated VF in the baseline state failed to achieve defibrillation
during epinephrine infusion in 4 out of 16 patients. Because the plasma epineph-
rine concentration in their study was within the physiological range, they con-
cluded that enhanced sympathetic tone could reduce defibrillation efficacy and
that adrenergic blockade may be a potent method for improving the clinical effi-
cacy of ICDs.\(^7\) Thus, the findings regarding adrenergic modulation of defibrilla-
tion have been rather conflicting.

There are only limited data available on how parasympathetic tone affects
defibrillation. Morillo, \textit{et al} found that both methacholine and carbacol (parasym-
pathomimetic drugs) decreased the DFT in pigs.\(^5\) Also, Wang, \textit{et al} demonstrated
that atropine increased the energy requirement for defibrillation by approxi-
mately 30\%.\(^4\) However, it was not clear whether acute VNS could affect the elec-
trophysiologic properties of ventricular myocardium in the same manner as that
cauised by systemic administration of parasympathomimetic drugs. Accordingly,
these studies did not indicate that VNS could markedly decrease DFT.

\textbf{Interpretation of the present results:} The extent of the decrease in DFT achieved
by unilateral right or left VNS was comparable. If the electrophysiologic influence
of the two vagi on the ventricles is appreciably different, their effects on
DFT should differ markedly. However, this was not the case.

Although VNS showed a pronounced effect on DFT, the VF interval did not
respond to VNS. An earlier study showed site-to-site and heart-to-heart variation
with regard to the effects of electrical sympathetic stimulation on local VF inter-
vals,\(^10\) and concluded that sympathetic stimulation heterogeneously modifies
the electrophysiologic properties of the ventricles because of regional variation in
each heart as well as interindivudual variation. A possible explanation of the
present observation is that due to its low sensitivity as an indicator of regional
refractoriness, the VF interval might have failed to reflect subtle changes in the
ventricular electrophysiologic properties caused by VNS.

Interestingly, bilateral VNS did not alter the DFT in dogs with intact vagi.
Inhibition of the vagotonic effect by the central nerve system was suggested because bilateral VNS decreased the DFT after decentralization. A similar observation was previously reported by Opthof, et al.\textsuperscript{11} In accordance with the results of the present study, they found that VNS did not influence the VF interval in dogs on cardiopulmonary bypass. Also, an antagonistic effect of bilateral VNS on the response of the VF interval to sympathetic stimulation was only observed after decentralization, and was not seen in neurally intact dogs.\textsuperscript{11} Because the sinus node and the atrioventricular node respond to bilateral VNS even in neurally intact dogs, apparent inhibition of the effect of bilateral VNS on DFT may be related to peculiarities of the autonomic innervation of the ventricles and the distribution of autonomically influenced ion channels. However, an explanation for this finding will require further investigation.

The decrease in DFT was dependent on the duration and the current used for VNS. Although some other parameters such as frequency may also be involved\textsuperscript{12}, the present results indicate that a relatively higher current with a duration of at least several seconds is necessary to substantially decrease DFT. The lack of any effect of VNS on DFT after treatment with propranolol was compatible, if not conclusive, with the view of sympathetic-parasympathetic “accentuated antagonism”.\textsuperscript{13} Because VNS reduced DFT to a similar extent in dogs with and without decentralization, the interaction between sympathetic and parasympathetic nerves during unilateral VNS, if it exists, seems to occur peripherally.

Limitations and implications: Although the effects of VNS on DFT did not differ between dogs treated with different anesthetics, extrapolation of the results obtained in our experimental models to diseased human hearts is necessarily limited. Because DFT was assessed 10 seconds after the onset of VF, the present finding that VNS decreases DFT is not equivalent to stating that VNS can influence the ultimate success of defibrillation. The role of VNS in prolonged resuscitation is unknown. Propranolol eliminated the effect of VNS on DFT. Although the dose of propranolol used in the present experiment (0.5 mg/kg + 0.01 mg/kg/min) was not equivalent to that administered in clinical practice, the value of VNS as a means to enhance defibrillation efficacy may be diminished in patients taking beta-blockers.

Conclusions: In conclusion, the results of the present study indicate that: 1) unilateral VNS but not bilateral VNS reduces DFT in neurally intact dogs; and 2) the effect of VNS on DFT is dependent on the electrical strength and duration of stimulation.
REFERENCES