The Effect of Vagus Nerve Stimulation upon Vulnerability of the Canine Ventricle

Role of Sympathetic-Parasympathetic Interactions

By Benet S. Kolman, M.D., Richard L. Verrier, Ph.D., and Bernard Lown, M.D.

SUMMARY

The effect of vagus nerve stimulation (VNS) upon ventricular vulnerability was studied in 30 mongrel dogs subjected to varying levels of adrenergic stimulation. Vulnerability was assessed both by determining the minimum current required to produce ventricular fibrillation (VF threshold) and by plotting VF threshold throughout the vulnerable period (VF zone). Chloralose-anesthetized animals were studied by means of sequential pulses applied to the apex of the right ventricular endocardium. Testing was carried out in closed-chest dogs, in open-chest dogs with and without left stellate ganglion stimulation (LSGS), and in open- and closed-chest dogs pretreated with propranolol. In the absence of adrenergic stimulation, VNS was without significant effect on either the VF threshold or the VF zone under closed- or open-chest conditions. During LSGS, however, VNS was associated with a 93 \pm 22% (mean \pm sE) increase in VF threshold (P < 0.01) and constriction of the VF zone. Vagus nerve stimulation combined with LSGS raised VF threshold to the control value, but not beyond. After beta-adrenergic blockade with propranolol, VNS was without effect on VF threshold in either open- or closed-chest animals. It is concluded that augmented sympathetic tone is a precondition for a VNS-induced elevation in VF threshold. The vagal effect is indirect and is expressed by opposing the effects of heightened adrenergic tone on ventricular vulnerability.

In their classic studies on cardiac excitability, Hoffman, Brooks, and co-workers¹⁻⁴ found that vagus nerve stimulation (VNS) was without significant effect on the electrical properties of the ventricle. Evidence to the contrary has recently been provided by Kent and Harrison et al.^{5, 6} When the ventricular fibrillation (VF) threshold was determined by means of a train of electrical pulses closely coupled to an antecedent paced beat, it was found that both VNS⁵ and edrophonium chloride⁶ consistently raised VF threshold in the normal as well as the ischemic canine ventricle. The protection against fibrillation was independent of vagally-mediated bradycardia.

Preliminary experiments by our group⁷ appeared to support the traditional view: we found that VNS had no effect on ventricular vulnerability in the non-ischemic heart. Furthermore, in animals subjected to beta-adrenergic blockade, hypothalamic stimulation,⁸

and reflex vagal activation by means of blood pressure elevation⁹ were without effect on VF threshold.

In intact animals, parasympathetic discharge does not occur in isolation, but rather concomitantly with activity of the sympathetic nervous system. Vagal effects on such inotropic and chronotropic parameters as sinus rate of the intact heart10 or contractile force of the isovolumic canine ventricle¹¹ are considerably influenced by the level of prevailing adrenergic tone. It may be that differing degrees of interaction between the two components of the autonomic nervous system account for the disparate findings as to the role of vagal stimulation on ventricular vulnerability. To test whether this is indeed the case, the present studies were conducted under conditions which corresponded to varying levels of adrenergic input: in closed-chest dogs, in open-chest dogs, in open-chest dogs during continuous supramaximal left stellate ganglion stimulation (LSGS), and finally in both closed- and open-chest dogs subjected to acute beta-adrenergic blockade. In these experiments, both quantitative and qualitative appraisal of susceptibility to induce VF was made possible by determining the over-all temporal configuration of vulnerability, as well as the VF threshold.

Material and Methods

Thirty healthy mongrel dogs, weighing 7-25 kg, were studied. The animals were anesthetized with i.v. administration of brevital (5 mg/kg), followed by 100 mg/kg alphachloralose. Additional booster doses of 50 mg/kg alphachloralose were given as required; a minimum of 30 min

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Address for reprints: Bernard Lown, M.D., Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

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separated the administration of anesthetic and electrical testing. Ventilation was maintained via a cuffed endotracheal tube attached to a Harvard constant-volume pump delivering a mixture of room air and $100\%~O_2$. Arterial pH was maintained in the range 7.30-7.55 and pO_2 greater than 100~mm~Hg. Abdominal aortic pressure was determined via a large lumen cannula inserted through a right femoral arteriotomy and connected to a Statham 23Db pressure transducer. The ECG was recorded from a unipolar right ventricular endocavitary lead. ECG and aortic pressure were continuously monitored by oscilloscope.

Vagus Nerve Stimulation

The cervical vagosympathetic trunks were decentralized approximately 2 cm below the carotid bifurcation; the distal cut ends were mounted in an insulated, teflon-coated, stainless-steel wire stimulator. Interrupted stimulation with pulse characteristics of 6–10 V, 40 Hz, 5 msec was applied separately to each nerve via separate channels of a Tektronix square-wave pulse generator.

The criterion of adequate vagal stimulation was asystole for a minimum of five seconds. This criterion was required even during simultaneous supramaximal left stellate ganglion stimulation. Each vagosympathetic trunk was tested individually at the start of every VF threshold test sequence. Adequacy of vagal stimulation was further assessed throughout the period of electrical testing by requiring that asystole be present during the 1.5–2.0 second pacing pause which followed each test sequence. It was found that adequate continuous vagal stimulation could readily be maintained for 10 minutes, the maximal time required for determination of VF threshold.

In keeping with the known negative inotropic effects of cholinergic stimulation, ¹² VNS occasionally resulted in a decrease in mean aortic pressure, aortic pulse pressure, and aortic pressure upstroke velocity. More commonly, these effects were observed when VNS was superimposed upon left stellate stimulation. A requirement for inclusion of data in the results was that vagal stimulation not reduce blood pressure by greater than 40 mm Hg, and in no case to values below 90 mm Hg. The hypotensive effect of VNS was usually of the order of 0–15 mm Hg, and was generally accompanied by either no change or by an increase in VF threshold.

Left Stellate Ganglion Stimulation

The LSG was exposed by a left lateral thoracotomy in the second intercostal space. An insulated, teflon-coated stainless-steel wire stimulator was positioned over the body of the decentralized ganglion. Pulse stimulus characteristics were 10 V, 10 Hz, 5 msec¹³ via a Grass SD-9 square-wave pulse generator. Criteria for adequate LSGS included a rise of at least 50% in aortic pulse pressure and 30% in mean aortic pressure, a sinus rate increase of at least 50 beats per minute, and a marked increase in upstroke velocity of the central aortic pulse tracing. With reference to these criteria, continuous LSGS could readily be maintained for 10 minutes, the maximal time required for determination of VF threshold. During stellate stimulation, concomitant vagal stimulation nearly always resulted in asystole, rarely with idioventricular escape beats.

Cardiac Testing

Bipolar, transvenous, fixed-rate, right ventricular pacing was employed throughout the experiments. Animals were paced with a bipolar catheter (Medtronics 5818), inserted via the right external jugular vein and positioned at the apex of the right ventricle under fluoroscopic control. The pacing stimulus was 5 ma in intensity. The pacing interval was 240 to 333 msec, corresponding to a ventricular rate of 180–250 beats per minute. These high pacing frequencies were required to override the animal's spontaneous rate following vagotomy and during LSGS.

A special-purpose stimulator, equipped with circuitry to inhibit the pacemaker output during electrical testing, permitted delivery of one, two, or three premature stimuli after the pacing impulse. Each stimulus was triggered from the upstroke of the preceding stimulus, and was delivered 15 msec after the effective refractory period (5 ma) for its antecedent beat. For each set of experimental conditions outlined below, the timing of the stimuli was readjusted at the outset of each separate determination of VF threshold, whether during the control state or the VNS intervention. The intensity as well as timing of the last stimulus in the sequence was varied in order to delineate the vulnerability characterististics at the endocardial test site.

Stimulus intervals were individually monitored via a digital timer arranged in parallel with the circuitry; stimuli could thus be timed with an accuracy of ± 1 msec and were continually monitored throughout the experiments. Stimulus configurations were continually checked during the experiments by display on a Sony Tektronix Type 323 oscilloscope arranged in parallel with the pacing catheter system. Stimuli preceding the test stimulus were each $\overline{2.0}$ msec in duration and 5.0 ma in amplitude. The intensity of the test stimulus was varied in stepwise increments as part of the test procedure. All stimuli were square-wave and bipolar. The distal catheter tip, wedged against the right ventricular apex, served as the cathode. At selected points during the experiments, stimulus characteristics were directly verified by means of a Tektronix P6021 AC current probe attached to a Tektronix 5102N oscilloscope. Each test sequence was triggered manually at 6-10 sec intervals after the antecedent test sequence. A variable 1.5-2.0 sec pacemaker delay followed the end of testing to allow the emergence of repetitive response patterns or VF.

The system described above thus permitted direct control of timing, duration, and intensity of a pacing simulus (S_0) , followed by one (S_1) , two $(S_1\,S_2)$, or three $(S_1\,S_2\,S_3)$ sequentially coupled stimuli. Each sequential stimulus progressively lowered the VF threshold for its associated response, ¹⁴⁻¹⁶ while the final test stimulus was used to determine VF threshold. This method of testing is a modification of the R/T sequential pulsing technique originally devised in this laboratory. ¹⁷

Defibrillation

In both closed- and open-chest animals, defibrillation was accomplished within 3-5 seconds of the onset of fibrillation in all but two instances, when it required 15-20 sec, by means of a DC current shock of 50-400 Wsec delivered from an American Optical Lown D4 DC defibrillator via 80 cm² copper plates secured to either side of the thorax. During inscription of the complete VF Zone (vide infra) a minimum of 2 min was allowed to elapse between defibrillation and successive VF threshold determinations; most often the recovery period was four to five minutes. This abbreviated recovery period was necessitated by the requirement for multiple defibrillations in the course of complete VF zone mapping. If immediate defibrillation were successful, repetitive VF determinations were found not to be significantly affected by a recovery interval of two minutes. During the scanning of the vulnerable period for the VF threshold (vide infra) the minimal period between defibrillation and the resumption of testing was extended to five minutes.

Determination of Vagal Effects on Ventricular Fibrillation Threshold

A test stimulus was used to scan, at 10 msec intervals and progressive 5 ma increments, the vulnerable period of the beat associated with an antecedent stimulus. The initial test stimulus of 5 ma was selected to fall 0-5 msec outside the 5 ma effective refractory period of the antecedent beat. Thereafter the test stimulus was moved by 10 msec increments progressively later in electrical diastole until at least 40-50 msec of the recovery cycle had been encompassed. This assured complete scanning of the vulnerable period. At the outer limit of the scanning region, the test current was increased by 5 ma, and scanning was resumed at 10 msec intervals by moving the test stimulus progressively earlier in diastole until the refractory period was encountered. In this fashion, current intensity was progressively increased in 5 ma increments until VF occurred. The current provoking sustained VF was designated as the VF threshold. Testing was carried out twice at each time setting and current intensity. The number of stimuli in the testing sequence was selected so as to yield a control VF threshold of 15 ma or greater. If the VF threshold with three stimuli was less than 15 ma, the number of stimuli was progressively reduced until a VF threshold of 15 ma or greater was obtained.

For any given animal, the various VF threshold test runs were integrated according to the following sequence: Initially, VF threshold in the closed-chest animal was determined with and without VNS. Then a left thoracotomy was performed and the LSG was decentralized. The effects on VF threshold of separate VNS and LSGS, as well as combined simultaneous LSGS and VNS, were then determined and compared to the basal control open-chest VF threshold. The order of testing was randomized. Four of 17 animals were tested under all of the above conditions; in the remaining 13 animals, testing was successfully completed under some, but not all conditions.

In order to assess whether a vagal effect on vulnerability could be elicited in the absence of sympathetic tone, six of the 17 animals were tested for a VNS-associated effect on VF threshold before and 15–30 min after the induction of acute beta-adrenergic blockade with 0.2 mg/kg intravenous propranolol.

For each of the above comparisons, determinations of VF threshold were made prior to and following each experimental intervention. Unless these values agreed within 5–10 ma, the experimental trial was repeated.

Determination of Vagal Effects on VF Zone Configuration

Thirteen animals were studied, seven under closed-chest and six under open-chest conditions. The vulnerable period was mapped by progressive stepwise increments in S_3 at 5–10 msec intervals throughout the recovery cycle. Initially, S_1 and S_2 were each set 15 msec outside the refractory period for a stimulus of 5 ma. S_3 was then set 10–15 msec outside its 5 ma refractory period, a range which was empirically found to approximate the minimum VF threshold. At this setting of S_3 , the amplitude of the test pulse was increased in 5 ma increments until sustained VF supervened. Testing was performed twice at each current level. The current just sufficient to evoke sustained VF was designated the VF threshold for that time in the recovery cycle at which testing

was performed. Then, with S₁, S₂, and S₃ still held constant in time, the vagi were stimulated and the procedure repeated in order to establish a VF threshold associated with vagal stimulation.

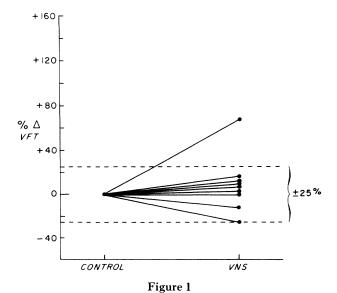
Ventricular fibrillation threshold determinations were carried out at each 5–10 msec interval in the recovery cycle, until the entire range of VF thresholds greater than 70–100 ma had been mapped for both the control and vagal-stimulated state. Such a continuous time sequence of VF thresholds defined the lower limit of the zone of vulnerability to fibrillation. The upper limit of the VF zone, demarcated in part by the so-called "no response" boundary, 18 was not determined in these experiments. The nadir of the VF zone lower limit, i.e., the point of maximum vulnerability, has been taken by numerous investigators as an index of the ventricular susceptibility to spontaneous fibrillation 19–21 and corresponds to ventricular fibrillation threshold as described in the previous section.

In all experiments, heart rate was set 10-20 beats per minute above the maximal rate associated with LSGS in a particular animal. For any set of test conditions in any given animal, the pacing rate, as well as the number of sequential stimuli was maintained constant. Statistical comparisons of paired samples were made using Student's t-test.

Results

Closed-chest Dogs

In nine closed-chest animals, VNS had no significant effect on VF threshold (fig. 1). The mean VNS-associated increase in VF threshold was $8\pm8\%$ (mean \pm se) of control. In but one of these animals did VNS raise VF threshold by greater than 25% of the control value. VF zones were mapped in seven additional closed-chest dogs. In these animals VNS shifted the entire VF zone 0–15 msec later into elec-



Percentage change in VF threshold, from control, during vagus nerve stimulation (VNS) in closed-chest dogs. In all but one animal the change in VF threshold associated with VNS was < 25% of control. In this animal, beta-adrenergic blockade with intravenous propranolol abolished the protective effect of VNS.

trical diastole, but did not affect either its over-all configuration or the magnitude of its nadir.

Open-chest Dogs

In ten open-chest animals, with left stellate ganglion decentralized, the mean VNS-associated increase in VF threshold was $26 \pm 22\%$, a value not significantly different from control. In but three of these dogs did VNS result in a rise in VF threshold greater than 25% of the control determination. VF zones were mapped in six additional open-chest animals. In no animal was the magnitude of the VF zone nadir or the over-all configuration of vulnerability affected by VNS.

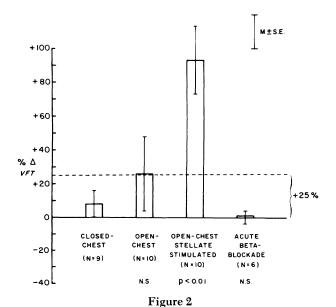
Stellate-stimulated Dogs

The effect of VNS on VF threshold during simultaneous LSGS was studied in ten open-chest animals. LSGS alone decreased VF threshold to 51% (P < 0.001) of the control value. VNS during concurrent LSGS resulted in a significant (P < 0.01) elevation of VF threshold (fig. 2). However, this elevation did not exceed the control value for VF threshold (table 1).

Ventricular fibrillation zones were mapped in four additional open-chest animals during sustained LSGS. VNS in stellate-stimulated dogs both elevated the VF zone nadir and narrowed the over-all configuration of vulnerability. The timing of the VF zone nadir was unaffected by VNS (fig. 3).

Acute Beta-adrenergic Blockade

The above observations were extended by assessing



Effect of VNS on VF threshold under varying conditions of adrenergic input. Only in stellate-stimulated animals was the effect of VNS on VF threshold significantly different from control (P < 0.01).

Table 1

Effect of Vagus Nerve Stimulation (VNS) on Ventricular Fibrillation (VF) Threshold During Concurrent Left Stellate Ganglion Stimulation (LSGS) in 10 Dogs

Dog N	Io (msec)	N Pulses	VF Threshold (ma)			
			Control	LSGS	VNS + LSGS	
1	280	3	35	18	14	
2	240	3	30	13	25	
	240	3	4.5	15	35	
3	240	1	50	25	45	
4	280	3	58	37	95	
6	280	3	37	13	15	
8	240	2	38	30	50	
9	240	1		17	35	
10	300	1		13	28	
11	240	1	23	10	22	
13	280	3	35	10	23	
Mean ± se			39 ± 4	19 ± 3	36 ± 1	
P				< 0.001	NS	

Abbreviations: I_o = pacing interval; P = P value relative to the basal control open-chest state, by Student's t-test; N = number.

the effects of VNS on VF threshold in six animals pretreated with intravenous propranolol. Three of the animals were closed-chest and three open-chest. In no animal with beta-adrenergic blockade did VNS significantly alter VF threshold (table 2). The mean VNS-associated change in VF threshold was $0\pm4\%$ of control (fig. 2). In two animals (#5 and #9) which had vagal-associated VF threshold elevations of 67%

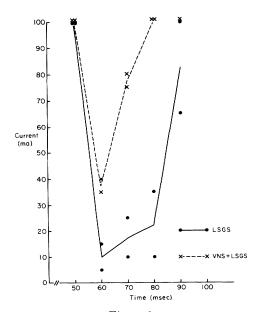


Figure 3

Effect of VNS on VF zone during left stellate ganglion stimulation (LSGS) in a representative experiment. During sustained LSGS, VNS elevated the VF zone nadir and narrowed the vulnerable period duration at any given stimulus intensity. The timing of the VF zone nadir was unaffected by VNS. The pacing interval in this animal was 240 msec.

Table 2

Effect of Vagus Nerve Stimulation (VNS) on Ventricular Fibrillation (VF) Threshold in Dogs Pretreated with Propranolol (0.2 mg/kg)

	${f I_o}$			VF Threshold (ma)		
$\operatorname{Dog}\mathbf{N}$	Prep*	(msec)	N pulses	C	P	VNS + P
		280	3	30	65	68
9	+	333	1	-	43	43
14	-	333	3	30	60	70
15	+	333	2	68	83	78
16	_	300	3		63	58
17	+	240	2	35	53	50
Mean ± se				41 ± 9	61 ± 5	$61 \pm .5$

Abbreviations: I_o = pacing interval; Prep = thoracotomy preparation; N = number; C = control; P = propranolol.

and 200%, respectively, in the control state, propranolol abolished the vagal effect.

Discussion

Considerable evidence exists indicating that parasympathetic nervous influences directly affect the chronotropic and inotropic properties of the ventricle. ²² Thus, Eliakim et al. ²³ have shown that VNS depresses the ventricular rate in A-V block dogs, while more recently Bailey et al. ²⁴ have demonstrated that acetylcholine in relatively small concentrations depresses phase 4 of the action potential of *in situ* proximal His-Purkinje fibers while enhancing conduction velocity. Similarly, DeGeest et al. ¹², ²⁵ and Priola and Fulton ²⁶ have demonstrated a distinct negative inotropic effect of vagal stimulation on the isovolumic canine ventricle.

Less clear, however, are the effects of vagal stimulation upon the electrical properties of the ventricle. While Hoffman and co-workers¹-⁴ found that VNS had no significant effect on either ventricular excitability or conduction velocity, Kent et al.⁵ have recently reported that VNS was associated with substantial (> 100-200%) elevations in VF threshold. Both investigators employed epicardial electrodes to study open-chest dogs subjected to barbiturate anesthesia. Hoffman and associates¹-⁴ assessed excitability by means of a single test pulse, whereas Kent et al.⁵ determined VF threshold with a train-of-pulses technique.

The present work originated as an attempt to define a vagal effect upon vulnerability in the closed-chest dog, inasmuch as this model was felt to be relevant to the occurrence of sudden death in man. Testing from the right ventricular endocardium eliminated the effects on vulnerability which might be associated with thoracotomy. Employing a single test pulse minimized the artifacts associated with delivery of suprathreshold trains of electrical stimuli²⁷ directly to

the myocardium. With this type of experimental design, our preliminary results⁷ showed no significant effect of VNS on VF threshold.

There remained the problem of accounting for our inability to confirm the persuasive findings of Kent and co-workers. 5 We postulated that the difference in results may have been due to varied states of sympathetic tone in the two studies. Kent et al. not only employed open-chest animals, but used a train-ofpulses technique²⁰ for assessing VF threshold; both these elements of experimental design are associated with enhanced sympathetic nervous activity. Nelemans,28 in 1951, suggested that faradization of the frog ventricle released acetylcholine and sympathin from local cardiac nerve terminals. Vincenzi and West²⁹ observed that subthreshold as well as threshold trains of electrical stimuli applied directly to the myocardium acted as potent releasers of neurohormones from endogenous cardiac stores. Brady et al. 30 demonstrated that a 100 msec pulsing train, consisting of 20 pulses, 80 ma/cm² in intensity, 1 msec in duration, and 5 msec apart, resulted in a sustained increase in contractility, exceeding 100% of control, in cat papillary-muscle strips; such potentiation was abolished by reserpine pretreatment. Thus the trainof-pulses technique may be associated with substantial catecholamine release.

The possibility that the effects of VNS on VF threshold were conditioned by concurrent levels of sympathetic activity finds support in other cardiovascular target areas wherein these systems interact. Numerous investigators^{10, 11, 31-34} have found that the negative inotropic and chronotropic effects of cholinergic stimulation are potentiated by elevation in the level of sympathetic activity. Levy et al. ¹¹ have shown that in the control isovolumic canine ventricle VNS diminished left ventricular systolic pressure $10.6 \pm 2.8\%$, as compared to $24.0 \pm 3.6\%$ during stellate stimulation (P < 0.005); when reflex enhance-

^{*-} = closed-chest; + = open-chest.

ment of sympathetic tone was effected by carotid sinus hypotension, the VNS-associated reduction in inotropy was altered from 23% to 34–45%. Hollenberg et al. 32 have observed an analogous inotropic effect upon infusion of acetylcholine into the left coronary artery of the dog. Equivalent potentiation of the negative chronotropic effect of parasympathetic influence by high levels of sympathetic tone has also been demonstrated. 10, 33, 34

Such interactions have also been shown to operate in relation to the occurrence of VF. As early as 1913, A. G. Levy³⁵ found that, in cats sensitized to catecholamines by light chloroform anesthesia, cervical vagal section resulted in the abrupt emergence of ventricular arrhythmias, including VF. These observations were later extended by Hoff and Nahum³⁶ who showed that, in cats presensitized by either benzol or chloroform inhalation, acetyl betamethylcholine afforded protection against ventricular extrasystoles, ventricular tachycardia, and VF provoked by catecholamine administration.

The investigations cited above encouraged the inference that a vagal effect on ventricular vulnerability, while absent under basal conditions, might be elicited during augmented sympathetic tone. Our initial experiments were therefore repeated under a variety of conditions: in closed- as well as in open-chest animals, with and without direct enhancement of sympathetic neural input by means of LSGS. VNS had no significant effect on VF threshold in closed-chest animals, nor was such an effect noted in control open-chest animals. However, in open-chest dogs with LSG stimulated, VNS resulted in significant (P < 0.01)elevations in VF threshold (fig. 2). Finally, the VNSassociated elevation in VF threshold was not observed in any of the animals subjected to beta-adrenergic blockade; while propranolol completely abolished the vagal protection observed in two non-stellatestimulated animals.

Qualitative appraisal of the effect of VNS on vulnerability was provided by mapping of the VF zone. The absence of a vagal effect on VF zone nadir in closed-chest animals confirmed the results obtained by means of the different technique of VF threshold determination. Moreover, VNS in open-chest, stellatestimulated animals elevated the VF zone (including its nadir) and narrowed the vulnerable period; this effect contrasts with that observed in closed-chest animals, in which VNS shifted the VF zone 0-15 msec later into electrical diastole, without affecting its nadir or over-all configuration. It may be that the VNSinduced displacement of the zone of vulnerability in closed-chest dogs is related to concurrent VNSassociated changes in ventricular excitability, which are abolished by maximal stellate stimulation.

We infer from these data that heightened sympathetic tone is a necessary condition for vagal enhancement of ventricular electrical stability.

This inference is questioned by more recent findings of Kent et al.37 In five animals depleted of cardiac catecholamines by pretreatment with 6-hydroxydopamine, VNS resulted in a moderate (48%) increase in VF threshold, as determined by the train-of-pulses technique. Interpretation of these experiments, however, is complicated by several technical considerations: intact adrenomedullary catecholamine stores, which would not be affected by 6-hydroxydopamine; post-denervation myocardial hypersensitivity to circulating adrenomedullary hormones, as well as to small amounts of residual ventricular norepinephrine which may be released by the train of electrical stimuli; thoracotomy; and stimulation of the intact rather than the decentralized cervical vagi. To date, therefore, a direct vagal effect on ventricular vulnerability, in the absence of adrenergic stimulation, has not been demonstrated.

Our studies also provide some insight regarding the mechanism of the vagal effect. In the stellate-stimulated group of dogs, LSGS resulted in a substantial lowering of VF threshold, whereas VNS simultaneous with LSGS raised VF threshold to the control value, but not beyond. Moreover, in propranolol-treated animals VNS was without effect. These observations suggest that the VNS-associated increase in VF threshold is indirect, and results from partial anullment of concomitant adrenergic influence, rather than from any direct cholinergic action on the ventricles.

Indeed, there is evidence at the molecular level to support this view. Murad et al.38 showed that acetylcholine reduced adenylcyclase-directed cyclic adenosine 3', 5' — monophosphate (cAMP) synthesis from a variety of broken-cell cardiac tissues, and that such a reduction was blocked by atropine. LaRaia and Sonnenblick³⁹ demonstrated that carbamylcholine blockade of cAMP synthesis was associated with a reduction in tension in isolated cat atrial and ventricular muscle strips, and that the effect was again abolished by atropine; norepinephrine increased cAMP synthesis in parallel with increases in tension development. More recently, Löffelholz, Muscholl et al. have shown in isolated rabbit hearts that VNS,40 as well as acetylcholine,41 markedly reduces norepinephrine production resulting from stimulation of cardiac sympathetic nerves.

At the turn of the century, Garrey⁴² demonstrated that vagal stimulation protected some dogs against ventricular fibrillation. Kent and co-workers^{5, 6} have provided a physiologic basis for such protection in demonstrating vagally-induced enhancement of ven-

tricular fibrillation threshold. This opens a possible new therapeutic approach to the formidable problem of sudden death in those afflicted with ischemic heart disease. But if such an approach is to be pursued successfully, it must take cognizance of the fact that vagal action on ventricular vulnerability is part of a complex autonomic interaction, in which the primary determinant is the sympathetic limb.

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