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Vagus nerve stimulation: from pre-clinical to clinical application: challenges and future directions

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Abstract Vagus nerve stimulation was performed experimentally for the first time more than 150 years ago. In the 1980s and 1990s, vagus nerve stimulation was shown, both in the anesthetized and in the conscious animal, to exert marked antiarrhythmic effects, particularly during acute myocardial ischemia. There is a strong rationale for a beneficial effect of augmented vagal activity in the setting of chronic heart failure. Studies in experimental models of heart failure showed that chronic vagus nerve stimulation exerts beneficial effects on left ventricular function and on survival. Vagus nerve stimulation is approved in man for refractory epilepsy and depression. The first-in-man study performed in 32 patients with chronic heart failure suggests that vagus nerve stimulation was safe and well tolerated. Six months of open-label treatment was associated with significant improvements ($P < 0.001$) in NYHA class, quality of life, 6-min walk test, LV ejection fraction (from 22 ± 7 to 29 ± 8%), and LV systolic volumes ($P = 0.02$). These improvements were maintained at 1 year. Mechanisms of action may include the following: heart rate, anti-adrenergic, anti-apoptotic, and anti-inflammatory effects as well as an increase in nitric oxide. Controlled clinical trials will start soon to assess whether vagus nerve stimulation can indeed represent a new non-pharmacological approach for the treatment of symptomatic heart failure.

Keywords Heart failure · Vagal stimulation · Ventricular arrhythmia

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Introduction

Research into vagus nerve stimulation has a long and storied history. Much of the early work was performed in animal models with the goal of describing its effects on either cardiovascular physiology or cardiac rhythm disturbances. We will therefore examine these latter studies and then focus on heart failure. We will also provide some concluding thoughts that help to synthesize many of the concepts raised in this issue of HF Reviews.

Vagal stimulation in experimental models of arrhythmias: historical and recent studies

The first study was performed more than 150 years ago. Einbrodt assessed the effects of an inductorium on heart beats and noticed that during vagal stimulation, the distance between the coils could be markedly reduced,

thereby increasing the current delivered, before ventricular fibrillation (VF) occurred and the dog died [1]. Despite this pioneering observation, dating back to 1859, the dominant view [2–4], with few exceptions [5, 6], was that vagal hyperactivity is proarrhythmic and favors the occurrence of VF. The proarrhythmic effect of vagal stimulation was not confirmed in dogs subjected to coronary artery occlusion by Scherlag et al. [7] and by Kerzner et al. [8]and was seriously questioned in the early 1970s [9–11]. In the chloralose-anesthetized cat, bilateral vagotomy increased the incidence of VF produced by occlusion of the left anterior descending (LAD) coronary artery from 20 to 55%, independently of heart rate effects [12]. Subsequently, Yoon et al. [13, 14] found in anesthetized dogs that heart rate reduction mediated the antiarrhythmic effects of vagal stimulation during coronary occlusion and that an anti-adrenergic mechanism played a major role in the increase in VF threshold (VFT). Similar conclusions were reached by Kolman et al. [15] and by Furey and Levy [16], who showed that vagal stimulation also counteracted the effect of isoproterenol infusion suggesting post-junctional antagonism. This was at variance with Kent et al. [9] and Yoon et al. [13], who showed an increase in VFT independent of sympathetic stimulation. Many years later, the question of whether vagal stimulation has biologically significant effects at ventricular level independent of its anti-adrenergic action is still a matter of debate.

Malignant arrhythmias also occur following reperfusion of the ischemic myocardium [17]. We evaluated the effects of bilateral vagotomy and of vagal stimulation on reperfusion arrhythmias in cats [18]. Vagal stimulation decreased the incidence of malignant arrhythmias dramatically when heart rate was allowed to decrease and moderately when heart rate was kept constant. Although reperfusion arrhythmias were considered to have limited clinical relevance, reperfusion of the ischemic myocardium produces a cascade of events resulting in cell death and dysfunction that are grouped under the definition of reperfusion injury [19], and it is likely that the mechanisms leading to electrical or mechanical abnormalities share common pathways that may be favorably affected by vagal stimulation. Indeed, a series of recent experimental studies have found promising results for the potential of vagal stimulation to attenuate reperfusion injury and subsequent cardiac remodeling (see section on future developments).

All experimental studies described above involved anesthetized animals and conditions distant from the one potentially encountered clinically. Therefore, we assessed the effects of vagal stimulation in a conscious animal model for sudden cardiac death [20] in which VF may be reproducibly induced for several months in approximately 55% of the animals ("susceptible"), allowing internal control studies. In this model, vagal activity was essential for the prevention of VF in 11 of 45 animals originally resistant to VF and tested after atropine [21]. Additionally, susceptible dogs underwent a further exercise and ischemia test with no additional intervention (control group) or with right vagal stimulation started few seconds after the beginning of coronary occlusion [22]. VF occurred in 23 of 25 (92%) control animals, but only in 3 of 26 (11.5%) vagally stimulated dogs. When heart rate was not allowed to decrease, 5 of 9 animals (55%) remained protected from VF. We stimulated the intact cervical vagus, and thus, both efferent and afferent fibers were stimulated. Since vagal afferent stimulation produces a reflex withdrawal of sympathetic efferent activity [23], this withdrawal might have significantly influenced our results. However, this appears unlikely since atropine prevented both the chronotropic and the antiarrhythmic effects of vagal stimulation in this model. Thus, in the exercising dog with high levels of circulating catecholamines, a transient decrease in the firing of sympathetic nerves is unlikely to grossly affect cardiac electrophysiology. Notably, the picture is likely to be different when dealing with long-term studies aiming, for instance, at providing anti-remodeling effects in patients with heart failure: in this setting, simultaneous sympathetic withdrawal may very well contribute to the beneficial effects of chronic vagal stimulation. Summarizing, vagal hyperactivity drastically reduces malignant arrhythmia, and the reduction in heart rate is not a crucial component in half of the protected animals. Favorable effects were also observed in this same animal model with pharmacological vagal activation [24].

In a more recent rat study [25], vagal stimulation confirmed a striking antiarrhythmic effect during myocardial ischemia and prevented >50% of the loss of connexin 43 induced by ischemia, a new potential mechanism involved in the vagally mediated increase in electrical stability.

Vagal stimulation and arrhythmias in patients

Until very recently, all information regarding vagal activation in patients with cardiac disorders was obtained from indirect evidence. The background regarding the predictive role of a marker of vagal reflexes such as baroreflex sensitivity is discussed elsewhere in this Supplement [26]. More relevant to the current topic are the few clinical studies examining the effects of reflexly induced vagal hyperactivity, mostly on ventricular arrhythmias. Waxman and colleagues provided the first evidence that some ventricular tachycardias (VTs) could respond to vagal activation, contrary to traditional belief [27, 28], and that ventricular automaticity was decreased by vagal activity [29].

We have assessed the antiarrhythmic effect of reflexly induced vagal activation, in patients with frequent, stable premature ventricular contractions (PVCs) [30]. When

heart rate was allowed to decrease, phenylephrine completely abolished ectopic activity in 9 of the 10 patients studied. During atrial pacing at the pre-drug rate, PVCs reappeared in most subjects. Their mean number, however, was still significantly less than the control values, which suggests that the antiarrhythmic effect of reflex vagal activation is only partially rate-dependent.

Vagal stimulation in experimental models of heart failure

Chronic electrical vagal stimulation has been assessed in three animal models of heart failure. Rats subjected to a large anterior myocardial infarction (MI) leading to heart failure were randomized to vagal and sham-stimulated groups 14 days post-MI. The vagus was stimulated for 10 s/min, with an intensity adjusted to reduce heart rate by 20–30 bpm. Rats randomized to vagal stimulation showed significant improvement in left ventricular (LV) hemodynamics and decreased mortality from 50 to 14% at 140 days (Fig. 1) [31]. In an established canine model of intracoronary microembolization-induced heart failure, vagal stimulation significantly improved LV function compared to sham-operated animals [32]. In the same animal model, therapy with vagus nerve electrical stimulation combined with beta-blockade improved left ventricular systolic function beyond that seen with beta-blockade alone [33].

More recently, the effects of chronic vagal stimulation in a canine pacing model of heart failure (HF) were presented [34]. These dogs were subjected to 8 weeks of high-rate ventricular pacing with concomitant vagus nerve stimulation in the active group and no stimulation in the control group. At the end of the 12-week study period, vagally stimulated animals had significantly lower LV end-diastolic and end-systolic volumes and higher LV ejection fraction (EF). This result was obtained in the absence of any heart rate effect provided by vagal stimulation since both groups were subjected to the same constant ventricular pacing.

Finally, vagus nerve stimulation at a low intensity, not causing any heart rate reduction, exerted positive effect on LV function and multiple biomarkers in the canine microembolization HF model [35].

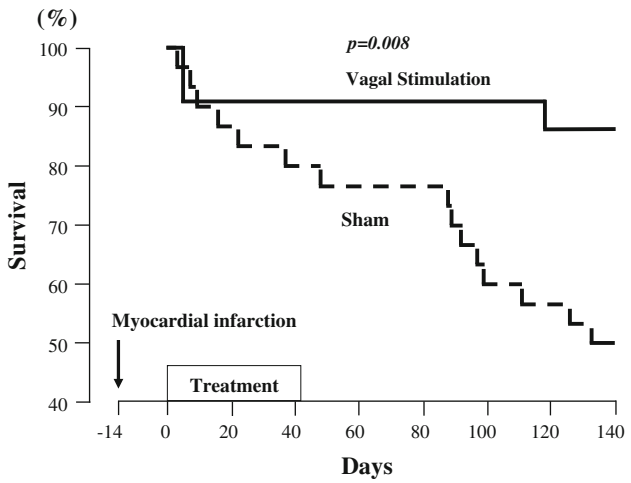

Fig. 1 Survival curves of rats subjected to a large anterior myocardial infarction leading to heart failure and randomized 14 days post-MI to vagal stimulation or sham stimulation. Rats randomized to vagal stimulation showed a significantly lower mortality. (Modified from Ref. [31])

Vagal stimulation and heart failure in patients

In patients, vagus nerve stimulation has been approved for the treatment of drug-refractory epilepsy [36–38] and, subsequently, depression [39, 40].

Given the strong rationale for vagal stimulation in patients with heart failure, we performed a single-arm open-label interventional phase II study that followed a 2-staged approach [41, 42]: a single-center feasibility phase followed by a multicenter phase assessing primarily safety and tolerability of chronic vagus nerve stimulation. A secondary objective of the study was to collect preliminary information on efficacy.

We enrolled 32 patients (94% men; mean age 56 ± 11 years) with a history of chronic heart failure in symptomatic NYHA class II-IV and average LVEF of 23 ± 8%. The patients were on a very comprehensive background medical treatment including beta-blockers, ACE inhibitors/ARBs, and loop diuretics in 31 out of 32; implantable cardioverter-defibrillators (ICDs) were previously implanted in 19 out of 32. The main inclusion and exclusion criteria are described in detail elsewhere [41, 42]. These patients underwent implantation of the CardioFit 5000 system (BioControl Medical, Yehud, Israel), including an implantable neurostimulator, capable of delivering low-current electrical pulses, with adjustable parameters, to stimulate the vagus nerve. The stimulator is designed to sense the heart rate (via an intracardiac implanted electrode) and deliver stimulation at preset delays from the R wave as well as to interrupt vagal stimulation when the heart rate reaches the bradycardia limit (e.g., 55 b/min). The stimulation lead is an asymmetric bipolar multi-contact cuff electrode specifically designed for cathodic induction of action potentials in the vagus nerve while simultaneously applying asymmetrical anodal blocks, which are expected to lead to preferential, but not exclusive, activation of efferent fibers.

Within 4 weeks of implantation, a 3-week stimulation up-titration phase was started with the goal of reaching 5.5 mAmp, a 5–10 b/min heart rate reduction or onset of side effects. The stimulation intensity reached 4.1 ± 1.2 mA and was limited by discomfort or pain in the majority of patients. Two serious adverse events (SAEs) were clearly related to the procedure: one acute pulmonary edema occurring after surgery and treated with iv diuretics and one need of surgical revision of the device. Two SAEs were possibly related to the experimental treatment: an episode of atrial fibrillation leading to electrical cardioversion and an episode of ulcer bleeding in a Helicobacter pylori-positive patient.

Heart rate changes observed during vagal stimulation (10-s ON time: red crosses, 30-s OFF time: blue crosses) in one patient are shown in Fig. 2. The average acute heart rate changes observed during vagal stimulation were modest (1.5 b/min). However, baseline resting heart rate decreased significantly during the study from 82 ± 13 to 76 ± 13 b/min. Most patients improved by at least one NYHA class both at 3 months (18/32, 56%) and at 6 months (19/32, 59%). Quality of life markedly improved at 3 months (from 49 ± 17 to 33 ± 16 with the Minnesota Living with Heart Failure® Questionnaire), thereafter remaining almost identical at 6 months (32 ± 19). The same was found for the 6-min walk test with an increase at 3 months from 411 ± 76 to 470 ± 99 m and subsequent stability. The blinded echocardiogram analysis disclosed a non-significant decrease in LV end-diastolic volume, a significant reduction in LV end-systolic volume (see Fig. 3), and a significant increase in LV ejection fraction (from 22 ± 7% to 29 ± 8%). A group of 23 patients

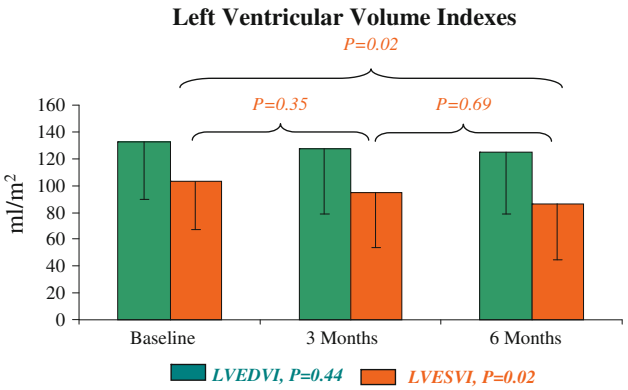

Fig. 3 Left ventricular volume indexes. LVEDVI: left ventricular end-diastolic volume index. LVESVI: left ventricular end-systolic volume index. (From Ref. [42])

continued their follow-up with active vagal stimulation. Analysis of clinical variables in this group of patients revealed maintenance and even magnification of the favorable effects of vagal stimulation at 1 year (especially LVEF from 21 to 34%).

This first human experience of chronic vagal stimulation in patients with heart failure suggested that the treatment is feasible, safe and tolerable and leads to a subjective clinical improvement. The study also provided the first evidence to suggest that this new therapeutic approach may produce favorable and long-lasting effects on left ventricular function. The preservation of these effects at 1-year follow-up strongly argues against a major role of a possible placebo effect.

Thus, this novel therapeutic approach appears promising and warrants further investigation. Accordingly, two trials

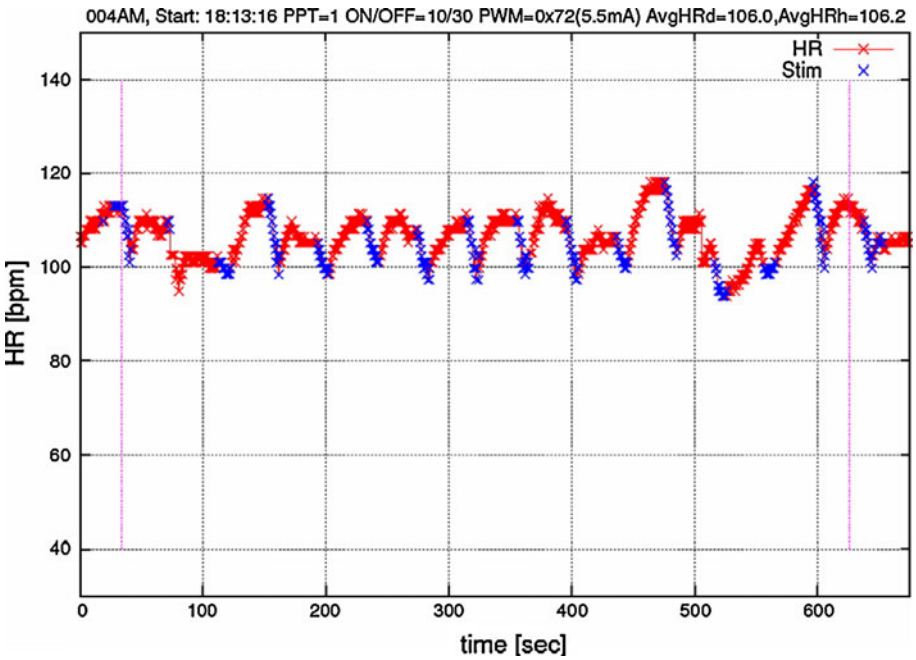

Fig. 2 Heart rate observed during vagal stimulation (5.5 mAmp, 10 s ON time: red crosses, 30 s OFF time: blue crosses) in one patient. A reduction of approximately 10 b/min, starting from a baseline heart rate of 110 b/min, occurred during the 10-s train of pulses. (From Ref. [41])

(a phase III study using this same device and a phase II study with a different device) will start soon. They will provide a more precise definition of the role of vagal stimulation in heart failure.

Mechanisms of favorable effect

Several mechanisms are likely to be involved in the beneficial effects of vagal stimulation. The first question is as follows: how important is the contribution of the heart rate decrease? In the arrhythmia literature, this issue has been analyzed in detail [43]. Briefly, although few studies indicate it as the sole cause of the antiarrhythmic effect, the majority of the investigations, including our own [18, 21, 22], suggest that heart rate modulation plays a significant but not exclusive role. It should be mentioned that several studies were performed during coronary artery occlusion, a condition in which higher heart rates are accompanied by greater degrees of myocardial ischemia [11, 44], thus obviously facilitating arrhythmias. However, the experience with isolated ventricular arrhythmias in patients in the absence of ischemia [30] is still consistent with this concept.

Among patients with heart failure, a heart-rate-mediated effect is likely to play a significant role. Results from clinical trials have suggested that the heart rate decrease during beta-blocker treatment is a major determinant of the favorable effect of this pharmacological approach [45].The recently reported beneficial effect of ivabradine, an agent acting almost exclusively by decreasing heart rate, also supports the concept of a favorable role of heart rate reduction [46]. Experimentally, heart rate during vagal stimulation was allowed to decrease in the first two models used [31–33], thus not allowing the assessment of a heart-rate-independent mechanism. However, in two recent studies, namely in dogs subjected to the same high-rate ventricular pacing in both vagal stimulation and control group [34] and in dogs with microembolization-induced HF subjected to vagus nerve stimulation at a low intensity [35], beneficial effects were found in the absence of any heart rate difference.

Several of the potential additional mechanisms contributing to the beneficial effect of vagal stimulation have been recently discussed in detail [47]. These may include anti-adrenergic effects that may occur at central level and at peripheral level (both pre-synaptic and post-synaptic), anti-apoptotic effects, an increase in nitric oxide and anti-inflammatory effects. Indeed, these intriguing additional mechanisms are related to the so-called inflammatory reflex, which shows that vagal stimulation inhibits macrophage activation, the synthesis of TNF, and inflammatory responses [48]. This particular effect is likely to be involved also in the beneficial results of vagal stimulation against myocardial ischemia/reperfusion injury.

Present challenges: identification of the best stimulation technique and the ideal patient

The demonstration of a beneficial effect of vagal stimulation in patients with heart failure clearly needs confirmation in a large randomized controlled clinical trial. At least two challenges exist: selection of the stimulation protocol and selection of the patient. It should be emphasized that simply stating that a patient will be assigned to vagus nerve stimulation therapy is very inexact. A list of more than ten parameters that may affect the clinical efficacy of the intervention is presented in the Table 1.

While most pharmacological interventions show a dose–response curve (with some doses ineffective or even detrimental), the same likely applies to neural modulation interventions such as vagal stimulation. To date, experimental studies have not adequately addressed this issue; thus, choices have to be made on the basis of the limited clinical experience.

Equally important is the selection of patients who are likely to respond better to this autonomic intervention. Again, most interventions in patients with heart failure show variable efficacy, and a non-negligible percentage of patients are generally considered to be non-responders. For instance, among candidates to cardiac resynchronization therapy, identification of responders and non-responders (still an open issue) would clearly allow the best use of resources and avoid unnecessary implantation of biventricular devices. Very limited data are available so far to

Table 1 Vagus nerve stimulation parameter that may be regulated

Variables in vagal nerve stimulation
Right vs left vs bilateral stimulation
Electrode and waveform configuration
Bidirectional efferent and afferent (technically easier), preferential efferent or preferential afferent stimulation (technically more complex)
Continuous stimulation versus pulse-synchronous stimulation
With pulse-synchronous stimulation: delay from the R wave (or other trigger) and number of pulses per cycle
With continuous stimulation: frequency of stimulation
Current amplitude, titration protocols, and maximum current
Target: heart rate reduction vs low-intensity vagal stimulation without heart rate target
Duration of the ON/OFF cycles
Presence or absence of long stimulation pauses
Heart-rate-dependent stimulation intensity and limits for stimulation withdrawal (e.g., low heart rate)

help identify the ideal candidate for vagus nerve stimulation. It appears that patients who, despite optimal medical therapy, still show signs of marked sympathetic activation such as higher heart rate and lower heart rate variability tend to show a better response [49]. Patients with diabetic neuropathy were excluded our study, but the question whether any type of diabetes reduces the responsiveness to vagal stimulation is still open. In addition, it appears reasonable that patients who present a very large LV scar and thus have a limited amount of viable tissue are unlikely to show a marked improvement in LV volumes and ejection fraction.

Future directions: possible alternative electrical stimulation techniques leading to an augmentation of vagal efferent activity

A shift in the autonomic balance among subjects with heart disease toward reduced sympathetic drive and increased vagal activity can be obtained both experimentally and clinically by several means including exercise training [50, 51] and pharmacologic modulation [52, 53] as detailed elsewhere in this issue of HF Reviews [54]. Here, we briefly focus on electrical stimulation techniques other than direct vagus nerve stimulation that can lead to increased vagal efferent activity.

Following the experimental demonstration in rats that electroneurostimulation of the ear endings and brainstem structures increases parasympathetic tone and exerts an antiarrhythmic effect [55], Zamotrinsky et al. [56, 57] performed clinical studies using acupuncture needles placed at a depth of 0.1–0.3 mm into an acupuncture point known as heart 1 (shin), corresponding to an area near the auditory passage that contains endings of the nerve auricolaris, a sensitive ramus of the vagus nerve. The treatment consisted of one daily application of low-intensity current for 15 min. Both studies involved patients with advanced coronary artery disease and severe angina. The first study [56] found a striking reduction in angina and the absence, in atrial tissue taken during the subsequent surgical revascularization intervention, of inducible heat-shock protein, present in all control patients not subjected to electrostimulation. The second paper [57] confirmed and extended these findings, also showing a significant decrease in heart rate and blood pressure, as well as an improvement in LVEF and diastolic properties.

An additional method involves electrical stimulation of carotid baroreceptors. This possibility was first introduced in the 1960s [58, 59] but was abandoned, mainly for technical reasons. More recently, an implantable device has been developed that may overcome most of these problems [60]. Chronic stimulation with this device has been shown to produce sustained hypotension experimentally [61] and to significantly decrease blood pressure in drug-resistant hypertensive patients in open-label investigations [62]. Although carotid baroreceptor stimulation likely increases significantly vagal efferent activity, the main mechanism for blood pressure reduction may be sympathetic inhibition. Indeed, Heusser et al. [63] measured muscle sympathetic nerve activity by microneurography in 12 hypertensive patients during carotid baroreceptor stimulation and found that sympathetic nerve activity decreased markedly during stimulation and that this decrease significantly correlated with the blood pressure decrease. Experimentally, in a canine model of pacing-induced heart failure, chronic baroreceptor activation reduced neurohormonal activation and prolonged survival from an average of 37 days in the control group to an average of 68 days [64].

A detailed description of the effects of spinal cord stimulation (SCS) goes beyond the scope of this paper. However, it should be mentioned that experimentally SCS has been shown to enhance parasympathetic activity, mediated via the vagus nerve [65]. This technique was shown to reduce ventricular arrhythmia and to markedly improve LV function in a canine post-infarction heart failure model over a several week period [66].

Vagal stimulation can also be accomplished by means of intravascular catheters. Schauerte et al. [67] have shown that cardiac parasympathetic nerves can be stimulated in conscious humans via a multipolar catheter placed in the superior vena cava or in the ostium of the coronary sinus (stimulating during the atrial refractory period to avoid inducing atrial fibrillation). The two distinct sites predominantly slowed sinus rate and AV conduction, respectively. Stimulation duration was very short, and patients perceived pain, particularly during stimulation in the superior vena cava. Despite these limitations, this approach appears interesting. For instance, atrial pacing leads implanted in appropriate areas of the right atrium may provide safe high-frequency stimulation recruiting vagal efferent fibers and slowing the ventricular rate during atrial fibrillation in patients [68].

Future directions: potential application in other clinical settings

At a time when the possibility of chronic, safe, and effective stimulation of the vagus nerve in cardiac patients is coming to reality, it should be emphasized that cardiac conditions other than heart failure may benefit from this technique. Given the wealth of experimental data on the antiarrhythmic potential of vagal stimulation (discussed above), an obvious clinical application may be the prevention of life-threatening arrhythmias in patients at high

risk, particularly if due to ischemic heart disease or the treatment of recurrent episodes of ventricular arrhythmias leading to multiple ICD shocks. In addition, following the pioneering experience of Braunwald [59], vagal stimulation may help patients with intractable angina pectoris. Indeed, the two more recent studies by Zamotrinsy et al. [56, 57] with electroneurostimulation of the ear endings (see above) suggest a striking anti-anginal effect among severely symptomatic patients.

Finally, as discussed earlier in this paper, myocardial ischemia/reperfusion injury may be attenuated by vagal stimulation. Multiple experimental studies demonstrate a beneficial effect of vagal stimulation in the reduction of infarct size following myocardial ischemia and a marked protection against myocardial ischemia/reperfusion injury [69, 70]. At least two clinical settings may be relevant. The first is related to myocardial reperfusion in patients undergoing surgical procedures such as coronary artery bypass grafting (CABG) and heart transplantation. Preliminary canine experimental studies have been performed to assess whether controlled intermittent asystole induced by high-intensity vagal stimulation, potentially useful to facilitate off-pump CABG, would impair post-asystolic coronary blood flow or myocardial function [71]. The authors found no negative acute effect of intermittent asystole; rather, a significant decrease in neutrophil accumulation in the ischemic myocardium was observed, in agreement with the hypothesis of vagally mediated decrease in reperfusion injury. Similarly, other situations requiring transient asystole, such as robotic CABG, endovascular deployment of aortic stents or valves might be applicable.

Reperfusion in the setting of acute MI could also be approached with vagal stimulation, possibly performed by means of an intravascular catheter [67] at the time of primary PCI, resulting in the activation of a protective pathway and in the reduction in myocardial damage following reperfusion.

Additional future applications of chronic vagal stimulation in primarily non-cardiologic conditions are conceivable. For instance, a case can be made for its use in patients with chronic renal failure. These patients have a poor prognosis characterized by a markedly increased cardiovascular mortality. Cardiovascular autonomic dysfunction has been proposed as a major contributing factor [72]. Interestingly, recent experimental data in rats subjected to surgical nephrectomy leading to chronic renal failure found marked autonomic imbalance characterized by diminished cardiac parasympathetic tone but by a completely preserved cardiac response to direct electrical vagus nerve stimulation [73]. Thus, vagus nerve stimulation might help to restore the autonomic imbalance and reduce the unacceptably high cardiovascular risk among this group of patients.

Conclusions

Vagal stimulation in patients with heart failure has a strong physiologic and experimental rationale and has been recently proven to be feasible and safe. Preliminary data suggest that this intervention provides subjective and objective improvements. These results require appropriate evaluation in randomized controlled clinical trials of adequate size. Should these trials confirm the promising results of the open-label evaluation, vagus nerve stimulation is likely to become an additional important tool for the treatment of patients with heart failure.

As an example of the potential of this new therapeutic strategy, a patient with chronic ischemic heart disease, a reduction in systolic LV function and the persistence of coronary stenoses, and angina might be a candidate for a vagal nerve stimulation device, possibly combined with defibrillator capacity for primary prevention. Indeed, in such a patient, chronic low-intensity vagal stimulation may provide an improvement in LV function, functional capacity, and quality of life, as well as reduce the risk of ventricular tachycardia/fibrillation. Angina, if present, might also respond favorably. In the case of myocardial ischemia (detected by a device sensor or eventually by the patient), the intensity of vagal stimulation could be increased by appropriate programming, thereby providing protection against ischemic arrhythmias, a reduction in the severity of ischemia, and, in case of prolonged ischemia, also in the amount of ischemia/reperfusion injury. Finally, the device could also provide higher-intensity vagal stimulation to reduce ventricular rate in case of fast ventricular response to atrial tachycardia/fibrillation.

This scenario may appear futuristic, but the same criticism could have been made to our statement, more that 15 years ago [43], that “the development of a chronically implantable electrode” was “within current technical possibilities”.

Therefore, although much clinical research is still required, we believe we are now at the beginning of the clinical use of electrical neuromodulation for the treatment of patients with heart failure and other related cardiac conditions.

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