Why Cardiologists are not using Devices to directly modulate the Nervous System

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Abstract

In spite of all the available evidence on the efficacy and safety of electrical neuromodulation for chronic refractory angina, the therapy is not generally accepted in the field of cardiology. Albeit that in both, European and US guidelines of cardiology, electrical neuromodulation, mainly executed through spinal cord stimulation, is adopted for treatment of chronic refractory angina, there is still a paucity in its acceptation. Here, we will discuss the putative major reasons why acceptance of electrical neuromodulation has not yet become common practice among cardiologist. Furthermore, we provide our reflections on how to achieve a better acceptation of electrical neuromodulation for cardiac diseases.

Rationale

The Achilles' heel of electrical neuromodulation for cardiovascular diseases seems to be its acceptance by cardiologists. Though direct electrical interference with cardiac function via artificial cardiac pacemakers, implantable defibrillators, and resynchronization therapy is widely accepted as effective therapies among cardiologists, the use of the nervous system to directly control cardiac function is largely overlooked. Thus, instead of indirectly using medication designed to adjust the disturbed (autonomic) nervous system to improve cardiac function, modulating the nervous system itself, may even be a superior strategy. For epochs of time the crucial role of the efferent nervous system has been recognized in the genesis and maintenance of many cardiac diseases, such as arrhythmias and heart failure. Since the first publication on electrical neuromodulation for angina by Eugene Braunwald in 1967, hundreds of articles followed. However, in contrast to the enormous growth of neuromodulation for other indications and irrespective of the acceptance of neuromodulation in US and European cardiology guidelines, the treatment is still of limited use.

In this article, we therefore are addressing concerns with regard to the limitations of neuromodulation for a broad acceptance among the cardiology community.

The problem of chronic refractory angina in the light of evidenced based medicine

Though evidenced based medicine has become widely adopted in the medical community there are still 'alternative facts' opposed, or even worse denial of an established treatment. An example is the scientific consensus that the Human immunodeficiency virus (HIV) infection causes acquired immune deficiency syndrome (AIDS). However, this cause-effect relation was challenged by Duesberg, a cell biologist, who hypothesized that HIV is a harmless passenger virus, not causing AIDS Although one manuscript can be addressed as incorrect, since Joan Shenton's book "Positively False – Exposing the Myths Around HIV and AIDS", more than 18,000,000 sites on the internet are proclaiming the denial of the HIV-AIDS relation!

From this perspective, it is highly unlikely that after hundreds of articles on neuromodulation for cardiac ischemic diseases, the method can be considered as 'fake', though the core evidence is still lacking large randomized control trials. On the other hand, after decades of consistent reports, we may conclude that cardiologists have a blind spot for the delicate restorative powers of the central nervous system (brain and spinal cord) on other organs and therefore do not foster the potential skills the nervous system offers, when used as a propelling beneficial remedy for functional improvement in affected organs.

Can patients with chronic refractory angina be accurately identified?

A consequence of the tremendous reduction in mortality from cardiovascular diseases is an increase in morbidity, during the last decades. Subsequently, patients live longer with their cardiac disease and as a result, many cardiac diseases have become chronic ailments. One of these chronic cardiac diseases concerns patients with chronic stable angina, resistant to the modern armamentarium of therapies. These no-option patients are not always under control of medical specialists anymore, since conventional therapies to control the patient's symptoms are exhausted.

The first and principal issue is, to address whether these patients can be identified, or in other words, whether they have specific characteristics. Though the answer depends on the definition of chronic refractory angina used, this question is well worth a discussion in a

separate paper. In brief, the joint study group of the European Society of Cardiology has defined refractory angina pectoris as *"a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months*." This definition is debatable since it excludes patients with cardiac syndrome X (microvascular angina), but more importantly, leaves a lot of freedom for individual therapeutic tailoring, specifically with respect to medication.

The same holds true for the success of revascularization of the coronaries, which also depends on the interventionist's opinions and skills. Finally, reversible myocardial ischemia is not always easy to demonstrate in patients with 3-vessel disease.

Regarding the characterization of patients with refractory angina, based on the literature, there is a consistent pattern showing that these patients are predominantly of male gender, have relatively good prognoses (annual mortality 5-7%), are of relatively young age (beginning of the sixties), suffering for a long period (about a decade) from their coronary artery, (most often 3 vessel) disease, while they maintain their left ventricular function. Therefore, these patients may be considered as survivors of their disease. The number of patients fulfilling this condition varies in the literature from 200,000-1,000,000, both in the USA and Europe Albeit that the condition of refractory angina has been defined, awareness of adjunct therapies such as electrical neuromodulation, is lacking among patients, physicians and health care providers.

Methods of Electrical Neuromodulation

The first report on electrical stimulation to treat chronic stable angina was reported by Braunwald *et al*, in 1967 The investigators modified an artificial cardiac pacemaker to stimulate the stellate ganglion, as an additional therapy to treat angina. Although the method was successful, it was gradually abandoned, since in the seventies of the 20th century coronary artery bypass surgery (CABS) became the therapy of choice. However, a decade later some patients developed refractory angina again, following a CABS procedure. As a consequence, newer neuromodulation techniques were developed.

Only one study addresses the effect of vagal nerve stimulation on angina The authors also claim improvement in left ventricular function, using an observational design.

In 1982, Transcutaneous electrical nervous stimulation (TENS) was reported for the first time as an effective method to reduce both intensity and frequency of angina attacks and to increase exercise capacity Even though TENS is an effective, safe and rather cheap therapy, the disadvantages of this external device, are that gel pads come off easily on hairy chests and during perspiration, and that it frequently induced skin irritation. Due to these disadvantages the use of the transcutaneous method of electrical stimulation to treat refractory angina increasingly shifted to a fully implanted system i.e. Spinal Cord Stimulation (SCS).

Anti-angina and Anti-ischemic Mechanism of Neuromodulation

The authors of six meta-analysis/ systematic reviews of 7-12 randomized control clinical trials on 270-518 patients have reported convincingly that electrical neuromodulation, executed through SCS, is producing long-term anti-angina effects and has an excellent safety profile. Observational studies and registries of the 'real world', confirming the RCTs, and

vary in size from incidental case reports to 1204 subjects

Given the clinical efficacy of SCS on complaints of angina, SCS can also be used to study interactions between the heart and the brain and so to assess the underlying mechanisms at the neural-cardiac axis. In addition, ample evidence is provided that electrical neuromodulation improves the ischemic tolerance of the heart (vide infra)

Since myocardial ischemia activates nociceptive sensory afferent fibers in the C7-T5 spinal segments, which fibers transmit information about chemical and mechanical changes in the heart, modulation of these fibers through electrical stimulation (i.e. SCS) is found to provide beneficial outcomes on both, angina and myocardial ischemia. The C7-T5 fibers excite cells of the spinothalamic tract, and cells of other ascending pathways, that also receive primarily muscle and to a less extent cutaneous input from overlying somatic structures such as the chest and upper arm, and contribute to pain perception. Neurotransmission of cardiac nociception in the spine is achievable through a mixture of compounds, specifically substance P, and receptors such as particularly the transient receptor potential vanilloid-1 (TRPV1). In addition, release of neurokinins, such as nuclear factor kappa b (NF-kb), modulate these neurotransmissions. A number of animal studies have provided better understanding of the underlying mechanisms, during the last decades. For instance, the results of experimental studies have shown that SCS of the C8-T1 dorsal columns reduced the number of action potentials of spinothalamic tract neurons evoked by administrating pericardial injections of bradykinin, a mediator of inflammation. The reduction in activity of these cells most likely occurs, because SCS antidromically activates dorsal column collaterals in the gray matter of the T3-T4 segments that release the *k*-opioid, dynorphin, which may directly and/or indirectly suppress spinal neuronal activity

During episodes of myocardial ischemia, dynorphin may also reduce the amount of Substance P, released in spinal neuronal circuits Further, since Braunwald *et al* demonstrated beneficial effects of stellate ganglion stimulation on angina, he retrospectively published his initial findings on its anti-ischemic effect. Thus, many clinical studies (for review of studies see) making use of a variety of research tools (exercise stress testing, ambulatory monitoring, right atrial pacing, nuclide studies, Positron Emission Tomography and invasive studies such as [fractional] flow measurements in coronary arteries) and recent experimental studies have shown that SCS indeed produces anti-ischemic effects that contribute to improved cardiac function. In this respect, in an animal model, SCS applied to the C8-T1 dorsal columns initiated prior to the onset of ischemic episodes (pre-emptive SCS), activates adrenergic mechanisms that reduce infarct size produced by ischemic stress, following 30 min of coronary occlusion.

Only rather recently scientific interest is growing about (modulation of) the afferent nervous system and the role of intrinsic cardiac nervous system (ICNS). The ICNS contains ganglia, which are highly complex ganglionic plexi, involved in the function of the heart. In the wake of neural hierarchy in cardiac control, the ICNS may also control cardiac function independently, because it has its own vasculature. The intrinsic cardiac nervous system, which is critical for coordinating regional cardiac function and providing rapid and timely reflex coordination of autonomic neuronal outflow to the heart also responds to SCS. An important observation in animal studies is that SCS stabilizes activity of these intrinsic cardiac neurons during ischemic stress resulting from a brief (15 min) occlusion of a coronary artery, and this stabilization can last for up to an hour after SCS is

terminated. Thus, electrical neuromodulation contributes to anti-angina effects by modulating pathways that are involved in pain perception and improved cardiac function to a considerable degree by regulating neural memory of the intrinsic cardiac nervous system as well as beneficially is affecting infarct size.

The present knowledge about electrical neuromodulation on the (patho-) physiology of the intrinsic cardiac nervous system and its subsequent effects on cardiac functioning is schematically presented in Figure 1 (vide infra).

Electrical Neuromodulation for Heart failure and arrhythmias

Given the neural hierarchy for cardiac control, executed through reflex networks, therapies focusing on adjusting a disturbed autonomic nervous system are warranted to consider for the management of chronic cardiac pathologies. In contrast to the concept that the autonomic nervous system plays a predominant role in heart failure and the subsequent encouraging outcomes of experimental studies, randomized trials on SCS and on vagal nerve stimulation (VNS) for heart failure have failed to demonstrate convincing beneficial effects (see Figure 2). The lack of effect may be due to, among others, inadequate patient and endpoint selection, non-optimal sites to influence the anatomical target, or simply electrical neuromodulation is not an effective therapy to treat end-stage systolic heart failure. However, studies on baroreflex modulation for heart failure are still pending.

Finally, neuromodulation therapies in experimental settings have clearly demonstrated that they can reduce the occurrence of both, atrial and ventricular arrhythmias.

Summary

SCS has been adopted in US and European guidelines for cardiology for many years, established by hundreds of manuscripts published, 12 RCTs and 5 meta-analyses, all pointing to a beneficial effect of SCS for angina, without any evidence for deleterious effects, such as masking the symptoms during a myocardial infarction. However, on the other hand, the RCTs are of relatively small size, varying from 13 to 102 patients.

So, since the efficacy of electrical neuromodulation on angina has been consistently demonstrated and because its beneficial anti-ischemic effects are reported in many studies, making use of different methods, it is difficult to understand for many scientists and clinicians in the field of neuromodulation that this therapy is not widely accepted among cardiologists.

Conclusions and future perspectives

In conclusion, given all the evidence, it may be more likely that additional setbacks have to be focused on, before electrical neuromodulation is accepted among cardiologists. Dr. Robert Levy, editor in-chief of Neuromodulation addressed in an Editorial, in 2011 the main concerns to get SCS generally accepted for angina. These difficulties are, among others: lack of public, patient and professional awareness of electrical neuromodulation, the lack of established referral pattern for these patients and most often, also difficulty with reimbursement. Subsequently, Dr. Levy recommended, educational and training programs on electrical neuromodulation for patients, physicians and cardiologists. In this respect, a major problem is that SCS is not common practice for cardiologists.

Subsequently, efforts have been made to evaluate subcutaneous electrical neuromodulation (SubQ) as an alternative, during the last decade. SubQ stimulation, making use of a parasternal or intercostal sub-cutaneous placed lead, is thought to represent the best of two worlds. The lead is connected to an implantable stimulator, which can be activated externally. For

SubQ there are no electrode pads necessary, which easily come off specifically during perspiration, it does not induce skin irritation and there is no need to carry an external device with electrodes, as with a transcutaneous electrical nervous stimulation system (TENS). In addition, there is no need to withhold anti-coagulants, as is required for SCS implantation. Moreover, cardiologists can do the implant themselves. However, a prerequisite to get (subcutaneous) electrical neuromodulation accepted among cardiologist, is a large trial to demonstrate the efficacy of SubQ electrical neuromodulation. Following a potential favorable outcome of such a study, cardiologists who seem to consider the heart more or less as an independent organ, may be convinced of the efficacy of neurostimulation when translational medicine comes more in focus and so the scope of cardiologists is broadened and so they can better accept the power of (modulation of) the nervous system. While awaiting such a study, training and education of the involved and interested persons remains warranted.

Other medical disciplines are using neurostimulation devices more frequently, resulting in an estimated number of 34,000 patients to undergo SCS implants each year, world-wide. Hence, also for cardio-logist it becomes indispensable to obtain knowledge about these neurostimulation devices, since interference with implant-able cardiac devices may occur, which may have, among others, medicolegal consequences. These concerns are discussed in a recent paper.

Finally, an observation from Scandinavia demonstrates that organiza-tional aspects are of vast importance. In Sweden implantations in the pioneering clinic in southern Sweden have drastically diminished to some few each year while implantation rate in a university setting in northern Sweden remains unchanged and amounts to at least 15-20 cases each year. The critical difference between the two centers is that in the first center implants were made at a pain center while at the latter unit everything was performed within the department of cardiology (i.e. all therapies; stents, by-pass and SCS were considered as complimentary therapies and were discussed and carried out by the same organization).

Thus, the take-home message is that these therapies should be seen as complimentary and be performed within the same organizational framework.

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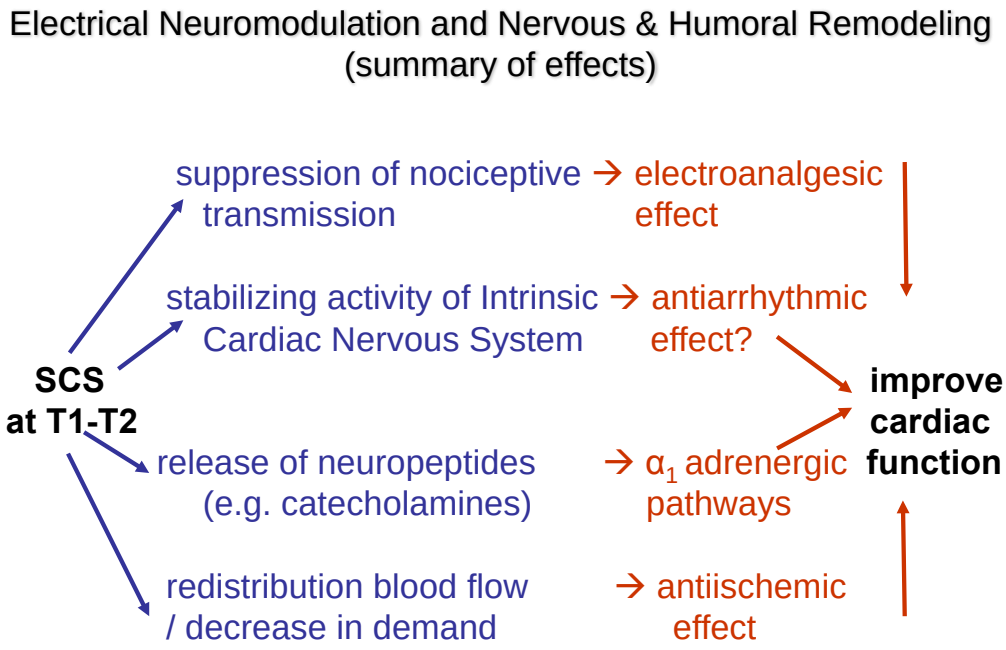

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Figure 1: Intrinsic Cardiac Nervous System

Randomized Controlled Trials				
Method	**Name study**	**#pt**	***Primary end points*** **Left Ventricular end diastolic volume /death/ hospitalization/ safety**	***Secondary end points*** **Quality of Live outcomes**
SCS (SB)	DEFEAT-HF	66	ns	ns
(DB)	Methodist	9	ns	ns
VNS (OL)	Inovate	730	Ns	↑ + 6MWD ↑
(DB)	Nectar-EF	96	Ns	↑
(OL)	Anthem-HF	60	ns (EF ↑)	↑
BRS (DB)	Rheos DHF	6	pending	pending
(OL)	Barostim neo HF	146	Ns	↑
(OL)	Beat-HF	800	Estimated 2021	

Figure 2: Neuromodulation for Heart Failure
Adapted from Byku M and Mann D. Neuromodulation of the Failing Heart: lost in Translation? *J Am Coll Cardiol. Basic Transl Sci, 2016;1(3):95-106 doi: 10.1016/j.jacbts.2016.03.004*
Legends: BRS = baroreceptor stimulation; DB = double blinded; OL = open label; SB = single blinded; SCS = spinal cord stimulation; VNS = vagal nerve stimulation.