

# Concept: Electrical Cardiac Stimulation is Detected by the Cardiac Autonomic Nervous System with Possible Effects on the Vasovagal Reflex

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## Abstract

A novel concept is described concerning the possible effect of right ventricular pacing stimulation being detected by the cardiac autonomic nervous system and through its afferent neuronal connection to the central autonomic nervous system (spinal cord) causing reversal or attenuation of the vasovagal reflex. This could be a direct effect of electrical stimulation or may occur by the known adverse consequences on ventricular synchrony induced by stimulation which could be right ventricular site and timing in the evolution of the vasovagal reflex dependent.

**Keywords:** Cardiac autonomic nervous system, electrical cardiac stimulation, interference in the vasovagal reflex, vagus nerve, vasovagal reflex

## INTRODUCTION

The cardiac autonomic nervous system wraps around the heart consisting of multiple ganglia connected by a network of neurones. It receives input as efferents from the sympathetic nervous system mainly but not exclusively through the stellate ganglion and from the vagus nerve. It connects afferently in the reverse direction. It is commonly stated that the two systems function in opposition to each other to create an appropriate balance for the prevailing body circumstances. It is additionally necessary to take into account the neuroendocrine system giving interplay by the release of epinephrine into the circulation and local release of norepinephrine from nerve endings around the heart. This description indicates a complex multifunctional system which is presently incompletely understood.

The hypothesis is that the vasovagal reflex involves primarily the vagus nerve which delivers its parasympathetic effect when triggered by the detection of reducing cardiac volume from baroreceptors mainly in the right atrium and right ventricle. This is one of several current explanations of the reflex and is used for the common form of vasovagal reflex occurring

in upright subjects. The triggering arising from baroreceptors in the right heart is assumed to pass through afferent nerves of the sympathetic system and, likely, the vagus nerve, completing the reflex through the vasomotor center in the brain with the effect delivered by the vagus nerve. Afferent traffic is difficult to assess as it is difficult to measure. The vagus nerve is rich in afferent fibers. These fibers exist to allow transmission of the status of the circulation in the case of the cardiovascular system. Activity of afferent vagal fibers has been demonstrated, for example, in hyperventilation, where these impulses modulate responses, recorded by electroencephalography, rather than local brain input. Many other examples exist.

Cardiac electrical stimulation has been employed to counteract the bradycardiac effect since the early days of cardiac pacing<sup>[1]</sup> with mixed results considered due to vasodepression, resulting in blood pooling in the splanchnic bed in the upright position.

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Cardiac pacing can offer no recognized benefit for this aspect of the reflex constituting the reason for modest or poor results.<sup>[2]</sup>

## CONCEPT

Cardiac stimulation has a hitherto unappreciated effect in modulating the vasovagal reflex.<sup>[3]</sup>

This concept has been enhanced by an increased understanding of the relatively new procedure of cardioneuroablation (CNA).<sup>[4]</sup> This procedure aims to prevent the vagus nerve exerting its bradycardiac influence by means of ablating extracardiac ganglia from within the atrial cavities across cardiac tissue. Data are accumulating that this can be successful in many patients.<sup>[5]</sup> These early data with, to date, only one positive relatively small randomized controlled trial (RCT)<sup>[6]</sup> risks prompting an explosion of procedures as has happened so often in medicine. This could be another example of unproven treatment being adopted as a new norm when our patients deserve to have a potentially dangerous therapy scientifically supported by thorough work including agreement on methodology and large RCTs.<sup>[7]</sup>

Despite these concerns, the procedure has prompted thought that if damaging radiation (radiofrequency) can achieve the effects demonstrated, much less powerful delivery of cardiac stimulation could indeed have significant effects on the cardiac autonomic system one of which might be modulation of the vasovagal reflex.<sup>[3]</sup> The site of stimulation may be very specific and individual for each patient. Thus, mapping of the effect combined with hemodynamic monitoring will be required. Hemodynamics are affected as we could understand even in the 1920s from the work of Wiggers<sup>[8]</sup> and have deeply learnt since the publication of the DAVID study<sup>[9]</sup> which destroyed assumptions that ventricular pacing is benign. Stimulation was found most potently adverse in already vulnerable ventricles.<sup>[9]</sup> There may be less adverse effects in subjects with normal ventricular function where hemodynamic deterioration due to the abnormal activation pattern may take time to develop. It has been demonstrated that apical right ventricular stimulation is an adverse site, perhaps greater in the upright position and worse than others in this chamber.<sup>[10]</sup> It must also be considered at what point in the evolution of the reflex, pacing is triggered. Early pacing delivery may coincide with high levels of epinephrine which tends to maximize ventricular performance, conversely, if pacing is delivered late in the evolution of the reflex, epinephrine levels are falling coinciding with reducing ventricular function.<sup>[11]</sup>

These ideas may be interpreted as any effect of cardiac pacing on the vasovagal reflex may vary between patients, stimulation sites, and timing of stimulation. It is possible that very precise positioning of the stimulus site may be required to achieve benefit by favorable influence on the reflex either directly or by adverse hemodynamic changes. If cardiac stimulation alone, along these proposed lines, could reverse the reflex, it may prove to be superior to CNA and indeed also to conventional cardiac pacing.

It has recently been shown that the vasovagal reflex evolves through life beginning in youth displaying intense cardioinhibition. With the passage of years, cardioinhibition diminishes in intensity and vasodepression becomes the dominant facet of the reflex.<sup>[12,13]</sup> With this in mind, a recent editorial has suggested that CNA may become the treatment of choice in young patients with demonstrated effect against cardioinhibition reserving pacing for older patients.<sup>[14]</sup> The proposed strategy requires proof especially when pacing in older patients is already proven effective by multiple trials<sup>[15]</sup> but recurrent syncope persists in about 20%, considered due to vasodepression.<sup>[16]</sup> Thus, pacing already has a place in the therapy of vasovagal syncope and its place could expand even among younger patients who could receive VVI leadless devices protecting them from lead failures.

Proof that ventricular stimulation is detected by cardiac ganglia may, perhaps, be attained during a CNA procedure with an assessment before and after ablation. However, exactly how the assessment is made requires thought and discussion.

## Author contributions

Richard Sutton came up with the concept and wrote the first draft of the manuscript. J. Gert Van Dijk contributed all neurological input. Both authors participated in the revision and have given final approval for the current version to be published.

## Ethical statement

The ethical statement is not applicable for this article.

## Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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## Conflicts of interest

Dr. Richard Sutton is an Editorial Board Member of *Heart and Mind*. The article was subject to the journal's standard procedures, with peer review handled independently of Dr. Richard Sutton and the research groups. There are no conflicts of interest.

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