AMPS-QT

The AMPS Quarterly - Issue n. 34 - 2Q2017 Editors: Fabio Badilini PhD, FACC and Martino Vaglio MS

AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

In this issue of AMPS QT, we proudly host a valuable contribution from Prof. Gaetano Maria De Ferrari, a prominent Italian cardiologist and a well-known figure in the world of scientific literature and research. Professor De Ferrari is currently Head of the Cardiac Intensive Care Unit and Director of the Cardiovascular Clinical Research Center at Fondazione IRCCS Policlinico "San Matteo" of Pavia and Director of the Postgraduate School of School of Cardiology at the University of Pavia, Italy. He has two main interests: clinical research and neuromodulation.

With AMPS-QT, it is our endeavor to bring you some of the most interesting and significant developments in the industry, publishing contributions from the clinical world, either because they are related to cardiac safety, or because of their innovative nature. To take this another step further, in this issue Prof. De Ferrari and his co-author Dr. Veronica Dusi present to our readers a thorough report on cardiac sympathetic denervation and its role in the prevention of life-threatening ventricular arrhythmias, which is currently an emerging area of investigation. On behalf of the entire AMPS team, we extend our gratitude to Prof. De Ferrari for this interesting article which we are sure our readers will greatly enjoy.

A Noteworthy Contribution:

Cardiac sympathetic denervation to prevent life-threatening ventricular arrhythmias: are we finally moving forward?

By Gaetano M De Ferrari, MD* and Veronica Dusi, MD.
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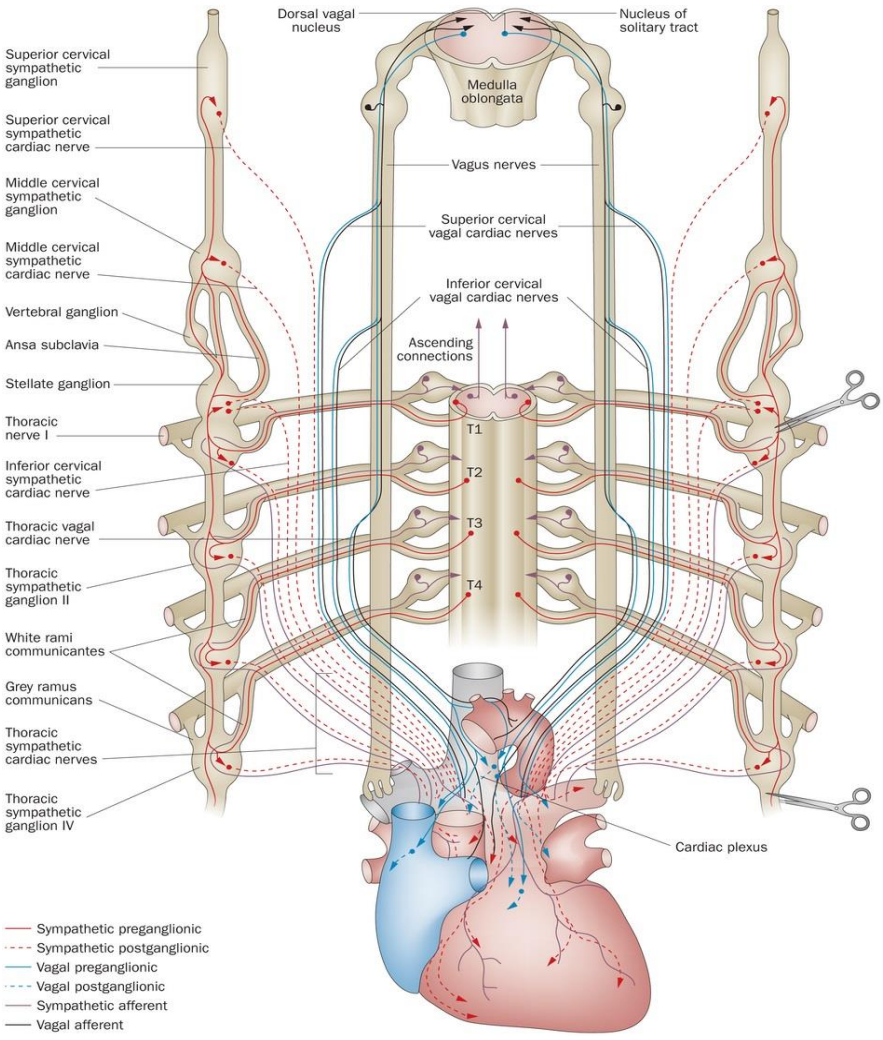
Almost 500 years ago, in 1628, through his renowned opera "Exercitatio de motu cordis et sanguinis" the English physician William Harvey was the first to provide a complete and detailed description of the systemic circulation and to finally conceive the heart as the pulsating pump providing blood to the brain and the entire body. Thereafter, a large body of experimental data has been accrued on the properties of the heart as a muscle and on the importance of the coronary artery flow in regulating its function, both in physiological and pathological condition. However, two more centuries were required to begin to understand that the cardiovascular system was much more complex and that all its function are finely modulated by the autonomic nervous system. Autonomic reflexes are crucial to acutely react to external stimuli and/or to internal pathological conditions such as myocardial ischemia, in order to increase or try to maintain cardiac output. Actually, the autonomic nervous system, composed by both afferent and efferent branches, is really never silent, showing a continuous, "tonic" activity and plays a major role in the pathophysiology and in the progression of heart disease, including heart failure and life-threatening arrhythmias. Efferent cardiac neurotransmission via the cardiac nerves intricately modulates nearly all physiological functions of the heart

(chronotropy, dromotropy, lusitropy, inotropy and coronary flow). Furthermore, afferent information is continuously transmitted to higher levels of the nervous system for processing resulting in efferent cardiomotor neural impulses (via the sympathetic and parasympathetic nerves). One century was required for the concept of "heart-brain interaction" to be widely accepted and to show a clear therapeutic potential. A pioneer of this approach was the Romanian surgeon and anatomist Thomas Jonnesco (1860-1926). As a surgeon, he was particularly interested in the perception pain and in means of achieving an effective analgesia. In 1909, he was the first to propose the use of general spinal block for surgeries of the skull, head, neck, and thorax, with impressive results. Few years later, in 1916, he happened to meet a patient suffering incapacitating angina associated with cardiac arrhythmias. Based on his personal experience in surgical analgesia and on previous studies by Francois-Frank (1) suggesting that removal of cervicothoracic sympathetic nervous system might be useful in patients with angina, he decided to perform a unilateral section of the left stellate ganglion (which is formed in man by the fusion of the last cervical ganglia, C8 (+ occasionally C7), and the first thoracic ganglion, T1).

Five years later neither angina nor arrhythmias had recurred and Jonnesco reported his results to the scientific community. As a consequence, in the following years other surgeon started to implement this procedure to treat angina pectoris with very good results. The initial fear about the potential detrimental effect of left stellectomy on coronary flow was definitively dismissed in 1929 by Leriche and Fontaine (2), who demonstrated that sympathetic nerves had a vasoconstrictive effect on the coronary arteries (instead of a vasodilator effect as previously thought). Indeed, several studies performed in both Europe and the USA between 40s and 60s, showed that left stellectomy was highly successful in preventing anginal attacks and improving performance during exercise stress testing. Concerning the optimal extension of left denervation, cervico-thoracic denervation (removal of stellate ganglion and T2 to T4 thoracic ganglia) proved to be the most effective to prevent angina. In humans, the last cervical ganglion (C8) is usually fused with the first thoracic ganglion to form the stellate ganglion (Figure 1).

Despite its efficacy, left cardiac sympathectomy was abandoned in the 60s, with the diffusion of β-adrenergic-receptor blockers and surgical coronary artery bypass graft to treat angina pectoris.

Shortly after, however, based on encouraging experimental results, interest in the antiarrhythmic potential of the technique had started to merge. In this setting the new developments in pharmacology of antiarrhythmic drugs, in antiarrhythmic implantable devices and in the ablation of ventricular arrhythmias have not cancelled its role. On the other hand, indications are currently expanding as we will briefly review hereafter.



<u>Figure 1</u>: Cardiac innervation and left sympathetic cardiac denervation. Schematic showing the sympathetic and parasympathetic innervation of the heart, and the points at which the sympathetic chain is sectioned during left sympathetic cardiac denervation (from T1 to T4 ganglia).

Electrical heart disease

Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are two diseases characterized by malignant ventricular arrhythmias occurring in structurally normal hearts and are among the leading causes of sudden death in the young. Symptoms typically manifest in the first decades of life and include palpitations, syncope and cardiac arrest, mainly precipitated by emotional or physical stress. LQTS is typically characterized by prolongation of the QT interval on the surface ECG and includes two hereditary variants: the autosomal-dominant Romano-Ward (RW) syndrome, first described in the early 1960s and the autosomal-recessive and extremely severe Jervell and Lange-Nielsen(JLN) syndrome, first described in 1957 in association with congenital deafness.

The interesting observation was made in the early 1970s that LQTS patients often showed the intriguing ECG pattern of T wave alternans prior to syncope, that this patter was clearly triggered by sympathetic activation and that it could be reproduced in anesthetized cats by electrically stimulating of the left stellate ganglion (Figure 2). This led Schwartz to suggest sympathetic imbalance with left-sided dominance as the pathophysiological mechanisms of LQTS (3).

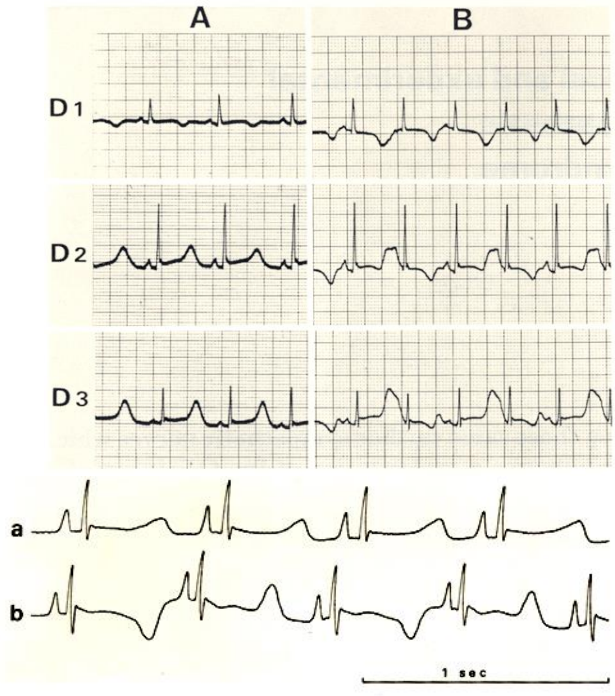


Figure 2: Top: T wave alternans preceding syncopal episodes in a child affected by LQTS (peripheral leads), Bottom: T wave alternans in an anesthetized cat evoked by electrical stimulation of the left stellate ganglion. Modified from Schwartz PJ, Malliani A. Electrical alternation of the T wave. Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. Am Heart J 1975; 89:45–50.

In agreement with this hypothesis, Moss and McDonald performed the first left cardiac sympathetic denervation (LCSD) procedure in an LQTS patient. Despite the subsequent demonstration of mutations in cardiac ion channels involved in ventricular repolarization as the pathogenetic mechanism of LQTS, the rule of the sympathetic nervous systems as the main trigger of arrhythmias was never questioned and LCSD become a therapeutic mainstay in in patients not completely protected by b-blockers. The largest series of LQTS patient treated with LCSD was reported in 2004 (4). It includes 147 LQTS with a very prolonged QTc interval (mean 546 ms) and a high prevalence of major cardiac events before (99%) and after (75%) beta-blockers. The average follow-up periods between first cardiac event and LCSD and post-LCSD were 4.6 and 7.8 years, respectively. After LCSD, 46% remained symptomatic, but only 7% of patients died suddenly. The mean yearly number of cardiac events per patient dropped by 91%. In 5 patients with preoperative implantable defibrillator and multiple discharges, the post-LCSD count of shocks decreased by 95% from a median number of 25 to 0 per patient.

Patients with CPVT patients not only show a structurally normal heart but also a normal resting ECG. The typical clinical feature of the disease is the reproducible and progressively worsening development of ventricular arrhythmias in response to adrenergic exposure and notably to exercise. The main autosomal-dominant form is caused by mutations in the RYR2-encoded cardiac ryanodine receptor, whereas the rare autosomal-recessive forms most often derive from homozygous or compound heterozygous mutations in the CASQ2-encoded calsequestrin 2 gene (CASQ2), both of which result in a net increase in intracellular diastolic calcium during sympathetic activation. Due to the compelling clinical and molecular association between adrenergic exposure and arrhythmias in CPVT pharmacological treatment with beta-blockers quickly became the first line treatment for the disease. Unfortunately, up to 30% of CPVT patients may fail to respond completely to beta-blockers, with recurrent ventricular arrhythmias including life-threatening forms. Moreover, implantable cardioverter defibrillators (ICDs) may be less effective in CPVT as compared to other arrhythmogenic diseases and may actually become part of the problem. The fear and the pain generated by the first ICD shock may promote an arrhythmic storm and result in multiple shocks, with major psychological consequences and potentially even death in case of exhaustion of ICD therapies. The first report of LCSD in patients with CPVT was published in 2008 in the New England Journal of Medicine (5), describing three patients

who continued to experience ventricular fibrillation and aborted cardiac arrest (ACA) despite full-dose β-blockers and become asymptomatic after LCSD. In 2015, we reported comprehensive data obtained from an International CPVT Registry confirming the strong antiarrhythmic properties of LCSD on top of beta-blockers in 63 CPVT patients (6). Among the 54 patients with major cardiac events before LCSD either on (n=38) or off (n=16) beta-blockers, the 1- and 2-year cumulative event-free survival rates after LCSD were 87% and 81% and among the 29 patients with a pre-surgical ICD, the rate of shocks dropped by 93% from 3.6 to 0.6 shocks per person per year (Figure 3).

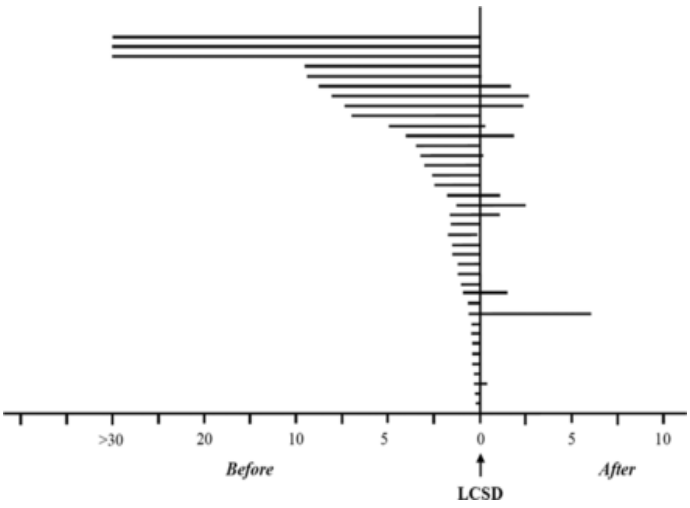


Figure 3: Incidence rate of major cardiac events (MCEs) before and after left cardiac sympathetic denervation (LCSD) for the 38 patients with catecholaminergic polymorphic ventricular tachycardia who continued to have symptoms despite optimal medical therapy (OMT). Each line on either side of the vertical line (time of LCSD) represents 1 patient and the corresponding number of MCEs per year occurring from the start of OMT to LCSD (left) and from LCSD to the last follow-up (right).

Seven patients underwent an incomplete denervation, sparing the lower half of the left stellate ganglion in order to avoid the risk of Horner's syndrome, (albeit very rare with an experienced surgeon). These patients had significantly more recurrences of arrhythmias (71% versus 17%; P<0.01) compared with patients who received the complete denervation LCSD. This concept of a therapeutic dose, also reported in patients with long-QT syndrome, should mandate comprehensive LCSD (from the lower half of the stellate ganglion to T4) and dissuade the execution of a suboptimal surgical procedure.

Structural heart disease

Recurrent ventricular tachycardia represents a rising problem for cardiological centers dealing with patients with heart failure and cardiomyopathies. Despite the use of beta-blockers, of amiodarone and of other antiarrhythmic agents, some patients have refractory arrhythmias and may experience also electrical storms (three or more major arrhythmias in 24 hours). In many of these cases, catheter ablation is the first choice and may be directed not only to the critical components of the arrhythmic circuit (in case of macro-reentry) or the focal origin of an ongoing ventricular tachycardia, but also to the anatomical and/or electrical abnormal myocardial areas, in the absence of a mapped arrhythmia. Despite this few patients continue to have ventricular arrhythmias and to receive ICD shocks.

Despite the fact that the experimental evidence for an antiarrhythmic role of sympathetic denervation is very strong, it was only in this millennium that the first report on cardiac sympathetic denervation in patients with structural heart disease and refractory ventricular arrhythmias was published (7). Forty-one patients who presented with either VT storm or recurrent ICD shocks refractory to medical therapy (median of 2 antiarrhythmic medications/pt including amiodarone) and catheter ablation (median of 2 ablation procedures/pt) underwent CSD. The vast majority of them had an idiopathic (54%) or ischemic (22%) cardiomyopathy, with a mean left ventricular ejection fraction of 31%; 80% of patients presented with monomorphic VT. Fourteen patients underwent left CSD only and 27 patients underwent bilateral CSD. ICD shocks were reduced from a mean of 19.6/pt in the 12 months pre-procedure to a mean of 2.3 post-procedure (P< 0.001). Survival free from ICD shock was shown to be higher in the bilateral group than in the left CSD group. No significant adverse impact of left or bilateral CSD on LV function was reported (albeit echocardiographic data were not available for all patients during follow-up).

This pioneering experience has just been extended with a second publication including additional patients from the group of Shivkumar at UCLA as well as patients recruited in four other centers (8). Overall, between 2009 and 2016, 121 patients (age 55±13 years, 26% female, mean LV ejection fraction 30±`13%) underwent left (19%) or bilateral CSD. The vast majority of them (71%) had non-ischemic cardiomyopathies; the same percentage (71%) presented with monomorphic VT only. Overall, 99% of patient were being treated with amiodarone before CSD and 66% had at least on VT ablation procedure (median of 2 VT ablations/patient). One-year freedom from sustained VT/ICD shock and ICD shock, transplant, and death were 58% and 50%, respectively. Once more it was shown that CSD significantly reduced the burden of ICD shocks: from a mean of 18 ± 30 (median 10) in the year before

study entry to 2.0 ± 4.3 (median 0) at a median follow-up of 1.1 years ($p<0.01$). The study suggested by multivariable analysis that pre-procedural advanced (III-IV) NYHA functional class and longer VT cycle lengths (more than 400 msec) predicted a higher likelihood of recurrence of ICD shocks. When looking at the combined endpoint of sustained VT/ICD shock recurrence, death, and transplantation, in addition to the two just mentioned variables also a left-sided–only procedure predicted the outcome. Finally, among the 120 patients taking antiarrhythmic medications before CSD, 32% no longer required them at follow-up.

Conclusion

Cardiac sympathetic denervation has been shown experimentally to have a very powerful antiarrhythmic potential. Its clinical indications have been recently expanding from the acknowledged use in patients with long QT syndrome to patients with CPVT and now to patients with refractory ventricular tachycardia in the setting of structural heart disease. Albeit non-controlled and retrospective, the studies show that the procedure provides an impressive reduction on the burden of ICD shocks also in these two additional clinical scenarios. Patients with non-ischemic cardiomyopathy and refractory recurrent ventricular tachycardia are particularly in need of additional strategies since the success rate of catheter ablation is relatively modest due to the very challenging arrhythmic substrate, characterized by epicardial and intramural scars.

More data are needed on the long-term results and the execution of a randomized controlled trial which would definitively clarify the role of CSD has been planned. In the meanwhile, cardiac sympathetic denervation should be considered as a valid option also among patients with cardiomyopathies and recurrent ventricular arrhythmias refractory to antiarrhythmic drugs and/or ablation.

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AMPS Notebook

Fabio Badilini attended the 44th International Congress on Electrocardiology. 2017 June 24-27, 2017 in Portland, Oregon where he presented the latest advancements of the PDF-ECG project.

AMPS will be looking forward to meet you at the 44th Computing in Cardiology Congress in Rennes, France.

Products News

New Product Launch

In Q2 2017 we introduced and launched **ECGSolve**, our new versatile command-line based complete ECG File Processing Software tool. **ECGSolve** is equipped with the following modules:

- ECG format conversion: accepts inputs in a variety of ECG formats
- Fully configurable ECG Image Generator that can generate a variety of ECG waveform images in various graphic formats, imposing different layouts and image resolution properties
- PDF ECG Report Generator: includes a fully configurable header, ECG waveforms layout, and demographic information details
- ECG Annotator Engine for automatic annotations using the latest version of the AMPS **BRAVO** algorithm

Latest Releases

In Q2 2017 we have released:

- A new version of **CER-S (v. 3.0.0)**, including the following new features:
  - Continuous ECG beat detection and classification, including fully renewed algorithm
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor,

  with the addition of measuring time intervals, amplitudes and ST elevation, both on beat-to-beat basis and averaged time-templates
- A new version of **CalECG (v. 4.0.0), Trial Perfect (v. 3.0.0)** and **Fat-QT (v. 2.0.0)**, including the latest version of AMPS **BRAVO** algorithm allowing the measurement of QTp, TpTe, QT, JT and JTp intervals using the FDA library

AMPS People

Rashmi Vohra joined AMPS in May 2017 as a Consultant. With a Master's degree in Pharmaceutical Sciences (specializing in Pharmacology), she has over 20 years of professional experience. She has a rich R&D experience in the highly regulated pharmaceutical industry, having worked for companies like Abbott Laboratories and Abbvie Pte Ltd. in Singapore as a Senior Scientist. While leading a team of scientists, she was not only responsible for analytical activities to support drug product development, but also for ensuring regulatory compliance in a multicultural global environment. Her earlier professional experience includes 13 years in Mumbai, India as faculty (Assistant Professor) in Pharmacy, having mentored and supervised pharmacy students at undergraduate as well as post-graduate levels.

Rashmi's foundation in pharmaceutical sciences, analytical and pharmacological concepts together with technical writing, communication and coordination skills, all strengthen her overall effectiveness as a technical leader. Rashmi has a passion for leadership development and for mentoring technical teams. In her leisure time, she enjoys reading and travelling to places that are closer to nature.

We welcome Rashmi onboard the AMPS team, and look forward to work with her on our various projects!