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Short communication

Cardiac sympathetic denervation 100 years later: Jonnesco would have never believed it

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ABSTRACT

One hundred years have elapsed since Thomas Jonnesco performed the first left cardiac sympathetic denervation (LCSD) in a patient with unmanageable angina pectoris and ventricular tachyarrhythmias, and the progress in the field has surpassed imagination. Here we will review the historic basis of cardiac sympathectomy for the management of life-threatening arrhythmias and will then discuss the often forgotten critical experimental studies that provided the rationale for the amazing growth of its role in clinical management. We will then mention the evolution in the surgical approaches, with their pros and cons. Similarly, we will address the existence of different views on the wisdom of starting with unilateral LCSD versus performing at outset bilateral CSD. The main results in the two diseases for which LCSD has already a definite role (namely the long QT syndrome and catecholaminergic polymorphic ventricular tachycardia) will be reviewed and discussed, touching also on the medico-legal implications descending from the clear efficacy of LCSD for these conditions. Finally, we will consider the potential value of LCSD for other clinical conditions and will close by mentioning a new randomized clinical trial in which LCSD is performed in patients with heart failure.

When, in 1916, Thomas Jonnesco convinced a patient with incapacitating angina accompanied by life-threatening cardiac arrhythmias to undergo, for the very first time, a left cardiac sympathetic denervation (CSD) he probably had no idea of how far reaching were going to be the consequences of his rather cavalier approach. He published his report (Fig. 1) only 5 years later (according to his admirers, because he was so cautious to require a long follow-up; according to his detractors, because no scientific journal wanted to publish his case-report) and he made the critical observation that also the cardiac arrhythmias had disappeared [1]. His life-long personal adversary, Danielopolou (another cardiologist from Bucharest in Romania, confirming the old saying that the worst enemies always come from close) kept his relentless campaign against sympathectomy (accused of depriving the patient of the warning represented by cardiac pain) for many years [2], but to no avail. If he had still been around, he would have been even more surprised than Jonnesco. In the long run, CSD has succeeded and is now integral part of the management of patients at high risk for sudden cardiac death.

The chronology of CSD for the prevention of life-threatening arrhythmias has been reported more than once [3,4] and this is not the place for repetitions. Here, the idea is to review very succinctly what has been conclusively proven so far, what is still unsettled, and where we are going. Most of the clinical studies have involved left CSD (LCSD) or bilateral CSD (BCSD). Also, the rationale for LCSD has been presented and, based on the large number of experimental studies, discussed extensively [3,4]. We will just remind the readers that probably the main effect of LCSD is the marked increase in the threshold for ventricular fibrillation [5], a gross but reliable marker of the propensity of a heart to fibrillate. This, as well as the other protective effects of LCSD [6], is the consequence of interrupting the release of norepinephrine in the ventricles by the left cardiac sympathetic nerves.

1. LCSD vs BCSD and retropleural vs thoracoscopy

The left-sided cardiac sympathetic nerves are quantitatively dominant at ventricular level [4]. Experimental studies have shown that whereas unilateral left stellate ganglion block decreases the likelihood of ventricular arrhythmias, unilateral right stellate ganglion block actually increases this probability [5,6]. Accordingly, most therapeutic interventions involve the left sided nerves. In the early-80s, prior to the ICD

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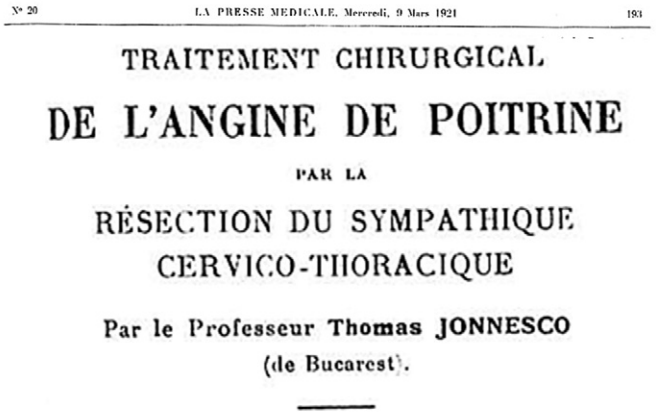

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TRAITEMENT CHIRURGICAL

DE L'ANGINE DE POITRINE

PAR LA

RÉSECTION DU SYMPATHIQUE CERVICO-THORACIQUE

Par le Professeur Thomas JONNESCO

(de Bucarest).

Fig. 1. Front page of the first report by Jonnesco, 1921.

era, we began to remove the right sided nerves in the few patients who continued with arrhythmia recurrences after LCSD. These cases represented our first use of BCSD and were met with mostly positive results. However, we cannot forget a German child with continuous and recurrent cardiac arrests in whom LCSD had only decreased the events; when right CSD was also performed all arrhythmic events stopped completely for 3 years, but one morning she was found dead in her bed.

For patients with channelopathies we are strongly convinced that LCSD should be performed first and that right CSD should be considered as subsequent step for the minority of patients who have not responded satisfactorily to the first intervention. This approach is in keeping with the general rule in medicine suggesting using the lowest effective dose, as there is always the possibility to increase dosage. Also, cardiac sympathetic nerves contribute importantly to myocardial contractility and, specifically, the right sided ones are critically important for the sympathetic control of heart rate [9]. If it is possible to control arrhythmias while avoiding depriving abruptly the hearts of our patients of all neural sympathetic support, so much the better.

The choice is more complex in patients with structural heart disease and recurrent ICD shocks. Shivkumar's group has reported very favourable results for CSD in various types of ischemic and non-ischemic cardiomyopathies [7,8], and has suggested a greater efficacy for BCSD than only LCSD. Their strategy to perform directly BCSD may also reflect the desire to maximize success rate in a single procedure in patients who have already undergone multiple ablation procedures and who may be reluctant to accept a stepwise approach. However, this attitude may partly reflect also difficulties specific to the American medical system, such as problems concerning the need for the patient to return a second time to that hospital. While we understand the rationale for BCSD, at this time one of us (PJS) still favours a step-wise approach.

Since 1973 our group has been using the retropleural approach [10] but we have recently shifted to video-assisted thoracic surgery (VATS) [11]. This approach is significantly less invasive, allows a better visualisation of the sympathetic chain and has better aesthetic results leaving almost no visible scar. We always remove the lower part of the left stellate ganglion with the second to fourth ganglia; in this way we perform an adequate CSD while avoiding the Horner syndrome. Its incidence in our hands is <2%. The only, but not always minor, limitation of the new approach seems to be a higher incidence of neuropathic pain (which was only exceptionally seen with the retropleural approach) that lasts between days and several weeks, and even a few months. This pain, which apparently tends to affect adult women more than other patients, seems to be counteracted rather effectively by gabapentin. In this subset of patients deemed at higher risk of pain development we now start this agent two days before surgery at 300 mg b.i.d. increasing it postoperatively to 300 mg t.i.d. if well tolerated as a pre-emptive treatment. Should pain occur, the dosage can be progressively increased until substantial response is obtained without significant adverse effects. In our experience this strategy appears to be effective. The pathogenesis of this complication, observed with the thoracoscopic technique more than with the supraclavicular approach, remains as yet unclear. Our initial suspicion that a causative role might have been played by excessive mechanical stretch on the sympathetic chain during the initial cases does not seem confirmed after significant changes had been implemented in the technique over time. Our group has performed during the last two years >15 LCSD using VATS in patients with Long QT Syndrome (LQTS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), and also in a few patients with ischemic cardiomyopathy. The latter cases underwent BCSD.

2. LCSD for LQTS and CPVT

There are two clinical conditions for which LCSD now plays a major role in proper management: LQTS and CPVT.

As LQTS is concerned, following the initial single case reports [12,13] in the early seventies the number of patients operated became so large [14,15] that the Guidelines could no longer ignore clinical reality [16]. Whenever a LQTS patient has syncope while on treatment with β-blockers, LCSD should be considered, prior to jump to an ICD implant. ICDs are associated with a dramatically high (31%) incidence of serious cardiac events within less 5 years [17]. LCSD can often usefully complement an ICD because it helps in preventing new arrhythmic events and thereby prevents arrhythmic storms and multiple shocks [17]. We also use LCSD in specific cases of still asymptomatic patients when either they do not tolerate β-blockers or when - despite β-blockers - they show signs of cardiac electrical instability such as macroscopic T wave alternans [13]. Our successful experience with LCSD in LQTS patients is fully confirmed by the growing number of patients studied at the Mayo Clinic [18].

For CPVT we published the first report on the value of LCSD in 2008 [19]. As this was based on only 3 patients (but with a significant follow-up), we felt necessary to follow with a much larger study, in order to confirm or dismiss the initial encouraging observation. Such a study, involving 63 CPVT patients, was published in 2015 [20]. As these data are relatively recent, a few details will be provided. In 54 of the 63 patients LCSD represented secondary prevention. The majority of these patients had either aborted cardiac arrest or appropriate ICD-discharges. Of them, 38 had continued to have these events despite optimal medical therapy. In this very high-risk group, the occurrence of major cardiac events dropped from 100% to 32% ($p < 0.001$). The results, with a median follow-up >3 years, showed a major decrease (>80%) in the number of events and no cardiac arrests. Importantly for the quality of life, in the 29 patients with an ICD implanted prior to LCSD, the rate of appropriate shocks dropped by 93% from 3.6 to 0.6 shocks/person/year ($p < 0.001$). Also, the incidence of the devastating electrical storms decreased by 63% (Fig. 2). A multicentre paediatric registry including 18 patients who underwent LCSD found that this procedure was successful in 89% of cases, thus fully confirming our results [21].

The evidence concerning the efficacy of LCSD for LQTS and for CPVT is so strong that, when considered together with the high incidence of major ICD-related adverse events, it has medico-legal implications [22]. The patients and their families have the right to know the pros and cons of both LCSD and ICDs; only in this way will they be able to make an informed choice, balancing almost full protection vs high protection and the demonstrated good quality of life [23,24]. Whenever, as it happens frequently, the ICD implant is accompanied by significant adverse events and the families realize that they have not been given correct information on LCSD as alternative therapy they may consider legal action. When a cardiologist deals with a LQTS or CPVT patient at risk for

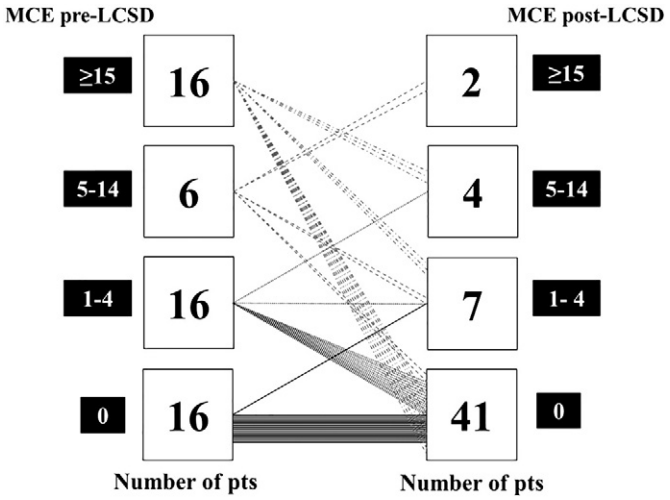

Fig. 2. Effect of LCSD on major cardiac events (MCEs) in the 54 symptomatic patients including the 16 with no MCEs on optimal medical therapy (OMT) in addition to the 38 with MCEs on OMT. The figure shows for each patient the number of MCEs, before and after LCSD. Each line represents one patient. The numbers in the squares represent the patients and those outside are clusters of MCEs of increasing frequency. (*From ref.* [20], *with permission*)

sudden death, it is no longer acceptable that the right to proper information about LCSD is denied.

3. Other clinical conditions

In the beginning it was logical to limit LCSD to conditions in which the arrhythmogenic role of sympathetic activation was very clear [25]. However, as LCSD raises the threshold for ventricular fibrillation, one can expect benefit in any condition associated with propensity for lethal arrhythmias. We have already demonstrated that LCSD reduces sudden death by close to 90% in a subset of post-MI patients at very high risk [26]. Anecdotal reports suggest a benefit of LCSD in patients with hypertrophic cardiomyopathy [27] or with arrhythmogenic right ventricular cardiomyopathy [28]. It is already evident that promising results are being obtained in patients with sustained ventricular tachycardia and cardiac arrest secondary to ischemic or dilated cardiomyopathy [7].

There is one more, and important, clinical condition that might benefit from LCSD; namely, heart failure. The initial suggestion was made just five years ago [29,30] and the full rationale was discussed in detail [30,31]. This has led to a clinical trial ("Left Cardiac Sympathetic Denervation for Cardiomyopathy Feasibility Pilot Study (LCSD), NCT03071653") in which we have already enrolled the initial patients and which takes place at the Groote Schuur Hospital – University of Cape Town (A. Chin et al. – manuscript in preparation).

4. Conclusion

Rivers start small but end up big: 100 years have elapsed since Jonnesco's pioneering LCSD in a patient with angina and arrhythmias and no one could have imagined that this surgical intervention would have become such a precious addition for the management of life-threatening arrhythmias. One of us felt rather lonely for many years while presenting both experimental and clinical data supporting the value of cardiac sympathetic denervation for specific patients [4,25] but now feels vindicated. At this time, standard of medical care requires that when dealing with patients at risk of malignant arrhythmias a cardiologist, together with antiarrhythmic drugs and ICDs, should also consider the specific pros and cons of cardiac sympathetic denervation, mostly left but also bilateral under specific circumstances or medical conditions.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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