# Endoscopic Left Sympathetic Blockade in the Treatment for Dilated Cardiomyopathy

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## Abstract

**Background: The level of sympathetic nervous activity is a major determinant of prognosis in patients with heart failure.**

**Objective: The purpose of this investigation was to perform a proof-of-principle trial of therapeutic endoscopic left thoracic sympathetic blockade in heart failure patients to assess safety and immediate effects.**

**Methods: Fifteen patients with dilated cardiomyopathy and left ventricular ejection fraction (LVEF) < 40%, New York Heart Association functional class II or III, and heart rate > 65 bpm, despite either adequate betablocker use or intolerant to it, were enrolled. Ten patients underwent left infra-stellate ganglion plus T3-T4 interspinal space clipping through videothoracoscopy, while the other five patients were randomized to a control group.**

**Results: None of the treated patients had any procedure-related adverse cardiovascular events at the perioperative period. Two patients from the surgical group died due to pulmonary thromboembolism or myocardial infarction within 6 months of the initial follow-up, while three patients from the control group had heart failure progression and died or developed cardiogenic shock during the same period. Treated patients presented improvement in quality of life, level of physical activity and LVEF (from 25 ± 9% to 32 ± 8%, p=0.024) at 6 months of follow-up, whereas these parameters did not change in control patients.**

**Conclusion: Endoscopic left thoracic sympathetic blockade is feasible and appears to be safe in severe heart failure patients. This initial study suggests that this procedure might be an effective alternative approach to sympathetic blockade in the treatment of dilated cardiomyopathies. (Arq Bras Cardiol 2010;95(6):685-690)**

**Keywords: Heart failure; cardiomyopathy, dilated; stroke volume; sympathectomy; thoracoscopy.**

## Introduction

The activation of the sympathetic nervous system is an important mechanism involved in the pathophysiology of systolic heart failure. Despite being an adaptive feature to support the failing myocardium, the chronic exposure of the heart to higher norepinephrine concentrations can cause several detrimental and maladaptive effects[1]. Based on this fact, the use of beta-blocker therapy is currently well established in chronic heart failure treatment and it is responsible for significant clinical and survival improvement in patients with left ventricular systolic dysfunction[2].

Bilateral endoscopic thoracic sympathectomy has been performed for the treatment of primary hyperhidrosis[3,4] and as a palliative approach to patients with severe angina pectoris[5]. Furthermore, left cardiac sympathetic denervation is described for the treatment of long QT syndrome[6] and catecholaminergic ventricular tachycardia[7]. Recent studies have demonstrated that these procedures decrease sympathetic nervous activity[5,8-10], while vagal and global cardiac autonomic functions seem to be improved after them[8]. The most significant effects on cardiac sympathetic activity seem to be particularly related to the excision or blockade of the left stellate ganglion and subsequent sympathetic chain[11]. On the other hand, another experimental study suggests that unilateral right sympathectomy can potentially increase the incidence of ventricular arrhythmias, in contrast with the left sympathetic blockade[12]. Furthermore, clinical studies have documented that sympatholytic agent administration can be maladaptive in patients with severely compromised hemodynamics in whom a minimal adrenergic tone is important, suggesting that excessive sympathetic inhibition may be deleterious in heart failure patients[13].

Based on these findings, we can speculate that the achievement of a partial sympathetic blockade including the left stellate ganglion in patients with systolic heart failure may represent an effective approach to decrease cardiac noradrenergic drive. This fact could occur while preserving some integrity of the sympathetic nervous function, a

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situation that can potentially provide clinical and ventricular function benefits without paradoxical deleterious effects. Therefore, the purpose of this study is to describe the technique of a reversible thoracoscopic left sympathetic blockade, which was used for the first time in the treatment of patients with severe systolic heart failure, in order to assess its feasibility and safety.

## Methods

### Patient selection criteria

Patients were selected by the Heart Failure Program of our Institution, among those with severe dilated cardiomyopathies and significant functional limitation with intermittent New York Heart Association functional class III or IV symptoms despite attempts to optimize medical therapy. They had had a diagnosis of dilated or ischemic cardiomyopathy for more than two years and also had reduced left ventricular function, characterized by echocardiographic ejection fraction < 0.4, and heart rate > 65 beats per minute at rest, despite either adequate beta-blocker use or intolerance to it. Patients using intravenous inotropic drugs or in persistent functional class IV were contraindicated for left sympathetic blockade, as well as those with complex or intractable arrhythmias and any life-threatening noncardiac disease. Informed consent according to our ethical and scientific review board was obtained after discussion of risks, alternatives and possible benefits of the operation.

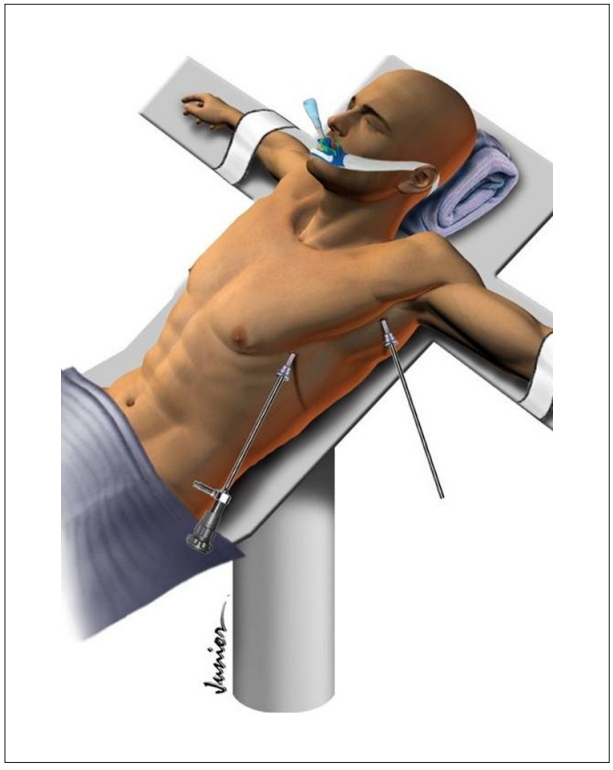

*Figure 1 - Schematic representation of patient positioning and pleural incisions for thoracoscopic sympathetic blockade.*

### Reversible endoscopic left sympathetic blockade

All procedures were performed under general anesthesia with single-lumen endotracheal intubation and all operations were performed by the same surgeon. The patients were placed in the supine position with the arms abducted. Surface defibrillator electrodes were routinely placed. The monitoring consisted of electrocardiogram, end-tidal $CO_2$ analyses, pulse oximeter, direct monitoring of arterial blood pressure, a flow-direct pulmonary artery catheter and transesophageal echocardiogram.

The pleural cavity was entered through two 1.0 cm incisions at the fifth intercostal space, where we inserted the 10-mm, 30-degree thoracoscope and the second 10-mm instrument port, which was introduced under direct vision in the midaxillary line. The incision at the fifth intercostal space was performed more laterally than in the projection of the anterior axillary line, due to risk of heart injury because of the important cardiomegaly (Figure 1). The anesthesiologist provided low-volume ventilation with 100% oxygen.

The sympathetic chain was easily identified under the transluminal parietal pleura. The parietal pleura overlying the desired level was incised. The left stellate ganglion was located in the first intercostal space and was much larger than the others, as it usually consisted of C7, C8 and T1 ganglia. The range of clipping included the lower third of the stellate ganglion and the T3-T4 interspinal space. The cephalic portion of the stellate ganglion was preserved to avoid Horner's syndrome and the electrocautery use was also avoided due to the same reason. The nerve was double-clipped at the two sites using a 10-mm Endoclip applier (Ethicon, San Angelo, Texas) (Figure 2). Hemodynamic and echocardiographic behaviors were continuously monitored during these surgical maneuvers.

After the clip application, 10 ml of 0.25% bupivacaine solution was injected along the site of the pleural dissection for postoperative analgesia. The lung was reinflated under direct vision and a small tube was inserted to remove the air through the upper incision, which was removed at the end of the operation. The two port sites were closed primarily with absorbable stitches.

### Study endpoints

The primary endpoint was to assess all adverse events secondary to thoracoscopic left sympathetic blockade during the surgical procedure and for the duration of the first 6 months of follow-up. Serious adverse events were defined as fatal or life-threatening events and events requiring unexpected hospitalization. A surgical reversal (clip removal) criterion was severe worsening of heart failure symptoms in the perioperative period. The secondary endpoint was to evaluate preliminary indicators of efficacy by improvement in the quality of life using the Minnesota Living with Heart Failure questionnaire[14], 6-minute walk test distance and ventricular function evaluation by Doppler-echocardiography.

Data are presented as means and standard deviation. Comparisons were made using Wilcoxon signed rank test. Randomization was performed by appropriate software.

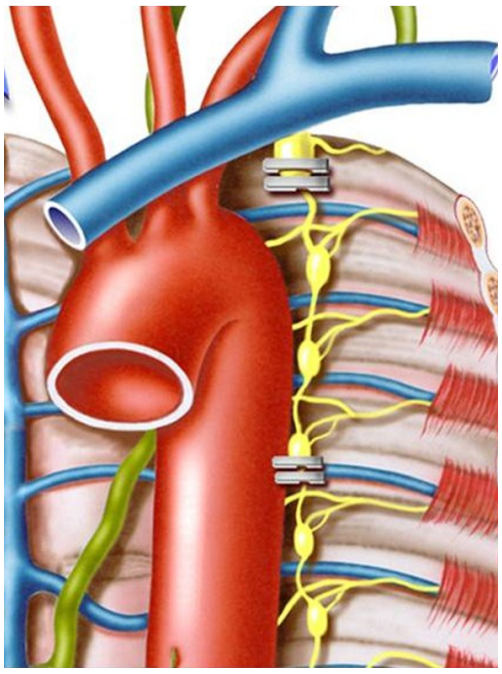

*Figure 2 - Schematic representation of double clipping of the stellate ganglion and T3-T4 interspinal space.*

## Results

Fifteen patients were enrolled in this phase I clinical trial (12 males, mean age = 52 ± 6 years) with a diagnosis of idiopathic (8) or ischemic (7) dilated cardiomyopathy. Previous history of acute myocardial infarction was documented in seven patients and three of them had been previosuly submitted to coronary artery bypass grafting. Four patients were in NYHA functional class III and 11 in class II immediately prior to the operation. All of them were receiving maximal doses of beta-blocker therapy and angiotensin converting enzyme inhibitor. Mean left ventricular ejection fraction obtained by echocardiography (Simpson´s method) was 22 ± 5% and the mean heart rate at rest was 81 ± 3 bpm.

Ten patients were randomized in a 2:1 approach to undergo left infrastellate ganglion plus T3-T4 interspinal space clipping through videothoracoscopy, while the other five patients were randomized to a control group. There were no differences between the two groups in relation to the preoperative variables. Two patients from the surgical group were in functional class III and eight in class II, while two patients from the control group were in class III and three in class II. Mean left ventricular ejection fraction was 25 ± 9% in the patients submitted to thoracic sympathetic blockade, while it was 23 ± 8% in the control group.

All surgical procedures were performed by the same surgeon. The mean duration of the operation was 48 ± 6 minutes and the hospitalization period was two days for every patient. There were no intra or immediate postoperative complications. Normal hemodynamic and left ventricular function behaviors were observed during sympathetic chain clipping and it was not necessary to reverse the surgical procedure at the perioperative period.

During the first 6-months of follow-up, two patients from the surgical group died suddenly due to acute myocardial infarction or pulmonary thromboembolism, while they were in NYHA functional class II. Heart failure improvement was also observed in other seven patients who were in functional class I (5) or II (2) and only one patient did not improve clinically and was maintained in functional class III. Three patients described slight compensatory sweat at the plantar area.

In the control group, two patients died due to heart failure progression at 3 and 4 months of follow-up. Another patient was hospitalized due to cardiogenic shock and was submitted to intra-aortic balloon pump implantation. The remaining two patients were in functional class II at 6 months of follow-up.

Postoperative evaluation performed in nine patients from the surgical group showed the decrease in the mean heart rate at Holter monitoring from 78 ± 8 to 72 ± 5 beats per minute (P=0.144). Minnesota Living with Heart Failure score decreased from 47 ± 16 to 39 ± 20 in the surviving patients at the 6-month evaluation (p=0.192) and the six-minute walk test distance significantly improved from 167 ± 55 to 197 ± 71 meters (p=0.029). Doppler-echocardiography documented the maintenance of left ventricular diastolic dimensions (from 70 ± 8 to 72 ± 10 mm, p=0.28) and the improvement in left ventricular ejection fraction from 25 ± 9 to 32 ± 7 % (p=0.024), as shown in Figure 3.

## Discussion

Surgical procedures have been proposed as alternatives to heart transplantation to provide palliative treatment for patients with dilated cardiomyopathies. These approaches are justified by the possibility to reverse the deleterious effects of different compensatory mechanisms that are activated to preserve cardiovascular homeostasis during heart failure progression. Allied with the great success of beta-blocker therapy, this proof-of-principle trial of therapeutic endoscopic left sympathetic blockade in heart failure patients showed promising results. It demonstrated the technical feasibility and safety of applying left infra-stellate ganglion plus T3-T4 interspinal space clipping through videothoracoscopy in patients with dilated cardiomyopathy. Furthermore, despite the occurrence of two nonrelated cardiac deaths, clinical and left ventricular function improvements were documented during the first six months of follow-up in the surviving patients.

Regardless of being just a feasibility study, the modifications observed in the follow-up of patients submitted to left sympathetic blockade were similar to those documented with other well established approaches in the treatment of chronic heart failure[15-17]. Furthermore, as a phase I clinical trial, the current experience represents a conservative approach in the surgical achievement of a sympathetic blockade. The technique could be potentially performed with cauterization or resection of the sympathetic chain or applied bilaterally, amplifying the blockade extent.

There have been no previous studies about the effects of surgical sympathetic blockade in heart failure patients. The

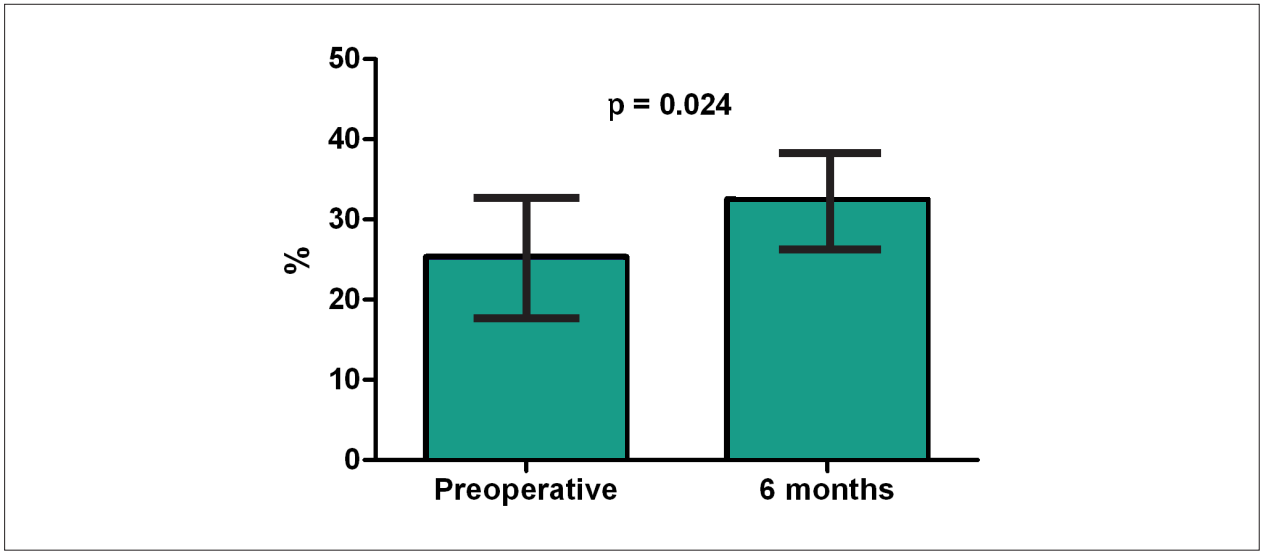


*Figure 3 - Echocardiographic left ventricular ejection fraction variation in patients submitted to thoracic sympathetic blockade. Mean values ± 95% confidence interval.*

real extent of the sympathetic chain disruption necessary to decrease the cardiac noradrenalin drive without important deleterious effects is therefore unknown. Several studies have documented the decrease in sympathetic tone after bilateral sympathectomy for primary hyperhidrosis or angina pectoris, without significant interference with the vagal and global cardiac autonomic activities[8-10]. Findings on $^{123}$I-metaiodobenzylguanidine imaging studies indicate that bilateral upper-thoracic sympathectomy slightly suppresses the activation of the sympathetic nervous system, similarly to beta-blocker therapy[18]. The decrease in cardiac sympathetic innervation density measured by 6-[$^{18}$F]Fluorodopamine positron emission tomographic scanning was also documented with bilateral upper-thoracic sympathectomy, whereas unilateral right-sided sympathectomy had no apparent effects on this finding[19].

The performance of an isolated left sympathetic blockade in this study may therefore represent only a minor modification in cardiac sympathetic activity, but this surgical approach was justified in this primary clinical investigation by the great risk represented by the excessive sympathetic inhibition for heart failure patients. The clinical use of sympatholytic agents such moxonidine was terminated prematurely due to increased mortality[13] and higher reductions in plasma norepinephrine concentrations after beta-blocker therapy were also related to higher mortality rates in the Beta Blocker Evaluation of Survival Trial (BEST) subgroup analysis[20].

Also in favor of the isolated left sympathetic blockade is the fact that this procedure has been successfully performed for the treatment of long QT syndrome[6] and catecholaminergic polymorphic ventricular tachycardia[7]. In this regard, left unilateral stellectomy is responsible for an increase in the ventricular refractory period similar to that obtained with the bilateral resection of stellate ganglion, whereas the isolated right stellectomy can produce a paradoxical decrease in refractoriness[11]. This fact can be responsible for the increase in ventricular arrhythmia incidence, a situation that need to be avoided and that is responsible for an important mechanism of death in heart failure patients.

The performance of the left sympathetic blockade using the clipping technique, instead of the sympathectomy with cauterization or resection of the sympathetic chain in this study was based on the possibility of procedure reversal in the presence of immediate deleterious effects[21]. Nevertheless, no procedure-related adverse events were observed in this initial trial and the intra-operative monitoring showed only a slight decrease in the peripheral vascular resistance without any period of hypotension, making it possible to perform the procedure in a more conventional and comprehensive way. The resection or cauterization of the sympathetic chain can be potentially performed in heart failure patients without any adverse complications, as it is observed in the treatment of long QT syndrome and catecholaminergic ventricular tachycardia[6,7]. Nevertheless, it is important to emphasize that similar results have been obtained with clipping or cauterization of the sympathetic chain in the treatment of primary hyperhidrosis[22]. The importance of actually interrupting the several nervous fibers that have connection with the heart is an open discussion and other studies will be necessary to adequately define the best technical approach to therapeutic sympathetic blockade in patients with heart failure.

Similar to other palliative treatments of heart failure, mortality in the follow-up can occur by different complications[15-17]. The occurrence of two late deaths due to myocardial infarction or pulmonary thromboembolism in this series was probably related to the underlying disease and not to the procedure itself. On the other hand, heart failure progression seems to have stabilized and the observed improvement in left ventricular function opens a real perspective for the use of this procedure as a complementary treatment for advanced heart failure due to dilated or ischemic cardiomyopathy.

In conclusion, thoracoscopic left thoracic sympathetic blockade is feasible and appears to be safe in severe heart failure patients. Exploratory data of this initial study suggest that this procedure may potentially represent an alternative approach in the treatment of dilated cardiomyopathies.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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