



## **Surgical Sympathectomy for the Treatment of Refractory Angina**

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## Introduction

There is an increasing number of patients with advanced long-standing coronary artery disease (CAD), that have severe debilitating angina despite receiving maximal medical therapy .[1] Chronic refractory angina is defined by the European Society of Cardiology (ESC) as a “chronic condition ( $\geq 3$  months) caused by clinically established reversible myocardial ischaemia in the presence of CAD, which cannot be adequately controlled by combination of medical therapy, angioplasty or coronary artery bypass grafting (CABG)”. [1] It is estimated up to 1.8 million Americans have refractory angina, with an incidence of  $\geq 50,000$  new cases per year in the United States .[2] In Europe it is estimated that 5%-10% of patients undergoing cardiac catheterization have refractory angina, with 30-50,000 new cases annually.[3] Traditional revascularisation via Percutaneous Coronary Intervention (PCI) or CABG is neither feasible nor favoured in these patients for numerous reasons, but is often secondary to prohibitively high surgical risk, lack of conduit and/or unfavourable coronary anatomy.

Appropriate management of these patients is challenging, driven by the complex interaction between coronary anatomy, myocardial perfusion abnormalities and clinical symptoms.[3,4] Such patients suffer from severely restricted levels of activity and compromised quality of life.[3-5] Precise prognosis is difficult to determine due to limited data regarding their natural history, and high variability of reported mortality rates. One-year mortality rates ranging from 1% to 22% are reported in randomised controlled studies concerning medical treatment of refractory angina.[6-9] These studies are predominantly more than a decade old, but a recent study from the Minneapolis Heart Institute of 1,200 patients shows a mortality of 3.9% at 1 year and 28.4% at 9 years with medical therapy.[10] Such results suggest that improved medical treatment has led to better survival in patients with refractory angina, prompting the authors to suggest that future focus of therapy should primarily be on enhancing quality of life. [4, 10] In the absence of suitable revascularisation options, therapeutic strategies are limited to secondary risk factor modification and anti-anginal pharmacotherapy. Understandably this has incited considerable interest into alternative/novel strategies targeting both the symptoms and mechanisms underlying angina. Numerous pharmacological, non-pharmacological, invasive and non-invasive options have been explored, and continue to evolve.[4]

One such surgical therapy is that of surgical sympathectomy of the cervical or thoracic sympathetic chain. In this review, we discuss the specific use of surgical sympathectomy in treatment of chronic refractory angina. We explore physiological principles and mechanisms underlying its use, and examine evidence supporting its potential role in treating this growing patient population.

## **Methods**

### **Search strategy**

In search for clinical evidence regarding the use of surgical sympathectomy in angina, an extensive search was performed using the MEDLINE, NHS Evidence and Web of Science databases. The search criteria were: (angina OR “refractory angina” OR “intractable angina”) AND (sympathectomy OR “cervical sympathectomy” OR “thoracic sympathectomy” OR “endoscopic sympathectomy”). Articles were limited to those in English, German and French. No date limit was enforced.

In total 278 articles were identified. Duplicates and false positives (totalling 234) were removed outright. Eight articles from pre-1950 were not accessible. Thirty-six papers from this search have been included in this review. Reference lists of these articles were screened for any further relevant papers, and also to inform the anatomical and physiological sections of this review.

## **Anatomical and Physiological Principles**

### **Anatomy**

It is long established that the sympathetic nerves are predominantly responsible for transmission of angina pain from an ischaemic heart to the brain.[11] Crucial to understanding the potential role of sympathectomy in angina treatment is knowledge of the underlying anatomy of cardiac sympathetic innervation. Sympathetic afferent fibres merge and form the cardiac sympathetic plexus. These nerves subsequently combine into the superior, middle and inferior cardiac nerves, which connect to adjacent swellings within the cervical region of the paravertebral sympathetic chain. The paravertebral chains of ganglia run on the anterolateral surfaces of the vertebrae on each side of the spinal column from the first cervical vertebra down to the lower end of the sacrum.

In the thoracic spine there is a ganglion for each individual vertebra. The first thoracic is usually attached by an isthmus to the larger inferior cervical ganglion. This dumbbell-shaped structure lies in contact with the costo-vertebral articulation of the first rib and is known as the stellate ganglion (Figure 1). Only 3 ganglia exist in the neck. These structures are predominantly left sided and termed the superior, middle and inferior/stellate cervical sympathetic ganglia, and are conveniently readily accessible for interventional procedures. The inferior or upper half of the stellate is connected with the middle cervical ganglion by a number of delicate fascicles that surround the subclavian artery (annulus of Vieussens). The sympathetic chain from this point upward consists of a single well-defined trunk lying posterior to the carotid sheath on the fascia over the longus colli and capitis muscles. Anterior to the second and third cervical vertebrae it broadens into a long fusiform superior cervical ganglion. The sympathetic pathways then unite with the intermediolateral gray column of the upper thoracic spinal cord via the white and grey rami communicantes. The majority of cell bodies from the cardiac sympathetic afferents are found in the dorsal root ganglia between T2 and T6 spinal segments [12].

### **Neurostimulation and Neuromodulation**

The exact triggers for neurostimulation of sympathetic afferents are incompletely understood and detailed discussion is beyond this review. Cardiac ischaemia releases a multitude of stimulatory chemicals, of which bradykinin and adenosine are considered pivotal.[12-16] As well as chemosensitive triggers, mechanosensitive pathways are also involved in pain transmission from heart to brain.

Neuromodulation describes the use of therapeutic means to interrupt afferent pain signal pathways between periphery and brain. [4,11] The strategy of interruption can be pharmacological, electrical or surgical. In addition to obvious analgesic effects of neuromodulation in treating refractory angina, anti-ischaemic effects of suppression of heightened cardiac sympathetic drive (i.e. efferent pathways) are beneficial.[4] Surgical sympathectomy represents a form of neuromodulation. However, its role in clinical treatment of chronic refractory angina is not established and this surgical therapy does not feature in any current therapeutic guideline, yet its potential for clinical use for patients with angina has attracted interest for many years.

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## Sympathetic Nervous System and the Heart

Aside from direct interruption of afferent pain pathways, disruption of the sympathetic chain has other physiological effects by virtue of its pivotal efferent activity. The sympathetic nervous system plays a critical role in myocardial ischaemia and arrhythmia vulnerability leading to sudden cardiac death.[17] Humoral activation increases serum catecholamine concentrations, and neurogenic activation elevates cardiac concentrations.[17] Detrimental effects of heightened adrenergic stimulation on cardiac structure, function and remodelling are well established by experimental and clinical studies.[17,18] Its importance is reflected by the inverse relationship between plasma noradrenaline levels and patient survival [19], the heightened noradrenaline levels seen in patients with unstable angina (20), the proven association of elevated heart rate (HR) and/or decreased HR variability (a marker of heightened sympathetic activity) with decreased survival [21, 22], and the incidence of plaque rupture.[23] This pathological basis underpins the proven clinical efficacy of pharmacological  $\beta$ -blockade in treatment of both heart failure and ischaemic heart disease.[24,25]. These studies show a decrease in morbidity, mortality, incidence of sudden cardiac death, rehospitalisation rate, and improved global systolic ventricular function.

Mechanisms underlying beneficial effects of  $\alpha$ -adrenergic receptor (AR) blockade are multiple, complex and incompletely understood, but are almost entirely secondary to blockade of detrimental  $\alpha$ -AR signalling.[26] They can be simply classed as being secondary to, (a) opposition of detrimental neurohumoral activation, (b) multiple cellular and sub-cellular effects improving cell survival, excitation-contraction coupling and myocardial gene expression, (c) anti-arrhythmic and vasodilatory effects, and (d) HR reduction-induced anti-ischaemic effects.[26,27]

### Heart rate reduction

Anti-ischaemic effects following HR reduction are considered important and merit discussion. HR reduction improves diastolic filling time, improves myocardial blood flow and decreases myocardial oxygen demand.[28, 29] HR reduction also improves endothelial function in diseased coronary vasculature with improved metabolic regulation of coronary blood flow.[29] Recovered re-distribution of altered regional blood flow to diseased post-stenotic coronary arteries, with shift from vasoconstriction to vasodilatation occurs following pharmacological HR reduction[28].

In addition, expansion of the capillary bed and novel angiogenesis accompany HR reduction with  $\beta$ -blockade.[30] It therefore is reasonable to expect surgical interruption of cardiac sympathetic innervation to yield beneficial physiological, structural, functional, anti-arrhythmic and anti-ischaemic effects, similar to those of  $\beta$ -adrenergic blockade. These effects are distinct to the pure analgesic effects of sympathectomy described above.

### **Historical Background of Surgical Sympathectomy**

The idea that interruption of sympathetic pathways can ameliorate angina is not new. Francois Frank Professor of Physiology in Paris proposed this notion in 1899. In 1916 almost 100 years ago, Jonnesco performed the first recorded sympathectomy for angina in Bucharest with excellent effect. Over the subsequent 50 years various surgical sympathectomy techniques were reported and associated with good analgesic effect.[12,14,31] During this period cervical and upper thoracic sympathectomy was used in treating hyperhidrosis and vasospastic conditions of the upper limb alone, and remained largely experimental and occasional in treating angina. Numerous anecdotal case reports were published and summary of the literature revealed that relief of cardiac symptoms was achievable in 65-90% of patients.[16,32,33]

Various surgical techniques were employed during this period.[16, 32-35] However, these early obliterative and invasive techniques were had high morbidity, irreversible complications and mortality rates of 7-10%.[16, 32-35] This inevitably discouraged their widespread use in refractory angina.

### **Physiological Effects of Surgical Sympathectomy**

As alluded to earlier, cardiac sympathectomy (via left stellate ganglionectomy) produces anti-arrhythmic changes equivalent to that of pharmacological  $\beta$ -adrenergic blockade in animals and humans. Increase in ventricular refractoriness and elevation of ventricular dysrhythmia threshold occurs.[36, 37]

In contrast, right sided sympathectomy is associated with pro-arrhythmic tendency [38], yet bilateral intervention enhances the “sympatholytic” effect of left sided sympathectomy in animal studies.[36]

## HR and BP reduction

In 1965 Birkett et al. showed in a prospective study of 52 patients with severe angina that bilateral surgical sympathectomy significantly reduced resting HR and both exercise induced blood pressure (BP) and chronotropic response; improving exercise performance up to 6 months post intervention.[14] Tygesen et al. reported in a non-controlled prospective study of 57 patients with refractory angina, that left sided surgical sympathectomy significantly reduced HR and restored HR variability up to 7 weeks post-surgery, suggesting a significant shift towards cardio-protective parasympathetic predominance.[39] This effect occurred in majority of patients; even those on maximal  $\beta$ -blockade therapy ( $\geq 95\%$ ), suggesting an additive clinical benefit when sympathectomy is combined with medical therapy. Similar findings were reported in a 24-patient study by the same group.[40] Another prospective 43 patient study showed a strongly reproducible reduction in HR, BP and ST segment depression following surgical sympathectomy [41], effects already demonstrated by an earlier series in the 1950s by Lingdren et al.[35] These results are re-enforced by a recent small 10 patient prospective study employing bilateral VATS sympathectomy performed in 2006.[42] In this study, at 6-month follow-up significant reduction in plasma noradrenaline, resting HR and incidence of VEs during exercise occurred, suggesting mid-term efficacy of the procedure.

In healthy patients undergoing sympathectomy for hyperhidrosis rather than for cardiac reasons, a reduction in resting HR, maximal HR response to exercise, and exercise induced systolic BP, but not mean or diastolic BP occurs. [43,44]. These changes are not associated with decrease in exercise performance capacity and peak VO<sub>2</sub> (43,44), and offer a clear anti-ischaemic protective mechanism in patients with angina.

## Clinical Efficacy and Safety of Surgical Sympathectomy in Treating Refractory Angina

Table 1 demonstrates a summary of all available case series of surgical sympathectomy as a treatment for angina to date. As discussed earlier, original attempts of open surgical sympathectomy proved it was a valid option for alleviating symptoms.[32,35] However, they were associated with high mortality (~7%-10%) and irreversible complications. This factor, combined with the advent of superior treatments, namely pharmacological  $\beta$ -blockade and CABG surgery, lead to a decline in enthusiasm for ~~sympathectomy in angina therapy.[45] With the continued development of less invasive, safer, video~~

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assisted thoracic surgery (VATS) interest in this therapeutic strategy has resurged. Thoracic sympathectomy has also shown excellent safety and improvement in functional status and cardiac function in dilated cardiomyopathy patients.[46]

### **Minimally Invasive and VATS Sympathectomy**

In the few reported modern series, it is overwhelmingly clear that surgical sympathectomy decreases angina severity and frequency, use of nitrates and demonstrable ischaemia in majority of patients [41,42,47-50] with persistent complete resolution of symptoms occurring in most. Unaltered and even improved exercise capacity is reported.[43,44] These studies show anti-anginal effects to be immediate and persistent for up to 10 years.[49] A similar effect is demonstrated in patients with intractable non-atherosclerotic vasospastic angina.[48] . In a 2019 prospective randomised controlled 79-patient study, Yaowang et al. showed that VATS sympathectomy reduced major adverse cardiac endpoints and all cause mortality in patients with refractory vasospastic angina at 2 year follow up; with no serious complications.[51] One initial barrier to employing this technique was the idea that removal of the protective pain sensation of angina would lead to decreased awareness of cardiac ischaemia and increased morbidity and mortality from silent cardiac events. However, most studies do not show this, with most subjects retaining a definite “warning sensation” during exercise ischaemia testing.[33,42,47]

### **Safety**

Minimally invasive VATS sympathectomy is an established safe and successful treatment for palmar and axillary hyperhidrosis. Numerous large series have shown zero perioperative mortality and low incidence of severe complications.[52-56]. The reported post-operative length of stay varies between 1-6 days, but safe day-case/ overnight procedure is achievable in a large number of patients.[54,55]

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A variety of early complications are reported including acute coronary syndrome, symptomatic

bradycardia, pleural complication requiring thoracostomy (including effusion, pneumothorax, haemothorax and chylothorax), oesophageal injury, seroma, transient Horner's syndrome, transient paraesthesia and wound infection. However, the incidence of these complications in experienced centres is low ( $\leq 4\%$ ).[52-55] Delayed compensatory hyperhidrosis is an inconvenient and highly subjective complication, with a widely variable incidence (3%-98%) depending on definition employed.[52,53,55,56] It is thought related to extent of sympathetic resection, and can be troublesome enough to interfere with quality of life, but often improves with time.[53.56] This delayed complication is an important consideration if VATS sympathectomy is to be employed in angina patients for enhancement of quality of life. In the few reported modern series of patients with refractory angina (n=240), VATS sympathectomy was achieved with zero peri-operative mortality and without severe complication, with length of stay between 2-6 days.[41,42, 47-49, 51]

### **Non-surgical Alternatives for Neuromodulation**

Numerous novel non-surgical treatments have been developed and tested for angina. These include pharmacological techniques, non-invasive techniques such as extracorporeal shockwave therapy and enhanced and external counterpulsation, and invasive techniques such as recanalisation of chronic total occlusions, transmyocardial laser revascularisation, coronary sinus reduction, and angiogenic, gene-based and cell-based therapies.[4] Few of these treatments receive a strong recommendation when assessed using contemporary level-of-evidence measures [57], and despite early promise, placebo-controlled trials have shown only modest improvements in angina relief. Of note, the majority of these novel anti-anginal treatments have been evaluated in the stable coronary artery disease population, not those with advanced refractory disease.[58] The focus of this review is surgical sympathectomy and therefore only a circumscribed overview of other neuromodulatory techniques is undertaken.

### **Invasive Neuromodulatory Techniques**

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A variety of other techniques for sympathetic blockade, both temporary and permanent, have been used clinically and are discussed below.

### **Stellate ganglion block**

This technique involves infiltration of local anaesthetic close to the medial cervical ganglion or stellate ganglion. Stellate ganglion blockade provides temporary relief of angina ranging from 2-12 weeks.[59] However, longer-term ( $\leq 2$  years) anti-anginal effect is reported following repeated interval procedures.[58] Original block techniques employed puncture between carotid artery and cricoid cartilage, and were associated with complications such as oesophageal injury, vertebral artery infiltration, and retropharyngeal haematoma. Newer ultrasound guided puncture is less hazardous.[60] This technique also provides valuable information prior to surgical sympathectomy.

Radio-frequency ablation of stellate or upper thoracic ganglion also shows good long-term effect.[61] This can be conducted under X-ray or CT guidance but treatment in angina is limited to few patients.[62] Permanent thermo-destruction is achieved and therefore the risk of permanent Horner syndrome is present.

### **Thoracic paravertebral block**

Another less targeted means of sympathetic neuromodulation is that of paravertebral block. Local anaesthetic is infiltrated into the left paravertebral space at the T2-T3 or T4 levels achieving sensory and sympathetic blocks to bordering segments. Older, small studies show efficacy in reducing evidence of ischaemia in angina patients but angina relief is not always certain.[63] Paravertebral block appears less effective than stellate ganglion block with shorter duration of action [32], and has been superseded by more focused blocks.

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### **Spinal cord stimulation (SCS)**

Spinal cord stimulation (SCS) interrupts perception of painful stimuli from the myocardium. Mechanism of action is incompletely understood, but is thought to involve both analgesic and anti-ischaemic effects.[64]. SCS has been used for 3 decades.[65, 66] In treatment of cardiac pain, a multipolar electrode is surgically positioned in the epidural space between the C7 and T4 vertebrae, close to the dorsal column, and SCS is considered to modify dorsal-horn neurochemistry, antagonising transmission of the nociceptive afferent signalling. In addition, sympatholytic effects causing improved coronary flow and distribution are seen, but a precise and consistent association is not established.[66] SCS involves an electrode being connected to a programmable pulse generator, with patient administered stimulation usually happening for an hour, a few times a day during angina occurrence.

Randomised trials of SCS in refractory angina show favourable results relating to symptoms, functional status and use of nitrates, and this is echoed by registry data.[67-69] Similar symptomatic relief is shown following SCS when compared to patients undergoing CABG, although surgical patients show superior functional status.[70] A meta-analysis reported a reduction in angina attacks in patients undergoing SCS.[64] The small randomised multi-centre RASCAL pilot study compared SCS + standard care versus standard care alone in refractory angina.[71] In this underpowered study; a trend for larger improvements in quality of life and exercise capacity with good safety was observed during addition of SCS. Many other non-randomised studies reinforce the benefits of SCS in refractory angina, with regards to reduction of symptoms, hospital admission rates, quality of life and functional status.[72,73] Severe complications associated with SCS, such as spinal canal haematoma, remain extremely rare. Rates of less severe complications such as electrode migration, breakage or epidural infections can approach 25%. One significant barrier opposing widespread use of SCS is the high cost, at approximately; ~£20,000 per patient, but original fears that SCS is dangerous due to masking of ischaemic symptoms are unsupported.[74]

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## **Non-invasive Neuromodulatory Techniques**

### **Subcutaneous electrical nerve stimulation**

Subcutaneous electrical nerve stimulation (SENS) is a relatively novel technique in refractory angina therapy, that focusses on subcutaneous nerve endings over the precordium. Subcutaneous multipolar electrodes are implanted in the parasternal area and tunnelled to a pulse generator in the upper abdomen. SENS is shown as safe and effective by two small series in which a total of 12 patients all reported subjective symptomatic relief following device implantation [75,76], This less invasive technique may prove useful in those with a contraindication to SCS such as elevated bleeding risk into the epidural space, but further larger scale evaluation of SENS is required

### **Transcutaneous electrical nerve stimulation**

Transcutaneous electrical nerve stimulation (TENS) involves the application of low intensity electrical current through the skin, producing vibration sensations that replace sensations of pain.[77] This technique was perfected 30 years ago and good efficacy is reported in treatment of angina.[77] Improved functional status, quality of life and reduced incidence of pain occurs, and reduction in systemic vascular resistance may partially contribute to these beneficial effects.[78] TENS can also be used as a test method prior to SCS implantation, to identify patients that may benefit from this more invasive therapy. Increased resistance of skin at electrode site decreases TENS effect and remains a major barrier to use.

## **Summary and Conclusions**

The population of patients with refractory angina unsuitable for revascularisation continues to expand. Recent evidence suggests medical therapy is improving survival of these patients, emphasising the need for new therapies directed at enhancing quality of life and alleviating symptoms.[10] In addition to palliative properties, continued interrogation of any novel therapy with potential to enhance prognosis is justified. Currently no European or North Atlantic guideline advocates or mentions potential use of surgical sympathectomy in treatment of refractory angina.[1,79] This is because a robust evidence base

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involving randomised controlled studies with medium to long-term follow up does not exist. This

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review re-highlights the obvious paucity of good studies in the last decade examining use of surgical sympathectomy in refractory angina. For a novel treatment to be recommended it must be necessary, effective, safe, of symptomatic and/or prognostic benefit and ideally cost-effective. Surgical sympathectomy shows promise in satisfying all these criteria.

Evidence presented in this brief review, mainly derived from small case series, suggests that surgical sympathectomy causes a persistent reduction of angina in majority of patients. Original fears relating to increase in silent ischaemic events following loss of protective pain sensation are unfounded. In experienced centres, minimally invasive VATS sympathectomy is now performed with zero mortality, with few significant complications and very short hospital stays. These factors make the proposition of surgery attractive and acceptable.

Surgical sympathectomy shows good symptomatic and analgesic efficacy. However, the potential prognostic benefit derived from the inherent anti-ischaemic effects described earlier needs to be established, and quantified by longer-term studies. We hypothesise that addition of surgical sympathectomy to current optimal medical therapy will further improve A) symptoms, B) functional status and C) survival in patients with chronic refractory angina.

### **Future Directions**

The concept that surgical sympathectomy is beneficial in treating angina is over 8 decades old, and is strongly supported by evidence in this review. This renders a proof-of-concept study unnecessary. The next potential useful step is to conduct a large long-term randomised controlled study comparing VATS sympathectomy as an adjunct to current optimal medical pharmacotherapy, with optimal medical therapy alone. Pivotal to the quality of a future study is A) use of a standardised anatomical and surgical resection technique in experienced high-volume centre(s) B) objective comparison of symptomatic, functional, and quality of life effects pre and post intervention and C) measurement of clinical/cardiac outcomes and survival. In addition, a simultaneous detailed temporal mechanistic interrogation of potential anti-ischaemic and sympatholytic effects of sympathectomy is essential. Effects on HR, HR variability, haemodynamics, myocardial blood flow, plasma and myocardial markers of sympathetic activation, chronotropic and coronary flow reserve, merit assessment.

**In conclusion:** D) Surgical sympathectomy shows efficacy in improving symptoms, quality of life

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and functional capacity in patients with chronic refractory angina. II) Current evidence is insufficient to advocate surgical sympathectomy as a potential widespread therapeutic option in patients with chronic refractory angina.

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