Chronic refractory angina pectoris treated by bilateral stereotactic radiosurgical stellate ganglion ablation: first-in-man case report

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Background
Refractory angina pectoris (AP) significantly impairs quality of life in patients with chronic coronary syndrome. Several minimally invasive methods (coronary sinus reducer, cell therapy, laser or shockwave revascularization, and spinal cord stimulation) or non-invasive methods (external counterpulzation) have been studied. However, their routine clinical use has not been widely implemented. Surgical or endoscopic sympathectomy is feasible for permanently relieving angina, but is often contraindicated due to the extent of complications associated with it. Neuromodulation by anaesthetic blockade of the left-sided stellate ganglion (SG) has been shown to relieve angina for days or weeks. To provide a long-term anti-anginal effect, novel pharmacological (phenol-based) or radiofrequency ablation techniques have been individually used to permanently destroy sympathetic pathways.

Case summary
We describe a first-in-man use of stereotactic radiosurgical SG ablation using a linear accelerator (CyberKnife) in a heart failure patient after myocardial infarction with chronic refractory AP. Repeated anaesthetic SG blockade in this patient resulted in a significant, but only short-term, clinical improvement. The left, and subsequently the right, SG was ablated by targeted irradiation. During the 1-year follow-up, the patient remained without angina. We did not observe any clinically relevant early or late complications. Atrial fibrillation that developed 2 months after the second procedure was deemed to be associated with a natural progression of co-existing heart failure.

Discussion
We conclude that stereotactic radiosurgical SG ablation has the potential to become a minimally invasive and low-risk procedure to treat refractory angina patients. However, this procedure needs to be evaluated in larger patient populations.

Keywords
Upper thoracic sympathetic system • Stellate ganglion blockade • Refractory angina • Stereotactic radiosurgery • Case report
Learning points

• Stereotactic radiosurgery of the left stellate ganglion (SG) is a technically feasible, well-tolerated, and clinically effective method to mitigate anginal symptoms in a patient with refractory angina pectoris. It can be applied as an outpatient procedure.

• Temporary anaesthetic blockade of the SG can be used to verify the treatment effect of unilateral radiosurgical ablation. Bilateral ablation may be required as the right-sided SG may also be involved in ischaemic cardiac pain perception.

Primary specialities involved other than cardiology

Anaesthesiology, radiation oncology.

Introduction

Refractory angina pectoris (AP) is defined as chest pain caused by coronary insufficiency that cannot be controlled despite the maximal coronary revascularization using percutaneous coronary intervention (PCI) or aorto-coronary bypass graft (CABG), together with optimal medical therapy that includes a combination of anti-ischaemic drugs. The symptoms need to last for at least 3 months, and evidence of reversible myocardial ischaemia is usually required to confirm the diagnosis.1,2 The estimated incidence of new cases of refractory AP in Europe is between 30 000 and 50 000 cases per year.3 Given improvements in interventional techniques and overall survivability of coronary heart disease, these numbers are set to rise.4 New techniques have been developed and individually applied to relieve angina, neuromodulation being one of them. One of the targets of interest are sympathetic stellate (cervicothoracic) ganglia (SGs) that are situated at the level of C7 vertebrae. These ganglia originate from the sympathetic afferent cardiac fibres and transmit signals from the heart atria and ventricles to the upper thoracic spinal cord and eventually to the pain centres of the brain. The majority of sympathetic pathways coalesce in the left-sided ganglion. Given this observation, left-sided SG anaesthetic blockade has been proposed and demonstrated to be effective for the treatment of arrhythmic storms and refractory angina as part of holistic care.4–6 The therapeutic effect of this approach is temporary, lasting from days to weeks, and repeated applications are often required.

The involvement of the right SG in left ventricle innervation is less understood and somewhat controversial. A case series described a positive effect of cervicothoracic sympathectomy with bilateral removal of both SGs in order to mitigate pro-arrhythmic neural signalling within the ganglia or myocardium. The left-sided, and eventually the right-sided, denervation was performed as the former was not clinically effective.7 The additive effect of the right-sided denervation on the decrease of malignant arrhythmia occurrence and mortality was demonstrated in a multicentre study.8 To the best of our knowledge, there are no published data about affecting the right SG in terms of ischaemic pain modulation. Nevertheless, experimental data confirming the right SG involvement in myocardial innervation9 and clinical data suggesting safety and a positive effect of right-sided denervation in patients with arrhythmias may serve as a rationale to target the right SG to mitigate ischaemic pain.

At Trinec-Podlesi Hospital, we have been practising anaesthetic puncture blockades of the left SG since 2016 in patients with electrical storm,5 and in 2018 we expanded the indication to those with refractory angina.

This report presents a case of a patient who had been suffering from refractory angina. After several attempts to relieve pain by anaesthetic puncture blockades of SGs, the first-in-man stereotactic radiosurgical ablation of the left SG was performed, and, eventually, of the right SG to provide long-term pain relief and improve his quality of life.

Timeline

| Year | Age | Event |
|------|-----|-------|
| 1987 | 33  | Inferolateral wall myocardial infarction: 2 × venous aorto-coronary bypass graft (CABG) [left anterior descending artery (LAD) and D1] |
| 1996 | 42  | Symptomatic angina pectoris: 3 × venous CABG [LAD, obtuse marginal, and posterior descending artery (PDA)] |
| 1999 | 45  | Bradycardia; pacemaker implantation |
| 2005 | 51  | Coronary angiography: all CABGs occluded but CABG–PDA, diffuse coronary disease, conservative approach |
| 2016 | 62  | Coronary angiography: same findings as in 2005, conservative approach |
| 2018 | 64  | Preventive biventricular internal cardioverter-defibrillator implantation |
| 12 October | 65 | Anaesthetic left stellate ganglion (SG) blockade: short-term clinical effect |
| 13 December | 65 | Left SG stereotactic radiosurgical ablation |
| 2019 | 66  | Anaesthetic left SG blockade: no clinical effect |
| 8 October | 66 | Anaesthetic right SG blockade: short-term clinical effect |
| 29 October | 66 | Anaesthetic right SG blockade: short-term clinical effect |
| 18 November | 66 | Right SG stereotactic radiosurgical ablation |
| 2020 | 66  | Atrial fibrillation diagnosed |
| 23 January | 66 | Electrical cardioversion: sinus rhythm restored |
| 31 January | 66 | Recurrence of atrial fibrillation |
| 22 May | 66 | Electrical cardioversion: not effective |

Bold formatting—milestones of the case report.
Case presentation

Patient’s history

The patient is a male born in 1954, obese (body mass index 36.84 kg/m²), with positive family history of myocardial infarction (MI), and a heavy smoker who suffered inferolateral wall MI at the age of 33. Venous CABGs to the left anterior descending artery (LAD) and its first diagonal branch (D1) were performed in 1987 (at the age of 33 years) to treat the patient. Then, in 1996, he underwent a reoperation—three venous CABGs to LAD, the left obtuse marginal (OM1), and the right posterior descending artery (PDA) due to recurrence of exertional angina. In 1999, a permanent pacemaker was implanted for bradycardia. Due to rapidly progressive angina in 2005, another coronary angiography was performed demonstrating just one venous graft (CABG–PDA). The other CABGs were occluded and the native coronary arteries were diffusely diseased. The Heart team recommended a conservative approach. The patient was followed at a different cardiac centre and his treating cardiologist consulted with a heart transplant centre regarding the case. However, he was rejected due to extra-cardiac comorbidities (peripheral artery disease, according to available documentation).

In August 2016, the patient was referred to our centre for re-coronarography for resting angina (CCS Class IV). The findings were unchanged and a conservative approach was recommended as the only possible treatment option (Figure 1 and Videos 1 and 2). In November 2016, the patient was examined one more time at the transplant centre, and spiroergometry was performed. The result verified ischaemic origin of the chest pain and a very low exercise tolerance. The values were as follows: maximal tolerated load of 88 W (0.8 W/kg), maximal heart rate of 104/min while pacemaker stimulated, VO₂ max of 10.6 mL/kg/min, O₂ saturation of 99% throughout the test, and ventricularextrasystoles on electrocardiogram (ECG) during maximal load. The test was terminated due to anginal pain with a need of two sublingual nitrate applications.

In 2017, apart from suffering from ischaemic heart disease with low left ventricular ejection fraction of 30%, hypertension, and hyperlipidaemia, he was also re-evaluated for previously diagnosed peripheral artery disease. Significant stenoses of femoral and tibial arteries and asymptomatic right internal carotid artery occlusion were found. No intervention was indicated and conservative pharmacological therapy was chosen.

Left stellate ganglion blockade

Due to the left ventricular dysfunction and 100% pacemaker dependency, cardiac resynchronization therapy (CRT) was indicated and a biventricular cardioverter-defibrillator was implanted on 11 October 2018. During this hospitalization, the patient complained of severe refractory angina despite the maximal pharmacotherapy (bisoprolol 10 mg daily, nitrate, molsidomine, and trimetazidine). He reported emergency nitrate spray use of 20–40 times a day.

Given the severity of anginal symptoms, ultrasound-guided anaesthetic blockade of the left SG was performed on 12 October 2018 (Figure 2 and Video 3). The technique was described previously. After application of 6 mL of 0.5% bupivacaine, temporary Horner’s syndrome and a slight left shoulder girdle paresis were observed, both resolving within 24 h. The patient was discharged 3 days after the procedure. At the ambulatory follow-up visit 31 days later, the patient reported complete resolution of AP for the initial 5 days. He then became symptomatic again. His angina rapidly graduated and reached the same level of severity within 14 days. Nevertheless, the patient’s responsiveness to therapy was verified. As ergometry was highly positive in this patient already in 2016, there was no need to repeat non-invasive stress testing to confirm ischaemic origin of the chest pain and place the patient at risk for malignant arrhythmias or heart failure symptom worsening, or to perform invasive functional testing (e.g. fractional flow reserve) of the last patent artery, i.e. CABG to PDA. This graft did not have a stenosis of >50%, and diffuse atherosclerosis of the distal right coronary artery was not suitable for
revascularization. As no other treatment option mentioned in the guidelines was available in the Czech Republic (one site had experience with radiofrequency SG ablation, but it was not manageable for logistical reasons) and surgical upper thoracic sympathectomy was contraindicated due to comorbidities, the case was discussed with an oncologist (J.C., co-author) experienced in radiosurgical techniques. The aim was to reach a longer-term anti-anginal effect. After mutual agreement, we opted for SG modulation by irradiation using a linear accelerator (CyberKnife).

### Left stellate ganglion ablation

The highly symptomatic patient at this time agreed to undergo the first-in-man stereotactic radiosurgical procedure in order to modulate the left SG sympathetic activity and possibly relieve limiting anginal symptoms. After signing an informed consent, a fiducial marker (a golden particle) was implanted into the left SG area under the ultrasound guidance to mark the position of SG for computed tomography (CT) imaging (Supplementary material online, Figure S1). After fixing the patient in a thermoplastic mask on 10 December 2018, the CT scan was performed and images were stored for subsequent offline analysis. The target volume and surrounding vital structures were identified based on a frame-by-frame analysis, and a 3D topographical reconstruction was created (Figures 3A and B and 4). No contrast agent was necessary. The clinical target volume included the left SG. CT imaging of immobile neck structures reached sub-millimetre accuracy. Thus, no safety margin was added and the planned target volume of 0.4 mL matched the clinical target volume. The Multiplan system (Accuray, Sunnyvale, CA, USA) was used to calculate the appropriate radiation dose for 6 MeV of high-frequency photons (Figure 5). To deliver the dose, the CyberKnife system (version 10.5, Accuray) and XsightSpine tracking technology were used due to the close proximity of the target to the cervical spine. XsightSpine tracking allows to control patient position (translation and rotation) according to spine structures. This methodology has been described in detail previously and reaches sub-millimetre accuracy. Detailed description of radiotherapy can be found in Table 1 (left). The dose was maximized according to the size of the targeted volume based on the oncologist’s experience with one-time ablation deliveries to treat trigeminal neuralgias. The procedure was carried out as outpatient without any periprocedural complications on 13 December 2018 (Figure 6). The patient experienced a mild headache that disappeared within 24 h. No early or late complications were observed. Neuron-specific enolase—a marker of a neuronal damage—was not increased.

During the next 3–4 months, the patient reported a significant overall improvement of his condition. He used nitrates 10–20 times a day, which was a 50% reduction compared to previous usage. He was able to manage his family, child, house, and garden. Based on this improvement, he applied for a job and eventually started working as a security guard. However, he had to quit the job 2 months later (6 months in total after irradiation), as he became progressively symptomatic again. In order to verify the possible residual involvement of the left SG, an anaesthetic blockade was performed again. This was carried out on 25 June 2019, resulting in temporary Horner’s syndrome. There was no change in anginal symptomatology after this procedure. Given the fact that this procedure had always been effective before the left-sided stereotactic irradiation, it was clear evidence of the complete elimination of the left SG function.

### Right stellate ganglion ablation

Despite the fact that cardiac sympathetic innervation is predominantly mediated by left-sided pathways, the involvement of the right-sided sympathetic chain must be considered, and its blockade might have
beneficial clinical effects. Thus, it was decided to challenge the patient’s response to the right SG blockade on 8 October 2019, which was again followed by temporary Horner’s syndrome. The patient was free of anginal symptoms and dyspnoea remained his only limitation for the period of 1 week. One more anaesthetic blockade of the right SG was performed on 29 October 2019 with the same result. This was sufficient proof that the right SG pathways were involved in ischaemic cardiac pain perception. With the patient’s signed consent, we proceeded to irradiate the right SG. Due to good ultrasound visibility and well-understood topographical anatomy of the right SG area, a CT scan was performed without the need for a prior introduction of the fiducial marker. After precise mapping of the landing zone (Figure 3C and D), the stereotactic irradiation was performed on 18 November 2019 as an outpatient procedure (Table 1, right). No early or late procedure-related complications were observed or reported by the patient.

**Follow-up**

The patient needed his nitrate 5–15 times a day for the first 10 days after the right SG ablation. At the 2-month visit he reported a complete resolution of angina, but complained of worsening dyspnoea and overall performance of basic daily activities. Atrial fibrillation with normal ventricular response was newly detected on ECG, without new valvular or structural changes on echocardiography. NT-proBNP level increased from a previous value of 400 ng/L (taken in a stable condition after the right SG ablation) to 1221 ng/L. An anticoagulant was introduced and after transoesophageal echocardiography excluding intracardiac thrombosis, the patient underwent a successful electrical cardioversion. At the next follow-up visit 2 months later, the patient reported relief from dyspnoea and non-specific nitrate non-responsive chest pain. NT-proBNP decreased to 769 ng/L. At the visit on 22 May 2020 (later than expected due to Covid-19 pandemic), recurrence of atrial fibrillation was found, and the patient reported New York Heart Association (NYHA) III dyspnoea with no anginal symptoms. The NT-proBNP level increased to 979 ng/L. A new attempt to restore sinus rhythm by electrical cardioversion failed this time. The patient was recommended to undergo radiofrequency ablation of atrial fibrillation. With his consent he was placed on the waiting list. The patient has been prescribed amiodarone as a rhythm control strategy, in addition to a chronic dose of bisoprolol at 10 mg/day that has been left unchanged since 2016. Another cardioversion was planned but never occurred due to Covid-19-related restrictions. Neither did the intended ablation procedure of atrial fibrillation. There is no solution in sight as the patient was hospitalized in November 2020 with suspected infective endocarditis on the CRT electrode system to be further managed. The
The latest NT-proBNP level reached 1687 ng/L. The patient is currently dyspnoeic NYHA III without anginal symptoms.

**Discussion**

Despite all of the improvements in technical aspects of PCI and CABG, there are still patients in whom effective revascularization cannot be achieved. The latest anti-anginal, ischaemia-modulating drugs (e.g. ivabradine, ranolazine) are not able to completely eliminate AP. For this reason there is a considerable effort to develop new methods to mitigate anginal symptoms. Various procedures have been tested. One of them is thoracic epidural anaesthesia, which has been proven effective but cannot be used in everyday practice due to frequent complications.¹⁴ Another method is transmyocardial laser revascularization, in which the risk outweighs the possible treatment benefit.¹⁵ The so-called external counterpulzation has been proven effective and safe. It is applied for 1 h a day, 35 h in total.¹⁶ Implantation of a special stent to the coronary sinus (coronary sinus reducer) is one of the invasive procedures that causes a certain degree of coronary sinus stenosis and thus increases the pressure gradient in coronary vessels. This leads to redistribution of blood flow from the less ischaemic epicardium to the more ischaemic endocardium.¹⁷ The application of autologous CD 34⁺ cells that stimulate neoangiogenesis also seems to be beneficial for refractory angina patients. A pooled analysis of three randomized trials confirmed improvements in exercise capacity, frequency of angina, and mortality reduction.¹⁸

Neuromodulation is probably the most ambitious and widely investigated topic of interest. Spinal cord neurostimulation is one of the currently approved methods the efficacy of which has been proven in clinical studies.¹⁹ This method, as well as external counterpulzation and coronary sinus reducer, have a IIb (level of evidence B) recommendation in the current Guidelines of European Society of Cardiology.¹

Neuromodulation also focuses on affecting the upper thoracic sympathetic system, of which SGs are components. Their anaesthetic blockade, particularly of the left SG, is used for many indications, for example, in a malignant storm.²⁵,²⁶ The effect of anaesthetic left SG blockade on AP recurrence was demonstrated many years ago.⁴ However, a double-blind clinical study showed that the effect on anginal symptoms might be due to mechanical compression caused by the applied volume rather than by anaesthetic properties of the solution.²⁰ Several studies aimed to destroy SG permanently using minimally invasive techniques, such as injection of phenol²¹ or radiofrequency energy.²² Video-assisted upper thoracic sympathectomy is a currently used surgical method of choice to eliminate adverse effects of cervical and upper thoracic sympathetic pathways.²³ However, this procedure is often contraindicated in patients with comorbidities due to the extent of complications that may arise.

The present case report described an option for refractory AP treatment using stereotactic radiosurgery. It is a minimally invasive

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**Figure 4** Computed tomography imaging of the left stellate ganglion—3D reconstruction.
procedure that is currently used in patients with brain tumours, arteriovenous malformations, and neuralgias. Contrary to applied surgical methods, CT-guided radiosurgery targeting structures of the neck has a very low incidence of acute (within 3 months), late, and very late complications. The radiation dose affecting the oesophagus is minimized and is far below the permitted limits to cause severe toxicity, such as necrosis or rupture. Nevertheless, acute focal mucositis of the oesophagus caused by scattered radiation may occur, usually manifested by cough and painful swallowing with a good clinical response to local antiseptics. Horner’s syndrome caused by cervical sympathetic neuritis is a very rare acute complication. An occurrence of acute local dermatitis, the typical complication after radiotherapy in oncological patients, cannot be expected to be clinically relevant due to a very low dose of radiation. Late complications include focal necrosis of the adjacent longus colli muscle (most likely asymptomatic), oesophageal fibrosis (very unlikely as the doses of radiation are...
incomparably lower than those used in radiation oncology), or accelerated atherosclerosis in adjacent major arteries caused by scattered radiation that may potentiate endothelial changes. Finally, carcinogenesis resulting from radiation exposure may theoretically be a very late complication of radiosurgery, but is very unlikely due to very small target volumes. Given the justifications above and to the best of our knowledge, this is the first time this method was used in a patient with refractory angina, as concomitant comorbidities excluded the patient from other available therapies. Our approach required a precise knowledge of the upper thoracic sympathetic chain topography, verification of SG involvement, a positive response to neuromodulation (anaesthetic blockade), and interdisciplinary cooperation with a radiation oncologist and anaesthesiologists.

When an irradiation strategy is being planned, the factors of irradiated area, target volume, safety margin, and dose determination are of utmost importance. In the present case, a dose of 40 Gy was
applied for safety reasons in order not to exceed a maximum dose for organs at risk, especially the oesophagus in case of contralateral radiosurgery. The repeated anaesthetic blockade had no additional effect on angina, thus confirming that 40 Gy was an appropriate dose. According to our experience arising from this case, unilateral SG ablation might not be sufficiently effective as both left- and right-sided sympathetic chains are involved in the sensory component of AP. Moreover, a higher dose of 60–70 Gy that is usually used in the treatment of trigeminal neuralgia might be needed. It is also important to look for a clear endpoint of a successfully performed procedure because the patient’s reported degree of anginal symptoms can be subjective. In this regard, heart rate variability, phase angle shift, and neuroECG are being investigated. The rationale for SG modulation/ablation can extend and be used to treat different parts of the sympathetic nervous system and secondarily impact the function of innervated tissues and organs.

**Conclusion**

This is the very first case report of stereotactic radiosurgery for bilateral SG ablation in a patient with refractory AP receiving optimal medical therapy and with no option for coronary revascularization. The method was found to be technically feasible, well tolerated by the patient, and clinically effective to ameliorate anginal symptoms. It can also be applied as an outpatient procedure. More studies are needed to justify its routine use in a refractory angina setting. The rationale for SG modulation/ablation by irradiation can also be applied to different sympathetic pathways.

**Lead author biography**

Miroslav Hudec, MD, graduated at Masaryk University Brno, Czechia, in 2002. Having completed his internal medicine and general cardiology residency, he has been focusing on interventional cardiology. Presently, he works as a cardiology consultant and performs both coronary and non-coronary interventions (Mitraclips, LAAO, PTMSA, PFO/ASD closures, PVL closures). He started a PhD program in 2019.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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