Sympathetic Ablations and Hyperhidrosis

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FOREWORD

In its inception 135 years ago, sympathetic surgery was part of general surgery. Over time, the development of specific surgical fields, along with evolving indications, led sympathetic surgery to become part of the curriculum of several emerging medical specialities. Since the sympathetic system is a neuroanatomical structure located in the neck, chest, and abdomen, it is performed today by some, but not all, neurosurgeons, thoracic surgeons, vascular surgeons, and still general surgeons. Although it is a restricted field, its complexity requires specially dedicated surgeons.

The advent of endoscopic surgery and the development of appropriate instruments stimulated the endothoracic sympathetic approach. Two vascular Swedish surgeons, Dr. Gøran Claes and Dr. Christer Drott, accumulated a vast experience in this new technique. In 1993, they organized in Borås, Sweden an International Symposium on Sympathetic Surgery. Avid to share and learn, the Symposium was attended by participants from all over the world. A second Symposium was organized in 1997 again in Borås, followed by a third one in 1999, Kanazawa, Japan. I attended all symposia and in a conversation with Drs. Claes and Drott, the idea of establishing a professional society emerged. We met again in Israel in 2000 and composed the Bylaws of the proposed society; the objectives being the advancement of the science and art of sympathetic surgery by research, education and nurturing of surgical practice throughout the world. The Bylaws were submitted to the audience of the fourth International Symposium in 2001, Tampere, Finland, and adopted by its attendees, thus establishing the International Society of Sympathetic Surgery. Dr. Drott was elected as its first President. I followed him as President and continued to serve the Society on the Board to the present. Up to now, fifteen Symposia have been held in Europe, North and South America, the Far East, and Australia.

For several years, I functioned as “Scientific Secretary”, currently reviewing the literature and accumulating a vast amount of published data. During these years, some major changes in the concepts and axioms of Sympathetic Surgery transpired. However, several questions and problems await a solution.

The purpose of this compendium is to present a digest of the accumulated data and knowledge in the field of sympathetic surgery and its principal present indication-hyperhidrosis, discuss the unsolved problems, and consider what could be expected for its future.

INTRODUCTORY NOTE

This book is addressed to any surgeon and physician who has an interest in sympathetic surgery and its major present indication-primary hyperhidrosis. It is meant to provide the reader with a detailed overview on the subjects, updated to 2024. It supplies the required background (anatomy and physiology) and the accumulated data on the evolving methods, techniques, indications, and results. The science and art of the subject is analyzed by discussing the what's, why's, and how's, indicating their advantages and drawbacks, pointing out the accepted and controversial items. Lastly, future directions to improve the state of this specific branch of surgery are provided.

The material is divided into eight chapters. Each chapter is a complete, independent presentation of the subject, as specified in its title, including the pertinent references. Only occasionally is the reader referred to another chapter for some specific secondary subject, to prevent a large repetition of text.

Finally, I hope that this compendium will stimulate the reader to undertake and pursue research, thus achieving further advancement in the science and art of sympathetic surgery.

CHAPTER 1

SURGICAL ANATOMY OF THE SYMPATHETIC SYSTEM

The anatomy, physiology, and pharmacology of the sympathetic nervous system, the largest subdivision of the autonomic nervous system, are described thoroughly in the literature.[1] The present exposition concisely describes the sympathetic system with special emphasis on the target sections of present-day sympathetic surgical procedures.

The Usual ('Normal') Anatomy of the Sympathetic System

The sympathetic nervous system is centrally controlled and innervates all the sweat glands, the muscle wall of all blood vessels, the erector muscles of the hairs, and all the viscera.[2]

The Ganglia

Unlike the somatic system, the efferent peripheral sympathetic system includes two neurons connected by a synapse. The first group of these neurons is located in the lateral column of the grey matter of all the thoracic (T) and upper two lumbar (L) segments of the spinal cord. The neurons of the second group are located either in the paravertebral or in the prevertebral ganglia.[2,3] The paravertebral ganglia are connected to form the sympathetic trunks, one on each side of the spine. They include twelve thoracic and two uppermost lumbar ganglia that receive the preganglionic efferent sympathetic fibres from the corresponding spine levels. In addition, the trunks extend cranially with the three cervical (inferior, middle, and superior) ganglia, and caudally with the remaining lumbar and three sacral ganglia. The first thoracic ganglion (T_1) is usually fused with the inferior cervical ganglion to form the cervicothoracic (stellate) ganglion.[3] It is typically located on the inferolateral border of the 7th cervical vertebra, the superolateral border of the 1st thoracic vertebra, the neck of the 1st rib, and the adjacent part of the 1st intercostal space.[4] The remaining thoracic

ganglia, except the lowermost two or three, rest against the heads of the ribs and are positioned in the corresponding number of lower rib borders and intercostal spaces. The last two or three thoracic ganglia are placed against the sides of the bodies of the corresponding vertebrae.[3] So is the lumbar section of the sympathetic trunk. It usually contains four ganglia located in the retroperitoneum, in front of the vertebral column, and along the medial border of the psoas major muscle. It is overlapped on the right by the inferior vena cava and on the left by the lateral aortic lymph nodes. The prevertebral ganglia are all located in the abdomen and include the coeliac, superior mesenteric, inferior mesenteric, and aortorenal ganglia.[3]

The Neural Pathways

Axons from neurons in the sympathetic central nervous system descend within the spinal cord and synapse with neurons of the first group located in the lateral horn of the spinal cord. Axons from these cells (the preganglionic fibres) exit the cord via the ventral roots of the spinal nerves. They leave these roots to join the sympathetic trunks via thin nerves (the white rami communicantes). Axons of the preganglionic fibres arborize with dendrites of nerve cells of the second group (one or more) located in the ganglia within the trunks at the same spinal segment level or ascend/descend in the trunk to synapse with cells at a higher or lower level, including neurons located in the superior, middle and lower cervical ganglia, and the lower lumbar and sacral ganglia. Some axons from the ganglionic group of cells (the postganglionic fibres) exit the sympathetic trunk via thin nerves (the grey rami communicantes) to join the somatic nerve of the corresponding level. These sympathetic fibres diverge from the somatic nerves along their course and form the sudomotor, vasomotor, and pilomotor nerves to somatic structures.[3] Some other axons of the ganglionic nerve cells exit via the cervical and thoracic cardiac nerves to join the thoracic viscera (heart, lungs, and oesophagus).[3] Some preganglionic fibres do not synapse with neurons in the sympathetic trunk. They exit to form the thoracic and lumbar splanchnic nerves and join the abdominal prevertebral and aortorenal ganglia, where they synapse with nerve cells of the second group.[3] The only exceptions are some of these preganglionic axons that cross the sympathetic trunk to join directly the adrenal medulla and synapse with the adrenaline-secreting cells, which are modified second-group sympathetic neurons.[2] Axons from the nerve cells in all the prevertebral ganglia form the postganglionic fibres that supply the sympathetic innervation to all the viscera and blood vessels in the abdomen.

In addition to the efferent fibres, the sympathetic system includes afferent pathways that refer sensory information from peripheral organs to the central nervous system.[1]

The 'Kuntz' Nerve

In 1927, Kuntz described an inconstant intrathoracic ramus connecting the first and second intercostal thoracic nerves.[5] He postulated that this ramus contained sympathetic fibres that leave the sympathetic trunk below the stellate (namely, below the first thoracic) ganglion to join the first intercostal nerve, finally becoming incorporated in nerves arising from the brachial plexus. They may represent sympathetic pathways to the upper limb that bypass the stellate ganglion. In a recent cadaveric study, the nerve of Kuntz was identified in 99 sides of 60 cadavers.[6] No similar fibres were found in the second, third, and fourth intercostal spaces. In another cadaveric study, grey rami communicantes connecting the T_2 ganglion to the first intercostal nerve were found in 53.6% and descending rami to the third intercostal nerve in 46.4%. The corresponding figures for the T_3 ganglion were 5.9% and 26.2%, and for the T_4 ganglion-4.8% and 4.3%.[7] All authors postulated that these irregular anatomic connections could explain incomplete sympathetic denervations or recurrences after sympathetic surgery.[5-7] Two reports by the same group of surgeons who performed sympathectomies for palmar hyperhidrosis provide clinical support for this concept. In the first report, the T_1-T_3 ganglia were resected by the supraclavicular approach[8]; in the second study, only the T_2-T_3 ganglia were resected endoscopically but in addition, the pleura over and the periosteum of the second rib was incised with diathermy along the rib for a length of about 3 cm, lateral to the sympathetic trunk.[9] All excised specimens had pathological confirmation. In the first study, the immediate failure rate was 2.4%, and recurrences occurred in 4.1% of limbs within 2 to 18 months.[8] In the second study, all limbs were completely dry after the procedures, and there were no recurrences at a follow-up ranging from 11 to 26 months.[9] This difference was attributed to the pleuro-periosteal incision in the second study, which, in addition to the T_2-T_3 resection, transected all the ascending fibres that bypassed the T_2 ganglion.

Anatomical Variations

The upper sympathetic trunk has substantial anatomical variability, mostly regarding the stellate and T_2 ganglia. The stellate ganglion, consisting of the fused inferior cervical and T_1 ganglia, was found in 70%,[10] 80%,[3,7] and

84.3% [4] of dissected sympathetic trunks. In another cadaveric study, the T_2 ganglion was found in the second intercostal space in 90.2% of dissections.[11] In the remaining cases, it was fused with the stellate ganglion in 4.9% of cases, fused with the T_1 ganglion (separated from the inferior cervical ganglion) over the neck of the second rib in 2.4% of cases, or fused with the T_1 ganglion and elongated to the border of the third rib in the remaining 2.4% of cases.[11] The authors of this study claimed that the stellate ganglion cannot be seen during thoracoscopy because it is typically covered by a pad of fat on the neck of the first rib. They also considered that during thoracoscopy, the second rib is the uppermost visible one. This view is supported by others,[12] but contested as well.[13] In this latter study, the first rib was visible in half of the patients and palpable with the diathermy bar in the remaining cases.[13] The author considers that, in doubt, rotating the 30° scope towards the anterior part of the chest dome always allows identification of the first rib. The variability of the lower ganglia is much less frequent.

The variability regarding the grey rami communicantes exiting the uppermost sympathetic ganglia[6,14] has clinical implications, possibly explaining early failures and late recurrences of sympathetic ablations. The nerve fibres that bypass the trunk, often referred to as "the nerve of Kuntz", differ from the original description of Kuntz.[5] Such a network of bypassing postganglionic fibres was reported with an incidence ranging from 38% to 75%.[6]

The Sympathetic Innervation of the Target Organs

The sympathetic ganglionic trunk and rarely the thoracic splanchnic nerves are the sections of the sympathetic system that are ablated for present-day surgical indications. Denervation of a target organ requires precise knowledge of the sympathetic pathways and levels of the spinal cord segments which supply the fibres that innervate this organ.

Head and Upper Limbs

In a recent overview of the autonomic sympathetic system, the cord segments that provide sympathetic innervation to the head and neck were reported to be T_1-T_5, and to the upper limbs T_3-T_6.[1] In an old study in humans reported by Hyndman and Wolkin, stimulation of the ventral root of the 1st thoracic nerve generated sweat over the face, stimulation of the anterior root of the 2nd thoracic nerve produced sweat over the neck and thorax, and stronger stimulation, over the face as well; stimulation of the

anterior root of the 3rd thoracic nerve caused upper limb sweating beginning in the axilla.[15] Similar stimulation down to the 6th nerve generated sweat over the arm. However, in another old study in humans, exposing the cervicothoracic region of the spinal cord during surgery, some variability was reported concerning the uppermost and the lowermost level of spinal cord segments supplying the head and upper limbs.[16] In this study, the anterior roots were electrically stimulated, and observations were made on the pupillary effect and diminished skin resistance in the hands. Variability in the sympathetic outflow to the hands between individuals and between sides of the same individual existed. The uppermost segment supplying the hands was found to be T_2, and the lowermost ranged down to T_{10}. The pupillary sympathetic pathways were derived from the C_8 (8th cervical) to the T_4 roots. In the "Gray's Anatomy" textbook,[17] the T2 is indicated as the uppermost spinal segment providing sympathetic input to the hand.

While some of the postganglionic fibres join the same level peripheral somatic nerves, the majority supplying the head and upper limbs ascend within the trunk through the second and the stellate ganglia to join the nerves and arteries of the head, neck, and upper extremities. This is why the stellate ganglion was ablated in the early period of sympathetic surgery. Later, to prevent Horner's syndrome, the T_2 ganglion replaced the stellate ganglion as the target of ablation.[18,19] Regarding the sympathetic pathways deriving from lower spinal cord segments and innervating the head and upper limbs, it is obvious that the lower the level of ablation is, the fewer channels will be interrupted and less sympathetic denervation be achieved. This compromise is largely adopted today. To reduce the incidence and gravity of compensatory hyperhidrosis (See Chapter 7), lowering the level of sympathetic ablation for palmar hyperhidrosis to T_3 or T_4 is recommended.

Thoracic Visceral Organs

The heart is supplied by sympathetic pathways deriving from the T_1-T_7 spinal cord segments.[1] The autonomic innervation of the heart is complex, as demonstrated in an old review of animal studies.[20] In humans, the stellate ganglion is the pivotal exit of postganglionic fibres to the heart. Stellate ganglion blockade is considered a temporary management of ventricular arrhythmias.[21] It allows stabilization of the patient until other medical or definite surgical treatments are supplied. On an anatomical basis, the cardiac improvement obtained by stellate ganglion block indicates that at least the majority of postganglionic fibres, deriving from the sympathetic trunk and targeting the heart, ascend the trunk up to and through the stellate ganglion. For permanent sympathetic denervation, ablation of the lower part of the

stellate ganglion, the T_1 segment, plus the T_2-T_4 ganglia has been recommended.[22] The cardiac sympathetic innervation is not symmetrical, and efferent fibres don't have identical receptors on each side. This explains the rewarding results of left unilateral sympathetic ablation for arrhythmias.[22] The stellate and upper sympathetic ganglia are also the ablation level of the afferent sympathetic fibres that convey painful stimuli from the heart in the treatment of refractory angina.[23]

The efferent pathways to the bronchi and lungs derive from the T_2-T_7 spinal segments.[1] They ascend the sympathetic trunk and exit through the stellate ganglion. Since the sympathetic treatment of asthma apparently became obsolete, the sympathetic anatomy of the bronchi lost its surgical relevance.

Lower Limbs

The preganglionic axons to the lower extremities derive from the T_{10}-L_2 spinal cord segments and synapse with the lumbar and sacral ganglionic neurons.[1] The postganglionic fibres exit the trunk to join the somatic nerves and descend the limbs. At various levels, they exit the nerves to join arteries and veins.[24] They also supply the sweat glands of the lower limbs. Clinical experience indicates that the postganglionic fibres to the foot exit the trunk at the L_3-L_4 level.[25]

Abdominal Visceral Organs

The preganglionic fibres that supply the abdominal viscera exit the ganglia of the sympathetic trunk as high as the T_4 and as low as the L_1 level to form the constant greater splanchnic nerve and the inconstant lesser and least splanchnic nerves.[26,27] These nerves penetrate the abdominal cavity to join the abdominal ganglia. Sympathetic innervation to the distal colon, rectum, bladder, and sex organs derives from the L_1-L_2 spinal segments. The splanchnic nerves also contain afferent nociceptive sensory fibres and are the target ablation site to treat intractable abdominal pain. The neurons of these afferent fibres are located in the spinal cord and their axons project through the ventral roots to join the sympathetic trunk. They exit the trunk via the splanchnic nerves, and travel through the prevertebral ganglia to join the sensory receptors in the serosal membrane covering the visceral organs, the parenchyma, and the vessels supplying the viscera.[28,29]

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CHAPTER 2

SURGICAL PHYSIOLOGY OF THE SYMPATHETIC SYSTEM

The sympathetic system is involved in the autonomic activity of all the human body organs. It includes two sets of efferent pathways. One group proceeds from the sympathetic trunk along the somatic nerves to the periphery, including sudomotor, vasomotor, and pilomotor fibres. In humans, the last ones have no significant physiological role. The second group of fibres supplies sympathetic innervation to all visceral organs. In addition, the sympathetic nerves relay nociceptive information via afferent fibres. Two physiological functions are carried out via the first group: thermoregulation and blood pressure control. The physiological function of visceral organs affected by sympathetic ablation is restricted mainly to the heart. The present chapter aims to briefly summarize the physiological functions that are affected by sympathetic surgery.

Thermoregulation

Thermoregulation is achieved in coordination by the sympathetic sudomotor control over sweat glands and the two branches of the vasomotor nerves, one exercising vasodilation and the second vasoconstriction of the skin blood vessels.[1] In addition, the somatic nervous system contributes to thermoregulation by shivering.[1] Increase in internal core temperature and warm external conditions intensify sweating and increase skin blood flow.[2] Heat is lost by sweat evaporation and by the increased exposure of warm blood in the skin to external air. When air temperature exceeds skin temperature, heat is lost only by sweating.[3] There is a difference in the thermoregulation mechanisms of nonglabrous and glabrous skin (palms, soles, face, and ears), due to the difference in the most peripheral vascular elements.[4] Heat activates sweat glands in the nonglabrous skin but usually does not activate sweat glands in the glabrous skin.[5] Thus, heat loss in the glabrous skin is achieved mainly by the skin's peripheral microcirculation, which is increased by heat. Capillaries are present in both nonglabrous and glabrous skin. However, in the glabrous skin, there are arteriovenous

anastomoses (AVA) as well, serving as short circuits between the arteriolar and venular networks.[4] Heat triggers vasodilation of both capillaries and AVAs. Activation of AVAs, in addition to the capillaries, significantly increases skin blood flow. Consequently, a much larger heat loss per surface unit ensues in the glabrous skin than in the hairy skin.[4] In contrast, sympathetic fibres induce vasoconstriction and reduce sweat secretion under cold conditions, thus limiting heat loss.[6]

Control of the Cardiovascular System

The brain centres of the cardiovascular system regulate blood pressure by two sets of postganglionic sympathetic fibres: fibres from the grey rami that innervate the smooth muscles of blood vessels and control their resistance via smooth muscle contraction, and afferent and efferent fibres from the sympathetic nerves that innervate the heart by monitoring the heart rate and the heart contraction intensity.[1] The vasomotor mechanism is triggered mostly by afferent information sent from baroreceptors in the carotid sinus and aortic arch to the brain regulatory centres, which control the blood vessel resistance, heart rate and contraction strength via the sympathetic (and parasympathetic) efferent pathways. In general, sympathetic stimulation constricts peripheral blood vessels, specifically those of the skin and abdominal viscera, and increases the heart rate and force of contraction.[7]

In the periphery, renal nerves contribute to the regulation of blood pressure and fluid volume through sympathetic efferent pathways, and the modulation of sympathetic outflow through afferent sensory pathways.[8] Thus, sympathetic renal activation plays a critical role in the development of hypertension and cardiovascular disease, including heart failure and arrhythmias.

Visceral Pain Control

Visceral pain is referred to the brain via nociceptive afferent sensory fibres that travel through the prevertebral ganglia and the splanchnic nerves. Prevertebral ganglion block[9] and splanchnicectomy[10] achieve abdominal pain control by interrupting these nociceptive sensory pathways, not by the concomitant ablation of the sympathetic efferent fibres.[11]

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CHAPTER 3

THE ORIGIN AND EVOLUTION OF SYMPATHETIC SURGERY

Initial Period

Sympathetic surgery was instigated following two major physiological observations regarding the pathophysiology of sympathetic ablation. The experiment of Claude Bernard showed that cervical sympathetic ablation resulted in miosis, enophthalmus, ptosis, and peripheral vasodilation.[1] The experiments of Gaskell demonstrated that section of the sympathetic supply to striated muscles resulted in vasodilation and temperature rise.[2] Based on the vasodilative effect of sympathetic ablation, on the hypothesis that **epilepsy** resulted from interference with the "brain nutrition," and on the presumption that improvement of brain perfusion could alleviate the fits, Alexander performed the first sympathetic ablation on humans with epilepsy by excising the upper cervical ganglion.[3] A discussion on the aetiology of epilepsy, the possible benefit of sympathetic ablation and a lengthy description of a series of cases was published by him in 1889.[3] The first sympathetic ablation for **ischaemic lesions** in the lower limb (periarterial denudation) was performed by Jaboulay and published in 1899.[4] The enophthalmic effect of cervical sympathetic ablation became another indication. Ionescu performed cervical sympathetic ablation for **exophthalmos** in 1896.[5] So did Jaboulay, who also reported in 1900 its use in the treatment of **goitre**.[6] François-Frank listed two more indications: **glaucoma** and what he named "**idiotie**".[7] Sympathectomy was also performed for **migraine.**[8] Ionescu added a further indication: **angina pectoris** (heart ischaemia).[9] Suppression of sweating, an additional observation of peripheral sympathetic denervation, incited Kozareff to treat **hyperhidrosis** by sympathetic ablation, published in 1920.[10] Most of these early indications soon became obsolete, and the only ones which persisted to the present are **ischaemia,**[4] **hyperhidrosis,**[10] and some other later occasionally used indications.

Following his demise in a train accident in 1913,[11] Jaboulay's pursuits in the field of sympathetic ablation for ischaemia were endorsed and extensively used by René Leriche.[12,13] Leriche also applied sympathectomy for **Raynaud phenomenon**.[13] Brüning applied sympathetic ablation for Raynaud phenomenon and **scleroderma**.[14] In the same year (1923), Royle performed in Australia the first lumbar sympathetic ablation for **spastic paralysis** (another obsolete indication) by ramicotomy.[15] In 1924, Diez performed a lumbosacral sympathetic ganglionic ablation for ischaemic lesions of the lower limb.[16] Finally, Adson and Brown extended this technique to vasospastic disorders.[17]

Persisting Indications

Hyperhidrosis

Today, hyperhidrosis is the foremost indication of sympathetic ablation. A detailed dissertation on this pathology is presented in a separate chapter (Chapter 5).

Ischaemia

Ischaemia results from several obstructive and spastic disorders.

Obstructive ischaemic disorders

Arteriosclerotic occlusive arterial disease is one of the most common progressive disorders that develops in the lower limbs with old age. In most cases, its early symptom is muscle pain in the lower limbs that appears while walking and disappears on rest (intermittent claudication). The mechanism is lactic acid accumulation in the muscles when shifting from aerobic to anaerobic release of energy occurs.[18] With the progressive increase in obstruction, a point is reached when the circulatory oxygen supply becomes insufficient even for the rest muscle requirements, resulting in rest pain. Finally, ulcers and gangrene develop.

Intermittent claudication: For the early stages of occlusive atherosclerotic disease in the lower limbs, namely intermittent claudication, sympathetic ablation as a treatment modality remained highly controversial. Despite occasional reports of clinical improvement,[19] studies like the series of Myers and Irvine[20] not only reported a lack of clinical improvement by sympathetic ablation but recorded no statistically significant change in the flow by strain-gauge plethysmography as well. Lastly, sympathetic ablation was not

included in a recent clinical review of all treatments for intermittent claudication.[21] Rheological studies concur with this standpoint. Hoffmann and Jepson studied human muscle blood flow using 133Xe clearance tests before and after lumbar sympathectomy, which showed no significant alteration.[22]

Acute ischaemic atherosclerotic occlusive events: Only rare studies recommend sympathetic ablation for acute ischaemic atherosclerotic occlusive vascular lesions.[23] The majority emphasize that there is no benefit of the procedure for this condition[23-28] or ischaemic diabetic foot,[29] even in the absence of any therapeutic option, including vascular reconstruction. Moreover, a negative ("paradoxical") response to sympathectomy has been reported in humans.[30-33] It was postulated that haemodynamic changes resulting from the procedure, namely increased skin blood flow "stealing" from and reducing muscular perfusion, were a trigger factor for the development of gangrene instead of improvement following sympathetic ablation.

Thromboangiitis obliterans (Burger's disease) is an inflammatory non-atheromatous obliterative disease that affects small and medium-sized arteries, veins, and nerves, and is strongly associated with smoking.[34,35] Because of the peripheral location of the lesions, arterial reconstruction is rarely possible. Sympathectomy remains the only surgical modality for these patients, although a few publications have questioned its efficacy.[34,36] It may promote wound healing and alleviate pain.[33-41] However, it neither cures nor limits the progression of the disease, especially if the patient persists in smoking, as shown in a recent study of 344 cases.[42]

Microembolism in digits from a proximal source is an acute event which may progress to gangrene. Sympathectomy proved beneficial by enhancing the healing of pregangrenous lesions and digital salvage.[43]

Vasoconstrictive ischaemic disorders

Raynaud's phenomenon: Ischaemia develops in a series of vasoconstrictive pathologies, which may be ***primary*** (Raynaud's disease) or ***secondary*** to underlying diseases: scleroderma, lupus erythematosus, rheumatoid arthritis, paraneoplastic syndrome, and other rare connective tissue, myeloproliferative, malignant, and haematological diseases.[44] The clinical presentation consists in intermittent episodes of digital ischaemia induced by cold or emotional stress, which may progress to gangrene. Sympathectomy is a therapeutic option for Raynaud's phenomenon. The

initial results are positive: the procedure may alleviate ischaemic pain, preserve tissue and prevent or limit amputation.[45-46] However, escape and recurrent symptoms are frequent. Therefore, initial sympathetic phenol block[47] or primary periarterial sympathectomy[26,48] may be sufficient, leaving the sympathetic trunk intact for future ganglionic ablation if subsequently required. Periarterial resympathectomy is possible and successful.[49]

Scleroderma, Rheumatoid arthritis, Lupus erythematosus: These disorders may engender vasoconstrictive ischaemia. Sympathectomy is sporadically used in these cases. Scleroderma is a rare autoimmune connective tissue disorder. Ischaemic ulcers may result and progress to gangrene and are occasionally treated by sympathetic ablation.[50,51] Periarterial denervation is particularly useful when orthopaedic digital procedures are required for the primary pathology.[52-53] In cases with multiple finger lesions when no orthopaedic surgery is indicated, ganglionic ablation is required. Digital ischaemia has also been reported and successfully treated by digital sympathetic neurectomy in rheumatoid arthritis and lupus erythematosus.[26]

Paraneoplastic Raynaud's phenomenon: Such a case, successfully treated by sympathectomy, has been published.[54] However, the trigger for the vascular pathology in this case could have been the chemotherapy rather than the malignancy itself.

Frostbite: The pathophysiology of frostbite injury was first described by Larrey, Surgeon-General of the Imperial French armies, who participated in the disastrous retreat of the Grande Armée from Moscow in 1812.[55] Frostbite injury results from direct cellular damage, hypoxia, and the release of toxic and vasoactive by-products.[56] The literature regarding the benefit of sympathetic ablation in such cases is controversial. Bouwman et al.[57] observed that sympathectomy did not improve the outcome, whereas others[58-63] reported a favourable effect of sympathetic ablation for frostbite injuries. Murphy et al. observed that, if performed in the first 24 hours, sympathetic ablation aggravated oedema and induced tissue damage, whereas if performed after 24-48 hours, an opposite effect was obtained.[61] Pain and paraesthesia were also reported to be ameliorated.[62] A more recent study confirmed the beneficial outcome of sympathectomy in treating Raynaud's phenomenon due to frostbite.[63]

Vibration or hand-arm white finger syndrome: This is a common occupational disorder developing in workers who use vibration tools.[64-67]

Prolonged exposure to vibration provokes blanching, numbness and pain in the fingers due to vasoconstriction.[65] In advanced cases, hypertrophy of vascular smooth muscle development may lead to trophic changes and gangrene.[64] Unlike other underlying diseases associated with secondary Raynaud's phenomenon, there is a striking scarcity of studies advising sympathetic ablation for this disorder. The good response to the disuse of vibrating tools may be the reason. However, for advanced cases of vibration syndrome, sympathetic ablation remains an option to be considered before irreversible damage develops.

Cardiac Indications

Angina

Based on the study of cardiac innervation by François-Frank,[7] and the understanding of the afferent cardiac sympathetic pathways, cervical sympathectomy was performed in the 1920s for angina.[9,68] Despite the development of coronary surgery and endovascular procedures, refractory cases of angina are still encountered and alleviated by sympathetic ablation. However, according to the elucidation of the sympathetic contribution to the cardiac plexus,[69] the level of the procedures is now T_2-T_4.[70] As their poor haemodynamic condition represents a surgical risk, Abbate et al. recommended a preliminary stellate ganglion block to confirm the efficacy of sympathetic ablation.[70] Repeated left stellate ganglion blocks remain a useful solution for patients unfit to undergo a surgical procedure.[71]

Arrhythmias

The role of cardiac sympathetic innervation in modulating cardiac electric activity has been elucidated by experimental research,[72,73] and by clinical studies of staged sympathetic ablations.[74] The accumulated data support sympathetic ablation to treat some cardiac rhythmic pathologies.[75]

Long QT syndrome is a group of ion channel disorders of ventricular myocytes due to genetic mutations,[76] presenting with prolonged QT interval on ECG, and clinical episodes of syncope, cardiac arrest and death often triggered by physical or emotional stress.[77] Treatment is often medical but may be insufficient to prevent arrhythmias. For these cases, left sympathetic ablation has been recommended.[78] Occasionally, the left unilateral procedure is insufficient in suppressing arrhythmias, and an additional right sympathetic cardiac denervation is required.[74] In the past, the stellate ganglion was targeted, resulting in Horner's syndrome. Thoracoscopic left

T1-T4 ablation was adopted to avoid it, resulting in excellent published outcomes.[79,80]

Ventricular tachycardia is treated by beta-blockers and, in refractory cases, by implanted cardioverter defibrillators. ***Electric storm*** is a life-threatening state of electric cardiac instability consisting in three or more daily episodes of ventricular tachycardia.[81,82] Refractory to management, electric storms can be beneficially treated by ablation of the cardiac sympathetic innervation.[83,84] It has been claimed that bilateral sympathetic ablation is superior to left-sided procedures alone. Its effect extended beyond the acute postoperative period, with a significant reduction in required defibrillator shocks in 90% of cases and, on long-term follow-up, it abolished the need for shocks in 46% of patients.[85]

Afferent unmyelinated fibres from the kidneys, which travel along with the sympathetic nerves, transmit sensory information from renal chemoreceptors and mechanoreceptors to regions in the brainstem involved in cardiovascular control.[86] Accordingly, renal sympathetic ablation has been found beneficial for ischaemia-induced ventricular arrhythmia in an animal study[87] and in humans.[86] Development of arterial catheterisation and catheter radiofrequency or ultrasound devices simplified renal sympathetic procedures.

Atrial fibrillation is the most common sustained arrhythmia. Renal sympathetic ablation to treat hypertension was reported to have a beneficial effect regarding atrial fibrillation as well.[88]

Cardiomyopathy is a medical condition. Nonetheless, sympathetic ablation has been beneficial. In an animal study on rats with doxorubicin-induced dilated cardiomyopathy, bilateral sympathectomy effectively prevented remodelling and left ventricular dysfunction.[89] In another study on rats with induced myocardial infarction, left sympathectomy increased end-diastolic volume, whereas bilateral sympathectomy increased ejection fraction.[90] In patients with dilated cardiomyopathy, additional treatment with high thoracic epidural sympathetic blockade reduced cardiac chamber dimension and increased left ventricular systolic function.[91,92]

Pain Syndromes

Complex regional pain syndrome (CRPS)

This is a poorly understood, bizarre and out-of-proportion painful condition following but unrelated directly to trauma, characterised by inflammatory

and autonomic features.[93] A plethora of synonyms are found in the literature: reflex dystrophy, post-traumatic sympathetic dystrophy, causalgia, Sudek's atrophy, post-traumatic atrophy, shoulder-hand syndrome, post-traumatic pain syndrome, pain syndrome, sympathetic neurovascular dystrophy, post-traumatic spreading neuralgia, etc.[94] At present, the term "Complex Regional Pain Syndrome" (CRPS) is used, encompassing all clinical presentations. In the early stages, the inflammatory features are dominant and the condition is called "warm CRPS". In the latter stages, the autonomic features become dominant, and the condition is named "cold CRPS". According to the traumatized organ, CRPS has been divided into two subgroups: I - following tissue trauma; II – following trauma to a nerve.[95] The pathogenesis is obscure. Multiple central and peripheral mechanisms seem to cause its development: peripheral and central sensitization, autonomic changes and sympatho-afferent coupling, inflammatory and immune alterations, brain changes, psychological, and possibly genetic factors.[90] There are several clinical signs, the foremost being pain presented as allodynia (the perception of a non-painful stimulus as painful) and hyperpathia (an exaggerated pain perception to a painful stimulus). With time, inflammatory symptoms regress while sympathetic overactivity becomes prominent. In the advanced stages, trophic changes develop, which may lead to irreversible loss of limb function.[93,95]

The multiple clinical presentations of CRPS and the multitude of documented treatments in the literature emphasize the complexity of this multifactorial syndrome and its recalcitrant therapeutic approach.[96,97] Sympathetic ablation is based on the sympathetic overactivity component of the syndrome, but its use for CRPS is disputed in the literature. Sympathetic ablation is effective in alleviating neuropathic pain. However, deterioration following sympathetic ablation for CRPS has been reported.[99] A few authors reject its use due to lack of evidence or efficacy.[100,101] Indeed, two systematic reviews retrieved only uncontrolled studies.[102,103] Substantial pain reduction by sympathetic ablation in CRPS is based mostly on personal reports.[96,104-108] Nevertheless, two series of CRPS patients treated one by sympathectomy[104] and one by ganglion blocks[109] reported good results. A preliminary block, which has a temporary effect, has been advised to evaluate the effectiveness of a subsequent surgical ablation.[110] Yet, another study questioned the predictive value of such blocks.[111] A note of caution is required. Sympathetic ablation may be effective in cases of CRPS with symptoms of sympathetic overactivity. However, with time, CRPS becomes independent of this activity and sympathetic ablation cannot be effective.[112] Accordingly, sympathetic ablation for CRPS may be effective only in the early stages of the syndrome, if at all.[113]

Erythromelalgia

Erythromelalgia is a rare syndrome characterized by burning pain, oedema, redness, and increased temperature in the upper, lower, or both limbs.[114] The syndrome may be primary or secondary to other pathologies like myeloproliferative or autoimmune disorders, and neuropathic conditions.[115,116] Gene mutations have been reported.[117] Microvascular arteriovenous shunts have been implicated.[118] Clinical investigations have shown distal small-fibre neuropathy with selective involvement of cutaneous sympathetic fibres.[111] Symptoms are usually intermittent, lasting minutes to days, and rarely permanent.[116,119] Treating erythromelalgia by sympathetic ablation (blocks or surgical procedures) is sporadically presented in the literature as case reports. Although in one of them[109] sympathectomy failed to achieve improvement, in most cases a favourable outcome was obtained.[114,117,120-122]

Visceral pain

Visceral pain is referred through autonomic afferent neural pathways. Therefore, sympathetic ablation can alleviate pain and has been used in some cases.

Acute necrotizing pancreatitis: The effects of pancreatic sympathetic denervation in acute necrotizing pancreatitis have been examined in dogs.[123] Greater splanchnic nerve transection improved the pathophysiological process of acute necrotizing pancreatitis. In humans, continuous thoracic epidural analgesia (producing segmental sympathetic block) not only controls pain but also lowers serum amylase and lipase levels, improves paralytic ileus, and thus hastens recovery.[124]

Chronic pancreatitis: For pain from chronic pancreatitis, the usual procedure is splanchnicectomy, either unilateral or bilateral.[125-129] Leksowski suggested operating the side of the abdominal pain.[127] For diffuse bilateral pain, left side ablation has been used but the high recurrence rate required a second procedure on the right side. It seems that for bilateral abdominal pain, a bilateral procedure should be performed in the first instance. Results are favourable, but not permanent in all cases. Buscher et al. reported ~50% recurrence of pain.[128] At six-month follow-up in Leksowski's series, only 4/24 patients were free of opioid use.[127] Maher et al. reported long-term pain relief in only 20% of patients.[126] To obtain better results, the timing of the procedure may be important. Issa et al. reported that opioid use before splanchnicectomy is associated with a worse

outcome.[130] Nevertheless, at present, there is no additional remedy for refractory pain in chronic pancreatitis than sympathetic ablation. The relative ease of thoracoscopy should further encourage its use.

Pancreatic cancer: One of the main symptoms of pancreatic cancer is pain, mostly of neuropathic origin, which significantly affects the patient's quality of life.[131] In two series of cases, left-sided thoracoscopic splanchnicectomy has been used with apparently good results,[132,133] although in some of them, a second operation on the other side was required.[133]

Abdominal malignancies: As pain due to all other abdominal malignancies is referred through the same neural pathways as pancreatic cancer pain, sympathetic ablation for that purpose is similarly efficient.[134] For abdominal malignancies of any origin, a laparotomy is often performed. In patients with intractable abdominal pain with stages of advanced peritoneal spread, an intraoperative splanchnicotomy is feasible.[135] An alternative procedure is an intraoperative coeliac block. A coeliac block may also be performed percutaneously.[136]

Other Miscellaneous Indications

Blushing

Blushing results from increased cutaneous blood flow caused by transient vasodilation. It may be triggered as a physiologic response to heat or by some other conditions.[137] Many are secondary to non-malignant easily recognised pathologies,[138] but sometimes, the underlying diseases (benign or malignant) may require a thorough diagnostic investigation.[137] Primary facial blushing is initiated by emotion. In some patients, facial reddening triggers social embarrassment, which may progress to a phobia[139] that should primarily be treated by psychotherapy[140] in addition to local[141] and systemic[142] pharmacotherapy. For recalcitrant cases, sympathetic ablation remains an option. First described for this indication in 1985,[143] sympathetic ablation gained extensive practice with favourable reported results.[144-146] On a long follow-up of 14.6 (2.4) years [mean (s.d.)] in 1700 out of 3015 operated patients, good results of endoscopic thoracic sympathectomy for facial blushing were reported in 72.8%.[147] However, a meticulous selection of well-informed patients is required. Facial blushing must be of considerable burden to the patient so that he may be prepared to take the significant risks of compensatory hyperhidrosis and gustatory sweating following upper thoracic sympathetic ablation.

Ménière's syndrome and tinnitus

In a series of 110 patients with Ménière's syndrome or tinnitus, sympathectomy obtained very good results.[148] The procedure was surgical ablation or block of the stellate or the superior cervical ganglion. An additional study reconfirmed the efficacy of sympathetic ablation in these conditions.[149] Recently, another article on patients treated for tinnitus by radiofrequency lesion of the superior cervical sympathetic ganglion reported relief in 64% of patients at 7-week follow-up, reduced to 40% two years later.[150] For patients with tinnitus who do not respond to conventional therapy, ablation of the superior cervical sympathetic ganglion may be appropriate.

Hypertension

Renal sympathetic denervation for the treatment of hypertension was already performed in the 1930s by a transthoracic[151] or a transabdominal[152] approach. Smithwick and Thompson compared 1266 hypertensive patients after thoracolumbar sympathectomy with 467 hypertensive controls.[153] On follow-up, they observed mortality of 19% and 54%, respectively. Significantly lower blood pressure was achieved in 45% of the surviving operated patients. With the development of new antihypertensive drugs in the 1960s that were effective and had minimal side effects, surgical sympathetic ablation to treat hypertension fell into disuse.[154] However, a small group of recalcitrant hypertensive patients persisted. With the development of arterial catheterisation, radiofrequency, and ultrasound, periarterial sympathetic ablation became a relatively easy procedure. Its use as a therapeutic approach for hypertension was reintroduced by the end of the 2010s and gained rapid popularity.[155] Three randomized trials followed. The first [Simplicity HTN-1][156] and the second [Simplicity HTN-2][157] showed some benefit of the procedure. Results of the third study [Simplicity HTN-3],[158] a multi-centre single-blinded trial comparing patients submitted to bilateral renal artery denervation with patients with sham procedures, are questionable. Three additional new studies [SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and RADIANCE HN SOLO] have shown positive outcomes.[159-161] Although no definitive results are available yet, these studies and recent emerging evidence will probably and finally approve renal artery sympathetic ablation to treat refractory hypertension.[162]

Thoracic outlet syndrome

Thoracic outlet syndrome results from compression of the neurovascular bundle at its transit from the thorax into the upper extremity. Compression