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REVIEW

The vagus nerve: current concepts in anaesthesia and ICU management

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The vagus nerve (XN) is a major component of the autonomic nervous system. It plays an important role both in the regulation of metabolic homeostasis and in inflammatory modulation. XN tone is dampened in stress conditions (either of inflammatory and/or infectious origin) and the preservation of parasympathetic function may serve as a biomarker of general health, longevity and vitality. COVID-19 remains a major healthcare issue worldwide. Excessive inflammation and its end organ consequences are key elements in the pathogenesis of COVID-19-induced multiple organ dysfunction, as well as post-COVID-19 syndrome (long COVID). XN stimulation has been hypothesised to control both the SARS-CoV-2 replication and the ensuing inflammation, and could improve the clinical outcomes as an adjunct treatment. Electrical stimulation of the auricular XN (AXNS) is an emerging technology, with few side effects and anaesthetic implications, and is showing promise with respect to the management of gastroparesis, epilepsy, migraine, autoimmune diseases, anxiety and major depressive disorders, obesity, SARS-CoV-2 infection in the intensive care unit (ICU), and long COVID. Continuous vagal tone monitoring in patients with COVID-19 may potentially also be used as a predictive marker of the COVID-19 illness course, and an evaluation of future therapies.

Keywords: vagus nerve, anaesthesia, intensive care unit

Anatomy, physiology and pathophysiology

The vagus nerve (XN) is a major component of the autonomic nervous system (ANS) and plays an important role both in the regulation of metabolic homeostasis and in the neuro-endocrine-immune axis.[1] The sympathetic and parasympathetic components of the ANS control and regulate the function of various organs, glands and involuntary muscles throughout the body, including vocalisation, swallowing, heart rate, respiration, gastric secretion and intestinal motility.[2] Through efferent and afferent fibres, the XN plays a role in maintaining cardiovascular homeostasis and in modulating inflammation.[3]

The XN is a mixed nerve composed of 20% efferent fibres and 80% afferent (sensory) fibres. The anatomy of the XN in the neck is shown in Figure 1. The efferent cholinergic fibres are the main parasympathetic component of the ANS. The right and left XN exit from the brainstem and course through the neck (in the carotid sheath between the carotid artery and jugular vein), upper chest (along the trachea), lower chest and diaphragm (along the oesophagus), and into the abdominal cavity. During this course, branches innervate various structures including the lungs, spleen, liver, heart, bladder and pancreas. The main XN branches are the inferior ganglion branch that innervates the pharynx and larynx, the superior ganglion branch that innervates the spine and ear, and the XN branch that innervates the heart, lungs and gastrointestinal tract. In the brainstem, the sensory afferent fibres terminate in the nucleus tractus solitarius, which then sends fibres that connect either directly or indirectly to the dorsal raphe nuclei, locus ceruleus, amygdala, hypothalamus, thalamus and orbitofrontal cortex. Within the central nervous system, the XN primarily projects to the nucleus of the solitary tract (NTS), releasing excitatory neurotransmitters (glutamate and aspartate), inhibitory neurotransmitter (gamma-aminobutyric acid), acetyl-choline, norepinephrine and neuropeptides implicated in signal transduction. In turn, the NTS has widespread efferent pathways to the parabrachial nucleus, reticular formation, basal forebrain, amygdala, hippocampus, hypothalamus, dorsal raphe, cerebellum and spinal cord.[1,2]

The ANS regulates the production of cytokines, through interactions with the hypothalamic–pituitary–adrenal axis, leading to the release of anti-inflammatory glucocorticoid hormones. Vagal efferent fibres also release acetylcholine (ACh), which, by

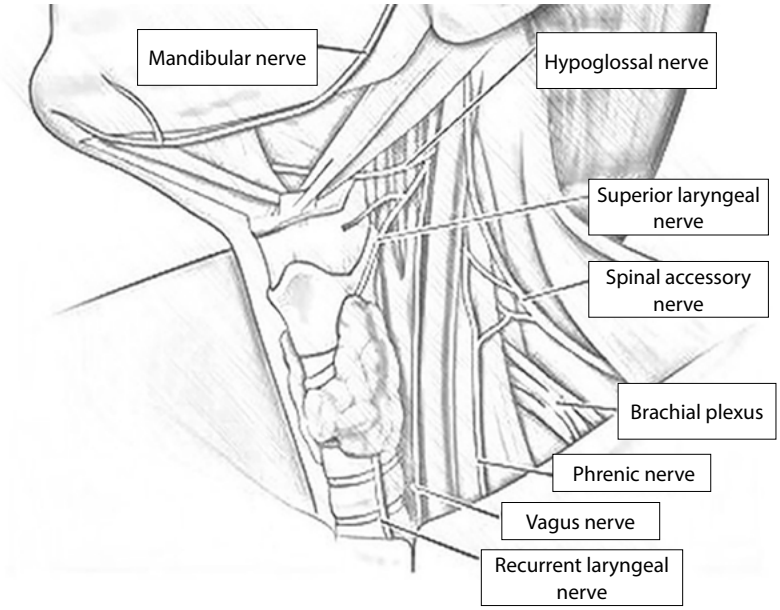

Figure 1: The anatomy of the neck showing the position of the vagus nerve (XN)[1,2]

interacting with α7-subunit-containing nicotinic receptors found in tissue macrophages, and dendritic cells, inhibit the release of proinflammatory cytokines such as tumour necrosis factor alpha (TNFα), IL-1β, IL-6 and IL-18.[4]

XN tone is dampened in stress conditions (either of inflammatory and/or infectious origin).[4] The level of resting vagal tone may give some indication as to an individual's vulnerability to stressors.[5] It has been postulated that severe traumatic life events (physical or emotional) may result in XN dysfunction.[6] Normal ageing is associated with an increase in sympathetic prevalence and/or a decrease in the vagal tone. A shift toward sympathetic prevalence may also contribute to age-related conditions, such as hypertension and heart failure.[7] The preservation of parasympathetic function may serve as a biomarker of general health, longevity and vitality.[7]

XN dysfunction has been found to be associated with the following:[3,6,8-13]

- Gastroparesis, abdominal pain, bloating and irritable bowel syndrome
- Dysmenorrhoea and perimenopausal hot flashes
- Abnormalities in glucose regulation, obesity and unexplained weight changes
- Gastroesophageal reflux disease
- Paroxysmal atrial tachyarrhythmia, dizziness, vertigo and syncopal episodes
- Abnormalities in blood pressure control (hyper- and hypotension) and vasculitis.
- Difficulties with swallowing, alterations of the gag reflex, and nausea and vomiting
- Hoarseness, wheezing and loss of voice
- Chronic fatigue syndrome, poor effort tolerance and limb weakness
- Chronic pain syndromes and fibromyalgia
- Chronic coughing, asthma and chronic obstructive lung disease
- Musculoskeletal pain, myalgia and hyperalgesia
- Cognitive impairments, insomnia, anxiety, panic attacks, depression and psychosis
- Anosmia and nasal obstruction
- Muscular tics and spasms

XN and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

COVID-19 remains a major healthcare issue worldwide. Excessive inflammation and its end organ consequences are key elements in the pathogenesis of COVID-19-induced multiple organ dysfunction, as well as post-COVID-19 syndrome (long COVID). Specific treatments for COVID-19 and long COVID are lacking.[14]

An exacerbated inflammatory response is believed to be one of the major causes of morbidity and mortality of a SARS-CoV-2 infection. Neuromodulation therapy, based on XN stimulation, has been hypothesised to control both the SARS-CoV-2 replication and the ensuing inflammation, likely through the inhibition of the nuclear factor kappa-light-chain-enhancer of the activated B cells pathway and could improve the clinical outcomes as an adjunct treatment. SARS-CoV-2 is prone to neuroinvasion from the lung along the XN up to the brainstem autonomic nervous centres involved in the coupling of cardiovascular and respiratory rhythms.[14]

The brainstem autonomic network allows SARS-CoV-2 to trigger a neurogenic switch to hypertension and hypoventilation, which may induce dysautonomia, together with an inflammatory "storm". The lethal outcomes of COVID-19 may rely on a critical hypoactivity of the efferent XN cholinergic pathway, which is involved in lowering cardiovascular pressure and systemic inflammation tone.[14]

SARS-CoV-2 is characterised by a dramatic cytokine storm in some patients. This storm is due to the release of high levels of proinflammatory cytokines such as interleukin (IL)-1 β, IL-6, tumour necrosis factor (TNF), and chemokines by respiratory epithelial and dendritic cells, and macrophages. It has been hypothesised that this cytokine storm and the worsening of a patient's health status can be dampened, or even prevented, by specifically targeting the vagal-driven cholinergic anti-inflammatory pathway (CAP). The CAP involves an anti-inflammatory effect of XN efferents by the release of ACh. The nicotinic acetylcholine receptor (nAChR) alpha7 subunit (α7nAChRs) is required for ACh inhibition of macrophage-TNF release and cytokine modulation. Alveolar macrophages, epithelial cells and inflammatory infiltrated neutrophils express α7nAChR and could be involved in the efferent arm of the pulmonary parasympathetic inflammatory reflex. XN stimulation (XNS) may also alleviate lung injury through the reduction of gut and lung permeability through the AChR.[14,15]

SARS-CoV-2 may infect the terminal areas of XN afferents or the origin of XN efferents inducing down-regulation of ACE2 and favouring local inflammation that could disrupt the CAP and dysregulate the inflammatory response. XNS might attenuate sepsis-related inflammatory processes leading to endothelial activation, impaired microcirculation, multiorgan failure and death. XNS may also exhibit favourable cardiovascular effects during sepsis, including anti-arrhythmogenic effects, decreased myocardial oxygen consumption and improved diastolic function. Therefore, targeting the α7nAChRs through XN stimulation may become part of the management of patients with SARS-CoV-2 infection in the intensive care unit (ICU) in the future.[14]

Long COVID is a potentially disabling syndrome affecting 10–15% of individuals infected with SARS-CoV-2. Symptoms associated with long COVID include dysphonia, dysphagia, dizziness, paroxysmal tachycardia, orthostatic hypotension and diarrhoea. In individuals with symptoms suggestive of long COVID, an ultrasound of the XN in the neck (Figure 2) may show

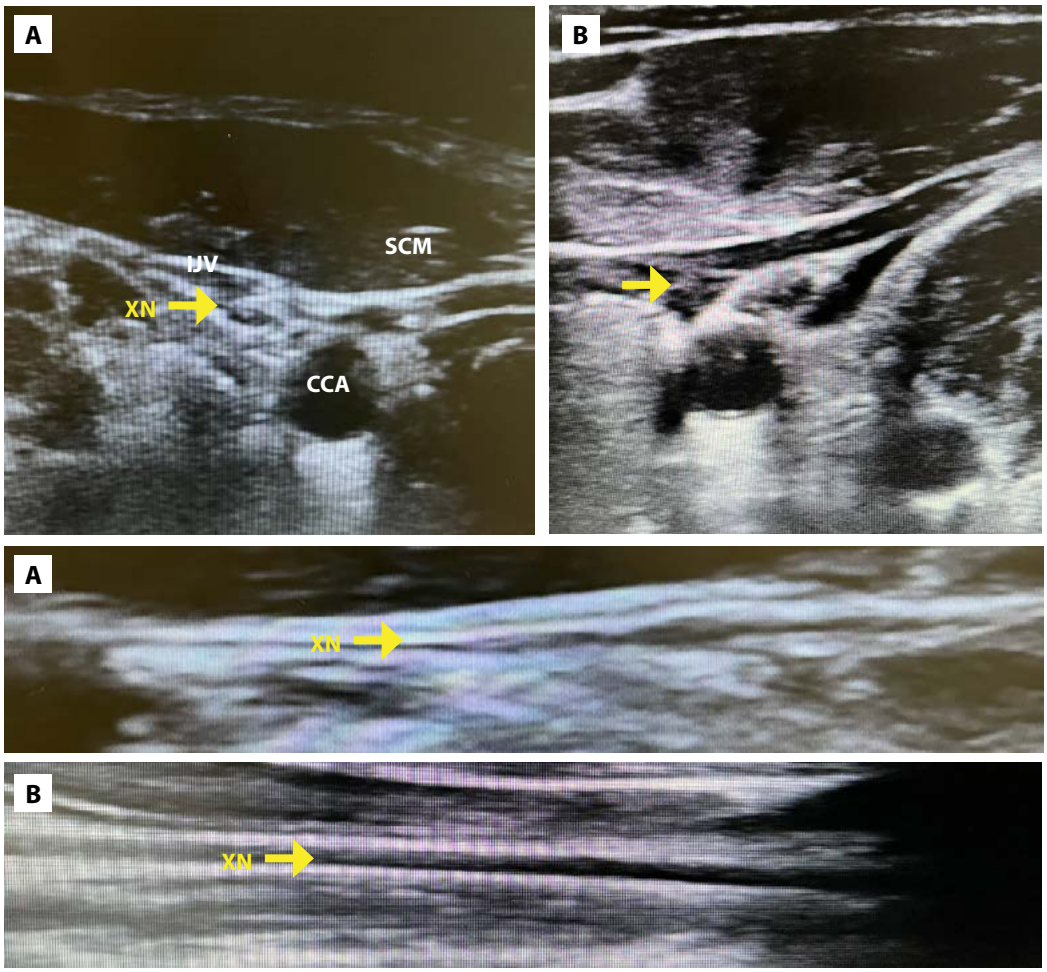

Figure 2: Ultrasound of the XN at the level of the neck in subjects with (A) and without (B) symptoms suggestive of long COVID syndrome
XN – vagus nerve, IJV – internal jugular vein, SCM – sternocleidomastoid muscle, CCA – common carotid artery

thickening of the XN as well as increased echogenicity indicative of mild inflammatory changes.[16]

XNS may be beneficial in the management of long COVID syndrome. Continuous vagal tone monitoring in patients with COVID-19 may potentially also be used as a predictive marker of the COVID-19 illness course, and an evaluation of therapies.[16,17]

Electrical nerve stimulation of the XN (eXNS)

Invasive electrical stimulation of the XN (IXNS) was established for epilepsy treatment in 1988 and has been investigated for several other therapeutic targets over the years. Electrical stimulation of the auricular XN (AXNS) is an emerging technology in the field of bioelectronic medicine with applications in therapy.[18]

AXNS is an evolving neuromodulation technology that has a wide range of therapeutic applications across multiple disciplines of medical science. Transcutaneous auricular XNS (TAXNS) has been investigated regarding its therapeutic properties in several conditions including gastroparesis, epilepsy, migraine and major depressive disorder, and has been shown to access similar neural pathways than those accessed through invasive XN stimulation.[18]

The outer ear is supplied with three sensory nerves, namely the auriculotemporal nerve, the great auricular nerve, and the auricular branch of the XN (ABXN). The ABXN and the great auricular nerve have been found to be solely on the antihelix in 73% of patients. The ABXN provides ramification for the crura antihelices in 9% of patients, for the cavity of conchae in 45% of patients, and for the cymba conchae in 100% of patients.[18,19]

In 55% of patients, the ABXN and the great auricular nerve have been identified in the cavity of conchae. The ABXN includes thick myelinated afferent fibres that project to the nucleus tractus solitarii which are considered essential for the clinical effectiveness of this neuromodulatory approach. Functional magnetic resonance imaging (fMRI) has shown that there is similar activation of the neural pathway in TAXNS to that in IXNS.[18,19] This is depicted in Figure 3.

It is traditionally believed that the XN efferent fibres leading to the heart are usually located on the right side, and most studies believe that it is safe to perform TAXNS only in the left ear. However, it has also been shown that right-sided stimulation does not increase the risk of adverse events, and based on increased sensory input to the brainstem, activation of both the left and right ABXN would potentially enhance the stimulation effect. Reported adverse events have been mild to moderate and include headache, ear pain, application site erythema, vertigo, fatigue and nausea.[18,19]

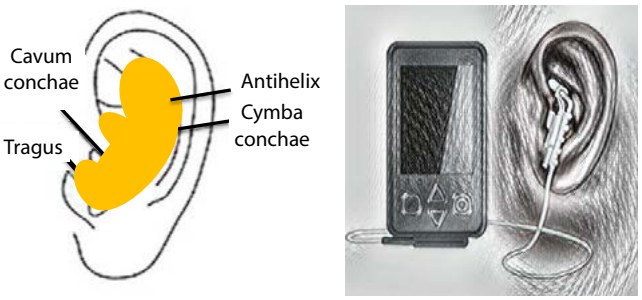

Figure 3: Transauricular vagus nerve stimulation (TAXNS) of the ear regions innervated by the cutaneous auricular branch of the XN

Anaesthesia for patients with XN stimulators

The perioperative concerns in patients with an XNS device include respiratory and cardiovascular side effects, as well as mechanical and electrical safety concerns.[20] The XNS device consists of a pulse generator, a lead wire and an electrode wrapped around the left XN (Figures 3 and 4). Intermittent electrical stimulation of the left XN via the lead from the pulse generator attenuates epileptic seizures. A dedicated magnet for the XNS device can be used either to deliver a burst of vagal stimulation by placing the magnet transiently over the generator or to temporarily inhibit output by leaving the magnet in place.[20]

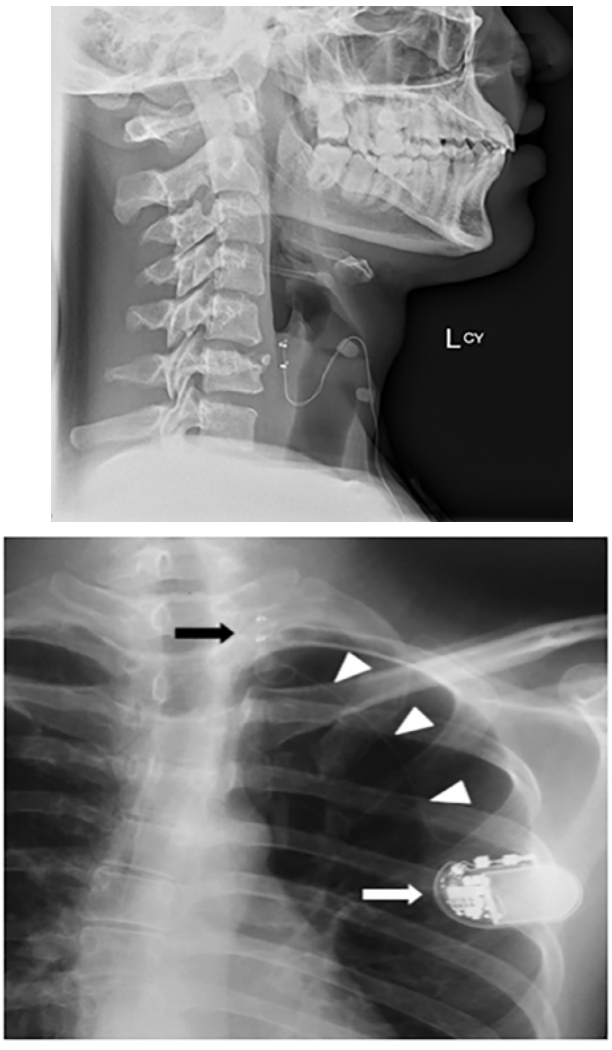

Figure 4: Lateral neck and chest x-ray showing the position of an implanted XN stimulator
Source: Courtesy of Dr Yahya Baba, Radiopaedia.org, rID57414

Following the onset of a seizure, application of the magnet by waving it over the generator for approximately a second activates the XNS device, thereby attenuating the seizure. The XNS device will return to its normal programmed mode once the magnet is removed.[20]

However, under certain conditions, XNS can also be proarrhythmic (e.g. increased vagal tone could trigger ventricular fibrillation in Brugada syndrome). High-frequency stimulation may be associated with tissue damage with long-term use.[20]

The antennae within the generators are controlled by radio frequency signals. Therefore, short wave diathermy, microwave diathermy and therapeutic ultrasound diathermy should not be used in patients with indwelling XNS devices. External defibrillation and electrical cardioversion may also damage the generator. If external defibrillation is required, the XNS manufacturer recommends using the lowest amount of appropriate energy during each electrical current delivery and that the defibrillation contact pads should be placed as far from the generator and implanted lead as possible. Contact pads should be placed so that current will travel in a vector perpendicular to the XNS system. With magnetic resonance imaging (MRI), the primary risks are excessive heating of the leads attached to the XN and damage to the stimulator.[20]

Other potential risks posed by MRI in patients with an implanted metallic device include spurious device stimulation due to magnetic field gradients, displacement due to static magnetic field interactions, and disruption of the XNS system.[20]

Chronic XNS therapy can lead to significant respiratory complications and has been associated with cases of laryngeal dysfunction such as altered voice, dyspnoea and cough. There have also been reports of an increased incidence of obstructive sleep apnoea (OSA) episodes with XNS. XNS may cause new onset sleep apnoea episodes in patients who have not previously been diagnosed with this condition. Lower stimulation frequencies, longer periods of off time, as well as device inactivation are associated with reduced respiratory events. Screening for sleep apnoea events before and after implantation, and careful perioperative risk assessment and management is required. Perioperative management of patients with OSA and XNS should aim to minimise postoperative respiratory risks, such as the use of an opiate-free anaesthesia technique, close postoperative monitoring in a high care or ICU, supplemental oxygen postoperatively, and discussion with neurology about turning off the XNS for the high-risk perioperative period.[20]

XNS can lead to abnormal movement of the vocal cords with resultant voice alterations, such as hoarseness, breathlessness and, in some cases, airway obstruction. Voice alterations are due to concurrent stimulation to two branches of the XN, the superior and recurrent laryngeal nerves which innervate the muscles of the larynx. This is usually mild and associated only

with periods of stimulation, but in some cases it may present with a sore throat or evidence of airway obstruction such as dyspnoea or stridor. Medial deviation of the left vocal cord and arytenoids has been documented on videoendoscopy during XNS. Recurrent intraoperative obstructive episodes as a result of tetanic contraction of the left-sided musculature of the larynx has been reported in patients in whom laryngeal mask airways were used. This potential complication must be considered when using supraglottic airways while under general anaesthesia and may require the XNS to be switched off preoperatively to reduce the risk of airway obstruction.[20]

Patients with XNS should be referred to a preoperative assessment clinic for review by an anaesthesiologist. Expert advice should be sought from neurology colleagues for specific advice around perioperative management, and patients should have the pulse generator interrogated after any unplanned or emergency deactivation with the magnet to ensure proper functioning and appropriate programming going forward. Familiarity with the device is important, both for patient safety as well as for avoidance of damage to the device.[20]

Conclusion

The XN, the tenth cranial nerve, is a major component of the ANS. It plays an important role both in the regulation of metabolic homeostasis and in inflammatory modulation. XN tone is dampened in stress conditions (either of inflammatory and/or infectious origin). The level of resting vagal tone may give some indications of a patient's vulnerability to stressors. The preservation of parasympathetic function may serve as a biomarker of general health, longevity and vitality. A shift toward sympathetic prevalence may contribute to age-related conditions, such as hypertension and heart failure. Electrical stimulation of the auricular XN (AXNS) is an emerging technology, with few side effects and anaesthetic implications, and is showing promise with respect to the management of gastroparesis, epilepsy, migraine, anxiety and major depressive disorders, obesity, SARS-CoV-2 infection in the ICU, and long COVID syndrome. Continuous vagal tone monitoring in patients with COVID-19 potentially may also be used as a predictive marker of the COVID-19 illness course, and an evaluation of future therapies.

Conflict of interest

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