The Evolution of Laryngeal Reinnervation, the Current State of Science and Thoughts for Future Treatments

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Summary: The treatment of unilateral vocal fold palsy (UVFP) or bilateral vocal fold palsy (BVFP) has been the subject of debate and experiment for 150 years. To date, dozens of different surgical methods have been described to reinnervate this most complex of organs, the larynx. As yet, there is no consensus on the most functionally effective method of reinnervation. However, it is a rapidly expanding area of research and remains an area of controversy. Indications for reinnervation for both UVFP and BVFP are still evolving and our understanding of the neuromuscular supply to the larynx continues to expand. What may have been considered unacceptable results from previous studies with one pathology may actually be of benefit in patients with different pathologies. This uncertainty of treatment options and potential outcomes can be confusing. In addition alternative techniques have been postulated as mainstays or adjuncts of treatment to the stalwart of reinnervation, neurorrhaphy. Determining what the correct treatment for an individual patient should be is still a gray area. With this in mind, this article reviews the evolution of laryngeal reinnervation, reviews the current state of the science, and suggests directions in which it might move in the future.

Key Words: Laryngeal reinnervation–Recurrent laryngeal nerve–Superior laryngeal nerve–Anastomosis of Galen–Neurrorhaphy–Vocal fold palsy.

INTRODUCTION AND ANTIQUITY

Galen (AD 129–199 [or 217]) is accredited with the first detailed description of the anatomy of the larynx and the description of laryngeal nerves. He understood that the voice came in part from vibration of the vocal folds. He dissected a series of mammals and discovered the same in each. Demonstrating on a pair of pigs to an audience in Rome, he described "… there is a pair [of nerves] in the muscles of the larynx on both left and right, which if ligated or cut render the animal speechless without damaging either its life or functional activity …"[1] To further his demonstration of the nervous system, with the pig strapped to a table in a Roman piazza, he would take a knife and plunge it into the lower spine. The hind legs would stop moving but the forelegs and head continued to. He would then insert the knife into the lower neck through the cervical spine. The forelegs would now stop moving but the pig still breathed and cried out. Finally, he would insert the knife through the high cervical spine, killing the animal, and throwing his knife onto the table (Figure 1).

Although Galen accurately identified what are now named the recurrent laryngeal nerves (RLNs), there is no record of him describing the superior laryngeal nerves (SLNs).

The study of the larynx and its mechanisms of action, in comparison with the rest of the body, progressed slowly until direct visualization using light and mirror was first described by Bozzini in 1807. Unfortunately, colleagues condemned his invention of a speculum that reflected light and the idea was lost for almost 50 years but due to the tenacity and detailed presentations concerning the direct visualization of his own larynx, Garcia became known as the father of laryngoscopy and the technique gained a foothold.[2] The introduction of photographic strobe lighting by Muybridge in the 1870s[3] and its adaptation to visualize the larynx by Oertal in 1895[4] allowed a greater understanding of the production of the voice. However, the clinician's increasing interest in disorders of the larynx ran in parallel with these innovations and by the turn of the century, vocal fold palsy had been well described and attempts were being made to correct this defect.

ANIMAL EXPERIMENTS

In 1893, writing in The Veterinarian, Cotterell described the division of the left RLN of three dogs and a donkey and direct anastomosis with the divided ipsilateral vagus nerve. Two dogs died, one dog had a partially working, synkinetic left vocal fold (LVF) and the donkey had an LVF described as working synchronously with the right vocal fold (RVF).[5] By any measure, this represents a partial success. One may consider that the sacrifice of one of the vagus nerves may have played a part in the demise of two of the dogs but with no published description, this is conjecture.

HUMAN CASE REPORT

The first description of a human laryngeal nerve reinnervation was by Horsley,[6] of Richmond VA, in 1909 published in the *Annals of Surgery*. He described the presentation of a lady who had been shot by a pistol. The ball had entered:

> … at the lower border of the chin about the median line and just grazing the bone. It was evidently deflected by the bone and took a course downward and to the left, just beneath the skin, to the larynx where it penetrated deeper in the neck. Just above the larynx the bullet so nearly penetrated to the surface that a keloid developed as a result of the injury to the deep layers of the skin. After striking the left side of the thyroid cartilage the bullet took a deeper course, wounding the left recurrent laryngeal nerve. There was only slight bleeding at the time, but the patient's voice was at once affected and was so hoarse that she could not speak above a whisper.

The reason the woman had been shot was not mentioned. Horsley went on to operate in August 1908, excising the scarred

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FIGURE 1. Image from the bottom panel of the title page to the 1541 Junta edition of "'Galen's Works." Depicts Galen demonstrating that the RLNs render an animal voiceless when cut.

portion of the RLN and anastomosing end-to-end with a sportingly large 0 catgut. Muscle was overlaid and the skin closed with silkworm gut. The patient was examined by Dr Clifton M. Miller, the regional Professor of Rhinology and Laryngology at the University of West Virginia after 2 and 15 months. At the first viewing, the LVF had slight movements, and at the second, there were almost normal movements. However, the LVF was noted to be lagging behind the RVF in its movements and there was an anteriorly based laryngeal web, presumably secondary to inflammation from the initial traumatic insult. One can assume that this was due to a mild degree of synkinesis.

To correct the lateralized vocal fold without reinnervating the affected muscles, surgeons started implanting material lateral to the fold in an attempt to metalize the fold into the midline. Bruening,[7] in 1911, described the first injection medialization laryngoplasty using paraffin, and Payr,[8] in 1915, the first external approach medialization thyroplasty. These techniques have remained the mainstay of treatment for unilateral vocal fold palsy (UVFP) until the present day.

ANATOMY

Every medical student knows that the RLN supplies motor innervation to all the muscle of the larynx except the cricothyroid and sensation to the larynx below the level of the vocal folds. The SLN supplies motor innervation to the cricothyroid and sensation larynx above the vocal folds. The folds themselves receive a mixed supply. However, as in most aspects of the human body, reality is not quite as simple as this. The RLN loops under the arch of the aorta on the left and under the subclavian artery on the right to run superiorly in the tracheo-oesophageal groove bilaterally. It curves antero-superiorly around the cricothyroid joint and enters the larynx. It divides, sometimes before and sometimes after the joint, into its adductor and abductor branches. The abductor branch runs posteriorly to supply the only abductor of the larynx, the posterior cricoarytenoid (PCA) and the adductor branch runs superiorly and further divides to supply the thyroarytenoid (TA) and interarytenoid muscles. Again, this division is not as simple in reality as it looks in the diagrams. There is cross-innervation of the PCA from the contralateral side and there are often interdigitations between all these end branches. A suitable analogy would be the interconnecting branches of the facial nerve within the parotid gland, not described in textbooks, found during a parotidectomy.

As well as the complex subdivisions of the RLN, the SLN also plays a part. A well-described anastomosis between the two nerves is the appropriately named anastomosis of Galen. A recent review suggested an incidence of this connection of 81% in 50 larynges.[9] In the event of RLN damage, the intrinsic muscles of the larynx will still receive some supply from the SLN. The review published in Clinical Anatomy also suggested that considering the morphometric contributions of the RLN and SLN, the SLN may be a larger contributor than previously thought. Which muscles this connection supplies and what ratio of abductor to adductor axons it carries are also unknown. Indeed, a 10-year study of the feline larynx published in 1992 by Yoshida et al[10] focused on the myotopical arrangements of the motoneurons, an astonishingly intricate piece of work, but even so their summation was that "most of this innervation, …, is unclear". The fact that the SLN and the anastomosis of Galen may play a part intuitively feels right although there is no evidence either way at present.

HORSES

Laryngeal reinnervation in humans did not advance until the later part of the 20th century. Before this, a number of experiments on horses had been attempted because of an unusual inherited trait. Almost all Western thoroughbred horses are descended from three Arabian stallions imported over the last 300 years. The Byerley Turk (1680s), the Darley Arabian (1704), and the Godolphin Arabian (1729) were all stallions brought to the UK with an aim to sire winning thoroughbreds. With this small number of stallions, there has inevitably been inbreeding, a consequence of which is the incidence of clinical and subclinical left vocal fold palsy. It is postulated that the weakened LVF flaps in the airway when the horse is at gallop making a noise known as roaring. This limits the racing capacity of the horse in question and veterinarians have tried to circumvent this to push forward this sport of kings.