Clinical and experimental aspects of tracheal stenosis

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Citation for published version (APA):
Introduction
Outline of the Thesis
Introduction

Narrowing of the major airway may have multiple causes, the most common being post-intubation lesions, trauma, chemical strictures, neoplastic lesions, inhalation injury, burns, and congenital anomalies. Although the etiologies of airway stenosis vary widely, the common denominator results in acute or insidious respiratory compromise which may be life threatening. Despite medical possibilities that allow for survival in a first instance, the ultimate pathway towards recovery passes by some sort of mechanical intervention, be it from within or externally, or directly on the diseased airway. This is classically in the form of surgery, with repair or replacement of the narrowed airway, or more recently with the adjunct of intraluminal stenting. The immediate goal of all interventions on airway lesions of any type is to facilitate adequate gas exchange, and secondarily to achieve proper healing and normal function. To illustrate the problems specifically related to post-surgical healing, and the efforts directed at improving the post-interventional results common to most tracheo-bronchial obstructive lesions, congenital diseases are representative, and will be used as a descriptive model in this thesis. Congenital diseases of the airway may be grossly divided into two categories on the basis of their etiology, either from intrinsic anomalies of the tracheo-bronchial wall with resultant narrowing, or by extrinsic compression by vascular malformations. The two may co-exist, and vascular malformations are often the cause of the former.

Classical surgical attempts at management of congenital narrowing are limited to the major airway, namely the trachea and the mainstem bronchi, as the distal broncho-alveolar tree is inaccessible. Surgical approaches may be schematically divided into 5 subgroups (Table 1):

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<th>Table 1</th>
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<td>1- Direct surgical repair of the airway wall by resection of obstructing lesions and/or augmentative patch plasty;</td>
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<td>2- Indirect relief of obstruction through division or rerouting of exterior compressive forces, namely vascular malformations;</td>
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<td>3- Intraluminal relief of compression by stenting or prosthetic materials designed to augment the intraluminal diameter by stretch mechanisms;</td>
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<td>4- Excision of the diseased portion of the airway and its replacement by a biological or prosthetic substitute;</td>
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<td>5- Novel experimental techniques: de novo formation of an airway, either by autologous tissue, or by biocompatible in vitro implants for long-lasting replacement/reconstruction.</td>
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Major advances have been made in the surgical results in the treatment of long segment congenital tracheal stenosis from complete tracheal rings, partly owing to improvements in surgical technique, the adjunct of cardiopulmonary bypass and extracorporeal circulatory support, but also to meticulous postoperative airway management. The multidisciplinary treatment package has allowed for enhanced survival in this previously fatal disease, but morbidity remains an omnipresent concern.

Although surgical reconstruction of the airway is almost always deemed feasible to restore immediate patency in the setting of narrowing from any cause, the mid to long-term results are disappointing. After what is hoped to be a surgical cure, an exaggerated healing cascade results in granulation tissue, which is a phenomenon particular to surgery of the airway. This is an obstructive and dysfunctional scar of obscure origin, which results in residual or recurrent stenosis. Most clinical and experimental research has focused on ways to prevent granulation tissue, with equivocal results. More recently, ways to influence or treat preexisting granulation tissue are being studied.

These considerations and others pertaining to the mechanisms in granulation tissue formation motivated the current research, in view of eventually elucidating the causing factors, and subsequently proposing ways to avoid or treat granulation tissue. The ultimate goal is to enhance the surgical and interventional results of major airway reconstruction, which are otherwise technically sound, reproducible, give initial excellent results, but are disappointing in the mid to long-term for reasons mentioned above.

In order to minimize or prevent granulation tissue, the true Achilles heel of airway repair, it is important to understand its etiology. To date, this is unsolved, although multiple hypotheses have been forwarded, and one of which is to be tested in this study. Potential mechanisms that could explain why granulation tissue is a more or less specific problem with the airway are shown in Table 2, and elaborated in more detail below:

**Table 2: Potential etiologies of impaired airway healing**

1. Continuous environmental contact
2a. Non-static organ
2b. Movement of particles within organ
3. Tension on repair
4. Poor vascularization
Introduction

1. The airway represents a unique target in terms of surgery or intervention, in that it is not physically excluded from the exterior environment. In contrary to other organs which are internal and for whom the principles of antisepsis and isolation are paramount, the airway is in continuous contact with moving ambient foreign air particles. This in itself may be a first source of ongoing stimulation and a potential source for chronic inflammation, with resultant granulation tissue. In order to test this hypothesis, a surgical model would have to be developed using a sterile peri and postoperative environment, hence excluding any contamination or infection from ambient air. This has not yet been performed to the author’s knowledge, and will not be further tested during the experiments presented herein.

2. Along the same lines implementing external mechanical stimulation and its potential role in the prevention of healing, the airway is not a static organ. In analogy with the skeleton and the lessons learned from orthopedic surgery and the beneficial effects of inertia for healing, the airway is unfortunately impossible to splint. There are two unavoidable intrinsic phenomena in the functioning airway; first (2a), the to-and-fro motion of airway particles which never allow the inner lining of epithelium to be at complete rest, and second (2b), the dilation/collapse of the trachea during respiration, be it spontaneous or mechanical, which does not allow for the wall to remain inert. In this sense, the airway is unique and presents a formidable challenge, in that an absolute "static state" may not be relied upon during the process of healing. Again, this hypothesis has not been previously tested to the author’s knowledge, and elaborating models that would avoid all movement of air or the airway itself do not seem clinically applicable. This will therefore not be undertaken in this study.

3. When extensive lengths of diseased trachea are involved and require resection, direct anastomosis or repair is not always possible without undue traction. Various studies have alluded to the importance of avoiding anastomotic tension, more for the fear of repair dehiscence, but also in view of avoiding an unstable healing ground that could lead to granulation tissue. Recommendations have been made as to the maximum safe length of diseased trachea that can be excised and still permit direct end-to-end anastomosis. Despite this, granulation tissue and recurrent airway stenosis have not been entirely prevented. Also, multiple repair techniques with interposition of bridging material exist, as well as total replacement of the major airway by autografts or prostheses that remove any source of anastomotic tension, without any effect on the avoidance of granulation tissue. Clearly, this surgical axiom is valid and should be applied, but it has to date not solved the problem of preventing granulation tissue.
A hypothesis common to all surgical disciplines relates to the importance of an adequate vascularization and the related supply and demand balance with regards to hemoglobin/oxygen transport capacity. Multiple efforts have been directed towards macroscopic conservation of the arterial pedicles during tracheal surgery, others towards enhancement of the preexisting vessels by omental wrapping, and more recently, by attempts at increasing microscopic blood vessels, either in number or by local vasodilation. Macroscopic preservation of major feeding vessels has yielded good results and is intuitively applied as a surgical principle by all physicians involved with this disease. However, its application with regards to prevention of granulation tissue has not eradicated the problem. As such, the microvascular hypothesis appears a more attractive one and represents the one target that is more easily approached and/or attained, which can be clinically relevant and reproducible if successful. Testing the microvascular hypothesis, namely the influence of increased vascularity by capillary vasodilation and de novo angiogenesis at a tissue level, and its potential beneficial effect on tracheal wall healing, will form the bulk of the experimental chapters in this thesis.

A case of congenital tracheal stenosis associated with a pulmonary arterial sling malformation, the two prime causes of congenital narrowing of the airway, known as the ring/sling complex, will be described (Chapter 2a) to set the basis for lesion description and the multidisciplinary approach. The diagnostic workup for congenital tracheal stenosis can be very simple, but must be complete in its full description of the anatomy, which may radically change the surgical or interventional options. In complex cases, extensive surgery with extracorporeal circulatory support may be necessary and requires careful preoperative planning to avoid fundamental pitfalls that may preclude patient survival. The multidisciplinary nature of treatment is crucial to implicate, as management issues pertaining to postoperative care may involve not only the cardiothoracic surgical team, but also specialists ranging from otolaryngologists performing bronchoscopy and intraluminal debridement, to interventional radiologists and the adjunct of intraluminal stenting (Chapter 2a).

This will be followed by a clinical illustration of an extreme surgical technique used in a bail out situation to repair long-segment congenital tracheal stenosis (Chapter 2b). It will cover the various available surgical solutions and repair materials, and will underline the importance of a thorough preoperative investigation that should be kept in mind by all clinicians caring for these difficult patients.

A brief historical overview of the surgical treatment of congenital tracheal stenosis is presented: Until the early 1980s, reports of congenital tracheal stenosis invariably described dismal survival,
and Benjamin et al. reported a 43% mortality when reviewing medical management of this disease. Kimura et al performed the first successful operation for tracheal stenosis from complete tracheal rings in 1982, using a rib cartilage graft as an anterior tracheoplasty graft. Following the successful experimental canine model of Bryant et al. in 1964, Idriss et al. reported a successful series of autologous pericardial patch repair in 1984. Their innovation in tracheal repair used the adjunct of cardiopulmonary bypass (CPB), which freed the surgical field of cumbersome ventilation cannulae, thus allowing a more precise repair. Hospital mortality after pericardial patch repair currently ranges from 6.7% -8.3%. The reoperation rate after this procedure is reported between 0-25%. In 1989, Jonas et al performed tracheal repair by resection and end-to-end anastomosis, in a patient with concomitant pulmonary artery sling. Resection with end-to-end anastomosis has the lowest surgical mortality in the literature, reported between 0-8%. However, this reflects less extensive disease, corresponding most often to lesser symptomatology. Furthermore, even after extensive mobilization of the trachea and adjacent structures, maximally to reduce tension on the future anastomotic line, this technique is judged optimal when eight or less tracheal rings are involved, and cannot be applied to patients with long segment disease. In 1989, Tsang and Goldstraw introduced the slide tracheoplasty technique, which involves an oblique transection through the diseased tracheal portion, and a subsequent oblique anastomosis, resulting in a trachea which is half as long and has four times the luminal diameter. The most recent reconstruction technique was introduced by the group at Children’s Memorial in Chicago, namely the autograft technique, first performed in 1996. The reported early surgical mortality combined with late death from autograft failure is 13.3%.

A classification of the most common congenital vascular malformations responsible for symptomatic and/or structural airway disease will be outlined (Chapter 3a), with emphasis on the diagnostic algorithm thereto related, and the surgical techniques and results which lead to the expected successful outcome of this otherwise potentially fatal disease. This will be followed by a clinical description of a rare vascular ring, which illustrates the additional caution the surgeon must entertain so as to push the diagnostic imagery as far as necessary, until the certainty is reached that will allow for the correct surgical approach (Chapter 3b).

The surgical treatment of congenital vascular malformations that create narrowing of the airway has evolved little in the last decades. The techniques have long been standardized and the results are excellent, not only in terms of operative mortality, but also in minimal postoperative morbidity and normal long-term functional status of the airway and lungs.
Chapter 1

The association of intracardiac anomalies and congenital diseases of the airway will be illustrated (Chapter 4), with a first glimpse at more alternative approaches to palliation/treatment of the tracheo-bronchial tree with intraluminal stenting.

Surgery may not always be an option in the management of airway stenosis, or at least may not resolve the problem completely and/or durably. In the first instance, anatomical lesions of the carina and distally are very difficult to access, and may preclude a surgical approach, or make the probability of restenosis higher, owing to extrinsic compression by surrounding mediastinal structures. Secondly, generalized poor condition of the patient, such as sepsis, bleeding disorders, or intrinsic trachea-bronchomalacia, may contraindicate a surgical solution. Also, in the setting of reoperation, difficulties may be anticipated that may highly discourage a second repair in the same area, such as extensive adhesions, lack of reconstruction materials, or lack of remaining tracheal length to allow for mobilization and repeat repair. The advent of interventional radiology with intraluminal balloononing and stent placement began in these settings, most often in desperate situations as a bail out procedure, before they were slowly introduced in the regular armamentarium in the treatment of long segment tracheal disease.

However, despite the attractiveness of a lesser invasive procedure than surgery, stenting has universally been complicated by the early troublesome onset of granulation tissue protruding into the lumen, with recurrent airway stenosis or obliteration, in as high as 100% of cases in certain series. Other complications include tracheal erosion or penetration into the great vessels with fatal hemorrhage. Lack of stent growth is an additional problem that may initially require redilation of the stent, but leads inevitably to patient-stent size mismatch, requiring extraction of the stent and major reconstruction. Efforts have been made to improve design and materials, namely with the advent of covered stents, in which protrusion of granulation tissue through the stent meshwork is hoped to be avoided by the covering layer. Other experimental animal trials have tested biodegradable stents, which are slowly absorbed by the local tracheal wall after insertion. Given the temporary relief of mechanical obstruction, intraluminal balloononing and the placement of stents are rarely indicated as a primary procedure, which could only complicate ulterior surgical repair. They are therefore preferably reserved for inoperable lesions, difficult reoperations, or in bail out situations.

The patterns of tracheal healing after surgery and measures taken to prevent postoperative granulation tissue will be studied in experimental animal models (Chapters 5 and 6). To test the microvascular hypothesis whereby improved vascularization or de novo formation of vessels
may improve healing and perhaps reduce granulation tissue, an angiogenic factor, vascular endothelial growth factor (VEGF), will be used topically during surgery. Furthermore, the different reconstruction materials commonly used in clinical practice will be studied, with or without topical VEGF pretreatment, to compare the relative healing patterns amongst them. Beyond the mechanical aspects of relieving obstruction, attempts to improve surgical results have focused on enhanced healing of the repair, at the site of tissue disruption, notably the loss of continuity of the specialized respiratory epithelium. Meticulous surgical technique aimed at minimizing surgical trauma, improvements in suture material, and postoperative care protocols for the airway have all contributed to better general results. However, the healing process of a traumatized airway wall is hampered by troublesome granulation tissue, which consists of an exaggerated healing response, formed after excessive inflammation, edema, and resultant fibrous ingrowth into the lumen. Granulation tissue typically originates at the site of epithelial disruption, and may progress to recurrent stenosis or even occlusion of the airway, thus undoing what would otherwise be a perfect technical repair. It would seem attractive to influence this abnormal healing mechanism by exogenous systemic or topical agents, that increase the local tissue hemoglobin/oxygen transport capacity by increased vascularization, either through vasodilation of preexisting vessels, or by angiogenesis. There are multiple vasoactive substances, some vasodilators, others angiogenic, whose list is steadily increasing, and that could influence the local vascular supply and demand balance. The newer interest and focus has been to apply substances that do not create adverse systemic reactions, for what should be a localized problem. In this sense, the topical application of substances is attractive, and will be attempted in animal models described herein.

A fully synthetic tracheal prosthesis with a biocompatible inner lining will be tested in an experimental rabbit model (Chapter 7), with attention to the potential for epithelial growth over the lining, and its potential for clinical use.

In extreme cases where the segment of diseased trachea is so long that primary or patch repair is not feasible, alternative replacement of the airway has been attempted with allograft tissue. In 1996, Jacobs, et al. used cadaveric tracheal homograft to reconstruct long-segment complete tracheal rings. The worldwide experience in 31 children was reported in 1999 at a follow-up ranging from 5 months to 14 years, with an 84% survival rate, and only one child requiring a tracheostomy. Encouragingly, the tracheal homografts were epithelialized, and hence speculatively should allow for continued long-term survival and minimal morbidity. However, these grafts are rare and remain expensive, are flacid and require prolonged
intraluminal stenting when longer portions have been implanted, and do not grow, a problem common to all prosthetic devices. Modifying the chemical or cryopreservation techniques may be an important path towards attaining a more rigid graft and the avoidance of stenting. Other experiences with allograft tissue have been obtained with aortic homografts as tracheal substitutes. Although these have been used mostly as patch repairs or in short segment replacements with encouraging results, their use in reconstruction of longer diseased tracheal segments is also limited by the lack of intrinsic rigidity, and the need for initial intraluminal stenting until the graft solidifies. When surgical repair or replacement with allograft tissue is not feasible, fully prosthetic substitutes may be considered. Efforts to find an optimal prosthesis are ongoing, and date back to a century. The list of various synthetic materials and their respective applications in animal experiments and even in clinical trials is a long one, and will not be presented herein.

In general, the ideal prosthesis should:

- stand the test of time
- grow or allow for patient somatic growth
- resist infection
- be biocompatible to avoid rejection phenomena
- be non-carcinogenic
- be flexible to avoid erosion into adjacent structures
- be sturdy enough to avoid collapse
- be air and waterproof
- allow for overgrowth of functional respiratory epithelium

To date, no fully prosthetic trachea fulfills all of these requirements, and both experimental and clinical trials have been relatively disappointing.

Finally, the discussion of Chapter 8 will try to give an overview on the development of newer biodegradable tracheal substitutes, using molecular and computer technology, and entertains the future prospects of bioengineering in the treatment of airway diseases in general.
Introduction

Outline of the Thesis

The main purpose of this thesis was to attempt to improve the intra and postoperative course of children with spontaneous narrowing of the major airway, either after tracheal surgery, after treatment of vascular abnormalities with extrinsic compression of the airway, or after intraluminal stenting as a bailout procedure.

The thesis is divided in three parts: the first, Chapter 2, describes the anatomy, diagnostic work-up, and therapeutic possibilities in a multidisciplinary setting, to treat long-segment congenital tracheal stenosis; the second, Chapter 3, deals with congenital vascular rings and the excellent surgical results with regards to relief of major airway narrowing. Chapter 4 is an intermediate part linking the clinical aspects described in Chapters 2 and 3, with the last part of the thesis, which is experimental. It describes the relative common association of certain intracardiac defects with narrowing of the airway, along with the description of concomitant intracardiac repair with the newer therapeutic adjunct of intraluminal stenting. Chapters 5, 6 and 7 make up the third part of the thesis, which attempts to explain the various potential etiologies of the post-operative recurrence of airway narrowing, despite initial surgical success, due to granulation tissue, an exaggerated scar tissue. These Chapters use an experimental animal model to test one hypothesis in the prevention of granulation tissue formation, namely the microvascular hypothesis, and seek potential ways to achieve perfect healing by promoting epithelialization of the airway lumen. Chapter 7 mainly discusses alternatives to tracheal reconstruction, and tests a new tracheal prosthesis with regards to its potential to support a living respiratory epithelial covering.

Finally, a summary and conclusions comment on the possible futures of airway reconstruction or replacement, followed by acknowledgements, a short curriculum of the author, and a list of publications.

References


