A new endoscopic standardized grading system for macroscopic central airway complications following lung transplantation: the MDS classification

Hervé Dutau\(^{a,b,c}\), Thomas Vandemoortele\(^{d}\), Sophie Laroumagne\(^{a,b}\), Carine Gomez\(^{e}\), Véronique Boussaoud\(^{c,f}\), Arnaud Cavailles\(^{b,c}\), Laurent Cellerin\(^{a,b}\), Arlette Colchen\(^{a,b}\), Tristan Degot\(^{a,b,c,i}\), François Goni\(^{b,c,h}\), Christophe Hermant\(^{a,j}\), Jacques Jougnot\(^{c,h}\), Romain Kessler\(^{c,i}\), François Phili\(^{a,c,l}\), Christophe Pison\(^{b,c,m}\), Christel Saint Raymond\(^{c,m}\), Delphine Wermert\(^{c,n}\), Philippe Astoul\(^{b}\), Pascal Thomas\(^{c,o}\), Martine Reynaud-Gaubert\(^{c,e}\) and Jean-Michel Vergnon\(^{b,p}\)\

Abstract

OBJECTIVES: After lung transplant, between 9 and 13% of bronchial anastomoses develop complications severe enough to warrant therapeutic intervention. These complications include stenosis, dehiscence, granulation tissue, bronchomalacia and fistula. Most of these have already been included in a classification or another, but none of these have been universally accepted. Moreover, no grading system has integrated all of these complications. The Groupe Transplantation (GT) (Transplant Group), from the Société de Pneumologie de Langue Française (SPLF) [French Language Pulmonology Society], maintains a prospective national registry of lung transplants performed in France. The GT has mandated the Groupe d'Endoscopie de Langue Française (GELF), also from the SPLF, to develop an endoscopic classification, in order to describe the macroscopic aspect of the bronchial anastomoses, and downhill airways, using a standardized and exhaustive grading system.

METHODS: An endoscopic classification that would take into account the three major aspects of the description of bronchial anastomoses was elaborated. The first parameter is the macroscopic aspect (M), the second, the diameter (D) of the anastomosis and the third, the sutures (S) of the anastomosis. This classification was then submitted to expert bronchoscopists from nine centres, responsible for lung transplants in France, for their opinion, using a five-item questionnaire, according to the Delphi methodology.

RESULTS: After the first round of consultation, all experts (100%) agreed on Questions 1 and 4. Answers were positive for Questions 2 (59%), 3 (56.25%) and 5 (70%). A modified classification, incorporating propositions from the first round, was then submitted. This second round allowed a consensus to be reached between all experts: the MDS classification. Each parameter (M, D and S) can be classified from 0 to 3. For M and D, it is possible to determine the extent of abnormalities downhill from the anastomosis into four subgroups (a, b, c or d). For S, the localization of abnormalities can be divided between two subgroups (e and f).

CONCLUSION: The MDS classification, established by a consensus of French experts in bronchoscopy, could represent a standardized, universally acceptable system to describe central airway complications after lung transplant.

Keywords: Lung transplantation • Anastomotic complications • Bronchial stenosis • Bronchial dehiscences • Bronchomalacia • Classification
INTRODUCTION

The reported incidence of central airway complications after lung transplant varies greatly, ranging from 1.6 to 33%, with an associated mortality rate of 2–4% [1]. This can be explained by the absence of standardized definitions and of a universally accepted classification system. Risk factors for post-lung transplant complications have been reported as follows: ischaemia of the donor bronchi in the immediate postoperative period; surgical technique used; length of the donor bronchi; presence of microbial agents before the transplant in the recipient and the donor; size incompatibilities between the recipient and the donor bronchi; postoperative infections; postoperative mechanical ventilation and use of immunosuppressant agents [1–4]. However, some of these risk factors are still controversial. Improvements in transplant preservation techniques, donor/recipient screening and medical and surgical advances have allowed a reduction in the frequency of bronchial complications.

There are primarily six different types of bronchial complications after lung transplant, some of which may be the consequence or the continuation of others. According to most studies, 9–13% of bronchial anastomoses will, at some point in time, develop complications severe enough to require treatment [5, 6]. The most common being bronchial stenosis. Other complications include bronchial dehiscence, obstructive granulomas, bronchomalacia, bronchial fistulae and endobronchial infections. Most of these complications have been the subject of gradations or classifications without any of them being universally accepted. Above all, no classification integrates all of these complications into one single entity.

Through this work, we present a new standardized classification, the most exhaustive possible, which integrates all bronchial complications except for infections, the diagnosis of which is not based on macroscopic endoscopic criteria.

MATERIALS AND METHODS

Groupe Transplantation (GT), a division of the Société de Pneumologie de Langue Française (SPLF) [French Language Pulmonology Society], has a prospective national register for the follow-up of lung transplants performed in France. In order to document and add anastomotic and, more broadly, central airway complications to this register, GT asked the Groupe d’Endoscopie de Langue Française (GELF) [French Language Endoscopy Group], another division of the SPLF, to conjointly design an endoscopic tool that would enable the description of the macroscopic appearance of bronchial and central airway anastomoses in a standardized and exhaustive manner.

A classification taking into account the three major aspects required for the endoscopic description of bronchial anastomoses was thus created. The first parameter concerns the macroscopic aspect (M), the second deals with the diameter (D) of the bronchial anastomosis and the third describes the appearance of the sutures (S). Each parameter can be ranked from 0 to 3. For the M and D components, it is possible to specify the extension of the abnormalities downstream from the anastomosis into sub-classes (a–d). For the S component, the location of the abnormalities can be specified using two sub-classes (e and f).

This classification was then submitted to the opinion of experts performing lung transplants who had agreed to participate, from the 11 centres where lung transplants are realized in France. The classification was emailed to one or more physicians who perform bronchial endoscopies in the participating lung transplant centres. There were 245 lung transplants performed by these centres for the year 2011.

A questionnaire was submitted with the classification to gather their opinions, suggestions or changes.

The questionnaire contained five questions:

(i) Is the classification of bronchial anastomosis complications into three parameters relevant (MDS)?
(ii) Is the subdivision of the M component into 4 sub-groups from 0 to 3 relevant?
(iii) Is the subdivision of the D component into 4 sub-groups from 0 to 3 relevant?
(iv) Is the sub-classification of the M and D components into 4 sub-groups: A, B, C, D relevant?
(v) Is the subdivision of the S component into 4 sub-groups from 0 to 3 relevant?

and three possible answers:

(a) Yes:
(b) No:
(c) What change(s) would you recommend?

RESULTS

During the first round of consultation, all of the physicians (100%) responded favourably to Questions 1 and 4. Favourable responses were 59, 56.25 and 70%, respectively, for Questions 2, 3 and 5.

The suggestions and proposals of the experts were then analysed by the two principal investigators coordinating the study (Hervé Dutau and Jean-Michel Vergnon). A new classification proposal, including the suggested changes, was then submitted to the expert physicians.

The need to keep four divisions per parameter, however, was imposed in order not to complicate the classification and to allow identification of the stages in which therapeutic management could be common when it is used.

The second round of consultation reached a consensus among all the experts for the following classification: The MDS endoscopic standardized grading system for macroscopic central airway complications following lung transplantation (Table 1).

Figures 1–4 give some graded examples of post-lung transplantation anastomosis with or without complications.

DISCUSSION

At least four classification systems concerning post-transplantation airway complications have been published, but none of them is universally accepted [5, 7–9].

Also, these complications could be classified as early (<3 months) or late (>3 months) [10]. Extensive necrosis and dehiscence tended to occur early as a consequence of bronchial ischaemia, whereas the other complications appeared late, after bronchial healing and remodelling, such as stenosis and malacia [11].

The first classification published by Coureaud et al. [7] describes the macroscopic endoscopic appearance of bronchial anastomosis, 15 days after lung transplantation. It includes five degrees of increasing severity of which the correlation with late complications was suggested but not confirmed. This classification is very
Dehiscence.

Figure 1: (R) M0D0S0 = R: right, M0: scar tissue, D0: normal to < 33%, S0: no dehiscence and days following transplant leading to early complications such as phenomena of ischaemia and necrosis of the anastomosis in the stages of evolution after lung transplant. It takes into account the accurate at an early stage, but is no longer adapted to the later stages of evolution after lung transplant. It takes into account the phenomena of ischaemia and necrosis of the anastomosis in the days following transplant leading to early complications such as dehiscence and fistulae as well as late complications such as stenosis and malacia.

Table 1: The MDS endoscopic standardized grading system for macroscopic central airway complications following lung transplantation

<table>
<thead>
<tr>
<th>M (macroscopic aspect)</th>
<th>M0: scar tissue</th>
<th>M1: protruding cartilage</th>
<th>M2: inflammation/granulomas</th>
<th>M3: ischaemia/necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of abnormalities in regard to the anastomosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Abnormalities localized to the anastomosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Abnormalities extending from the anastomosis to the bronchus intermedius or to the extremity of the left main bronchus, without lobar involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Abnormalities extending from the anastomosis to lobar or segmental bronchi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (diameter)</td>
<td>D0: normal to a fixed reduction &lt;33%</td>
<td>D1: expiratory reduction (malacia) &gt;50%</td>
<td>D2: fixed reduction from 33 to 66%</td>
<td>D3: fixed reduction &gt;66%</td>
</tr>
<tr>
<td>Extent of abnormalities in regard to the anastomosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Abnormalities localized to the anastomosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Abnormalities extending from the anastomosis to the truncus intermedius or to the extremity of the left main bronchus, without lobar involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Abnormalities extending from the anastomosis to lobar or segmental bronchi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Abnormalities affecting the lobar and/or segmental bronchi, without anastomotic involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (sutures)</td>
<td>S0: absence of dehiscence</td>
<td>S1: limited dehiscence (&lt;25% of circumference)</td>
<td>S2: extensive dehiscence (from 25 to 50%)</td>
<td>S3: very extensive dehiscence (&gt;50%)</td>
</tr>
<tr>
<td>Localization: e: anteriorly; f: other localizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

According to Shennib and Massard [5], ischaemia is also the most significant factor, as it influences healing of the bronchial anastomosis after lung transplant. They suggested a new classification of the different stages of healing of the anastomosis at early and late stages, including five divisions (Table 2). This classification is more complete than the previous one [7], because it lists the macroscopic consequences of the phenomena of ischaemia and necrosis at an early stage, the phenomena of healing with granulation tissue and delayed consequences such as fibrotic stenosis and malacia. However, it does not take into account that some of the stages described can coexist at any given time.

Bronchial stenosis is the most common complication, with an estimated incidence between 1.6 and 32% [12–14]. It generally occurs after extensive necrosis, dehiscence and infections, particularly with aspergillus species [1]. Telestoming anastomoses are associated with a rate of stenosis around 7% [10]. However, stenoses can develop without previously documented lesions [15]. Two types of bronchial stenosis have been described: the first is located at the anastomosis, while the second type affects the bronchi distal to the anastomosis, with or without anastomotic stenosis. These distal stenoses are rare and not well documented; their incidence is estimated at 2.5–3% [13, 16, 17]. The problem is the lack of differentiation between these two types of stenosis in published studies, which does not allow distinction between their respective aetiologies and physiopathologies [10, 16]. Furthermore, it should be noted that these distal stenoses most commonly affect the bronchus intermedius [13, 14] where they can even lead to complete stenosis in nearly 2% of cases (vanishing bronchus intermedius syndrome [18]). Bronchial stenosis generally occurs between 2 and 9 months after the transplant [2, 10, 19]. Thistlethwaite et al. [9] proposed classifying airway stenosis into four types. Type 1 represents stenoses located at the anastomosis; Type 2 groups the stenoses of the anastomosis which extend to >1 cm from the anastomotic suture; Type 3 represents distal stenoses which do not involve the anastomosis; while Type 4 concerns diffuse airway stenoses (anastomotic and distal). In their study, on 22 patients with post-transplantation stenosis, 54.5% were Type 1, 22.7% were Type 2, 13.6% were Type 3 and 9.1% were Type 4.

Bronchial dehiscence represents a potentially disastrous complication associated with a high mortality [20, 21]. Dehiscence is the result of mucosal necrosis, which occurs soon after transplantation, typically between 1 and 5 weeks [22]. Necrotic changes peak early and resolve rapidly because the airways cannot remain

Figure 2: (L) M0D3aS0 = L: left, M0: scar tissue, D3a: D < 66%, localized at the anastomotic site, S0: no dehiscence.

Figure 1: (R) M0D0S0 = R: right, M0: scar tissue, D0: normal to < 33%, S0: no dehiscence.
ischaemic for a long period without either repair or dehiscence [22]. A certain degree of ischaemia and necrosis is generally the rule after transplantation, usually circumferentially at the anastomosis with possible extension to the lobar bronchi. Dehiscence can be partial or complete. The reported incidence of dehiscence is between 1 and 10% [23], and at least some degree of dehiscence was described in 24% of transplants in one study [12]. The majority of patients presenting with complete dehiscence died, secondary to severe sepsis. Dehiscence can be complicated by infections or by the formation of peribronchial abscesses. Granulation tissue can lead to a significant reduction in the bronchial calibre in >20% of patients, classically in the anastomotic area, during the months following transplant [1]. The unproven physiopathology involves excessive stimulation of the inflammation mediators and the recruitment of macrophages at the bronchial suture, a process similar to that of cheloid scars formation [1, 24]. Additionally, aspergillus infection seems to increase the problem and could lead to resistance to treatment [11].

Expiratory collapse (malacia) can be present in a generalized manner throughout the airways or at the anastomosis, where it can be associated with fixed stenosis [1]. Malacia is defined as a reduction of >50% on expiration [1]. It is important to differentiate between perianastomotic malacia and the distal, diffuse form of bronchomalacia; the latter can be associated with bronchiolitis obliterans [1]. Changes in the structure of the cartilage have been described. However, the implications of these changes are uncertain. Malacia is usually objectified within 4 months after transplant.

Chhajed et al. [8] also suggested another classification: Thickness, Extent of injury, Granulation tissue, Loose sutures, Anastomotic/airway complications (TEGLA) classification for bronchoscopic reporting of airway ischaemic injury after lung transplantaion.

### Table 2: Shennib's classification

- **(i)** No necrosis (primary healing mucosa to mucosa)
- **(ii)** Ulceration or granulation
  - (a) Mucosal ulceration (<50% of circumference)
  - (b) Mucosal ulceration (>50% of circumference)
  - (c) Mucosal granulation (<50% narrowing of airway in diameter)
  - (d) Mucosal granulation (>50% narrowing of airway in diameter)
- **(iii)** Partial-thickness necrosis
  - (a) Submucosal and cartilage necrosis (<50% of circumference)
  - (b) Submucosal and cartilage necrosis (>50% of circumference)
  - (c) Healing by granulation (<50% narrowing of diameter)
  - (d) Healing by granulation (>50% narrowing of diameter)
- **(iv)** Full-thickness necrosis
  - (a) Full-thickness necrosis (<50% of circumference)
  - (b) Full-thickness necrosis (>50% of circumference)
  - (c) Healing by granulation (<50% narrowing of diameter)
  - (d) Healing by granulation (>50% narrowing of diameter)
- **(v)** Stricture and malacia
  - (a) Fibrotic stricture (<50% narrowing of airway in diameter)
  - (b) Fibrotic stricture (>50% narrowing of airway in diameter)
  - (c) Anastomotic malacia (restricted to anastomosis and 1 cm proximal and distal to it)
  - (d) Diffuse malacia (involving all donor proximal airways)
transplantation (Fig. 5). It involves five parameters: the consequences of ischaemia on the bronchial wall (thickness), the extension of lesions on the circumference of the anastomosis and distally (extent of injury), the existence of granulation tissue (granulation tissue), the appearance of sutures (loose sutures) and anastomotic or distal complications (anastomotic/airway complications). Each parameter can be coded as absent or present. In the latter case, specifications can be made by free text. This classification is similar to ours by its exhaustiveness, since it includes immediate complications, particularly with the description of ischaemic lesions and regeneration (granulations), as well as fixed stenotic and expiratory complications (malacia) and dehiscence.

However, it does not allow a synthetic code to identify lesions found during bronchoscopy.

Fistula between the bronchial tree and the neighbouring structures after transplant are serious and complex complications, requiring a multidisciplinary management. Three types of fistula can be mentioned [1]: bronchopulmonary fistulae, bronchomediastinal fistulae and bronchovascular fistulae (broncho-aortic, broncho-cardiac and between the bronchus and the pulmonary arterial system), which are most often lethal. Fistulae are in fact the result of dehiscence and thus, we opted not to include them in our strictly endoscopic classification. Indeed, endoscopy cannot, in the majority of cases, evaluate the fistulous tract completely even if it allows orientation. Additional imaging techniques are needed to diagnose fistulae.

The four previously described classifications [5, 7–9] were very useful in the design of ours. Indeed, each one was incorporated in the MDS classification in one way or another. The M parameter of our classification is divided into four sub-classes. M0 (healed scar aspect) is considered, by the experts interviewed, to represent the normal aspect of an anastomosis. In fact, even in cases of complete re-epithelialization of the anastomosis, a scar is always visible. M1 (cartilaginous protrusion) is classically found in cases of discrepancy between the calibre of the donor and recipient bronchi leading to a telescoping anastomosis. The appearance of this type of anastomosis can give an impression of anastomotic pseudostenosis, but in these cases, the diameter of the donor bronchi should be gauged carefully, which is, in our opinion, what must be evaluated to guide therapeutic decision. In our classification, an inflammatory appearance or that of granulations is grouped into sub-division M2. In fact, granulations are the ultimate consequence of inflammatory phenomena. As such, a description of the M1 type, without repercussion in terms of diameter, generally does not require any therapeutic steps in the absence of associated infection which must be treated. In case of reduction in calibre, assessed by parameter D, an endoscopic procedure may be performed. The MDS classification is less exhaustive than the classifications of Couraud, Shennib and Chhajed to precisely describe the different types of ischaemic, ulcerative and necrotic (M3) lesions which are mostly present at an early stage. This is a deliberate choice from our part in order to keep the classification simple, but also because these details do not automatically lead to a well-coded treatment approach. In fact, most often, the presence of ischaemic or necrotic lesions, in the absence of dehiscence, results in increased endoscopic monitoring with a conservative, wait-and-see attitude. It is for that reason that the M parameter of our classification is limited to the description of ischaemic and/or necrotic aspects with the possibility of specifying its extension into a, b, c or d as in the other classifications. The presence of dehiscence associated with ischaemia/necrosis could be specified by the S parameter.

Parameter D, thanks to its four sub-classes as well as the possibility of specifying the topography from a to d, allows the integration of all types of stenosis, proximal and distal, as well as their severity in terms of reduction in calibre (Fig. 6). The creation of each sub-class of parameter D was the subject of debate among the experts interviewed for the definition of the reduction thresholds. Indeed, it appeared that the therapeutic attitude of the experts could vary rather appreciably according to the level of reduction in calibre. Reduction in calibre alone is not in itself the only factor for therapeutic decision-making. The latter is based primarily on the clinical symptoms as well as the parameters of respiratory function, in addition to the endoscopic aspect.

Regarding parameter S, the experts agreed rather unanimously on the four sub-classes but the discussion was on the location of the dehiscence. In fact, it appeared to some experts that a dehiscence of the anterior wall, with the risks of vascular fistulae, had more pejorative prognostic significance. Therefore, we decided to specify the location of the dehiscence (e = anterior and f = other locations).

The concept of increasing severity is present in this classification in all of the parameters studied. For M, the ischaemic or necrotic character seems to be the most pejorative with the risks of dehiscence or fistulation. For D and S, the increasing severity is clear in our classification.

Thus, this classification is not supposed to correlate with clinical outcomes. Its primary objective is the use of a common language to describe endoscopic findings using a synthetic code universally understandable.

However, we hope, thanks to prospective studies, to be able to determine the stages of common outcome and/or management, as in oncology with the tumor, node, metastasis (TNM) classification. In fact, some stages could lead to a more conservative attitude (monitoring in the majority of cases), other stages could require endoscopic treatment (mechanical resection, laser, thrombocoagulation, endobronchial dilatation, stent insertion etc.) and others would require surgical treatment.

At first, prospective validation of this classification is the next study that the GT and the GELF are going to conduct.
In conclusion, we believe that the MDS classification, established by a consensus of French experts, could represent a standardized, universally acceptable system of description of central airway complications after lung transplantation, thanks to its exhaustiveness and its synthetic character, as was adopted for the TNM classification in oncology.

Conflict of interest: none declared.

REFERENCES