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Pulmonary cuff dysfunction after lung transplant surgery: A systematic review of the evidence and analysis of its clinical implications

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primary graft dysfunction

BACKGROUND: Pulmonary cuff dysfunction, either due to pulmonary vein obstruction, pulmonary vein stenosis, or pulmonary vein thrombosis, is an uncommon, yet serious complication after lung transplantation. Although there have been numerous reports of its occurrence, there is little consensus regarding the hemodynamic parameters associated with its presentation and diagnostic considerations. This systematic review summarizes the evidence surrounding pulmonary cuff dysfunction after lung transplantation surgery and empirically analyzes its implications.

METHODS: Databases were examined for all articles and abstracts reporting on pulmonary cuff dysfunction. Data collected included: number of patients studied; patients' characteristics; incidences of pulmonary vein stenosis and pulmonary vein thrombosis; and timing and imaging modality utilized for diagnosis.

RESULTS: Thirty-four full-text citations were included in this review. The point prevalence of pulmonary vein stenosis and thrombosis were 1.4% and 2.5%, respectively. The peak pulmonary cuff velocity associated with dysfunction was found to be 1.59 ± 0.66 m/sec. The diameter of the dysfunctional pulmonary vein was noted to be 0.48 ± 0.20 cm. The majority of diagnoses were made in the early post-operative period using transesophageal echocardiography. Overall, 41.3% of patients (26 of 63) required emergent procedural reintervention, and 32% of patients (20 of 63) diagnosed with pulmonary cuff dysfunction died during their hospital stay.

CONCLUSIONS: This systematic review underscores the importance of identifying pulmonary cuff dysfunction after lung transplant surgery, and the usefulness of transesophageal echocardiography for detection of this complication. The clinical implications of these results warrant the further development of identification and management strategies for lung transplant patients.

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Lung transplant surgery is an intricate procedure that remains the chief last-line therapeutic option for patients with end-stage lung disease.[1] After the anastomosis of the bronchus, anastomosis of the pulmonary cuff of the donor lung (i.e., left atrial wall with the surrounding pulmonary veins)[2,3] to the wall of recipient's left atrium, and finally the pulmonary artery anastomosis are completed.[4] The patency of the pulmonary cuff and anastomosis are crucial because blockage of either component can result in allograft dysfunction and, in severe cases, hemorrhagic infarction of the pulmonary lobes.[5] This condition, known as pulmonary cuff dysfunction, can be catastrophic and may lead to graft failure, stroke, and death.[6,7]

Pulmonary cuff dysfunction is thought to be an underreported, yet serious complication that may arise after lung transplant surgery.[1,5,7] Although the incidence of pulmonary vein thrombosis in the early post-transplant period has been estimated to be approximately 15%, data on pulmonary vein stenosis is scarce.[8] The difficulties with diagnosing pulmonary cuff dysfunction stem from several factors, including: the lack of clarity surrounding the time frame in which pulmonary cuff dysfunction occurs[1]; the broad clinical presentation of patients presenting with this complication[9]; and the uncertainty surrounding the optimal diagnostic modality.[5,8−11] As a result, the timely diagnosis of pulmonary cuff dysfunction has been noted to be challenging and can often be missed. For this reason, it is likely that the true incidence of this condition is underreported.

Within the literature, there exist numerous discrepancies in the reporting and diagnostic recommendations of pulmonary cuff dysfunction.[3,12] Thus, our aim in this systematic review was to provide a comprehensive analysis of the published literature on pulmonary cuff dysfunction, specifically pulmonary vein thrombosis and pulmonary vein stenosis, after lung transplant surgery. There was a specific emphasis on the timing of diagnosis, the optimal diagnostic modality, the clinical presentation of patients, and the presenting hemodynamic parameters. The second aim of our review was to empirically analyze the implications of the evidence on the peri- and post-operative management of patients undergoing lung transplant surgery.

Methods

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[13] Studies that assessed the incidence of pulmonary vein stenosis or pulmonary vein thrombosis after lung transplantation were evaluated using a pre-designed protocol. This protocol was not registered with the International Prospective Register of Systematic Reviews.

Eligibility criteria

Clinical studies of any study design reporting on pulmonary vein stenosis or pulmonary vein thrombosis in adult patients (≥18 years of age) who had undergone single or bilateral lung transplant surgery were considered for inclusion. Studies were also considered for inclusion regardless of the timing of diagnosis of pulmonary vein stenosis or pulmonary vein thrombosis, or the diagnostic modality used. Any study that exclusively assessed pulmonary artery stenosis or pulmonary artery thrombosis was excluded. Studies were included regardless of country of publication or language of original print.

Search strategy

An evidence-based medicinal librarian (T.S.) created a systematic search strategy for the United States National Library of Medicine Database (Medline) and Excerpta Medica Database (EMBASE), from inception until September 6, 2018. The medical subject headings and keywords included in each search strategy related to pulmonary vein stenosis, pulmonary vein thrombosis, and lung transplantation. The full-search strategy for each respective database can be viewed in Appendix A. In addition, the abstracts for the following international meetings were hand-searched: Cardiac Society of Australia & New Zealand (CSANZ) (2013 to 2017) and the Society of Cardiovascular Anesthesiologists (SCA) (2014 to 2017). The reference lists of all included citations were also hand-searched to identify any additional studies that satisfied the inclusion criteria.

Selection of included studies

Two independent reviewers (N.H. and N.K.) screened the results generated from the electronic literature search. The initial screening strategy was based on the articles' title and abstract alone. Next, the full-text versions of all potentially eligible citations were retrieved. The full-text versions of all potentially eligible citations were screened again by the same 2 independent reviewers (N.H. and N.K.). The ultimate decision for a study's inclusion was based on its relevance or contribution of new information regarding pulmonary vein stenosis or thrombosis. The overall study design, level of evidence, or sample size was not considered for inclusion. In the case of disagreement between the 2 independent reviewers on inclusion of a potentially eligible citation, a third reviewer (M.E.) judged the study in question and an ultimate decision was reached by consensus. The initial agreement between the 2 independent reviewers on full-text inclusion was assessed through the calculation of an unweighted kappa (κ).

Risk of bias assessment

Risk-of-bias assessment was performed using specific critical appraisal tools varying based on study design. For any included randomized controlled trial, methodological quality was assessed using the Cochrane Collaboration's Risk of Bias questionnaire.[14] Items in this questionnaire relate to randomization, subject allocation, blinding of study investigators, loss to follow-up, and outcome data reporting.[14] Each parameter is rated on this tool as having a low, unclear, or high risk of bias.[14]

For any included observational study (i.e. cohort or case-control study), methodological quality was assessed using the Newcastle–Ottawa Scale (NOS).[15] Items in this scale relate to case selection, case–control comparability, and exposure or outcome assessment.[15] This tool uses a "star system" to denote higher quality observational studies with regard to selection, comparability of study participants, and outcome assessment. The follow criteria are assessed: case definition (1 star); representativeness of cases (1 star); control definition (1 star); control selection (1 star);

comparability of cases and controls on the basis of design or analysis (2 stars); ascertainment of exposure (1 star); same method of ascertainment (1 star); and non-response rate (1 star).[15] The NOS rating was then converted to conform to Agency for Healthcare Research & Quality standards for study quality (i.e., *poor, fair*, or *good*). A *poor* quality study earned either no or 1 star in the selection domain, no stars in the comparability domain, or no or 1 star in the outcome domain; a *fair* quality study earned 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome domain; and a *good* quality study earned 3 or 4 stars in selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome domain.[15]

A risk-of-bias assessment was not performed for any case study included in this review, given that there is no well-defined critical appraisal tool.

Data extraction

A standardized data extraction form was created and piloted by an independent reviewer (N.K.). Data extraction was then carried out in duplicate by 2 independent reviewers (N.H. and N.K.). In any case of disagreement during data extraction, a third reviewer (M.E.) assessed the data point in question and made a final decision. The data extraction form collected information regarding the following variables: author and year of publication; number of patients included in study; number of lung transplantations performed during study timeframe; lung transplant laterality; age and gender of study participants; documented cases of pulmonary vein stenosis; documented cases of pulmonary vein thrombosis; timing of diagnosis; method of diagnosis; pulmonary vein parameters, including site of occlusion, measured velocity, pressure gradient at site of stenosis or obstruction, absence or presence of turbulent flow, and diameter of vessel; and clinical outcome data, including nature of symptoms, timing of clinical presentation, documented interventions with timing, and overall mortality.

Given that the current literature describing pulmonary vein stenosis and pulmonary vein thrombosis after lung transplant surgery exists as either case reports or retrospective studies, it was expected that the primary source of data would be in textual form. As a result, for the purposes of this review, data were primarily sought from text-based results. In cases of data presented in table form, all relevant information was extracted. The corresponding authors of all included studies were contacted for additional data, when needed.

Primary and secondary outcomes

The primary outcome of this systematic review was the point prevalence of pulmonary vein stenosis or pulmonary vein thrombosis. An accurate diagnosis of pulmonary vein stenosis mandates an anatomic examination of the pulmonary vein; therefore, for the purpose of this review, pulmonary vein stenosis, if not otherwise stated, was defined as a peak pulmonary cuff velocity of ≥1 meter/second (m/sec), or a remaining functional pulmonary vein luminal diameter <0.5 cm and/or a 50% reduction in comparison to the contralateral pulmonary vein. These criteria were chosen as they represent those that are commonly reported in the literature.[16−19] Likewise, pulmonary vein thrombosis, if not otherwise stated, was defined as the discovery of thrombus obstructing normal venous flow leading to a significantly elevated pulmonary cuff velocity (≥1 m/sec) or a remaining functional pulmonary vein luminal diameter <0.5 cm and/or a 50% reduction in comparison to the contralateral pulmonary vein.[5,19] Finally, for this review, pulmonary cuff dysfunction was defined as an event that occured due to either pulmonary vein stenosis or pulmonary vein thrombosis.

The secondary outcomes of this systematic review were to evaluate: (1) the timing, and modality used, for the diagnosis of pulmonary cuff dysfunction; (2) the hemodynamic parameters associated with pulmonary cuff dysfunction, including the occlusion site, peak pulmonary cuff velocity, pulmonary vein diameter, and pressure gradient or presence of turbulent flow; (3) the clinical presentation of patients; and (4) the mortality and reintervention rates. Diagnostic times were classified as intraoperative, early post-operative, and late post-operative. An intraoperative diagnosis was defined as the discovery of pulmonary vein stenosis or pulmonary vein thrombosis in the operating room before fascial closure; an early post-operative diagnosis was defined as a diagnosis of pulmonary vein stenosis or pulmonary vein thrombosis within the first 72 hours upon arrival to the intensive care unit (ICU) after completion of lung transplantation; and a late post-operative diagnosis was defined as the discovery of pulmonary vein stenosis or pulmonary vein thrombosis after the initial 72 hours of post-operative ICU care.

Statistical analysis

For the quantitative outcomes of this review, a percent frequency with 95% confidence interval (CI) was calculated for the point prevalence/proportion of the following outcomes: pulmonary vein stenosis; pulmonary vein thrombosis; combined pulmonary cuff anastomosis dysfunction due to either stenosis or thrombosis; reintervention rate; overall mortality after diagnosis; and occurrence of post-operative hypoxemia, edema, or pulmonary hypertension.

In addition, a weighted mean with standard deviation (SD) was calculated for the reported pulmonary cuff velocities and pulmonary vein diameters across all included studies. Mean peak velocities for pulmonary cuff dysfunction were further stratified into pulmonary stenosis and pulmonary thrombosis velocities. The differences between the 2 groups were compared by calculating a weighted mean difference (WMD) with 95% CI. The difference in mean peak velocities for pulmonary cuff dysfunction were also compared for single versus bilateral lung transplant recipients using a WMD with 95% CI. For pulmonary vein diameter, a WMD with 95% CI was calculated to compare patients with pulmonary vein stenosis and pulmonary vein thrombosis. For all analyses a $p < 0.05$ was considered significant, and all tests of significance were two-tailed.

Empirical analysis

Finally, an empirical analysis of the clinical implications of diagnosed and undiagnosed pulmonary vein stenosis or thrombosis after single or bilateral lung transplant surgery was performed. The aims of this analysis were to demonstrate the need for standardized clinical guidelines and to highlight the possible need for an adjustment to anesthetic management during lung transplant surgery. Based on the findings of this analysis and the experiences described in the studies included in this review, a clinical decision tree will be created to help physicians identify and properly diagnose pulmonary cuff dysfunction after lung transplant surgery. The preceding systematic review will serve as the qualitative and quantitative evidence supporting the empirical analysis and clinical decision tree. The goal of this systematic review is to guide the theoretical portion of the empirical analysis. We further aim to interpret the potential impact of timely diagnosis of pulmonary cuff dysfunction and its overall economic implications.

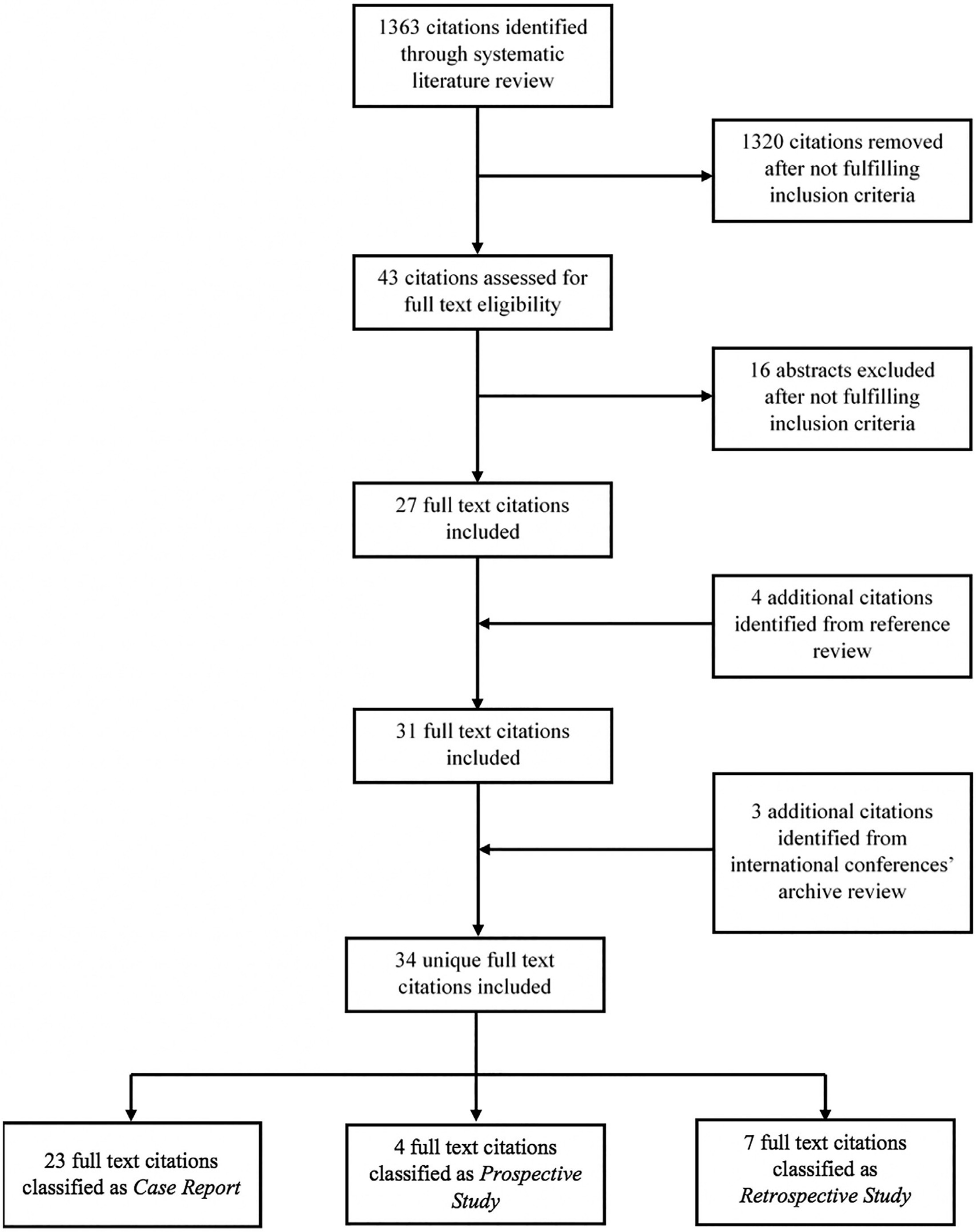

Figure 1 Study flow diagram for study inclusion.

Data management

All data analyses were calculated using SPSS version 21.0 (IBM, Armonk, NY).

Results

After the removal of any duplicate citations, the primary literature search yielded a total of 1,363 citations. Of the potentially eligible abstracts identified, 1,320 did not satisfy the inclusion criteria based on title and abstract screening alone. Thus, a total of 43 abstracts had their full-text citations retrieved for review. Of the full-text citations, a total of 16 were excluded due to the following reasons: review article ($n = 5$); evaluation of only pulmonary artery stenosis ($n = 8$); and evaluation of pulmonary vein stenosis after cardiac procedures ($n = 3$). From the primary literature search, a total of 27 full-text citations[1,5,6,8−11,19−38] were included in the review. Additional hand-searching of conference proceedings, citations of included articles, and gray literature revealed an additional 7 citations[39−45] that satisfied the inclusion criteria. Ultimately, a total of 34[1,5,6,8−11,19−46] full-text citations were included in the qualitative review. For full-text eligibility, the unweighted κ was calculated to be 0.73 between the 2 independent reviewers. A full flow diagram for study inclusion is presented in Figure 1.

Study characteristics

A total of 34 studies[1,5,6,8–11,19–46] satisfied the inclusion criteria for this review. These included 23 case reports,[1,5,6,9,10,22–25,27–30,33,35–42,44] 7 retrospective studies,[5,19,21,32,34,43,45] and 4 prospective studies.[11,20,26,31] Key study variables included: number of patients studied; patients' characteristics; outcomes analyzed; cases reported of pulmonary vein stenosis and pulmonary vein thrombosis; and timing and modality of diagnosis (Table 1).

Across all included studies, a total of 1,415 patients were included, and 1,618 lung transplants were performed. Seven hundred eighty-five patients underwent bilateral lung transplantation,[1,5,10,11,19,21–28,30–34,43,45] 21 underwent combined heart–lung transplantation,[30,31,43] and 608 underwent single lung transplantation.[5,6,8,9,19,20,26,29–44] Of the 608 patients who underwent single lung transplantation, 61 underwent right-sided lung transplantation,[6,8,19,20,26,29,30,32,33,35,37,39,43] and 57 underwent left-sided lung transplantation[5,9,19,20,26,29,30,32,33,36,38,40–44]; the laterality of the lung transplant was unspecified in 489 cases.[5,21,30,31,34,42,45] Five surgical teams reported performing the transplantation with cardiopulmonary bypass support,[6,22,23,25,35] whereas 14 surgical teams reported performing the procedure off bypass.[5,8–10,24,27,36–38,40,42–44]

Risk of bias assessment

The risk of bias assessment for the included studies in this review can be seen in Table 2. Of the 34 studies,[1,5,6,8–11,19–46] 7 were retrospective[5,19,21,32,34,43,45] and 4 were prospective[11,20,26,31] observational studies. In line with the NOS rating scale,[15] the methodology of 2 studies[20,32] was categorized as *fair,* whereas 9 studies[5,11,19,21,26,31,34,43,45] were categorized as having *good* methodology.

Prevalence of pulmonary cuff dysfunction

Of the 34 included studies in this review, 22 reported cases of pulmonary vein thrombosis,[1,10,11,20,25–32,35,40–45] and 17 studies reported cases of pulmonary vein stenosis.[5,6,9,19,21,22,29,31,33–39,42,45] Across all lung transplants performed ($n = 1,618$), a total of 22 cases of pulmonary vein stenosis[5,6,9,19,21,22,29,31,33–39,42,45] and 41 cases of pulmonary vein thrombosis[1,10,11,20,25–32,35,40–45] were reported, for a point prevalence of 1.4% (95% CI 0.8%, 2%) and 2.5% (95% CI 1.8%, 3.4%), respectively (Table 3). Overall, the proportion of patients developing pulmonary cuff dysfunction for any cause was 63 of 1,618, or 3.9% (95% CI 3.0%, 4.9%).

Diagnosis of pulmonary cuff dysfunction

The timing of diagnosis of pulmonary cuff dysfunction varied across all studies in this review (Table 3). Of the 63 reported cases of pulmonary cuff dysfunction, 10 were diagnosed in the intraoperative period[1,6,11,19,22,25,34]; 30 were diagnosed in the early post-operative period[5,8,10,20,26–28,30–32,40,42,45]; and 15 were diagnosed in the late post-operative period.[9,23,24,29–31,33,35,37–39,44] The diagnostic period was unspecified for 8 patients.[21,36,41–43] The range of timing of diagnosis was intraoperative (0 minutes)[1,6,11,19,22,25,34] to 27 months[29] post-operatively.

The method used for diagnosis also varied across all included studies. Transesophageal echocardiography (TEE) alone was employed by the majority of studies to aid in the diagnosis of pulmonary cuff dysfunction in 47 patients (Table 3).[1,5,6,8–10,19,20,22,24–32,34,41,42,45] Chest computed tomography (CCT) was used as the sole diagnostic modality in 6 patients,[35–38,40,44] followed by pulmonary angiography in 1 patient.[33] Four studies utilized 2 modalities to confirm the diagnosis of pulmonary cuff dysfunction: 2 of the studies used both TEE and CCT to diagnose 2 patients,[23,39] and the other 2 studies used TEE and transthoracic echocardiography to diagnose 3 patients.[11,21] Transthoracic echocardiography was not used as a sole diagnostic modality in any study. Two studies did not specify the diagnostic modality used to identify pulmonary cuff dysfunction.[42,43]

Hemodynamic parameters of pulmonary cuff dysfunction

Some form of quantification of pulmonary cuff dysfunction was reported by all 34 studies[1,5,6,8–11,19–45] included in this review. Specifically, descriptions of: (1) occlusion site were provided by 33 studies[1,5,6,8–11,19,20,22–45]; (2) peak pulmonary cuff velocities were provided by 12 studies[6,8,9,19,21,22,26–29,31,40]; (3) presence or absence of turbulent flow were provided by 8 studies[1,6,10,20,22,26,29,31]; (4) pressure gradients across the pulmonary vein obstruction were provided by 9 studies[5,9,10,19,22,31,35,36,38]; (5) residual pulmonary vein luminal diameter were provided by 9 studies[1,5,19,26,29–31,35,40]; and (6) residual cross-sectional area of the pulmonary vein lumen was provided by 1 study (Table 3).[36]

Occlusion site

The pulmonary cuff occlusion site was reported in 33 of the 34 studies (Table 3).[1,5,6,8–11,19,20,22–45] With regard to left-sided occlusions, the most commonly reported occlusion site was the left superior pulmonary vein, which was reported in 20 patients.[1,5,22,25,26,28–32,41] The left inferior pulmonary vein was occluded in only 6 patients.[9,23,32,36,40,42] The occlusion was reported to be at the junction of the left common pulmonary vein and the left atrium in 8 patients.[9,33,34,38,43–45]

Table 1 Study Characteristics and Outcomes Assessed

Study	Number of patients	Patients' characteristics: Gender (*n*) (M/F)	Patients' characteristics: Age (mean ± SD)	Patients' characteristics: Performance of CPB	Patients' characteristics: Type of lung transplant (*n*) (R-SLT/L-SLT/BLT/H-L)	Patients with pulmonary vein stenosis	Patients with pulmonary vein thrombosis	Timing of diagnosis: (1) intraoperative; (2) early post-operative; (3) late post-operative; (4) post-operative period, unspecified	Modality of diagnosis	Patients requiring intervention (*n*)	Mortality (*n*)
Hausmann et al 1992[32]	10	7 / 3	35.9 ± 12.6	NS	4 / 4 / 3 / 0	0	1	2	TEE	0	0
Sarsam et al 1993[42]	1	0 / 1	22	No	0 / 1 / 0 / 0	0	1	2	TEE	1	1
Yacoub et al [42]	3	NS	NS	NS	3 single	3	0	3	NS	1	3
Griffith et al 1994[45]	134	NS	NS	NS	70 SLT, 74 BLT	1	1	2	TEE	2	0
Leibowitz et al 1994[31]	21	14 / 7	44.8 ± 13.1	NS	16 SLT, 4 BLT bilateral, 1 H-L	1	5	2, 3	TEE	3	4
Clark et al 1995[33]	5	4 / 1	43 ± 8.6	NS	1 / 3 / 1 / 0	1	0	3	Pulmonary angiogram	1	5
Shah et al 1995[30]	106	NS	NS	No	1 / 1 / 0 / 0	0	2	2, 3	TEE	2	2
Medalion et al 1996[43]	10	5 / 5	45.4 ± 10.1	No	3 / 5 / 1 / 1	0	1	2	NS	NS	1
Michel-Cherqui et al 1997[19]	18	5 / 13	43.1 ± 13.6	NS	9 / 5 / 4 / 0	1	NS	1	TEE	1	2
Liguori et al 1997[29]	2	1 / 1	55 ± 7.5	NS	1 / 1 / 0 / 0	1	1	3	TEE	0	2
Nahar et al 1998[28]	2	0 / 2	42.5 ± 11.5	NS	0 / 0 / 2 / 0	0	2	2	TEE	0	0
Reilly 1998[10]	1	0 / 1	20	No	0 / 0 / 1 / 0	0	1	2	TTE, TEE	0	0
Huang et al 2000[6]	1	1 / 0	52	Yes	1 / 0 / 0 / 0	1	0	1	TEE	0	1
Boyd et al 2001[20]	18	6 / 12	50.1 ± 9.2	NS	12 / 6 / 0 / 0	0	1	2, 3	TEE	0	0
Schulman et al 2001[26]	87	50 / 37	53 ± 9.9	NS	25 / 23 / 39	0	13	2	TEE	NS	5
Nagahiro et al 2002[27]	1	0 / 1	35	No	0 / 0 / 1 / 0	0	1	3	TEE	1	0
Cywinski et al 2005[25]	1	1 / 0	31	Yes	0 / 0 / 1 / 0	0	1	1	TEE	0	0
McIlroy et al 2006[1]	3	0 / 3	42.3 ± 11.9	NS	0 / 0 / 3 / 0	0	3	1	TEE	0	0
Fadel et al 2007[8]	1	1 / 0	32	No	1 / 0 / 0 / 0	0	1	2	TEE	1	0
Myles et al 2008[22]	1	1 / 0	22	Yes	0 / 0 / 1 / 0	1	0	1	TEE	0	0
Uhlmann et al 2009[24]	1	1 / 0	31	No	0 / 0 / 1 / 0	0	1	3	TEE	0	0
Zimmermann et al 2009[37]	1	0 / 1	42	No	1 / 0 / 0 / 0	1	0	3	CT scan	1	0
Gonzalez-Fernandez et al 2009[5]	132	37 / 95	52.4 ± 12.0	No	0 / 2 / 82 / 0 (48 unspecified SLT)	2	0	2	TEE, pulmonary angiogram	2	2
Pazos-Lopez et al 2010[9]	1	1 / 0	31	No	0 / 1 / 0 / 0	1	0	3	TEE, CT scan	0	0
Felten et al 2012[11]	18	7 / 11	36.1 ± 13.4	NS	0 / 0 / 18 / 0	0	1	1	TEE, TTE	NS	NS
Loyalka et al 2012[36]	1	0 / 1	56	No	0 / 1 / 0 / 0	1	0	4	CT scan	1	0
Mydin et al 2012[35]	1	0 / 1	62	Yes	1 / 0 / 0 / 0	1	0	3	TEE, CT scan	1	1
Hillier et al 2013[21]	108	NS	NS	NS	5 SLT, 103 BLT	2	0	4	TTE, TEE	NS	NS
Siddique et al 2013[34]	720	334 / 386	NS	NS	289 SLT, 431 BLT	2	0	1	TEE	0	3
McCall et al 2014[41]	1	0 / 1	54	NS	0 / 1 / 0 / 0	0	1	4	TEE	1	NS

(*continued on next page*)

Table 1 (*Continued*)

Study	Number of patients	Patients' characteristics: Gender (*n*) (M/F)	Age (mean ± SD)	Performance of CPB	Type of lung transplant (*n*) (R-SLT/L-SLT/BLT/H-L)	Patients with pulmonary vein stenosis	Patients with pulmonary vein thrombosis	Timing of diagnosis: (1) intraoperative; (2) early post-operative; (3) late post-operative; (4) post-operative period, unspecified	Modality of diagnosis	Patients requiring intervention (*n*)	Mortality (*n*)
Weder et al 2015[44]	1	1 / 0	66	No	0 / 1 / 0 / 0	0	1	3	CT scan	1	0
Denton et al 201623	1	0 / 1	64	Yes	0 / 0 / 1 / 0	0	1	3	TEE, CT scan	1	0
Daly et al 2017[40]	1	0 / 1	41	No	0 / 1 / 0 / 0	0	1	2	CT scan	1	0
Jobanputra et al 2017[38]	1	1 / 0	60	No	0 / 1 / 0 / 0	1	0	3	CT scan	1	0
Lonial et al 2017[39]	1	1 / 0	64	NS	1 / 0 / 0 / 0	1	0	3	TEE, CT scan	1	0

CT, computed tomography; NS, not specified; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

Table 2 Risk of Bias Assessment

Study	Selection: Case definition[a]	Case representative[a]	Control selection[a]	Control definition[a]	Comparability: Case/control comparability[b]	Outcome: Ascertainment[a]	Same method[a]	<10% lost to follow-up[a]	Study quality[c]
Hausmann et al 1992[32]	★	N/A	N/A	★	★	N/A	★	★	Fair
Griffith et al 1994[45]	★	★	N/A	★	★	N/A	★	★	Good
Leibowitz et al 1994[31]	★	★	N/A	★	★★	★	★	★	Good
Medalion et al 1996[43]	★	★	N/A	★	★★	★	★	★	Good
Michel-Cherqui et al 1997[19]	★	★	N/A	★	★	N/A	★	★	Good
Boyd et al 2001[20]	★	N/A	N/A	★	★	★	★	★	Fair
Schulman et al 2001[26]	★	★	N/A	★	★	★	★	★	Good
Gonzalez-Fernandez et al 2009[5]	★	★	N/A	★	★	N/A	★	★	Good
Felten et al 2012[11]	★	★	N/A	★	★★	N/A	★	★	Good
Hillier et al 2013[21]	★	★	N/A	★	★	N/A	★	★	Good
Siddique et al 2013[34]	★	★	N/A	★	★	N/A	★	★	Good

CT, computed tomography; N/A, not applicable; NS, not specified; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

[a]One ★ maximum.

[b]Two ★ maximum.

[c]Conversion from the Newcastle–Ottawa Scale to study quality (good, fair, and poor) per the Agency for Healthcare Research & Quality standards: 15 Good quality, 3 or 4 ★ in selection domain AND 1 or 2 ★ in comparability domain AND 2 or 3 ★ in outcome domain; Fair quality, 2 ★ in selection domain AND 1 or 2 ★ in comparability domain AND 2 or 3 ★ in outcome domain; Poor quality, 0 or 1 ★ in selection domain OR 0 ★ in comparability domain OR 0 or 1 ★ in outcome domain.

Table 3 Pulmonary Cuff Dysfunction Characteristics

Study	Occlusion site(s)	Pulmonary vein cuff velocity (m/s) (mean ± SD)		Pulmonary vein diameter (cm) (mean ± SD)		Pulmonary vein surface area (cm^2) (mean ± SD)		Pulmonary vein pressure gradient (mm Hg) (mean ± SD)		Presence of turbulent flow (yes/no)	Clinical symptoms reported: (1) dyspnea and hypoxemia; (2) pulmonary edema; (3) hypotension; (4) other	Reintervention required: (1) anastomosis revision; (2) stent placement; (3) thrombectomy; (4) lobectomy; (5) other
		Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side			
Hausmann et al 1992[32]	LUPV, LLPV	—	—	—	—	—	—	—	—	—	2	—
Sarsam et al 1993[42]	LLPV	—	—	—	—	—	—	—	—	—	1, 2	4, 5
Yacoub et al [42]	NS	—	—	—	—	—	—	—	—	—	—	—
Griffith et al 1994[45]	LAA, RAA	—	—	—	—	—	—	—	—	—	2	1, 3
Leibowitz et al 1994[31]	LUPV, RUPV, RLPV	—	—	0.79 ± 0.03	0.32 ± 0.36	—	—	8	12	—	1, 4	3, 5
Clark et al 1995[33]	LPVA	—	—	—	—	—	—	—	—	—	1	2
Shah et al 1995[30]	LUPV, RUPV	—	—	25%	—	—	—	—	—	—	1, 3, 4	3
Medalion et al 1996[43]	LCPV	—	—	—	—	—	—	—	—	—	—	—
Michel-Cherqui et al 1997[19]	RSU	—	1.40	—	0.25	—	—	—	<12	—	—	1
Liguori et al 1997[29]	LUPV, RUPV	—	3.70	—	0.40	—	—	—	—	Yes	1	—
Nahar et al 1998[28]	LUPV	0.95 ± 0.05	—	—	—	—	—	—	—	—	—	—
Reilly et al 1998[10]	RUPV	—	—	—	—	—	—	—	0	No	4	—
Huang et al 2000[6]	RLPV	—	1.60	—	—	—	—	—	—	Yes	1, 3, 4	—
Boyd et al 2001[20]	RUPV	—	—	—	—	—	—	—	—	—	—	—
Schulman et al 2001[26]	LUPV, RUPV, RLPV	1.22 ± 0.23	1.33 ± 0.18	0.46 ± 0.11	0.51 ± 0.08	—	—	—	—	Yes	—	—
Nagahiro et al 2002[27]	RCPV	"Significant"	—	—	—	—	—	—	—	—	1, 4	3
Cywinski et al 2005[25]	LUPV, RCPV	—	—	—	—	—	—	—	—	—	3	—
McIlroy et al 2006[1]	LUPV	—	—	1.10	—	—	—	—	—	No	—	—
Fadel et al 2007[8]	RUPV, RLPV	—	1.80	—	—	—	—	—	—	—	1, 3	3
Myles et al 2008[22]	LUPV	2.67	—	—	—	—	—	28	—	Yes	—	1
Uhlmann et al 2009[24]	RUPV	—	—	—	—	—	—	—	—	—	4	—
Zimmermann et al 2009[37]	RUPV	—	—	—	—	—	—	—	—	—	1, 2	2
Gonzalez-Fernandez et al 2009[5]	LUPV, LLPV	1.2	—	0.60	—	—	—	6	—	—	1, 2	3
Pazos-Lopez et al 2010[9]	LCPV	—	—	—	—	—	—	25	—	—	1	2
Felten et al 2012[11]	RUPV	—	—	—	—	—	—	—	—	—	—	—
Loyalka et al 2012[36]	LLPV	—	—	—	—	0.17	—	8	—	—	1	2
Mydin et al 2012[35]	RLPV	—	—	—	0.20	—	—	—	7	—	1	2

(continued on next page)

Table 3 (*Continued*)

Study	Occlusion site(s)	Pulmonary vein cuff velocity (m/s) (mean ± SD)		Pulmonary vein diameter (cm) (mean ± SD)		Pulmonary vein surface area (cm^2) (mean ± SD)		Pulmonary vein pressure gradient (mm Hg) (mean ± SD)		Presence of turbulent flow (yes/no)	Clinical symptoms reported: (1) dyspnea and hypoxemia; (2) pulmonary edema; (3) hypotension; (4) other	Reintervention required: (1) anastomosis revision; (2) stent placement; (3) thrombectomy; (4) lobectomy; (5) other
		Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side			
Hillier et al 2013[21]	NS	2.00 ± 0.20	—	—	—	—	—	—	—	—	—	—
Siddique et al 2013[34]	LCPV, RCPV	—	—	—	—	—	—	"Significant"	"Significant"	—	—	1
McCall et al 2014[41]	LUPV	—	—	—	—	—	—	—	—	—	1, 3, 4	3
Weder et al 2015[44]	LAA	—	—	—	—	—	—	—	—	—	1	3
Denton et al 2016[23]	LLPV, RUPV	2.20	—	—	—	—	—	—	—	—	1, 2, 3, 4	3
Daly et al 2017[40]	LLPV	0	—	—	—	—	—	—	—	—	1, 2	3
Jobanputra et al 2017[38]	LCPV	—	—	0.55	—	—	—	—	16	—	1, 4	2
Lonial et al 2017[39]	RUPV, RLPV	—	—	—	—	—	—	—	—	—	1, 2	2

LCPV, left common pulmonary vein; LUPV, left upper pulmonary vein; LLPV, left lower pulmonary vein; NS, not specified; RCPV, right common pulmonary vein; RLPV, right lower pulmonary vein; RSU, right-side unspecified; RUPV, right upper pulmonary vein.

With regard to right-sided occlusions, the most commonly reported occlusion site was of the right superior pulmonary vein, which was reported in 20 patients.[8,10,11,20,23,24,26,29,31,39] The right inferior pulmonary vein was occluded in only 7 patients.[6,8,26,30,31,35,39] The occlusion was reported to be at the junction of the right common pulmonary vein and the left atrium in 6 patients.[27,32–34,39,45] One patient[19] had stenosis of the right-sided pulmonary cuff, but further details on occlusion site were not provided in the study.

Peak pulmonary cuff velocities

Peak velocities across the pulmonary cuff were reported by 13 of the 34 studies[6,8,9,19,21–23,26–29,31,40]; 12 of these studies reported numerical values of peak pulmonary cuff velocities,[6,8,9,19,21–23,26,28,29,31,40] whereas 1 study noted an unspecified "significant increase in inflow velocity" in 1 patient (Table 3).[27] Pulmonary cuff velocities were only acquired when TEE was used as the diagnostic modality by the included studies.[6,8,9,19,21,22,26–29,31,40] Collectively, pulmonary cuff velocities coinciding with pulmonary cuff dysfunction ranged from 0.9 m/sec[26,28] to 3.7 m/sec,[29] with a weighted mean of 1.59 ± 0.66 m/sec. In stratifying these data based on pulmonary vein stenosis vs pulmonary vein thrombosis, the peak pulmonary cuff velocities associated with pulmonary vein stenosis ranged from 1.2 m/sec[5] to 3.7 m/sec,[29] with a weighted mean of 2.08 ± 0.86 m/sec,[5,6,19,21,22,29] and for pulmonary vein thrombosis from 0.9 m/sec[26,28] to 2.2 m/sec,[23] with a weighted mean of 1.32 ± 0.33 m/sec.[8,23,26,28] In comparing both these groups, patients with pulmonary vein stenosis were found to have a significantly higher peak pulmonary cuff velocity by a WMD [95% CI] of 0.76 m/sec [0.10, 1.42] (p=0.02).

When comparing the peak pulmonary cuff velocities after single lung transplantation vs bilateral lung transplantation, the range was noted to be 1.1 m/sec[26] to 3.7 m/sec[29] and 0.9 m/sec[26,28] to 2.67 m/sec,[22] respectively. For single lung transplantation specifically, the weighted mean pulmonary cuff velocity was found to be 1.55 ± 0.66 m/sec. In contrast, for bilateral lung transplantation, the weighted mean pulmonary cuff velocity was noted to be 1.53 ± 0.84 m/sec. This difference was not found to be statistically significant (WMD 0.19 m/sec, 95% CI −0.91, 0.95) (p = 0.97).

Three instances of pulmonary cuff velocities of 0 m/sec, all measured after a single lung transplant surgery, were representative of a complete occlusion of the pulmonary cuff.[8,31,40]

Pulmonary vein diameter

A pulmonary vein diameter of <0.5 cm, or a >50% reduction in pulmonary vein luminal diameter in comparison to the contralateral pulmonary vein, may be indicative of pulmonary vein stenosis or thrombosis.[19] Six patients[5,19,29,31,35] were reported to have a diminished pulmonary vein diameter due to pulmonary vein stenosis; in contrast, 21 patients were reported to have a diminished diameter due to thrombus formation at the anastomotic suture lines (Table 3).[1,26,30,31,40] One study reported narrowing of the pulmonary vein as a 75% reduction in luminal diameter.[30] Overall, the luminal diameter of the compromised pulmonary vein ranged from 0 cm[30,31,40] to 1.2 cm,[31] with a mean of 0.48 ± 0.20 cm. In stratifying the data, for pulmonary vein stenosis the diameter ranged from 0 to 0.6 cm, with a mean of 0.33 ± 0.22 cm. In contrast, for pulmonary vein thrombosis, the diameter ranged from 0 to 1.1 cm, with a mean of 0.54 ± 0.18 cm. In comparing both these groups, patients with pulmonary vein thrombosis were found to have a significantly larger pulmonary vein diameter by a WMD [95% CI] of 0.21 cm [0.02, 0.40] (p=0.03). A discrete pulmonary vein diameter was acquired in the majority of patients (n=26) using TEE[1,5,19,26,29,35] CCT was only utilized to evaluate pulmonary diameter in 5 patients.[35,36,38]

Pressure gradient and turbulent flow across the pulmonary cuff

Nine studies, comprising 10 patients,[5,9,10,19,22,31,35,36,38] provided a measured pressure gradient across the obstructed pulmonary cuff, and 1 study[34] noted an unspecified "significant gradient" in 1 patient (Table 3). Pressure gradients across the compromised pulmonary cuff ranged from 0 mm Hg[10] to 28 mm Hg.[22] A pressure gradient of 0 mm Hg corresponded to a complete blockage of the pulmonary cuff.[10] A measured pressure gradient across the pulmonary cuff anastomosis was acquired in 7 patients by TEE.[5,9,10,19,22,31] In contrast, a multipurpose guide catheter was used in 3 patients[35,36,38] to measure the pressure gradient across the pulmonary cuff.

Eight studies,[1,6,10,20,22,26,29,31] comprising 19 patients, reported the presence or absence of turbulent flow across the dysfunctional pulmonary cuff (Table 3). All 8 studies evaluated for turbulent flow using TEE's color flow Doppler function.[1,6,10,20,22,26,29,31] Five studies,[6,22,26,29,31] inclusive of 16 patients, reported that turbulent flow was used as an indication of a derailment at the pulmonary cuff. In contrast, 3 studies,[1,10,20] inclusive of 3 patients, did not report viewing any turbulent flow despite the presence of a thrombus.

Clinical presentation and symptoms of patients

With 24 of the 34 studies[5,6,8−10,23−25,27,29−33,35−42,44,45] having made the diagnosis of pulmonary cuff dysfunction during the post-operative period, clinicians relied on patient symptoms to advise them on further care. The most commonly reported clinical symptoms and signs of pulmonary cuff dysfunction included dyspnea and hypoxemia (21 of 30 patients, proportion 70%, 95% CI 50%, 85%),[5,6,8,9,23,27,29–31,33,35–42,44] pulmonary edema (9 of 30 patients, proportion 30%, 95% CI 14%, 49%),[5,23,32,37,39,40,42,45] and systemic hypotension (8 of 30 patients, proportion 26%, 95% CI 12%, 46%) (Table 3).[5,6,8,23,25,30,41] Clinical symptoms and signs were not found to differ in patients ultimately diagnosed with pulmonary vein stenosis or pulmonary vein thrombosis.

The timing of symptom manifestation was reported for 14 patients across 11 studies.[5,9,10,23,30,31,33,35,38,40,44] Six patients[5,10,30,31,40] presented with symptoms within the time frame of the early post-operative period (i.e., within 72 hours post-operatively). In contrast, 8 patients presented with symptoms within the time frame of the late post-operative period.[9,23,30,31,33,35,38,44] The times at which symptoms began to appear in the late post-operative period ranged from 6 days to 1 year post-operatively.[9,23,30,31,33,35,38,44]

Reintervention and mortality rates

A total of 26 out of 63 patients (Proportion 41%, 95% CI 29%, 53%)[5,8,9,19,22,23,27,30,31,33−42,44,45] diagnosed with pulmonary cuff dysfunction from either pulmonary vein stenosis or thrombosis required additional procedural intervention. Specifically, patients with pulmonary vein stenosis (13 patients)[9,19,22,31,33−39,42,45] either required refashioning of the pulmonary cuff anastomosis (4 patients)[19,22,34,45]; pulmonary vein stent placement (7 patients)[9,33,35−39]; enlargement of the pulmonary cuff anastomosis with a pericardial gusset (1 patient)[42]; or thoracotomy to relieve external pressure from the pulmonary cuff anastomosis (1 patient).[31] Likewise, 13 patients with pulmonary vein thrombosis[5,8,23,27,30,31,40−42,44,45] required either thrombectomy (12 patients)[5,8,23,27,30,31,40,41,44,45] or lobectomy (1 patient).[42]

Overall, 20 of the 63 patients diagnosed with pulmonary cuff dysfunction died during their hospital stay,[5,6,26,29−31,33−35,42,43] corresponding to a mortality rate of 32% (95% CI 21%, 44%). In stratifying these data, 10 of the 22 patients diagnosed with pulmonary vein stenosis died during their hospital stay,[5,6,29,33−35,42] corresponding to a mortality rate of 45% (95% CI 24%, 68%). In contrast, 10 of the 41 patients with pulmonary vein thrombosis died during their hospital stay,[26,29−31,42,43] corresponding to a mortality rate of 24% (95% CI 12%, 40%).

Discussion

A recent editorial[3] and response[12] have highlighted the controversy regarding the estimated incidence of pulmonary cuff dysfunction after lung transplant surgery. Alongside this debate, important questions arise regarding the diagnosis and clinical implications of this complication. This systematic review is among the first and largest series investigating pulmonary cuff dysfunction after lung transplant surgery.

The main findings of this review are: (1) despite the low prevalence of pulmonary cuff dysfunction after lung transplant surgery, the condition is associated with a high mortality rate, at approximately 32%, or 1 in every 3 patients; (2) the diagnosis of pulmonary cuff dysfunction mainly occurs in the post-operative period through the use of TEE imaging; and (3) pulmonary cuff dysfunction requires reintervention in the majority of patients and requires timely detection. Our review is also the first to highlight and elucidate the hemodynamic parameters, as identified by TEE, which are associated with pulmonary cuff dysfunction. Clinically meaningful symptoms of pulmonary cuff dysfunction appear to occur when peak pulmonary cuff velocities are >1.5 m/sec or with pulmonary vein luminal diameters <0.5 cm, during or after lung transplant surgery.

Prevalence, clinical presentation, and diagnosis of pulmonary cuff dysfunction

Whether underreported[1,26,31,32] or a truly uncommon occurrence,[12,33,34] pulmonary cuff dysfunction appears to be an underrated and deadly complication after lung transplant surgery. Our systematic review has demonstrated that the prevalence of pulmonary cuff dysfunction is approximately 4% among patients undergoing lung transplant surgery, with pulmonary vein thrombosis being more prevalent than pulmonary vein stenosis, at 2.5% and 1.4%, respectively. More importantly, we found that patients with pulmonary cuff dysfunction have high mortality rates, at approximately 32%, which once again highlights the fatality of this condition if left untreated.[6] Clinically, almost 50% of cases were diagnosed, and appeared to present with symptoms, in the post-operative period. Astonishingly, only 10 of 63 cases were diagnosed intraoperatively with TEE. The discrepancy between the number of cases diagnosed intra- and post-operatively is of particular interest. First, the formation of a thrombus in the pulmonary vein may be influenced by several factors, including quality of the suture line, the presence of flow restriction, hypercoagulable conditions, endothelial injury, and fibrosis.[5] As a result, thrombus formation is likely to be delayed, and thus found in the post-operative period.[5] In contrast, the occurrence of pulmonary vein stenosis is thought to be more predictable as it may be a direct consequence of dynamic mechanical obstruction of the pulmonary cuff and less likely due to surgical technique.[5,36,45] Given this, in theory, it would be expected that more cases of stenosis would be diagnosed intraoperatively in comparison to thrombosis, but the results of this review suggest that this may not be the case. We suspect that this may have been due to the nature of diagnosis of pulmonary cuff dysfunction by the included studies, as many did not perform intraoperative TEE.[33,35−38,40,42−44] This creates the possibility that cases of pulmonary vein stenosis may have been missed and subsequently diagnosed in the post-operative period. If performed, intraoperative screening may expedite the identification of pulmonary vein stenosis.[35] Finally, the higher incidence of post-operative diagnosis could have been due to mechanical obstruction of the pulmonary cuff and anastomosis due to pathologies causing higher intrathoracic pressure after chest closure, such as pulmonary edema, bleeding, posterior chest wall thrombus, and pneumonia.[5,47]

Another important discovery is the clinical presentation of pulmonary cuff dysfunction. In our review we found that the common symptoms and clinical signs of pulmonary cuff dysfunction mimicked those of primary graft dysfunction, which include dyspnea, hypoxemia, pulmonary edema, and systemic hypotension.[9,40] As such, it may be entirely possible that patients presenting with primary graft dysfunction may have initially had undiagnosed pulmonary cuff dysfunction.[6,48] Indeed, it has been reported that in a number of cases a pulmonary venous obstruction could not be excluded as the etiology of primary graft failure.[48] As result, in patients presenting with primary graft dysfunction, clinicians should have a low threshold for conducting additional testing geared toward evaluating the pulmonary cuff, as immediate treatment may prevent progression to overt graft failure.

Hemodynamic parameters of pulmonary cuff dysfunction

Although there are no established quantitative clinical reference values associated with pulmonary cuff dysfunction,[3] the results from our review suggest that clinically meaningful symptoms of pulmonary cuff dysfunction occur when pulmonary cuff peak velocities are >1.59 m/sec, or with pulmonary vein luminal diameters <0.5 cm on TEE imaging.

A number of normal[21,49−51] or threshold[5,7,19] peak pulmonary vein velocities have been proposed in the literature, which include: (i) 0.41 m/sec in healthy volunteers[49]; (ii) 0.63 m/sec in coronary artery bypass graft surgery patients[50]; (iii) 0.69 ± 0.34 m/sec for the right pulmonary veins and 0.79 ± 0.37 m/s for the left pulmonary vein in lung transplant patients not developing pulmonary vein stenosis[21]; and (iv) 0.50 ± 0.10 m/sec for transplanted pulmonary veins in single lung transplant patients not diagnosed with pulmonary vein thrombosis.[51] With the lack of clearly defined cut-off values, clinicians may face challenges in identifying high-risk patients during lung transplant surgery. Most of the studies included in our review did not disclose a threshold value above which physicians would suspect pulmonary cuff dysfunction. To identify cases of pulmonary cuff dysfunction, our review utilized a conservative peak pulmonary cuff velocity of ≥1 m/sec to be indicative of dysfunction based on the current literature.[5,7,19] We decided to use this estimate to capture all cases of pulmonary cuff dysfunction reported in the literature; however, it is entirely possible that this may underestimate the true threshold. Indeed, we found that the mean peak pulmonary cuff velocity associated with dysfunction was 1.59 m/sec, which is 1.5 times greater than what is reported in the literature.[5,19] Although using this cut-off would reduce the sensitivity of identifying pulmonary cuff dysfunction, it is currently the only available estimate in the literature that is based on available data. Further, it is worth considering that using a ≥1m/sec peak pulmonary vein cuff velocity threshold for dysfunction may not be applicable after lung reperfusion due to the occurrence of hyperdynamic circulation in the majority of lung transplant patients.[3,5,21,49,50,52] This is particularly common in bilateral lung transplant surgery, in which elevated pulmonary cuff velocities may be recorded until the second donor lung has been implanted and reperfused.[7,52] Thus, having a higher threshold, as found by our review, may be more generalizable to lung transplant patients as a whole.

Previous studies have also reported other pulmonary vein diameter thresholds for pulmonary cuff dysfunction, which are different from those described in our review, such as (i) <0.5 to 0.75 cm,[5] (ii) 0.5 cm,[9] (iii) 0.25 cm,[6] and (iv) 50% of that of the neighboring pulmonary vein.[19] The large variation, and lack of clearly defined thresholds, again makes it difficult for clinicians to identify concerning pulmonary vein diameters. However, this also highlights the difficulties in establishing such cut-offs. For instance, when viewed categorically, our results suggest that pulmonary vein stenosis was associated with a residual luminal diameter $<0.3 \pm 0.2$ cm, whereas pulmonary vein thrombosis was associated with slightly larger residual luminal diameters, at $<0.5 \pm 0.2$ cm. Such a difference suggests that there may be a range of pulmonary vein diameters that are indicative of dysfunction. Challenges in establishing pulmonary vein diameter thresholds may also be due to the algorithm by which TEE visualizes the pulmonary vein lumen. The pulmonary veins appear elliptical on TEE due to the angle at which the ultrasound beam interrogates the pulmonary cuff.[11,19] The oblong shape may lead some anesthesiologists to overestimate the cross-sectional area of the lumen, whereas other providers are inclined to underestimate the cross-sectional of the same lumen when only considering the narrowest width of the vein.[5] To further complicate this issue, the diameter of the pulmonary vein can also be derived from color flow Doppler, which provides a "functional diameter" of the pulmonary vein. As a result, this may be an over- or underestimation of the true pulmonary vein diameter.[11,19] The current discrepancies in determining pulmonary vein diameter illustrate the need for comprehensive TEE analysis and standardized diagnostic guidelines for lung transplantation.

Site of occlusion

The current data suggest that the superior pulmonary veins are at higher risk for stenosis and/or thrombosis than the inferior pulmonary veins. The left superior pulmonary vein was at the highest risk of occlusion (59%) in comparison to the left common pulmonary vein (24%) and the left inferior pulmonary vein (18%). Similar findings were seen for right-sided occlusions, with most occurring in the right superior pulmonary vein (61%) in comparison to the right inferior pulmonary vein (21%) and right common pulmonary vein (18%). Although surgical technique may play a role in this discrepancy, the most likely cause is the difficulty in identifying the inferior pulmonary veins with TEE.[7,25] In fact, it has been hypothesized that this difficulty may be due to sub-optimal angles of interrogation of the ultrasound beam, or to the gravitational effects on the pulmonary veins, which are dependent on surgical positioning of the patient.[52] Given that TEE is highly user- and situation-dependent, many factors need to be taken into account when operating and interpreting TEE parameters.

Role of transesophageal echocardiography

Despite the number of studies on the anesthetic care for lung transplant patients, there has been limited discussion and analysis on the important role of TEE, specifically surrounding pulmonary cuff patency.[3,4,7,53,54] In the present systematic review, TEE was instrumental for diagnosis in 83% of cases of pulmonary cuff dysfunction. Further, it was the sole imaging tool in 75% of patients. Considering that surgical intervention may be needed to correct hemodynamically significant pulmonary cuff dysfunction, intraoperative monitoring with TEE deserves consideration as a standard of care to assess the pulmonary cuff.[5,7,52,53] Currently, TEE is not routinely utilized to make intraoperative assessments of pulmonary cuff function since this practice is only categorized as a Class IIb recommendation, with little evidence or expert opinion supporting its routine use.[52,55] However, when TEE is used for evaluating the pulmonary cuff, special considerations should be made. Continuous wave Doppler assessment of flow from the pulmonary cuff into the left atrium should be performed precisely, with optimal Doppler alignment, to limit the potential for underestimation of velocities and gradients across the anastomosis.[54] Color flow Doppler assessment further provides data regarding the likelihood for flow acceleration from the pulmonary veins into the left atrium.[5] Turbulent flow may exist in the presence of pulmonary cuff dysfunction, but is not specific for this condition as hyperdynamic circulation may cause flow acceleration in the pulmonary cuff.[22] As such, when turbulence is evident, more specific TEE parameters should be used to evaluate the pulmonary cuff for stenosis or thrombosis.[6,7,32] The absence of turbulence, however, does not rule out pulmonary cuff dysfunction, especially if complete obstruction from a thrombus or stenosis exists.[10,22] More importantly, these TEE measurements are best performed after the reperfusion of both lungs in double lung transplantation to avoid confounding from the iatrogenic increase in blood flow from contralateral cross-clamp application.[7]

Clinical implications and empirical analysis

The possible clinical implications of detecting pulmonary cuff dysfunction are worth noting. Our results suggest that pulmonary cuff dysfunction is associated with a high mortality rate. Evidence from the collected studies in this review suggest that the risk of patient mortality may be attenuated by the timely diagnosis and subsequent intervention in patients with pulmonary cuff dysfunction. Although delayed identification has implications in post-operative care, it remains unclear whether all cases of pulmonary vein thrombosis or pulmonary vein stenosis can even be detected and rectified intraoperatively.[5] This issue is of particular importance as delayed diagnosis and correction of pulmonary cuff anastomosis dysfunction can result in

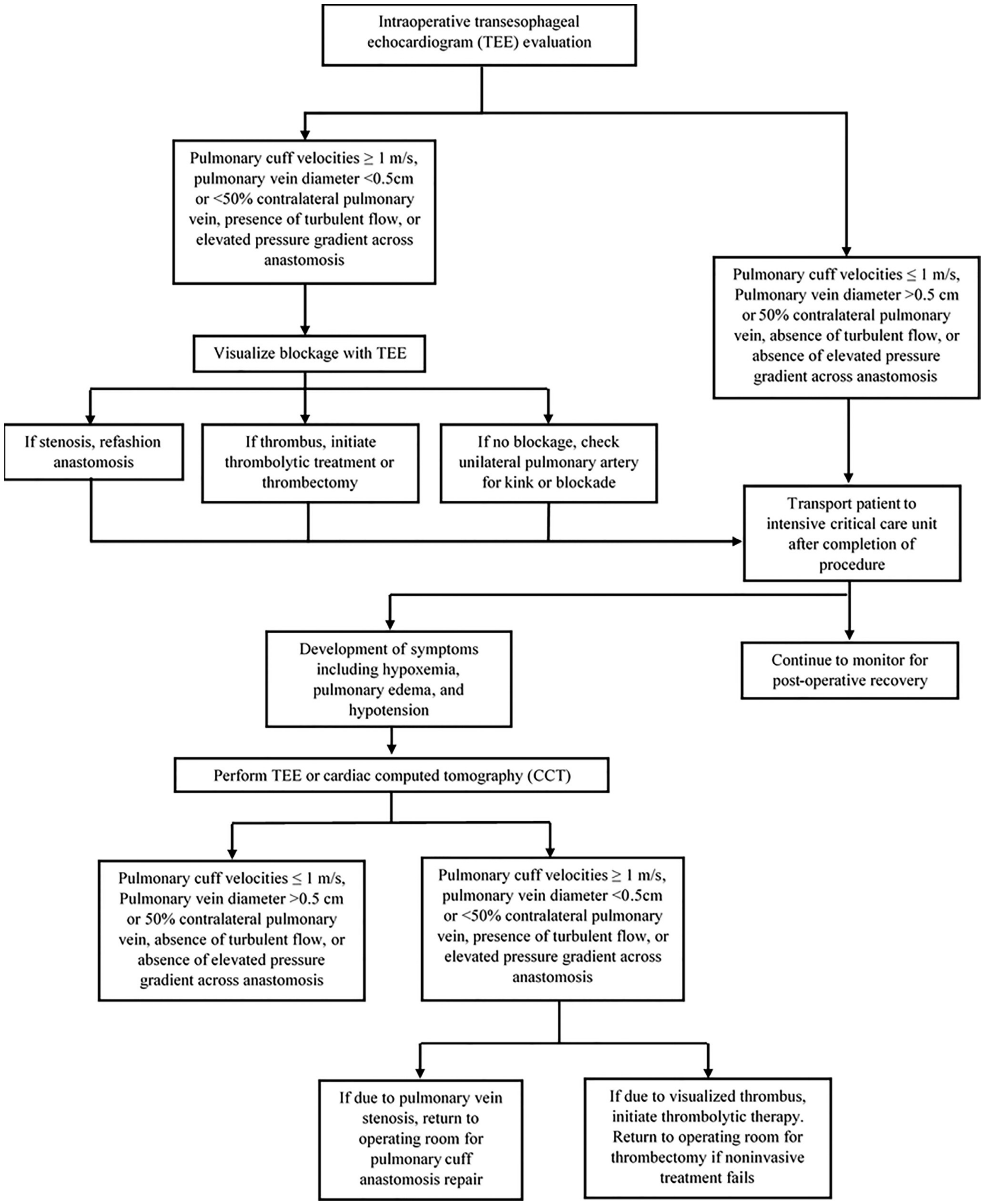

Figure 2 Intra- and post-operative clinical decision tree for physicians treating patients undergoing lung transplant surgrery who are at risk of developing pulmonary cuff dysfunction.

hemodynamic impairment and ventilatory failure, leading to several days in the ICU without adequate time to return to the operating room for reintervention.[19] The use of intraoperative TEE monitoring during lung transplant surgery may help reduce this burden. Specifically, to enable timely detection and surgical correction of pulmonary cuff dysfunction, TEE should be strongly considered during lung transplantation, not only for anastomotic assessment but also to guide hemodynamic management and fluid administration.[7,54] Although the earliest studies collected for this systematic review date back to the early 1990s,[32,42] intraoperative TEE monitoring has since been established as a standard of care in cardiothoracic surgery at a growing number of transplant centers.[3,5,6,32,52] Although CCT can diagnose pulmonary cuff dysfunction, as evidenced by this review, it has no value for intraoperative guidance.[5,52] Moreover, despite the exorbitant cost and radiation risk associated with CCT, it only provides morphologic assessments and, thus, has no utility in the hemodynamic assessment of the pulmonary cuff.[52]

Currently, no clinical recommendations exist regarding the diagnosis and treatment of pulmonary cuff dysfunction after lung transplant surgery. However, based on the findings of this systematic review, we have created a clinical decision tree to help guide practice when encountering a lung transplant patient with concerns of pulmonary cuff dysfunction (Figure 2).

Study limitations

To our knowledge, this systematic review is the first to tabulate all published reports of pulmonary cuff dysfunction after lung transplantation surgery and, as such, provides useful quantitative and qualitative data regarding pulmonary cuff dysfunction after lung transplant surgery. However, our review has some limitations that need to be addressed. Despite the usefulness of the data presented, included data was mostly from retrospective studies and case series, which inherently are lower quality evidence. Also, many of the included studies had small sample sizes, which may negatively impact the validity of our results. Another important issue is the current challenge in assessing the pulmonary cuff due to the lack of consensus on quantitative threshold parameters. Some of this difficulty can be explained by the dependency of these parameters on patient-specific factors, including cardiac output, extracorporeal support, mitral insufficiency, diastolic dysfunction, and the inability to adequately determine the diameter of the 4 pulmonary veins.[3] Thus, the topic of monitoring the patency of the pulmonary cuff with intraoperative TEE warrants further investigation. As result, the point prevalence estimates of pulmonary vein stenosis and pulmonary vein thrombosis found in our review should be employed conservatively given that they may be an overestimation of the true prevalence.

In conclusion, evidence on the topic is evolving; however, the results of our systematic review are an initial step for providing clinicians with hemodynamic parameters and diagnostic criteria that can be used to help identify patients before the development of catastrophic complications from pulmonary cuff dysfunction. Our study also suggests that TEE is of significant value and supports its routine use during lung transplantation. The clinical implications of these results warrant the further development of identification and management strategies for pulmonary cuff dysfunction in lung transplant patients.

Disclosure statement

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2019.01.005.

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