

Does the use of extended criteria donors influence early and long-term results of lung transplantation?

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Summary

A best evidence topic was constructed according to a structured protocol. The question addressed was whether the presence of extended criteria donors influences the early and long-term results in patients referred for lung transplantation. Of the 30 papers found using a report search, 14 presented the best evidence to answer the clinical question. The authors, journal, date, country of publication, study type, group studied, relevant outcomes and results of these papers are given. In total, we recorded 10 retrospective studies that considered all the donor criteria for comparing marginal donors (MDs) and standard donors. On the one hand, six of them showed no difference between the two groups in terms of early and long-term results. On the other hand, four studies demonstrated a negative impact of MDs on various early outcomes (mortality, primary graft dysfunction, duration of mechanical ventilation, length of stay in intensive care unit), whereas no significant negative influence on survival has ever been described when screening MD results. More precisely, when analysing the role of individual factors of marginality, as done in two of the 14 studies, a significant negative impact was observed for a low level of PaO₂ at the time of harvesting, positive bronchoscopy and smoking history. More specifically, the first two criteria have been validated by several authors, both in multicentre and cohort studies. Finally, the importance of avoiding the donation of the lung from an MD to a high-risk recipient emerged, whereas the association with single or bilateral transplants remains more controversial. Hence, current evidence suggests that there are no contraindications—given the absence of negative impact on survival—for the use of MDs for the transplant of a proposed standard receiver. However, given the low level of evidence of published studies, caution is necessary in order to avoid organ shortage, despite these encouraging results.

Keywords: Thoracic surgery • Lung transplantation • Extended donor criteria • Early results • Long-term results

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients undergoing lung transplantation], does receiving [routinely acceptable donor lungs], when compared with [extended criteria donor lungs], affect [mortality and morbidity]?

CLINICAL SCENARIO

You are called to assess a lung donor (58-year-old man, deceased from a spontaneous cerebral haemorrhage after 2 days in ICU), suitable for a patient aged 57, affected by pulmonary fibrosis and candidate for bilateral lung transplantation (LTx). The chest X-ray revealed a right pulmonary infiltrate. The bronchoscopy did not show the presence of bronchial secretions. The analysis of donor arterial blood gas, performed with FiO₂ = 1 and PEEP of 5 cmH₂O, revealed a value of PaO₂ of 310 mmHg.

The donor presents ABO compatibility and appropriate size match with the prospective recipient. Clinical data revealed a smoking history of 20 pack-years, and no history of malignancy, previous cardio-thoracic surgery or other systemic pathology was reported. While deciding whether to accept the proposal for LTx, we wonder if the presence of extended donor criteria could influence the early and long-term LTx results. Therefore, we decide to look up the evidence in the literature.

SEARCH STRATEGY

The extended donor criteria were defined according to the standard criteria, which are the following: age <55, clear chest radiograph, PO₂ > 300 mmHg with an FIO₂ of 100%, smoking history <20 pack-years, no evidence of aspiration, absence of chest trauma, absence of organisms in sputum and no purulent secretions on bronchoscopy.

Medline 1989–June 2011, using the OVID, Pubmed, Pascal and Cochrane interfaces, with results limited to English language articles: ('lung transplantation'[MeSH Terms]) AND ('extended criteria donor'[MeSH Terms]) OR ('marginal donors'[MeSH Terms]) AND ('early results'[MeSH Terms]) OR ('long-term results'

Table 1: Overview of the studies

Author, date, country, study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Kron <i>et al.</i> , 1993, USA [2] Prospective study (level 3)	11 MDs; period: 1990–92	Hospital survival	Nine of the ten lung transplant did well Donor pool expanded by 36%	First report in the literature; small number of patients; follow-up not specified
Sundaresan <i>et al.</i> , 1995, USA [3] Cohort study (level 3)	Study group: 44 MDs; Control group: 89 SDs; Period: 1991–94	Hospital outcomes (A-a gradient, MV duration, 30 days mortality) Survival	No differences between the groups. CPB used more frequently to implant the second lung when MDs (20 vs 13%, $P = ns$) Study group: 86.4%; control group: 83.2%; $P = ns$	Pioneer work; analysis restricted to MDs with $PO_2 < 300$ mmHg; recipient severity of illness was not considered in the analysis
Gabbay <i>et al.</i> , 1999, Australia [4] Cohort study (level 3)	Study group: 64 MDs (subgroup of 20 with initial suboptimal gas exchange); Control group: 48 SDs; Period: 1995–98	Hospital outcomes (ICU stay, PaO_2/FiO_2 at T0 and T24 h, 30-day mortality) Survival (1, 2 and 3 years)	No differences between groups. Graft ischaemic time predict the recipient PaO_2/FiO_2 ratio No differences between groups	High MD percentage (57%); large number of donors with two criteria of marginality
Bhorade <i>et al.</i> , 2000, USA [5] Cohort studies (level 3)	Study group: 52 MDs; Control group: 62 SDs; Period: 1996–99	Short-term outcomes (OR and ICU complications) Middle- and long-term outcomes (acute rejection episodes, 1-year pulmonary function and survival)	No differences between groups No differences between groups	Exclusion of SLT or HLT; first report concerning follow-up at 1 year; difference in sex recipients (>female in the MD group, $P < 0.05$)
Pierre <i>et al.</i> , 2002, Canada [6] Cohort study (level 3)	Study group: 63 MDs; Control group: 60 SDs; Period: 1997–2000	Hospital outcomes (time on CPB, 30- and 90-day mortality, PaO_2/FiO_2 in ICU, ICU length of stay)	Higher 30-day mortality (17.5 vs 6.2%, $P = 0.047$) and 90-day mortality (22.2 vs 7.7%, $P = 0.0391$) in the MD group Higher mortality associated with bronchoscopy and chest X-ray alterations RR = 1.92 for SD and NG recipients vs MD and NG recipients	High MD percentage (51%); lack of intermediate and long-term outcomes; study not adjusted for differences in recipient severity of illness
Thabut <i>et al.</i> , 2005, France [7] Multicenter retrospective study (level 3)	785 patients ($n = 270$ SLT; $n = 251$ BLT; $n = 264$ HLT)	Early graft function (best recipient PaO_2/FiO_2 ratio within the first 6 PO hours and MV duration); long-term survival	Donor gas exchange before harvest was significantly associated with recipient early gas exchange, duration of MV and survival Increase RR of death when donor PaO_2/FiO_2 before harvest < 350 mmHg (RR = 1.43; $P = 0.01$) Donor and recipient sex mismatch significantly associated with survival	Smoking history of most lung donor was not recorded; duration of MV only available in three centres (380 patients)
Lardinois <i>et al.</i> , 2005, Switzerland [8] Cohort study (level 3)	Study group: 63 MDs; Control group: 85 SDs; Period: 1992–2003	Hospital outcomes (MV duration, ICU stay, PO complications, 30-day mortality) Intermediate outcomes: spirometry at 6 months, 1-year mortality)	No differences between groups in hospital or intermediate outcomes No differences in survival when analysing the different periods or the number of MD criteria Low PO_2 level and positive bronchoscopy associated with higher risk of 30-day and 1-year mortality	First report that analyses the impact of MDs with one or more than one criteria; more female and higher age in the MD group

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Table 1: Continued

Author, date, country, study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Aigner <i>et al.</i> , 2005, Austria [9], Cohort study (level 3)	Study group: 23 MDs; Control group: 60 SDs; Period: 2001–02	Hospital outcomes (surgical procedure and complications, 30-day mortality, ICU and hospital stay) 3 Months and actuarial survival BOS incidence Lung function test after transplantation	No differences between groups in hospital or intermediate outcomes	Small sample size in the study group; introduction of inhalative drug abuse as extended criteria
Kawut <i>et al.</i> , 2005, USA [10], Cohort study (level 3)	Study group: 27 MDs; Control group: 24 SDs; Period: 2001–03	Primary endpoints: MV and ICU-free days, time to hospital discharge, spirometry at 1 year Secondary endpoints: intra-operative complications, pneumonia, sepsis and survival	Recipient of MDs had less ICU-free days ($P = 0.002$), longer time to hospital discharge ($P = 0.007$) and worsen pulmonary function (FEV1%, FEV1/FVC, FEF25–75, $P < 0.05$) at 1 year No difference in survival: 30-day survival = 96% in both group	Small sample size; eight deaths in the cohort limiting the power to detect a difference in survival
Luckraz <i>et al.</i> , 2005, UK [11], Cohort study (level 3)	Study group: 50 MDs with PO ₂ level <300 mmHg; Control group: 312 SDs with PO ₂ level >300 mmHg; Period: 1984–2001	Hospital outcomes (CPB and ischaemic time, MV duration, 30-day mortality) Infectious and rejection rate, risk of BOS 1- and 5-year survival	Recipient of MDs had higher 30-day mortality (22 vs 13%, $P = 0.08$) and a lower rejection rate after 3 months ($P = 0.05$) No differences in other outcomes between groups	Long period of analysis; higher age of the donor and lower age of the recipient in the MD group
Botha <i>et al.</i> , 2006, UK [12], Cohort study (level 3)	Study group: 83 MDs; Control group: 118 SDs; Period: 2000–2004	Hospital outcomes (ischaemic time, 30- and 90-day mortality, PGD score, A-a gradient, MV duration, ICU stay) Intermediate outcomes (survival, incidence of BOS, BOS-free survival)	Recipient of MDs had a higher rate of grade 3 PGD (43.9 vs 27.4%, $P = 0.015$), higher mean A-a gradient at 24 h (148 vs 115 mmHg, $P = 0.021$), higher 90-day organ-specific mortality (15.7 vs 5.1%, $P = 0.012$) and on BLT higher 30- and 90-day mortality No differences in other outcomes (survival, incidence of BOS, BOS-free survival) between groups	Larger number of patients; MDs with more than 1 criteria were 30%; recipient of MDs had higher mean age
Meers <i>et al.</i> , 2010, Belgium [13], Cohort study (level 3)	Study group: 27 MDs; Control group: 23 SDs; Period: 2006–07	Hospital outcomes (use of CPB, PGD, mortality, ICU and hospital stay) 1- and 2-year survival	Recipient of MDs had higher ICU stay (7 vs 4 days, $P < 0.03$) and the PGD rate at 24 h ($P < 0.04$) No differences in the other early and intermediate outcomes	Small number of patients; minority of MDs with low PO ₂ levels and more than 1 extended criteria
Berman <i>et al.</i> , 2010, UK [14], Cohort study (level 3)	Study group: 184 MDs based on smoking status; Control group: 240 non-smoking donors; Period: 1995–2008	Hospital outcomes (ICU stay, MV duration) Intermediate and long-term outcomes (3 months and 1-year survival, 3 months and 1-year chronic rejection and infectious rates)	Recipient for smoking donors had higher ICU stay (>2 days, $P = 0.004$), lower 3 months survival (13 vs 21%, $P = 0.04$), 20% higher risk of MV > 10 days ($P = ns$) No difference in rejection or infection rates	Smoking donors are older than non-smoking donors

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Table 1: Continued

Author, date, country, study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Pizanis <i>et al.</i> , 2010, Germany [15] Cohort study (level 3)	Study group: 19 MDs based on age ≥ 55 years; Control group: 186 SDs (age < 55 years); Period: 2000–08	Hospital outcomes (ischaemia time, time on CPB, initial oxygenation capacity, ICU and hospital stay, MV duration, mortality) Intermediate and long-term outcomes (spirometry at 6, 12, 36, 60 months; 1-, 3- and 5-year survival; the BOS occurrence rate after 5 years)	No significant differences in early, intermediate and long-term outcomes Spirometric function: trend towards a lower percentage from 36 months PO in the MD group	Small number of patients in the MD group; all BLT performed with CPB

A-a, alveolar arterial; BLT, bilateral lung transplantation; BOS, bronchiolitis obliterans syndrome; CPB, cardiopulmonary bypass; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF25–75, mean forced expiratory flow during the middle half of forced vital capacity; HLT, heart-lung transplantation; ICU, intensive care unit; MD, marginal donor; MV, mechanical ventilation; NG, non-guideline; OR, operating room; PGD, primary graft dysfunction; PO, post-operative; RR, relative risk; SD, standard donor; SLT, single lung transplantation.

[MeSH Terms]). Finally, a hand search was used to follow-up references from the retrieved studies.

SEARCH OUTCOME

A total of 30 abstracts were found, from which 14 papers were selected to provide the best evidence on the topic. These papers are documented in Table 1.

RESULTS

Kron [2] reported the first experience with the clinical use of extended criteria donors in LTx. The authors highlighted the lack of an increased risk of mortality. Sundaresan *et al.* [3] published the first retrospective study comparing standard donors (SDs) and marginal donors (MDs). No difference in the early outcome was found, but in the case of MDs, cardiopulmonary bypass was required more frequently. The authors only recommend the use of MDs for emphysema recipients. Gabbay *et al.* [4] reported their experiences with 112 donors (48 SDs and 64 MDs). No significant differences in gas exchange, ICU stay, early mortality and long-term survival were found. The authors observed that graft ischaemic time predicted the recipient PaO₂/FIO₂ ratio at T0 and T24 h after LTx. Comparing SDs and MDs, Bhorade *et al.* [5] found no difference in early and intermediate-term outcomes and survival. They observed a trend towards a difference in spirometry in single-marginal lung recipients. For this reason, they cautioned against the use of single lungs from MDs. The retrospective study of Pierre *et al.* [6] was the first to document a higher early mortality using MDs. The authors cautioned against the use of MDs in high-risk patients, especially recipients of advanced age. The multicentric work of Thabut *et al.* [7] evaluated the effect of donor characteristics on short- and long-term outcomes after LTx. Donor gas exchange before harvest was the only factor significantly associated with recipient early gas exchange, duration of mechanical ventilation (MV) and long-

term survival. A non-linear model showed a steep increase in the relative risk of death when donor PaO₂/FIO₂ before harvest was below 350 mmHg. Lardinois *et al.* [8] evaluated the impact of MDs over a long period. This was the first report that compared the effect of donors with multiple criteria of marginality to SDs and MDs presenting only one criterium. The authors did not find any difference in early and intermediate results when they analysed survival among the different periods of activity, or the number of MD criteria. Aigner *et al.* [9] and Kawut *et al.* [10] compared SDs and MDs during a 2-year period of time. The analysis of major outcomes in the short and the medium term did not show any differences between the groups in Aigner *et al.*'s study [9]. In contrast, significant differences between the two groups in many primary endpoints were shown in Kawut *et al.*'s study [10]. Recipients from MDs had less ICU-free days and had to remain in the hospital for a longer period of time before being discharged. Patients developed worse pulmonary function at 1 year. No differences were observed for survival. Luckraz *et al.* [11] analysed donors with low levels of PaO₂ (< 300 mmHg) in comparison to donors with normal gas exchange. They observed, in the MD group, a higher but not significant 30-day mortality rate (OR = 1.92) and a lower rejection rate after 3 months ($P = 0.05$). Botha *et al.* [12] reported their retrospective experience with 202 donors (83 MDs). Recipients of MDs had a higher mean alveolar-arterial gradient at 24 h, a higher rate of primary graft dysfunction (PGD) of grade 3, and an increased 90-day mortality caused by respiratory or multiorgan failure. Meers *et al.* [13] observed a negative impact of MDs in terms of ICU stay and the PGD rate. A smoking history or chest X-ray abnormalities were the most frequent retrieved criteria (71%). The study of Bergman [14] was based on smoking donors and their impact on LTx. Over a period of 13 years, 454 patients were included. A significant association between smoking history and lower 3 months survival, and also ICU stay for > 2 days, was found. Pizanis *et al.* [15] focused their attention on donors aged > 55 , in comparison to younger donors. No significant impact on early, intermediate and long-term results was observed.

CLINICAL BOTTOM LINE

On the whole, we recorded 10 papers that considered all the donor criteria for comparing MDs and SDs. On the one hand, six studies showed no difference between MDs and SDs in terms of early and long-term results. On the other hand, four studies observed a negative impact of MDs on various early outcomes (mortality, PGD, MV length and ICU stay), while no significant influence on survival was described. When analysing the role of individual factors of marginality, a negative impact was observed for a low level of PaO₂ at harvesting, positive bronchoscopy and smoking history. The first two criteria have been validated by several authors, both in multicentre and cohort studies. Finally, the importance of avoiding the donation of the lung from an MD to a high-risk recipient emerged, while the association with single or bilateral transplants remains more controversial. Hence, the current evidence shows that there are no contraindications for the use of MDs for the transplantation of a proposed standard receiver.

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