Lung donors selection criteria: a review

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Lung transplantation has had increasing success worldwide and it became an acceptable treatment modality in end-stage pulmonary diseases. The insufficient supply of donor lungs, resulting in prolonged waiting time, and the significant rise of patients on the waiting list, have forced the most experienced transplantation centers to redefine the acceptable lung donor criteria including marginal allografts. Existing standard lung donor criteria have been established in the first period of lung transplantation activity, based mainly on opinions and individual experiences rather than on existing evidences: the paucity of donors may be also explained by the rigid application of these criteria. The quality of donor organs has a significant impact on early and long-term recipient outcome. Recent studies have demonstrated that the use of marginal donors did not affect early and late recipient outcome, and significantly increased the number of transplants performed. The aim of this paper is to review how the main lung donor selection criteria have been changed and how they influence the recipient outcome.

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Nowadays, lung transplantation is an acceptable treatment for end-stage pulmonary diseases, with 75% and 50% one-year and five-years survival rate, respectively. But donor organ availability continues to be a serious problem worldwide. This shortage has forced the transplant community to redefine the acceptable lung donor portrayed in the development of the following strategies: live-lobar donors, non-beating-heart donors, and an expansion of the acceptable criteria for the traditional brainstem-dead donor, by using marginal allograft.

Despite a significant rise in the number of patients on the waiting list, a similar rise in number of lung transplantations performed has not occurred. On the contrary, the number of patients dead while on waiting list is, unfortunately, increased.

Currently, only 25% of available donors are identified for transplantation, and of these, 20-25% only are considered suitable for lung transplantation. The limited donor supply may be, in part, caused by the application of the rigid donor selection criteria that were established in the first period of lung transplantation activity.

The pressure to expand the donor pool has influenced the donor acceptability criteria of several experienced centers; marginal or extended donors have been very frequently used, without adverse early and late complicances in recipients.

The purpose of this paper is to identify the evidences and supporting the recommendations for donor lung acceptability, on the basis of several donors characteristics (age, gender, cause of death, length of time on mechanical ventilation, arterial blood gas levels, radiographic evidences, presence of secretions and smoking history).

Physiologic changes during brain death and consequences on the lung functionality

The physiological changes during and after brain death are responsible of a high incidence of potentially

transplantable organs complicances. The lung is probably the weakest organ, deeply suffering the haemodinamic changes. A correct medical management of lung donors can directly influence the recipient outcome, possibly increasing the number of tranplantations.

Immediately after the brain death the intense sympathetic outflow leads to a rise in circulating catecholamine blood levels. This is known as the "sympathetic storm", which causes intense vasoconstriction that leads to hypertension, tachycardia and an increase in myocardial oxygen demand. In some cases, subendocardial ischemia may occur.

Pulmonary dysfunction is common after brain death, and it includes pneumonia, aspiration, neurogenic pulmonary edema and pulmonary trauma.[1]

A direct pulmonary damage is done by the "sympathetic storm": the increase of left atrial pressure, systemic hypertension and pulmonary vasoconstriction cause an increase pressure in pulmonary capillary bed, with an endotelial serious damage. Pulmonary capillary permeability is increased, and fluid volume overload occurring during the cardiovascular resuscitation maneuvres tends to precipitate the pulmonary edema.[2]

The hormonal system is deeply impaired, and it reflects the early anterior and posterior pituitarian gland failure.

There is an early depletion of antidiuretic hormone (ADH), with the development of diabetes insipidus in almost 80% of brain death organ donors.[3] It is characterized by inappropriate diuresis, severe hypovolemia, hyperosmolarity and hypernatremia. These changes exacerbate the neurogenic pulmonary edema, seriously damaging the lungs.

Significant decreases in cortisol levels occur after brain death, impairing the donor stress response and tissue perfusion. An early exogenous corticosteroid administration has been described as correct procedure, resulting in stabilization of the organ function.

The correct donor medical management protocol recognizes, first of all, the hypotension correction. The goal of hemodynamic management is to maintain an adequate circulating blood volume, a proper cardiac output and a good organ perfusion. Following the hemodynamic changes fluid resuscitation is considered the first step in correcting the hypotension. The goal standard is to achieve euvolaemia, not hypervolemia. Fluid overload can increase lung parenchyma damage induced by the neurogenic pulmonary edema. An adequate fluid replacement could be guided by mon-

itoring the central venous pressure (CVP); a CVP < 10 mm/Hg is usually recommended in clinical practice.[4]

In case of low blood pressure after adequate fluid administration, vasopressor can be started. Low dose dopamine is the drug of first choice in this case; low dose (5 U every time) vasopressin is preferred in case of severe ADH decrease, diabetes insipidus and organ donor hemodynamic instability.[5-8] Vasopressin, in fact, has shown to stabilise the systemic blood pressure, allowing a reduction of vasopressor administration in multiorgan cadaveric donors.

Hormonal substitution includes early methylprednisolone and triiodothyronine administration.[9, 10]

The lung requires a particular care to avoid severe damages: a correct ventilation assessment with FiO_2 <50%, positive end-expiratory pressure (PEEP) of 5-10 cm H_2O and a tidal volume of 10 mL/kg should be adopted avoiding ventilation-induced lung injuries.

FiO_2 should be as low as possible to maintain a PaO_2 of 90 to 110 mm/Hg. Atelectasis are avoided by applying the PEEP.

Bronchoscopy should be routinely performed, and more frequently if aspiration or purulent secretion are expected. Chest X-ray should be performed twice a day, monitoring the evolution of possible infiltrates. Donor's antibiotic early coverage is useful to prevent pneumonia; a more aggressive therapy is mandatory when aspiration or purulent bronchial secretion are observed.

Recruitment maneuvres are recommended every 3-4 h, especially after the apnea test.

Ideal and extended lung donors

The acceptability lung donor criteria were firstly defined by Sundaresan[11] in 1993 and resulted in "ideal donor" characteristics (Table I). "Marginal donors" were considered those who did not completely meet these criteria.

For many years lung donors were evaluated and accepted strictly following these guidelines. In particular, the presence of lung contusions at chest X-ray, or purulent secretions at the preharvesting bronchoscopy contraindicate their use. All this even if in 1992 Puskas et al.[12] described a successful single lung transplantation from 4 donors with unilateral lung dysfunction, whose arterial oxygen tension were lower than 300 mmHg.

A number of strategies have been advocated in

order to increase the number of lung donors. The persistence of shortage in lung donors has led to increasing interest in re-evaluating the existing lung donors' criteria. Recently, some experienced centers safely expanded the selection criteria, considering the so called "marginal" and "extended" donors.[13, 14]

Bhorade *et al.*[15] studied donors who did not fulfil one of "ideal donor" classification criteria. The one-year post-transplantation outcome when those donors were used, was not different from ideal donor's one. In Bhorade's paper the oxygenation was maintained high before lung procurement (PaO_2/FiO_2 ratio maintained >300).

Straznicka *et al.*[16] considered "extended donors" those who did not meet one or more than one usual criteria and with PaO_2/FiO_2 ratio < 150. Those donors were commonly considered unacceptable for lung procurement, earlier.

Donor selection main criteria

The first criteria considered for lung selection is donor age. Generally accepted donor age is <55 years.[11, 17] Novick *et al.*[18] demonstrated that donor age <10 or >50 years was associated with a limited increase in one-month and one-year recipient mortality. Moreover, they concluded that there is a negative association between extended graft ischemic time and donor age, particularly when the first is > than 6 h and the second is >55 years.

The same results are reported in the last International Society for Heart and Lung Transplantation (ISHLT) registry [19] in which the strong interaction between donor age and graft ischemic time is still stressed.

Bhorade *et al.*[15] did not osserve a negative recipient outcome when donors higher than 55 years were used.

Recently Fisher *et al.*[20] report their experience with lung donors older than 50 years, compared with younger ones. Recipients lung functions (early perioperative period and in the first year after transplantation) were similar in the 2 groups, and this does not underline the theoretically reported reduced "functional reserve" in elderly lung grafts.[18] This paper is the first in which all retrieved lungs received the same perfusion solution (low-potassium dextrane solution, Perfadex®); in previous reports lungs were perfused with different solutions.

TABLE I.—*Currently accepted "ideal donor".*

— Age <55 years
— ABO compatibility
— Clear chest radiography
— PaO_2 >300 on FiO_2=1.0 and PEEP 5 cm H_2O
— Tobacco history <20 pack-years
— Absence of chest trauma
— No evidence of aspiration/sepsis
— No prior cardiopulmonary surgery
— Sputum gram stain – absence of organisms
— Absence of purulent secretions at bronchoscopy

Older donors might have beneficial effects, due to the reduced immune system in older lungs, which may be less prone to rejection. On the other hand, older lungs may develop emphysematous changes, with reduced lung function, or may have increased susceptibility to cancer and infections.

Generally, care is mandatory for a correct "old" lung allocation: the organ of an old donor should be transplantated into an old recipient, even if, at moment, no evidence exists to support this practice.

The lower donor arterial blood gas acceptance limit is PaO_2/FiO_2 ratio not lower than 250. The most frequent causes of deterioration in donor gas excanges are neurogenic pulmonary edema, fat embolism or thromboembolism.

Managing potential multiorgan donors with high-dose steroids (methylprednisolone, mean 14.5±0.06 mg/kg), Follette *et al.*[21] demonstrated an important increase in PaO_2/FiO_2 ratio, resulting in a significant increase in the number of lung transplanted. On the contrary, there was a significant decrease in PaO_2/FiO_2 ratio in those donors not treated with steroids. Recently Luckraz *et al.*[22] report that the use of donors with low PaO_2 had an adverse effect on early mortality in recipient, but the difference did not extend beyond 30 days. The risk of morbidity (pulmonary infections, bronchiolitis obliterans syndrome development) was similar in the 2 groups, with a tendency to lower rejection rates in the low PaO_2 group. Low PaO_2 donors use allowed a 14% expansion of donor pool, in Luckraz' s experience.

The presence of clear chest X-ray is a well recognized criteria for donor selection. Chest X-ray abnormalities are a great variability, difficultly valuable because they depend on subjective evaluations by the harvest equipe. Chest X-ray abnormalities may reflect the state of hydration, the presence of neurogenic pulmonary edema, the presence of lung contusions, of atelectasis, or sepsis.

Pierre,[23] Gabbay,[14] and Bhorade *et al*.[15] reported the same results using donors with chest X-ray infiltrates: no adverse recipient outcome was evident when the infiltrates were not extended.

Sekine *et al*.[24] demonstrated that a donor lung with bilateral infiltrates at chest X-ray, purulent secretions or signs of aspiration at the bronchoscopic preharvesting evaluation were significant risk factors for 30-day mortality and prolonged ICU stay at univariate and multivariate analyses.

One of the main criteria for donor selection is the absence of infection in donor lung. An intrapulmonary infection has been a major cause of early morbidity and mortality in lung transplantation.[25] On the contrary, the aggressive use of broad-spectrum antibiotics in donors and recipients has reduced the incidence of recipient pneumonia.[26, 27] Positive Gram stain of donor tracheal aspirates may not reflect ongoing pneumonia, but, simply, they are a collection of purulent secretions in the upper airways.

The brain-dead donor is at high risk for lung bacterial colonization. The cause of death (*e.g.* trauma), the endotracheal intubation, the possible aspiration, the length of intubation and ICU recovery and the brain-death process as well, associated with bacteria colonization of the airways, and predispose to the risk of ventilation-acquired pneumonia. Intubation time > 3 days and grossly purulent secretions at pre lung procurement broncoscopy represent a contraindication to the donor use. On the other hand, sterile bronchial secretion are rare in multiorgan donors: series from different transplant centers report that the incidence of tracheal colonization in donors was approximately 80%.[28-30]

Recent studies have demonstrated that a positive Gram stain in donor upper airway secretions does not predict worse recipient outcome.[14, 27]

A recent study from Avlonitis *et al*.[31] reports the utility of bronchoalveolar lavage (BAL) performed in donor lungs immediately before the implantation. The advantage of this technique is that it provides informations about bacteria colonizing the lower donor airways, at the opposite of tracheal secretions, collected from the upper airways. Transplantation of lungs with positive BAL results in poor early graft function and lower recipient survival. This suggests that lungs with positive BAL are of inferior quality. Bacteria make a subclinical infections in donor lungs, which is amplified by the ischemia-reperfusion process, and results in poor recipient outcome.

The demonstration that the recipient early pneumonia is generally caused by bacteria different from those collected from donor lungs, may be explicated by a subclinical donor lung injury which makes the lung prone to be infected by different organisms in the recipient.[32, 33]

In the clinical practice it is recommended that the first recipient antibiotic coverage should be guided on the basis of donor lungs Gram stain results, early modified according to the cultures obtained from the donor lungs.[34]

Transplanted lungs remain vulnerable to reperfusion injury, with severe graft dysfunction, despite organ preservation techniques and solutions. To reduce the incidence of primary graft failure and other acute adverse events following lung transplantation, current target lung graft ischemic time ranges from 4 to 6 h. A longer one is tolerated in case of use of organs from distant locations, increasing national organs allocation.

In literature there are not evidences that prolonged ischemic time alone may increase one-month or one-year mortality in recipients. Novick *et al*.[18] report increased adverse recipients events when prolonged ischemic time (>6 h) is associated with old donor age (>55 years). Gammie *et al*.[35] and Fiser *et al*.[36] document no increase in mortality for recipients with ischemic time >6 h. In particular, no correlations are observed with prolonged ischemic time and postoperative lung function, risk of lung infections, risk of bronchiolitis obliterans syndrome.[35-37] Current ischemic time guideline (4-6 h) may be too conservative, especially when low potassium dextrane organ preservation solution is used.

Although it has been speculated that the cause of donor death may influence the recipient outcome, there is only a paper published in literature about this topic.[38] Ciccone *et al*. observed that there were any differences in recipient outcome after lung transplantation, in length of hospital stay or in hospital mortality in the 2 donors groups (traumatic *vs* non traumatic donors). Traumatic recipients seem to have an increased frequency of acute rejection episodes in the first year after transplantation. But the five-year survival is not different from nontraumatic recipients.

The causes of this phenomenon must be researched in the physiologic and hemodynamic consequences of acute traumatic brain death. Moreover, traumatic donors usually receive high number of blood trans-

fusions or blood products, which could render the graft at a higher level of antigenicity. Moreover, traumatic donors may have higher aspiration, with high frequency of Gram negative infections. Traumatic donors more frequently are intubated at the scene of the accident, potentially in a less sterile environment. All these circumstances may amplify the risk of donor infections.

The donor length of mechanical ventilation is directly related with nosocomial pneumonia and lung injury high risk. The crude rate of ventilator-associated pneumonia has been estimated as 1-3% per day of mechanical ventilation.[39]

The use of donors intubated for > 5 days, but with clear chest X-ray, good oxygenation and without mucopurulent bronchial secretions did not affect recipients outcome. Moreover, these lungs are more acceptable than others intubated after a traumatic death, or with sequelae of aspiration, or pneumonia or other tissutal injuries.

The ABO incompatibility between donor and recipient is an absolute contraindication to donor use in solid organ transplantation. Patients transplanted with organs from ABO-incompatible donors develop a hyperacute rejection.

In lung transplantation ABO-identical organs are generally preferred, but occasionally the use of ABO-compatible, but not identical organs could be warranted. In these patients haemolysis by donor-derived red blood cell antibodies may occur.

There is not a particular gender matching in lung transplantation. Due to lung size considerations, large male generally receive lungs from male donors, and small female, from female donors. In literature no published paper report a correlation between donor gender and recipient outcome.

Conclusions

There is a clear indication for the extension of the traditional lung donor selection criteria, to contrast the profound shortage of donors. The ultimate decision if a lung should be transplanted or not must be made on the basis of donor and recipient clinic characteristics, and must be done by an expert surgeon team.

Recipient strict follow-up is mandatory, to validate the results of extended donors use.

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