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LUNG DONATION AFTER CARDIAC ARREST. CHALLENGES AND OPPORTUNITIES. LITERATURE REVIEW

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The global development of transplantology faces several objective obstacles. One of the major ones is widespread organ shortage. This is most pronounced in clinical lung transplantation (LT). The development of this area is directly connected with more intensive development of available donor resources and search for new sources of donor organs that are suitable for transplantation. Along with the existing methods of increasing the number of lungs suitable for transplantation, LT with donation after cardiac death (DCD) is attracting increasing attention. The effectiveness of this approach has been confirmed by the International Society for Heart and Lung Transplantation and deserves more attention from Russian specialists.

Keywords: lung transplantation, lung donation, effective circulatory arrest, brain death, cardiac arrest, hypoxic necrobiosis.

LT is the only effective way to cure terminal respiratory failure against the background of refractory chronic lung diseases of various etiologies.

In Russia, LT can be characterized as a relatively young field. The number of transplants performed (national experience) is much lower than in Europe and North America in contrast to the transplants of other solid organs. As of January 2024, 207 lung transplants have been performed in the Russian Federation, including 17 transplants of heart-lung complexes.

Finding ways to solve the problem of shortage of donor lungs suitable for transplantation is a priority task for further development of this area of clinical transplantology.

Accumulated international experience demonstrates several promising areas for improving the quantitative and qualitative indicators of LT associated with improved surgical approaches to operations on recipients. It is possible to use the available donor resource more intensively by performing two single-lung transplants instead of one double-lung, the outcomes of which, according to some authors, are comparable [1]; performing lobar LT [2], split LT for patients with small anthropometric parameters [3], transplantation of two lung lobes from 2 living donors [4–6].

Another way involves expanding the criteria of organ donors for transplantation without compromising transplant outcomes [7, 8], namely, the use of lung recruitment methods within the framework of multi-organ donor conditioning [9, 10]; the use of lungs of a suboptimal donor followed by normothermic extracorporeal lung perfusion [11, 12].

The listed options are used mainly in conditions of donation after brain death (hereinafter referred to as "brain-dead donor", BDD) with preserved blood circulation in the donor.

Irreversible injury to human organs and tissues as a result of cardiac arrest occurs due to hypoxia and ischemia. Tolerance of solid organs to the hypoxic effects varies widely. Hypoxia impairs cellular respiration (oxidative phosphorylation) resulting in acute deficiency of macroergic compounds (primarily adenosine triphosphate, ATP) and elevated levels of its metabolites (adenosine diphosphate, ADP; adenosine monophosphate, AMP; etc.). In connection with this, further energy supply is carried out anaerobically. ATP deficiency is replenished by the reaction of anaerobic glycolysis. There is a rapid depletion of glycogen reserves, accumulation of products (metabolites) of glycolytic reactions – lactic and pyruvic acid – which leads to acidification of the intracellular environment and suppression of anaerobic glycolysis. Cellular energy supply completely stops. All cellular energy-dependent reactions stop. Transmembrane transport of potassium and sodium ions against a concentration gradient is impaired. Cellular homeostasis is disrupted. Passive cell membrane permeability leads to increased intracellular sodium and potassium deficiency, impaired repolarization processes, suppression of functional activity, and loss of action potential. Excessive intracellular sodium content leads to cellular hyperhydration. High intracellular concentration of calcium entering through inactive voltage-gated calcium channels activates membrane phospholipases and nuclear endonucleases. The totality of the occurring processes, a cascade of bioche-

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mical reactions, leads to damage of cell membranes and its structural elements up to cell death [13, 14].

Thus, the mechanism described above limits the acceptable time frame for obtaining a viable donor organ, and in some cases makes it basically impossible.

In this context, lungs have an undeniable advantage over other solid organs. Under certain conditions, the lungs can resist warm ischemia effects, because lung parenchyma cells are initially adapted to absorb oxygen from alveolar gas, and, therefore, need less oxygenation by perfusion. Thus, in relation to the lungs, warm ischemia is not identical to tissue hypoxia.

This hypothesis has been confirmed in several experimental studies.

Using a dog model, Egan et al. demonstrated the principal possibility of transplanting lungs procured within 4 hours after circulatory arrest. The experimental design consisted of left LT from donors 1, 2, 4 hours after cardiac arrest. One hour after transplantation, the pulmonary artery and right main bronchus were ligated, after which respiratory function and gas exchange were performed exclusively by the single transplanted lung. The best survival and gas exchange rates were obtained in the group with the shortest warm ischemic time. All recipients of 1-hour cadaver lungs safely survived the 8-hour follow-up period with satisfactory gas exchange rates. Two of 5 animals in group 2 (2-hour cadaver) showed similar outcomes. In group 3, gas exchange and survival rates were unsatisfactory [15].

Two years later, Ulicny Jr et al. supplemented the design of the Egan et al. experiment with postmortem lung ventilation during a 4-hour warm ischemic period, which, all other things being equal, resulted in a 100% 8-hour survival rate, whereas in the non-ventilated group, survival rates were significantly lower [16].

In a series of experiments, D'Armini et al. evaluated and compared the number of viable lung cells of laboratory rats and their metabolic activity depending on the use of artificial ventilation. The number of non-viable lung cells at 2, 4, and 12 hours after circulatory arrest and in the absence of artificial ventilation amounted to 36%, 52%, 77% respectively, while postmortem ventilation achieved significantly better values: 13%, 10%, 26% at similar control points ($p < 0.01$). Evaluation of the levels of ATP and its metabolites in the experimental groups showed that in the case of lung ventilation with oxygen, the process of aerobic oxidation and oxidative phosphorylation is preserved (comparatively higher level of ATP at control points), i.e. to preservation of metabolic activity, hence viability is preserved [17].

Thus, postmortem lung ventilation in the experiment made it possible to preserve the viability and functional activity of lung parenchyma cells (if not avoided, but significantly reduced the intensity of cell death). These results can be achieved only during artificial ventilation with high oxygen content in the respiratory mixture [18].

The possibility to maintain lung oxygenation after biological death and cessation of spontaneous breathing in the donor by continuing artificial lung ventilation is an important advantage in comparison with other solid organs in the context of organ transplantation from a donor after circulatory death (DCD).

The listed research results demonstrate the fundamental possibility of performing transplantation of lungs subjected to warm ischemia in the donor's body. The effectiveness of this approach is determined by warm ischemic time. According to some reports, acceptable ischemia periods are up to 4 hours, which allows to consider a donor with circulatory arrest as a lung donor as well.

The concept of lung donation after circulatory arrest has a clear physiologic rationale and has important advantages with respect to lung donation after brain death.

Today, postmortem organ donation from a BDD is the generally accepted gold standard of clinical transplantology. The events leading to the development of this condition are most often acute in nature – direct traumatic impact with destruction of the brain matter, vascular accidents, which have an impact both due to mass effect with dislocation of structures and due to lesion of brain stem structures.

Considering brain death not as an end result but as a process, we can identify a number of regular sequential events, the key to which is development of cerebral edema with subsequent brain stem compression and herniation, which leads to loss of central regulation of the parasympathetic (autonomic) nervous system. These circumstances naturally lead to impairment of systemic hemodynamics, development of systemic inflammatory reactions (catecholamine and cytokine storms), water-electrolyte disorders and other events that have a direct damaging effect on the donor's lungs. The combined effect of the above factors can lead to the so-called "neurogenic pulmonary edema".

The nature and structure of morphological changes in the lungs of patients who died within 12 hours after traumatic brain injury correspond to acute respiratory distress syndrome [19]. The incidence of pulmonary edema associated with damage to brain structures of various etiologies differs depending on the time from development of brain death. According to Rogers et al, pulmonary edema on autopsy of patients who died on the spot as a result of traumatic brain injury was observed in 32% of cases, whereas after 96 hours these changes were observed in 50% of cases [20]. Several factors have been identified as having a damaging effect on the lungs of the patient and donor. They are: increased plasma levels of endogenous catecholamines resulting from sympathetic nervous system activation, which occurs during acute brain injury, and has been called "catecholamine storm"; pulmonary edema due to hypertension in the pulmonary circulation against the background of acute left ventricu-

lar failure; increased permeability of pulmonary capillaries as a response to intracranial hypertension. Systemic inflammatory reaction that has a damaging effect on the endothelium of the pulmonary vascular bed due to circulating proinflammatory cytokines, mediators of systemic inflammatory response, the source of which can be the damaged brain matter, has been called "cytokine storm" [21]. The absence of the above-mentioned damaging factors is an important advantage of lungs from donors after circulatory death.

Donors after circulatory death represent a heterogeneous group of patients, clinical circumstances, timing and types of care. The earliest attempts at systematization date back to 1995, when a classification of donors after circulatory death, named after the place of its adoption, Maastricht, was formulated (Table 1) [22].

In principle, there are 2 classes of donors: patients with uncontrolled (categories I and II) and those with controlled circulatory arrest (categories III and IV). The first category includes patients found without signs of cardiac and respiratory activity, with no known timing of the onset of circulatory arrest or other events (circumstances) leading to it. The second category includes patients found with other comparable circumstances, but with witnesses available to determine the time of onset of circulatory arrest. The third and fourth categories include hospitalized patients for whom cardiac arrest is foreseeable and expected. These are patients whose vital signs can be maintained with ventilator support, including patients with confirmed brain death. Later, the classification was extended to category V – donors after euthanasia.

Category 3 controlled donors are most often used for clinical transplantation. Controlled donors have several advantages, because their stay in the hospital implies the availability of clinically relevant information for the transplantologist, such as infectious status, presence or absence of clinically significant diseases and conditions that influence the decision on organ transplantation. The period of functioning of life support systems can be used to conduct fundamentally important studies that determine the quality of the donor organ. The process of interrupting life support is clearly regulated and allows all necessary technical and organizational measures to be taken in advance to prepare the recipient in order to minimize warm ischemia time. Working with controlled donors is strictly regulated by national laws.

Table 1

Classification of donors after circulatory death (Maastricht, 1995)

Dead on arrival	Category I
Unsuccessful cardiopulmonary resuscitation	Category II
Expected cardiac arrest	Category III
Cardiac arrest with established diagnosis of brain death	Category IV

Within the framework of national clinical transplantology, the existence of category 3 (expected, actually planned cardiac arrest by stopping the functioning of life support systems) is not regulated by the current legislation.

The current legal "window of opportunity" allows for implementation of activities related to the conditioning and removal of organs from donors corresponding to Maastricht I and II categories [23].

In 2011, The International Society for Heart and Lung Transplantation (ISHLT) formed a working group to create a registry of lung transplants from donors after circulatory arrest. The first attempts to estimate the contribution of this lung source to the total number of globally performed lung transplants date back to 2015. A team of authors led by Marcelo Cypel evaluated the current experience between 2003 and 2013. There were 10 transplant centers in North America, Europe and Australia.

The article retrospectively evaluates the efficacy and safety of LT technique on the example of 306 DCD cases in comparison with the classical concept of BDD lung transplantation (totaling 3,992 cases) [24].

Of the 306 DCDs, the vast majority were categorized as Maastricht 3 (94.8%), Maastricht 4 (4%), and Maastricht 5 (euthanasia, 1.2%). It is noteworthy that there is no record of lung transplants from Maastricht category 1 and 2 DCDs in the first registry.

The immediate efficacy of lung donation in the absence of circulation was evaluated by the level of 30-day survival (DCD, 96%; BDD, 97%), 1-year survival (DCD, 89%; BDD, 88%; $p = 0.59$), and 5-year survival, which in both groups was 61%.

Of note is the limited use of ex vivo lung perfusion (EVLP) (only 12%), which most likely reflected the availability of this technique at that time. On the other hand, the overwhelming use of Maastricht category 3 donors in DCD fundamentally allows to obtain high outcomes even without EVLP, because with proper organization, the duration of warm ischemia of DCD lungs can be minimized to a time comparable with BDD. However, the authors suggest that extracorporeal normothermic lung perfusion has great prospects, especially within the framework of Maastricht categories 1 and 2 [24].

The next revision of the registry and its results was in 2019 and covers the period from 2003 to 2017. It demonstrates a positive trend of a twofold increase in the number of transplant centers over a 5-year period (from 11 centers in 2013 to 22 centers in 2017). The registry includes 11,516 lung transplants, of which 1,090 (9.5%) were performed in a DCD setting. The vast majority (94.1%) fell under Maastricht category 3, while categories 1 and 2 featured less than 1% (Fig.).

On the other hand, in the period from 2005 to 2016, Spanish and Italian authors, demonstrating their own

Table 2 Number of DCD Lung Transplants at Participating Hospitals by Category between January 1, 2003 and June 30, 2017

Maastricht category	N	%
(I) Dead on arrival (uncontrolled)	1	0.1
(II) Unsuccessful resuscitation (uncontrolled)	6	0.6
(III) Awaiting cardiac arrest (controlled)	1,026	94.1
(IV) Cardiac arrest in a brain dead donor (controlled)	43	3.9
(V) Euthanasia (controlled)	14	1.3
All	1,090	100.0

Abbreviations: DCD, donation after circulatory death
Adapted from Kootstra et al.[1995] and Detry et al.[2012]

Fig. Lung transplants from donors after effective circulatory arrest depending on the Maastricht category [25]

experience and outcomes of LT from DCD categories M1 and M2, published a number of studies [26–29].

The dynamics of growth of the specific volume of lung transplants from DCD in the period from 2003 (0.6%, 3 out of 530 lung transplants) to 2016 (13.5%, 146 of 1,081 lung transplants) is clear. At individual transplant centers, the number of lung transplants performed from donors after circulatory arrest reaches 28% to 40% [25, 30].

It is noteworthy that only 4 hospitals performed over 100 DCD transplants during this period (2003–2017). The undoubted leaders are Toronto General Hospital (160); Alfred hospital, Australia (148); University Hospital Gasthuisberg Leuven, Belgium (116); Universitair Medisch centrum Groningen, Netherlands (111). The largest number of transplant centers demonstrating their own experience within the framework of ISHLT DCD registry is located in the US (8), the UK (6), and Australia (4). Other clinics are represented in their own countries with one transplant center each.

Still noteworthy is the absence of hospitals and authors specializing in Maastricht categories 1 and 2 patients in the registry, despite a significant number of publications devoted to this topic [31, 32].

The second edition of the DCD registry allowed us to demonstrate the effectiveness of LT from the classical donation after brain death (DBD) and donation after cardiac death (DCD) based on more evidence (Table 2).

Table 2

Comparative outcomes of lung transplantation with donation after cardiac death (DCD) and with donation after brain death (DBD) [25]

	30-day survival	1-year survival	5-year survival
DCD	96%	89%	63%
DBD	97%	88%	61%
p	(p = 0.30)	(p = 0.44)	(p = 0.72)

The present results provide a compelling rationale for the use of donors after circulatory arrest as lung donors, as patient survival rates obtained are comparable to those of LT from brain-dead donors.

CONCLUSION

Accumulated experience of LT from DCD donors within the international community of heart and lung transplantation, demonstration of comparable immediate and long-term outcomes and increased number of such transplant surgeries at leading transplant centers, suggest that this source of donor lungs is a possible and prospective one. Development of this direction in Russia, especially in regions with high donor activity (for example, Moscow) will increase the number of lung transplants performed, thereby increasing the availability of such a complex type of transplantation in the hospital.

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