Diploma thesis

Effects of reduced pressure on organ quality in airborne organ transport

Flights without pressurized cabins

submitted by

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Univ.-Ass.in Mag.a rer.nat. Dr.in scient.med. Bettina Leber

Graz, 25.01.2021

Statutory Declaration

I declare on my honor that I have written the present work independently and without outside help, that I have not used sources other than those specified and that I have identified the passages, taken verbatim or in terms of content, as such.

Graz, on 25.01.2021 *Christian Kellner e.h.*

Danksagung

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Glossary and abbreviations

A	Austria (member state of ET)
Allocation	Distribution of organs within member states of an organization
B	Belgium (member state of ET)
BKTW	handicapped patient transport vehicle
Burgenland	Federal State of Austria
Carinthia	Federal State of Austria
D	Germany (member state of ET)
en-bloc	when other organs and tissues in addition to the actual organ are removed "in one piece" during the same surgical procedure
ET	Eurotransplant
ex situ	"not on the spot" or in the figurative sense "outside the natural anatomical position
ft	feet, 1ft = 30,48cm = 0,3048m
H	Hungary (member state of ET)
HR	Croatia (member state of ET)
in situ	"on the spot" or in the figurative sense "at the given anatomical position" or "in the correct anatomical position
Ischemia time	Time in which a removed organ is transported – while stored in perfusion solution at approx. 4°C) –, transferred to the organ recipient and supplied with blood again, so that it is ensured that this organ is not damaged and functions properly again
L	Luxemburg (member state of ET)
M	meter, 1m = 100cm = 3,28ft
N	Newton; SI unit for the physical quantity of force
NL	Netherlands (member state of ET)
Non ET	non Eurotransplant; not a member state of ET
OTPG	Organ transplantation law
Pa	Pascal; SI unit of pressure and mechanical tension
Styria	Federal State of Austria
SLO	Slovenia (member state of ET)
TCG	Transplant Center Graz

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Zusammenfassung

Hintergrund: Im 19. Jahrhundert entdeckten Wissenschaftler, Mediziner und Naturwissenschaftler, dass es möglich ist, ein menschliches Organ zu transplantieren. Seit damals wird stetig versucht, den Weg einer Organtransplantation bei Menschen zu verbessern und zu optimieren. Die Transplantation eines oder mehrerer Organe ist die Therapie der Wahl für eine Vielzahl von Erkrankungen. Die immer größer werdende Nachfrage an transplantierbaren Organen steigt im Gegensatz zum Angebot stetig an. Die Aufgabenstellung, jedes einzelne Organ bestmöglich zu nutzen, Richtlinien und Zeiten einzuhalten, ein gutes Ergebnis zu erzielen und ethischen Grundsätze genau zu beachten sind wichtige Eckpfeiler. Einen weiteren großen Aspekt stellen die entstehenden Kosten für Personal, Verpackungs- und Transportmittel, physikalische Einflüsse auf das Organ und die medizinischen Herausforderungen dar. Für zeitkritischere Organe, wie Herz, Lunge und Leber wird, um eine möglichst kurze Ischämiezeit garantieren zu können, öfter der Luftweg für den Transport gewählt. Hierbei stehen sich medizinischer Nutzen und anfallende Kosten gegenüber.

Methode und Studie: In der Literatur gibt es keine Angaben darüber, ob der potentiell negative Einfluss des fehlenden Druckausgleichs, von kleineren Flugzeugen ohne Druckkabine, auf die lebensrettenden Organe ausgeschlossen werden kann. Um die möglichen Veränderungen an Organen während eines Fluges in einem nicht druckausgleichenden Flugzeug evaluieren zu können, wurden Versuche an Schweineorganen im Rahmen einer Studie durchgeführt. In dieser Studie wurden drei Flüge, zu annähernd gleichen Bedingungen, mit einer kleinen Schulungsmaschine durchgeführt. An Bord waren bei jedem einzelnen Flug verpackte Organe (Herz, Lunge, Leber, Pankreas und Nieren), in vorschriftsmäßiger Art und Weise, dem Gesetz und Richtlinien entsprechend. Von den einzelnen Organen wurde vor und nach dem Transport eine Gewebeprobe entnommen und im Anschluss histologisch untersucht.

Ergebnisse: Es wurde ein Zeitlimit von maximal zwei Stunden für den Transport der Organe eingehalten, die Proben vorher und nachher verglichen und keinerlei makroskopische oder histologische Veränderungen festgestellt.

Diskussion: Trotz der Wichtigkeit der Transplantationsmedizin darf man ökonomische Punkte nicht außer Acht lassen. Um die Kosten eines Organtransportfluges zu minimieren stehen verschiedene Möglichkeiten zu Verfügung. Eine Idee ist es, kleinere, nicht druckausgeglichene Flugzeuge für den Organtransport einzusetzen und somit die Kosten eines Fluges zu verringern.

Abstract

Background: In the 19th century, scientists, doctors and natural scientists discovered that it was possible to transplant a human organ. Since then, constant attempts have been made to improve and optimise the way of transplanting a human organ. The transplantation of one or more organs is the therapy of choice for a variety of diseases. The demand for transplantable organs is constantly rising, while the supply in contrast to the supply. The task of making the best possible use of each individual organ, adhering to guidelines and timescales, achieving a good outcome and paying close attention to ethical principles are important cornerstones to guarantee successful transplantations. Other vital aspects comprise the costs due for personnel, packaging and transport, physical influences on the organ and the medical challenges. For more time-critical organs, such as the heart, lungs and liver, air transport is often chosen in order to guarantee the shortest possible ischaemic period. In this case, medical benefits contrast accruing costs.

Methods and study: Information upon the potentially negative influence of the lack of pressure equalisation from smaller aircrafts without pressurised cabins on the life-saving organs is scarce in literature. In order to evaluate the possible changes to organs during a flight in a non-pressurised aircraft, experiments were conducted in a study on porcine organs. In this study, three flights, under approximately the same conditions, were conducted with a small training aircraft. During each flight, organs (heart, lungs, liver, pancreas and kidneys) were packed in a manner compliant with the law and with regulations on board. A tissue sample was taken from each organ before and after transport and subsequently examined histologically.

Results: A time limit of a maximum of two hours for the transport of the organs was observed. The organ quality before and after the flight was compared and no macroscopic or histological changes were detected.

Discussion: Despite the importance of transplantation medicine, economic aspects cannot be ignored. In order to minimise the costs of an organ transport flight, various options are available. One possible approach is the use of smaller, non-pressure balanced airplanes for organ transport, thus reducing the transport costs.

1 General part

1.1 Introduction

In modern medicine, under certain organic, medical, ethical, legal and organisational conditions a non-functioning organ of a human body is replaced with another, healthy organ (1). For a successful transplantation, a precise and coordinated procedure is essential. So-called transplant coordinators are responsible for the organization of the explantation, transport and transplantation of an organ and have to guarantee a smooth process. In Austria several hospitals are involved in the transplantation sector. The cities of Vienna, Graz, Innsbruck and Linz have established and organised their own transplant centres, dividing Austria into regions which deal with all aspects of organ transplantation. ÖBIG (Austrian Federal Institute of Health) is the umbrella organisation for these divided regions. Graz, as a supervising institution of Region South, is responsible for transplantations in the provinces of Styria, Carinthia and southern Burgenland. Moreover, Austria is a member state of Eurotransplant, one of several foundations to ensure a fair distribution of organs in Europe. Within the member states, available organs are centrally reported and further distributed according to the guidelines. Coordinators of the respective competent communicate with Eurotransplant, thereby ensuring a controlled workflow. Finally, yet importantly, it is also the task of these coordinators to correctly pack the organs and coordinate the transport. They are also responsible for receiving an organ as well as the organization and coordination of the implantation or transplantation procedures. In order to be able to guarantee a smooth process and to successfully transplant an organ, guidelines, medical knowledge, laws, historical experience and physical and histological research and improvements must be constantly observed. Consequently, a great effort and high costs are inevitable. (1)

The aim of this study is to shed light on a small sub-area of organ transplantation, namely air transport, and to pave the way for possible cost reduction by means of a pilot study.

1.2 History of transplantation

At the beginning of the 19th century, the first successful attempts were made to transplant skin, especially in plastic surgery. The first verifiable skin transplantation on humans was carried out in 1817 by Astley Cooper at the Guys Hospital in London. In 1883, a thyroid gland was transplanted for the first time, thus implementing the idea of transplantation to cure internal carcinomas. Hence, early transplantation medicine focused on the thyroid gland before the interest to transplant other organs such as heart, lung, pancreas, liver and kidneys increased. Around 1900 transplantation medicine and the concept of organ replacement were generally accepted, but scientists and surgeons failed in the practical implementation. The problem of immune defence was considered unsolvable at that time, which consequently slowed down the early progress in the history of transplantation. (2)

It was only in the 20th century, when organ transplantation finally became a regular procedure. This was the case, due to the further development of medical techniques and drugs in the fight against pathological germs. Particularly in hospitals, pathogenic germs were often not treatable after major operations. The Ukrainian surgeon Yuriy Voronoy transplanted the first kidney in 1933, but the procedure was unsuccessful due to a rejection reaction of the patient. Almost 20 years later, in 1954, Joseph Murray transplanted a kidney between identical twins, thus avoiding a rejection reaction. In 1960, the first drugs and biological methods became available in order to suppress immune responses, paving the way for the first heart transplantation in 1967, the first lung in 1985 and the first partial liver transplant in 1988. Transplantation medicine is constantly improving to this day. (1)

Charles Lindbergh was the first designer of a perfusion pump (Figure 1) - a mouth-blown, 18-inch high, clear Pyrex glass configuration used to keep organs functioning outside the body. He created it in 1935 together with Nobel Prize winner Alexis Carrel. (2)

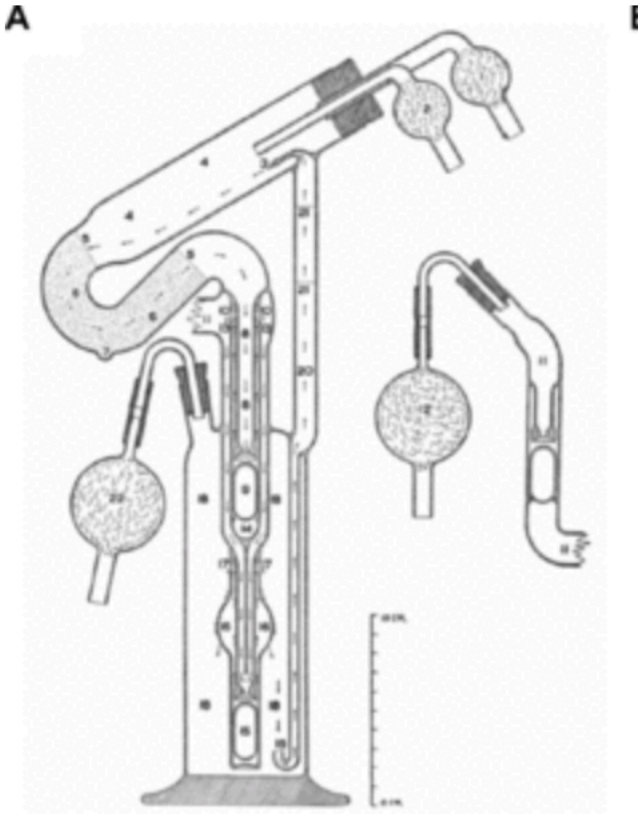


Figure 1: Lindbergh-Carrel Perfusion machine 1935 (3)

1.3 Eurotransplant

Eurotransplant is a European foundation for organ donation founded in 1967, which is responsible for organising the distribution and allocation of organs in eight countries. The following states are members of the foundation: Austria, Germany, Hungary, Croatia, Slovenia, Belgium, Luxemburg and the Netherlands. The specific tasks of Eurotransplant include the allocation, transport, accounting, statistics and vigilance of organs and transplants within the member states. (4) Organ transplantation offers lifesaving and quality-of-life enhancing treatment options to patients with end-stage organ failure. Aiming to fulfil this potential, Eurotransplant was established and acts as a mediator between donor hospitals and transplant centres, for the benefit of patients. More specifically, it is a non-profit international service organisation that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs at the service of its member states. As such, it manages the complex process of achieving the best possible match between available donor organs and patients on the transplant waiting list {table 1}. The

organisation acts transparently and in accordance with European Union regulations as well as ethical principles, and fully complies with national member states legislation. Eurotransplant is actively engaged in developing best practice recommendations and policies to constantly improve organ allocation and transplant outcomes, based on robust data collection and state-of-the-art scientific research. (5) The transplantation figures using Austria as an example show the great need for organs. In 2019, 72 hearts, 149 lungs, 138 livers, 298 kidneys and 14 pancreases were transplanted in Austria {table 2}. (7)

The needs of the individual institutions in Austria must also be considered when reflecting the imbalance between supply and demand. (6)

Despite the high number of transplantations, the waiting lists in Austria are still long. At the end of 2019, for example, 45 patients were on the heart, 60 on the lung, 99 on the liver and 616 on the kidney waiting list {table 3}. (7) The provided table refers to all member states of Eurotransplant as well as organs available in countries which are not part of the foundation (A-Austria, B-Belgium, D-Germany, H-Hungary, HR-Croatia, L-Luxemburg, NL-Netherlands, SLO-Slovenia, non ET-not a Member of Eurotransplant).

Yearly Statistics Overview Eurotransplant, 2019

Deceased donors used for transplant in 2019, by donor country

		A	B	D	H	HR	L	NL	SLO	Non-ET	Total
2019	donors	180	312	899	178	128	5	250	38	52	2042
2019	multi-organ	142	217	708	123	85	4	173	27	7	1486
2019	% multi-organ	78.9%	69.6%	78.8%	69.1%	66.4%	80.0%	69.2%	71.1%	13.5%	72.8%
2019	kidney	159	228	798	151	89	4	232	31		1692
2019	heart	72	87	324	79	34	3	40	14	16	669
2019	lung	76	114	320	33	17	3	96	9	30	698
2019	liver	134	267	705	108	119	4	162	24	13	1536
2019	pancreas	15	25	88	5	5	1	38			177

statistics.eurotransplant.org : 9023P_2019 : 06.05.2020 : based on date of donor registration

Table 1: Yearly overview Eurotransplant, deceased donors, 2019 (6)

Deceased donor organs used for transplant in 2019, by donor country										
		A	B	D	H	HR	L	NL	SLO	Non-ET	Total
2019	kidney	298	426	1536	281	158	8	445	53		3205
2019	heart	72	87	324	79	34	3	40	14	16	669
2019	lung	149	225	631	64	33	6	191	18	60	1377
2019	liver	138	272	726	112	119	4	165	26	14	1576
2019	pancreas	14	15	88	5	5	1	29			157
2019	pancreas islets	1	10					9			20
statistics.eurotransplant.org : 9023P_2019 : 06.05.2020 : by donor registration date, counting individual organs (lung, kidney)										

Table 2: Yearly overview Eurotransplant, used organs, 2019 (6)

Yearly Statistics Overview Eurotransplant, 2019

Active waiting list (at year-end) 2019, by country									
		A	B	D	H	HR	NL	SLO	Total
2019	kidney	616	870	6881	824	231	803	95	10320
2019	heart	45	82	706	62	38	115	42	1090
2019	lung	60	159	268			171		658
2019	liver	99	155	838	75	99	134	17	1417
2019	pancreas	2	25	34			19		80
2019	pancreas + kidney	10	24	231	34	6	27	1	333
2019	heart + lung		3	5			1		9
2019	heart + kidney	3	6	11					20
2019	lung + liver		1	3					4
2019	liver + pancreas		2	2					4
2019	liver + kidney	2	14	25	5	2	1	1	50
statistics.eurotransplant.org : 9023P_2019 : 06.05.2020 : at year-end, only including active patients									

Table 3: Yearly overview Eurotransplant, active waiting list, 2019 (6)

1.4 Procedure of organ donation

To ensure the best possible communication between Eurotransplant and the respective transplant centre, transplant coordinators are appointed. The tasks of these specially recruited people are manifold and include all the necessary aspects of explantation, packaging, transport management, scheduling, communication between all involved parties, the planning of the surgery in the operating rooms and invoicing. In order to guarantee the best possible outcome, it is essential to comply with laws and to plan and enforce a smooth procedure. Thus, the process starts with a donor notification at a hospital and ends with the transplantation of the organ, which, in Austria, is conducted by the organisation Eurotransplant {figure 2}.

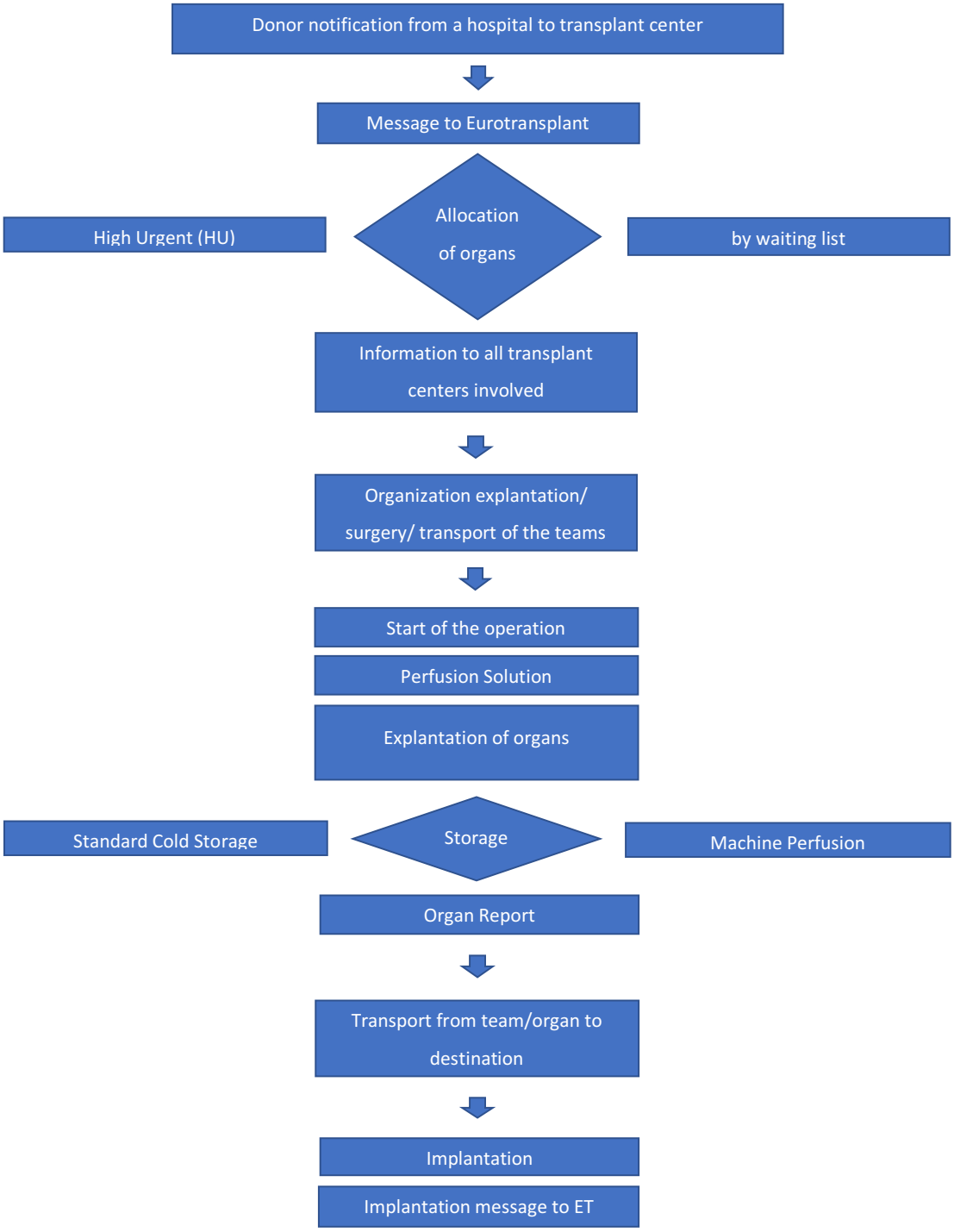


Figure 2: Organ Donation Overview, organized by transplant coordinators (7)

1.4.1 International organ exchange

By maintaining a central waiting list and a cross-border donor notification system, an improved allocation of organs to suitable recipients is guaranteed. Especially in the case of a particularly urgent organ transplantation, this system increases the chances of rapid allocation and availability of a suitable organ. Particularly people with rare blood types and children benefit from this system of international cooperation between several transplant centres. (8)

1.4.2 Logistics of transportation

The logistics of organ transport are a demanding task as often long distances have to be covered between donor and recipient, including the crossing of country borders. In the case of organ donation, it is almost always necessary to transport the donated organs to the recipient. Only with a live organ donation can doctors coordinate the removal and transplantation of the donor organ so that both procedures occur in the same place. The international agency Eurotransplant is involved in and responsible for international transports. (7)

1.4.3 Organ transplantation law

The scope of the Austrian organ transplantation law comprises donation, testing, characterization, provision, preservation, transport and transplantation of organs, which are intended for transplantation into the human body. Thus, the protection of the donor/recipient, the principles of donation, the objection register, the removal of organs, the obligation of the removal units as well as life donations are regulated in the Organ Transplantation Act (OTPG). It also contains procedural instructions on the quality and safety of organs, transport and organ characteristics. An essential part of the OTPG describes the traceability, organ vigilance and reporting, as well as the international exchange of organs and the administrative penal conditions. (7) During transport, the safety and a reasonable duration for teams and organs must be ensured. In addition to comprehensible documentation, which is usually carried out by a coordinator at one of the centres, important information must also be noted on each individual transport box. The hospital, address, telephone number and email address of the transplant centre, as well as the donor number and "Handle

with care" are to be attached to the transport box. Every person involved in a transplant transport is obliged to maintain confidentiality and must ensure that the provision and transplantation of an organ is fully traceable. (8)

1.4.4 Organ transportation

Organ donation requires organizational skills and the participation of many well-trained employees. The donation as well as the transplantation of an organ is associated with high costs and requires specialist knowledge. The organization of the transport is a vital part of the process and should, on the one hand, be performed as quickly and with as little delay as possible, and should, on the other hand, be done cost-efficiently. It is essential to have reliable partners both for the respective centres and the entire Eurotransplant area, namely in the form of ground-based and air-bound resources, as well as to be able to work with these partners seamlessly. In most cases, not only an organ, but also a team of doctors and coordinators must be brought to and from the explant. In these cases, rescue cars and charter planes are available. Apart from the legal regulations for organ transports, the top priority is to keep the so-called ischemia times, the time an organ remains outside the body without blood circulation, as short as possible. Short ischemia times are essential to guarantee a satisfying outcome of the transplantation. (5)

1.4.5 Organ donation

The procedure begins with a median laparotomy, and in the case of a planned removal of the liver, pancreas, heart or lungs, an additional median sternotomy is performed. First, the distal abdominal aorta and the branches of the iliac artery are prepared and tightened in order to be able to perform an immediate aortic perfusion if necessary. The inferior vena cava will also be bridled to provide access to the venous system for organ perfusion in the entry area of the pelvis. Further abdominal preparation depends on whether the organs are to be displayed in-situ or whether the visceral organs are to be harvested en-bloc and prepared ex-situ after perfusion. After that, the perfusion systems for the cannulation of the vessels for abdominal arterial perfusion or for cannulation of the ascending aorta for heart perfusion or the pulmonary artery for lung perfusion are being prepared. Synchronously, the thoracic and visceral organs are perfused with the cooled preservative solution. The venous

circulatory system is relieved by draining the vena cava intrapericardially or intraperitoneally. Surface cooling and perfusion lead to rapid cooling, to a reduction in oxygen consumption, and thus, to a maximum reduction of the metabolism, which allows the organs to remain functional under anoxia for a limited period of time. After perfusion and cooling, the thoracic organs are first removed. This is followed by the removal of the liver and pancreas, possibly en-bloc, and finally both kidneys are procured. For a necessary vascular reconstruction, the distal aorta with its division of the iliac vessels and the distal vena cava are removed and packed separately and added to the transplants. After organ removal, the thorax and abdomen are closed and bandaged. In this way the corpse does not show that organs have been removed. (1)

1.5 Pathophysiological processes

Clinical studies in animal experiments have shown that pathophysiological changes in the entire body occur relatively fast after brain death. The release of inflammatory mediators, activated enzyme systems (lipases, protease, NO-synthetases) and free oxygen radicals damage the cell surfaces of the entire body. After a further phase and with the release of proinflammatory cytokines, a generalized inflammatory reaction already damages organs. This means that organ perfusion disturbance occurs already before explantation. These mechanisms present medicine with major challenges and a need for rapid action even before the planned organ removal (9). During explantation the aspect of ischemia times becomes relevant, which can be differentiated into two parts, namely warm and cold ischemia (10).

1.5.1 Time of ischemia

The ultimate goal in organ transplantation is to achieve a careful and complication-free harvest with good perfusion and minimisation of the cold ischaemic time, so that minimisation of ischaemic perfusion damage and better graft function can be guaranteed. The use of special preservation solutions and additional surface cooling during organ removal currently define the standard of organ preservation and organ protection. (11)

The period of ischaemia, i.e. the time when an organ is not supplied with blood, and thus, not sufficiently oxygenated, plays an essential role in the entire transplantation

surgery. The shorter the ischemia time, the better the organ quality and the less damage is caused to the explant. (12)

A lack of oxygen leads to the blood being less oxygenated. Tissues with a high oxygen demand are particularly sensitive, the brain being the most important. This imbalance in supply leads to unprogrammed cell death and the respective organ is damaged. (13)

Cooling and cold storage reduces the cell metabolism and especially the oxygen consumption of the donor organs. The lack of perfusion/reperfusion leads to ischemia, which causes intra- and extracellular changes in the donor organs. Interstitial edema and intracellular acidosis are the result. (11)

In order to slow down and prevent this process from happening, special perfusion solutions are used for explantations. Another possibility to minimise cell death and keep cell changes as low as possible is the machine perfusion. (12)

Recent studies suggest to replace the traditional method of organ preservation with continuous machine perfusion. In view of the existing shortage of donors and organs, this would allow the possibility to react, and also to improve the acceptance of so-called marginal organs. (11)

The periods allowed between removal and transplantation in organs are the following: heart 4-6 hours, lungs 4-6 hours, liver 10-12 hours, pancreas/kidney 10-12 hours, kidneys 0-24 hours. (8) The table below provides an overview of the maximum ischemia times {table 4}.

Organ	Number of hours (approx.)
Heart	6
Lung	8
Small bowel	12
Liver	16
Pancreas	24
Kidney	36

Table 4: maximum time of ischemia (11)

Warm ischemia

Warm ischemia describes the period of time during the operation in which the organs remain in the body without blood supply, at body temperature. (11)

Cold ischemia

The cold ischaemic period in transplantation medicine refers to the time between the removal of an organ from the donor and its implantation in the recipient, i.e. the beginning of the anastomotic sutures. Removal may only take place after perfusion with a suitable special perfusion solution. (12)

1.6 Cold static storage

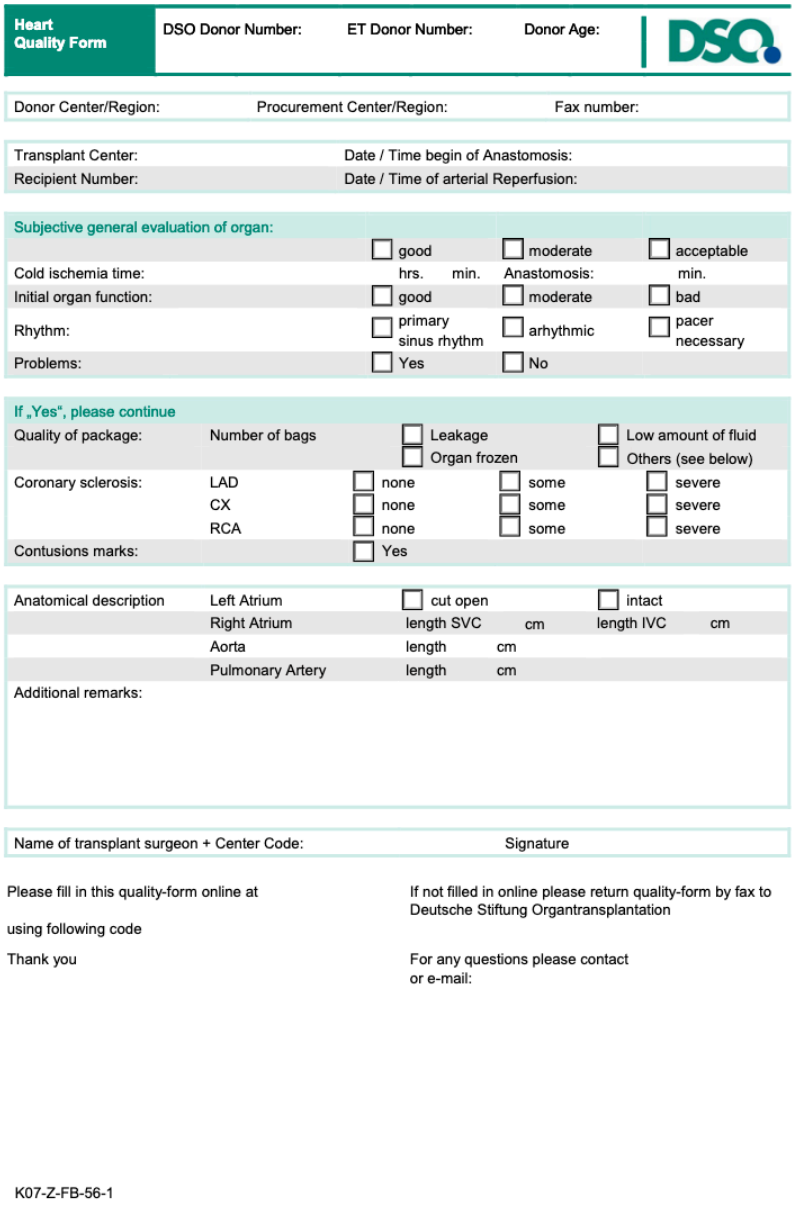
Until the ever-increasing demand for machine perfusion can be covered, the conventional, cold static cooling will continue to be used. (11) If no machine perfusion is available, the previously standardized and common packaging of organs in the Eurotransplant area must be available both for transport and for intermediate storage in order to guarantee and maintain the highest possible organ quality. (4)

1.6.1 Packaging of organs

All organs, tissue and blood samples procured from the body must be packaged and preserved in accordance with the current guidelines of Eurotransplant. Specially trained personnel, so-called transplant coordinators, carry out and control the packaging process. (3)

Immediately after removal, the organs are examined for organ perfusion, organ quality, anatomy, fatness, arteriosclerosis and any lesions that may have developed. All of the mentioned factors have to be documented on the organ report. For further transport, the organs are sterilely packed using a so-called three-chamber bag system and stored in a cool place. In the first bag, the organ is sterilely and airtightly packed together with preservative solution and then sealed. The first bag is packed into a second bag, filled with two litres of a 4°C cold Ringer's solution, and then sealed as well. The two bags are then packed airtight in a third bag. The same packaging procedure applies to removed containers. After packaging, the three-chamber bag system containing the organ is stored on crushed ice in a polystyrene or Styrofoam box and sealed for transport. (11)

Packaging, similar to all other aspects in the transplantation process, is regulated in detail in the Organ Transplantation Law (OTPG), which has to be followed at all times. (7) As already mentioned earlier, each packaged organ has to be accompanied by a corresponding organ report and must be traceable at all times. This organ report describes the organ quality, removal times, anatomy, arteriosclerosis signs, packaging, special features and problems during removal, as well as specifies the surgeon and the transplant centre performing the procedure. (7) Figure 3 shows how an organ report usually looks like.



Heart Quality Form | DSO Donor Number: | ET Donor Number: | Donor Age: | DSO

Donor Center/Region: | Procurement Center/Region: | Fax number:

Transplant Center: | Date / Time begin of Anastomosis:
Recipient Number: | Date / Time of arterial Reperfusion:

Subjective general evaluation of organ:

	☐ good	☐ moderate	☐ acceptable
Cold ischemia time:	hrs. min.	Anastomosis:	min.
Initial organ function:	☐ good	☐ moderate	☐ bad
Rhythm:	☐ primary sinus rhythm	☐ arhythmic	☐ pacer necessary
Problems:	☐ Yes	☐ No	

If „Yes", please continue

Quality of package:	Number of bags	☐ Leakage ☐ Organ frozen	☐ Low amount of fluid ☐ Others (see below)	
Coronary sclerosis:	LAD	☐ none	☐ some	☐ severe
	CX	☐ none	☐ some	☐ severe
	RCA	☐ none	☐ some	☐ severe
Contusions marks:		☐ Yes		

Anatomical description	Left Atrium	☐ cut open	☐ intact
	Right Atrium	length SVC cm	length IVC cm
	Aorta	length cm	
	Pulmonary Artery	length cm	

Additional remarks:

Name of transplant surgeon + Center Code: | Signature

Please fill in this quality-form online at

using following code

Thank you

If not filled in online please return quality-form by fax to Deutsche Stiftung Organtransplantation

For any questions please contact or e-mail:

K07-Z-FB-56-1

Figure 3: organ report heart, DSO (7)

1.6.2 Boxes for transport

The removal team carefully prepares the donor organ for transport, rinses it with a cooled preservation solution and puts it in the solution. The organ is then packed in sterile bag systems and transported in special Styrofoam boxes filled with crushed ice. Figure 4 shows typical examples of the described transport boxes. The temperature in the box during transport has to remain at four degrees Celsius, which creates optimal conditions for the preservation of the donor organ. At the end of the transport, the organ is handed over to the transplant centre and transplanted there (7).

Figure 4: box for organ transportation (12)

1.6.3 Advantages and disadvantages of cold storage

The advantage of the conventional packaging of organs is primarily the inexpensive and fast execution. The required ice, perfusion solution, organ bags and polystyrene boxes do not pose an immense organizational challenge and can be transported easily and without much effort. Due to the standardized dimensions of the transport boxes, small vehicles can be used for organ transport since the boxes do not need much space (13). One disadvantage of cold storage is the lack of permanent organ perfusion between explantation and implantation. This problem could be solved by using the technique of mechanical perfusion instead. While machine perfusion would guarantee a higher quality of the organ, it is also much more expensive. Compared to the conventional transport box method, the purchase of a suitable machine, the entire organ removal procedure with the following transport and the surgical and personnel costs are extremely high (14). Hence, it is important to not only consider and weigh up the costs and the organizational effort, but also to figure out a good and justifiable way to reduce the resulting pathophysiological processes to a minimum. (9)

1.7 Machine Perfusion

The demand for transplant organs has shown a steady upward trend in recent years. The ischemia times of the individual organs and the associated cell death, and thus, a functional limitation of individual cells has been the motivation for intensive research (9). One possible alternative to cold storage to preserve organs extracorporeally is machine perfusion (15). Due to the current shortage of donor organs worldwide, concepts, such as machine perfusion, which has already existed in the early days of transplantation medicine, have gained importance again. The current approach using normo- or hypothermic machine perfusion prolongs the preservation time, optimises the transplantation process between procurement and transplantation and provides more precise information concerning the quality of the organ, and consequently, the possibility to reconsider a previous assessment. Machine perfusion can be considered a suitable alternative, especially in times of organ shortage, also because several recent studies advocate a switch to machine perfusion (11).

1.7.1 Systems for machine perfusion

The following chapters present the currently available solutions and their specifications of machine perfusion. Also, special features, such as airworthiness, will be described. These perfusion systems differ in method, size, weight as well as transport possibilities and can usually only be used for one specific organ. The different methods of perfusion, including hypo-, normo-, hyponormothermal and pulsatile, are the distinguishing features of the perfusion machines available so far. Three suppliers are currently represented on the world market which are briefly described below.

1.7.1.1 Organ Assist

www.organ-assist.nl

The company Organ Assist was founded in 2005 and is based in Groningen, Netherlands. Their perfusion system was developed in collaboration with the Medical University of Groningen. The company's portfolio includes five different machines for donor, liver, lung and kidney perfusion and a device developed for kidney transport. Images of how the different perfusion systems look like are shown in figure 5. Except for the kidney transport perfusion device, all devices are intended for stationary use and are not designed for transport by car or plane (16). The stationary devices both support explantation and prolong the ischemia time through permanent cooling and perfusion, which leads to reduced cell damage. All the machines work either hypo- or normothermal or pulsatile. A majority of the company’s devices are part of several studies of the University of Groningen in order to improve not only the development of the machines, but also the perfusion process in general (13).

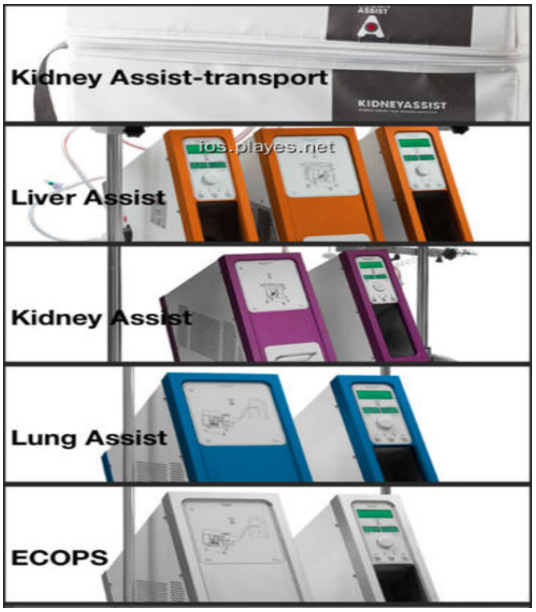


Figure 5: OrganAssist Machine Perfusion Systems (13)

1.7.1.2 Organ Ox

www.organox.com

The company OrganOx was founded in Oxford, Great Britain in 2008 and their perfusion device was developed in cooperation with the University of Oxford. OrganOx only offers a device for permanent liver perfusion. The special feature is the independently designed carbon casing, which enables transport by car at any time. The machine also allows for a longer transport of donor livers with minimised cell damage and permanent perfusion. This system works with normothermal temperatures, but it is not suitable for pulsatile applications and is not designed for air transport (15). Figure 6 provides an impression of the above described device.

Figure 6: OrganOx Machine Perfusion (14)

1.7.1.3 TransMedics

www.transmedics.com

TransMedics was founded in 1998 in Andover, Massachusetts (USA). The company's portfolio consists of three different perfusion machines that support heart, lung and liver perfusion. An example of a TransMedics device is presented in figure 7. All machines are designed for both car and air transport and work normothermally, pulsatile and, especially for the lungs, also with ventilation. The special feature of the device is the possibility of air transport, which was approved by Europe as well as Australia (15).

Figure 7: TransMedics Machine Perfusion (16)

1.7.1.4 Advantages and disadvantages of machine perfusion

There are a number of differences between machine perfusion and the methods of permanent, pulsatile and cooled perfusion used during explantation and the following storage of the organ at 0°-4° Celsius.

Several studies have shown a significantly better organ quality and a limited increase in liver enzymes when using a perfusion machine. However, this fact is quickly neutralized considering the effort of machine perfusion and the costs of such a device (19). A significant limitation is currently still the transportability of the

available perfusion machines. Even though the devices guarantee better organ quality, developers still face a number of challenges; these include the size of the devices, the handling, the changing physical conditions, such as temperature and air pressure, and the power or battery supply. Due to these problems, the development of newer technologies is running at full speed (20).

1.8 Transportation by plane

Airborne transport by plane is a faster alternative to ambulance vehicles. However, the resulting costs of this form of transport are also considerably higher. In order to keep the ischemia times of international transports at a minimum, transportation by plane is the only option. Air transport allows the coverage of long distances in a short time and ensures a steady supply of organs in the Eurotransplant area. The guidelines and laws stipulated in the organ transplantation law apply here as well (8).

For national or international shipments of organs by plane, a ground-based transport to a suitable airport is required before and after the transplantation. Both the removal team and the organs, especially the heart, lungs and liver, are often transported in an air-bound manner to guarantee a short ischemia time (7). The exchange of organs and transport, under the time pressure associated with it, can be better managed by airplane and ischemia times can be kept lower than with ground-based transport by car. In order to be able to guarantee international organ exchange as fast as possible within the countries covered by Eurotransplant {figure 8}, the transplant team as well as the organ have to be transported by a suitable aircraft (17).

Figure 8: Member States Eurotransplant to reach by plane (17)

1.8.1 Physical basics of pressure

Pressure is described by the fact that a certain force acts on a certain area (A). If the force (F) is evenly distributed over the area (A), the ratio of force (F) to the area (A) is called pressure (p).

pressure = force (F) / area (A)

p = F / A

unit Pascal (Pa): 1 Pa= 1 N/m^2

For most purposes, the unit of 1 Pa is too small and therefore the unit bar is used instead.

1 bar = 10^5 Pa; 100 Pa = 10^2 Pa = 1 mbar

How a body reacts to deformation depends on its physical properties, such as physical state, strength, elasticity, type of material, etc. and the structure of atoms,

particles and molecules (18). In solid bodies the particles are tightly packed, which means that they are relatively close to each other. In addition, the mutual forces are so strong that the particles occupy fixed positions and have a fixed shape. The shape changes only slightly and temporarily at low loads when exerting pressure or tension. This change is referred to as elastic deformation. Under high pressure and tension, bodies deform permanently. This is referred to as plastic deformation. If the cohesion of the mentioned particles is insufficient, the body breaks or tears. Particles are also densely packed in liquids, but, unlike in solid substances, they can be moved. For this reason, liquids do not have a solid shape and as soon as pressure is exerted on them in a closed vessel, forces are passed on equally on the whole area. Both solid bodies and liquids cannot be compressed, they are incompressible (18). In gases, the particles are relatively far apart, so they have no specific shape and fill closed vessels completely. This property allows gases to be compressed very well (18).

1.8.2 Effects of air pressure on the human body

The air in the atmosphere has mass and weight. Man lives at the bottom of a so-called “air sea”. The medium air pressure at sea level, what is referred to as normal pressure, is approx. 105 Pa (1 bar). Each square meter of earth therefore has a weight of approximately 10^5 N.

The air pressure in the atmosphere decreases with increasing altitude.

This is the case, because, on the one hand, the air column becomes shorter, and, on the other hand, the density of the air also decreases with height. This pressure change of rapid height differences can be felt in the human body, especially in the throat, nose, ears and the lung area. The partial pressure of oxygen decreases with increasing altitude as well. While the pressure is 160 mmHg at sea level, it halves to 80 mmHg at 5 800 m altitude. Although the oxygen concentration at this altitude corresponds to that at valley level, the body can absorb less oxygen per breath due to the reduced O2 partial pressure, which leads to hypobaric hypoxia. Up to a flight altitude of 2438m the body is able to manage the reduced partial pressure and adapts to the changing environment. Above the mentioned height limit, the partial pressure of oxygen is no longer sufficient to supply the human body with enough oxygen. Initially, this lack of oxygen is compensated by hyperventilation and, during longer periods of exertion, counteracted by the formation of more erythrocytes.

However, if the erythrocyte count exceeds a certain level, unconsciousness is the result. The human body responds to this with pressure equalization and acid base shifts (19). In airplanes that are intended for passenger transport, the air pressure must be stable at all times. Therefore, a pressure of 0.8 bar, corresponding to a height of 2200m, is maintained in pressure-balanced aircrafts. Such pressurized cabins are used less frequently in smaller aircrafts since they cannot exceed a flight altitude of 3000 m (18). For the subsequent study one of these smaller planes was used for transport.

1.8.3 Flight altitude vs. cabin altitude

The flight altitude of a non-pressurised aircraft is approximately the same as the cabin altitude. In order to reach a certain height with the aircraft, and thus, be able to fly more efficiently and faster, it is necessary to increase the cabin pressure so that it does not have a detrimental effect on the health of passengers (22).
As described above, the air pressure can be physically assigned to an exact altitude, which helps us to determine the necessary flight altitude. It is therefore all the more obvious that the flight altitude can be measured with a barometer, which in turn "only" shows the changes in air pressure on an altimeter scale (21). If the air pressure in the cabin increases, the cabin height decreases. This is called the descent of the cabin. This is necessary in order to successfully compensate for the decreasing pressure ratios at altitude and to avoid damage to the body (23). In passenger flight operations, a pressurised cabin is usually provided for the aircraft. It has a stabilized pressure at about 2100m (24). Between 0-100m flight altitude one can find birds, bats or insects. Between 150-1500m one can find air sports equipment, hang gliders, paragliders, hot air balloons, helicopters or airships. Between 1500m-3000m altitude small aircrafts in cruising flight, gliders in cross-country flights and commercial aircrafts in holding patterns for landing approach can be met. Between 3000m-5000m altitude business jets and some migratory birds can be found. The altitude between 5000m-10000m is reserved for business aviation, jets and turboprop aircrafts in cruising flight. Jet aircrafts in cruising flight are underway between 10000m and 15000m altitude. And the altitude between 15000m and 18000m is reserved for supersonic passenger aircrafts, such as the Concorde and Tupolew (22).

1.9 Time and costs, car vs. plane

Several types of planes are used in Austria for organ transport and the transport of the medical personnel involved. Regardless of the manufacturer, all charter aircrafts are equipped with conventional pressurized cabins common in commercial flights. Accordingly, airborne transport is associated with higher costs because of airport charges, pilots, fuel as well as wear and tear, than ground-based transport with an emergency vehicle. The resulting costs must always be compared to the time factor and the ischemia times which have to be observed. Experience has shown that air-bound transports within Austria and nearby international cities like Zagreb, Budapest or Munich, have a decisive advantage in terms of time. Other target hospitals can also be reached in a timely manner by car. Heart transplants, for example, are primarily transported by plane, because they are time critical. In the international exchange of organs, air traffic with scheduled or charter flights has proven to be definitely faster, although more expensive (7). The data provided are subject to the trade secret of the companies, are to be considered as guidelines and may vary in individual cases. Hence, the charged prices in the table below have to be considered as representative and not as fixed prices for every transport. Table 5 shows that one driven kilometre with a ground-bound transport of an employment organization in Austria costs on average 0.85€, without waiting periods or toll and without developing costs of additional personnel, overnight accommodation and travel time subsidy (20). In contrast to this, transport from LKH Graz with an approved pressure balanced organ transport jet, including pilots and airport fees, but without any additional charges, costs on average 31€/km, which equals 140€ per flight minute (20).

	Skoda Octavia	Diamond DA42	Eclipse 550
costs without tolls and fees/ km	**0,85€/ km**	**18€/ km**	**31€/ km**
costs without tolls and fees/ min		44€/min	140€/ min
km per minute		2,5 km/min	4,5 km/ min

Table 5: comparison costs per km car vs. plane (18,19)

2 Aim of the study

Considering the above described physical property of air pressure, the aim of this pilot study is to investigate the transport method of non-pressure balanced aircrafts for donor organs and to shed light on pathophysiological mechanisms and changes. This focus on transport cost optimization is only a small part of the effort to minimize the total cost of organ transplantation. With the steadily increasing demand for transplantable organs in Austria, the provision of planes and their maintenance and flight costs will also play a major role in the future. In order to reduce costs, smaller, non-pressurized planes would be the more efficient alternative to use.

Minimization of transportation costs

Due to the use of less expensive aircrafts and savings on airport fees, the total costs can be reduced considerably. In addition to significant cost savings for the flights, the transport would also need much less time compared to ground-based transport by car. In view of the shorter ischemia time and manageable settlements, the switch to small aircrafts should be considered in the future. Also, in view of the increasing volume of road traffic, the described alternative by air is necessary to guarantee secure and fast transport (18). The costs for organ transport after explantation could be minimized or optimized by using smaller non-pressurised cabin aircrafts.

3 Methods

3.1 Overview

In this pilot study, a pig model was used to demonstrate pathophysiological changes in explanted organs. In compliance with ethical guidelines, three pigs were prepared in the LKH Graz area and explanted on three different days in the Surgical Research Department of the Surgical Department of the Klinikum Graz. In the presence of a veterinarian, the sterile guidelines, as prescribed in the operating room, were observed and controlled. The entire procedure of the organ removal was performed according to the guidelines and instructions of OTPG and Eurotransplant. After the operation, the deceased pigs were sent to the carcass disposal. After the study, also the removed organs were passed on to be disposed.

3.2 Porcine organs

For this pilot study, the three animals used have already been prepared for another study and their organs could thus be used further. In consultation with the veterinarian, the surgeons, the pilots and the transport driver three explantations were performed. Specifically, the heart, lungs, liver, pancreas and both kidneys were explanted, packed and transported. After transport and further histological sampling, the organs were disposed.

3.3 Explantation of porcine organs

The pigs have a minimum stay in a quiet environment in the LKH Graz area in accordance with ethical aspects. The pig, whose organs will be explanted, is prepared, anesthetized and intubated by a veterinarian. A median laparotomy is performed first, and in case of a planned removal of kidneys, liver, pancreas, heart or lungs, an additional median sternotomy is performed. First the distal abdominal aorta and the branches of the iliac artery are prepared. The inferior vena cava is prepared as an access for the relief of the venous system during organ perfusion in the entry area of the pelvis. If the heart or lungs are harvested, a Y-shaped incision of the pericardium is made, the ascending aorta is looped, and the superior vena cava is looped twice. After opening the pleura on both sides, the pericardium is split

as far as the superior vena cava to the junction of the azygos vein. Also, the ascending aorta is separated from the pulmonary artery. Then, the perfusion systems for the cannulation of the vessels for abdominal arterial perfusion, for cannulation of the ascending aorta for heart perfusion and the pulmonary artery for lung perfusion are prepared.

Synchronously, the thoracic and visceral organs are perfused with the cooled preservative solution. The venous circulatory system is relieved by draining the vena cava intrapericardially or intraperitoneally. Surface cooling with ice and custodiol perfusion lead to rapid cooling, to a reduction in oxygen consumption, and thus, to a maximum reduction of the metabolism, which allows the organs to remain functional under anoxia for a limited period of time. After perfusion and cooling, the thoracic organs are removed first. This is followed by the liver and pancreas, and finally, both kidneys are procured. After the organs have been removed, the thorax and abdomen are closed and sutured with wire, as is common in veterinary medicine. The pig carcass is then sent to rendering.

3.4 Aircrafts used in the study

Diamond DA42 aircraft

The aircraft is characterized by two powerful engines and good and smooth flight characteristics. The DA42 is powered by the Austro Engine 168hp AE300 with a single power lever control. The three blade MT hydraulic constant speed propellers feature advanced blade geometry for efficient performance, smoothness and low noise. Automatically controlled by each engine's digital engine control, feathering is as simple as flipping a single switch (22). For this reason, this specific plane is used worldwide for training and transport. It is easy to fly and burns fuel like a single engine, but with the added safety of a second engine (23). A picture of the aircraft is presented below {figure 9}.

The Diamond DA42 is regularly used for training flights in Graz. These training flights made it possible to study the effect of a one-hour flight on the explanted pig organs. Specifically, three flights under the exact same conditions took place in the airspace of Graz.

Figure 9: Diamond DA42 (22)

This aircraft is considered to be one of the most efficient in its class. The interior holds up to four people, who can travel with light luggage. The maximum flight altitude is 5486m above sea level. For an altitude above 2500m two oxygen cylinders are permanently mounted in the cockpit (23). From an altitude of 6000m upwards a pressurized cabin is mandatory for passenger transport (17). Due to the relatively low fuel consumption this specific plane is particularly suitable for training and for the national transport of persons or organs (23).

3.5 Perfusion und baggaging

The perfusion with custodiol solution as well as the packaging were carried out professionally, as defined in the official guidelines. The organs were perfused in situ with a total of five litres of irrigation fluid and then packed in three organ bags each. Before packing, a tissue sample was taken from each organ. For the packaging of the organs the three-chamber bag system was used. The first bag, which contains the organ, was air-evacuated, filled with custodiol solution and tied up; then, the second bag, was again air-evacuated, filled with cooled sodium chloride solution and tied up; finally, the third bag was air-evacuated and then tied up without any added liquid.

After the standard packaging procedure, the bags were stored on crashed ice and put in polystyrene boxes, which are closed with adhesive tape. The boxes are labeled and marked in detail and handed over to the transport service.

3.6 Transport/ flight

The transport of the sealed and marked transport boxes was carried out by a transport company, which took the boxes from LKH Graz to Graz Airport.
At the airport, the boxes were handed over to the pilot and lashed down in the luggage compartment of the aircraft. Figure 10 provides an impression of how the compartment of the plane looks like. After a flight of one hour, which was executed in compliance with the specified guidelines and flight altitudes, the boxes were handed over to the same transport driver at Graz Airport and returned to LKH Graz. At the LKH, the transport boxes were reopened for the first time after transport and two more tissue samples were taken from each organ.

Figure 10: Luggage compartment Diamond DA42 (23)

3.6.1 Time of transportation

We tried to carry out the ground-based transport from Graz hospital to the airport as quickly as possible and within a time frame of 20-25 minutes driving time {figure 11}. In order to avoid delays, the pilot was informed at departure from the hospital, and hence, already expected the organ boxes. After the one-hour test flight, the organs were handed over to the ground-based transport and they were returned to LKH

Graz. Thus, each of the three organ boxes was back at the hospital after a maximum of two hours. When the boxes were returned the second sample could be taken from the organs.

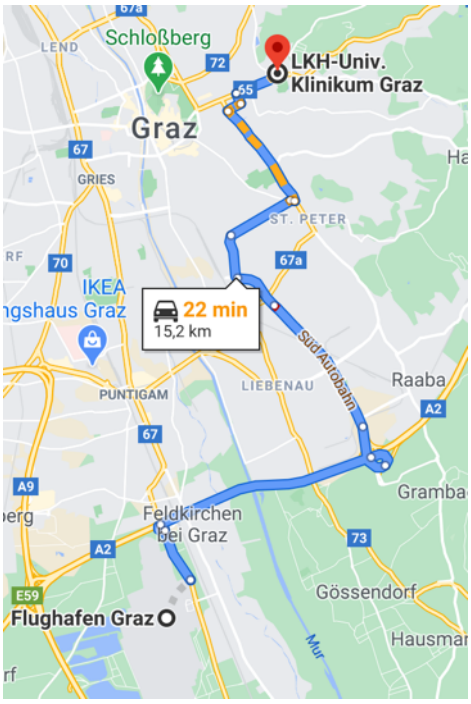


Figure 11: LKH Graz to Airport Graz (24)

3.6.2 Flight altitude and flight time

All three test flights with organ boxes had the same sequence of packaging, transport, flight altitude and flight duration. Also, as far as controllable, the three flights took place under nearly the same weather and air pressure conditions. The goal of the test flights was to achieve an altitude of 7000ft (2133m), because this altitude describes the physical value of a pressurized cabin during scheduled flights. Also, this is the altitude at which today's air balance cabins are calibrated (17). After the launch phase, the slow rise from ground to 3000ft over 4500ft to 7000ft took place. The aircraft remained at the altitude of 7000ft (2133m) for one to two minutes before slowly descending to 4500ft and further to 3000ft. After reaching 2133m above ground the landing approach was initiated and the aircraft returned to Graz Thalerhof Airport. Table 6 below shows the detailed records of the three organ flights. An attempt was made to create equal to similar conditions, which were only slightly influenced by traffic and weather.

date	27.03.18	24.04.18	22.05.18
Skin incision	08:00 a.m.	07:55 a.m.	08:38 a.m.
heparin	08:22 a.m.	08:28 a.m.	09:11 a.m.
heparin dose in i.U.	10.000	10.000	10.000
perfusion	08:25 to 08:35 a.m., 10 min	08:31 to 08:43 a.m., 12 min	09:15 to 09:30 a.m., 15 min
custodiol solution in ml	5000	5000	5000
explantation time	09:00 a.m.	09:12 a.m.	10:00 a.m.
start transport with car	09:30 a.m.	09:41 a.m.	10:28 a.m.
delivery at airport	09:45 a.m.	09:53 a.m.	10:41 a.m.
flight Nr.	1	2	3
pilot	C. W.	C. W.	C. W.
take off	10:00 a.m.	10:15 a.m.	10:50 a.m.
reaching and maintaining 3000 ft	10:04 a.m.	10:21 a.m.	10:56 a.m.
reaching and maintaining 4500 ft	10:13 a.m.	10:30 a.m.	11:04 a.m.
reaching and maintaining 7000 ft	10:24 a.m.	10:41 a.m.	11:14 a.m.
top of descent	10:39 a.m.	10:56 a.m.	11:29 a.m.
reaching and maintaining 4500 ft	10:45 a.m.	11:02 a.m.	11:35 a.m.
reaching and maintaining 3000 ft	10:51 a.m.	11:08 a.m.	11:40 a.m.
landing	10:56 a.m.	11:13 a.m.	11:46 a.m.
flight time	1:03 hrs	1:09 hrs	1:06 hrs
air time	56 min	58 min	56 min
level flight 7000 ft	15 min	15 min	15 min
start transport to hospital	11:00 a.m.	11:18 a.m.	11:51 a.m.
deliver at laboratory in hospital	11:14 a.m.	11:31 a.m.	12:02 p.m.

Table 6: Overview of explantation and transport data in study

The data presented in table 7 and shows a comparison of the three test flights. The data focuses on the changes in air pressure as the altitude of the aircraft increased and decreased during the individual test flights. Also, the data shows a comparison of the air temperature at the airport.

flight no. 1, weather: partly cloudy, 14,8°C	**airport**	**climb**	**climb**	**top of descent**	**descent**	**descent**	**airport**
flight altitude	1190ft	3000ft	4500ft	7000ft	4500ft	3000ft	1190ft
pressure	1029hPa	894hPa	849hPa	755hPa	849hPa	894hPa	1029hPa
flight no. 2, weather: sunny, 21°C	**airport**	**climb**	**climb**	**top of descent**	**descent**	**descent**	**airport**
flight altitude	1190ft	3000ft	4500ft	7000ft	4500ft	3000ft	1190ft
pressure	1033hPa	898hPa	852hPa	760hPa	852hPa	898hPa	1033hPa
flight no. 3, weather: sunny, 23°C	**airport**	**climb**	**climb**	**top of descent**	**descent**	**descent**	**airport**
flight altitude	1190ft	3000ft	4500ft	7000ft	3000ft	4500ft	1190ft
pressure	1032hPa	897hPa	851hPa	759hPa	851hPa	897hPa	1032hPa

Table 7: flight altitude vs. pressure data in study

3.6.3 Procedure after arrival at laboratory

After the arrival of the driver with the organ boxes, the organ bags were extracted from the cooled container, dried and checked for external damage.

Starting with the packaging of the heart, followed by the lungs, the liver, the pancreas, and finally, the kidneys, the outermost, non-liquid filled bag was removed. Then, the second bag filled with saline solution was disposed of and the innermost bag with the organ floating inside was set down. In the next step, the last bag was opened, and the organ was examined macroscopically to determine whether any external abnormalities were already visible. After that, one sample per organ was taken. After the procedure was completed on all organs, the organs and the packaging were disposed of according to regulations and the taken samples were sent to the pathology department at the LKH Graz for further histological examination. The exact same procedure was performed on all organs after they were returned to the hospital. After completion of the explantation, a total of 30 specimens were collected for histological examination at the pathology department.

3.6.4 Histological samples

Samples of each organ were fixed in 4% formaldehyde solution for a time period of 24 hours, cleaned with distilled water, dehydrated with 80% ethanol, infiltrated with wax and embedded in paraffin blocks. All samples were then cut in two µm thick sections, stained for hematoxylin and eosin and examined under light microscope by a pathologist.

4 Results

Three organ transports with porcine organs were used to find abnormalities in the transport box or the inside packaging and to identify macroscopic or histological changes of the organs in order to declare a transport with non-pressure-balanced airplanes as medically unacceptable. The previous knowledge regarding organ transplantation and preservation of organs was taken into account and attempts were made to find a cheap and fast transport alternative.

4.1 Macroscopic change

A total of three transports with two organ boxes each were performed. One of the boxes contained the heart and lung, while the second box contained the liver, pancreas and a kidney. A total of 15 organs were perfused, removed, packaged, transported and flown in standard packaging. Each of the organ boxes was returned to LKH Graz within 1.5 hours and was subsequently examined. Keeping the time of transport to a minimum, especially for the heart, is a top priority. After receiving the organ boxes, both the boxes as well as the organ bags were checked for external damage. No damage could be found on either of the bags or on the outside of the transport boxes. The sodium chloride solution used in the second organ bag showed no contamination or color changes during any of the transports. The innermost bag, which also contains the organ, was undamaged in all samples and the perfusion solution was not contaminated or discolored. Each organ was checked for external macroscopic abnormalities and changes, but no deviation from the condition before packaging and transport could be detected.

All organs were in the same macroscopic condition as shortly after explantation. No indication of changes could be detected. Table 9 presents a summary of all findings.

organ	Heart	Lungs	Liver	Pancreas	Kidney
box damaged	NO	NO	NO	NO	NO
package damaged	NO	NO	NO	NO	NO
solution difference	NO	NO	NO	NO	NO
any other conspicuity	NO	NO	NO	NO	NO
transported organs	3	3	3	3	3
histological samples taken	12	12	12	12	12
macroskopic change	NO	NO	NO	NO	NO

Table 8: macroscopical overview

4.2 Histological change

A histological sample was obtained from each organ before packing and upon return to the laboratory. All organ samples were examined in the Pathology Institute of the Medical University of Graz for histological changes before and after transport. As shown in the following tables no significant changes before and after the test flight could be detected {table 10-13}. Each organ had an unchanged normal architecture both before and after the flight and no inflammatory processes were detectable. No ischemic processes were detected either. The histological images did not show any abnormalities when images from before and after transport were compared. For better representation, evaluation and analysis, pictures of all histological sections were taken. As an example of this picture gallery the kidney sections before and after the flight are presented below {figure 12,13}.

	Liver	Heart	Kidney
flight 1	Normal architecture, mild portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, no interstitial inflammation, no signs of ischemia
flight 2	Normal architecture, no portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, no interstitial inflammation, no signs of ischemia
flight 3	Normal architecture, no portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, no interstitial inflammation, no signs of ischemia

Table 9: pre flight histology summary liver, heart, kidney

	Lung	Pancreas
flight 1	Normal architecture, mild peribronchial lymphocytic inflammation	Normal architecture, no inflammation
flight 2	Normal architecture, mild peribronchial lymphocytic inflammation	Normal architecture, no inflammation
flight 3	Normal architecture, mild peribronchial lymphocytic inflammation	Normal architecture, no inflammation

Table 10: pre flight histology summary lung, pancreas

	Liver	Heart	Kidney
flight 1	Normal architecture, mild portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, no interstitial inflammation, no signs of ischemia
flight 2	Normal architecture, no portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, no interstitial inflammation, no signs of ischemia
flight 3	Normal architecture, no portal inflammation	No signs of ischemia, no inflammation	Normal glomeruli, mild lymphocytic interstitial inflammation, no signs of ischemia

Table 11: After-flight histology summary liver, heart, kidney

	Lung	Pancreas
flight 1	Normal architecture, mild peribronchial lymphocytic inflammation	Normal architecture, no inflammation
flight 2	Normal architecture, mild to moderate peribronchial lymphocytic inflammation	Normal architecture, no inflammation
flight 3	Normal architecture, moderate peribronchial lymphocytic inflammation, focal calcifications	Normal architecture, no inflammation

Table 12: After-flight histology summary lung, pancreas

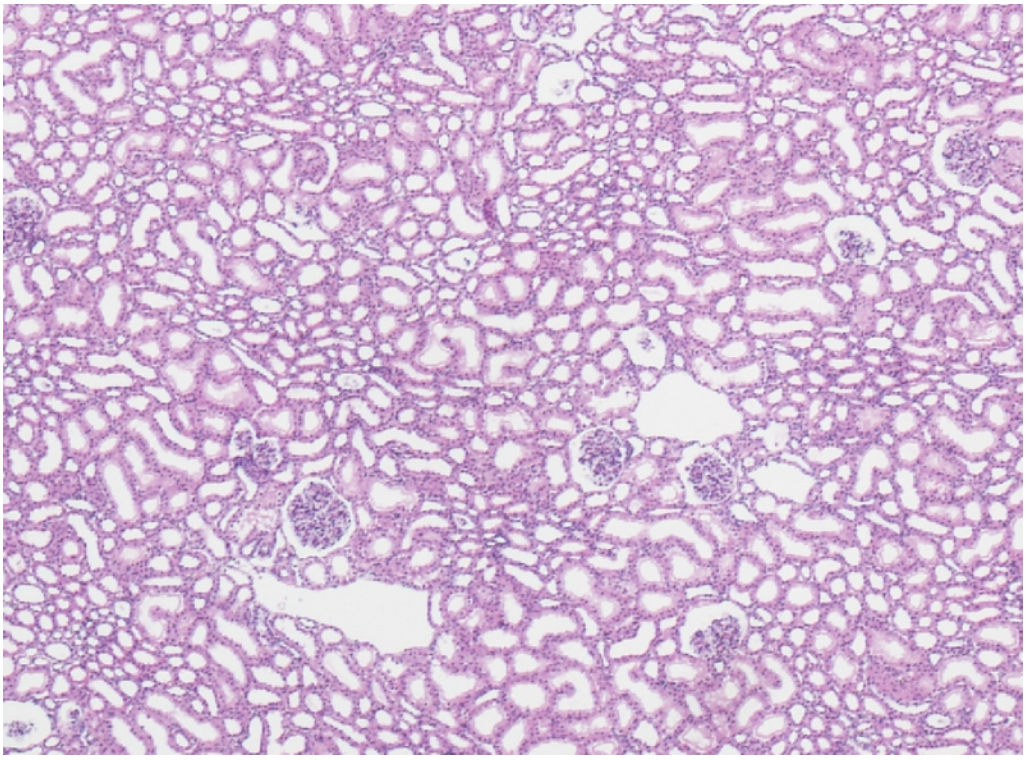


Figure 12: histological picture**,** pre-flight, flight 1, kidney, HE colouring, 300x enlarged

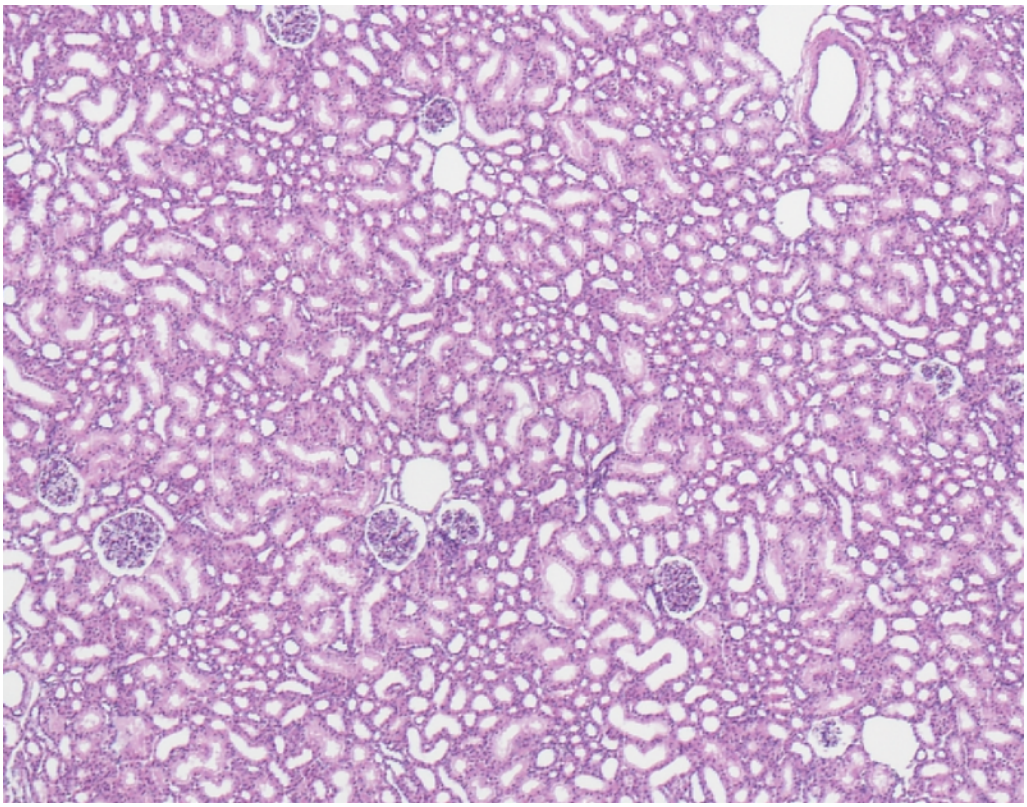


Figure 13: histological picture**,** post-flight, flight 1, kidney, HE colouring, 300x enlarged

4.3 Comparison of time and costs: aircrafts vs. cars

Using the example of an organ transport from LKH Graz to Munich, one can compare the resulting costs well in a table {table 14,15}. The given data are subject to the trade secret of the companies and have to be seen as a guideline; costs for individual cases can hence slightly differ. Therefore, the charged prices have to be considered as representative and not as fixed prices for this fictitious transport. The following aspects were included in the comparison: the kilometres to be covered, the time span, the costs, the locations, namely from Graz to Munich, ground-based transport with an emergency vehicle, a small airplane that is not pressure balanced and a previously used, common, pressure balanced transport jet {figure 14-16}. Here it is clearly evident that due to the long distance, the ground-bound transport and the consequently prolonged ischemic times, only the transport of kidneys would be reasonable and inexpensive. A travel time of 4.5 hours, without traffic delays, would exceed the tolerable ischemia time for any other organ. In this case, it would only be possible to cover the distance by car using machine perfusion; otherwise the organ will be damaged (14). It is obvious that air-bound transport in general would save much time. However, when comparing the two airplanes available, the enormous cost savings when using the smaller unpressurised plane are evident. The unpressurised propeller aircraft only needs 40 minutes more to cover the same distance and it only costs half the price. Still, prices may vary due to changes in wind and weather conditions.

This example comparison can be used for any city in Austria as well as cities in the immediate vicinity. These considerations could be groundbreaking in the future to decrease the total costs of organ transplantations and to keep the ischemia times of one or more organs to a minimum.

	car	**aircraft without pressure cabin**	**aircraft within pressure cabin**
	Skoda Octavia Combi	Diamond DA42	Eclipse 550
distance	386 km	225 km	225 km
needed time for distance	**4,5 hours**	**1,5 hours**	**50 minutes**
costs (within toll und tax fee)	**728 €**	**3400-4000 €**	**6400-7000 €**

Table 13: comparison of costs Graz to Munich car vs. plane (20,21)

	Skoda Octavia	Diamond DA42	Eclipse 550
costs without tolls and fees/ km	**0,85€/ km**	**18€/ km**	**31€/ km**
costs without tolls and fees/ min		44€/min	140€/ min
km per minute		2,5 km/min	4,5 km/ min

Table 14: comparison costs per km (20,21)

Figure 14: BKTW RK Graz (25) and Google Maps Graz to Munich by car (26)

Figure 15: Diamond DA42 (22) and Google Maps Graz to Munich by plane (27)

Figure 16: Eclipse 550 jet, pressurized (28)

5 Discussion

The total costs from explantation to the transplantation of an organ, including all transport, personnel and material costs, add up to large amounts of money (17). The complex process and coordination of an organ transplantation offers opportunities to minimize costs and save resources on certain levels since time management must be the top priority. Due to the fast availability of necessary vehicles and airplanes it is usually impossible to reduce costs (18). The idea for this investigation and study arose during my work as a transplant coordinator, because of several discussions with our pilot and flight provider for organ transports. The possibility of using smaller non-pressurized cabin balanced aircrafts for the national and international transport of organs, and thus, saving costs was the main focus. For the flight providers it would be possible to use several smaller airplanes for organ transports. Furthermore, due to the lower weight and the legal requirements, it would be viable to use smaller airports for take-off and landing procedures, and hence, more money could be saved regarding landing and usage costs at airports. In order to be able to use smaller airplanes, first of all the pathophysiological and histological changes of organs have to be investigated. Flight times and flight altitude are an important point as well, which were determined in the preliminary discussion with all people involved. One way to save costs and increase efficiency would be to use smaller, less fuel-efficient aircrafts that are not pressure-balanced. These means of transport would only be marginally slower and would hardly prolong the ischemic time compared to ground-based transport. Especially in connection with the increasingly researched machine perfusion, this is a path that should prove itself in the future (7). The use of machine perfusion shows considerable progress in the regeneration and also conservation of explanted organs. Many studies show the successful application of these devices and trend-setting results will follow soon. The current attempt to force transport by air still fails due to higher costs and the persisting research focus on the technology of perfusion machines (11–13).

It is possible to use smaller, non-pressure balanced airplanes for organ transport and thus minimize costs. Taking into account the distance and the associated change in ischemia times, the transport of organs could be coordinated and carried out more cost-efficiently without losing too much time and without damage to the organ in question (9). Research into machine perfusion will certainly be accompanied by research into the transport compatibility of the devices with aircrafts

(12). The resulting costs for the choice of the transport method, namely ground- or air-bound, could not be more different. Thus, the costs for ground-based transport are calculated with approx. 0,85€/ km and the air-bound transport with non-pressure-balanced airplanes with approx. 108€/ flight minute (20,21).

Likewise, the macroscopic examination of the organs, their packaging and the histological evaluation of the frozen samples showed that no pathological changes in the transported organs could be identified. For these temporally justifiable organ transports, no pathology of the samples could be detected overall. It would be important to consider this aspect in the future.

It will certainly be necessary to continue research on this topic, especially to take a closer look at the pathophysiological processes in organs. To consider these processes in the coordination and organization will a challenge for the future, also with regard to the acquisition and availability of smaller aircrafts in the national and international setting (1).

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