

Organ Perfusion for Uterus Transplantation in Non-Human Primates With Assumed Procurement of a Uterus From a Brain-Dead Donor

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ABSTRACT

Background. Clinical studies of uterus transplantation have been performed to treat uterine factor infertility. Because the uterus is a pelvic visceral organ, the method of perfusion for the procurement of vital organs from a brain-dead donor should be modified for removal of the uterus. Herein, we report the results of a preliminary study in cynomolgus monkeys of a new perfusion method for uterus transplantation with assumed procurement of a uterus from a brain-dead donor.

Methods. Cynomolgus monkeys were used; thoracolaparotomy was performed on the donor. A perfusion catheter was then placed into the unilateral femoral artery and/or external iliac artery. Cross-clamping was performed for the aorta under the diaphragm and the inferior vena cava was divided in the pleural space. The perfusion solution was then administered via the catheter to perfuse all organs in the abdominal cavity, including those in the pelvic cavity. After the perfusion, gross observation and histopathological examination of abdominal organs were conducted.

Results. Gross findings showed that all abdominal organs turned white in all specimens, indicating favorable perfusion of the uterus and all other organs in the abdomen. Pathological findings showed that almost no hemocytes were observed in the vessels of each organ.

Conclusions. With perfusion via the femoral artery and/or external iliac artery, all organs in the abdominal cavity, including the uterus, could be perfused. It was suggested that this technique could be useful for uterus transplantation assuming the procurement of a uterus from a brain-dead donor.

UTERUS TRANSPLANTATION (UTx) has become a potential option for women with uterine factor infertility to have a child [1,2]. A total of 11 cases of UTx have been conducted in Saudi Arabia [3] in 2000, Turkey [4,5] in 2011, and Sweden [6–8] in 2012, with a living donor, a brain-dead donor, and living donors, respectively. Brännström et al [7] achieved the first human delivery after UTx in 2014, and, to date, 4 babies have been born after UTx from living donors [9]. There is only 1 case of UTx from a deceased donor at present [4]; however, UTx from deceased donors should be given priority over UTx from living donors, based on the risks for living donors [10].

Therefore, UTx from deceased donors is likely to become common in many countries.

Abdominal organs that are currently removed from deceased donors are vital (life-supporting) organs outside

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the pelvis, although the uterus is located inside the pelvis. The current perfusion method does not target organs inside the pelvis, and thus the uterus is not perfused. Therefore, a new system is required to perfuse organs inside the pelvis during performance of UTx. Such a system should also maintain sufficient perfusion of vital organs and have no adverse effects on these organs. Herein, we report the results of a preliminary study in cynomolgus monkeys of a new perfusion method for UTx with assumed procurement of a uterus from a brain-dead donor.

METHODS

Animals

Three female cynomolgus monkeys (*Macaca fascicularis*) ages 6 to 9 years and with an average body weight of 3.33 ± 0.45 kg were used in the study. Anatomical pelvic structures in cynomolgus monkeys are almost the same as those in humans [11]. The study was performed in accordance with the recommendations in the *Guide for the Care and Use of Laboratory Animals* of the National Research Council. The original experimental protocols were approved by the Animal Care and Use Committee of the Research Center for Animal Life Science, Shiga University of Medical Science, Japan (permit No. 2013-4-2).

Surgical Procedure

Thoracotomy was performed, and vessels of the aorta under the diaphragm, of the inferior vena cava in the pleural space, and those surrounding the uterus were exposed. Perfusion catheter placement was attempted in the unilateral femoral artery first, then the external iliac artery. Because the femoral arteries in the 3- to 4-kg cynomolgus monkeys were too narrow to insert a catheter and administer the perfusate (except for 1 case), the unilateral external iliac artery in the abdominal cavity was used for catheterization in all 3 cases. After intravenous administration of heparin, cross-clamping was performed by clamping the supra-iliac aorta under the diaphragm and dividing the inferior vena cava in the pleural space, allowing the decompression of the intra-abdominal inferior vena cava. Simultaneously, the abdominal and pelvic cavities were filled with crushed ice and the abdominal organs were cooled. The administration of the perfusion solution (histidine + tryptophan + ketoglutarate at 4°C, 200–300 mL) was started right after the cross-clamping via the catheter to perfuse all organs in the abdomen (Fig 1). Flushing was stopped once the color of organs and discharged fluid were changed to lighter, white, or clear.

Gross Observation and Histopathological Findings

After perfusion, the color of abdominal organs (small intestine, liver, pancreas, kidney, uterus) was observed. Subsequently, these organs were removed and samples were fixed with 10% formalin neutral buffer solution, dehydrated, embedded in paraffin, and cut into 4- μ m sections. The sections were stained with hematoxylin and eosin. A histopathological examination was conducted to determine whether blood had been replaced by perfusion solution in vessels of organs.

RESULTS

With organ perfusion via the unilateral external iliac artery in 2 cases and the femoral artery and contralateral external

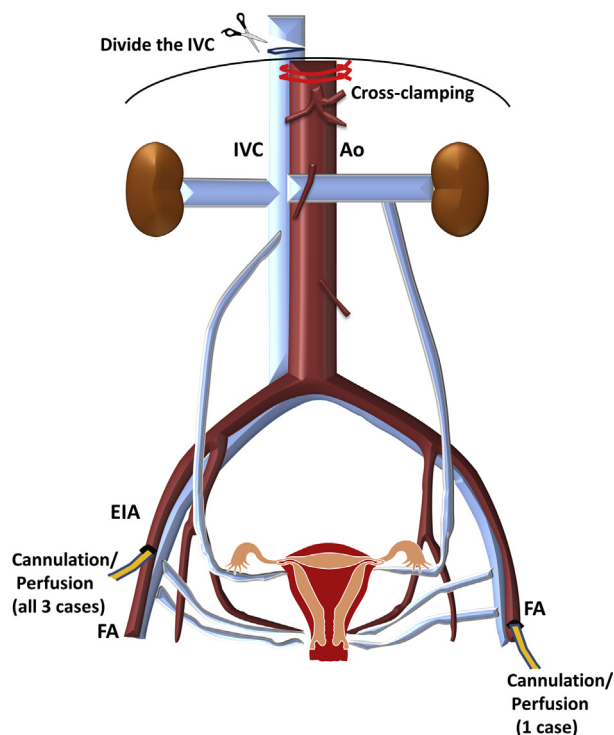


Fig 1. Surgical procedure for organ perfusion. Sites of cross-clamping of the aorta, dividing of the IVC, and placement of the catheter in the femoral artery and/or external iliac artery. Ao, aorta; IVC, inferior vena cava; FA, femoral artery; EIA, external iliac artery.

iliac artery in 1 case, gross findings showed that all abdominal organs turned white or lighter in all specimens, indicating favorable perfusion of the uterus and all other organs in the abdomen (Fig 2). There was no difference for organ perfusion between via the unilateral external iliac artery and via the femoral artery and contralateral external iliac artery. Pathological findings showed that the veins and lymphatic vessels of each organ were expanded, but almost no hemocytes were observed in these vessels, indicating sufficient perfusion in tissues (Fig 3).

DISCUSSION

UTx is an option for women with uterine factor infertility to have a child, and the uterus can be removed after delivery; therefore, UTx is a temporary transplantation. This differs markedly from transplantation of vital organs, for which lifetime treatment with immunosuppressants is often required. Therefore, vital organs should be removed from deceased donors in order, with the uterus as the last organ to be removed. In an evaluation of the feasibility of human uterus retrieval in a brain-dead donor, Gauthier et al [12] found that the cold ischemic time was prolonged to about 70 minutes by removing the uterus last; however, human uterine myometrial tissue was found to be resistant to cold

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