Uterus transplantation in the baboon: methodology and long-term function after auto-transplantation

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BACKGROUND: Techniques for uterus transplantation (UTx) have been developed in rodent/domestic animals towards future clinical introduction of UTx to treat uterine factor infertility. The aim of this study was to extend the UTx research into a non-human primate species by developing surgical techniques for uterus retrieval and transplantation in the baboon.

METHODS: Female baboons (n = 15) underwent surgery, with the initial five animals used for studies of pelvic vascular anatomy. Retrieval surgery included isolation of the ovarian veins and the uterine arteries together with the anterior branches of the internal iliacs. The utero-tubal-ovarian specimen was removed, flushed and kept ex vivo for 2 h when the two arterial ends and two venous ends were anastomosed side-to-side to construct one arterial and one venous end. These were, at auto-transplantation, anastomosed end-to-side to the external iliacs and the animals (n = 10) were evaluated concerning cyclicity and later by laparoscopy/laparotomy.

RESULTS: The total duration of organ retrieval, backtable preparation and transplantation was around 6 h with an overall ischaemic time of the specimen of about 3 h. One animal died due to cardiomyopathy. Five out of the nine surviving animals resumed menstruation, indicating re-established ovarian and uterine function. Laparoscopy confirmed normal-sized uteri in these two animals.

CONCLUSIONS: This study demonstrates the feasibility of UTx by vascular anastomosis in a non-human primate species. The low success rate demonstrates the complexity involved in UTx surgery and the need for further methodological developments.

Key words: baboon / infertility / transplantation / uterus

Introduction

Uterus transplantation (UTx) may in the future become a treatment for permanent uterine factor infertility (Brännström et al., 2003; Altchek, 2003; Brännström and Wranning, 2007) and thereby an alternative to gestational surrogacy, which is not allowed in large parts of the world due to legal, ethical or religious issues (Nakash and Herdiman, 2007). The causes of uterine factor infertility may be either congenital Müllerian anomaly, such as the Rokitansky syndrome (Guerrier et al., 2006), previous hysterectomy (Kwee et al., 2006; Sonoda et al., 2004), or a non-functional uterus due to intrauterine adhesions (Al-Inany, 2001) or leiomyoma (Oliveira et al., 2004). The total group of patients with uterine factor infertility comprises a relatively small group among infertile patients (Grimbizis et al., 2001), but since no treatment has been available, more than 12 000 potential UTx patients may exist in the UK alone (Sieunarine et al., 2005).

To find treatments for tubal factor infertility, the dog was initially used in research involving utero-tubal transplantation (Eraslan et al., 1966; Barzilai et al., 1973; Paldi et al., 1975). The successful introduction of IVF was most likely the cause of a closedown of the research activity within this research field, which however was reinitiated less than 10 years ago after the first and so far only human UTx attempt (Fageeh et al., 2002). Our opinion is that a non-life-saving surgical innovation, such as UTx, should be introduced in a human setting only after extensive research and training in several animal species. Thus, we and others have, during the last decade, developed UTx models in the mouse (Racho El-Akouri et al., 2002; Racho El-Akouri et al., 2003), the rat (Jiga et al., 2003; Wranning et al., 2008a), the pig (Sieunarine et al., 2005 Wranning et al., 2006; Avison et al., 2009) and the sheep (Ramirez et al., 2008; Dahm-Kähler et al., 2008). However, it is necessary to extend these animal studies to also include studies in a non-human primate model before a second
human UTx is attempted, as also stated in recent FIGO ethical guidelines concerning UTx (Milliez, 2009). For our research purpose, we choose the baboon as a suitable primate model because of its relatively large size and because its uterine anatomy and reproductive physiology closely resemble that of the human (Nyachieo et al., 2007).

**Materials and Methods**

**Animals**

The study protocol was approved by the Institutional Scientific Evaluation and Review Committee (ISERC) and the Animal Care and Use Committee of the Institute of Primate Research, Nairobi, Kenya. Fifteen healthy adult female olive baboons (Papio Anubis; 9.5–16.6 kg) with regular menstrual cycles over the last months were included. The animals were fed a commercial monkey diet with additional supplementation of fruits and vegetables three times weekly.

**Anaesthesia**

On the day of the surgery, the animal was given an im injection [100 mg for body weight (bw) < 10 kg and 200 mg for bw > 10 kg] of ketamine (Agraket®), Agrar Holland BV, Soest, Holland combined with 10 mg xylazine (Ilium Xylazil®, Troy Lab Pty Limited, Smithfield, Australia) to induce anaesthesia and was then brought into the operating theatre. After administration of Xylocain spray orally, the animal was intubated. Anaesthesia was maintained using halothane to minimal alveolar concentration of 1.3 and an oxygen/nitrous oxide mixture to secure the haemoglobin saturation to above 97%. Sulfadoxine with trimetoprim (15 mg/kg bw; Bimotrim®, CEVA Vetpharma, Lund, Sweden) and metronidazol (5 mg/kg bw; Flagyl®, Sanofi-Aventis, Bromma, Sweden) were given iv after induction of anaesthesia as initial prophylactic antibiotics. To compensate for fluid loss during surgery, the animal received continuous iv infusion of 0.163 M NaCl at a rate of 3 ml/kg/h according to our local tradition for iv fluid during surgery in children (The Queen Silvia Children’s Hospital, Stockholm, Sweden) and Review Committee (ISERC) and the Animal Care and Use Committee (Animal Welfare Act, Sweden). Heparin (3000 IU; LEO Pharma, Malmö, Sweden) was given iv 15 min before clamping of blood vessels that were severed were doubly ligated (5–0 Vicryl®, Johnson & Johnson, New Brunswick, NJ, USA) or closed by surgical clips (Premium Surgiclip II®, Covidien, Gosport, UK). The dissection then continued on the pelvic sidewall and the umbilical artery was divided around 5 mm distal to the uterine artery bifurcation. The small stump of the umbilical artery was then used as a point for upward traction of the uterine artery during subsequent dissection of the artery proximally to the point of the branching between the anterior and posterior portions of the internal iliac artery and distally to a point around 1 cm above the plane of the ureter. Generally, there were 3–4 arteries with accompanying veins that branched anteriorly from the uterine vessels on each side (Fig. 1). These branches were severed after ligations on the side towards the uterine artery and after bipolar diathermic coagulation on the side towards the pelvic sidewall. The ureter was then dissected free from its attachments to the cervix and the uterine vessels all the way to its inflow into the bladder. This procedure also involved severance of the ureteric artery and vein, branching from the uterine vessels. The entire dissection procedures of the vessels and the ureter were then repeated on the contralateral side.

The rectum was separated from the upper vagina by unipolar diathermy. The large vaginal veins and arteries, which run on the lateral aspects of the vagina and anastomose with the descending branches of the uterine vessels, were mobilized from the vagina and severed at a level around 5 mm caudal to the portion of the cervix. The vagina was then closed using surgical loupes (magnification ×2.3). A midline incision from the pubic bone up to the level of the umbilicus was performed and the intestines were packed into the upper abdomen. The vascular anatomy of the internal genitals organs of the baboon resembles that of the human female, as illustrated in Fig. 1.

**Primary surgery and backtable preparation**

The baboon was positioned in dorsi-ventral recumbency position and the abdomen was shaved, disinfected with 1% chlorohexidine solution and draped. The vagina was cleaned with 0.1% chlorohexidine solution and the urinary bladder was emptied by a transurethral catheter, which was kept during surgery to enable measurement of urinary output. All surgical procedures were performed using sterile techniques and the two surgeons used surgical loupes (magnification ×2.3). A midline incision from the pubic bone up to the level of the umbilicus was performed and the intestines were packed into the upper abdomen. The vascular anatomy of the internal genitals organs of the baboon resembles that of the human female, as illustrated in Fig. 1.

During the dissection procedures, unipolar (20–40 W; ValleyLab Force, ValleyLab, Boulder, CO, USA) and bipolar (8–16 W; CoaComp Biocoagulator, Instrumenta AB, Bilidal, Sweden) diathermy were used to minimize bleeding. The initial steps of the retrieval surgery were dissection of the bladder peritoneum from the anterior portion of the cervix and mobilization of the largest ovarian vein of the infundibulopelvic ligament in a cranial direction up to the level where it crosses the ureter. All blood vessels that were severed were doubly ligated (5–0 Vicryl®, Johnson & Johnson, New Brunswick, NJ, USA) or closed by surgical clips (Premium Surgiclip II®, Covidien, Gosport, UK). The dissection then continued on the pelvic sidewall and the umbilical artery was divided around 5 mm distal to the uterine artery bifurcation. The small stump of the umbilical artery was then used as a point for upward traction of the uterine artery during subsequent dissection of the artery proximally to the point of the branching between the anterior and posterior portions of the internal iliac artery and distally to a point around 1 cm above the plane of the ureter. Generally, there were 3–4 arteries with accompanying veins that branched anteriorly from the uterine vessels on each side (Fig. 1). These branches were severed after ligations on the side towards the uterine artery and after bipolar diathermic coagulation on the side towards the pelvic sidewall. The ureter was then dissected free from its attachments to the cervix and the uterine vessels all the way to its inflow into the bladder. This procedure also involved severance of the ureteric artery and vein, branching from the uterine vessels. The entire dissection procedures of the vessels and the ureter were then repeated on the contralateral side.

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then divided by unipolar diathermy at that level. Blood flow through the uterus remained throughout the entire dissection part of the surgery, also at the end when the uterus only was attached by the uterine arteries and the infundibulopelvic ligaments (Fig. 2). The infundibulopelvic ligaments and the anterior portions of the iliac arteries were then clamped and severed. The specimen, including the uterus with a vaginal rim, the oviducts and the ovaries, was removed from the abdominal cavity and put on sterile ice slush of 0.163 M NaCl.

During backtable preparation, which is described below, the uterus was positioned with its posterior side facing upwards and kept on ice slush during the entire procedure. The surgeon was aided by surgical loupes (magnification × 6). To remove blood from the organ, Teflon catheters (inner diameter 0.64 mm; Terumo, Leuven, Belgium) were inserted through the distal ends of the anterior divisions of the internal iliac arteries and advanced into the uterine arteries followed by ligatures around the vessel ends and catheters. The specimen was then gently flushed with approximately 40 ml Ringer-Acetate through each uterine artery. The largest ovarian vein on each side was identified and the end of this vein was dissected free for a distance of around 10 mm. Other ovarian veins and the ovarian artery were ligated or coagulated by bipolar diathermy. The ovarian veins to be used were then cleaved for a distance of around 7 mm and then joined by interrupted sutures (9-0 nylon; S&T AG, Neuhausen, Switzerland) to create a larger vessel (Fig. 3). A similar procedure was performed on the uterine artery (Fig. 3) using interrupted suture (8-0 nylon; S&T AG).

The external iliac artery and vein on the left side of the animal were dissected free over a distance of about 30 mm. Vascular clamps were placed on both ends of the isolated segments of the external iliac vein and artery. Incisions were made in the external iliac vessels and the vein and the artery of the specimen were anastomosed end-to-side (Fig. 4a) by continuous sutures (8-0 Prolene®, Johnson & Johnson). The vaginal cuff was then reattached to the vagina by continuous suture (4-0 Vicryl®, Johnson & Johnson) and the same kind of suture was used to attach the uterine body to the round ligaments. Adequate uterine bloodflow after reanastomosis was judged by pulsations of the uterine arteries and capillary refill of the serosal surface of the uterus. The abdomen was closed by continuous sutures of the fascia (1-0 polydioxanone; Johnson & Johnson) and the skin (3-0 Vicryl®, Johnson & Johnson).

**Monitoring of cyclicity and mating**

In the baboon, the perineum changes its appearance in a cyclic manner which is related to the hormonal changes of the menstrual cycle. The baboon menstrual cycle length is generally 33 ± 2 days and is determined by counting the days from the first day when perineal turgescence appears of one cycle until the day of reappearance in the following cycle (Stevens, 1997). The cycle can be divided into nine stages, where Stage 0 is the menstrual phase, Stages 2–6 are follicular phases, Stages 7 and 1 are luteal phases and Stage 8 is pregnancy phase. During the postmenstrual phase (Stage 2), the perineum is at rest (deflated) and during the following two stages the perineum increasingly inflates. Post-ovulation/secretory phase (Stage 5) is characterized by maximal perineal inflation and is followed by the luteal/secretory phase (Stages 7 and 1) with increasing turgescence. The perineal area starts to deflate during the premenstrual phase (Stage 1) and ends up in the menstrual phase (Stage 0) if pregnancy phase (Stage 8) does not occur. The changes in perineal appearance were determined by daily observations by experienced animal technicians using the numerical grading system, as described above, and noted on a chart for each baboon.

**Second-look laparoscopy and laparotomy**

The anaesthesia was identical to that used for primary surgery. At laparoscopy, insufflation was performed through a Verres needle to an intra-abdominal pressure of 10 mmHg. The laparoscope was introduced via an umbilical incision. Antibiotics or anti-coagulants were not given. The animals were euthanized during anaesthesia by i.v. fenobarbital (Fenemal Recip®, Recip AB, Solna, Sweden).

**Histology**

Biopsies (uterus and ovary) were fixed in formaldehyde, embedded in paraffin, sectioned and stained with haematoxylin and eosin.
Results

Surgical parameters
During the initial dissection studies in five animals, it was found that the ovarian veins were considerably larger in diameter than the uterine veins. Consequently, we decided to use the ovarian veins for end-to-side anastomosis on the external iliac veins in the auto-transplanted animals (n = 10). The durations of anesthesia and surgery in the auto-transplanted animals (n = 10) were 7 h 11 ± 29 min (mean ± SEM) and 6 h 1 ± 29 min, respectively. The procedure of utero-tubo-ovarian retrieval lasted for 2 h 43 ± 20 min and bleeding was minimal. When the specimen had been retrieved, flushing through the two uterine arteries ex vivo resulted in outflow of blood through the ovarian veins and blanching of the specimen in all cases. The duration of backtable preparation was 1 h 43 ± 28 min.

Dissection of the anastomosis site of left external iliacs lasted for around 30 min. The duration of anastomosis surgery (Fig. 4b), a time period when the specimen was gradually warmed up after cold ischaemia, was 1 h 7 ± 13 min. The total ischaemic (cold plus warm) period lasted for 2 h 51 ± 21 min. In all the 10 animals, immediate blood flow through the organ occurred after anastomosis and removal of vascular clamps, with transition of the organ from whitish to reddish, pulsations through the uterine artery and a filled outflow vein.

Overall outcome and cyclicity
The overall outcome of the 15 baboons used in the present study is summarized in Fig. 5. One of the 10 auto-transplanted animals had frequent periods of tachycardia of around 130 bpm during surgery and died during the first post-operative night. An autopsy showed a clear hypertrophy of the left cardiac ventricle (sign of cardiomyopathy). Intra-abdominal bleeding or pulmonary embolism was not present. Out of the remaining nine animals, five showed resumed cyclicity after auto-transplantation. Two of these five animals exhibited cyclicity within the first two post-operative weeks and menstrual stage (Stage 0) was also seen in these animals (Fig. 6a). In the other three animals, the cyclic pattern appeared after a post-operative lag phase of 2–4 months and menstruation stage did not appear (Fig. 6b).

Second-look surgery observations and histology
In the four animals, which did not show any signs of a cyclic pattern, a laparotomy was performed around 4 months after primary surgery. In these animals, there were no signs of any remnant of the utero-tubal-ovarian specimen. The omentum was adhered to the area of the vaginal vault, the rectum and the pelvic sidewalls.

In the five animals exhibiting a cyclic pattern after autotransplantation, laparoscopy was performed 2–3 months after primary surgery. In the three animals with cyclic pattern, but with
initiation after a lag phase and with no menstruation (Fig. 6a), the uterus could not be visualized also after omental adhesions to the lower pelvic region had been removed. A subsequent laparotomy 4 months after primary surgery revealed absence of the uterus but ovaries could be seen on the pelvic sidewall and the presence of ovarian tissue was confirmed by light microscopy (Fig. 7a).

In the two animals with immediate cyclic pattern (Fig. 6b), laparoscopy 4 months after primary surgery revealed some omental adhesions and, loosely attached to the pelvic side wall, a normal-sized uterus with normal-sized ovaries was seen. These two animals were allocated for timed mating for repeated cycles for >10 months but no pregnancy occurred. Subsequent laparotomy (17 and 19 months after primary surgery) revealed adhesions around the ovaries and the animals were on these occasions euthanized. Light microscopy confirmed the presence of viable endometrium (Fig. 7b).

Discussion

Research on experimental UTx is ongoing at several research centres worldwide. The UTx research within our group started 10 years ago and was initiated by a suggestion from a patient that had undergone a radical hysterectomy due to cervical cancer. Since that time several animal models for UTx research have been put forward and one single case of human UTx (Fageeh et al., 2002) has also been presented. This human case failed and a necrotic uterus, which had been retrieved from a living donor, was removed 3 months after transplantation. It is not clear whether the vascular thrombosis of the uterine arteries/veins and the necrosis of the allogenic transplanted uterus were due to factors related to surgery, ischaemia–reperfusion injury or rejection. Nevertheless, the poor outcome of this human UTx case clearly demonstrated that a new innovative surgical procedure such as UTx should reach the clinical stage only after solid research in experimental animals have optimized the procedure to minimize the risks. The patient groups that may benefit from UTx are those that are absolute uterine factor infertile due to lack of

![Figure 6](image-url) Graphs of cycle patterns of one transplanted animal with onset of cyclicity after a lag phase and with no menstruation (a) and another transplanted animal with signs of immediate resumption of cyclicity after transplantation and with menstruation (b). The different cycle phases are described in Materials and Methods.

![Figure 7](image-url) Representative light micrographs of ovary (a) and uterus (b) obtained after auto-transplantation. The ovarian sample (a) is taken 6 months after transplantation in an animal that showed ovarian tissue but no uterus remnant at second-look laparoscopy. A small follicle with an oocyte is seen. The uterine biopsy (b) is taken at laparotomy 18 months after transplantation in an animal that showed immediate and continuous cyclicity after transplantation. Normal endometrium and myometrium are seen.
the human female are of a reasonable diameter, with some overriding study. However, the uterine veins that follow the uterine artery in course not be feasible to use the ovarian veins as in the present donor. In a human UTx situation with living donor, it would of gacy to acquire genetic motherhood, but this procedure is not erable leiomyoma). An alternative to UTx would be gestational surro-

gacy of this species. The initial plan was to obtain arterial vascular pedicles up to and including the anterior branch of the internal iliac artery and venous vascular pedicles including the largest uterine vein on each side. However, we found that the uterine veins that accompany the uterine artery towards the pelvic sidewall in the baboon were in most cases thin. Instead, the largest venous outflow from the uterus seemed to be through the ovarian veins and through veins that run in close proximity to the vaginal arteries, on the lateral aspect of the cervix and vagina. Since, the vagina would be transected as part of the transplantation procedure with severance of the vaginal arteries and veins at a level just below the cervix, a potential venous anastomosis site involving the vaginal veins would be at this level. This site, deep in the pelvis, is fairly inaccessible for vascular microsurgery and it would also be at a location immediately adjacent to the vaginal anastomosis, which is a potential site for post-operative infections. The ovarian veins are prominent and extended vascular pedicles can easily be obtained, which in turn will facilitate vascular anastomosis surgery at transplantation.

The auto-transplantation method used in the present study has similarities to a clinical situation with organ retrieval from a living donor. In a human UTx situation with living donor, it would of course not be feasible to use the ovarian veins as in the present study. However, the uterine veins that follow the uterine artery in the human female are of a reasonable diameter, with some overriding the ureter together with the uterine artery and some passing in between the ureter and the cervix. Thus, in a human UTx situation, it would be quite realistic to use the largest uterine vein on each side and that would avoid oophorectomy at uterus retrieval.

The ovaries and the oviducts were included in the specimen that was auto-transplanted. In a human UTx situation, only the uterus will be transplanted. It would of course have been possible to auto-transplant only the baboon uterus but then the ovaries and oviducts would have to be removed at surgery, since the ovarian veins were used with the technique that we developed. However, the inclusion of the ovaries was evaluated to be beneficial for purposes of non-invasive follow-up of the animals. Hence, resumed cyclicity would indi-
cate a successful auto-transplantation procedure. In line with this, the four animals with no signs of cyclicity proved to have a total elimination of the uterus and also no ovaries at second-look laparoscopy. The results of the study also showed that in the cases with a late resumed cyclic pattern, after a lag-phase of 2–3 months, the uterus had disappeared but viable ovarian tissue was still present. Since both the transplanted uterus and the ovaries were supplied by the uterine arteries, the interpretation of these results is that the capacity of survival for a long period of warm ischaemia and then to become re-vascularized is greater concerning the ovary than the uterus. In the human setting, it is known that ovarian cortical strips that are transplanted fresh (Silber et al., 2005) or after freeze–thawing (Donnez et al., 2004) survive after avascular transplantation to the pelvis, although detailed studies in the sheep indicate that >60% of the primordial follicles do not survive the ischaemic conditions that may exist for some days (Baird et al., 1999). The lag phase of 2–3 months before resumed cyclicity in the animals with surviving ovarian tissue but disappearance of uterus of the present study indi-
cate that the larger follicles do not survive the ischaemic conditions and that the new wave of larger follicles and corpora lutea that give rise to the cyclic pattern are recruited from the pool of immature fol-
icles, with a developmental time to the antral stage of 60–90 days. In spite of cyclic pattern and menstruation in the two successfully trans-
planted baboons, repeated time mating did not result in any pregnan-
cies. At the final laparotomy of these animals, around 1.5 years after transplantation, abundant adhesions were noted around the ovaries and the oviducts. Thus, the chance for spontaneous pregnancy was accordingly low. In the old studies of UTx by omental wrapping in the rhesus macaque, resumed menstruation was also seen but mating trials did not result in any pregnancy (Scott et al., 1971). It was speculated that this was due to an inability to preserve tubal patency. Thus, the ischaemic damage to the tissue that occurs after vascular or avascular transplantation seems be especially harmful to the oviducts.

The results of the present study with two of nine animals exhibiting surviving uteri show that this type of surgery is difficult. The poor results are in spite of the surgeons of the team having wide experience of vascular UTx in rats (Wranning et al., 2008a), sheep (Dahm-Kähler et al., 2008) and pigs (Wranning et al., 2006).

Out of the 10 animals that were intended for auto-transplantation, all survived surgery but one death occurred during the first post-operative day. That animal showed periods of tachycardia during the operative day. That animal showed periods of tachycardia during the operative day.
rate of the animals in this initial study in the baboon is considerably higher than we previously experienced in syngenic UTx in the mouse (Racho El-Akouri et al., 2002) and rat (Wranning et al., 2008a, b) as well as in utero-tubal-ovarian auto-transplantation in the sheep (Wranning et al., 2010). The long-term survival of the remaining nine animals indicates that a living donor concept in a human situation would be reasonable.

The duration of surgery in the present study was around 6 h, but this involved retrieval surgery, backtable preparation and transplantation. In a human situation, we think that the retrieval surgery of the donor would be somewhat shorter than the surgical time for retrieval of around 2 h 45 min of the present study. The shorter time would be because the blood vessels would be considerably larger, the surgeons would be more familiar with the human anatomy and the surgical instruments used would be optimized for human use.

There exist of course several alternatives for vascular anastomosis and placement of a transplanted uterus. In the present study, the uterus was transplanted to an orthotopic position, although with the uterus somewhat lateral to the midline to allow vascular connections to the external iliac vessels. This is a similar approach to that which we have used for auto-transplantation of the uterus in the sheep, where fertility has been also demonstrated (Wranning et al., 2010).

There exist other alternative non-human primate species that could be considered for UTx research. The most widely used animal for research in reproductive biology is the rhesus macaque, which also has the advantage of existence of IVF protocols with reasonable pregnancy rates (Zelinski-Wooten et al., 1994). In a future human UTx situation, we would recommend that IVF is carried out before the UTx procedure to ensure fertility within the couple and to minimize exposure of the oocyte to immunosuppressive medication. Moreover, the oviducts would preferably not be transplanted. Concerning the baboon model, a disadvantage is the lack of an efficient IVF protocol for this species. The benefit of the baboon model in comparison with the rhesus macaque is the greater body size, with the accompanying larger blood vessels. The animals used in the present study had an average weight of 13.1 kg, which is considerably larger than the typical weight of about 5 kg in female rhesus macaques that are used in reproductive biology research (R.L. Stouffer, personal communication).

It is not possible to fully understand the causes of the demise of the majority of the auto-transplanted uteri in the present study, but it was most likely due to secondary stenosis of the arterial or venous anastomosis sites.

In conclusion, this initial effort of vascular transplantation of the uterus in the baboon indicates that the procedure is difficult and should be modified and improved before any attempt of UTx in the human is performed. However, the partial success is a proof of concept for this major surgical procedure in large non-human primates, which has not been shown before.

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