Abstract: Uterine transplantation may be a solution for infertility of uterine origin. Nevertheless, only three pregnancies with a live birth have so far been possible involving a uterine transplant from a brain-dead donor. Particularly, the impact of ischemia needs a better understanding. Analysis of mitochondrial respiration and production of reactive oxygen species (ROS) in muscle are of interest since they are pertinent markers of the harmful effects of ischemia. We therefore studied both uterine fundus and horn muscle mitochondrial use of oxygen and ROS production in eight women needing hysterectomy. High resolution respirometry and electron paramagnetic resonance allowed the determination of, respectively, myometrium oxidative capacity, hydrogen peroxide, mitochondrial free radical leak and superoxide anion production early (2 and 7 h) and late (24 h) following surgery. Mitochondrial oxygen consumption of the uterine fundus and horn tended to decrease with time but this was not statistically significant. Concerning ROS production, globally, we observed no significant change for H₂O₂, superoxide anion and free radical leak. In conclusion, a long period of cold ischemia did not impair myometrium mitochondrial respiration, only generating a transient H₂O₂ increase in uterine fundus. These data support that cold ischemia, even when prolonged, does not significantly alter uterine muscle oxidative capacity.

Keywords: oxygen; uterus; ischemia; myometrium; muscle; mitochondria; reactive oxygen species

1. Introduction

Almost 200 women of reproductive age per million are suffering from uterine infertility that need uterine transplantation to allow pregnancy [1]. Proposed in cases of absent or dys-functionning uterus (agenesia, hysterectomy, diverse malformations, Asherman syndrome, or endometriosis), uterus transplantation is still relatively rare. To date, about 24 healthy children are born after uterine transplantation, resulting from over than 70 attempts worldwide. In general, uterus was obtained from live donors. Brain-dead donors have only given rise to three live birth [2–20]. This clearly raises the issue uterine viability when subjected to long-lasting ischemia. Although they are placed in a hypothermic preservation medium, all organs can be significantly impaired by cold ischemia depending on its duration. In fact, organ characteristics modulate the tolerance to cold ischemia. Experimental and human studies investigating the uterine tolerance to cold ischemia demonstrated a lack of significant change in markers of necrosis and apoptosis till 6 and 24 h after cold ischemia [21–23].
Interestingly, studies of ischemia reperfusion performed upon skeletal muscle showed an early mitochondrial dysfunction suggesting that such a parameter might also demonstrate an eventual ischemia-induced uterine alteration [24,25].

Accordingly, mitochondrion is an important organelle producing energy and its dysfunction causes depletion in ATP and increased reactive oxygen species (ROS) production, particularly in the case of ischemia reperfusion [26]. Oxygen consumption by mitochondria is therefore widely used as a biological marker of its functionality.

Currently, little is known about the fate of mitochondria in the human uterus during transplantation and the purpose of this study was to determine the kinetics of mitochondrial respiration and of ROS production (2, 7 and 24 h after surgery) in two different segments of uterine myometrium subjected to cold ischemia as potentially observed during the clinical setting. Indeed, in skeletal muscles, the sensitivity to ischemia depend on muscles characteristics [27] and it appears to interestingly challenge the hypothesis of a differential effect of ischemia on either uterine fundus or horn, localizations often involved in embryo implantation.

2. Population and Methods

Eight women needing hysterectomy gave their informed consent and participated in the study carried out in the university teaching hospital of Strasbourg CHU and approved by the French Committee for the Protection of Persons (CPP) and registered on clinicaltrials.gov (RIN 2018–HUS N 7222).

2.1. Study Design

Inclusion criteria were patient >18 years old, affiliated to a social security regime and undergoing scheduled hysterectomy for an ostensibly benign pathology.

Tissue samples were provided by the surgeon immediately following surgical removal of the uterus during a total hysterectomy procedure conducted vaginally, laparoscopically or by laparotomy in the gynecological surgical service at the Strasbourg University Hospitals, France. The exact time at which the second uterine artery was ligated was recorded (ischemia T0). The surgeon cut the tissue directly post-operatively, with a cold scalpel to remove two samples of one cm³ myometrium per uterus, one at the fundal midline and the other at the right uterine horn (Figure 1).

![Figure 1. Surgical design. Two samples of one cm³ myometrium per uterus was removed, one at the fundal midline and the other at the right uterine horn.](image-url)
These sites were readily identifiable and therefore reproducible, and corresponded to myometrium-rich areas where embryo implantation characteristically takes place. Samples were dissected and consisted only of myometrium, without mucosa or serosa, and any macroscopically pathological myometrium (myoma, adenomyosis) was avoided.

Tissues were immediately placed in Krebs Hepes Buffer (NaCl 99 mM; KCl 4.69 mM; CaCl$_2$ 2.5 mM; MgSO$_4$ 1.2 mM; NaHCO$_3$ 25 mM; KH$_2$PO$_4$ 1.03 mM; D(+)-glucose 5.6 mM; Na-Hepes 20 mM; pH 7.4) in a beaker in an ice-bucket.

Three samples per tissue were obtained at three different times: 2, 7, and 24 h after cold ischemia.

2.2. Parameters Determined

2.2.1. Mitochondrial Use of Oxygen

A total of 10 mg wet tissue was placed in the oxygraphic chamber at 37 °C with 2 mL stirred MirO$_5$ (Mitochondrial respiration medium) + creatine solution (EGTA (0.5 mM), MgCl$_2$ (3 mM), K lactobionate (60 mM), taurine (20 mM), KH$_2$PO$_4$ (10 mM), Heps (20 mM), sucrose (110 mM), creatine (20 mM), BSA (1 g/L)), and saponin (125 µg/mL).

Additionally, tissue was permeabilized with saponin directly in the oroboros. Then, mitochondrial respiration was analyzed using a high-resolution oxygraph (Oxygraph-2k; Oroboros Instruments, Innsbruck, Austria) [28].

Thus, glutamate (10 mM) and malate (2.5 mM) were added to support electron flow through complex I (CI) of the electron transport system (ETS). Then, the addition of ADP (2 mM) stimulated respiration and oxidative phosphorylation (OXPHOS by CI). Finally, succinate was added (25 mM) to activate the complex II (OXPHOS by CI&II). DatLab software 4.3 was used to determine the oxygen flow (Oroboros Instruments, Innsbruck, Austria). Data are expressed in pmol O$_2$/s/mg wet weight.

2.2.2. Reactive Oxygen Species Production

Reactive Oxygen Species (ROS) comprise several moieties such as the superoxide anion (O$_2^{•−}$) or hydrogen peroxide (H$_2$O$_2$). Hydrogen peroxide production was measured using combined AmplexRed and horseradish peroxidase (HRP). AmplexRed reacts with H$_2$O$_2$ (1:1) and is catalyzed by HRP into resorufin, a fluorescent molecule. Resorufin is detected at 563/587 nm. Fluorescence was measured simultaneously with mitochondrial respiration on the high-resolution oxygraph. AmplexRed (20 µM) and HRP (1 U/mL) were thus added into the Oroboros chambers at the beginning of the experiment. Results are expressed in pmol/min/mg wet weight.

To analyze superoxide anion, electron paramagnetic resonance (EPR) is the gold standard. In this technique, ROS concentration is directly determined using a specific spin probe: 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine hydrochloride (CMH).

Tissues were sectioned in Krebs Hepes buffer containing deferoxamine (25 µM) and diethylthiocarbamate (DETC, 5 µM) and incubated with the spin probe CMH (200 µM) for 30 min. Temperature and oxygen pressure were controlled (37 °C, 20 mmHg) using a gas controller (Noxygen Sciences Transfer, Elzach, Germany). Then, 40 µL supernatant was analyzed in a capillary tube, and results recorded using an e-scan spectrometer (Bruker, Elzach, Germany) at 15 °C. EPR settings were: centerfield 3482.579 × g, microwave power 21.85 mW, modulation amplitude 2.40 G, sweep time 5.24 s (10 scans), sweep width 60 G, number of lag curve points 1. Tissues were finally harvested and dried at 150 °C for 15 min. ROS production was expressed in µmol/min/mg dry weight, as previously reported [29].

2.2.3. Free Radical Leak

Hydrogen peroxide and O$_2$ consumption were measured simultaneously. This allowed the calculation of the fraction of out-of-sequence electrons serving to oxidize O$_2$ into ROS in the respiratory chain. The Free Radical Leak (FRL) is therefore the rate of H$_2$O$_2$ production divided by twice the rate of O$_2$ consumption, expressed as a percentage.
2.3. Statistical Analysis

All data are expressed as mean ± standard error of the mean (SEM) and were analyzed using Prism software (GraphPad Prism 5, Graph Pad Software, San Diego, CA, USA). We tested normality for all groups, based on the Shapiro-Wilk test. When normality was not observed, the non-parametric test for repeated values (Friedman test) was applied followed by a posttest (Dunn’s multiple tests). A p value < 0.05 was considered significant.

3. Results

3.1. Clinical Characteristics of the Patients

The clinical characteristics of the eight women participating in the study are summarized in Table 1.

| Clinical Data            | Mean ± SD, Min–Max |
|--------------------------|--------------------|
| Age (mean ± SD, min–max) | 47.6 ± 3.9 (44–57) |
| Gravidity (mean ± SD, min–max) * | 2.37 ± 1.49 (0–5) |
| Parity (mean ± SD, min–max) ** | 2 ± 1.1 (0–4) |
| Smoker (n/8)             | 1                  |
| Post–menopausal (n/8)    | 0                  |
| Cardiovascular disease (n/8) | 2              |
| Indication (n/8)         | 4 myomas–3 adenomyosis–1 prolapse |
| Type of hysterectomy (n/8) | 5 laparoscopic–3 vaginal–0 laparotomy |
| Histology(n/8)           | 2                  |

* number of previous pregnancies; ** number of previous deliveries.

The mean patient age was 47.6 years, and mean gravidity 2.4. Two women were treated for hypertension and one was smoker. The indications for hysterectomy were myomatous uterus causing symptoms, symptomatic adenomyosis, and treatment of a prolapse in, respectively, four, three and one patients. A sarcoma was discovered on histological examination in one patient. No patient was menopaused.

3.2. Mitochondrial Oxygen Consumption in Uterine Fundus and Horn after Two, Seven, and Twenty-Four Hours of Cold Ischemia

3.2.1. Uterine Fundus

OXPHOS by complex I state of the uterine fundus tended to decrease with time but this was not statistically significant (1.65 ± 0.28, 1.52 ± 0.21, 1.25 ± 0.18 pmol/s/mg ww, after 2, 7, and 24 h of cold ischemia, respectively, Figure 2a). Moreover, the OXPHOS by complex I&II state was not altered after 2, 7, and 24 h of cold ischemia (4.90 ± 0.47, 5.03 ± 0.34, 4.32 ± 0.34 pmol/s/mg ww, after 2, 7, and 24 h of cold ischemia, respectively, Figure 2b).

3.2.2. Uterine Horn

Similarly, OXPHOS by complex I state tended to decrease not significantly, after 2, 7, and 24 h of cold ischemia (2.26 ± 0.37, 1.93 ± 0.39, 1.73 ± 0.33 pmol/s/mg ww, respectively, Figure 2a). Moreover, the OXPHOS by complex I&II state was not altered after 2, 7, and 24 h of cold ischemia (5.18 ± 0.70, 5.33 ± 0.97, 4.95 ± 0.48 pmol/s/mg ww, after 2, 7, and 24 h of cold ischemia, respectively, Figure 2b).
3.3. ROS Production at the Uterine Fundus and Horn after Two, Seven, and Twenty-Four Hours of Cold Ischemia

3.3.1. Uterine Fundus

Concerning H$_2$O$_2$ production, a significant but transient increase was observed after 7 h of ischemia (3.57 ± 0.18, 4.09 ± 0.25 pmol/min/mg ww, $p < 0.05$), the values at 24 h after ischemia being close then that observed after 2 h of ischemia (3.36 ± 0.17 pmol/min/mg ww, $p < 0.01$, Figure 3a).

Superoxide anion production was unchanged, regardless of the duration of cold ischemia (13.15 ± 1.66, 10.43 ± 1.07, 14.83 ± 2.42 pmol/min/mg dw, after 2, 7, 24 h of cold ischemia, respectively, Figure 3b).

Finally, the free radical leak (FRL), which indicates the number of oxygen molecules preferentially required to produce ROS (Figure 3c), did not change significantly (2.16 ± 0.53, 3.06 ± 0.52, 3.29 ± 1.05, after 2, 7, and 24 h of cold ischemia, respectively).
Finally, the free radical leak (FRL), which indicates the number of oxygen molecules preferentially required to produce ROS (Figure 3c), did not change significantly (2.16 ± 0.53, 3.06 ± 0.52, 3.29 ± 1.05, after 2, 7, and 24 h of cold ischemia, respectively).

Figure 3. ROS production measured in the different tissues and at different times of ischemia (2, 7, 24 h ischemia). (a) H$_2$O$_2$ production measured by high resolution oxygraphy, during complex I-linked OXPHOS state after 2, 7, and 24 h of cold ischemia (n = 8 per group). (b) Superoxide anion production measured by EPR at different times: after 2, 7 and 24 h of cold ischemia. (n = 7–8 per group). (c) Free radical leak at the uterine fundus and horn. These graphs represent the fraction of out-of-sequence electrons required to oxidize O$_2$ into ROS in the respiratory chain (n = 8 per group). Results are presented as mean ± sem. *p < 0.05.
3.3.2. Uterine Horn

$\text{H}_2\text{O}_2$ production was not modified regardless of the duration of ischemia (3.81 ± 0.19, 4.36 ± 0.19, 4.12 ± 0.11 pmol/min/mg ww, after 2, 7, and 24 h of ischemia, respectively, Figure 3a).

Superoxide anion production did not change significantly when comparing 2, 7 and 24 h of cold ischemia (20.93 ± 3.97, 11.90 ± 1.28 and 13.44 ± 2.74 pmol/min/mg dw, respectively). (Figure 2b).

Considering the FRL, again no significant change was observed (2.01 ± 0.33, 3.40 ± 0.84, 2.93 ± 0.61 after 2, 7, and 24 h of ischemia, respectively, Figure 3c).

4. Discussion

This study is the first to examine the kinetic of myometrial mitochondrial respiration and reactive oxygen production at both uterine fundus and horn, two, seven and twenty-four h after cold ischemia (CI). The main results are that mitochondrial oxidative capacity remains preserved over a long period, together with a lack of major rise in ROS production. These data support that cold ischemia is relatively well tolerated by human uterine myometrium.

Ischemia is a complex pathophysiological process leading progressively to impairments in the mitochondrial respiratory chain, intracellular edema, acidosis, oxidative stress, and finally cell death. Often studied in many organs such as the heart, brain, kidney, lungs, skeletal muscle etc. [27,30–33], there are relatively few data investigating uterine muscle ischemia-induced change in mitochondrial function [34]. Accordingly, mainly other methods were used to analyze uterine ischemia effects [35]. However, since to date, no transplant has produced a viable pregnancy after more than 6 h of cold ischemia, there is still an urgent need to better understand CI effect on uterine muscle, and particularly on mitochondria that are largely involved in many key cellular mechanisms. Interestingly, our results demonstrate that cold ischemia (better corresponding to the clinical setting than warm ischemia) did not significantly alter uterine myometrium mitochondrial respiration, whatever the site analyzed. Thus, although porcine uterine regions might have different sensitivities to hypoxia [36], both human uterine fundus and horn remained unaltered by short term and prolonged CI supporting that if present, an eventual mitochondrial dysfunction should have been minimal. In agreement with these data, Del Priore et al. did not observe any histological modification as assessed by electron microscopy after 12 h of cold ischemia [37]. Similarly, no histological modification or increased apoptosis, as assessed by TUNEL assay, was shown after 24 h of CI [21]. In 2005, Wranning et al. studied changes in energy metabolism (ATP) and in the capacity of human uterus to contract after various lengths of CI [38]. They observed a decrease in the spontaneous contractility, irrespective of the duration of ischemia. No histological modification was observed on electron microscopy, but degeneration of the vesicular cytoplasm and chromatin condensation were observed after 24 h of CI mainly when a protective solution was not used. The authors concluded that that human myometrial tissue can tolerate cold ischaemia for at least 6 h, but mitochondrial respiration determination was not performed. Further, the fact that swollen mitochondria were observed after 8 h of warm uterine ischemia [34] suggests that warm ischemia is likely to be much more harmful than cold ischemia which reduces tissue metabolism.

Oxidative stress is also a key mechanism in ischemia pathophysiology [38]. When investigating glutathione pathway in uterine myometrium in humans or ewes, respectively, an increased oxidative stress was observed mainly after 24 h of CI [39,40]. On the other hand, in our study, despite using three complementary approaches as often suggested, we observed no significant increase in hydrogen peroxide, superoxide anion productions or mitochondrial free radical leak during this experiment except at 7 h in uterine fundus for $\text{H}_2\text{O}_2$. However, such an increase was transient and concerned only one marker of oxidative stress. Therefore, the general picture is that no major change in ROS production occurred in this experiment, although further studies will be useful to determine the antioxidant status.
in such a setting. This is in agreement with the lack of mitochondrial dysfunction observed since mitochondria are known to be also largely involved in ROS production, particularly in the ones we studied here. Globally, these findings confirm that uterine muscle has a marked ability to tolerate cold ischemia well, corresponding to its physiological exposure to ischemia, particularly during menstrual cycles and labor.

5. Conclusions

In conclusion, although mitochondrial respiration tended to decrease over time, this was not statistically significant and this study shows that uterus mitochondria are relatively resistant to long periods of ischemia. We nevertheless cannot totally exclude evidence of other mitochondrial dysfunction potentially involving mitochondrial dynamic, calcium handling etc. Further, no major increase in ROS production was observed until 24h after surgery. Thus, other predictive markers of uterine function should be investigated, probably including studies on metabolomics or progenitor stem cells of the endometrium which play an essential role in physiological remodeling and regeneration of the human uterus and might be impaired by prolonged ischemia. Additionally, reperfusion studies will be useful since it is a critical time, allowing increased oxidative stress related to oxygen reflow.

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