Temperature-Controlled Organ Cooling Jacket System for Open and Robotic-assisted Surgeries

by

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Temperature-Controlled Organ Cooling Jacket System for Open and Robotic-assisted Surgeries

Koç University

Graduate School Sciences and Engineering

This is to certify that I have examined this copy of a master's thesis by

Mert Azak

and have found that it is complete and satisfactory in all respects,

and that any revisions required by the final

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Date: 23.01.2024

I dedicate this thesis to my wife, Selin Azak, my father, Mehmet Azak, my mother, Şule Azak, and my brother Mete Azak

ABSTRACT

Temperature-Controlled Organ Cooling Jacket System for Open and Robotic-assisted Surgeries

Mert Azak
Master of Science in Mechanical Engineering
January 23, 2024

Cold ischemia plays a crucial role in open and robotic-assisted kidney transplants and partial nephrectomy surgeries, not only minimizing the risk of renal injuries but also extending the duration of the operation. Traditionally, the cooling process relies on the application of ice slush to the donor kidney during operation, a method prone to variability as the amount of ice slush is determined arbitrarily by the operating doctor. To address this issue, a novel approach is proposed, introducing a temperature-controlled organ cooling jacket. This innovative design incorporates auxiliary liquid circulation and refrigeration units, providing a controlled and consistent cooling environment. The cooling jacket, crafted from biocompatible materials through negative molding with 3D-printed molds, represents a significant departure from the temperature-uncontrolled procedures prevalent in current practices. The development of the device is detailed in this study, covering the entire process from design conception to manufacturing techniques. The materials and methods employed in the production of the organ cooling jacket are discussed, highlighting the adherence to design constraints. The efficiency of the device is examined through ex vivo testing, shedding light on the promising results achieved. This comprehensive exploration encompasses the evolution of the proposed solution, offering valuable insights into its potential application in enhancing and implementing temperature-controlled cold ischemia in open and robotic-assisted kidney surgeries.

ÖZETÇE

Açık ve Robot-Destekli Ameliyatlar için Sıcaklık Kontrollü Organ Soğutma Ceketi Sistemi

Mert Azak
Makine Mühendisliği, Yüksek Lisans
23 Ocak 2024

Soğuk iskemi, açık ve robot destekli böbrek nakilleri ile kısmi nefrektomi ameliyatlarında hayati bir rol oynar; sadece böbrek yaralanma riskini en aza indirgemeyle kalmaz, aynı zamanda operasyon süresini uzatır. Geleneksel olarak soğutma süreci, operasyon sırasında donör böbreğine buzlu su uygulamasına dayanır; ancak bu yöntem, buz karışımının miktarının operasyonu yapan doktorun inisiyatifinde olması nedeniyle değişkenlik gösteren bir yöntemdir. Bu sorunu ele almak için, sıcaklık kontrollü bir organ soğutma ceketi tanıtan yeni bir yaklaşım önerilmektedir. Bu yenilikçi tasarım, yardımcı sıvı dolaşımı ve soğutma ünitelerini içerir, kontrol edilebilir ve tutarlı bir soğutma ortamı sağlar. Biyouyumlu malzemelerden oluşturulan soğutma ceketi, negatif kalıp kullanılarak 3D baskılı kalıplarla üretilir ve mevcut uygulamalardaki sıcaklık kontrolsüz prosedürlerden önemli bir sapma temsil eder. Cihazın gelişimi, tasarım kavramından üretim tekniklerine kadar geniş bir şekilde bu çalışmada detaylandırılmıştır. Organ soğutma ceketi üretiminde kullanılan malzemeler ve yöntemler tartışılarak tasarım kısıtlamalarına uygunluğu vurgulanmıştır. Cihazın etkinliği ex-vivo testleriyle incelenmiş, elde edilen umut verici sonuçlara ışık tutulmuştur. Bu kapsamlı keşif, önerilen çözümün evrimini içerir ve açık ve robot destekli böbrek ameliyatlarında sıcaklık kontrollü soğuk iskeminin geliştirilmesi ve uygulanması konusunda değerli içgörüler sunar.

ACKNOWLEDGEMENTS

I completed this thesis during my two-year tenure as a research assistant at Koç University Manufacturing and Automation Research Center (MARC). I want to express my deep gratitude to my advisor, Prof. Dr. İsmail Lazoğlu, for his unwavering support throughout my master's degree journey. His guidance, supervision in my research, and overall mentorship not only facilitated the completion of my Master's degree but also empowered me to apply for a patent and write an article in my research field. These contributions form the foundation of the majority of the chapters in this thesis, and I anticipate that they will provide a significant advantage in my professional endeavors.

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I reserve my deepest thanks for my parents, Mehmet and Şule Azak, who not only raised me to be the person I am today but also provided unwavering emotional and financial support through every milestone of my life. To them, I owe a debt that allows me to rise stronger from every setback. My gratitude extends to my good friend and brother, Mete Azak, for his invaluable support, even from a distance. Above all, I am thankful to my life partner, Selin Azak, who became my wife during my Master's. Our love, respect, and mutual support in every aspect of life have consistently strengthened us as individuals in the face of challenges. We have never given up, and we never will. This thesis is dedicated to my family, the pillars of my strength.

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ABBREVIATIONS

CAD	Computer-Aided Design
CT	Computer Tomography
MRI	Magnetic resonance imaging
PVA	Polyvinyl Alcohol
OCJ	Organ Cooling Jacket
R&D&I	Research And Development And Innovation
3D	Three-Dimensional
STL	Standard Tessellation Language
CID	Cold Ischemia Device
OKT	Open Kidney Transplantation
RAKT	Robotic-Assisted Kidney Transplantation
RPM	Revolution Per Minute
σ_h	Hoop (Circumferential) Stress
P	Pressure Inside Cylinder
Dm	Cylinder Diameter
t	Cylinder Thickness

CHAPTER 1: INTRODUCTION

1.1 Overview

Medicine is a field that will ensure its continuity as long as human beings exist. Like all areas of the industry and our lives, it needs research and development. It aims to improve and facilitate human health in an ever-changing world. Another area whose sustainability will continue with medicine is the medical device sector. It offers conveniences for surgeons and patients in the healthcare industry. It speeds up the healing process for patients while easing the responsibility of doctors [1].

Recently, the orientation to the medical device sector has increased. Various inventions have been made and used in the main topics such as biomedical signal analysis, imaging, infrared imaging, medical informatics, biomedical sensors, medical instruments, and devices [2] While the sector's narrow margin of error poses challenges, achieving successful outcomes is unavoidable through effective research and development along with a sound production approach.

One of the more challenging yet intriguing parts of the medical field is the medical device design. There is a regulation stage applied from the design stage to the final product of medical devices, as seen in Figure 1.1. After the prototype of the required device is designed and fabricated based on the emerging medical need, pre-clinical and clinical studies are carried out and developed. The final product, which is subjected to rigorous tests, is manufactured if it is successful. It is launched with a good marketing method and post-marketing surveillance is done. If a more advanced device is produced and released, the previously manufactured product becomes obsolete. In this case, the obsolescence device goes through the development and production process again, then it is marketed [3].

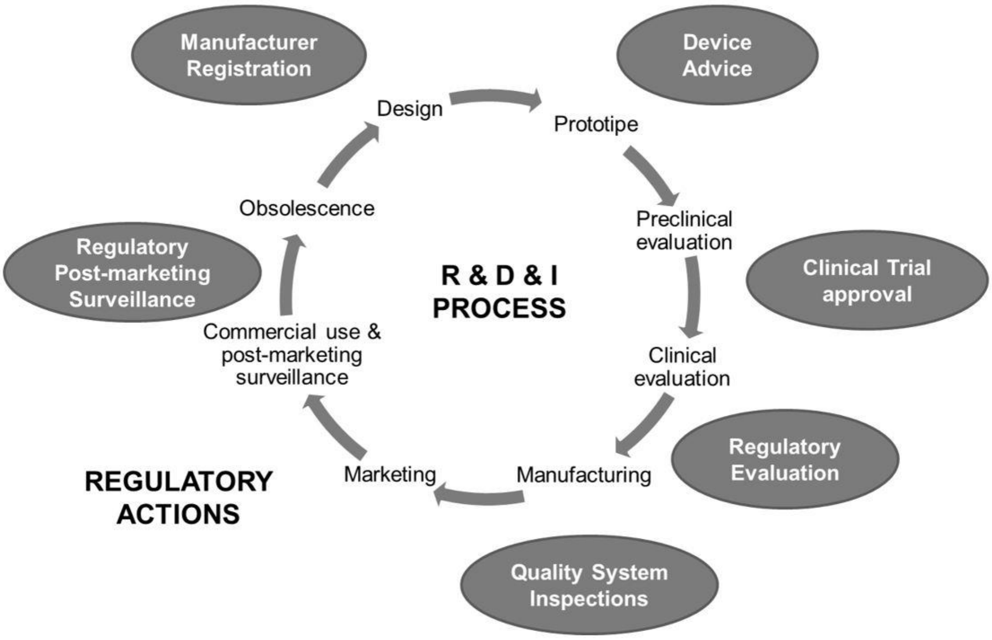

Figure 1. 1 Regulation Stage of Medical Devices [1]

The future of the medical industry is bright. Utilizing state-of-the-art 3D printing technology will enable the cost-effective production of medical components, offering convenience across various medical fields. Instead of large and expensive production lines, production is possible with an advanced 3D printing machine and compatible material. 3D-printed implants, prosthetic parts, and devices produced with the 3D printing method, which are used as auxiliary factors in many human anatomy parts, will be replaced by stem cell-based 3D-printed artificial organs in the future [4].

Organ transplantation has revolutionized the field of medicine, offering a life-saving option for individuals suffering from end-stage organ failure. One critical aspect that significantly influences the success of organ transplantation is the duration of ischemia, the period during which blood flow to the organ is restricted. Ischemia is broadly categorized into two types: cold ischemia and warm ischemia. Cold ischemia involves the preservation of organs at lower temperatures, typically through methods such as cold storage, while warm ischemia occurs when organs are exposed to ambient temperatures during procurement and transplantation. Understanding the differences between cold and warm ischemia is crucial for optimizing organ transplantation outcomes.[29]

Cold ischemia emerges as a crucial method for minimizing the risk of renal injury during kidney transplantation. Cold ischemia is applied before surgeries to prevent hypoxic injuries in the patient's organs and extend the operation time. Effective cooling, especially within the first 12 hours, proves essential for preventing renal injury in kidney transplantation. The application of cold ischemia involves ice-cooling, a common method during kidney transplant and open Nephrectomy surgeries. The donor kidney is covered with ice, enclosed in a gauze jacket, and introduced into the body, and the anastomosis process commences. Ice slush application is a prevalent technique, though it lacks precision in calculating ice amount and cooling time. The uneven distribution of ice pieces on the organ's surface leads to temperature variations, posing potential life-threatening dangers during the operation. [30]

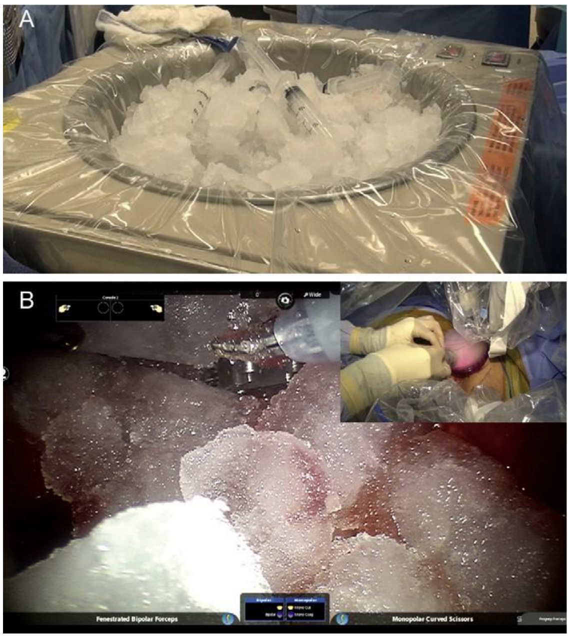

Figure 1. 2 – (A) Modified syringes prefilled with ice slush for cold ischemia. (B) Internal view of kidney covered with ice slush while the renal artery is clamped with a robotic bulldog clamp. The Inset picture demonstrates the external view of the injection of ice slush through the Gelpoint [30]

To address these challenges, a more advanced technique, the temperature-controlled organ cooling jacket, is introduced. This innovative solution aims to cool the organ homogeneously, allowing for prolonged operation times in both robotic-assisted and open surgeries. By preventing hypoxic injuries at body temperature, the organ cooling jacket represents a promising alternative to the less controlled ice-cooling technique. The objective of the cold ischemia device is to additionally expand the cold ischemia time and keep the donor organ in the range of cold ischemia temperatures. The cooling jacket operates on the principles of fluid mechanics and heat transfer, with various designs created through the application of these principles and diverse production methods. While the overarching goal of these designs remains consistent, variations arise based on factors such as the chosen material, cooling technique, refrigerant, and the production process. The organ cooling innovations are described in the literature review section.

1.2 Outline

This thesis discusses a novel organ cooling jacket system, which is designed to prevent hypoxia-induced renal or hypoxic injuries before the operation, reduce renal damage, and prolong the operation time. The main field that comprises the thesis is the organ cooling jacket system which is a cold ischemia device. In the medical field, while the cooling process is applied manually with ice slush, a cooling device with temperature control and uniform heat transfer is required. A common shortcoming of other cold ischemia devices is that the coolant circulating in the cooling jacket is not continuously cooled. In general, despite good designs in the studies carried out, the coolant temperature and subsequently the organ temperature increase during the operation. These studies, which are beneficial in the short term, increase the risk of injury to the organ in the long term.

This thesis focuses on the operation of a temperature-controlled and manageable constant flow novel organ cooling jacket system to prevent renal injuries and extend the operation duration in open and robot-assisted transplantations, as well as partial nephrectomy surgeries. The thesis emphasizes the organ cooling jacket system; a literature review, silicone kidney model, novel organ cooling jacket innovation with its refrigeration and liquid circulation systems, temperature-time result of animal graft organs, pros and cons, discussion, and conclusion are presented in chapter 2.

Chapter 2: DEVELOPMENT AND ASSESSMENT OF AN ORGAN COOLING JACKET SYSTEM

2.1 Background

Open and robotic-assisted Nephrectomy and partial Nephrectomy surgeries are treatment methods for common kidney diseases [24]. Nephrectomy is the procedure of removing the kidney. It may be necessary to remove the kidney due to reasons such as stones, infection, decay as a result of the kidney becoming unable to function, cancer developing in the kidney, or being attached to another person [24]. On the other hand, partial nephrectomy is a treatment option for localized kidney cancer. The goal is to remove the part of the kidney affected by the tumor and leave as much healthy kidney tissue as possible. The most optimized and quickest procedure used in these surgeries is laparoscopic surgery [24]. The general purpose of this application is to perform local surgery on the patient through small facias without making deep incisions as in open surgery. Before starting the laparoscopic surgery, the patient is laid down with the damaged organ on top, and the patient's arms are positioned at the head. [24]

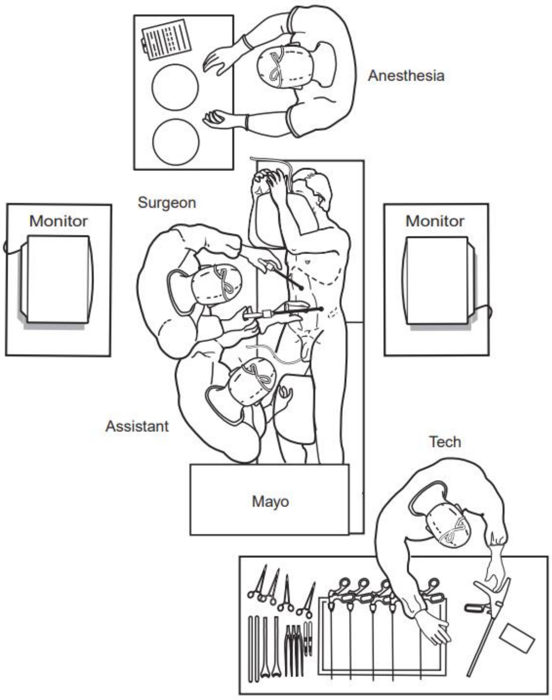

Figure 2. 1 Nephrectomy operation sample [24]

As seen in Figure 2.1, the patient whose left kidney will be operated on is lying on his right side. After the patient is anesthetized with general anesthesia, one of the most important points of the surgery is to determine the trocar areas.[24] In this procedure, generally, five points are determined: two of them are for the laparoscopic surgery tool of the doctor managing the operation, one is for the camera that provides a clear view inside the patient, one is for the retraction tool used by the assistant doctor, and one for to balance the body internal-external air pressure (figure 2.2). [26]

Trocar locations might differ depending on the location of the area to be worked on the organ. Additionally, the fascia length might vary related to the diameter of the trocar used (figure 2.3). [24] By taking advantage of the flexibility of human skin, instruments inserted through the trocar hole can be moved easily.

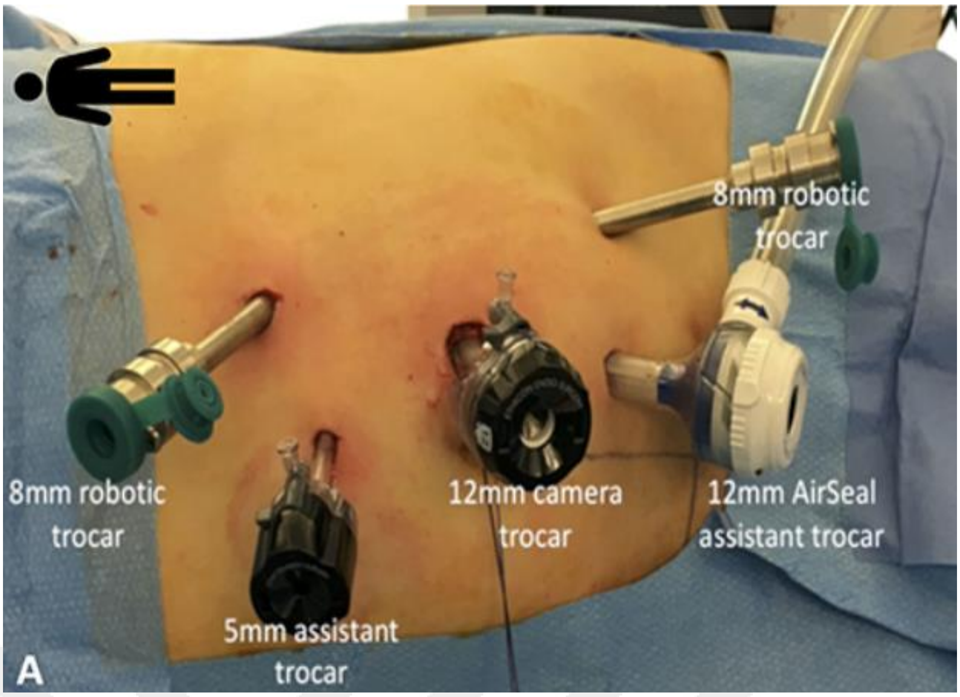

Figure 2. 2 Robotic-assisted surgery-port placement on the body. Robotic, camera, assistant and air seal trocars are represented with their diameters. The surgical procedure initiates with marking the incision site; however, the actual incision is executed after complete mobilization of the kidney, right before the examination of the renal vessels. [26]

While a large incision is not required in partial nephrectomy surgeries, this may of course vary depending on the size of the removed part. The situation is slightly different in nephrectomy and transplant surgeries. After the kidney is separated from the vessels and external tissue, it is placed in the endobag. After this procedure, another deep incision is usually made to remove the organ. If the doctor can remove this bag from the incision where the air seal system, which balances internal and external body pressure, was previously installed, there is no need for an extra incision. Likewise, in transplant surgeries, the kidney is taken in for anastomosis with the same process.

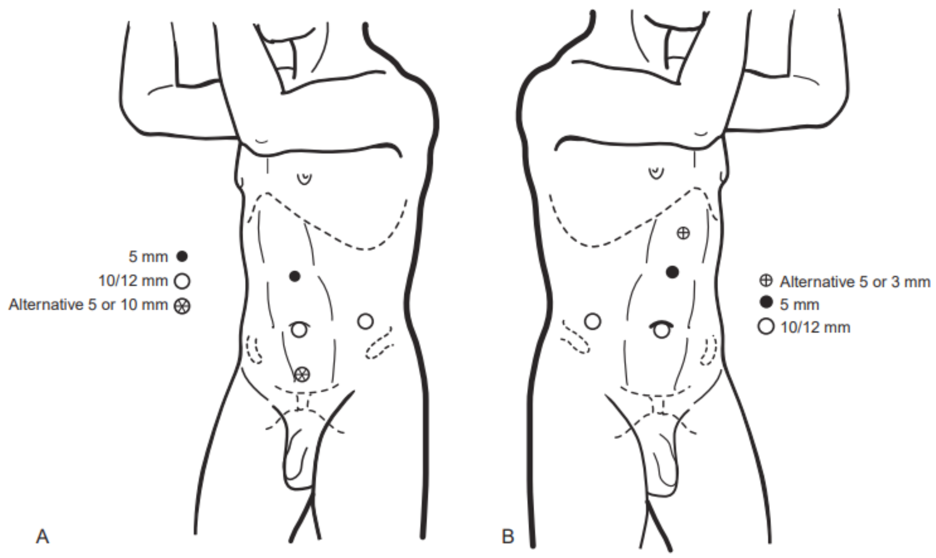

Figure 2. 3 Trocar sites for left-sided (A) and right-sided (B) procedures, and its dimensions [24]

The donor kidney is placed in the area to be anastomosed and the anastomosis process of the vessels is started as shown in Figure 2.4. This process takes time because it must be performed without errors at the micron level. Rosales et al. As stated, the first transplant surgeries took an average of 240 minutes. Most of this is due to the anastomosis process of the new healthy kidney. After taking the kidney, which had previously been kept in ice saline water, into the body, the critical process for the vital functions of the kidney begins. [25]

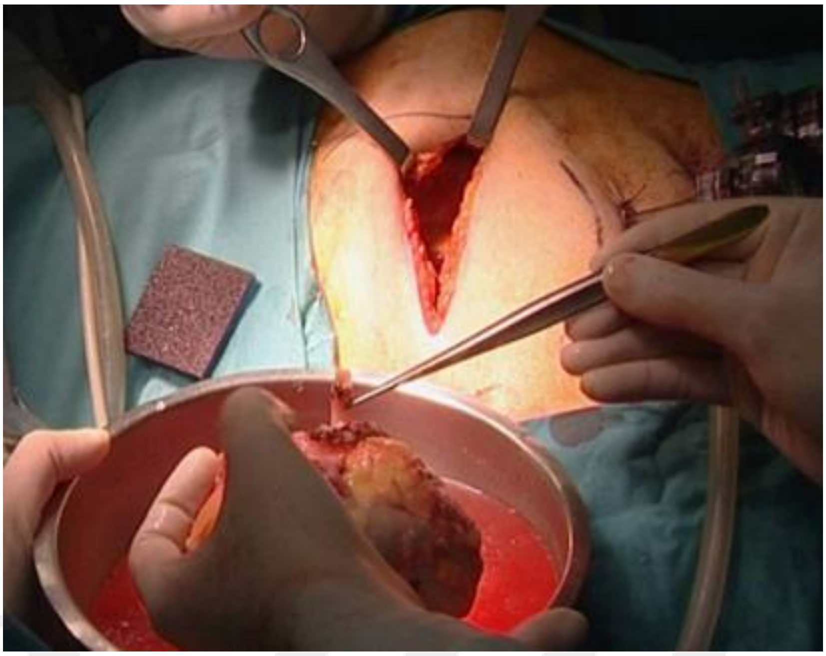

Figure 2. 4 Kidney graft through an incision [25]

Cold ischemia is a method known to reduce the risk of renal injury to the kidney. Before the surgeries, cold ischemia is applied to prevent hypoxic injuries in the patient's organ and prolong the operation time [8]. While the kidneys can be preserved for up to 72 hours, with cold ischemia, it may do well in the recipient after 36 to 48 hours. However, the longer the process, the higher the risk of renal injury.

While a renal injury is not observed for up to 12 hours of cold ischemia time in a kidney transplantation with accurate cooling, a kidney without cooling should be transplanted within 15 minutes of warm ischemia time [9]. The operated kidney must be cooled to an average of 4-20 ^{o}C to prevent renal injuries before the surgery [10,11].

The frequent method for temperature reduction in the operated kidney is ice-cooling. During both transplant and open Nephrectomy surgeries, following organ rejection in kidney transplant procedures, the donor kidney is covered with ice, encased in a gauze jacket, introduced into the body, and then the anastomosis process begins. Afterward, an uncontrolled temperature-time cooling process continues to be performed with gauge ice, nonuniformly distributed on the kidney by passing through the fissure opened by a doctor or from the port inserted into the fissure to keep the donor kidney at a low temperature [12].

Ice slush application is done without calculating the amount of ice used and the cooling time, the specific temperature at which the organ should be kept is not certain. Since the ice pieces delivered from the port to the organ surface are not spread homogeneously on the surface, Temperature differences are observed between different regions of the surface. While the amount of ice to be used is not known, the cooling time is an element determined by the doctor. In this uncontrolled cooling technique, the cooled organ may encounter life-threatening dangers during the operation. [12]

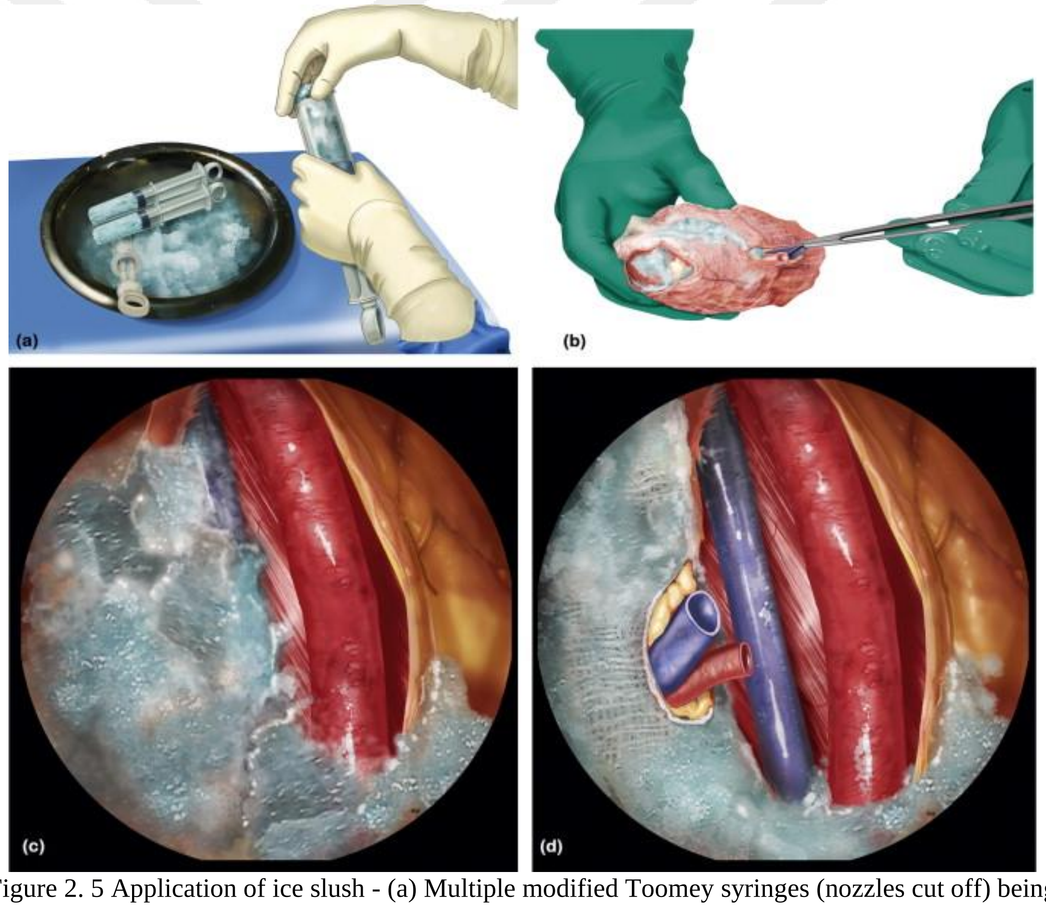

Figure 2. 5 Application of ice slush - (a) Multiple modified Toomey syringes (nozzles cut off) being readied for rapid delivery of ice slush. (b) Graft kidney wrapped in a gauze jacket filled with ice slush. (c) The pelvic bed lined with ice slush to achieve pelvic-bed cooling before the introduction of the graft kidney. (d) Additional ice slush is delivered onto the graft kidney immediately after its introduction, to achieve uniform cooling [12]

A more advanced technique, the temperature-controlled organ cooling jacket, is the current solution that can be an alternate methodology to the ice cooling technique. An organ cooling jacket is a product that aims to cool the organ homogenously to prolong the operation time in laparoscopic and open surgeries. The proposed invention is aimed to prevent hypoxic injuries in the patient's organ at body temperature.

The working principle of the cooling jacket is based on fluid mechanics and heat transfer. Several designs have been made by applying the principles and different production methods. Although the main purpose of the designs is the same, the jackets are designed according to different standards and constraints vary according to parameters such as the material used, the cooling technique, the refrigerant, and the production method.

The organ cooling system consists of a cooling jacket, a reservoir containing the refrigerant, a water pump that circulates the fluid in the jacket, and a tubing system that will ensure the transmission of the fluid. This system, which consists of four main parts, may vary according to the design and constraints. The organ cooling jacket, which is produced generally with elastic biocompatible materials, has channels or spaces on which the cooling liquid can circulate. It has inlets and outlets that allow the cooling liquid to circulate inside; the position and location of the inlet and outlet might vary according to the channel design of the cooling jacket and the organ to be used.

The refrigerant, prepared with several solutions or pure materials, is circulated in the channels inside the jacket with automatic and manual systems. While the circulation process is done using a water pump in an automatic system, in a manual system it is done with simple tools such as an injector that pushes the water by creating pressure.

In existing cooling jacket systems, the circulated refrigerant is kept in a cold environment and used during the process. A reservoir filled with refrigerant is used for each organ because heat transfer occurs over time between the fluid in the reservoir and the organ and its environment, and the coolant temperature increases. The reservoir to be used in the new surgery is taken from the cold environment and connected to the system.

2.2 Literature Review

2.2.1 An Effective Cooling Device for Minimal-Incision Kidney Transplantation

Li et al [13] designed a plastic cooling bag with an inlet and outlet as shown in Figure 2.6. The inside of this bag is empty and coolant circulation is provided inside by a tubing system. The circulation process is done manually by the injection of the coolant with the help of two assistants. While one assistant draws the fluid from the saline water with a syringe, the other assistant injects the fluid from the inlet of the cooler bag. Since this process is manual, it has no continuity. In addition, the saline water is cooled to 0-4 ^{o}C before the treatment; however, cooling is not continued during the circulation process. In this process, there is no controlled temperature as the amounts of water, salt, and ice are at the discretion of the person preparing it.

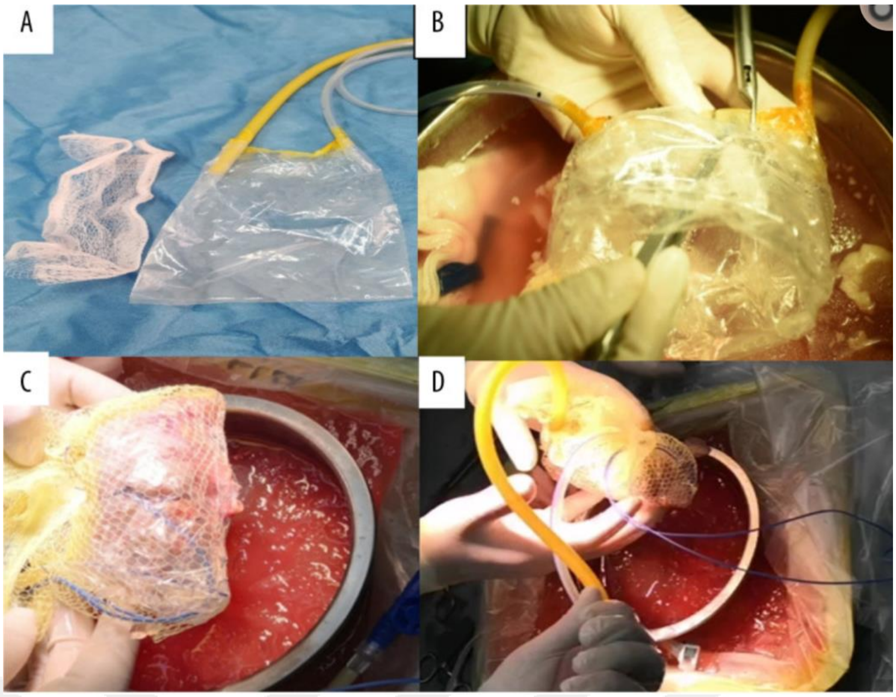

Figure 2. 6 Net-restrictive plastic cooling jacket, its components and visualisation (A) Components: plastic bag and plastic net. (B) Denting the bottom of the sealed plastic bag to form a new cavity. (C) The kidney is placed into the cavity of plastic bag. Wrapping the kidney with the plastic with mesh bag, and creating a gap for vessels to place them outside (D) Net-restrictive plastic cooling jacket with probes and tubes[13]

Before the cooling process is performed, the kidney is placed in the middle of the bag and wrapped. During wrapping, a gap is left in the area where the kidney vessels are located for anastomosis. The cooler bag is also more tightly wrapped and tied with a mesh bag. Likewise, for anastomosis, the mesh bag is cut, and the vessels are released. A thermocouple is attached to the upside and underside of the graft kidney from the empty area where the vessels are located, and temperature measurements are taken. There are temperature differences on the bottom and upper surfaces as seen in Figure 2.7 since the circulated refrigerant in the bag does not show a homogeneous flow distribution. Similarly, since a manual cycle is performed during the cold ischemia process, the temperature both increases and decreases nonuniformly. On the other hand, it has not been observed how long the cooling bag reduces the temperature of the graft kidney to the desired temperature thus efficiency cannot be commented [13].

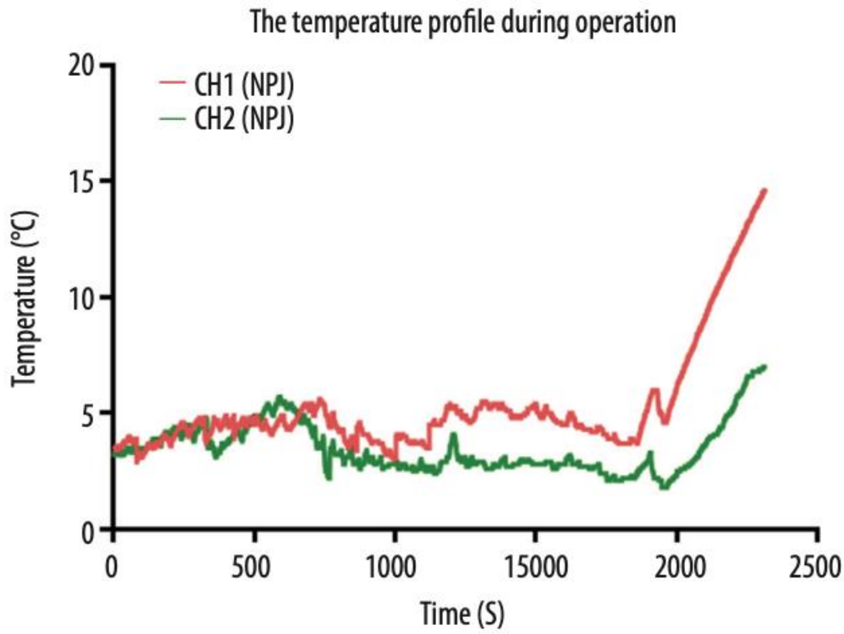

Figure 2. 7 Donor kidney temperatures taken kidney into plastic cooling bag to kidney revascularization CH1(NPJ): Net restrictive plastic jacket cooling surgery, underside. CH2(NPJ): Net-restrictive plastic jacket cooling surgery, upside [13]

2.2.2 Impact of an intra-abdominal cooling device during open kidney transplantation in pigs

Longchamp et al. [14] designed a cooling jacket made of silicone rubber as shown in Figure 2.8 to cool the donor organ before the operation in kidney transplant surgeries. In this design, the cooling process is aimed at circulating ethanol and methylene blue at 4 ^{o}C in the silicon tubing system. Instead of designing a path inside the cooling jacket, they passed the tubing system through the jacket and cooled it. The inner and outer thicknesses of the jacket are 0.8 mm and 5 mm, respectively. The difference between thickness is aimed to increase the heat transfer between the kidney and the jacket, on the contrary, to provide insulation with the external environment. Heat transfer is not efficient since the cooling jacket is made of an insulating material and the piping system is rotated inside the jacket. As seen in the figure 2.9, the flushing time is as long as 250 minutes.

The graph also shows the slope of the curve. From this slope, the temperature drop per minute can be found.

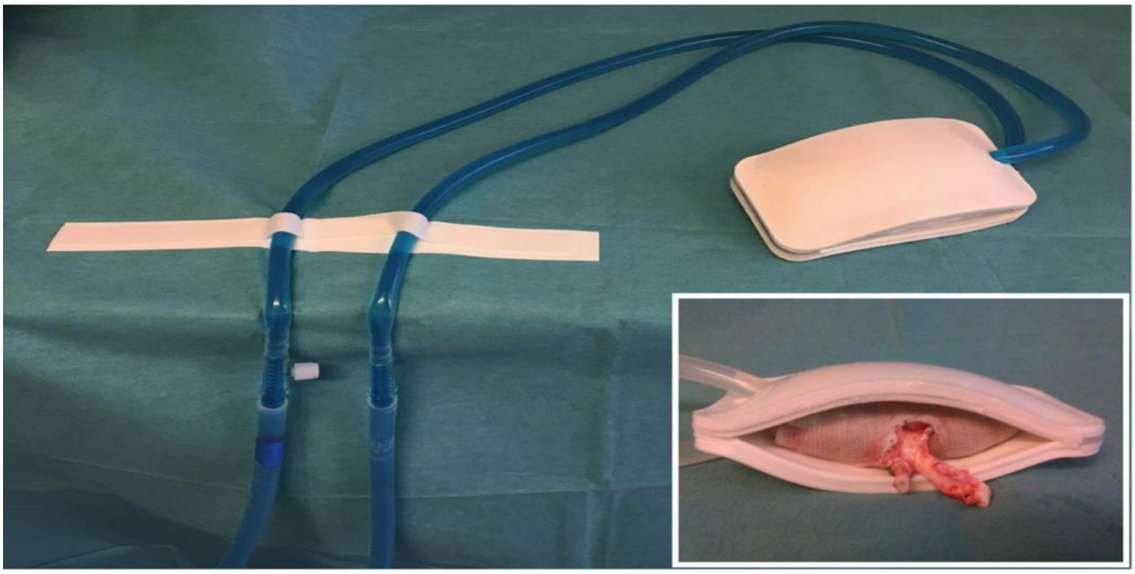

Figure 2. 8 The cooling device. The cooling device is a watertight double sheath of silicone surrounding the kidney and is continuously perfused via a tubing system with ethanol and methylene blue at 4°C. Inset: kidney with the perfused cooling device [14]

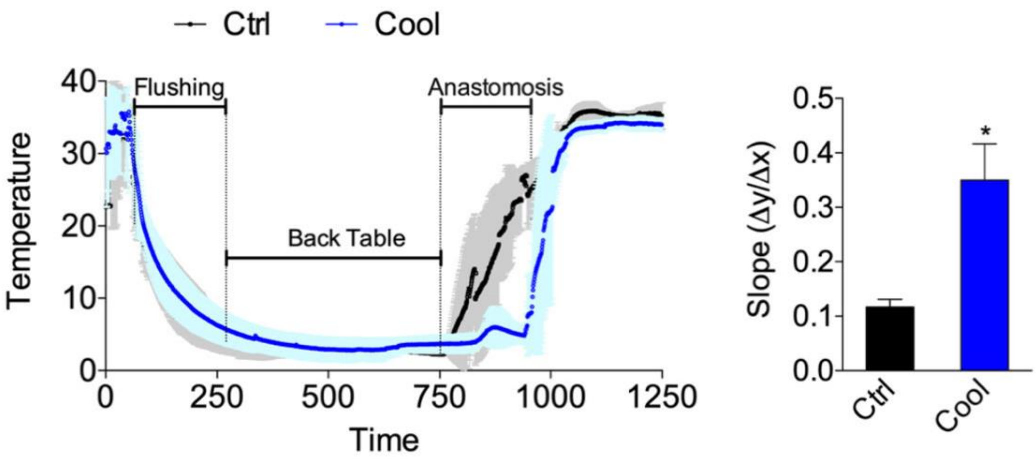

Figure 2. 9 Temperature curve from procurement to reperfusion. Curve (left) and slope during anastomosis (right) in the control [14]

2.2.3 Step-by-step Development of a Cold Ischemia Device for Open and Robotic-assisted Renal Transplantation

Territo et al [15] recommend an enhanced cooling jacket as shown in Figure 2.10 A. The jacket created is made of an elastic and flexible material. The aim is to create a path that the refrigerant can follow in the designed jacket and cool. Different parts of the material are combined in line with an unexplained method and a path is created. Initially, an ex vivo test was performed on the grafted kidney in the designed device and its temperature was recorded.

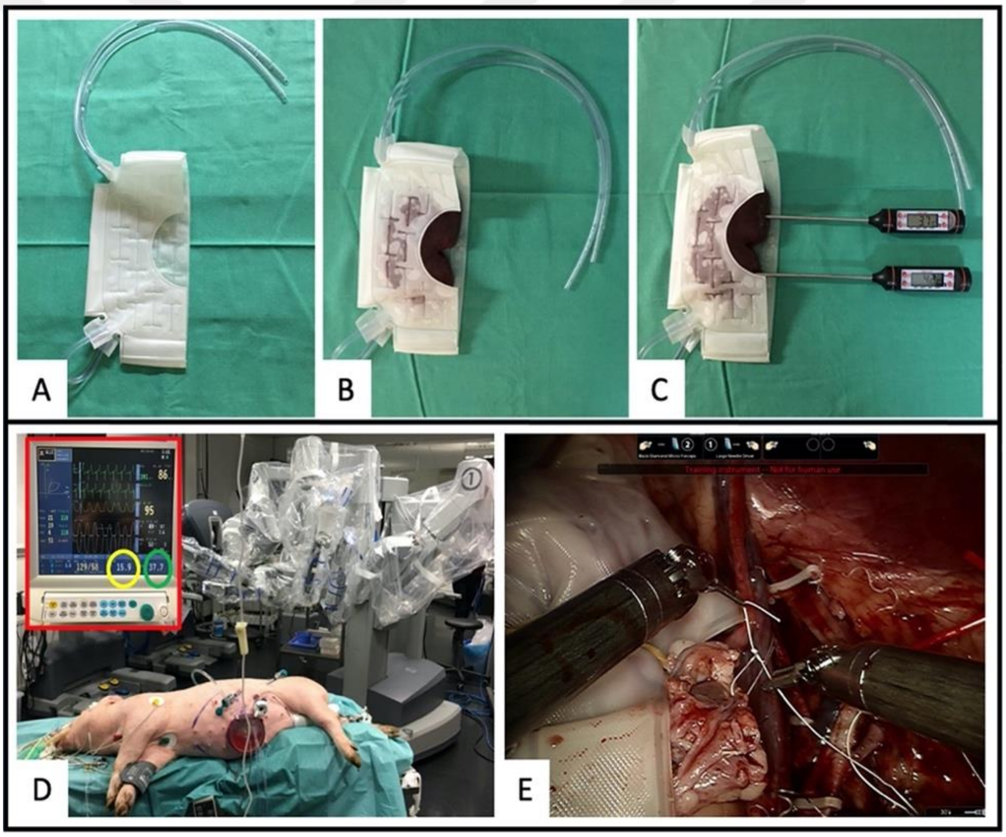

Figure 2. 10 (A) Cold ischemia jacket that has two silicone layers between in which the coolant can pass Filling CID with refrigerant, the distance between the two thin films is around 10 mm. (B) CID with graft, and (C) temperature measurement of donor kidney after coolant perfusion in CID: (D) thermocouples used and temperature data taken (E) Removing the cooling jacket after the vessel anastomosis and blood perfusing [15]

Natrium chloratum (NaCl) conditioned to 4 degrees is circulated continuously in the jacket by a peristaltic dosing pump as shown in Figure 2.11 C. The refrigerant in a reservoir is drawn by a dosing pump and circulated inside the jacket with the help of a closed-loop piping system. The process is not temperature-controlled as a previously cooled fluid is used which is not cooled to keep the temperature constant during the process. Since heat transfer takes place continuously during the process, the temperature of the refrigerant at 4 °C increases as seen in Figure 2.11 A, B [15].

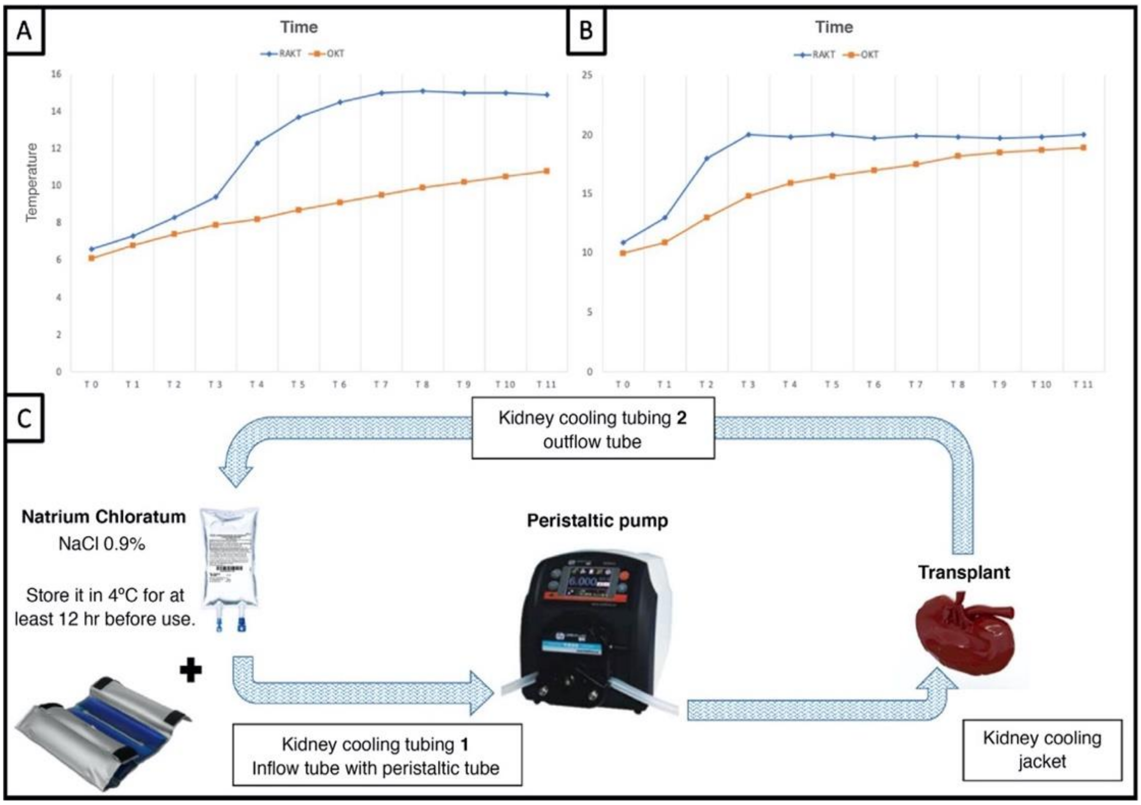

Figure 2. 11 (A) (IDEAL phase 0) Absolute temperatures at spesific times (B) (IDEAL phase 1) Absolute temperatures at spesific times (C) The closed-loop circulation system schematic shows the circulation of saline coolant inside tubing system by the help of peristaltic pump [15]

In addition, the liquid does not follow a smooth flow in the path created due to the stretching of the device as shown in Figure 2.12 A, therefore, heat transfer between the kidney and the jacket is not homogeneous. The coolant is changed approximately per 10 minutes to keep the coolant cold. Changing the refrigerant constantly limits the continuity of the system and might be extra costly, moreover, it is a time-consuming process [15].

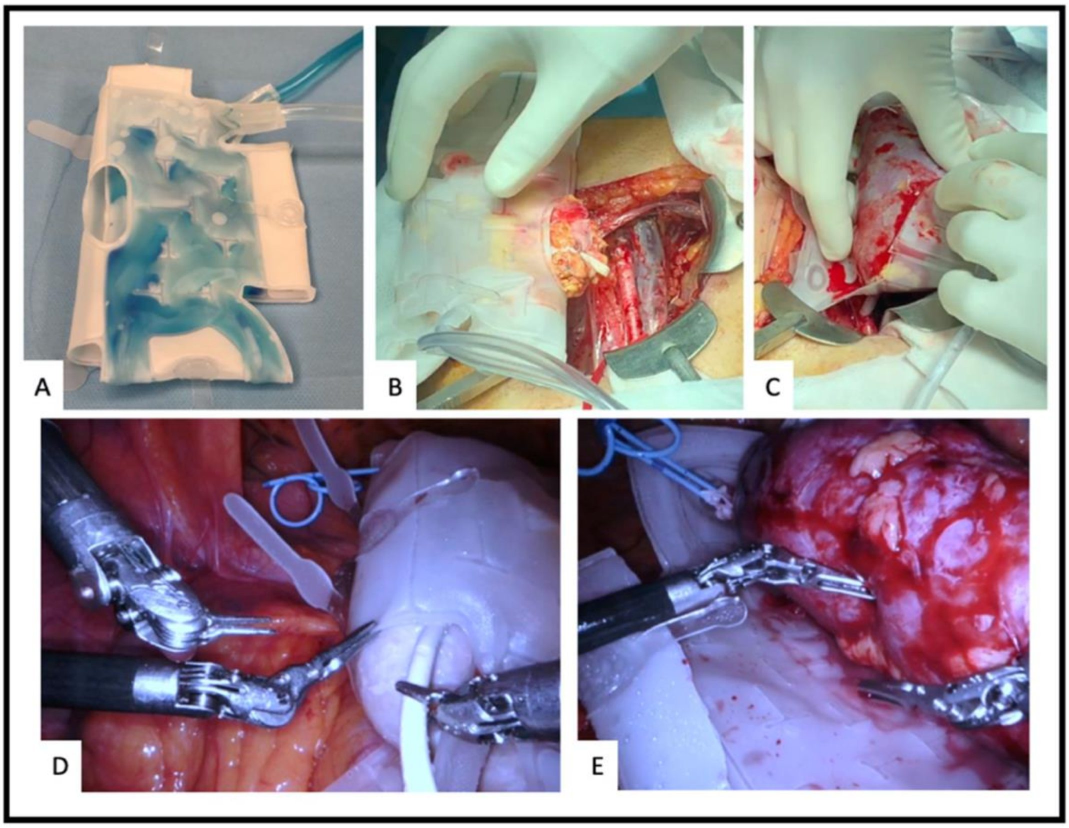

Figure 2. 12 (A) Saline perfused CID that has two silicone layers between in which the coolant can pass Filling CID with refrigerant, the distance between the two thin films is around 10 mm. (B) before carrying out a vascular anastomosis, and (C) removal process of CID after anastomosis (D) CID in RAKT surgery in human body and (E) Removing the cooling jacket after the vessel anastomosis and blood perfusing [15]

Table 2. 1 (IDEAL phase 0, ex vivo test) Absolute temperature values (deg C) at spesific times[15]

	T0 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	T3 Mean (SD)	T4 Mean (SD)	T5 Mean (SD)	T6 Mean (SD)	T7 Mean (SD)	T8 Mean (SD)	T8 Mean (SD)	T10 Mean (SD)	T11 Mean (SD)
Device (group 1)	3.1 (0.8)	3.5 (1)	4.9 (1.9)	7.7 (3.5)	10.5 (4)	12.4 (4.1)	14 (3.9)	15.1 (3.4)	16.8 (3.2)	17.7 (2.7)	19 (2)	19.9 (1.9)
Gauze jacket (group 2)	3.1 (0.3)	3.6 (0.5)	5.5 (0.8	8.2 (0.8)	11.2 (1.1)	13.9 (1.9)	16.2 (2.1)	18.4 (2.4)	20.1 (2.8)	22.4 (3.2)	24.4 (3.7)	26.1 (3.7)
No device nor gauze (group 3)	3.8 (0.7)	4.7 (0.9)	7.7 (2.3)	11.2 (3.3)	14.6 (3.3)	17.6 (3.1)	19.9 (3.2)	21.8 (3)	23.5 (2.8)	24.6 (2.7)	25.8 (2.3)	27 (2)
p value [a]	0.178	0.072	0.071	0.152	0.116	0.063	0.035 [b]	0.013 [b]	0.012 [b]	0.008 [b,c]	0.005 [b,c]	0.002 [b,c]

SD = standard deviation; T0 = baseline; T1 = 1st minute; T2 = 5th minute; T3 = 10th minute; T4 = 15th minute; T5 = 20th minute; T6 = 25th minute; T7 = 30th minute; T8 = 35th minute; T9 = 40th minute; T10 = 45th minute; T11 = 50th minute.
[a] *p* value for difference between the three groups at each time point (analysis of variance).
[b] Post hoc pairwise comparison of group 1 versus group 3, $p < 0.05$.
[c] Post hoc pairwise comparison of group 1 versus group 2, $p < 0.05$.
[d] Post hoc pairwise comparison of group 3 versus group 2, $p < 0.05$.

The graft kidney temperature is measured at around 37.5^{o}C and recorded. Subsequently, the CID was tested with a porcine model, followed by a graft human kidney. While conducting the tests, they chose three different test methods: with a cooling device, ice-filled gauze, and no device no gauze conditions. After the refrigerant, which was stored in cold storage before performing the test, was connected to the system, the liquid cycle system was operated, and kidney temperature measurements were made at certain time intervals. The ex vivo test shown in Table 2.1 proves that cooling is more efficient using a cooling device than in other cases. On the other hand, the temperature constantly increases as shown in seen in Figure 2.11 A, B, and Table 2.1 since there is no temperature-controlled coolant used for the cooling device [15].

2.3 Methodology

A more advanced technique, the temperature-controlled organ cooling jacket, is the current solution that can be an alternate methodology to the ice cooling technique. An organ cooling jacket is a product that aims to cool the organ homogenously to prolong the operation time in laparoscopic and open surgeries. The proposed invention is aimed to prevent hypoxic injuries in the patient’s organ at body temperature.

The working principle of the cooling jacket is based on fluid mechanics and heat transfer. Several designs have been made by applying the principles and different production methods. Although the main purpose of the designs is the same, the jackets are designed according to different standards and constraints vary according to parameters such as the material used, the cooling technique, the refrigerant, and the production method.

The organ cooling system consists of a cooling jacket, a reservoir containing the refrigerant, a water pump that circulates the fluid in the jacket, and a tubing system that will ensure the transmission of the fluid. This system, which consists of four main parts, may vary according to the design and constraints. The organ cooling jacket, which is produced generally with elastic biocompatible materials, has channels or spaces on which the cooling liquid can circulate. It has inlets and outlets that allow the cooling liquid to circulate inside; the position and location of the inlet and outlet might vary according to the channel design of the cooling jacket and the organ to be used.

The refrigerant, prepared with several solutions or pure materials, is circulated in the channels inside the jacket with automatic and manual systems. While the circulation process is done using a water pump in an automatic system, in a manual system it is done with simple tools such as an injector that pushes the water by creating pressure.

In existing cooling jacket systems, the circulated refrigerant is kept in a cold environment and used during the process. A reservoir filled with refrigerant is used for each organ because heat transfer occurs over time between the fluid in the reservoir and the organ and its environment, and the coolant temperature increases. The reservoir to be used in the new surgery is taken from the cold environment and connected to the system.

2.4 Produced Silicone Kidney Model for Designing Organ Cooling Jacket

2.4.1 Background

An anatomical model is a three-dimensional representation of human or animal anatomy, used for medical and biological education. Pre-surgery demonstration for the patient and instructive visualization of the procedure for the surgeon is made possible with the use of these anatomical models. Anatomical models can also be used for testing medical instruments such as surgical robots. [5,6,7]

The steps to be followed to create a 3D organ model are shown in the figure 2.13. In the first stage, MRI or CT imaging is performed on the organ to be modeled. The purpose of these imaging techniques is to capture the spatial information of the organ in a 3D cloud space which could be further assessed of manipulated in 3D software. The image sent to the computer environment is displayed using one of the 3D model segmentation programs thus the tissues and organs in the displayed image are colored and separated from each other. Since 3D model division programs do not have an advanced tissue recognition system, tissues, and organs are separated from each other manually by the user. The desired texture among the separated textures is divided into layers by the software, and the divided layers are arranged to reveal a 3-dimensional virtual model of the texture or organ. Minor deviations in the part of determining the boundaries of the organ and unexpected meshes that occur on the model during segmentation are cleaned at the mesh adjustment stage. This process is also called post-processing. At the final stage, the post-processed model is ready to be 3D printed. The model whose STL file is created is printed on a 3D printer with the help of the Ultimaker Cura software. [6]

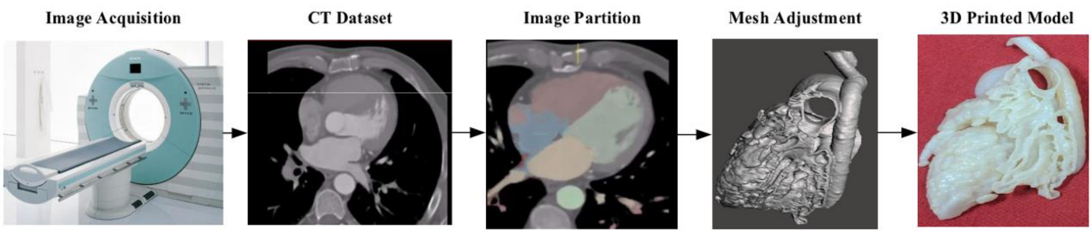

Figure 2. 13 The steps for creating a 3D organ model [6]

The Standard Prosthetic Production Cycle (SPPC) as shown in Figure 2.14 involves acquiring 3D data for prostheses using a 3D scanner, generating a digital 3D mold through software like 3D Max or SolidWorks, converting the model into G code using slicing software, and printing it with a desktop 3D printer. The resulting mold is filled with silicone, and the soft prostheses can be easily demolded after solidification due to the added strength and elasticity provided by the silicone. [31]

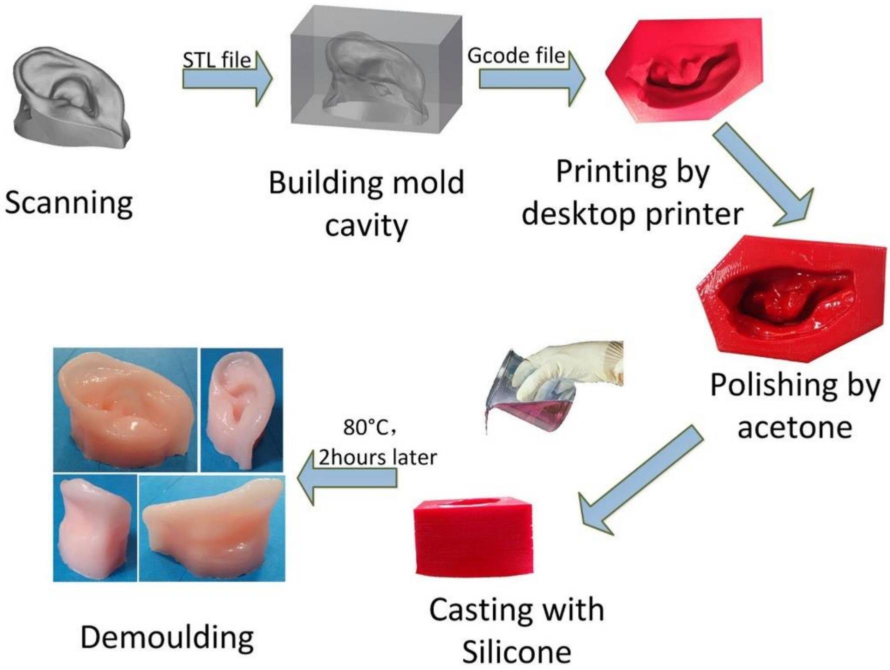

Figure 2. 14 The Standard Prosthetic Production Cycle (SPPC) Process [31]

2.4.2 Materials and Methods

CT scanning was performed using the 3D Slicer software. After securing all ethical permissions, we obtained a kidney model from the CT image of a kidney patient sent to us by Koç University Hospital. As seen in Figure 2.15, the kidney model is colored and segmented by applying CT imaging in 3D Slicer software.

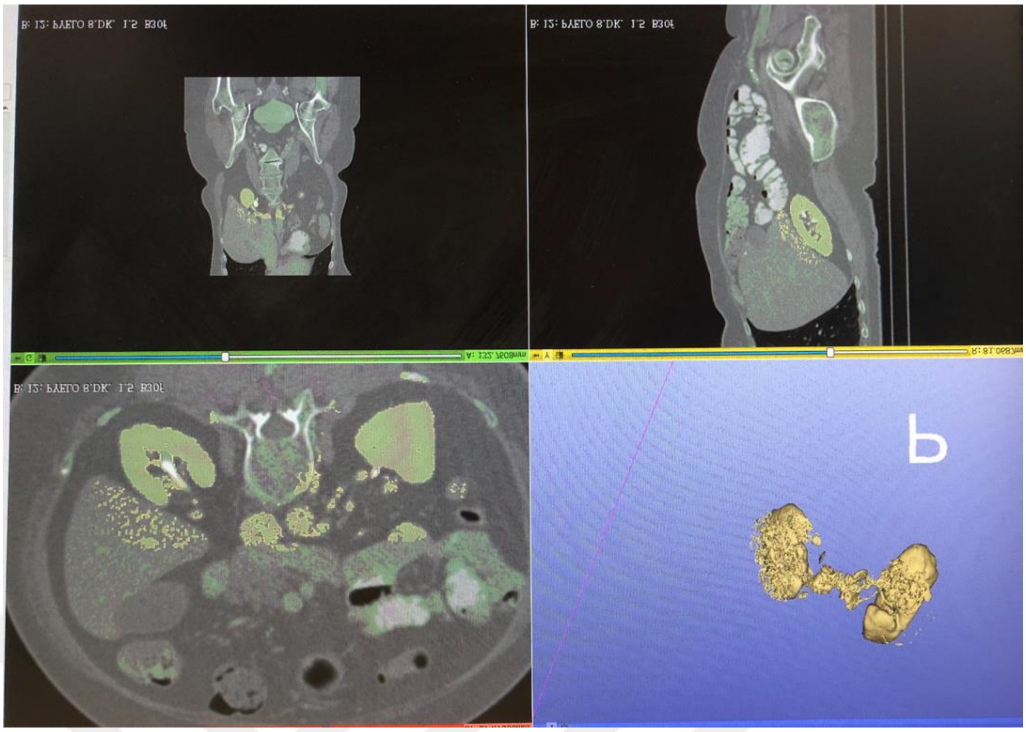

Figure 2. 15 The colored and segmented CT kidney image

In the complex model obtained, the right kidney was surgically removed as it has a tumor as seen in Figure 2.16 Therefore, the healthy left kidney was used in the model. The left kidney was isolated from the complex model and then post-processed. The STL format of the final model obtained is shown in Figure 2.17.

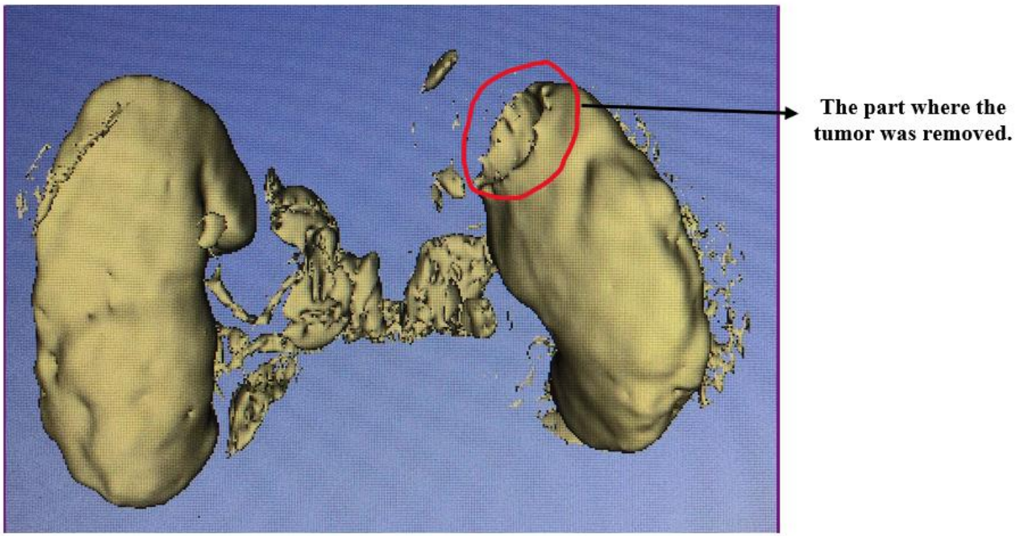

Figure 2. 16 The pair of kidneys from the CT image

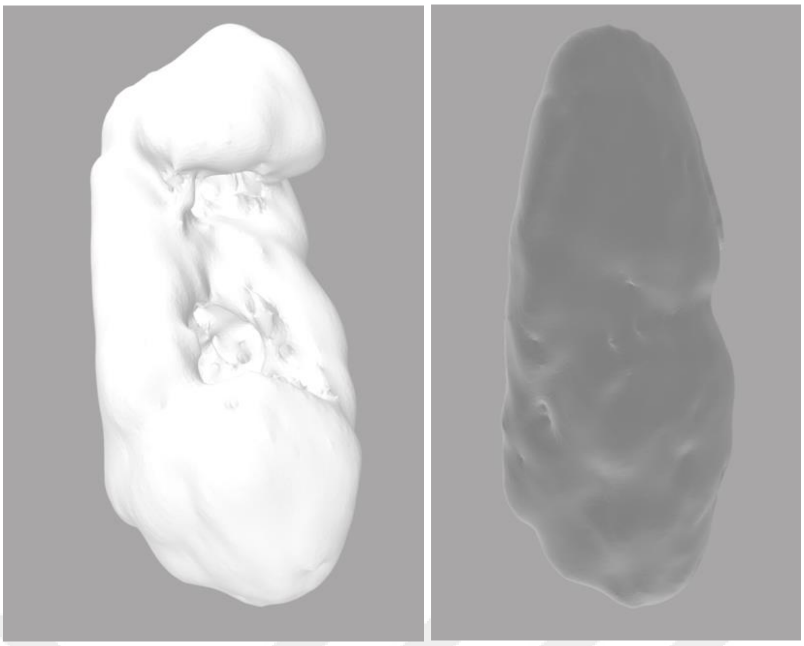

Figure 2. 17 STL Format of Obtained Kidney

2.4.3 Result and Discussion

The FDM 3D printing technique was used to create the 3D organ model [29]. In contrast to the conventional approach of directly 3D printing the model, this application involves the creation of two-part molds for producing the organ model, which are then molded with RTV mold silicone. The decision to use silicone in the printed mold instead of the direct model printing process is driven by the limitation that 3D printers cannot effectively print soft materials like silicone. The patterns, initially designed in the NTop software, were 3D printed, and a kidney model placed in the resulting block underwent negative molding. The resulting mold, described in Figure 2.18, was divided into two parts, as illustrated in Figure 2.19. Subsequently, both parts were printed using a 3D printer and molded with liquid silicone. The rationale behind dividing the mold into two parts is to facilitate the easier removal of the cured silicone model from the interior.

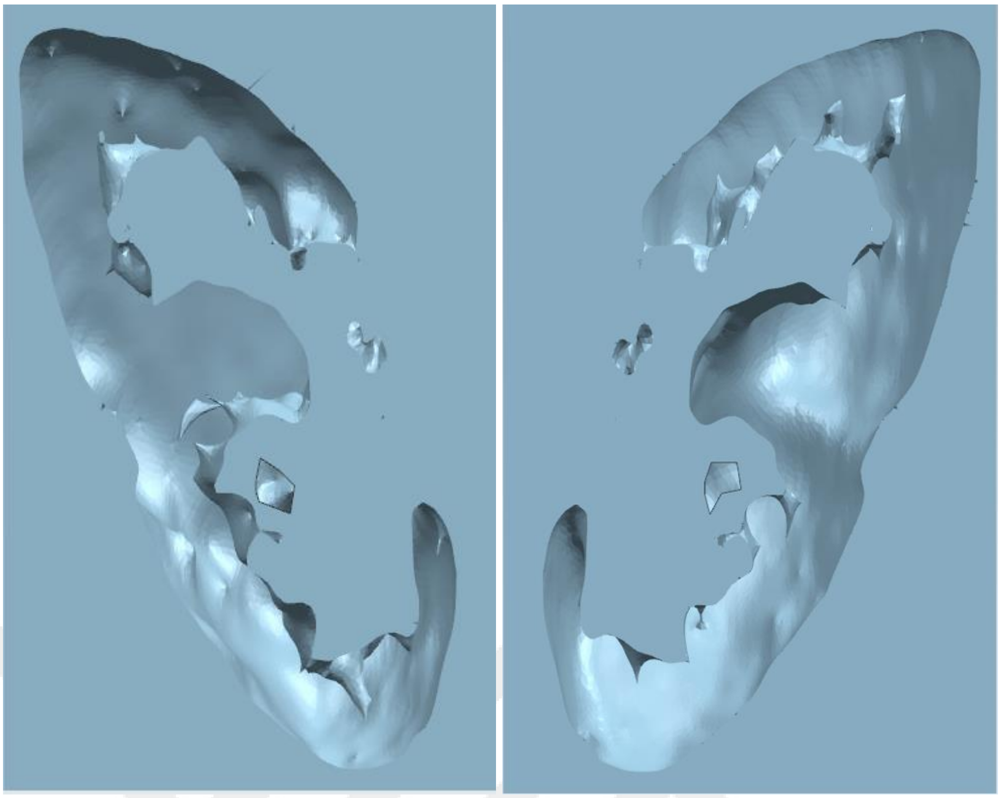

Figure 2. 18 Molds CAD

Figure 2. 19 The 3D printed molds and molding process

After the silicone was cured and hardened, the two half kidneys were removed from the mold. The two removed pieces were bonded with the same silicone material and the entire model was obtained. The real silicone kidney model is shown in the figure 2.20.

Figure 2. 20 Silicone-produced kidney model

2.5 Organ Cooling Jacket Design Considerations

Several design ideas have been thought for the production part, which is the most challenging part of the work. It was very critical to first choose the material to be able to produce, and then decide which production method would be used to form the material. The most critical and eliminative part of material selection is that the cooling jacket is in contact with the kidney. In this case, working with biocompatible materials, which is one of the material subgroups, is the best solution. The reason for this is that biocompatible materials are compatible with living tissues and cells, and when they come into contact with a part of the body, no malignant bacteria formation is observed on their surfaces. Biocompatible materials are categorized according to their chemical composition. Biocompatible polymers are soft and flexible materials that can be easily shaped [16].

2.5.1 Limitations

- The small incision diameter of the patient where the material input-output port is installed.
- The movement limitations of robot arms
- The space to wrap the donor kidney with a cooling jacket from outside.
- How to import OCJ from the port into the body in laparoscopic surgeries
- How to put the coolant liquid inside the kidney cooling jacket
- How to export kidney cooling jacket after cold ischemia

3.5.2 Phase 1: Silicone Jacket with Silicone Pipes

In the first design as seen in Figure 2.21, 1 mm thick RTV silicone was chosen to produce a cooling jacket. Silicone tubes which have a 3 mm inner and 5 mm outer diameter are used to circulate coolant inside the jacket. In this trial, the silicone tubes are placed inside the jacket. This design has an inlet and outlet silicone tubes; therefore, water can follow a path from the inlet to the outlet of the jacket by using a tubing system inside the jacket. In this design, constraints such as the use of biocompatible materials and the liquid to follow a certain path were provided. However, the measured diameter (around 40 mm) of the jacket is more than 20 mm (the maximum diameter of the used port) and cannot pass from the port used for laparoscopic kidney operations. In addition, this jacket is not flexible enough to be rolled up and inserted into the human body through the port thus it is failed.

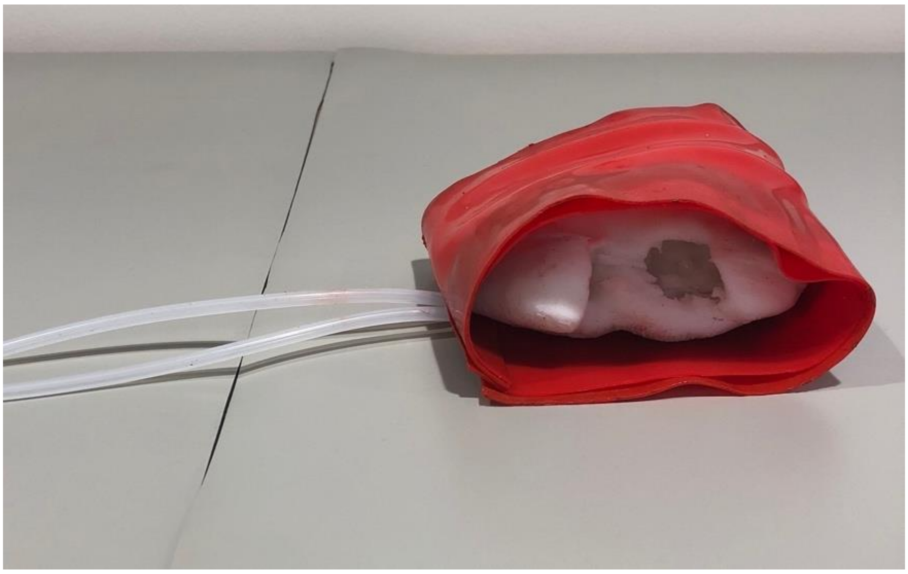
Figure 2. 21 The designed cooling jacket with 1 mm thick silicone rubber

2.5.3 Phase 2: Teflon Jacket with Silicone Pipes

In the second design as seen in Figure 2.22, elastic Teflon with a thickness of 260 microns was chosen. Here, the use of biocompatible materials, which is an important point of the study, was complied with. In this experiment, the refrigerant was circulated in a closed loop by a tubing system. Moreover, the working temperature of the material is also suitable as it covers the working temperatures required in this project. The tubing system is optimally designed as seen in Figure 2.23 thus the cooling jacket is the most thermally conductive. The design has been manufactured and tested. According to the flexibility and size of the cooling jacket, it is not convenient to perform it in laparoscopic kidney surgeries. Once the cooling jacket was rolled, it could not pass through the port since the jacket could not be folded to the smallest optimal diameter due to the insufficient flexibility of the material. In addition, due to the wall thickness of the silicone tubing, the thermal conductivity is not efficient in cooling the kidney. An efficient heat transfer could not be achieved.

Figure 2. 22 The designed cooling jacket with 260 microns sheet teflon

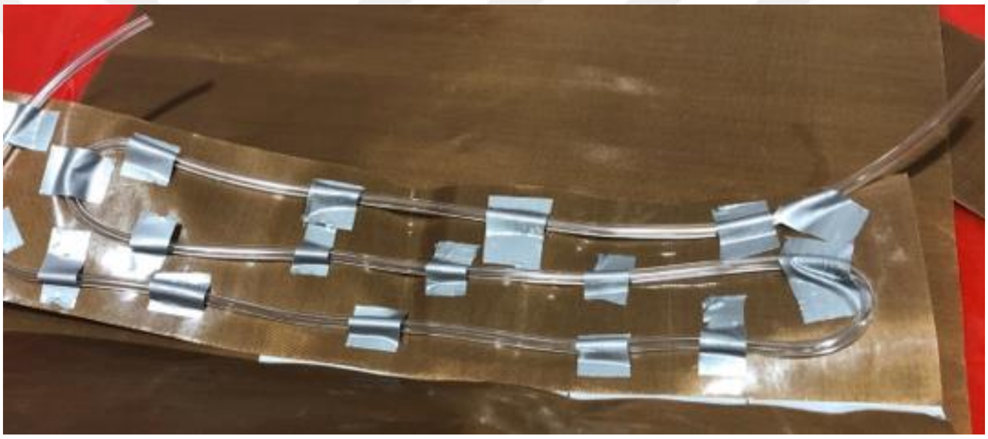

Figure 2. 23 Optimally placed tubing system in the 260 microns sheet Teflon jacket

2.5.4 Phase 3: Creating Water Channels by Implementing Super Glue

In the third design, a different refrigerant circulation method is considered compared to the previous designs. The main problems of other designs were evaluated and accordingly, a completely different production method was considered. In this study, it was desired to create a path in which the refrigerant can circulate in the flexible nylon material instead of using silicone tubing. Firstly, the melting method was tried to create a path in nylon. In this experiment, a production method was tried by melting the nylon together at the high temperature provided by the soldering device, but the edge of the soldering tool had a point area, and the nylon material was pierced. Subsequently, a soldering edge with a larger surface area was designed and tested to avoid piercing the material. This experiment, it was aimed to bond the material with the force applied by our hand and the pressure created by the designed edge on the material; However, since a homogeneous pressure could not be obtained in this process, both non-joining and perforation were observed in various parts of the material. Since the idea of bonding by heating was not successful, this process was tried with strong adhesives. For this bonding process, adhesives that can form a strong bond between nylon-nylon were researched and it was decided to use super glue. Initially, the path dimensions were decided and drawn on nylon. Afterward, super glue was applied on the sheet nylon part so that it would not pour out and it was cured. As a result, it has been observed that due to the weight of the nylon on the adhesive, it pours out of the lines, is into the spaces where the coolant will circulate, over time. Admittedly, the idea of producing a cooling jacket using glue was too optimistic.

2.5.5 Phase 4: Water-Soluble PVA Tunnels Between Two Layers

In this design, a theory was formed by utilizing the water-soluble property of polyvinyl alcohol. The main purpose of this design idea is to circulate water in the tunnels printed by a 3D printer from PVA material and to dissolve it thanks to the water solubility of the material. Initially, 500-micron silicone was chosen as the material to form the cooling jacket, and CAD of the tunnels was sketched in NX Siemens software as shown in Figure 2.24. The designed tunnels were converted into STL files and manufactured with the help of a 3D printer as seen in Figure 2.25. The critical point of this study is to keep the tunnels between the sheet silicone rubbers stationary and bond the two layers strongly. Based on this basic principle, tunnels formed between two sheet silicone rubbers are positioned as seen in Figure 2.26. To achieve this, two methods were considered. Firstly, forming silicone rubber at deformation temperatures was presented. This method could not be tried since both a hot press machine and molds for the press machine are required for this type of production. This method is very costly to produce the cooling jacket. Therefore, another consideration is to use a special adhesive to bond the silicone rubber layers. This method was also not successful, as the strong rubber adhesives available on the market were expensive and sufficient to produce a single jacket. For these reasons, the theory failed.

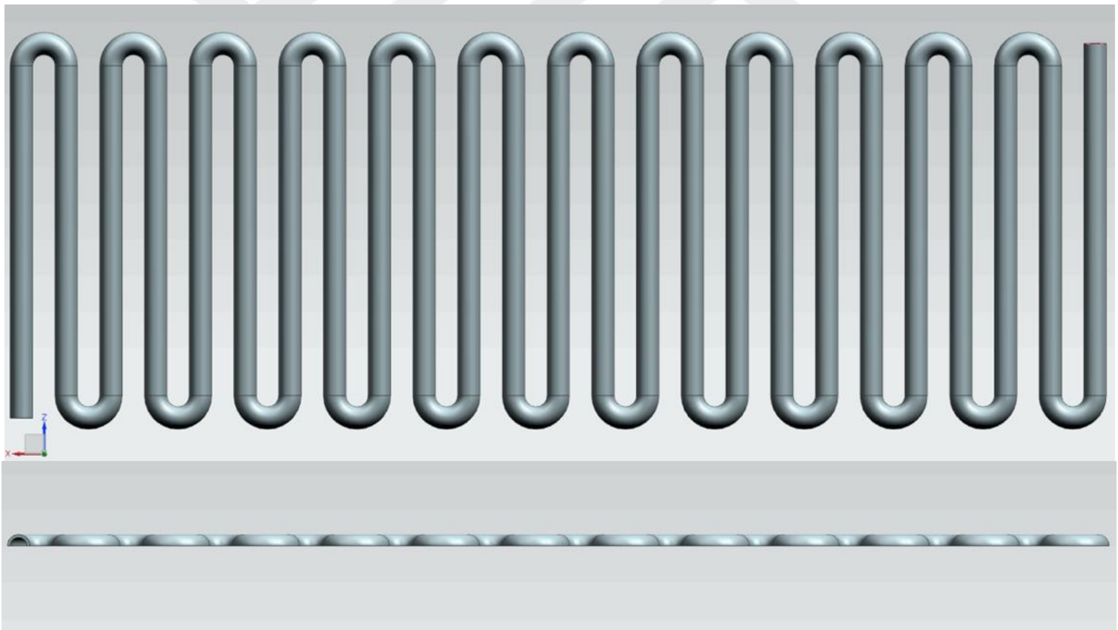

Figure 2. 24 Water Channel CAD

Figure 2. 25 3D printed PVA channel

Figure 2. 26 Positioning of PVA tunnels in between two silicone sheets

2.5.6 Phase 5: EPDM Elastic Organ Cooling Jacket by Negative Molding

Figure 2. 27 RTV Mold Silicone

In this design, a completely different production method is followed by observing the mistakes and deficiencies made in previous trials. Instead of ideas such as using a tubing system inside the cooling jacket and bonding rubbers by using adhesives, molding is applied by using 3D printed molds to manufacture the organ cooling jacket which can pass through the port, is thermal conductive, and most importantly, is easily shaped. The most critical part of the design is the molds. Since it is aimed to create a path in which water circulates, the RTV mold silicone material as shown in Figure 2.27, which is in a fluid state, should not flow and close the tunnels to be created in the mold. It is technically possible to create empty paths in which water can flow in a single mold; however, it is impossible to remove a cooling jacket with tunnels made of silicone from the single mold in one piece and undamaged. Therefore, the purpose is to produce the cooling jacket from two pieces and followingly assemble it. The critical question at this point is how to bond the silicone jacket produced in two parts. The same material can be used again to assemble parts produced with RTV mold silicone, which has been applied and observed in previous silicone organ model studies.

In this study, which was thought through in detail, the CAD designs of the molds were initially sketched in NX Siemens software. Four different mold designs were manufactured; two of them are used to form the upper part of the kidney cooling jacket, while the other two are used to form the bottom part. While the kidney cooling jacket is planned to be wrapped on the kidney with a 3-sided closed design, the open version of this jacket was first molded. To design the molds that form the upper part of the jacket, which consists of two pieces, the dimensioning must be done accurately. First, to determine the size of the jacket, the size of the adult kidney was evaluated according to gender, the side of the kidney in the human body, and its tolerances. Real normal kidney sizes are 108.5 ± 12.2 mm for the right kidney and 111.3 ± 12.6 mm for the left kidney [17]. The jacket to be produced is intended to cover even the largest kidney.

2.6 Production Method: Negative Molding with 3D Printed Molds

The production method of molding is implemented to manufacture the organ cooling jacket. The jacket, which is composed of upper and bottom pieces at the beginning, is produced by negative molding. Molds in which elastic material is molded are sketched in CAD software and printed by a 3D printer. While molds 1 (figure 2.28) and 2 (figure 2.29) are used to form the upper part of the jacket, parts 3 (figure 2.30) and 4 (figure 2.31) are used to form the bottom part.

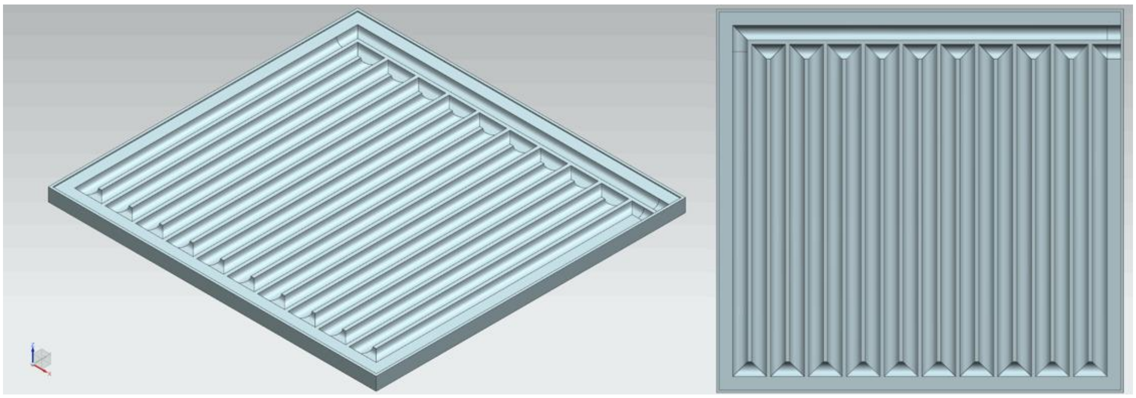

Figure 2. 28 CAD mold 1 for OCJ upper part

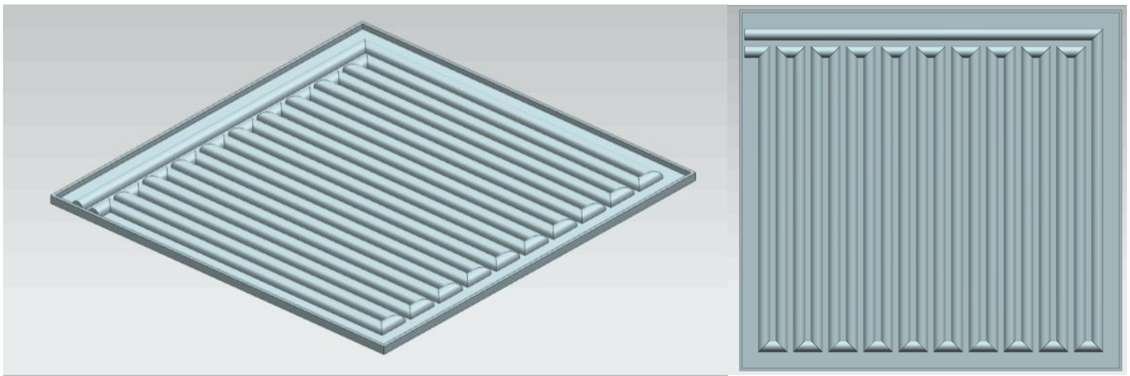

Figure 2. 29 CAD mold 2 for OCJ upper part

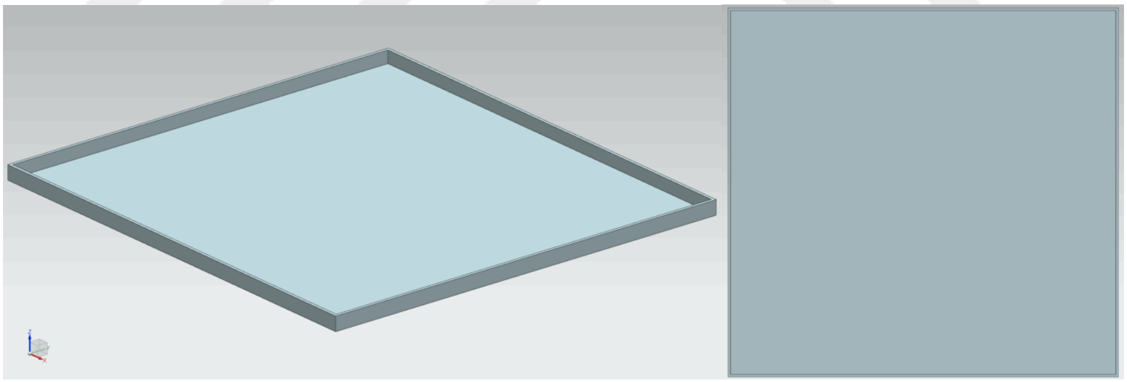

Figure 2. 30 CAD mold 3 for OCJ bottom part

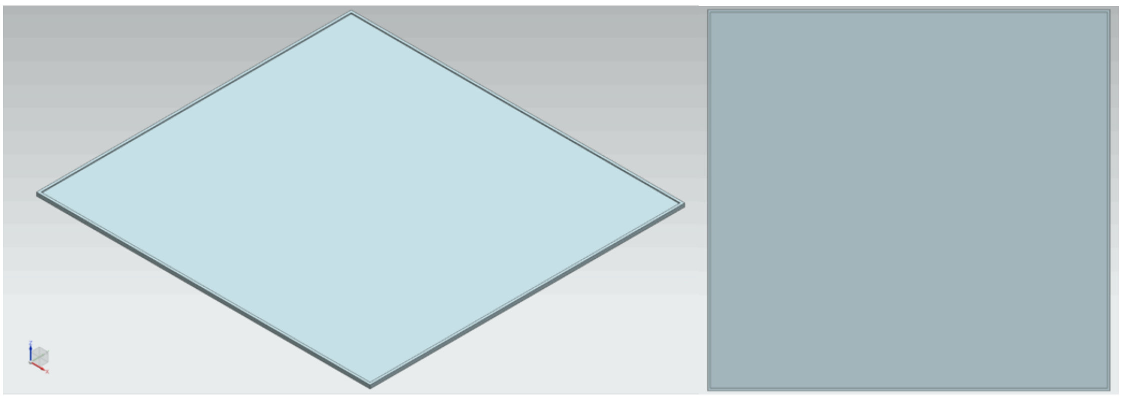

Figure 2. 31 CAD mold 4 for OCJ bottom part

There is a male and female mold forming each jacket piece, and they form the material to be cured by intertwining after pouring the liquid elastic material into them. Intertwining parts to manufacture both upper and bottom pieces of OCJ are shown in Figures 2.32 and 2.33. After curing, the upper and bottom pieces of OCJ are applied post-processing and made ready to form a single-form OCJ. The parts produced are bonded by using the same material which forms upper and bottom pieces or several adhesives for rubbers; form the OCJ.

Figure 2. 32 - (A) 3D printed female mold 1 1 (142x162x7 mm), (B) 3D printed male mold 2 (143x163x4mm), Intertwining of female and male mold to manufacture OCJ upper piece.

Figure 2. 33 - (A) 3D printed mold 3, (B) 3D printed mold 4, Intertwining of mold 3 and 4 to manufacture OCJ bottom piece.

The molds that produce the upper part of OCJ are more shaped as they are the ones that form the tunnels. Initially, the 1000 microns height between the surface and edge of mold 1 is given to form the thickness of the upper part. In addition, the tunnel radius of the female mold 1 is larger than the tunnel radius of the male mold 2 as much as the height value given between the surface and the edge for mold 1 which is 1000 microns. The purpose of this is to keep the thickness equal in all areas of the upper part of the jacket. The distance between the edges of the mold 2 is equal to the sum of the distance between the edges of the mold 1 and its edge thicknesses. The purpose of this design is to fix the edges of the mold 2 by wrapping the edges of mold 1 from the outside and to prevent the thickness differences in the jacket that might occur due to possible slips during the molding process. Analogically, mold 3 and mold 4 are used to create the bottom part. There is a 500-micron height difference between the edges and the surface of mold 3 to similarly create the thickness of the lower part. Likewise, the sum of the distance between two edges and the thickness of the edges of mold 4 is equal to the distance between the edges of mold 3 to prevent possible slipping during the molding process. After pouring the liquid mold material on the surface of mold 3, mold 4 is placed in the female mold and fixed.

2.7 Temperature-Controlled Organ Cooling Jacket

The organ cooling jacket (OCJ) comprises multiple cooling channels, an inlet, and an outlet, a 3D model of the jacket is presented in Fig 2.34. The coolant enters the OCJ from the inlet channel, circulates through the jacket, and exits from the outlet channel. Since the refrigerant is circulated with a constant flow in the organ cooling jacket, the jacket temperature is kept constant. Heat transfer takes place at the surface interaction of the jacket channels and the organ homogeneously. The design of the jacket takes into consideration the anastomosis process during renal transplant and ensures there is no intrusion to access the hilum region. The organ cooling jacket presented in the paper experiments with two varying inlet channel diameters. The smaller jacket mentioned in the paper refers to the jacket with an inlet diameter of 4.5mm and a wall thickness of 1mm.

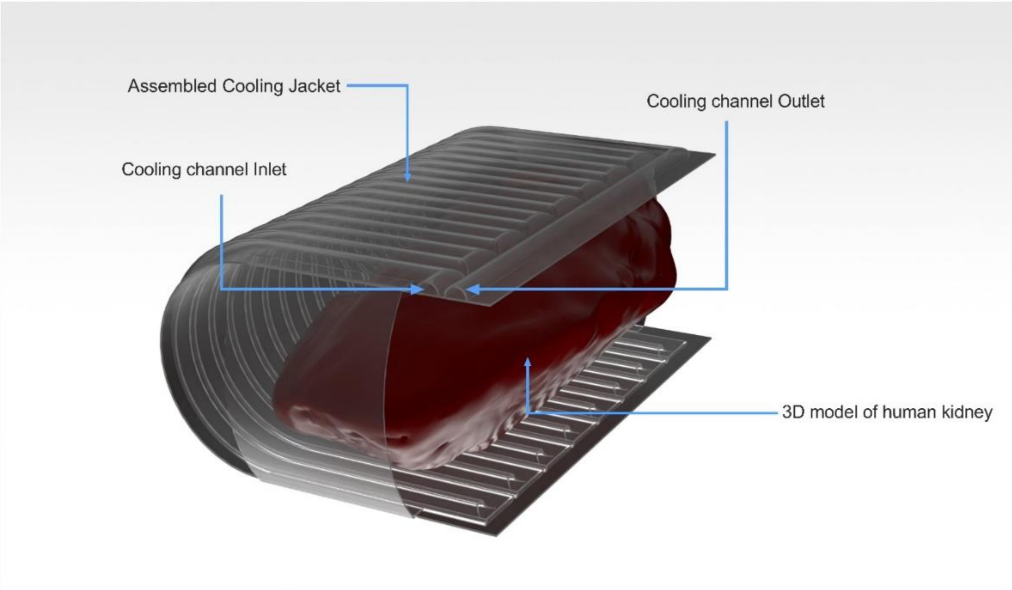

Figure 2. 34 3D model presentation of the organ cooling jacket enclosed around a 3D model of a human kidney

CAD of the kidney cooling jacket as shown in Figure 2.35 is provided with an inlet (1.1) and outlet (1.2), which are in one corner of the jacket. The position of the inlet-outlet is designed in a position not to inhibit the doctor from operating the cold ischemia of the graft organ (1.3). The coolant entering the OCJ from the inlet (1.1) circulates in the channel and exits from the outlet (1.2), therefore the constant flow cools the OCJ. Heat transfer takes place between the OCJ and the graft organ which is wrapped by the jacket. In this procedure, the organ to be operated on is cooled and its vital risks are eliminated.

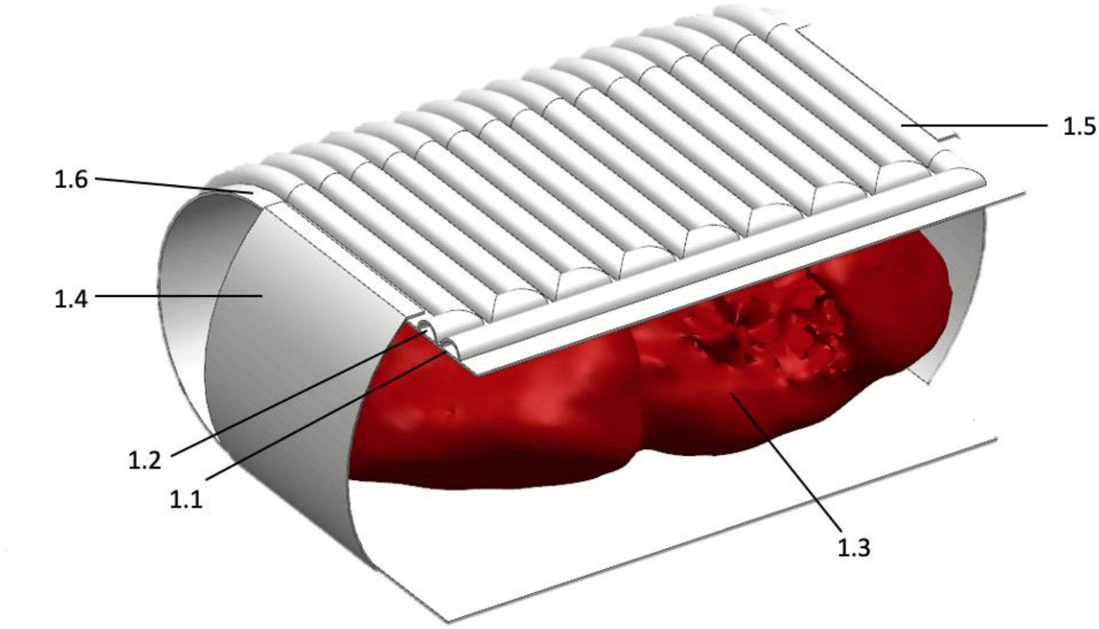

Figure 2. 35 -3D model of the organ cooling jacket enclosed around a 3D model of a human kidney, 1.1) inlet, 1.2) outlet, 1.3) human graft kidney model, 1.4) stretch band, 1.5) hollow half channels, 1.6) margin

Stretch bands (1.4) made of thin elastic material on both sides are used to hold and wrap donor kidneys of different sizes in OCJ. After the OCJ is wrapped around the graft organ, it can be sutured and fixed from two sides instead of using stretch bands. That's why the manufactured OCJ as shown in Figure 2.36 is without the stretch band. Thanks to the compressive force created by the bands, the jacket wraps the graft organ and prevents it from slipping. In addition, an elastic material is chosen to form the jacket easily and to wrap the organ.

While the upper part of the jacket consists of hollow half channels (1.5), the bottom part has a flat structure. This is due to the fact that two parts can be compounded more tightly by implementing a negative molding production method. The channel on the jacket is designed to achieve maximum thermal efficiency when the entire jacket is wrapped. In addition, the channel design is aimed that the liquid follows a unidirectional path and spreads the temperature evenly over the surface where heat transfer will take place with the graft organ. Due to the pressure created by the circulating liquid inside the channels, a margin (1.6) is left on the edges of OCJ. In this way, leaks that may originate from the pressure created inside are prevented. The 1000 microns' outer thickness of the produced jacket is more than the 500 microns inner thickness. The purpose of this application is to increase the heat transfer between the graft kidney and the jacket while reducing the heat transfer with the external environment.

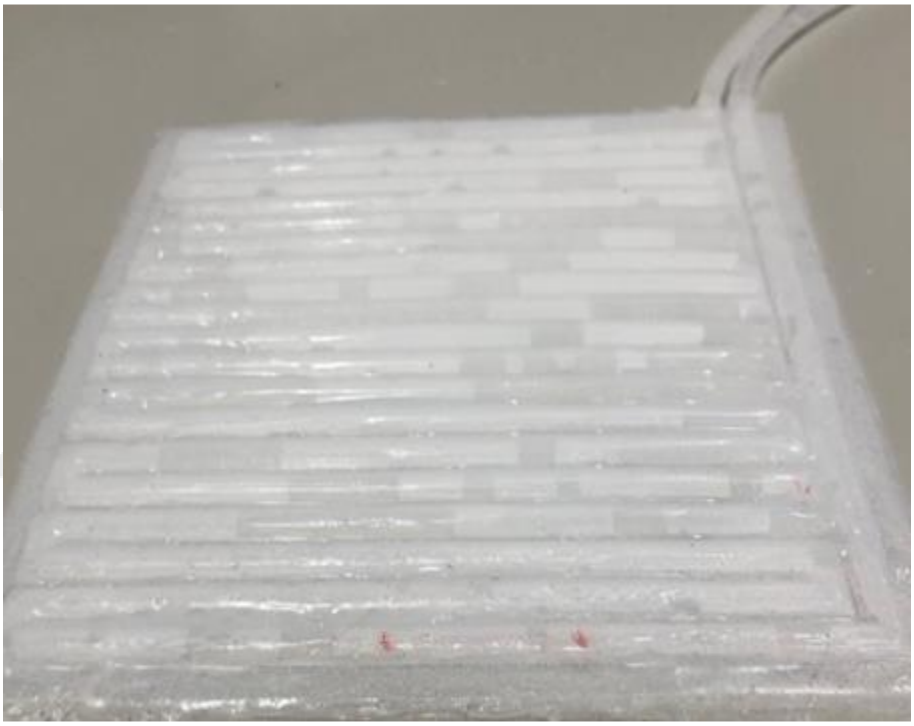

Figure 2. 36 Manufactured OCJ with inlet-outlet silicone pipes

The inlet and outlet pipes of the water circulation system are connected inside the inlet and outlet of OCJ using the hoop stress in equation 3.1[18]:

$$\boldsymbol{h = PDm / 2t} \quad (3.1)$$

caused by the stretching of the elastic material forming the cooling jacket, the diameter of the channel created on the jacket is designed smaller than the diameter of the inlet and outlet pipes. In this way, the entering inlet and outlet pipes are immobilized, and leakage is prevented by using the hoop stress by stretching OCJ on the pipes. In addition, an elastic material is chosen to form the jacket easily and to wrap the organ.

2.8 Auxiliary Systems

2.8.1 Liquid Circulation System

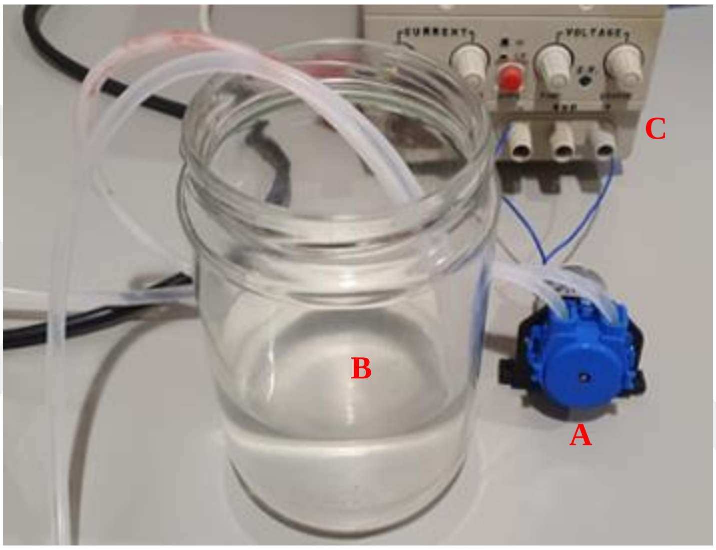

Figure 2. 37 Liquid Circulation System, A- Peristaltic pump, B- Liquid reservoir, C- power supplier

The liquid circulation system as described in Figure 2.37 allows the liquid to pass through the channels in the OCJ to be used to cool the graft organ. This system consists of a peristaltic dosing pump, a liquid-filled reservoir, and a tubing system. A peristaltic dosing pump with an adjustable flow rate according to the rpm of the motor provides a constant flow rate. The refrigerant from the liquid-filled reservoir is drawn by the pump and circulated within the system. In addition, the liquid to be passed through the OCJ is first cooled by circulating it in a controlled manner at a constant temperature in the reservoir of the cooling system. Distilled water, returned in the tubing system in a completely closed cycle, cools as it circulates through the reservoir of the cooling system.

In this process, the water rotating in the pipe does not come into direct contact with the refrigerant in the cooling system reservoir.

2.8.2 Refrigeration System

The built refrigeration system [19] as shown in Figure 2.38 is a simple system consisting of a compressor, condenser, expansion valve, and evaporator that is used to provide cooling of the liquid in the refrigeration system reservoir which circulates inside the tubing system. The temperature of the cooled liquid is aimed to be kept constant in this process.

Figure 2. 38 Figure 3. 2 Components of the Auxiliary cooling system for controlled fluid flow temperature across the jacket

The pipes, in which fluid rotates in the liquid circulation system, are kept in the cold liquid in the reservoir and chilled This temperature-controlled cooling process is the main purpose of the refrigeration system.

2.9 System Schematic

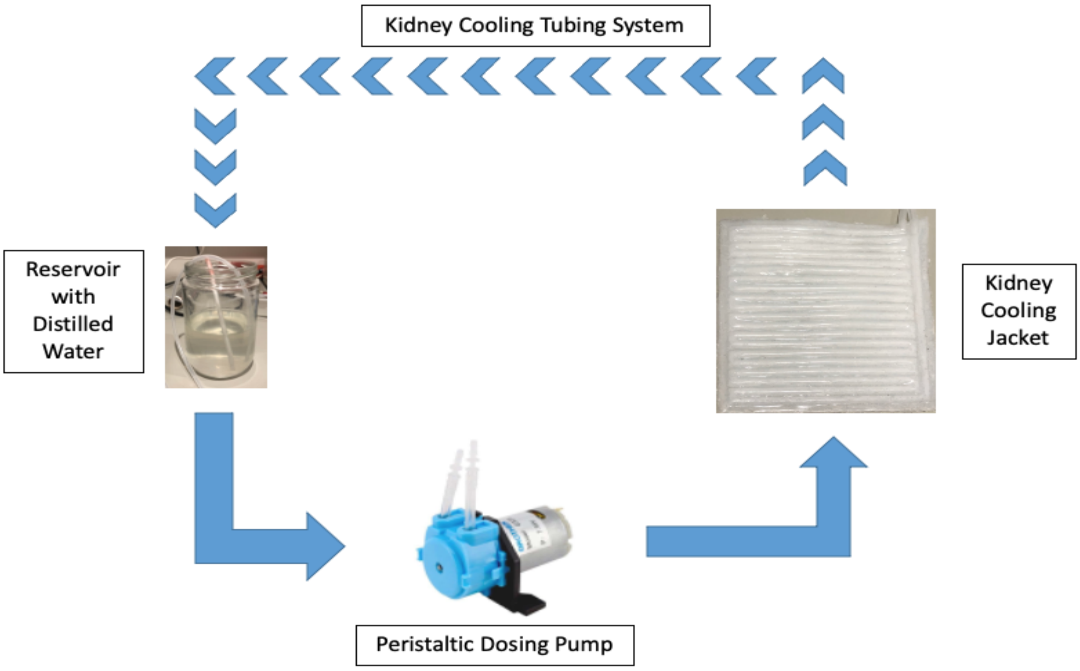

Figure 2. 39 Organ Cooling Jacket Liquid Flow Cycle

The liquid circulation system, which is an important part of the system, allows the liquid to pass through the channels in the cooling jacket to be used to cool the graft organ. Circulating distilled water in a reservoir to the cooling jacket by a pump and then back to the reservoir is the flow path of the refrigerant in a closed loop as presented in Figure 2.39. In addition, during the flow, the piping system is passed through the cooling system reservoir, the liquid inside is cooled and its temperature is kept constant.

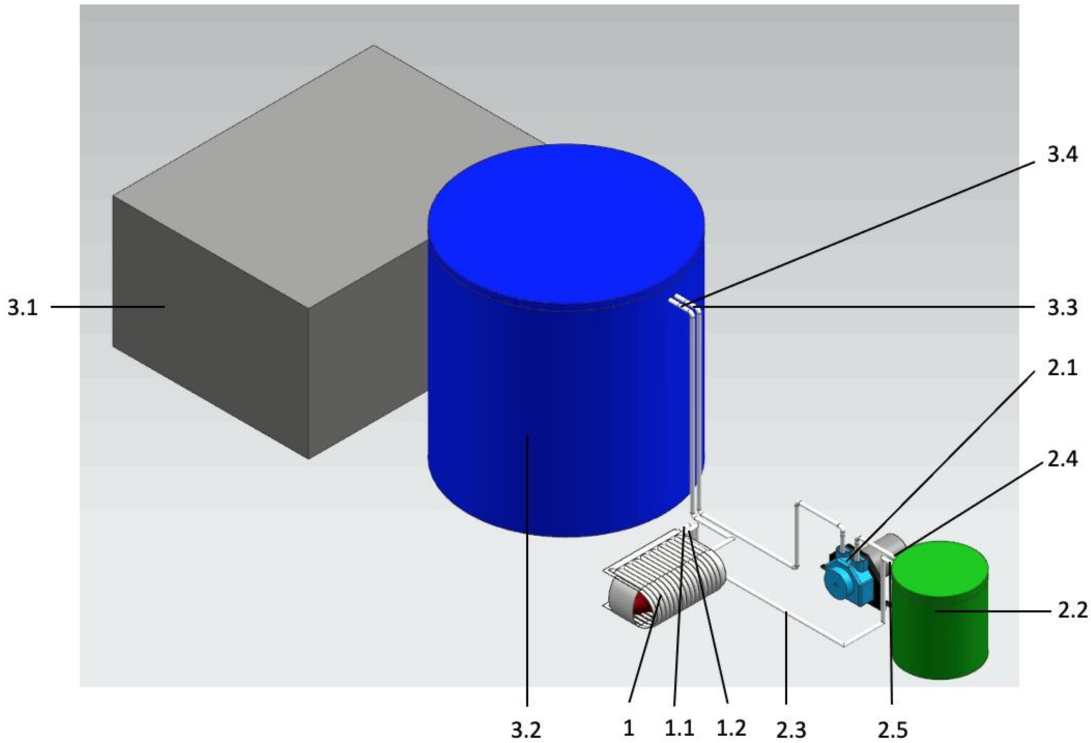

Figure 2. 40 - CAD visualization of complete OCJ system – (1) Organ cooling jacket, (1.1) Organ cooling jacket inlet, (1.2) Organ cooling jacket outlet, (2.1) Peristaltic dosing pump, (2.2) Liquid-filled reservoir, (2.3) Tubing system, (2.4) Liquid-filled reservoir outlet, (2.5) Liquid-filled reservoir inlet, (3.1) Refrigeration system, (3.2) Refrigeration system reservoir, (3.3) Refrigeration system reservoir inlet, (3.4) Refrigeration system reservoir outlet

The CAD design of the system as seen in Figure 2.40 consists of a peristaltic dosing pump (2.1), a liquid-filled reservoir (2.2), and a tubing system (2.3). Peristaltic dosing pump (2.1) with an adjustable flow rate according to the rpm of its motor provides a constant flow rate. In detail, initially, the liquid-filled reservoir (2.2), is drawn by the pump (2.1) from the liquid-filled reservoir outlet (2.4) and rotated the liquid to the refrigeration system reservoir (3.2). After the liquid enters the refrigeration system reservoir (3.2) from the refrigeration system reservoir inlet (3.3), the liquid in the tubing system (2.3) circulates inside the coolant in the reservoir and cools. From the refrigeration system reservoir outlet (3.4), the fluid inside the pipe enters the organ cooling jacket through its inlet (1.1) and continues to flow inside. The refrigerant, which completes its circulation in OCJ, exits from its outlet (1.2) flows through the liquid-filled reservoir, and enters from its inlet (2.5). Here the loop ends and repeats continuously. The complete physical system is presented in Figure 2.41.

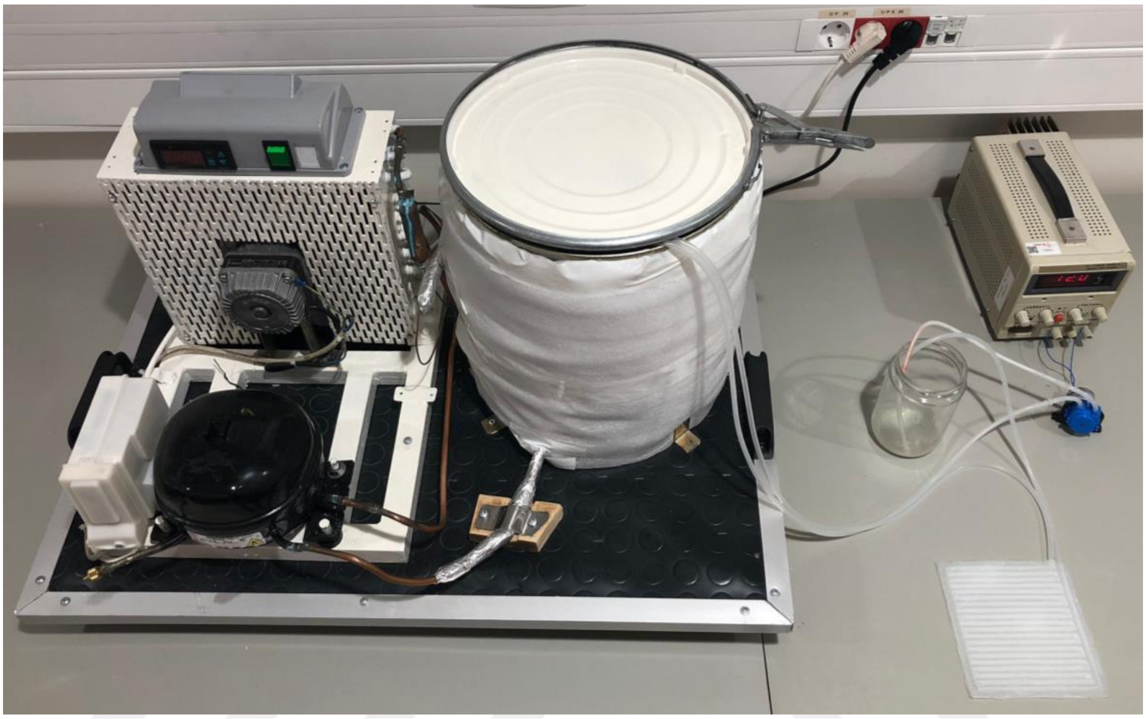

Figure 2. 41 Complete Physical OCJ System

2.10 Experimental Setup

The designed and manufactured OCJ is tested with animal kidneys. In the laboratory of Koç University Hospital for testing the device in porcine model, temperature-time tests will be carried out on donor pig kidneys and then trials will be conducted on real donor human kidneys. Temperature-time tests on calf kidneys were performed at around real human kidney temperature which is 36.5-37 ^{o}C.


Figure 2. 42 Graft calf kidney as the size of real human kidneys

At the beginning of the experiment, the calf kidneys obtained from the butcher were cut in the same dimensions concerning the 3D kidney model used for OCJ production. The cut kidney has a similar size as the human kidney and is also a similar shape as shown in Figure 2.42.

The block diagram with connection types and organ sensor placement is presented in Figure 2.43. There are 5 J-type thermocouple sensors which are inserted in the graft calf and sheep kidneys for the temperature measurements. Whereas SC represents a calibration sensor to validate the sensors connected with the data acquisition system, S1-S4 are data acquisition sensors. S1 is placed at the center of the organ, S2 is at the boundary, S3 is at the top surface, and S4 is at the back side of the calf kidney. Instead of S1, all the thermocouples are placed near the surface of the organ.

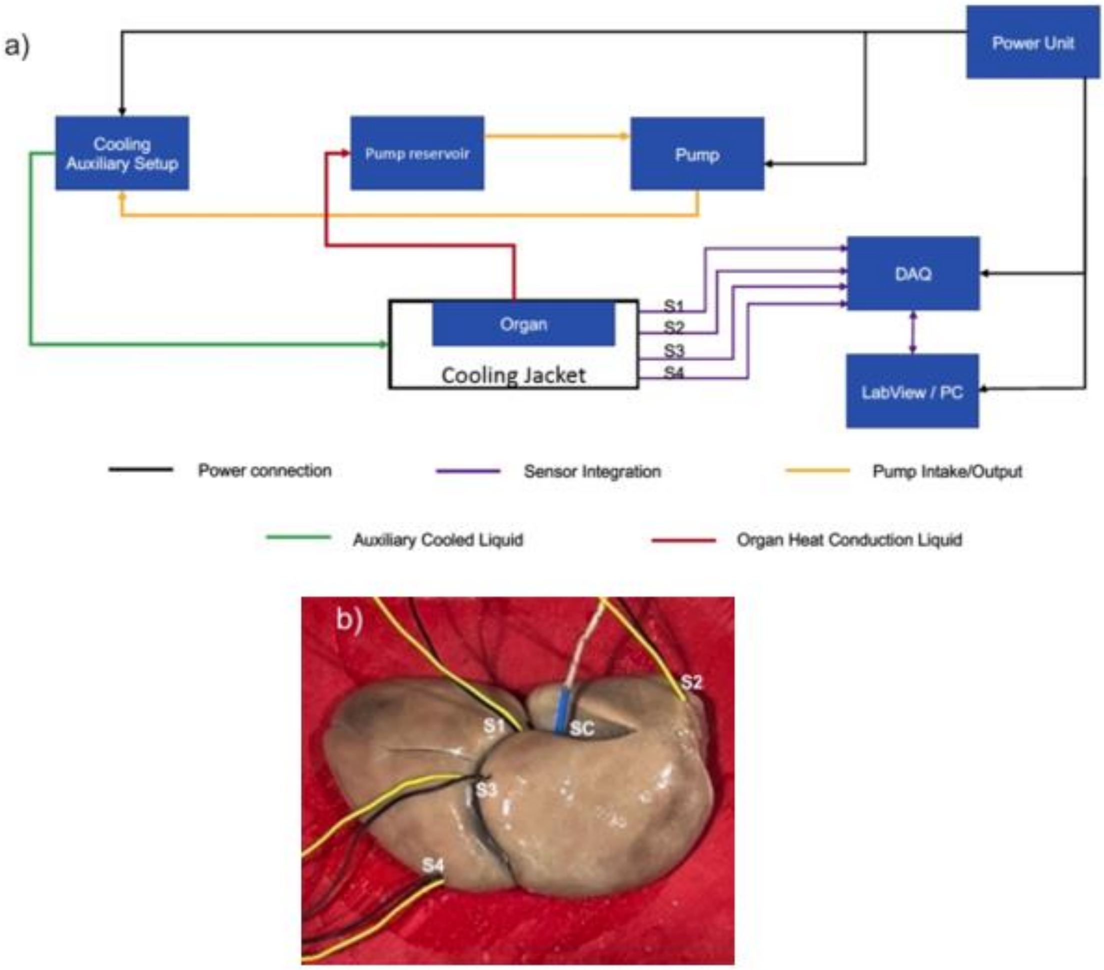

Figure 2. 43 a: Block diagram of the designed setup, b: Sensor placement in a calf kidney with sensor S1-S4. Connected to the Data Acquisition System, SC represents a Calibration Sensor to validate the sensors connected with the data acquisition system.

New organs were acquired for same-day experimentation. Organs were pre-heated to match internal body temperature of around 37°C by submerging in a controlled heated water bed. Four temperature sensors were embedded into the organ, and Figure 2.43 b represents the location of the sensors. Organ cooling at relative room temperature (22°C) without any cooling intervention was also recorded for comparative analysis. The organ was allowed to reach a steady state i.e., room temperature for all experiments. After the room temperature test, the organ was heated in the waterbed to 37°C. A cooling jacket was applied to the organ for the experiment. Figure 2.44 represents the implementation of a cooling jacket on the calf and sheep kidney with smaller and larger channel jackets, respectively. The average reservoir temperature was maintained at around 5^{o}C. All the experiments were repeated three times. Experiments were repeated in case of water leakage, pump cessation, or temperature reading errors. Calf kidneys were reduced to the average size of a human kidney to fit inside the jacket designed for the average human kidney.

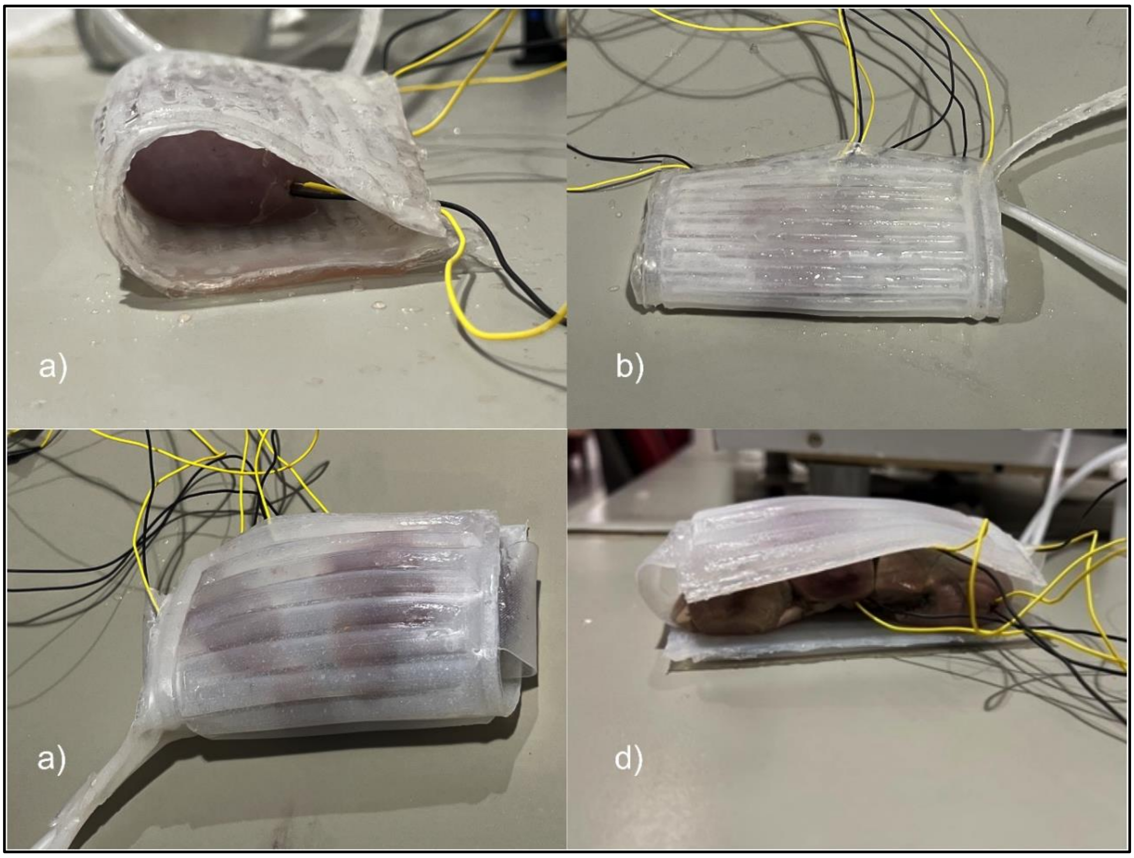

Figure 2. 44 a: Sheep Kidney with smaller channel Jacket; b: Implementation of smaller channel jacket with calf kidney; c and d: the larger cooling jacket implemented on the calf kidney with a top view and right-angle view of the jacket, respectively. Black and Yellow leads in the images represent the thermal sensors that are connected to the Data acquisition system for real-time temperature monitoring.

2.11 Data Acquisition:

Four waterproof temperature sensors (Thermistors) were connected to the LabVIEW software with a sampling frequency of 1KHz for each sensor. Data acquisition began after removing the organs from the waterbed at the start of each experiment. Thermal data for each sensor from each experiment for the same organ was averaged to remove any outliers, and only statistically significant ($p < 0.05$) data was considered. The results are presented as the mean and standard deviation of the averaged sensor reading for the entirety of the experiment.

The average mass and dimensions of the organs are presented in Table 3.2.

Table 2. 2 Average size and mass of the organs.

Organ	Length (mm) Mean	Width (mm) Mean	Thickness(mm) Mean	Mass (g) Mean
Sheep Kidney	72.5	29.5	52	64.35
Sheep Heart	70	31	95	139.7
Calf Kidney	62	30	114	153.9

2.12 Results

Experimental results for Calf Kidneys with the implementation of cooling jackets are presented in Fig. 2.45 & and Fig. 2.46, respectively. The initial Temperature (Ti) is 36.5℃ ± 0.5 for each experimental study. For non-jacket room cooling, the steady state temperature (final temperature Tf) achieved after 100 min of the experiment is at 23℃ ± 1. The sensor's relative position to the center of the organ reflects the conduction rate of the organ at different levels. Sensors 2, 3, and 4 are placed adjacent to the surface, and near the kidney-jacket contact region, thus their quicker thermal decay is apparent in the case of the calf (with both jackets) and sheep kidney as compared to Sensor 1, which is embedded further into the organ surrounded by layers of tissue. The results present the average of each temperature sensor for three experiments, each for three calf kidney organs. The cooling rate from a smaller cooling jacket is more effective on average as compared to a larger cooling jacket, as presented in Fig. 2.47. Further experiments were performed with smaller channel cooling jacket on sheep organs, i.e., sheep kidneys and sheep heart. The results of the experiments for the cooling jacket and non-jacket thermal decay are presented in Fig. 2.48 and 2.49 respectively. Results were similar to the calf kidney, with the outer tissue region of the organ cooling down much earlier than the medial region of the organ. However, with the smaller size of the sheep kidney, all sensors reached a steady state value under 10℃. Temperature drops of 5℃ starting from 30℃ to 10℃ as the mean for each sensor for the tested organs are presented in Table II.

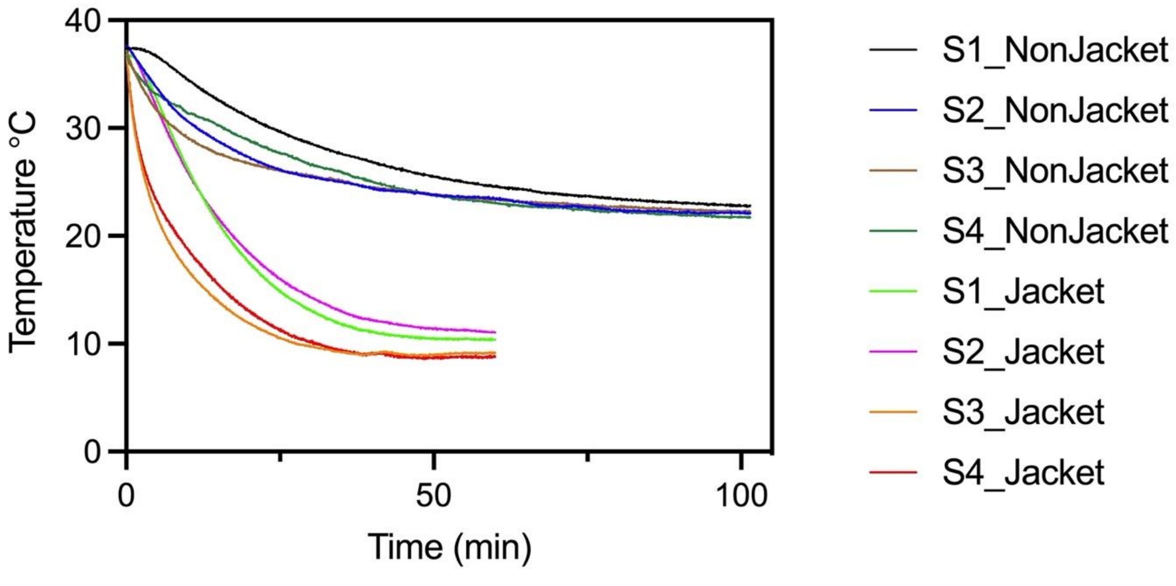

Figure 2. 45 Thermal decay for the cooling jacket and non-cooling jacket for calf kidney with smaller jacket. The mean values of 3 experiments were presented. Non-jacket and jacket cooling experiments were conducted for 100 minutes and 60 minutes each, respectively

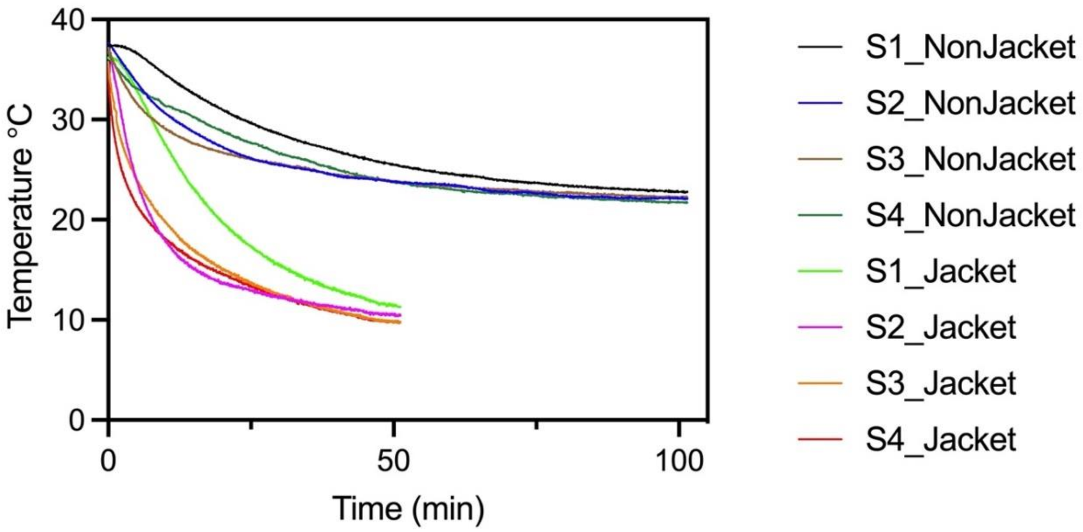

Figure 2. 46 Thermal decay for the cooling jacket and non-cooling jacket for calf kidney with larger jacket. The mean values of the 3 experiments are presented. Non-jacket and jacket cooling experiments were conducted for 100 minutes and 60 minutes each, respectively

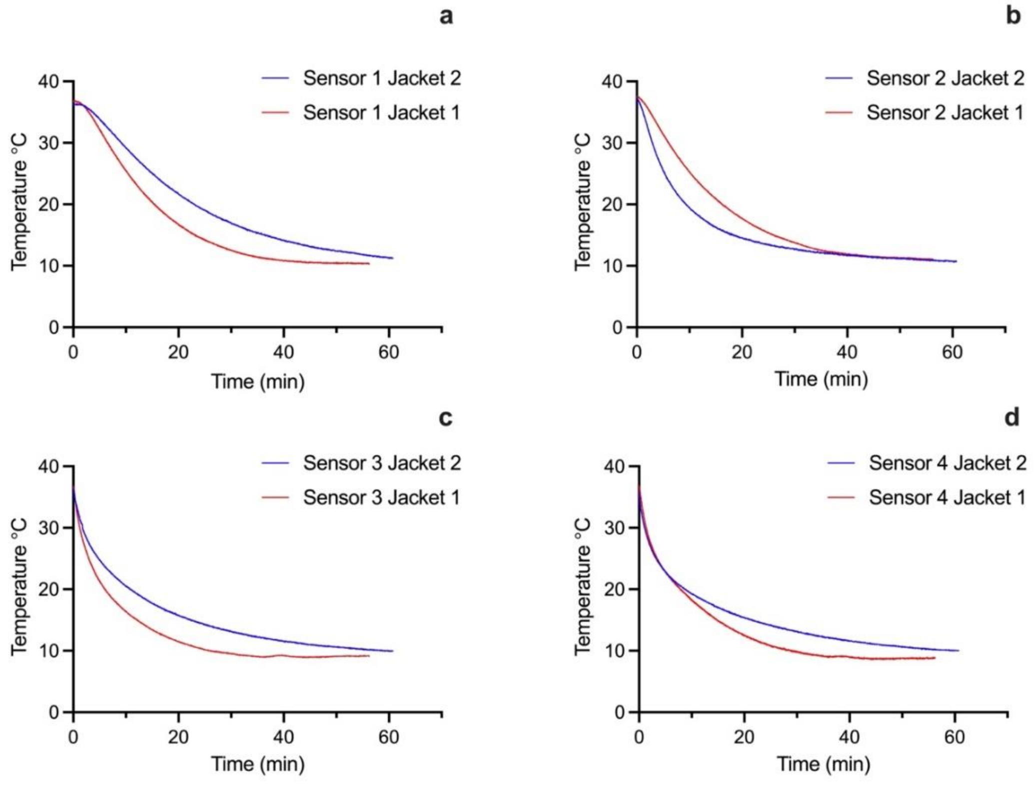

Figure 2. 47 presents a comparison between the 6.5 mm and 4.5 mm channel jackets, labeled as Jacket 2 and Jacket 1, respectively. Figure 2.47 a-d represents individual sensors comparison for both jackets.

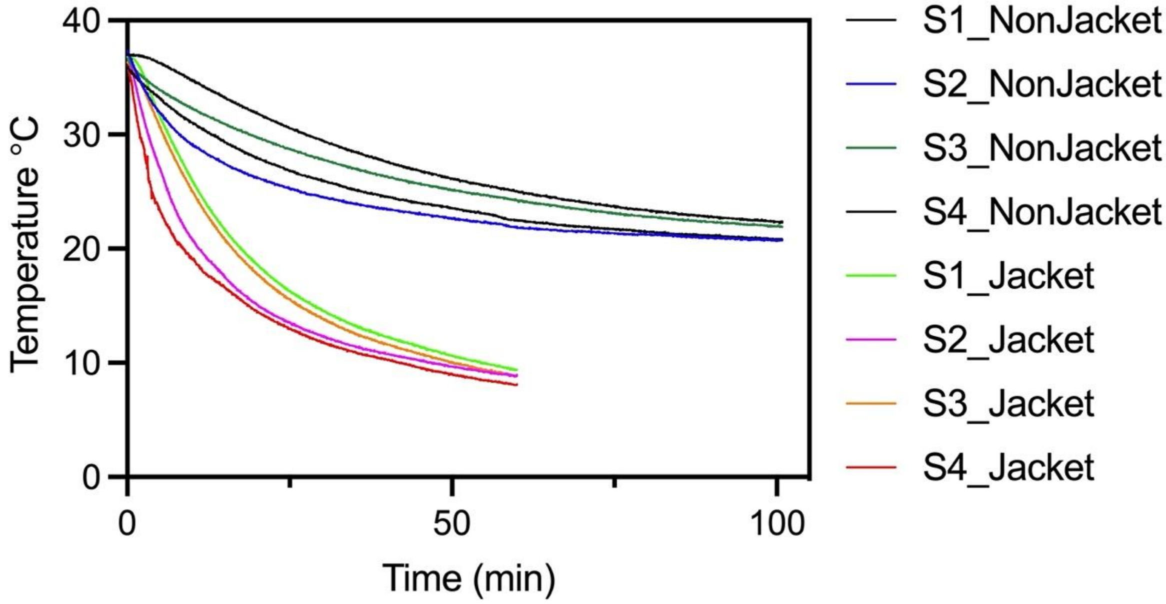

Figure 2. 48 Thermal decay for the cooling jacket and non-cooling jacket for sheep heart with 4.5mm jacket. The mean values of the three experiments are presented. Non-jacket and jacket cooling experiments were conducted for 100 minutes and 60 minutes each, respectively

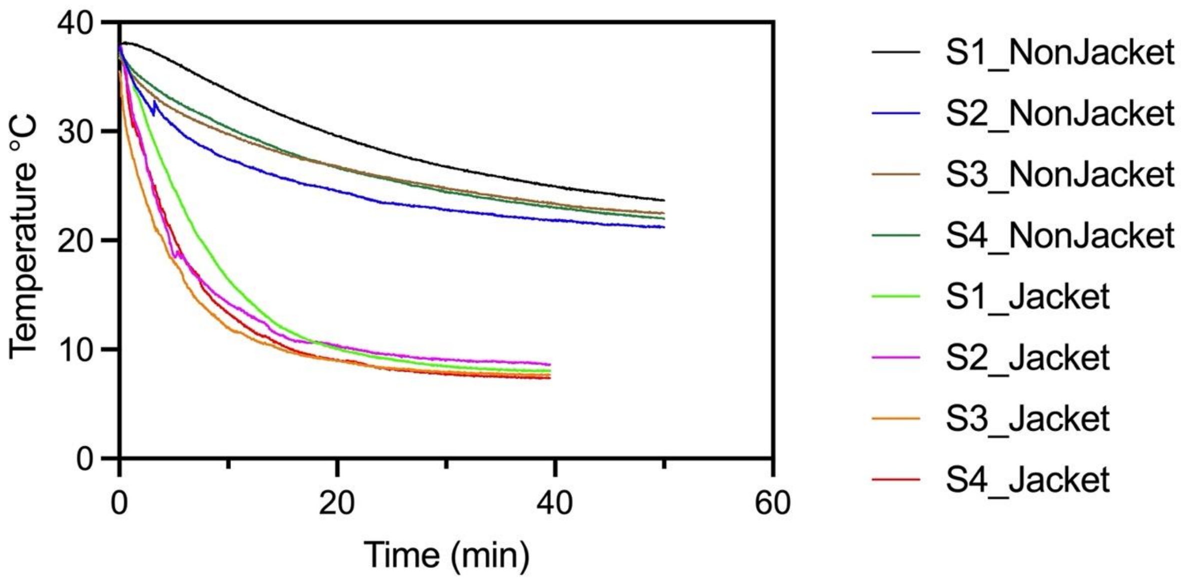

Figure 2. 49 Thermal decay for the cooling jacket and non-cooling jacket for sheep kidney with 4.5mm jacket. The mean values of the three experiments are presented. Non-jacket and jacket cooling experiments for 50 minutes are presented in the graph.

Table 2. 3 Time to Temperature: 30 - 10℃ for four temperature sensors: S1 - S4, for sheep kidney and heart with smaller channel OCJ, and calf kidney with smaller and larger channel OCJ, respectively.

	(30℃)	(25℃)	(20℃)	(15℃)	(10℃)
Sheep Kidney	Min	Min	Min	Min	Min
S1	3.488	6.142	9.352	14.09	25.11
S2	2.17	3.789	5.75	11.19	26.45
S3	0.87	2.469	5.08	8.387	18.61
S4	1.91	3.87	6.361	10.13	19.64
Sheep Heart					
S1	6.238	10.86	17.33	28.32	53.56
S2	3.21	6.189	10.84	19.85	45.69
S3	5.479	9.905	16.05	26.22	49.25
S4	1.918	9.708	8.503	18.3	41.1
Calf Kidney (Smaller channel)					
S1	6.852	11.06	16.23	24.22	N/A
S2	6.338	10.92	17.14	27.22	N/A
S3	1.286	3.114	6.32	12.67	26.85
S4	1.416	3.487	8.183	15.47	29.98
Calf Kidney (Larger channel)					
S1	9.65	15.65	23.51	37.46	N/A
S2	3.15	5.65	10.19	20.77	N/A
S3	1.85	4.827	10.76	22.13	58.64
S4	0.76	2.62	7.25	15.09	54.92

2.13 Discussion

The current research presents the design and ex-vivo studies of an organ cooling jacket, which can be used in laparoscopic, robot-assisted, and open surgeries, to minimize the risk of complications arising from hypothermia in the graft organ. Experiments performed on calf and sheep kidneys with varying cooling channels presented in Fig. 2.45 – 2.46 represent the efficacy of the novel cooling jacket, which can allow doctors to perform renal anastomosis in vivo while the cooling jacket provides controlled cooling to the organ.

According to the literature, the risk of complications due to regional hypothermia increases after 15 minutes of warm ischemia [9]. Therefore, the graft organ must be kept between 4-20^{o}C cold ischemia temperature to protect the organ from injury during transplantation [10]. There are essential criteria to be considered when applying the cooling process in the graft organ, and the most critical factor is temperature-controlled cold ischemia such as the one deployed in the present novel research with the implementation of the cooling system. Since the recently produced and developed organ cooling jackets have not yet entered the market, the old application, the renal hypothermia technique with ice, is applied. Menon et al. [12] applied to cool with the renal hypothermia technique in their IDEAL Phase 2a study. They wrapped the donor kidney in a gauze jacket filled with ice slush to cool the organ and reduce tissue damage caused by warm ischemia during anastomosis. The restrictions of this study are the local hypothermia-induced renal injuries caused by the failure to detect whether the mixture is homogeneously distributed over the organ in the ice-water technique applied, continuous melting of the ice, and an uncontrolled cooling process.

Due to the limitations of the ice-cooling method, studies have been carried out on the cold ischemia device as a robust and sophisticated approach. Within the bounds of possibility, several studies have been tried and tested in the porcine model. Three studies in this area were reviewed and reported. Li et al. [13] designed a simple plastic cooling bag with an inlet and outlet; the 0-4^{o}C saline water was perfused into the system manually by implementing an injection method. In the donor kidney, which is wrapped with a cooling bag, the vessels are exposed for anastomosis and tightly wrapped with an additional mesh bag. There is no path for the liquid to follow in the cooling bag. According to the limitations of this study, the temperature is not constant since an equal amount of refrigerant cannot be continuously perfused into the system. In addition, since it is not feasible for the coolant injected into the cooler bag to have a homogeneous distribution inside, it is infeasible to observe an equal temperature distribution in different textures of the graft kidney. In another study, Meier et al. [23] designed and reported a silicone kidney cooling jacket, and continuously, 4^{o}C ethanol and methylene blue were circulated inside the closed-loop system. The reported cold ischemia temperature versus time indicates that studies in this area are promising for the future. The cooled graft organ was analyzed with MRI, and limited renal injury due to cold ischemia was detected; the results show that it is more reliable than the cooling method applied with ice water [14]. The restrictions of this study are the vital risks of ethanol in possible leakage, the fact that the pipes placed inside the jacket do not show a homogeneous distribution, and the relatively large thickness of the device. In another study, Territo et al. [15] reported an advanced cold ischemia device continuously perfused with a saline solution which is stored in storage before use in the system. As reported in the study, graph kidney temperature measurements were examined in 3 groups with device, gauze, and without any equipment; the temperature of the graft kidney increases proportionally with time, even when the device is used, since a refrigerant that is kept at a low temperature is not used. Since the refrigerant temperature increased over time, they constantly replaced the used coolant with a new one. The limitations of this study are the limited control of temperature regulation in real time, the device designed in the path of the liquid cannot reach the corners due to the stretching, and therefore the liquid cannot distribute evenly in the path.

In contrast to open surgeries and topical ice pouring techniques, the use of laparoscopic incisions and the use of cooling methods hereby complement the laparoscopic and robot-assisted surgeries are going to become a standard practice in the coming years. In their study about robot-assisted partial nephrectomy with the use of ice pieces for cold ischemia, Canda AE et al. presented a promising case study where ice bags were introduced into the abdominal cavity created by small incisions using a laparoscopic setup, the intended use of ice bags introduced the desired cold ischemia affect while the mass was excised. No perioperative and postoperative complications were observed. The study reflects the potential benefits of robotic-assisted surgery over open surgeries as well the potential to introduce smart cooling techniques through the smaller incisions of laparoscopic setup [27].

Bio-compatible cooling jackets can be easily introduced into the abdominal cavity during laparoscopic or robot-assisted procedures through 5 - 12 cm sized incisions where ports are located (i.e. Alexis port, Applied Medical). The cooling jackets designed from biocompatible materials can also be sterilized before their implementation at the target site.

The current setup proposes the application of a kidney cooling jacket, with additional liquid circulation and refrigeration systems to keep the temperature constant during cold ischemia. In addition, the design of the OCJ was optimized by the use of optimal cooling channels for efficient heat transfer from the surface of the graft organ homogeneously. With the liquid circulation system used, a constant refrigerant is continuously circulated inside the cooling jacket, thus providing accurate and reliable information about ischemia time and temperature.

The OCJ was stress tested with a continuous operating time of up to 10 hours without any leakages or defects. The device was operated with the liquid pump operating at the highest flow rate (250mL/min) available. No possible leakages were detected even when manually occluding the channels to disrupt the uniform flow of the coolant. The manufacturing of the OCJ conforms to the average size of the human kidney, with the possibility to adapt to any organ size due to the elastic property of the material for larger than average organs and the enclosure bands to maximize surface contact for smaller scale factors. The jacket design utilizes the FDM technique [28, 29] for negative mold manufacturing, thus allowing the possibility to adapt and manufacture kidney/organ jacket for customized patient operations. The contact layer of the OCJ with the organ is designed to be as thin as possible while maintaining internal pressure to maximize thermal conduction; the ends of the jacket are thicker in comparison to provide structural integrity and add thermal insulation from the surrounding tissues.

2.13.1 Advantages of the Proposed Device

The organ cooling jacket system has many advantages. It can be evaluated under many headings such as applicability, function, ergonomics, cost, etc. In this study, the prominent advantages compared to other studies are listed:

1. The coolant in which the fluid circulation is provided follows a homogeneous unidirectional path.
2. Cold ischemia can be performed in short time intervals to the donor kidney.

3. It is a complete system with an organ cooling jacket, liquid circulation system, refrigerating system, and silicone tubing.
4. It has a circulation system that ensures that the coolant circulates at a constant speed inside.
5. It has a cooling system that allows the coolant to enter inside OCJ at a constant temperature.
6. It consists of an elastic material that is easily wrapped.
7. Cost-effective and customizable solution.
8. It is efficient and cools fast.
9. Easy to produce.
10. It can be used in both robotic-assisted and open surgeries.

In addition to being an elastic cooling jacket, the important points are that it is a complete system, that it is easy to manufacture, and that it provides efficient cooling by keeping the temperature constant. Additionally, its low cost is an important item in the sector. Providing homogeneous and constant flow, this jacket provides a controlled heat transfer between the organ and the body.

CHAPTER 3: CONCLUSION

In this thesis, a novel organ cooling jacket design is proposed for controlling the temperature and kidney cold ischemia time, moreover, decreasing the cooling time of the donor kidney. An organ cooling jacket is a product that aims to cool the organ to prolong the operation time in robot-assisted and open surgeries. The invention is aimed to prevent hypoxic injuries in the patient’s organ at body temperature.

Chapter 2 discusses the development of the kidney model, initially conceived as a supporting element. The creation of a life-sized model involved the utilization of CT imaging and negative molding, followed by practical testing on an actual kidney. This model played a pivotal role in assessing the cooling jacket's ergonomic aspects. Moreover, medical professionals sought the kidney model to experiment with the anastomosis feasibility of the silicone material. Concurrently, it is envisioned to serve as a benchmark kidney model for ongoing research on a remote-control surgical robot.

As outlined in Chapter 3, the proposed innovation is an adaptable system for cooling organs, specifically an elastic organ cooling jacket. This system incorporates channels for closed-loop circulation of refrigerant, along with an inlet and outlet for the refrigerant. The jacket, rectangular in shape, provides comprehensive coverage to all organs slated for cooling before surgery. Distinguished by its advanced features, the system includes auxiliary components which are refrigeration and liquid circulation units. Fundamentally, it operates by cooling liquid drawn from a reservoir in the refrigeration system, circulating it within the kidney cooling jacket, and subsequently returning the liquid to the reservoir.

In this research, a cooling jacket was meticulously designed and manufactured using negative molding. Ex-vivo testing was conducted to analyze the temporal variation in absolute temperature values concerning the kidney cooling jacket. The findings discussed in this study exhibit great promise for future applications in the realm of medical advancements. The presented research marks a significant advancement in the field of organ transplantation and surgical procedures, particularly in addressing the critical issue of hypothermia-related complications during surgeries involving graft organs. The design and ex-vivo studies of the organ cooling jacket (OCJ) showcase a novel approach that has the potential to revolutionize current practices in laparoscopic, robot-assisted, and open surgeries.

The literature review highlights the limitations of existing cooling methods, such as the ice-cooling technique, which suffers from issues like uncontrolled cooling, local hypothermia-induced injuries, and an inability to achieve homogeneous temperature distribution. Various studies, including those using plastic cooling bags, silicone kidney cooling jackets, and saline-based devices, have attempted to overcome these limitations in different ways. While some show promise, each has its own set of restrictions, ranging from inconsistent temperature control to the risks associated with the coolant used.

In contrast, the OCJ presented in this research addresses many of these limitations. The continuous circulation of a refrigerant within the cooling jacket, coupled with high-pressure leakage testing that demonstrates its reliability over extended operating times, sets it apart as a robust and sophisticated solution. The use of a liquid circulation system ensures a constant refrigerant flow, providing accurate information about ischemia time and temperature. The high-pressure leakage tests, operating for up to 10 hours without leakages or defects, demonstrate the practicality and durability of the OCJ under demanding conditions.

Moreover, the adaptability of the OCJ to different organ sizes is a crucial feature, allowing customization for various patient needs. The use of the FDM technique for negative mold manufacturing adds a layer of flexibility, enabling the production of customized jackets tailored to specific patient requirements. The thin contact layer with the organ maximizes thermal conduction, while the thicker ends provide structural integrity and insulation from surrounding tissues.

The experiments conducted on calf and sheep kidneys demonstrate the effectiveness of the OCJ in providing controlled and constant cooling to the graft organ. The importance of maintaining the organ temperature within the optimal range of 4-20°C during cold ischemia is emphasized, as exceeding this range can lead to complications, especially after 15 minutes of warm ischemia. The OCJ, with its temperature-controlled cold ischemia, addresses this critical criterion, setting it apart from traditional methods like the renal hypothermia technique with ice.

Based on the ex-vivo temperature study conducted on calf and lamb kidneys, the durations required to lower the central temperature of the graft kidney to the 20ºC cold ischemia limit were recorded as follows: 9.35 minutes for lamb kidneys, 16.23 minutes for calf kidneys in a small-channel cooling jacket, and 23.51 minutes for calf kidneys in a large-channel cooling jacket. Analyzing these recorded values, it can be inferred that the narrow-channel cooling jacket facilitates a faster flow, resulting in reduced heat loss and enhanced cooling efficiency.

In the initial phase of the experiment, the organs were heated to 36.5ºC ± 0.5. Subsequent tests conducted at room temperature (around 23ºC ± 1) compared the effectiveness of cooling with a jacket versus without a jacket, as well as the performance distinctions between a narrow-channel and a wide-channel jacket. Notably, the experiments involved graft calf kidneys being cooled with an organ cooling jacket for 60 minutes and, alternatively, left at room temperature without a jacket for 100 minutes. The findings of these tests present promising outcomes for the study.

The future trajectory of surgical procedures, especially in the context of laparoscopic, robot-assisted, and open surgeries, is anticipated to see a standard integration of cooling methods like the OCJ. The potential benefits observed in robot-assisted partial nephrectomy, where OCJ was introduced laparoscopically, highlight the promising avenues for incorporating smart cooling techniques through minimally invasive procedures. The introduction of bio-compatible cooling jackets into the abdominal cavity during laparoscopic or robot-assisted surgeries is projected to become standard practice, given their ease of implementation through small incisions and compatibility with existing surgical ports.

In conclusion, the organ cooling jacket represents a significant leap forward in mitigating the risks associated with hypothermia during organ transplantation and partial nephrectomy surgeries. The combination of innovative design, testing reliability, and adaptability to different organ sizes positions the OCJ as a potential game-changer in the field of surgical interventions involving graft organs. As this research lays the groundwork for further exploration and clinical trials, the prospect of improving patient outcomes and reducing complications associated with hypothermia becomes an exciting avenue for future advancements in surgical technology.

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