

Guiding Principles

PARAGONIX®



Advance
Organ
Preservation



Improve
Patient
Outcomes



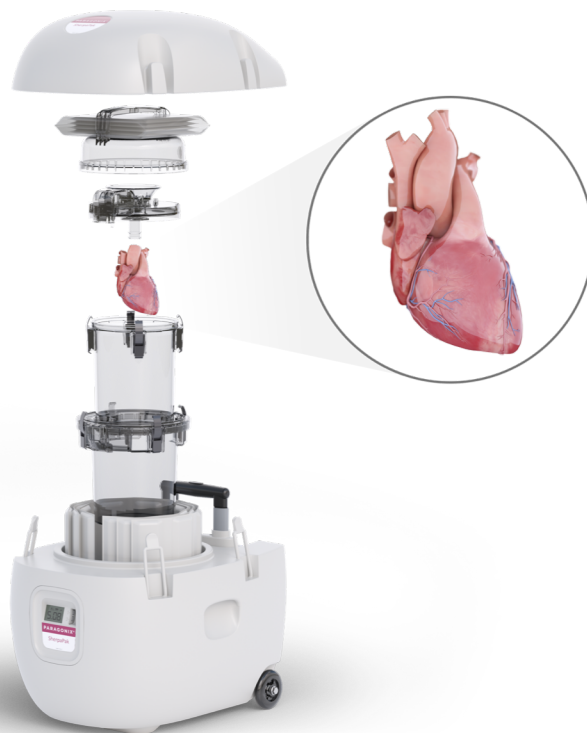
Do No
Harm



Reduce
Healthcare
Costs

Paragonix SherpaPak™ Cardiac Transport System

Clinical Overview



**Preventing
Cold Injury
in Transplants**

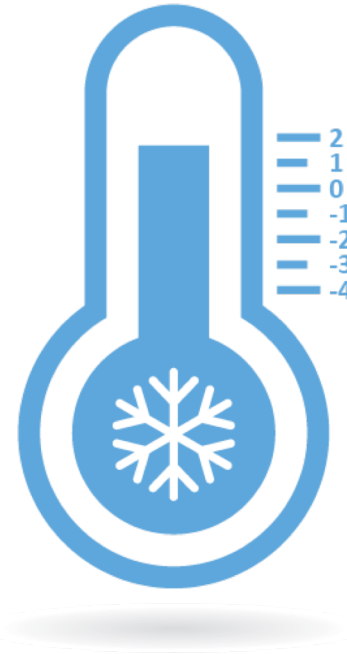
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Cold Injury In Transplantation

Perception: The Colder the Better

Reality:

- “Most mammalian cells can withstand low temperatures for short periods of time when ice is not present.”¹
- “Temperatures below 2°C significantly increase the risk of cold injury with some proteins denaturing below 0°C.”²⁻⁴
- “[It] is evident that the [diastolic function of the heart and elastance of those muscles] is irreversibly suppressed following exposure to temperatures of 1°C...”^{5,6}



Risks: <2°C

- <2°C: Cold injury¹⁻³
- 1°C: Irreversible suppression of diastolic function^{4,5}
- 0°C: Proteins denature¹⁻³

1. Michel et al., Heart, Lung, and Vessels 2015; 7(3):246-255.
2. Ingemansson, et al., Ann Thorac Surg. 1996; 61: 1413-7.
3. Mankad, et al., J Thorac Cardiovasc Surg 1992; 104: 1618-1624.
4. Keon et al. Ann Thorac Surg 1988; 46:337-341.
5. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers.
6. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers.

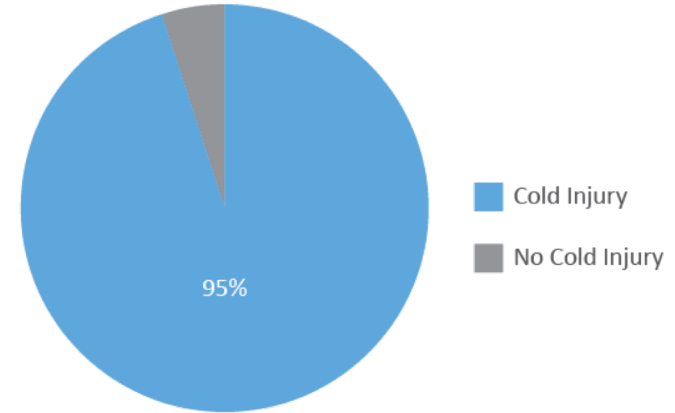
Challenges with the Cooler Method

- In less than 30 minutes, the heart reaches $<2^{\circ}\text{C}$ and risks cold injury^{2-4,7}
- Uncontrolled and uneven cooling¹⁻⁷
- Unknown temperature with no data reporting

“Heart transplantation has been around for over 50 years now....[and] it’s time to be a little more scientific about how we do this.”⁶

Dr. David D’Alessandro, Cardiothoracic Surgeon,
Massachusetts General Hospital (Boston, MA)

Cooler Method: Estimated Incidence of Cold Injury for Donor Hearts



The survey results from an ISHLT Symposium indicate that 95% of cardiothoracic surgeons and cardiologists report cold injury with the cooler method which may be of concern.⁶

“Current cold storage heart preservation technique is associated with wide fluctuation of organ temperature and may result in freeze injury.”

Dr. David D’Alessandro et al.
Massachusetts General Hospital (Boston, MA)

The Journal of Heart and Lung Transplantation, April 2019; Volume 38, Issue 4, S44.



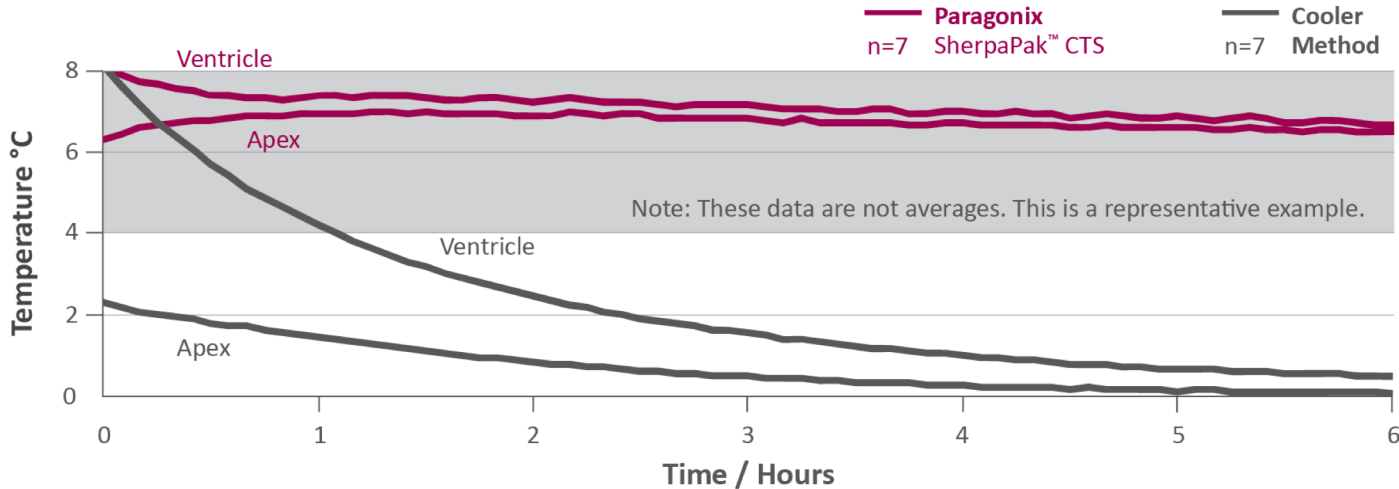
Cooler Method (<2°C and 0°C) vs. Preservation Solution Requirements (2-8°C or 2-6°C)

- An important factor for successful organ transplantation is cold ischemia, which ... [includes] cooling of the organ, followed by transportation...¹
- “[**Preservation solution**] manufacturer’s instructions call for a storage and transportation temperature of between **2°C to 8°C** [or **2°C to 6°C**]....”¹⁻⁴
 - The labeling of two preservation solutions also states “do not freeze”^{3,4} and one states “do not use if frozen.”⁴
- “We tested the usual packing procedure following the ET transaction guidelines. Surprisingly, organ temperature was maintained **at below 0°C** in all packing procedures.”¹
- “The average organ temperature during transportation (n=186) was **below 2°C**, and **after 6 hours below 0°C**, as previously verified experimentally.”¹

Validation Data: Paragonix SherpaPak™ CTS vs. Cooler Method

Side-by-side comparison: Ventricular and apical temperatures measured with probes placed inside a pig heart in Paragonix SherpaPak™ CTS and the cooler method.¹

- Paragonix SherpaPak™ CTS provides a controlled temperature outside the range for cold injury (<2°C).¹⁻⁴
- In contrast, the cooler method allows a wide temperature gradient within the heart and reaches the temperature range for cold injury (<2°C).¹⁻⁴



1. Data on file. 2. Michel et al., Heart, Lung, and Vessels 2015; 7(3):246-255. 3. Ingemansson et al., Ann Thorac Surg. 1996; 61: 1413-7. 4. Mankad et al., J Thorac Cardiovasc Surg 1992; 104: 1618-1624.

Cooler Method and Preservation Solution: Crystallization and Potential Graft Injury

- “When a preservation solution reaches $<2^{\circ}\text{C}$, “histidine may flocculate and crystallize... [which] may cause serious damage to the organs.”¹
- At **subzero temperatures**, “macroscopically visible and indissoluble particles have been observed” (Fig. 1).²

“Adequate storage temperatures of both grafts and perfusion solutions [...] seem of major importance in avoiding potential graft injuries.”²

Dr. Tullius et al. Department of Surgery, Charité Virchow Clinic
Department of Clinical Chemistry, Charité (Berlin, Germany)

Fig. 1: Indissoluble crystal particles in organ stored in preservation solution at subzero °C

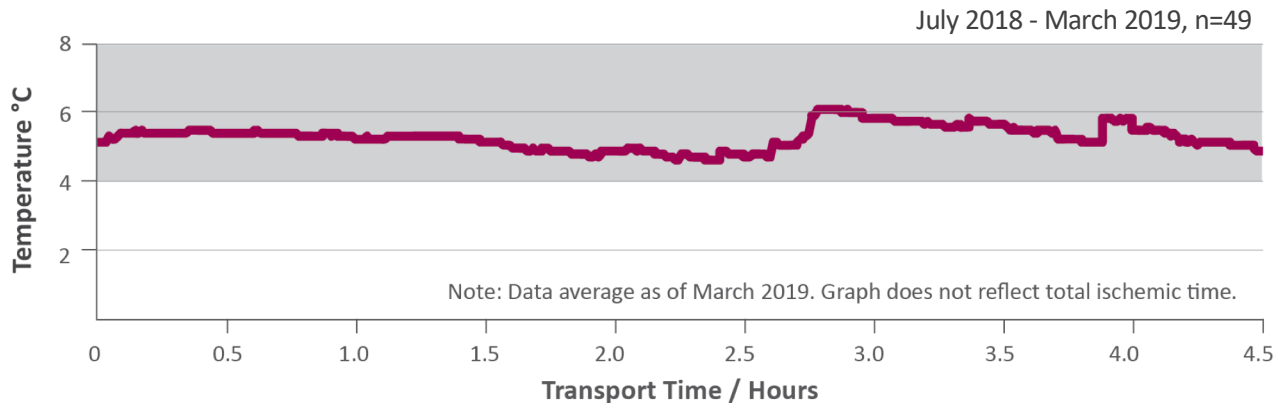


Indissoluble crystal particles (white specs below) were observed in an organ stored in preservation solution at subzero temperatures (d/polarization microscopy at 125x)

1. Letter on file from manufacturer of Custodial HTK, Essential Pharmaceuticals, from Deputy Head of Quality Assurance, April 17, 2019. 2. Tullius et al. American Journal of Transplantation 2002; 2: 627–630.

Human Data: Paragonix SherpaPak™ CTS

Paragonix SherpaPak™ CTS provides a controlled and consistent temperature outside the range for cold injury <2°C).



US and EU Clinical Experience			
Paragonix SherpaPak CTS™ Internal Temperature (°C)	Mean: 5.2	Min (Mean): 4.1	Max (Mean): 6.0
Paragonix SherpaPak CTS™ Transport Time (minutes)	Mean: 134	Min: 7	Max: 279*
Total Ischemic Time (minutes)**	Mean: 236	Min: 87	Max: 420
% of Transports where >4 Hours of Total Ischemic Time**	43%		
# Adverse Events / # Device Failures	0 / 0		

**n=37 *Indications for Use: The Paragonix SherpaPak™ Cardiac Transport System is intended to be used for the static hypothermic preservation of hearts during transportation and eventual transplantation into a recipient using cold storage solutions indicated for use with the heart. The intended organ storage time for the Paragonix SherpaPak™ Cardiac Transport System is up to 4 hours. Donor hearts exceeding clinically accepted static hypothermic preservation times should be evaluated by the transplant surgeon to determine transplantability in accordance with accepted clinical guidelines and in the best medical interest of the intended recipient.

The First Clinical Use of a Novel Cold Storage System of Donor Hearts

Authors: N. Naito¹, M. Funamoto¹, R. Pierson¹, M. Villavicencio¹, W. Riley², G. Lewis³, D. D'Alessandro¹. ¹Cardiac Surgery, Massachusetts General Hospital, Boston, MA, ²Perfusion Services, Massachusetts General Hospital, Boston, MA, ³Cardiology, Massachusetts General Hospital, Boston, MA.

Disclosures: N. Naito: None. M. Funamoto: None. R. Pierson: None. M. Villavicencio: None. W. Riley: None. G. Lewis: None. D. D'Alessandro: None.

The Journal of Heart and Lung Transplantation, April 2019; Volume 38, Issue 4, S44.

Abstract

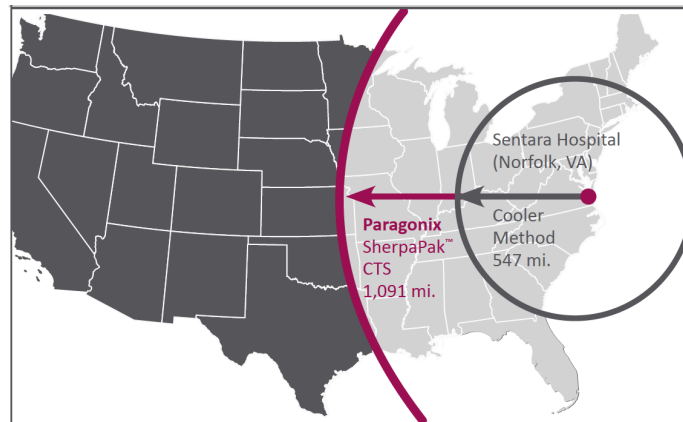
- **Purpose:** “Current cold storage heart preservation technique is associated with wide fluctuation of organ temperature and may result in freeze injury. Paragonix SherpaPak™ Cardiac Transport System (CTS) (Paragonix Technologies, MA, USA) was recently approved in the United States for clinical use. This single-use disposable device is designed for static hypothermic preservation of a donor heart during transport. We report the first clinical use of the Paragonix SherpaPak™ CTS.”
- **Methods:** “Since July 2018, the Paragonix SherpaPak™ CTS has been used in 6, non-consecutive heart transplant procedures at a single institution. All organs were procured from brain dead donors and had normal systolic function. Donor hearts were procured in standard fashion and positioned within the Paragonix SherpaPak™ CTS per the manufacturer’s instructions. The hearts were removed from the system in the recipient operating room and prepared for implantation in standard fashion.”
- **Results:** “Six recipients (5 male; mean age 60.3 ± 19.1 years) underwent heart transplantation using donor hearts transported with Paragonix SherpaPak™ CTS. All donors were categorized as PHS high risk and 5 of them were hepatitis C positive. Donor heart transportation time within the shipper was 24 to 205 (109.67 ± 66.60) min and donor heart total ischemic time was 116 to 312 (225 ± 70) min. Donor hearts were preserved at static hypothermia with a mean temperature of 5.99 ± 0.52°C. Among the patients transplanted there was no observed primary graft failure, and the ICU length of stay ranged from 3 to 21 (8.5 ± 6.3) days. All recipients are alive and well beyond 30 days with normal systolic function at discharge (LVEF 72± 6%).”
- **Conclusion:** “The Paragonix SherpaPak™ CTS provides consistent organ temperature regulation throughout the transport observed process. Organs transported using this system demonstrated normal perioperative function even including an organ with more than 5 hours of total ischemic time. This system may decrease cold injury during organ transportation and increase the safe interval of tolerable cold ischemia.”

Expanding Ischemic Time and Donor Opportunity with Paragonix SherpaPak™ CTS vs. Cooler Method^{1,2}

Sentara Hospital transplant program was able to expand their opportunity for donor hearts by 55% (>67M potential donors, 10 additional US states) using Paragonix SherpaPak™ CTS that provides a controlled and consistent temperature for 40+ hours.*

*“We had this discussion about who do we use it on — just short or long runs? ... After seeing the results being so good, we immediately started using it for everybody.”**

Dr. Jonathan Philpott, Cardiothoracic Surgeon, Sentara Hospital (Norfolk, VA)



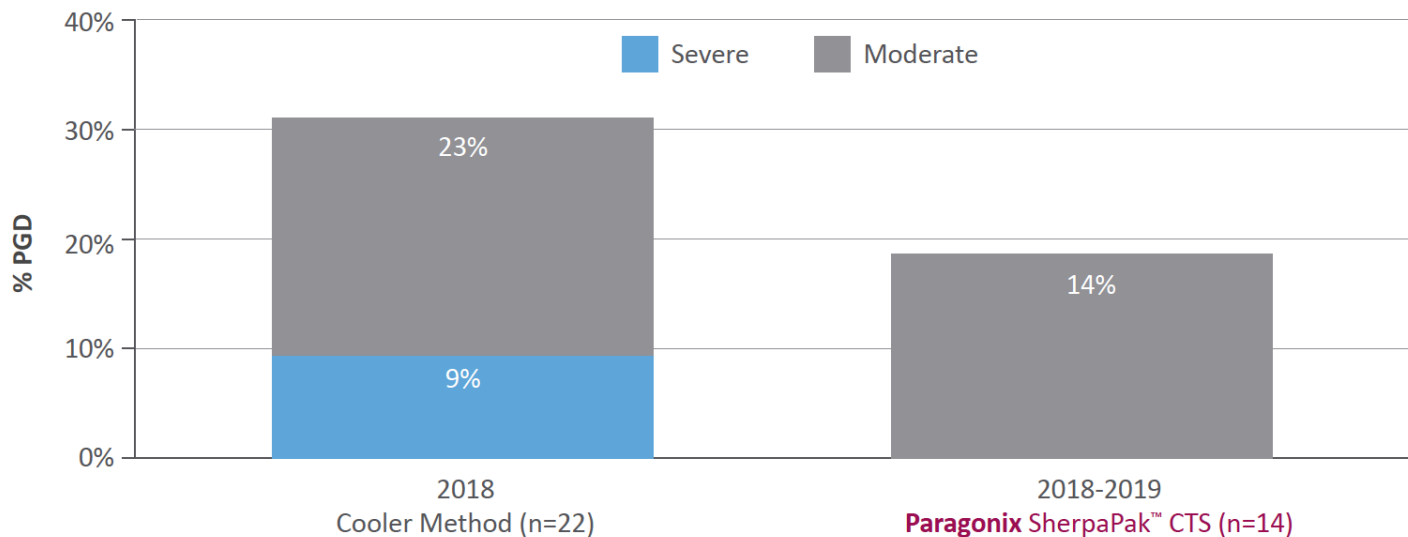
Inner Circle = maximum distance traveled with cooler method vs. Outer Circle = maximum distance traveled with **Paragonix SherpaPak™ CTS**.

1. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers. 2. United States Census Bureau. State Population Totals and Components of Change: 2010-2018. Note: Some states had only had part of the territory included with the cooler method or Paragonix SherpaPak CTS. A visual estimate was made to determine the percentage of population that was included for each group. Downloaded on 04/12/2019 at https://www.census.gov/data/tables/time-series/demo/popst/2010s-state-total.html#par_texti_image_1574439295.

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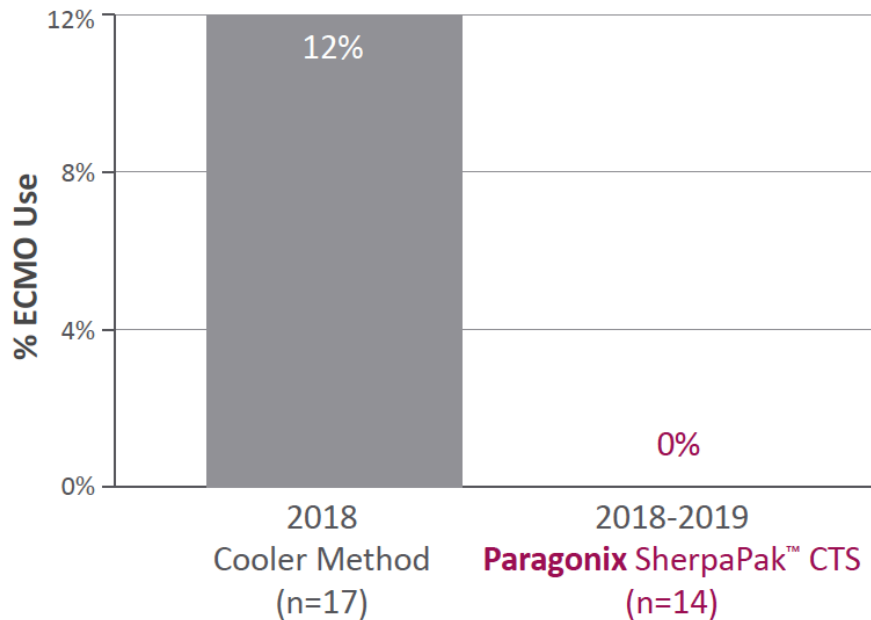
71% Reduction in Primary Graft Dysfunction (PGD): Paragonix SherpaPak™ CTS vs. Cooler Method

Paragonix SherpaPak™ CTS has shown a 71% reduction in PGD (moderate and severe) when compared to the cooler method at a single center. There was 0% severe PGD with the use of the Paragonix SherpaPak™ CTS.^{1,2}



1. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers. 2. Data collected in comparable time periods.

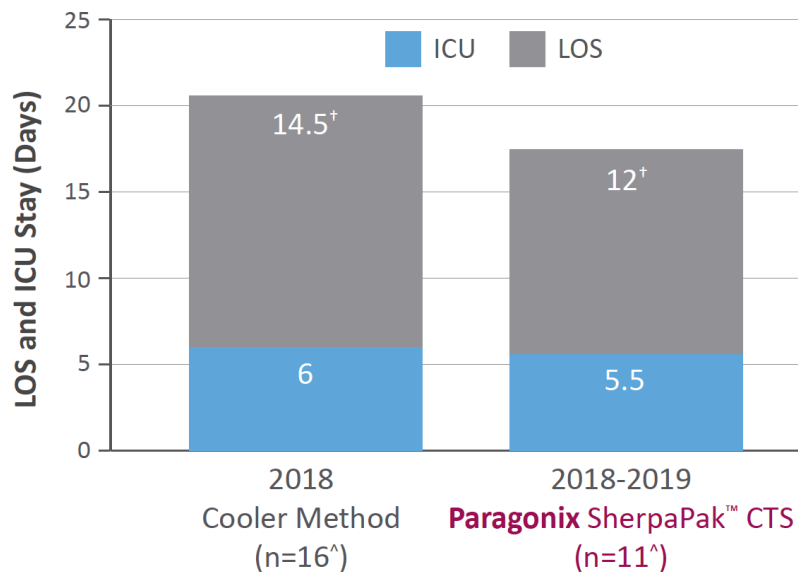
0% Incidence of ECMO (Extracorporeal Membrane Oxygenation): Paragonix SherpaPak™ CTS vs. Cooler Method



- Paragonix SherpaPak™ CTS has shown a 0% incidence of ECMO use compared to a 12% ECMO use with the cooler method at a single center.^{1,2}
- With the average total cost of ECMO being \$105,035 to \$335,565, the cost savings of going from 12% to 0% ECMO use is \$210,070 to \$671,130.^{1,3,4}

1. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers. 2. Data collected in comparable time periods. 3. Harvey et al., Appl Health Econ Health Policy 2015; 13:341-357. 4. Costs were rounded up to the nearest \$5 increment.

15% Reduction in LOS (Length of Stay) and ICU (Intensive Care Unit) Stay: Paragonix SherpaPak™ CTS vs. Cooler Method



- Paragonix SherpaPak™ CTS has shown a 15% reduction in LOS (2.5 days[†]) and ICU stay (0.5 days) when compared to the cooler method at a single center.^{1,2}
- With the average cost of per inpatient day and ICU day being \$7,500 and \$18,040, the cost savings for a reduction of 2.5 inpatient days[†] and a 0.5 ICU day is \$27,770.^{1,3}

Clinical Feedback: Paragonix SherpaPak™ CTS

"Definitely a game-changer. The hearts are different when they come back. They are soft, not frozen, not stiff."

"After you take the cross-clamp off, the first beat is different... it's like a hammer is being dropped which is radically different than what I was used to."

Dr. Jonathan Philpott, Cardiothoracic Surgeon,
Sentara Hospital (Norfolk, VA)

Paragonix SherpaPak™ CTS in Clinical Use¹



Donor heart is fully suspended and immersed for even cooling in preservation solution (left image) and then removed (right image) from the Paragonix SherpaPak™ CTS dual-cannister assembly. (Photo: Medical Univ. Innsbruck)

Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers.

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Cost Savings and Reimbursement: Paragonix SherpaPak™ CTS

Cost Savings

- Paragonix SherpaPak™ CTS has shown a cost savings by reducing ECMO use, ICU stay, and LOS at a single center.¹⁻⁴



Reimbursement

Paragonix SherpaPak™ CTS is reimbursable via a pass-through charge either through the US Medicare Transplant Cost Report or private payer organ acquisition costs.

1. Paragonix SherpaPak CTS International Heart Summit, ISHLT Annual Meeting, April 4, 2019. Note: The experience from a single center may not necessarily represent the experience of other centers. 2. Harvey et al., Appl Health Econ Health Policy 2015; 13:341-357. 3. Costs were rounded up to the nearest \$5 increment. 4. AOR/BOR file accessed on 4/16/19 at: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2019-IPPS-Final-Rule-Home-Page-Items/FY2019-IPPS-Final-Rule-Data-Files.html>



GUARDIAN is a post-market registry study which will assess patient survival and clinical outcomes of heart transplantation that involves donor heart preservation using the Paragonix SherpaPak™ CTS.

- **Learn more at:** www.GuardianHeartRegistry.com
- **Request to enroll at:** info@guardianheartregistry.com

Principal Investigator	Dr. Andreas Zuckermann, AKH, Vienna, Austria
Co-Investigator	Dr. David D'Alessandro, Massachusetts General Hospital, Boston, MA
Protocol	Paragonix SherpaPak™ CTS for preservation. No change in standard care protocols.
Objectives	Assess clinical parameters in the following time periods: 24 hours, 30 days, 1 year post-implant
# of Clinical Parameters Captured	>200
# of Centers	No limit
Follow-up Period	12 months