Innovations in pediatric cardiac surgery

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COLUMBIA | VAGELOS COLLEGE OF PHYSICIANS AND SURGEONS

Financial Disclosure

- I have no relevant financial disclosures

1. Living heart valve transplant

2. Robotically assisted pediatric cardiac surgery

1. Living heart valve transplant

2. Robotically assisted pediatric cardiac surgery

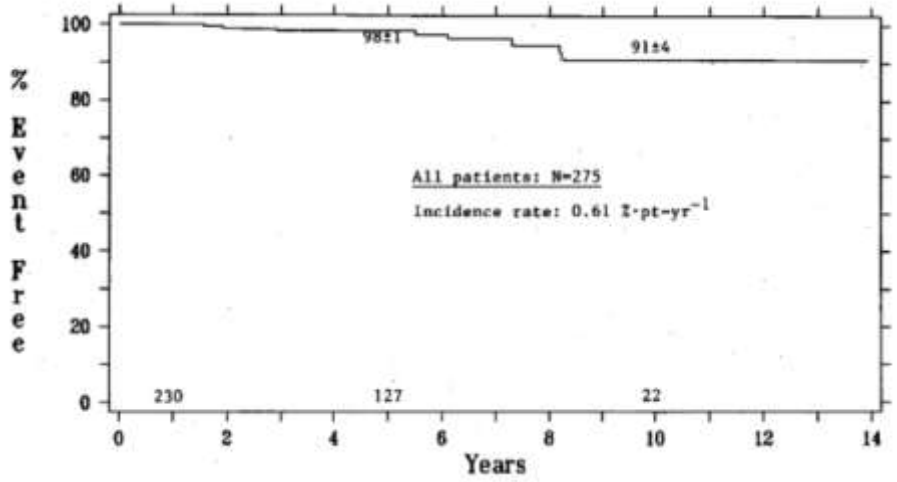
History – the “homovital homograft”

“Homovital” homografts were pioneered in the second half of the 20th century

These fresh allografts were wet-stored in electrolyte solution or nutrient medium at 4C and re-implanted at the first opportunity

Homovital homografts demonstrated **excellent durability**, with minimal stenosis

Freedom from reoperation (*14 years follow up*)



Yacoub et al., *J Thoracic Cardiovasc Surg*, 1995

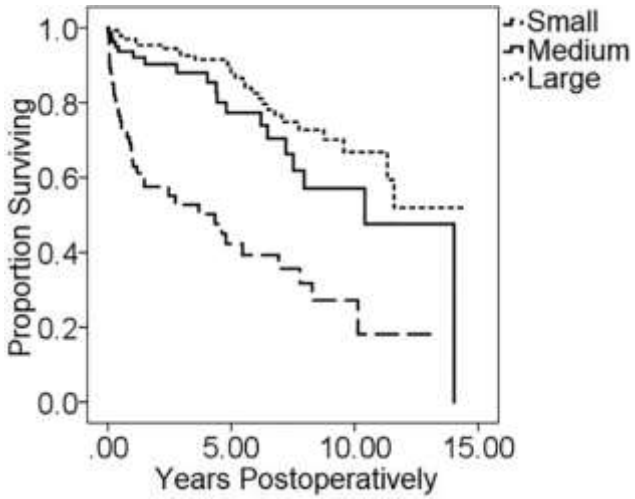
Valve-related late complications (*7 years follow up*)

Complication	*Number*
Valve regurgitation	31
Trivial 17	
Mild 13	
Moderate 1	
Cerebral embolism (minor)	3
Heart block (tenth month)	1
Cusp rupture (forty-sixth month)	1
Endocarditis (miliary tuberculosis)	1
Valve stenosis	0
Leaflet calcification	0

Khanna, Ross, Monro, *Thorax*, 1981

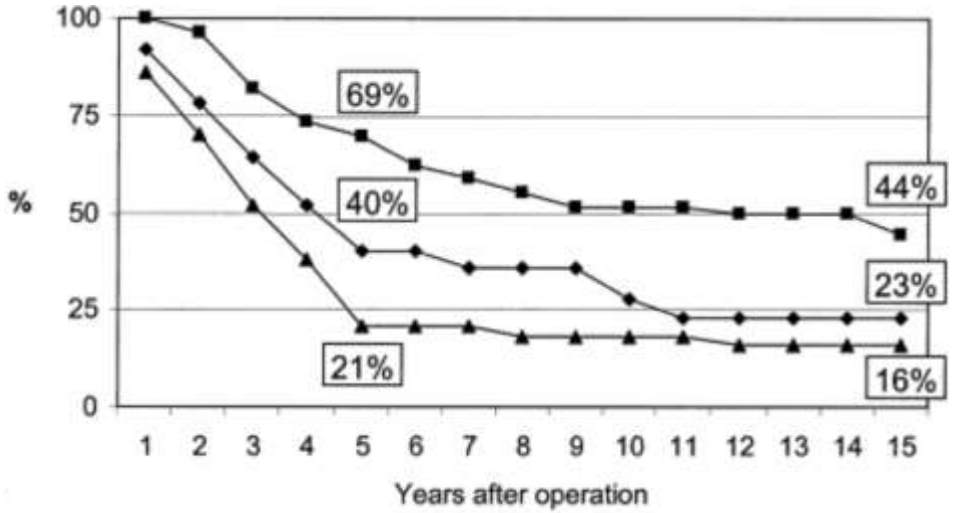
Cryopreserved homograft” – Risk factors and failure modes for pediatric patients receiving a valve replacement

Freedom from Pulmonary Valve Dysfunction – Bovine Conduits



Small conduits, 12-14 mm; medium 16-18 mm; large 20-22 mm
Patel et al., *World Journal for Pediatric and Congenital Heart Surgery*, 2018

Freedom from Pulmonary Valve Dysfunction – Cryopreserved Homografts



Diamonds, entire group; squares, older than one year; triangles, less than one year
Brown et al., *The Annals of Thoracic Surgery*, 2005

Common risk factors for valve dysfunction and failure:

- Smaller valve/conduit size
- Younger age at time of surgery
- Complexity of congenital heart disease

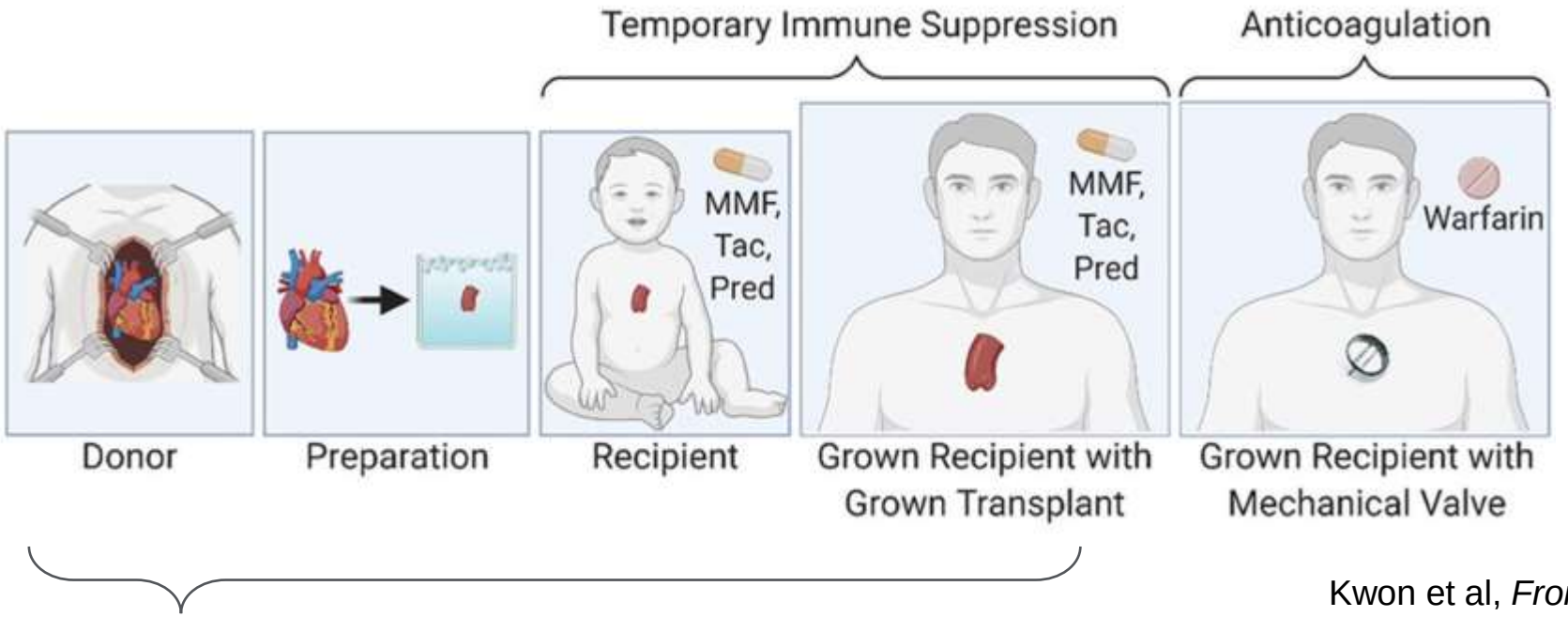
Common failure modes:

- Calcification
- Non-calcific structural valve degradation

Younger patients receiving smaller grafts are at highest risk of reintervention or reoperation following a tissue-based valve replacement

Partial heart transplant or Living Allogenic Heart Valve: A homograft capable of growth and repair?

Recent work highlights “partial heart transplants” as a means of offering living valvular homograft



Kwon et al, *Frontiers in Surgery*, 2021
Rajab, *Surgery*, 2021

Concept:

1. Valvular homograft is collected from a donor
2. Homograft is prepared for implantation
3. Once implanted, the recipient is given temporary immunosuppression to prevent homograft rejection

INVITED EXPERT OPINION

Living allogenic heart valve transplantation: Relative advantages and unanswered questions

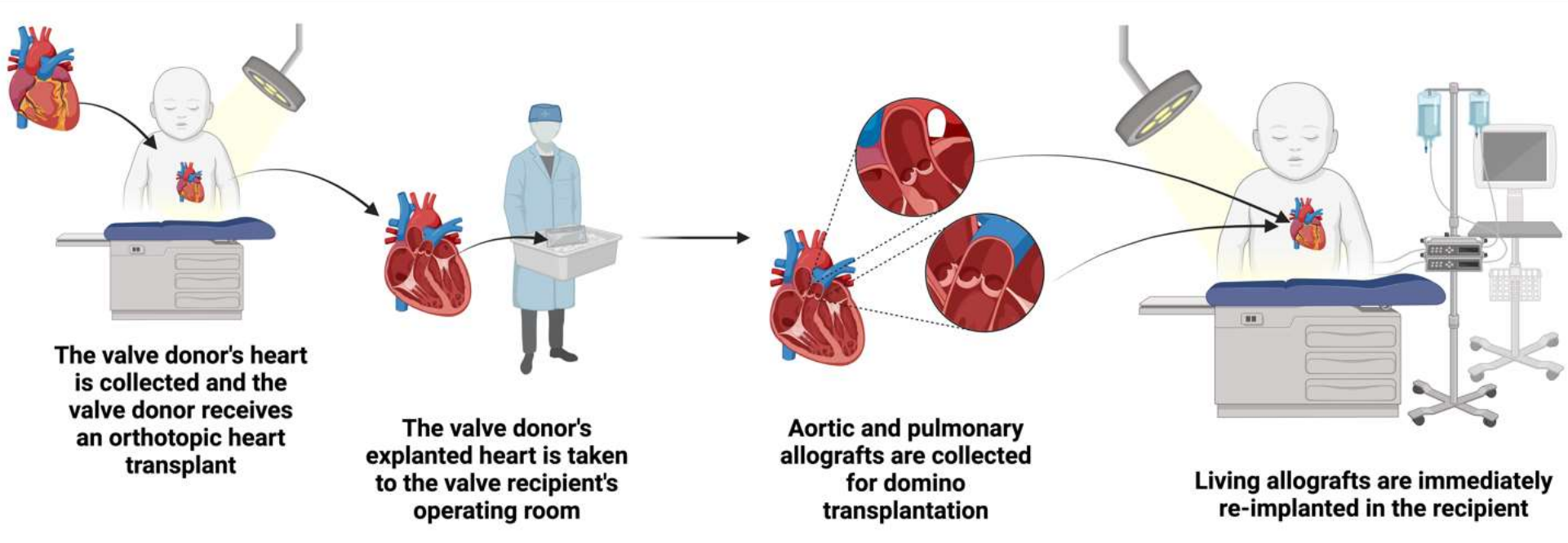
David Kalfa, MD, PhD,[a] Taufiek K. Rajab, MD,[b] Elizabeth Cordoves, BA,[c] Sitaram Emani, MD,[d] Emile Bacha, MD,[a] James Jaggers, MD,[e] Andrew Goldstone, MD, PhD,[a] Pirooz Eghtesady, MD, PhD,[f] and Joseph Turek, MD, PhD, MBA[g]

Key advantage: the living valvular homograft can grow and self-repair with the patient

Key limitations: donor availability, limited ex vivo viability, immunogenicity

May 2023
World First Domino infant partial heart transplant

Advantages of domino heart valve transplantation



Collecting valvular tissue from transplant patients **improves the spatiotemporal availability** of HVT

Minimizes the cold ischemic period to the time required for inter-operative room transport and back-table allograft preparation

Introduces unique advantages inherent to a **known valve donor**

Minimizes variables in a currently unregulated space

Our Experience in Living Allogenic Valve Transplantation: A Case Series of 6 Patients

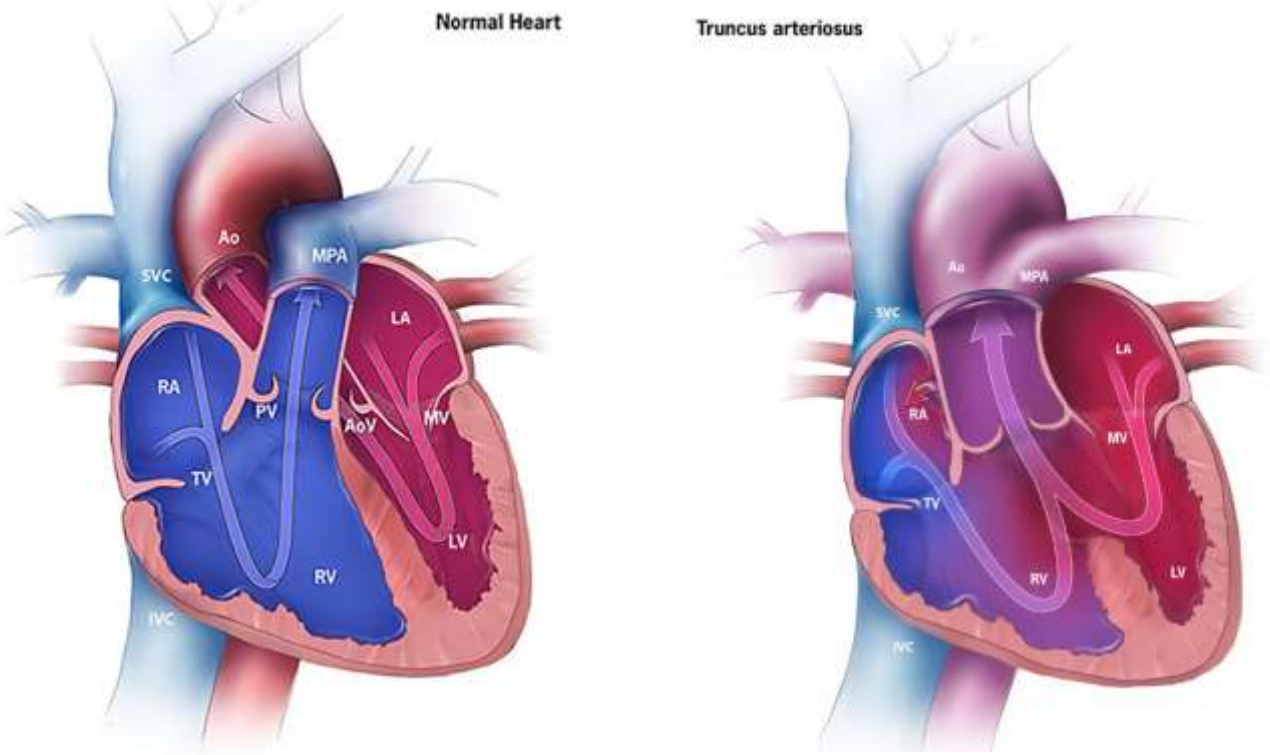
Patient 1

2-month-old F prenatally diagnosed with **TA Type 1** and left PA stenosis

Previous Surgeries: TA repair with RVOT reconstruction, left PA plasty on DOL 4 (02/21/23)

Clinical status (moderate-severe truncal valve insufficiency) discussed at multidisciplinary conference, at which point intervention was recommended

Underwent **ABO-incompatible domino aortic and pulmonary valve and root transplantation on 05/10/23** (CBP: 275 mins, XCT: 220 mins)
LOS: 15 days



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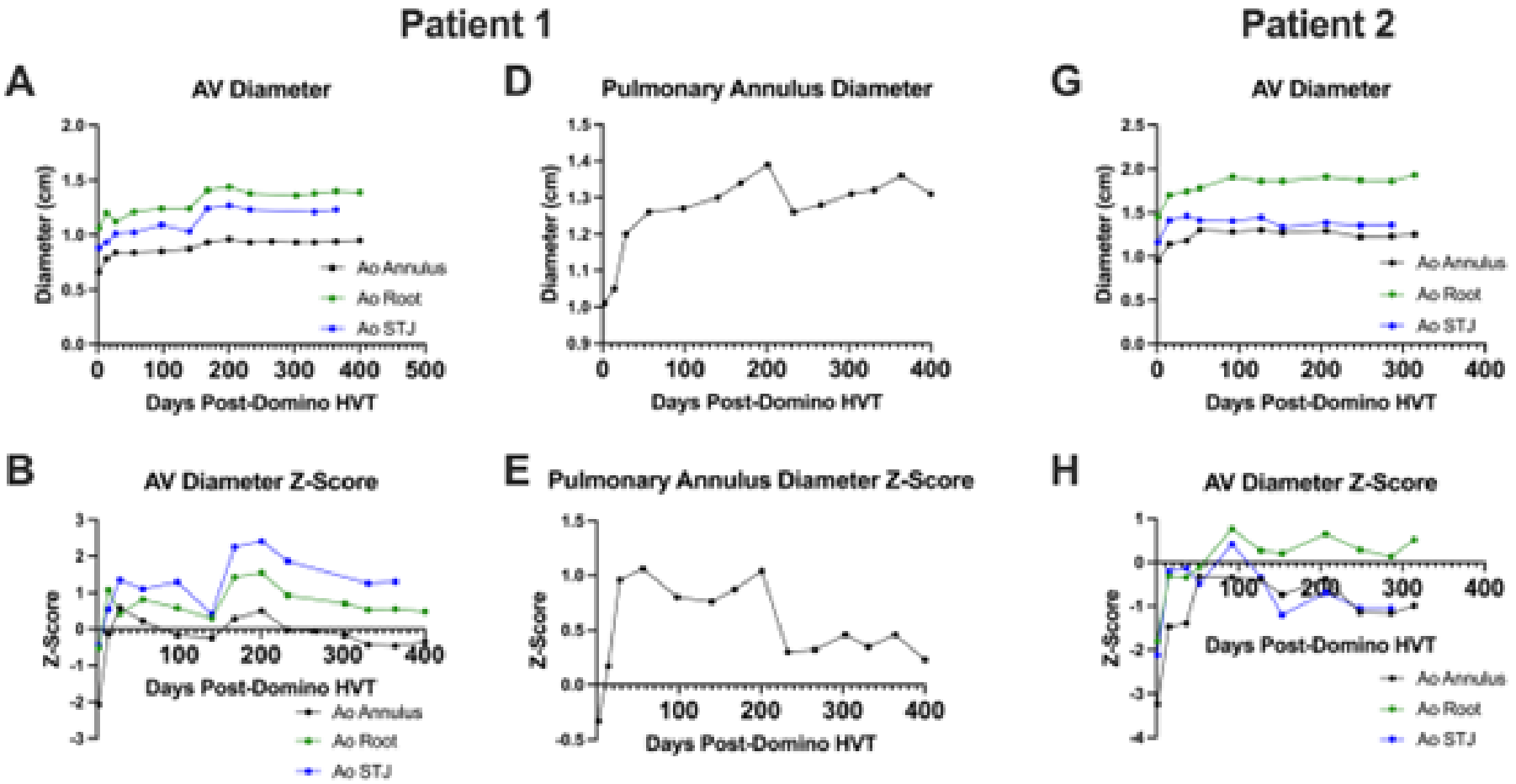
Patient 2

3-year-old M with congenital **bicuspid valve**, noted on echo to have severe AV regurgitation and a moderate-severely dilated left ventricle

Previous Surgeries: Balloon valvuloplasty at 3 months old (02/21/20)

Underwent **domino aortic valve/root transplantation on 07/11/23**, with aortic annuloplasty to prevent excessive root dilation (CPB: 131 min, XCT: 110)
LOS: 11 days

Early clinical outcomes support the growth capacity of transplanted valves

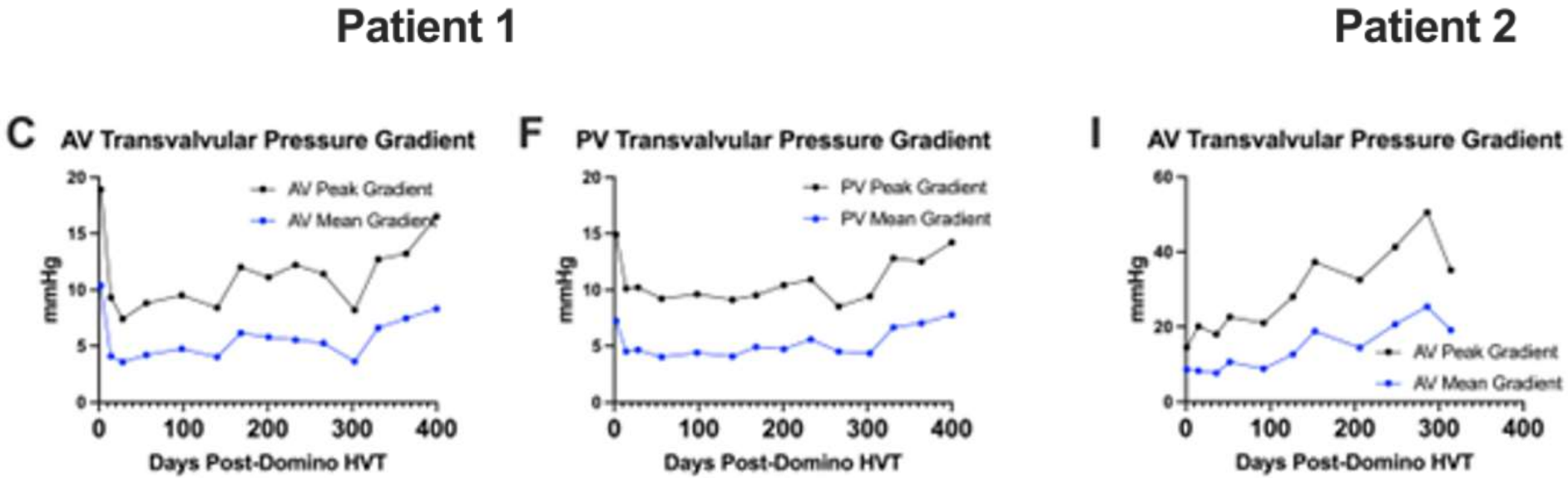


Valve diameter Z-scores trend towards normal within one-month postoperatively

HVT = heart valve transplant
AV = aortic valve
STJ = sinotubular junction

D Kalfa et al. JACC submission

Early clinical outcomes demonstrate the preserved function of transplanted valves



Transvalvular pressure gradients have remained within normal/mild levels throughout follow-up

HVT = heart valve transplant
AV = aortic valve
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D Kalfa et al. JACC submission

Early clinical outcomes demonstrate the preserved function of transplanted valves

	Patient 1					Patient 2		
Time Post-Domino HVT	AV Regurg	LV Dys-function	LV Dilation	PV Regurg	RV Dys-function	AV Regurg	LV Dys-function	LV Dilation
1-2 Days	Trivial	Moderate	Moderate	Trivial	Mild	Trivial	Moderate	Moderate
1-2 Weeks	Trivial	Mild	Mild	Trivial	Mild	Trivial	None	None
1-2 Months	Trivial	Mild	None	Trivial	Mild	Trivial	None	None
2-3 Months	Trivial	None	None	Trivial	Mild	Mild	None	None
3-4 Months	Trivial	None	Mild	Trivial	Mild	Mild	None	None
4-5 Months	None	None	Mild	Trivial	Mild	Mild	None	None
5-6 Months	None	None	Mild	Trivial	Mild	Mild	None	None
6-7 Months	None	None	Mild	Trivial	Mild	Mild	None	None
7-8 Months	None	None	Mild	Trivial	Mild	Mild	None	None
8-9 Months	None	None	Mild	Trivial	Mild	Mild-Mod	None	None
9-10 Months	None	None	Mild	Trivial	Mild	Mild-Mod	None	None
10-11 Months	None	None	Mild	Trivial	Mild	Mild-Mod	None	None
11-12 Months	None	None	None	Trivial	None			
12-13 Months	None	None	None	Trivial	None			

HVT = heart valve transplant
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D Kalfa et al. JACC submission

Patients #3- #6

	Age	diagnosis	Indication	Valve transplanted	Valve origin	Last postop follow-up	regurgitation at last follow	Gradient at last follow-up	growth
Patient 3	2y	Truncus s/p repair	Truncal regurgitation and RV –PA conduit failure	Aortic and pulmonary	Domino	4 months	Trivial AI, mild PI	No AS, peak radient PV 22mmHg	AoV 14mm→ 18mm (z score 3→1.5)
Patient 4	3y	Supra and valvar AS post repair	AS/AI	aortic	Domino split	2 months	No AI	No AS	AoV 1.3 →1.4
Patient 5	18 months	Truncus s/p repair	RV-PA conduit failure	pulmonary	Domino split	2 months	Trivial PI	No PS	?
Patient 6	8 day	Truncus s/p bilateral PA band	Truncal regurgitation	Aortic and pulmonary	Non-domino	1 month	Trivial AI/PI	Mild AS, mild to moderate subPS	?

Heart valve transplant recipient immunosuppression

Patients are discharged on triple-therapy immunosuppression, with the **overall goal of transitioning to a Tacrolimus-only regimen**

Important **“exit strategy”** of eliminating immunosuppression if significant complications arise

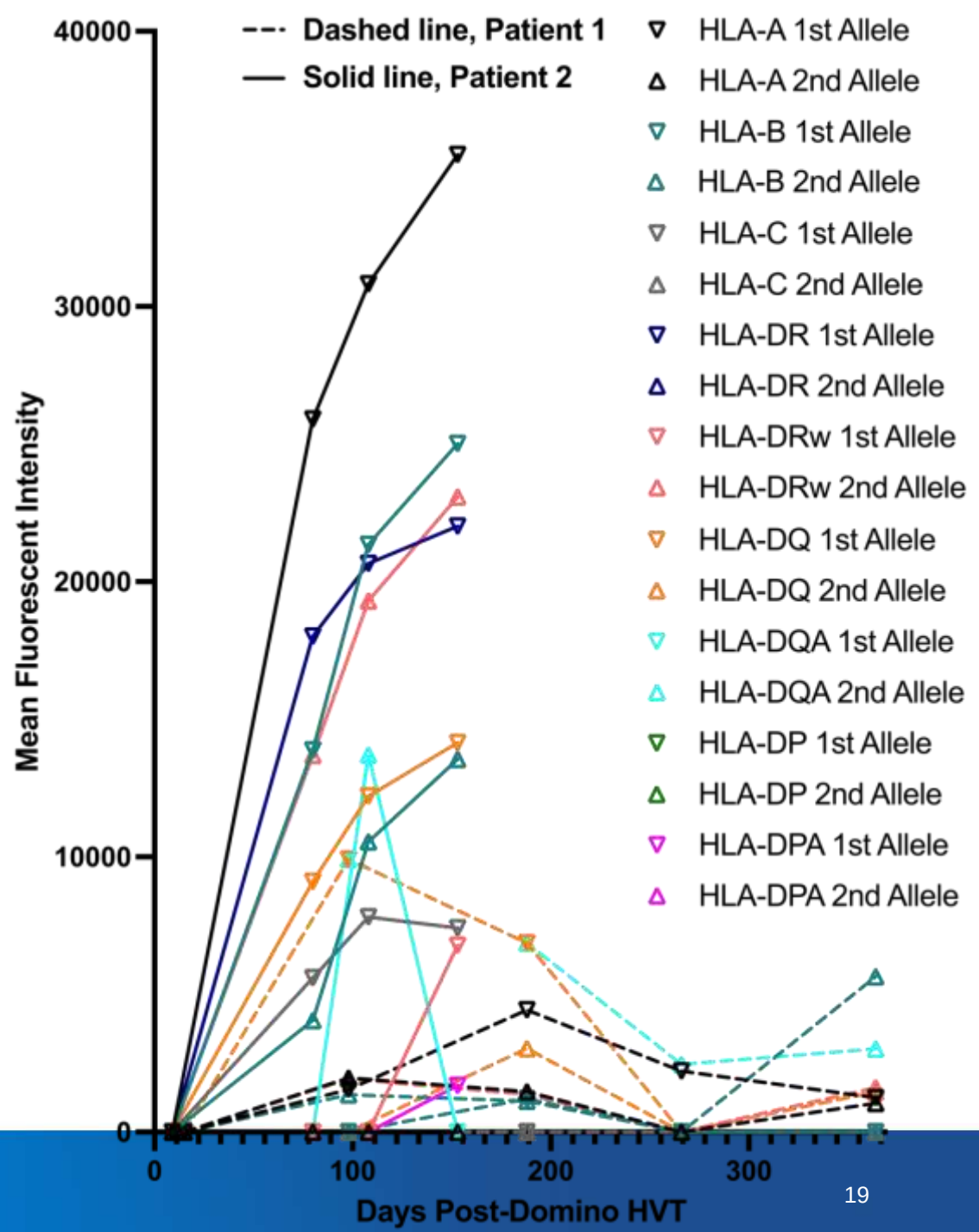
Without immunosuppression, predict outcomes no worse than standard cadaveric homograft

Postoperative Immunosuppression

	Patient 1			Patient 2		
Months Post-Domino HVT	**MMF**	**Tacrolimus**	**Prednisone**	**MMF**	**Tacrolimus**	**Prednisone**
0 - 1	Full-dose	Full-dose	Full-dose	Full-dose	Full-dose	Full-dose
1 - 2	62.5% of Full-dose*		75% Full-dose	Held**		50% Full-dose
			50% Full-dose	50% Full-dose		12.5% Full-dose
2 - 3	Held**		25% Full-dose	Full-dose		6.25% Full-dose
3 - 4		Goal Level Decreased By 20%			Goal Level Decreased By 20%	
4 - 5						
5 - 6	62.5% of Full-dose					
6 - 7						
7 - 8	Full dose		12.5% Full-dose			
8 – 9			Off			

Detecting Allograft Rejection

- Donor Fraction Cell-free DNA
  - Heart transplant Threshold is <0.14%
  - Both patients <0.08% and decreasing over time
- Donor Specific Antibodies
  - Developed at 2 months post
  - ?association with decrease in steroids?
  - Persistent stable antibody titers
- Non-invasive methods
  - MRI
  - PET



Living allogenic valve replacements demonstrate preserved **function** and **growth** with the recipient at short-term follow-up

first-ever infant domino heart valve transplant

Current indications

Truncal valve and aortic valve +/- pulmonary valve

Ross not feasible
Bad indication for a Ross: PI, RHD, severe AI, severe aortic root dilation
Neonatal Ross
Interest of the parents/cardiologist

The younger, the higher the benefit is for growth → up to 8-10 yo?

Self repair and remodeling (living valve) at all ages

Isolated RV PA conduit replacement in young children

Mitral valve replacement if not (re)-repairable (avoid coumadin / reop / survival?)

“Listing”

n=4 aortic valve, n=2 mitral valve

Multidisciplinary discussion and assessment: Surgeon/ HF/ cardiology

Criteria for “ranking”

- **age/size match (echo recipient/donor)**
- **clinical status**
- **timing of listing**

Multidisciplinary counseling of parent

Current clinical effort

1. Multicentric study
    1. N=19 (10 Duke, 6 Columbia, 1 Boston, 1 Austin, 1 south Carolina)
    2. DUA and IRB -> AATS abstract

2. Registry:
    1. US-based
    2. Invited expert opinion paper for JTCVS
    3. Columbia (Sherlanski) and Cornell (Gaudino) statistical and registry effort

Evaluating Safety and Outcomes of Living Allogenic Heart Valve Transplantation: The Case for a Multicenter Prospective Clinical Registry

Elizabeth M. Cordoves, BA[1,*], V. Reed LaSala, MD[1,*], Alexander Gregg, MD[2], Mario Gaudino, MD, PhD[2], Michael Shelanski, MD, PhD[3,4], Marc Richmond, MD[5], Emile Bacha, MD[1], David M. Kalfa, MD, PhD[1]

3. Regulatory considerations
    1. Organ vs tissue regulation

Why partial heart transplantation could be regulated as organ transplantation.

Glazier AK, Dafflisio G, Rajab TK, **Kalfa D**, Jaggers J, Emani S, Greenwald MA.

Am J Transplant. 2024 Jun 13:S1600-6135(24)00372-1. doi: 10.1016/j.ajt.2024.06.003. Online ahead of print.

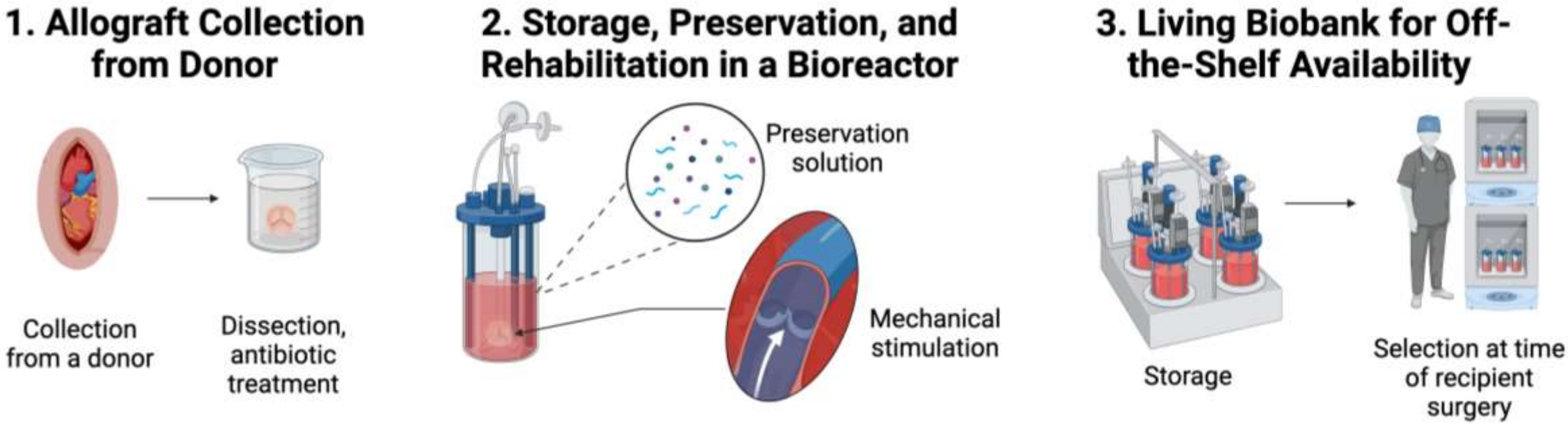
Questions about indications and listing?

Translational research:

Long term storage, preservation and rehabilitation of living allogenic valve

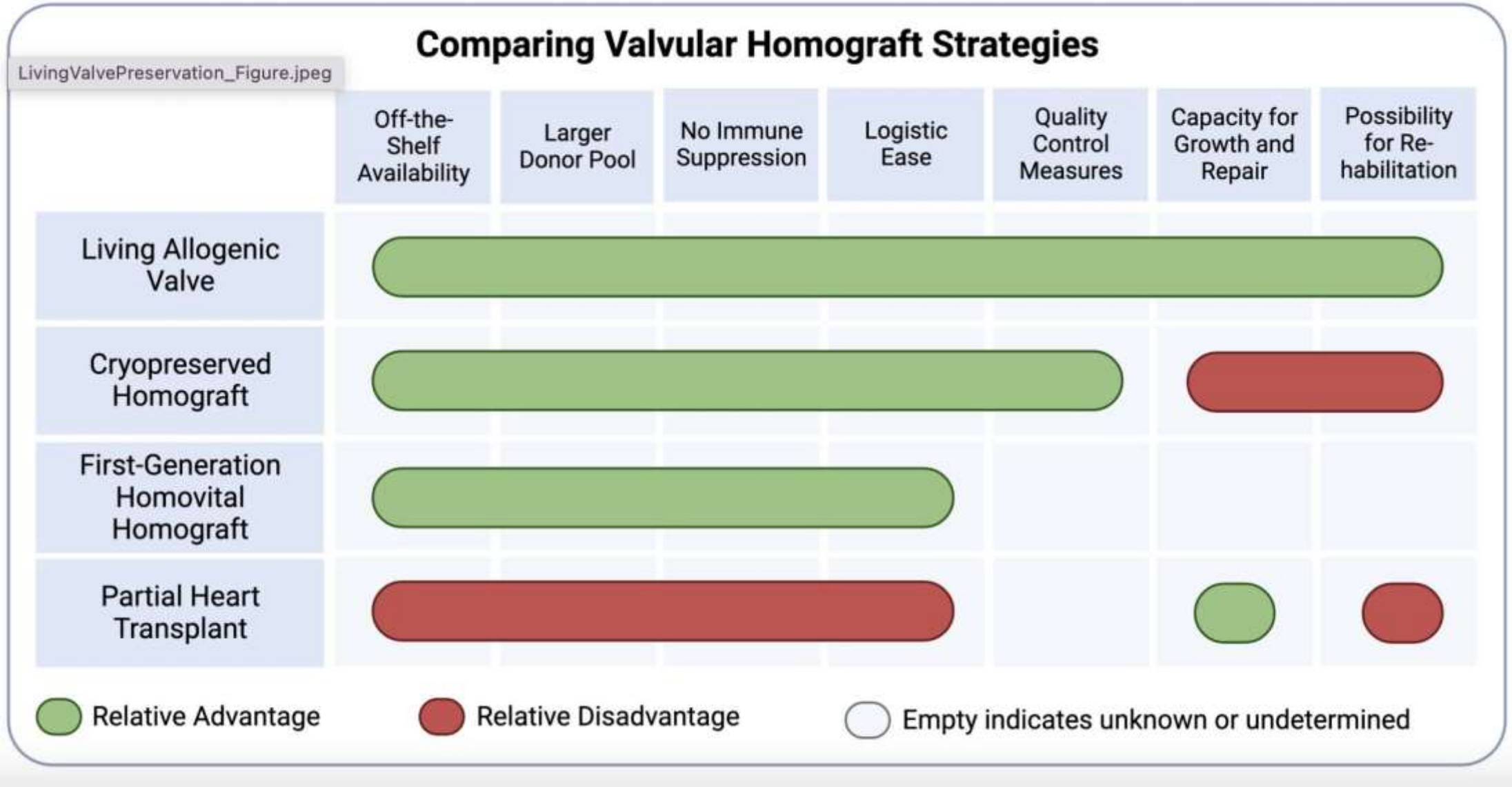
Kalfa Lab

The next-generation homograft: A living allogenic heart valve replacement (LAV)



Heart valve allografts can be kept viable in long-term storage, providing an “off-the-shelf” source of living valve replacements capable of growth and repair

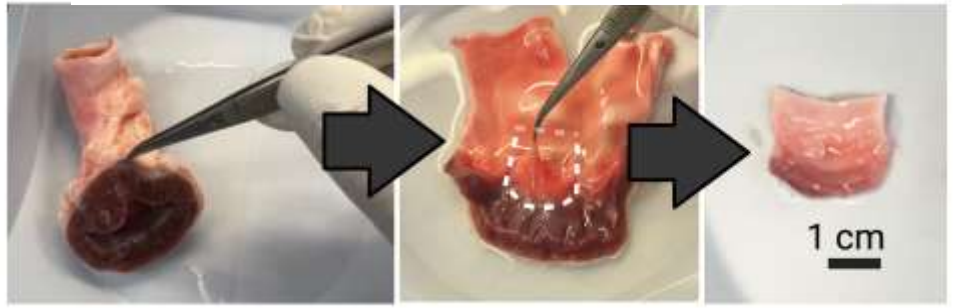
Cordoves E, Kalfa D et al, Med. 2024



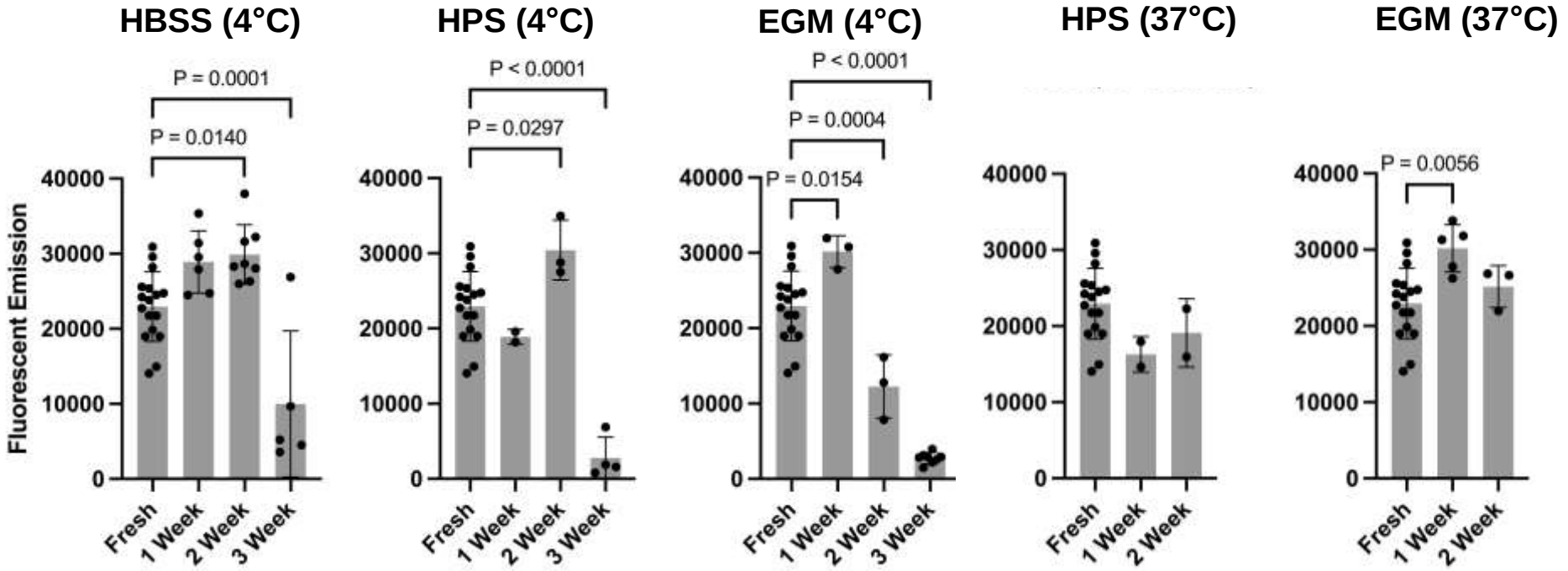
Cordoves E, Kalfa D et al, Med. 2024

Pulmonary allograft collection and viability testing

Porcine sample collection process



Living valvular tissue can be preserved for up to 2 weeks *ex vivo*



Now 7 weeks!

HBSS = Hank's Balanced Salt Solution
HPS = Heart Preservation Solution
EGM = Endothelial Growth Medium

Tissue viability data from Alamar blue assays. N = 2-17, ≥3 technical replicates per datapoint
Mean +/- SD, one-way ANOVA, each group compared to fresh tissues

A bioreactor for physiologically-relevant allograft storage

Valve open/close cycles as-imaged through the viewing window

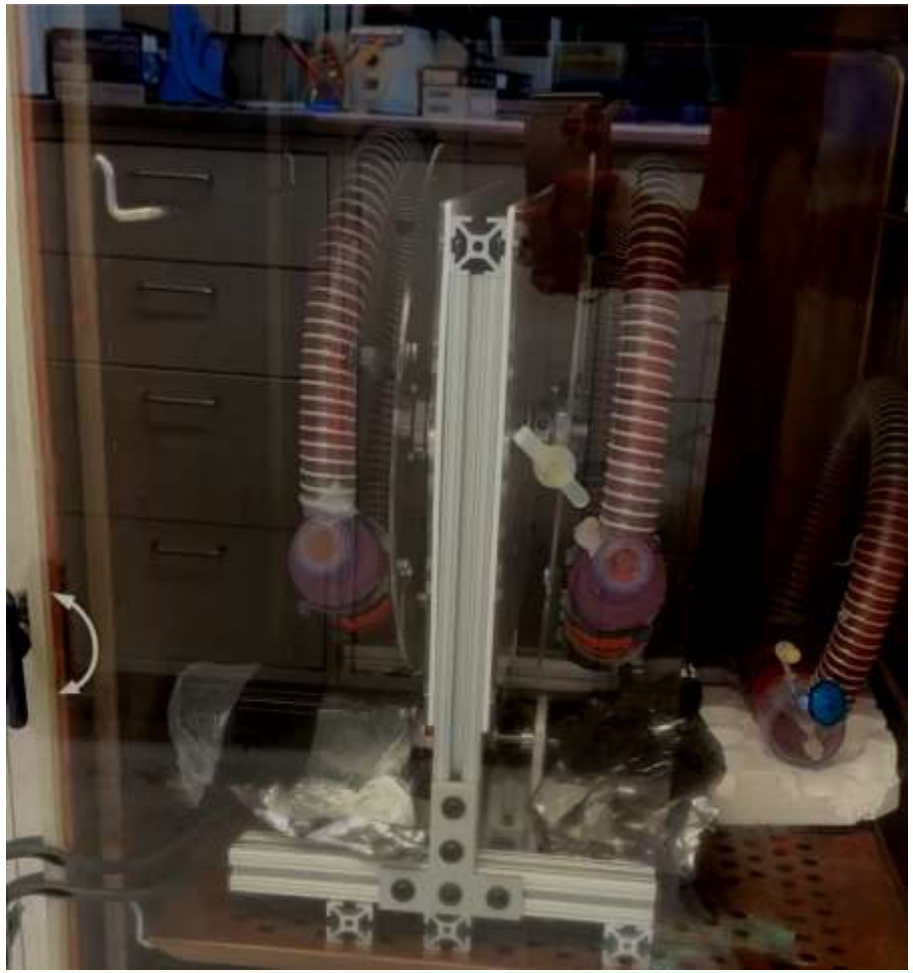
Valve viewing window

Valve held in place here

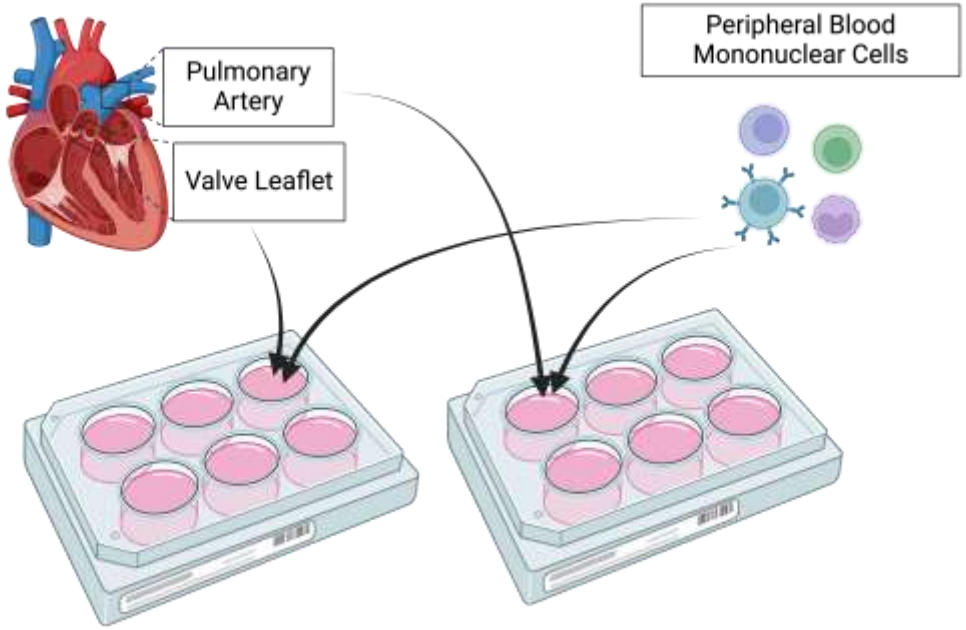
Construct is filled with valve preservation solution

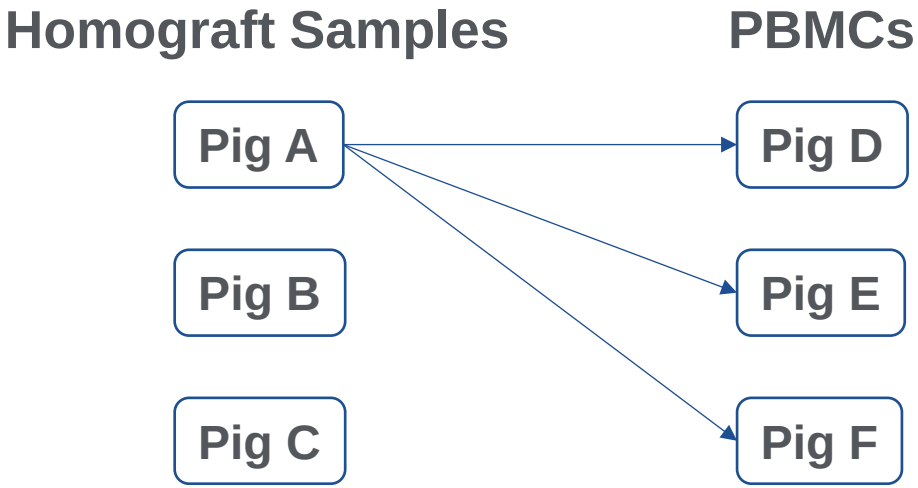
The prototyped bioreactor can induce valvular open/close cycles in a uniquely pumpless format

A high-throughput rotating motor for culturing multiple valves simultaneously was created



Updated analysis of valvular immunogenicity





Groups of Interest

1. Tissue-only (negative control)
2. Tissue + PBMCs
3. Tissue + PBMCs with Phytohemagglutinin
4. PBMCs-only (negative control)

Readouts

Alamar Blue
LDH

In vivo evaluations of the viability, growth-capacity and immune response to valvular allografts

Experimental Model:

Orthotopic transplantation of a pulmonary homograft in a 3-month-old piglet

2 month follow up

Readouts of Interest:

Valve growth, function over time

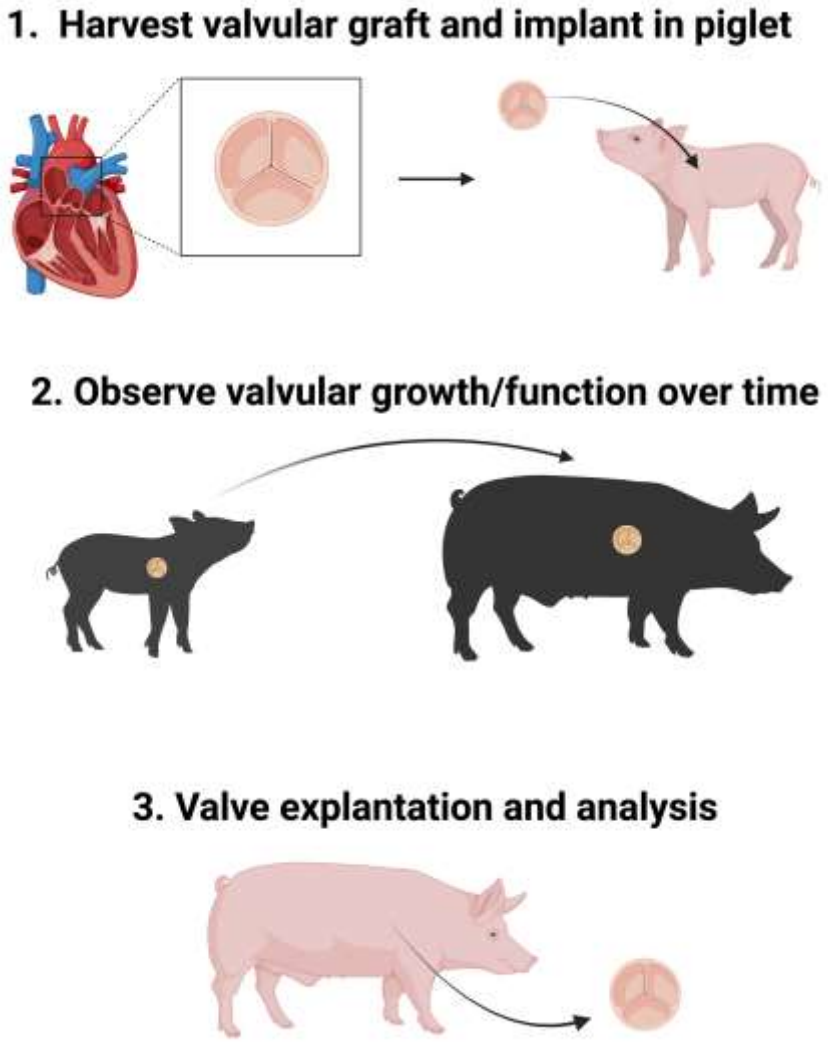
Valvular microarchitecture, cell phenotype

Immunogenicity

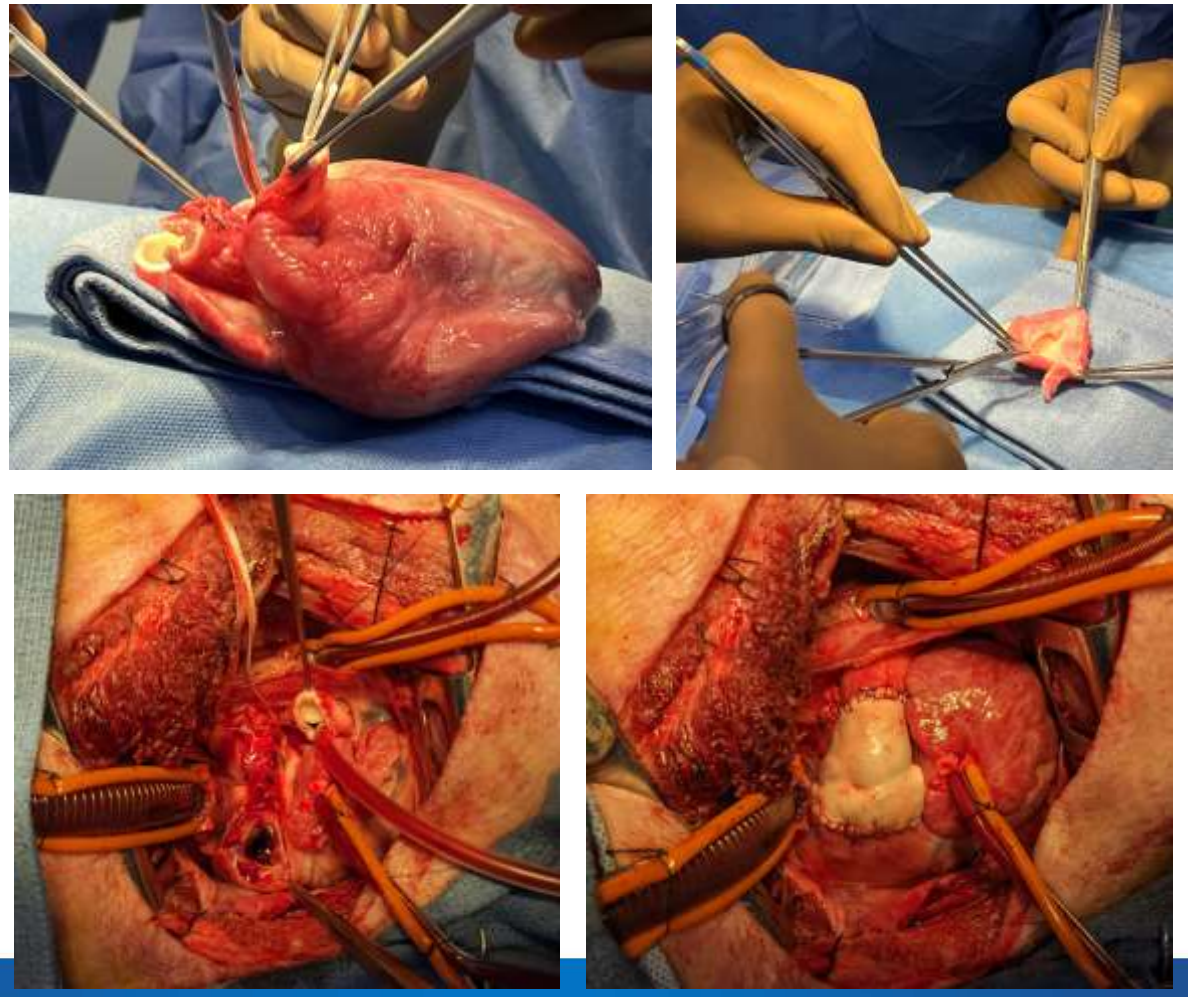
Experiments Performed:

N=2 Fresh Heart Valve Transplants

N=1 Cold-Stored Valve (4 weeks in PBS at 4°C)



Pulmonary homografts were freshly isolated in an adjacent operating room and reimplanted orthotopically in the recipient



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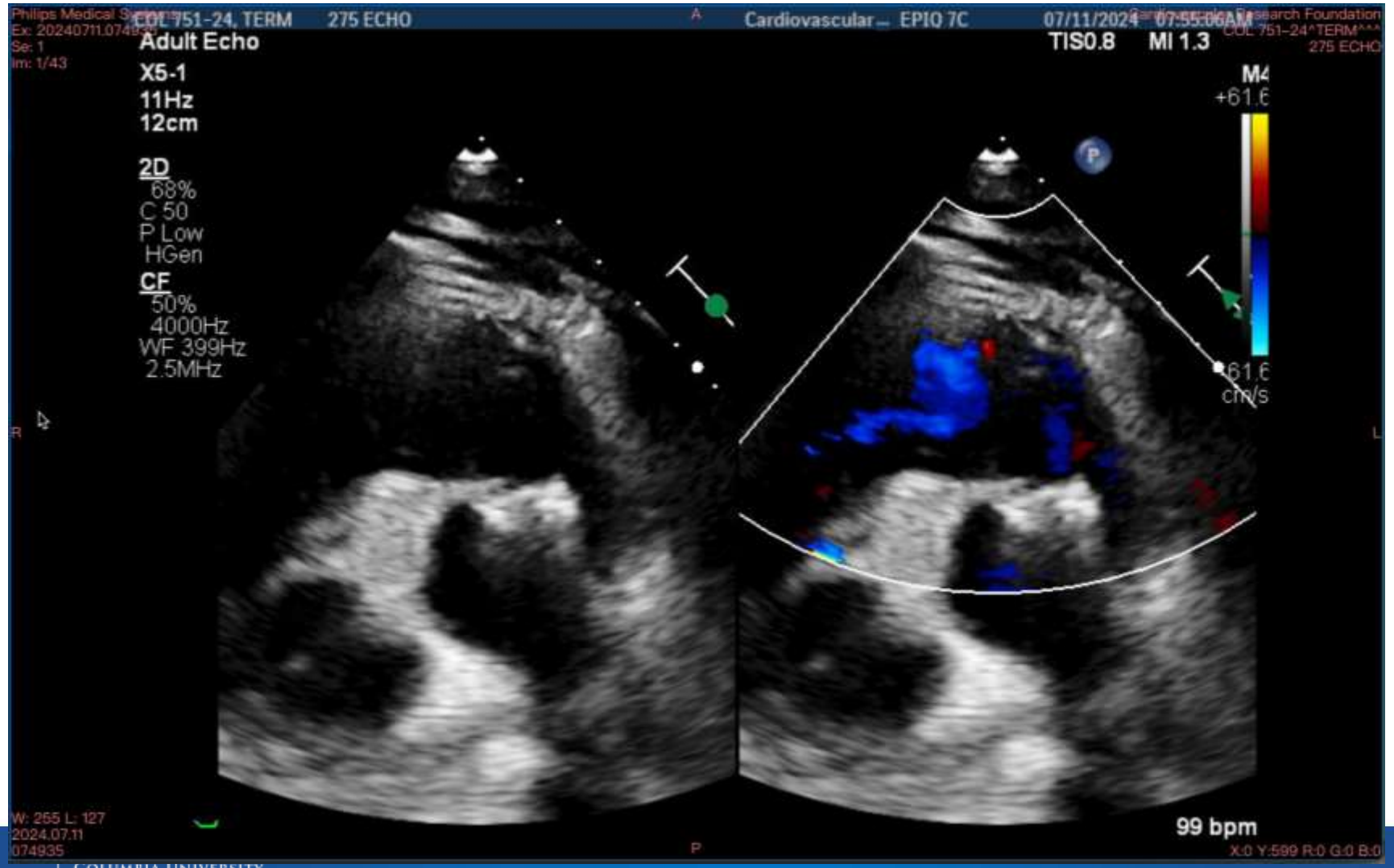
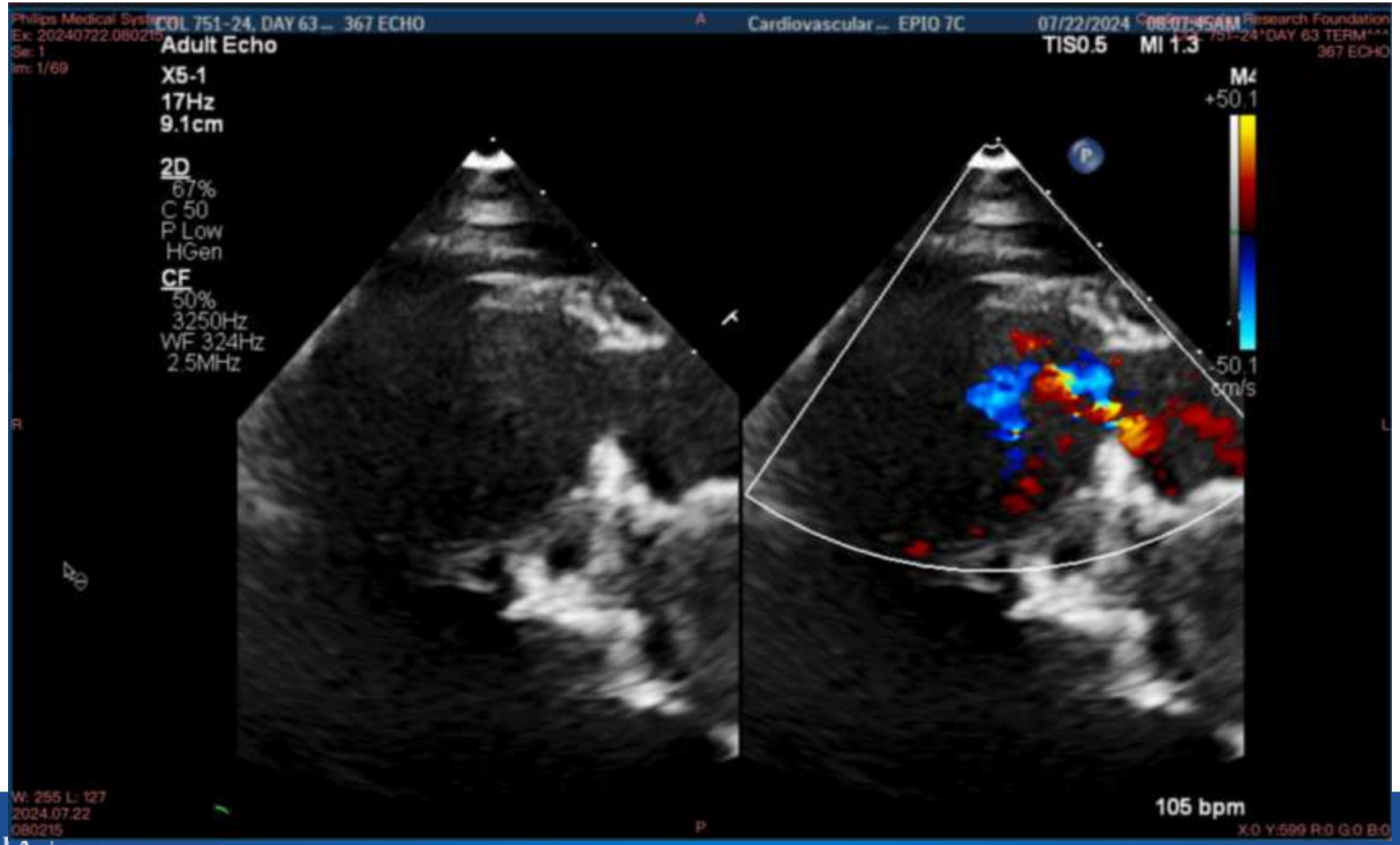
Term echo for the second freshly-transplanted valve demonstrated trivial/physiologic regurgitation



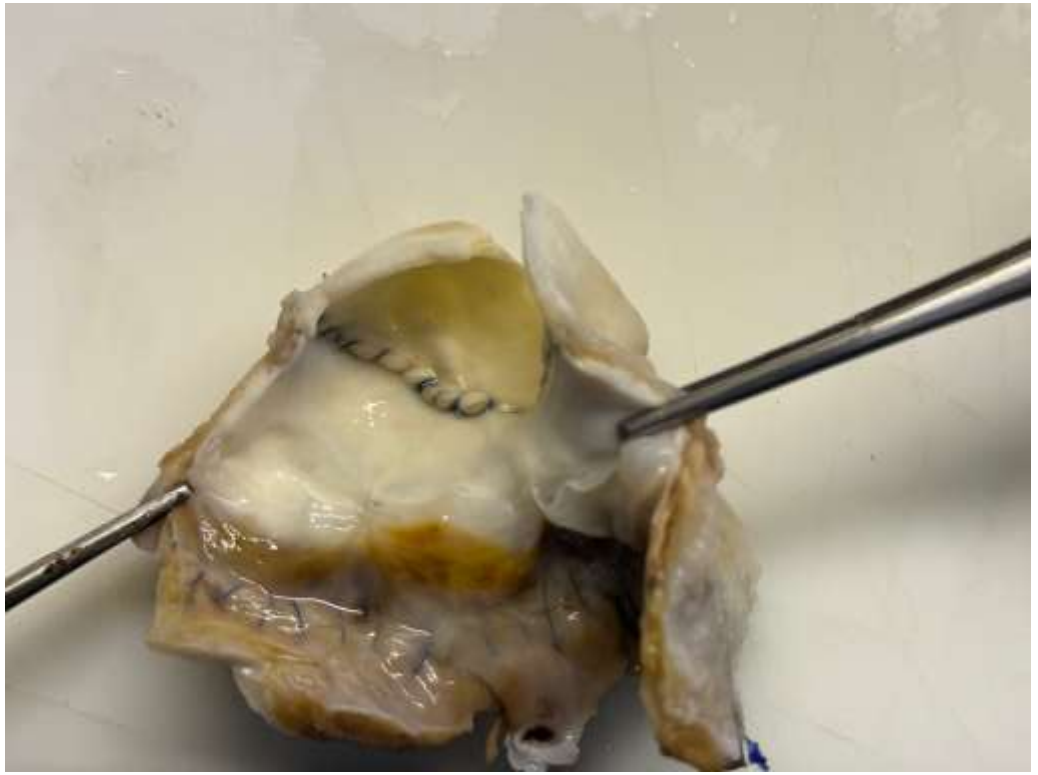
Echos were evaluated by the cardiologist on-site at Skirball

Term echo for the cold-stored valve demonstrated severe regurgitation



Echos were evaluated by the cardiologist on-site at Skirball

Grossly, explanted fresh pulmonary valve transplants demonstrated normal morphology and leaflet geometry



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Joint Award - Department of Surgery Innovation Fund and Columbia Technology Ventures (CTV) / CUIMC Validation Fund ($100,000)

1F30HL174098 - 01A1, Ruth L. Kirschstein National Research Service Award Individual Fellowship for Students at Institutions with NIH-Funded Institutional Predoctoral Dual-Degree Training Programs
National Heart, Lung and Blood Institute (NHLBI)

1F31HL178343-01, Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship to Promote Diversity in Health-Related Research
National Heart, Lung and Blood Institute (NHLBI)

R01 submission – to be reviewed in two weeks

AHA Established Investigator award – to be reviewed in 2 months

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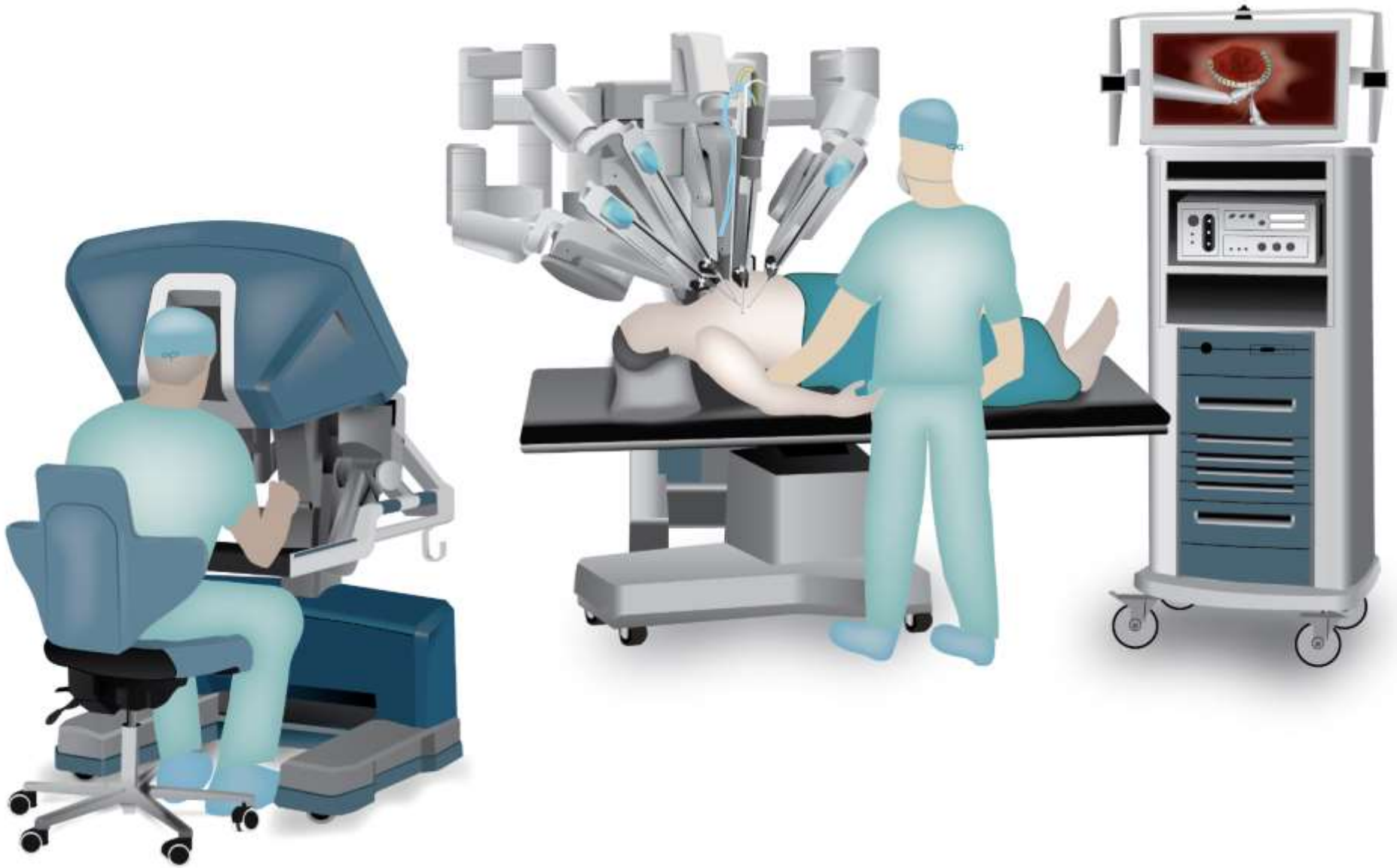
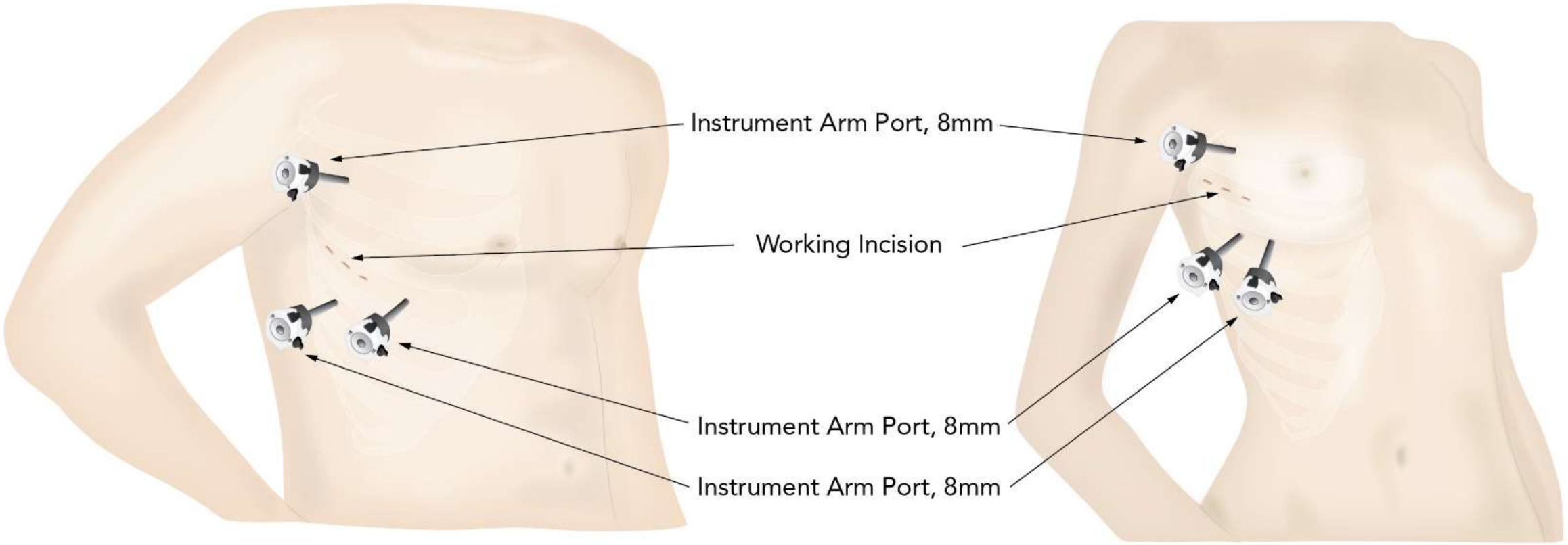
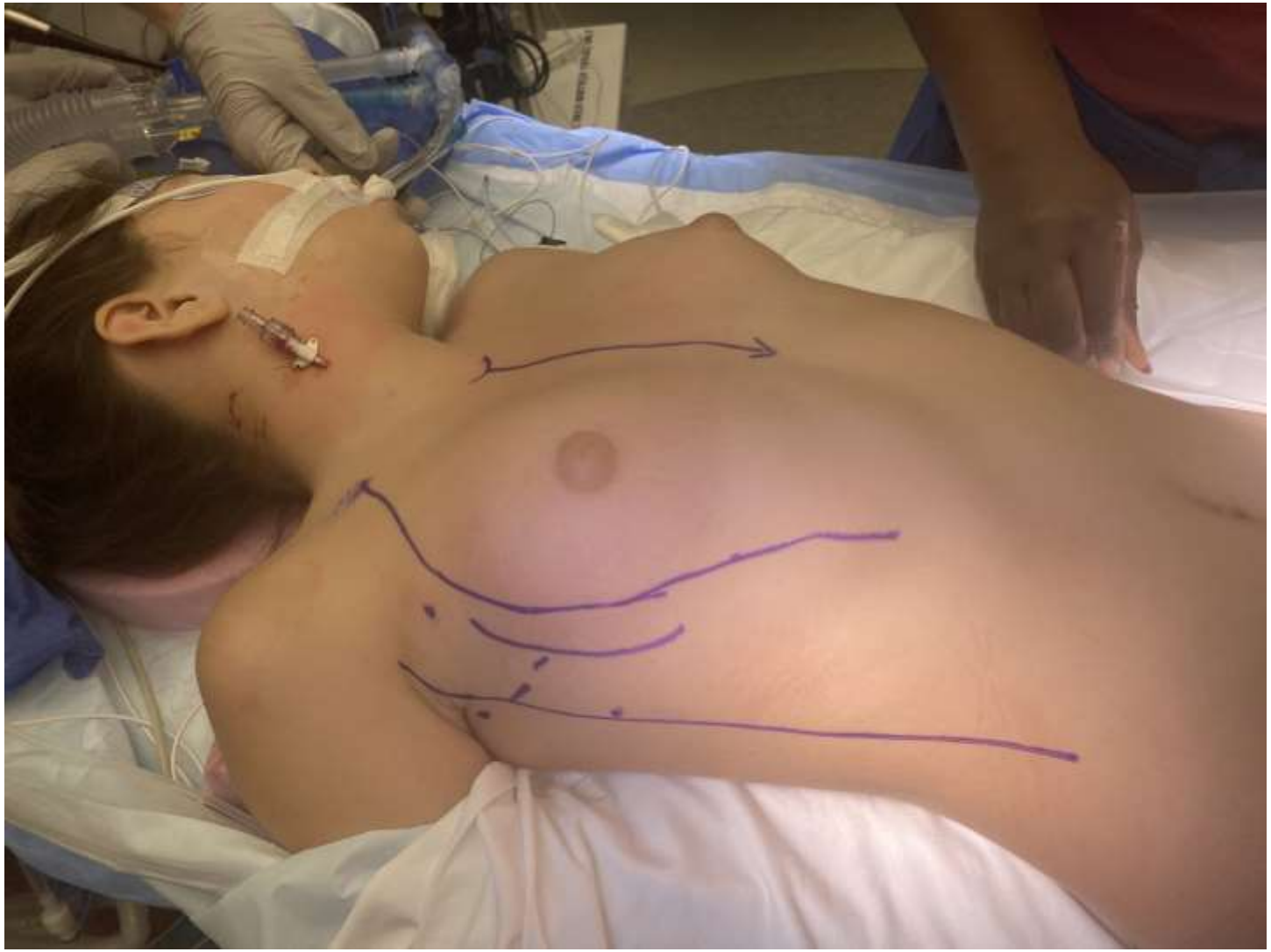




Kalfa D, Nature cardiology review



Our series

- 11 ACHD
  - Ostium secundum ASD
  - Sinus venosus ASD /PAPVR
  - Scimitar
  - MV repair
- 6 children
  - Ostium secundum ASD
  - PAPVR
  - double aortic arch

  - No death
  - No complications

Indications in congenital

- ASD OS and SV
- PAPVR
- Scimitar
- TVr
- Simple MVr
- Cor triatriatum
- Vascular ring

- Children >25kg
- Youngest 6 yo so far: youngest robotic open-heart surgery worldwide – June 2024

Thank you