

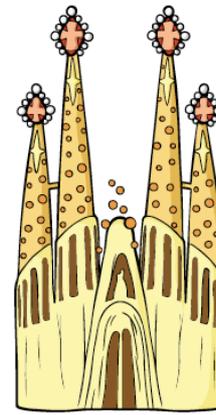
THE CATALAN  
TRANSPLANTATION  
SOCIETY



SOCIETAT  
CATALANA DE  
TRASPLANTAMENT



BANFF FOUNDATION  
FOR ALLOGRAFT PATHOLOGY



**2017 BANFF-SCT**  
Joint Scientific Meeting

**BARCELONA**  
27-31 March 2017



BANFF CONCURRENT:

HEART

The contribution  
of the pathologist  
to expand the donor pool  
in cardiac transplantation

*Ornella Leone*  
*Azienda Ospedaliero-Universitaria*  
*S.Orsola-Malpighi*  
*Bologna, Italy*

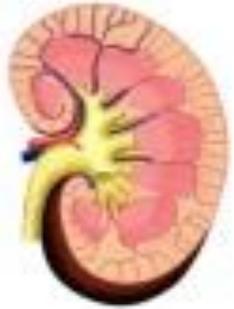
## Faculty / Presenter Disclosure

- Faculty: Ornella Leone, MD
- I have no past, actual or potential conflicts of interest concerning this program/presentation

## Pathology's contribution to assessing donor heart suitability

- rarely discussed
- very different from that for other solid organs

# Predictive value of donor organ histology during assessment:



## **DONOR RENAL BIOPSY**

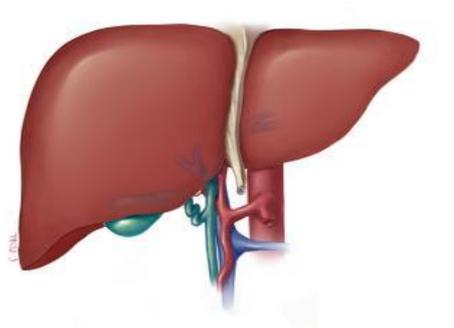
histologic scoring to evaluate the sum of

- interstitial fibrosis
- tubular atrophy
- glomerulosclerosis
- vascular damage



prediction of delayed graft function risk

# Predictive value of donor organ histology during assessment:



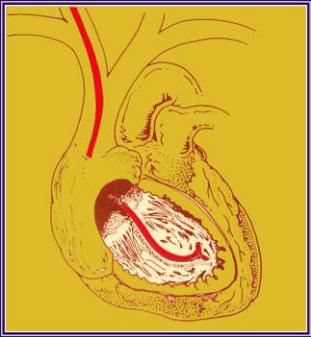
## **ALLOGRAFT LIVER BIOPSY**

histologic analysis of

- steatosis
- fibrosis
- necrosis



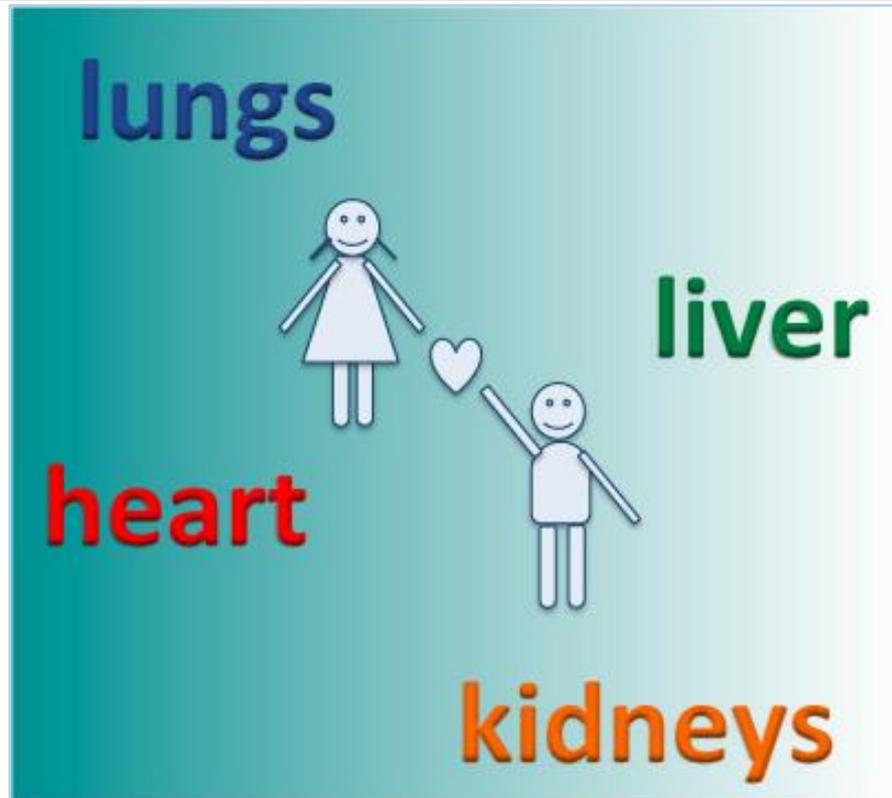
risk of development  
of primary non-function or poor function or allograft dysfunction



## The heart is not biopsied during routine donation work-up

- ischemic time must be as short as possible (adequate sample processing, even the rapid process, requires around 2 hours)
- the type of histologic lesions to assess cannot be using only extemporary frozen sections
- small biopsy samples are poorly representative because lesion extent throughout the whole myocardium is an essential parameter

# ORGAN DONATION



donor shortage  
compared to worldwide need  
is the main limitation to increasing transplant numbers



# HEART TRANSPLANTATION

two additional aspects

## DONOR AGE

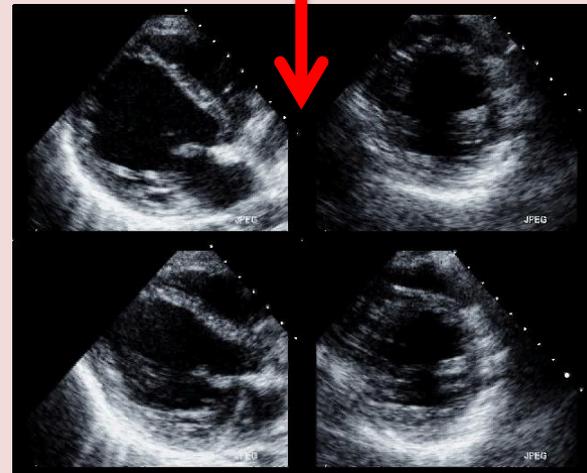
closely related to age-dependent risk of transmission of donor subclinical diseases



coronary artery atherosclerosis

## EFFECTS

of potentially reversible myocardial abnormalities in the immediate/early post-operative period on an organ



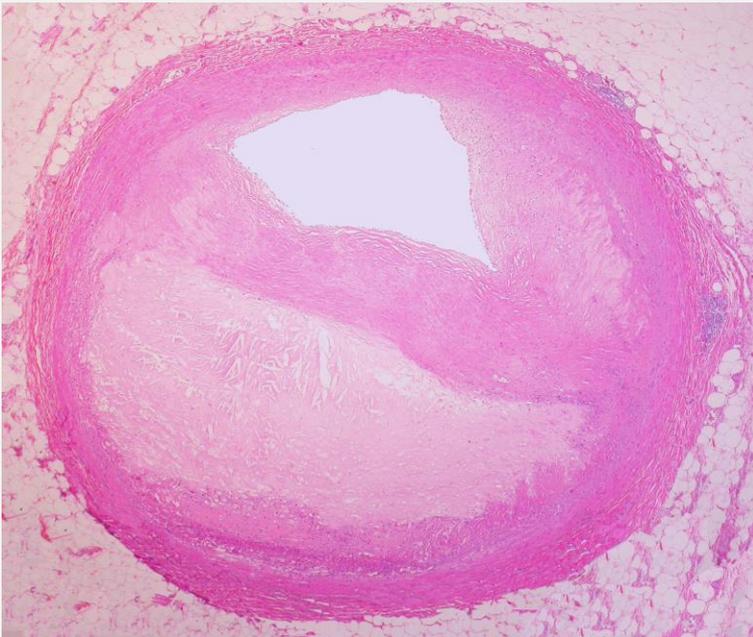
with largely mechanical properties

# More complex profile of today's heart donor pool

older donors  
with co-morbidities



higher number of grafts  
with coronary atherosclerosis



Brain-dead donors  
(more critical management)



Pathophysiology  
of brain death



negatively affect the heart

# Clinical decisions on heart suitability

- donor age
- donor size and weight
- donor history and cardiovascular risk factors
  - hypertension
  - diabetes mellitus
  - smoking and drinking
  - possible intake of cardiotoxic substances (cocaine, cardiotoxic medication, previous chemotherapy, etc)
- family history
- cause of death
- malignancies
- donor infection status

# Currently available or potentially available tools for cardiovascular diagnostics

- electrocardiography
- right heart catheterization
- echocardiography (now routinely performed in most hospitals)
- coronary angiography (not routinely performed everywhere)
- stress echocardiography (available only as experimental projects)

# Donor vasopressor and/or inotropic support in Intensive Care is another key issue

as higher catecholamine dosage is associated with potential organ damage

Ideally inotropic support should not exceed:

- 7.5 g/kg/min dopamine/dobutamine
- 0.4 g/kg/min norepinephrine

# Eurotransplant International Foundation Registry 2012

## REGISTERED DONORS

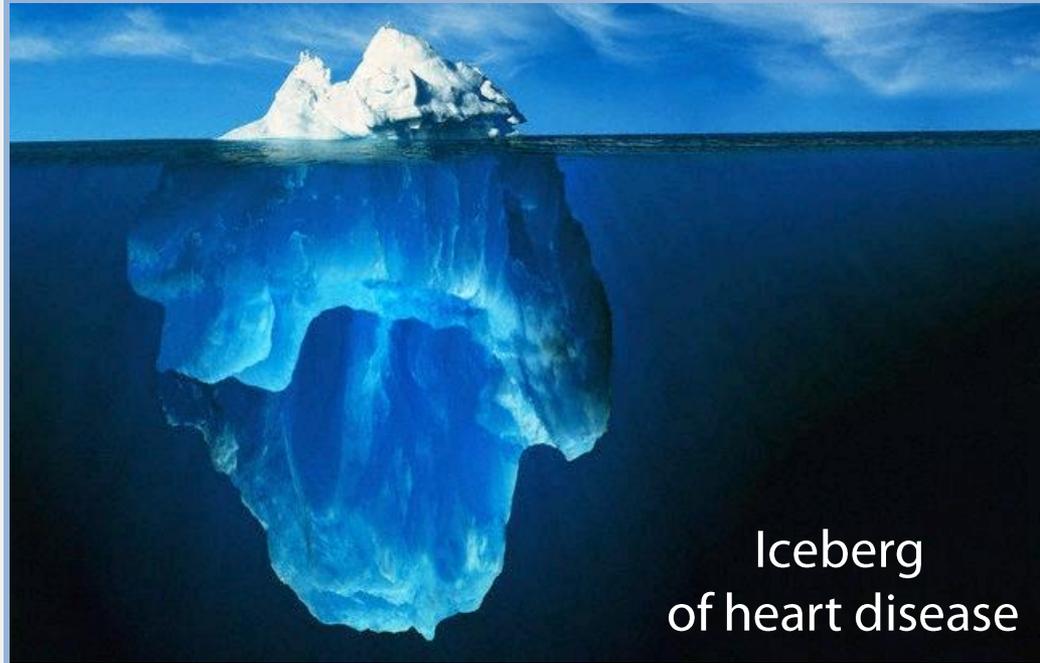
Potential heart donor candidates	36.9%
Hearts ultimately used for transplantation	64.6%

Why are so many discarded  
in spite of the lack of hearts?

more objective and reproducible  
donor assessment tool

would be desirable

to supplement clinical experience  
when deciding  
whether to accept a donor heart



Iceberg  
of heart disease

# Pathology and donor discarded hearts

substantial contribution with the routine examination of unsuitable or discarded hearts

in order to collect data on



- the spectrum of possible pathological alterations
- correlate them to previously obtained clinical-instrumental data

helping to identify  
a subgroup of potentially usable organs, currently discarded

# Pathology evaluation of non-procured donor hearts or fragments is not routine procedure in transplant centers

- the value of autopsy or any histological examination of tissue remnants to improve the safety for all types of tissue transplantation

*Visser et al. Cell Tissue Bank 2012;13:37-46*



- for heart valve homografts

*Heng WL et al. J Cytol Histol 2014; S4:003*



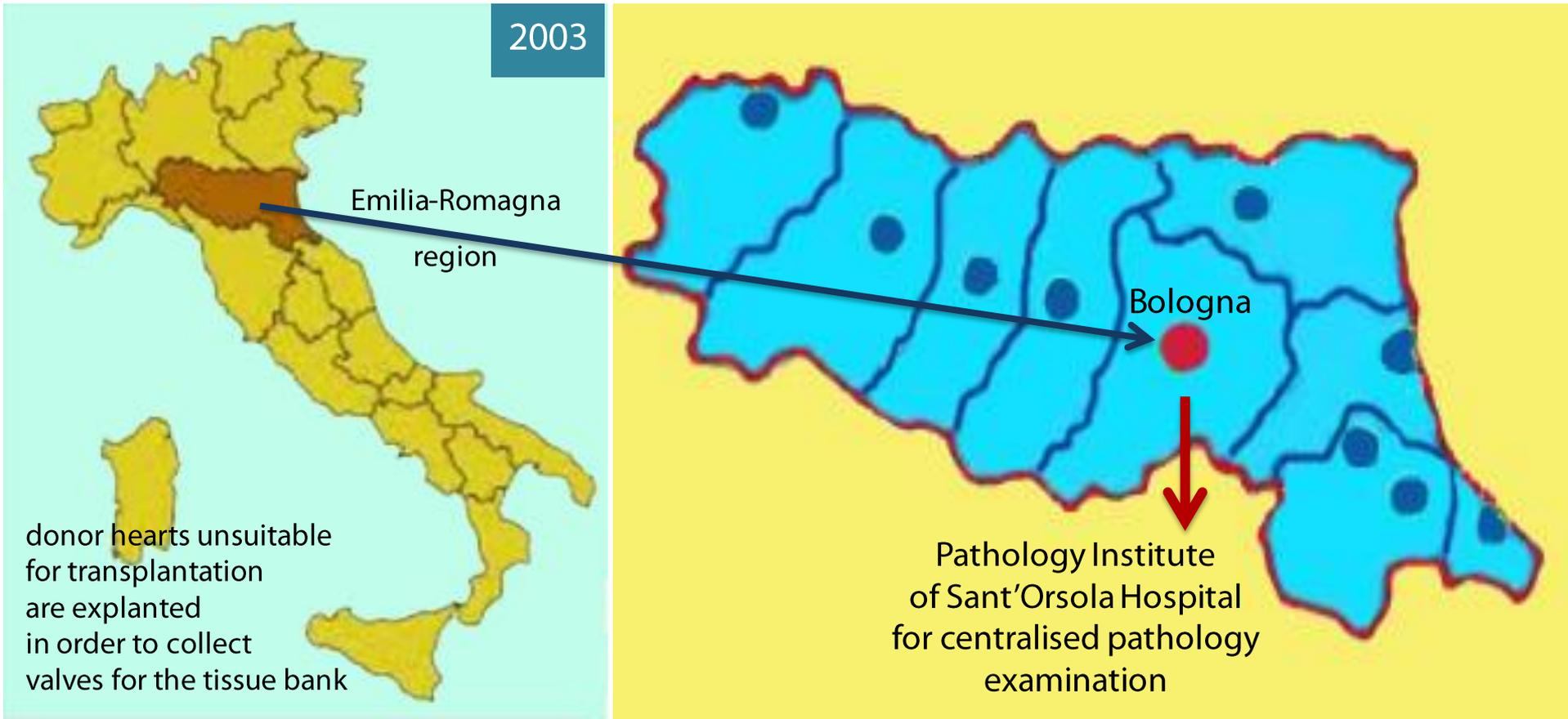
Doroshov RW et al. Availability and selection of donors for pediatric heart transplantation.  
*J Heart Lung Transplant 1995; 14 : 52-8*

potential role of myocardial pathology evaluation in brain-dead infant donors who have undergone autopsy to research more accurate predictors in assessment of donor suitability

# Potential of donor heart pathology evaluation

## BOLOGNA HEART TRANSPLANT CENTER

### Valve tissue bank project



# STUDY POOL

standard donors  
(non neoplastic, non infectious)  
approved for donation

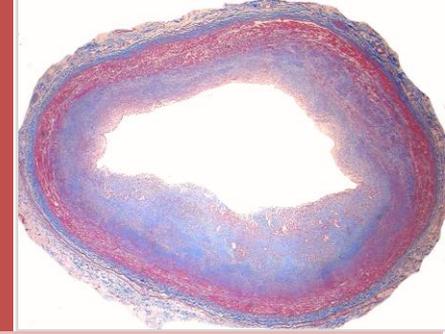
- multi-tissue donors: 35.5%
- multi-organ donors (at least one organ offered or transplanted): 64.7%



the heart was judged unsuitable for transplantation

- anamnesis results
- after clinical-instrumental evaluation

# Protocols for pathology examination of hearts unsuitable for transplantation



Cardiovasc Pathol 2012; 21: 2-16

CARDIOVASCULAR  
PATHOLOGY

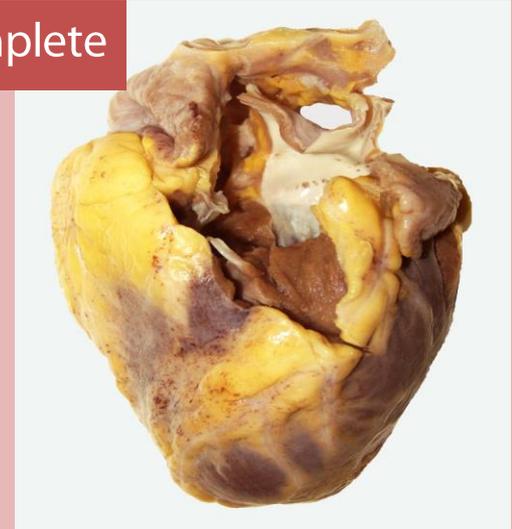
Original Article

Recommendations for processing cardiovascular surgical pathology specimens: a consensus statement from the Standards and Definitions Committee of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology

James R. Stone<sup>a,\*</sup>, Cristina Basso<sup>b,\*</sup>, Ulrik T. Baandrup<sup>c</sup>, Patrick Bruneval<sup>d</sup>, Jagdish Butany<sup>e</sup>, Patrick J. Gallagher<sup>f</sup>, Marc K. Halushka<sup>g</sup>, Dylan V. Miller<sup>h</sup>, Robert F. Padera<sup>i</sup>, Stanley J. Radio<sup>j</sup>, Mary N. Sheppard<sup>k</sup>, Kim Suvama<sup>l</sup>, Carmela D. Tan<sup>m</sup>, Gaetano Thiene<sup>n</sup>, Allard C. van der Wal<sup>o</sup>, John P. Veinot<sup>p</sup>



incomplete



fragmented



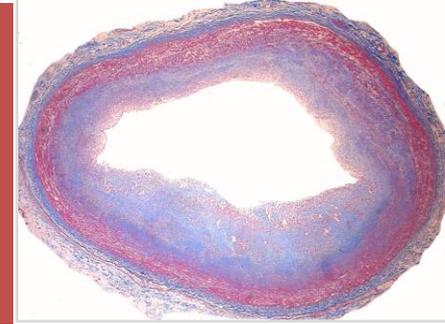
Virchows Arch (2008) 452:11–18  
DOI 10.1007/s00428-007-0505-5

REVIEW AND PERSPECTIVE

## Guidelines for autopsy investigation of sudden cardiac death

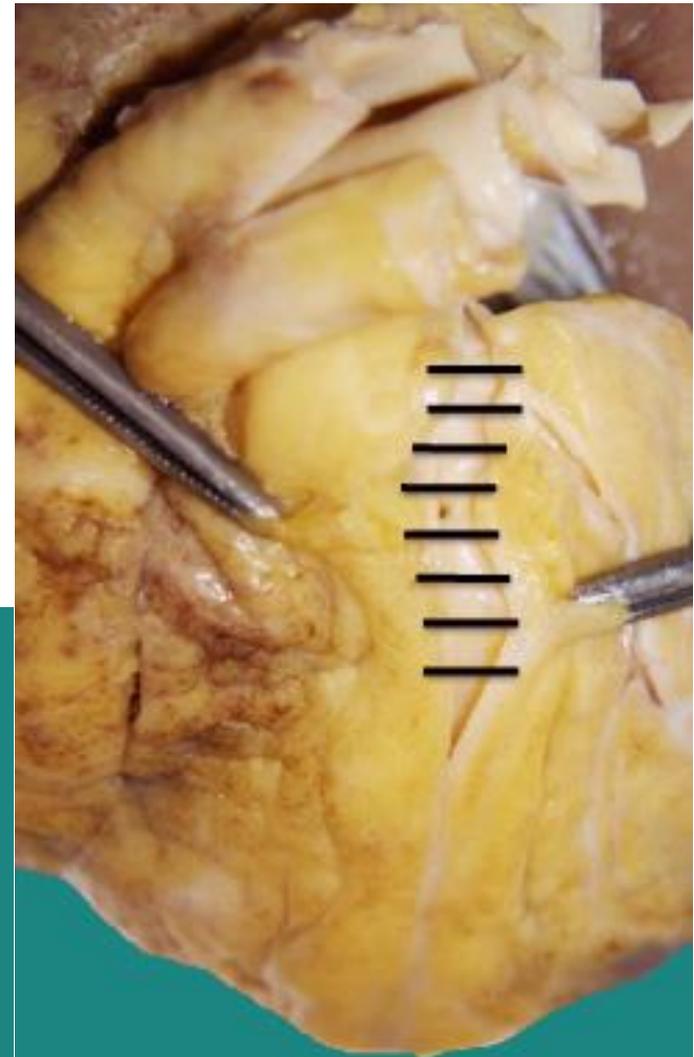
Cristina Basso · Margaret Burke · Paul Fornes ·  
Patrick J Gallagher · Rosa Henriques de Gouveia ·  
Mary Sheppard · Gaetano Thiene ·  
Allard van der Wal ·  
on behalf of the Association for European  
Cardiovascular Pathology\*

# Protocols for pathology examination of hearts unsuitable for transplantation



Non-pressure-fixed  
main subepicardial coronary arteries

- left main
- left anterior descending
- left obtuse marginal and circumflex branches
- right coronary

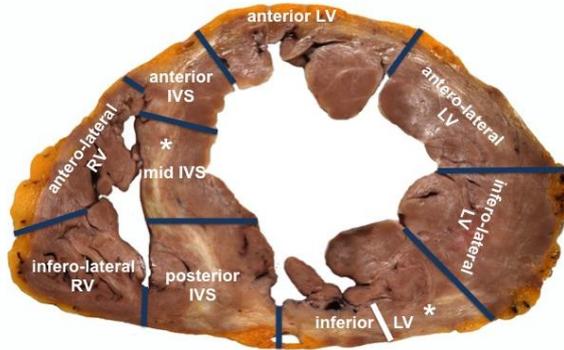


opening vessels  
with multiple transverse cuts  
at 3 mm intervals along the course



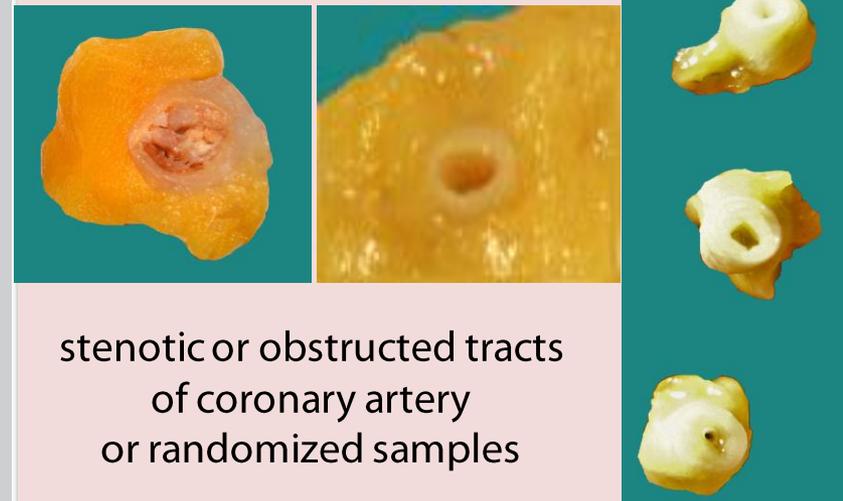
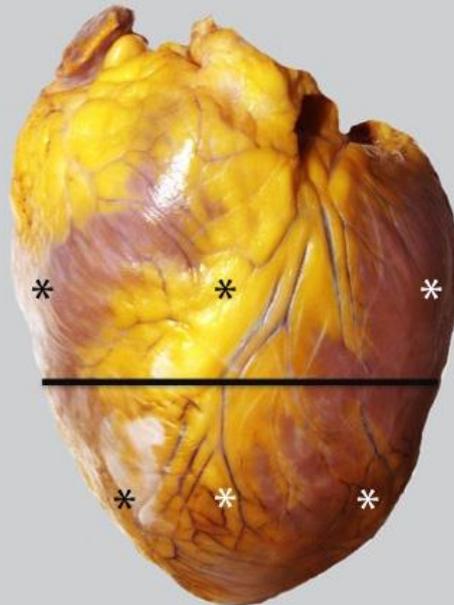
# Pathology examination of hearts unsuitable for transplantation SAMPLING

entire  
representative  
transverse slice  
of the heart



all macroscopically  
altered areas

further specimens  
from each right and left  
ventricle and septum



stenotic or obstructed tracts  
of coronary artery  
or randomized samples

300 hearts examined

# Bologna Heart Transplant Centre Valve tissue bank project pool

OVERVIEW

Preliminary data  
(2003-2016)

- 65% males; 35% females
- median age of 48 years (range 11-66 years)

## Causes of death

### Brain death: 60.3%

Brain death due to haemorrhagic/ischemic ictus: 60.3%

Brain death due to road/workplace accident/suicide: 33.7%

After cardiac arrest resuscitation: 5%

Miscellaneous: 1%

### Cardiac death: 39.7%

Cardiac death due to road/workplace accident/suicide: 69%

Sudden cardiac death: 23.5%

Cardiac death due to bulbar ictus: 5%

Miscellaneous: 2.5%

# Bologna Heart Transplant Centre: Valve tissue bank project pool

## Reasons for excluding a heart from donation

**① Hearts refused  
by the Transplant Center: 38.3%**

**② Hearts excluded after  
Intensive Care Unit screening: 61.7%**

Heart pathology after clinical-instrumental  
evaluation (including stress-echo): 48.6%

Cardiac arrest mainly following road accident:  
50%

Age: 17.8%

Cardiac arrest due to sudden death: 15.8%

Haemodynamic instability/hypotension:  
16.8%

Heart pathology known on the basis of  
anamnestic data: 28%

Surgical examination: 13.1%

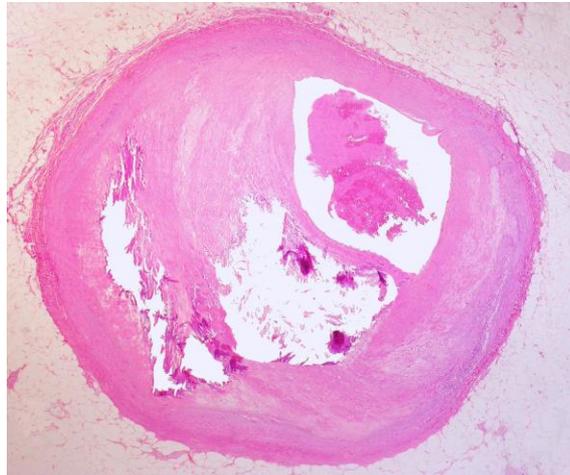
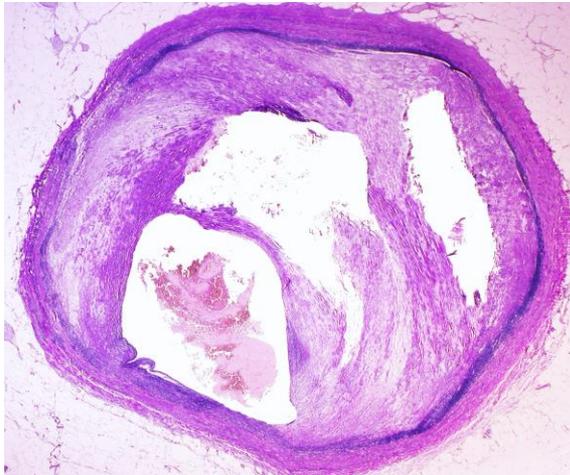
Lack of information/consent  
withdrawal/organizational issue: 6.2%

Lack of recipients: 3.7 %

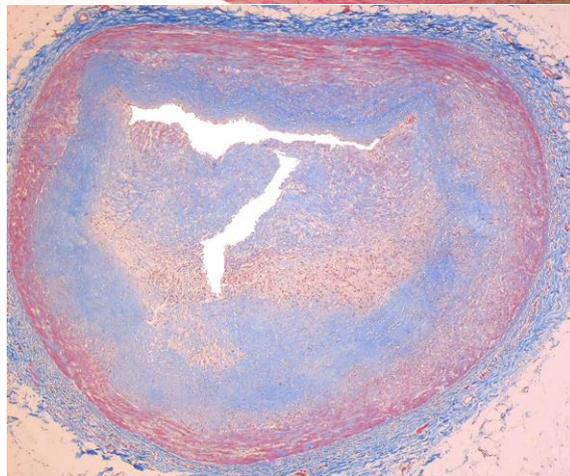
# Pathology abnormalities

## Bologna Heart Transplant Centre

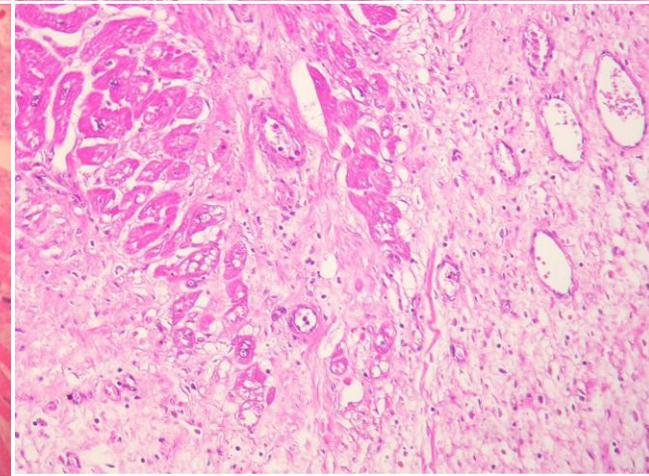
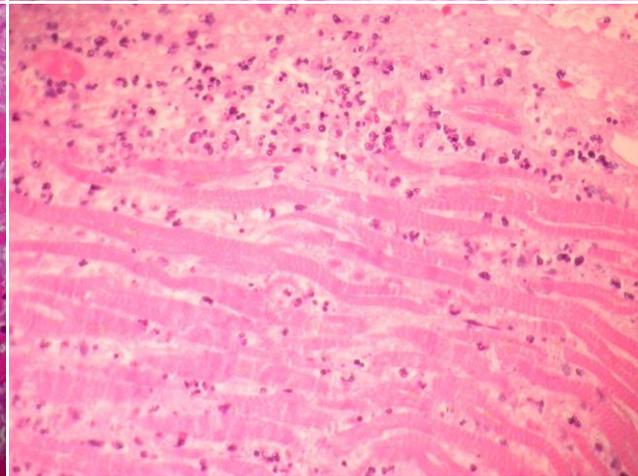
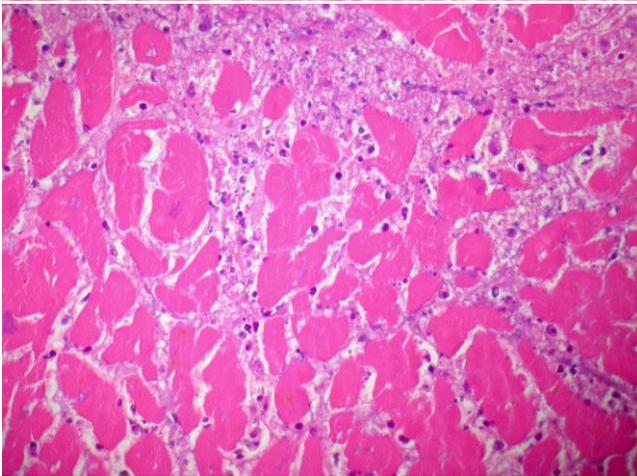
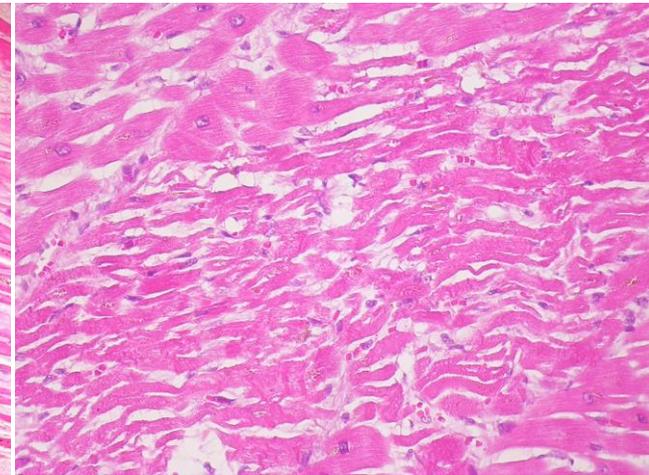
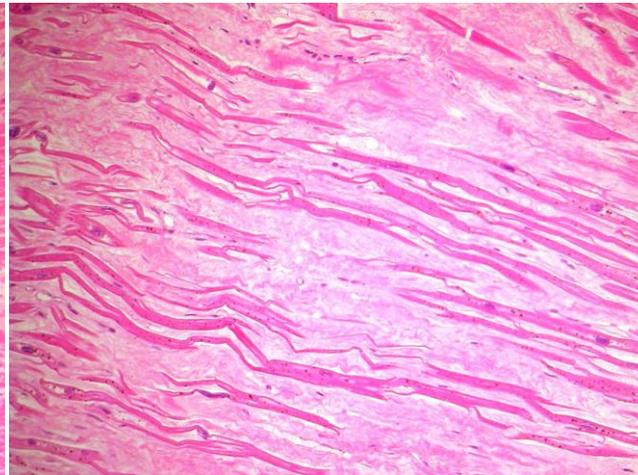
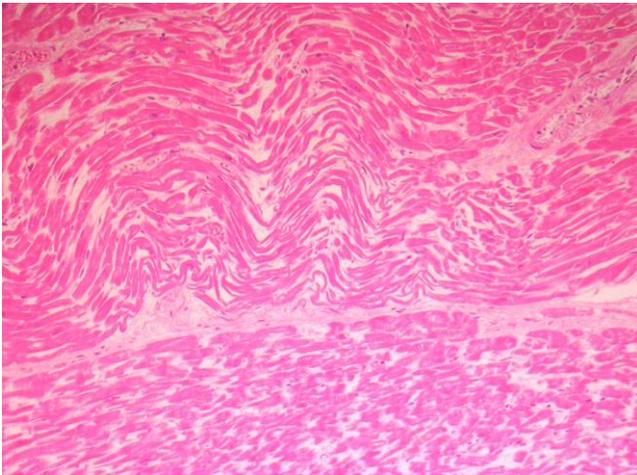
- **hearts with significant disease/damage (74%):**
  - pathologies pre-existing donation (54%)
  - pathologies arising during donation (20%)
- **hearts with no significant damage/pathologic findings (i.e. pathologically normal hearts) (26%)**



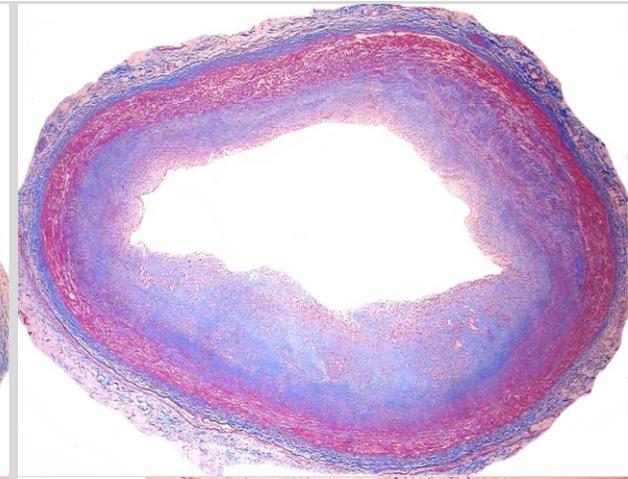
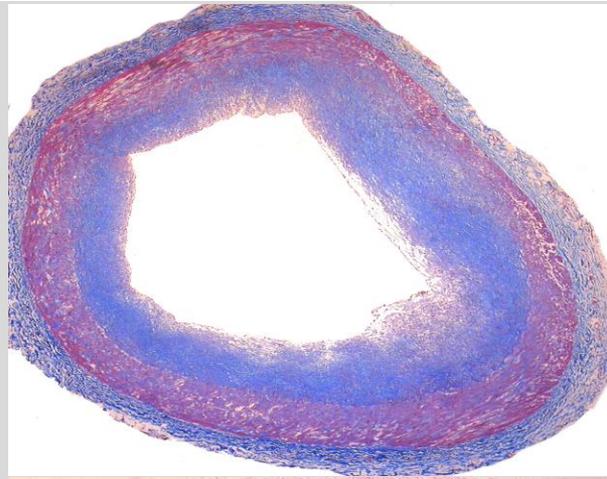
Major pre-existing disease:  
coronary artery  
atherosclerosis



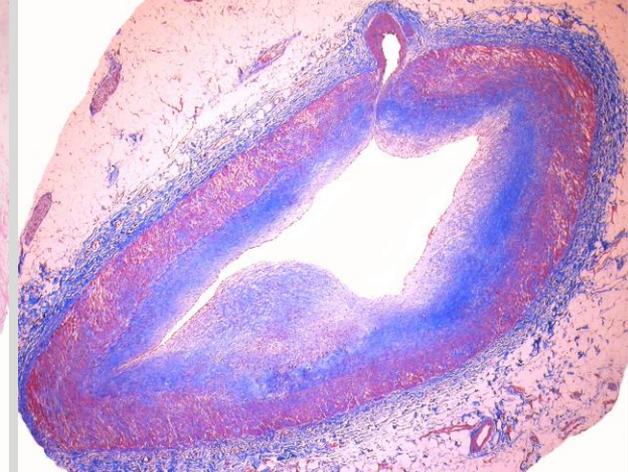
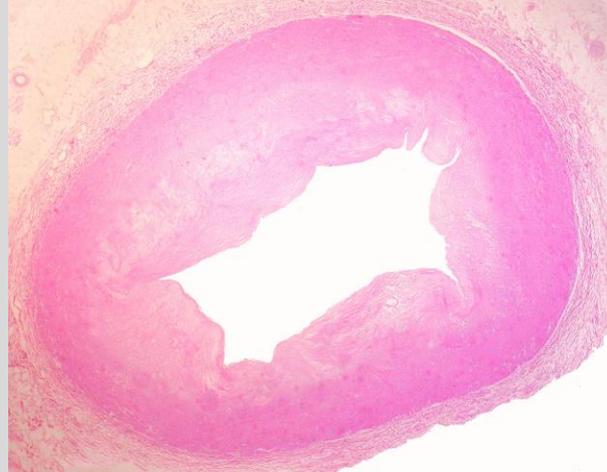
# myocardial signs of ischemia/hypoperfusion in varying degrees and stages of evolution



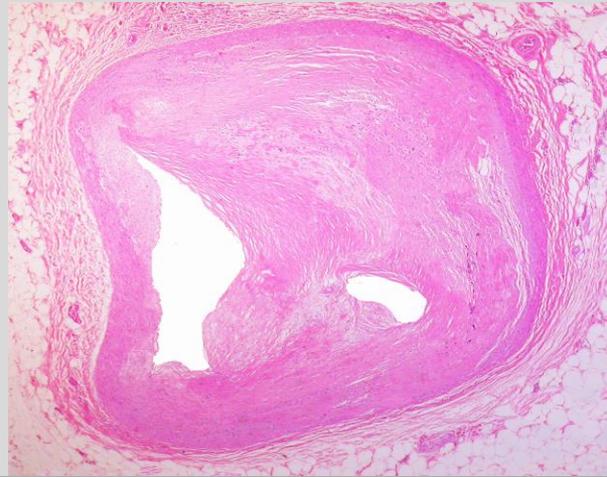
Mild: stenosis < 50%



Subcritical: stenosis 50-75%



Critical/significant:  
stenosis 75-100%





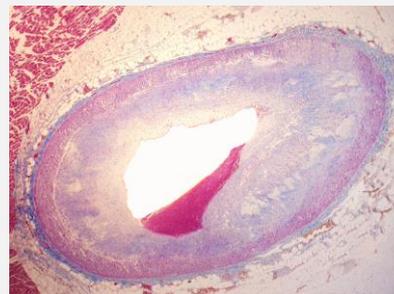
## Limitations of pathology examination of coronary atherosclerosis

non-physiological conditions of  
non-pressure-distended arteries

non-pressure-fixed vessels

inevitable collapse of the medial  
layer where it is uninvolved by  
eccentric plaque

Bologna Heart Transplant Centre  
Pathology of hearts excluded  
from donation



**36%: coronary artery atherosclerosis**

**Critical/significant stenosis (>75%)**

**33% of patients**

single coronary vessel (monovalsal)

70% of patients

double or triple vessel involvement

30% of patients

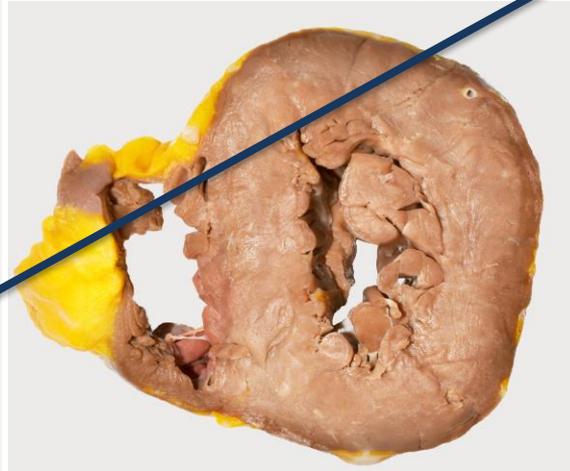
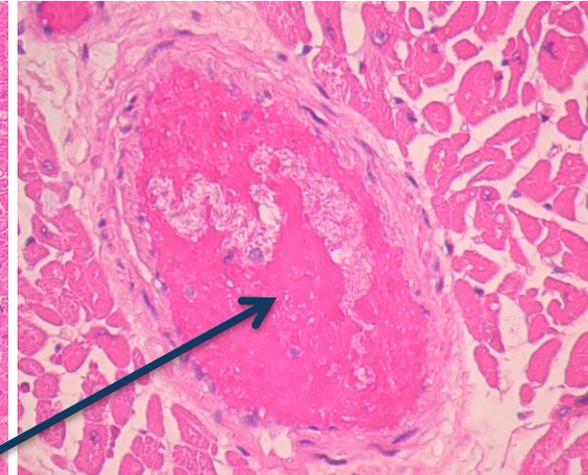
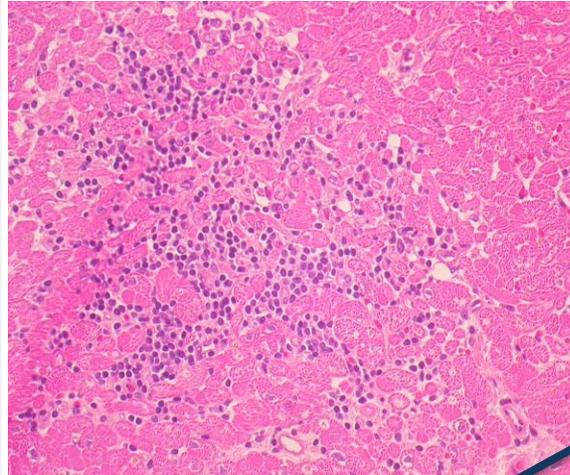
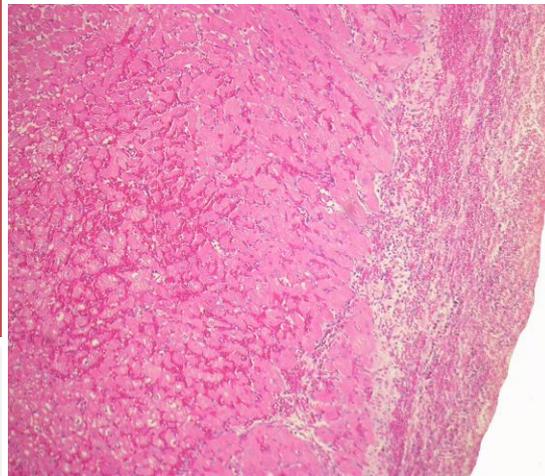
- 22.5% bivasal
- 7.5% trivasal

Median age of donors with significant CAD:  
51.3 years

Media age of the entire group:  
42 years

## Other pathologies pre-existing donation

- hypertensive heart disease
- cardiac trauma
- lymphocytic myocarditis
- myocardial bridging
- anomalous origin of coronary arteries
- an unusual case of diffuse microvascular thrombosis



# Damage attributable to events during donation

## **CATHECOLAMINE INJURY**

due to both

neurogenic stunned myocardium  
and inotropic therapy

# BRAIN DEATH

- *Am J Physiol.* 1992; 263: H784-H791
- *Circulation.* 1990; 82:723-738
- *J Heart Lung Transpl* 2004; 23: S217-22
- *Curr Neurol Neurosci Rep* 2009, 9: 486–491
- *J Am Coll Cardiol* 2010; 56: 352 -61

profound  
pathophysiological changes



“adrenergic storm”  
neuro-hormonal derangement

neurogenic stunned  
myocardium

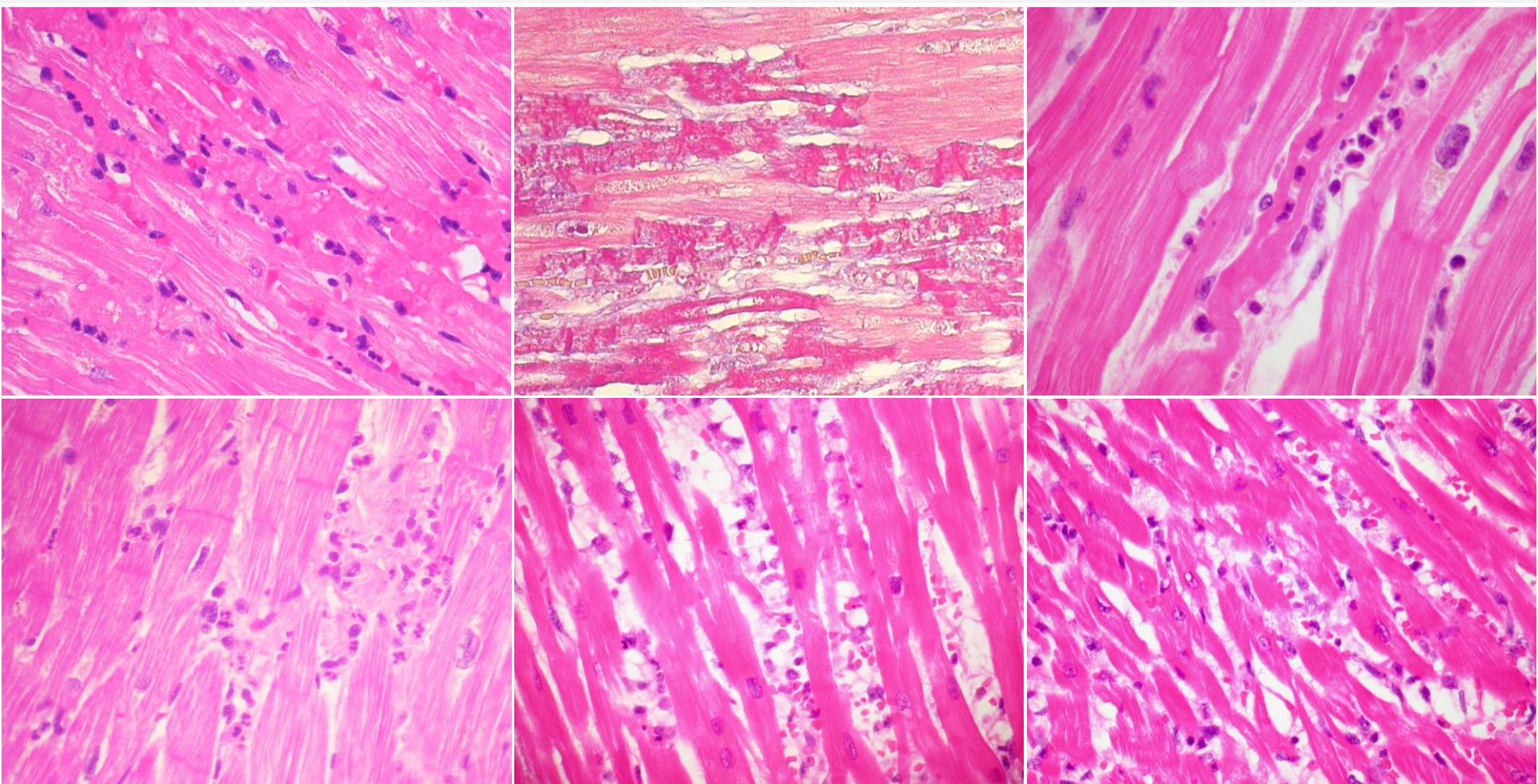


segmental or global  
myocardial  
dysfunction

stress-related myocardial microscopic multifocal necrosis



- contraction band necrosis or diffuse sarcoplasmic hyper-eosinophilia
- ruptured myocells
- real coagulative-type cardiomyocyte necrosis



- foci of toxic myocarditis: small aggregates of eosinophilic/fragmented myocells surrounded by scarce inflammatory infiltrates (macrophages, granulocytes, sporadic lymphocytes or mixed inflammation)

These small and typically multifocal  
necrotic-inflammatory lesions  
were present in a significant number of cases!

- in isolation
- as the main lesion in non altered hearts
- in association with other disease

PERSPECTIVE

**Is stress cardiomyopathy the underlying cause of ventricular dysfunction associated with brain death?**

Marius Berman, MD,<sup>a</sup> Ayyaz Ali, MRCS,<sup>a</sup> Euan Ashley, PhD, MD, FRCP,<sup>b</sup> Darren Freed, PhD, MD,<sup>c</sup> Kieran Clarke, PhD,<sup>d</sup> Steven Tsui, MD, FRCS,<sup>a</sup> Jayan Parameshwar, FRCP,<sup>a</sup> and Stephen Large, FRCP, FRCS<sup>a</sup>

- can these myocardial lesions underlying ventricular dysfunction associated with brain death be considered as an extreme variant of stress cardiomyopathy?
- if so, can they, like stress cardiomyopathy, be reversed?

Can we therefore expect recovery of the dysfunctional donor heart over time, thereby permitting increased use of hearts offered for transplantation?

## Summary of the major points emerging from the pathology data of the hearts

- coronary atherosclerosis is a major issue in older donors with a significant cardiovascular risk profile
- a significant number of hearts from younger donors with a low cardiovascular risk profile are pathologically normal and potentially suitable for acceptance
- the need for further research into the phenomenon of catecholamine-associated ventricular dysfunction and related myocardial damage which seems to be acquired during the process of brain death and donor management

*Berman M et al. J Heart Lung Transplant 2010; 29 (9): 957-65*

*Casartelli M et al. Cardiovascular Ultrasound 2012, 10: 25-32*

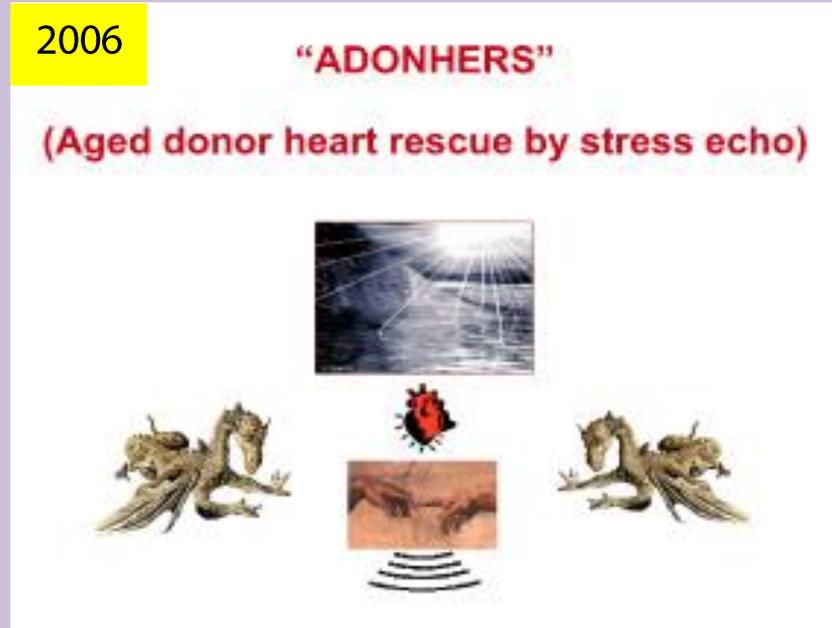
What practical use can we make  
of pathology information from these discarded hearts  
in order to improve criteria for accepting hearts?

# Bologna Heart Transplant Centre

2006

**“ADONHERS”**

**(Aged donor heart rescue by stress echo)**



screens marginal donors  
using pharmacological stress echocardiography  
to identify healthy donor hearts  
that would historically have been rejected  
due to patient age or transient left ventricular dysfunction

# Aged Donor Heart Rescue by Stress Echo Project Adonhers Protocol

## MARGINAL CANDIDATE DONORS

Patients aged > 50 years

or < 50 years with concomitant risk factors

- history of cocaine use
- three risk factors
  - hypertension
  - diabetes
  - smoking history
  - dyslipidemia
  - family history of premature coronary artery disease

# Candidate marginal donors (brain death)

# ADONHERS PROTOCOL

- regional wall motion
- global ventricular function
- ventricular mass

resting 2D echo

normal

dipyridamole  
dobutamine

stress echo

normal

Donor hearts

abnormal → excluded →

abnormal → excluded →

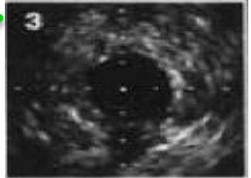
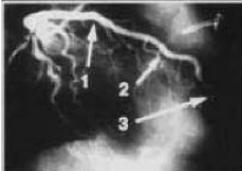


Heart transplantation

eligible hearts not used due to lack of a suitable recipient

pathologic substrate underlying the echo alterations

Angiography/IVUS at 1 month post-transplant

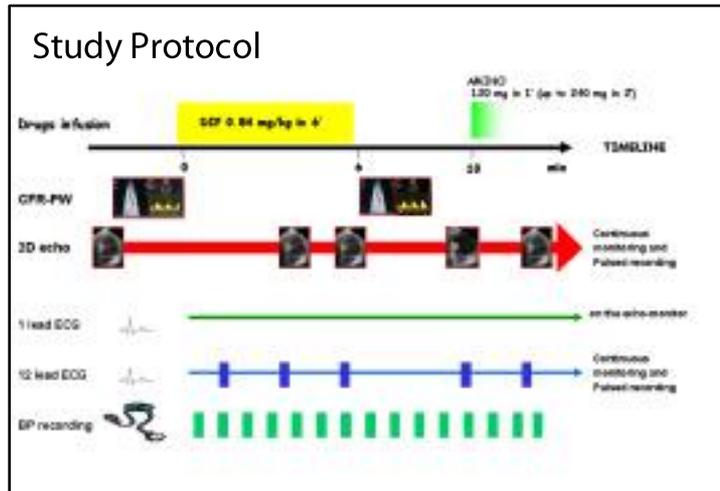


# ADONHERS

Eligible

CANDIDATE DONORS

Normal  
baseline echo



By coupling coronary flow and myocardial function stress echocardiography allows simultaneous evaluation of **inducible ischemia** (evaluated by wall motion score index = WMSI) and **contractile reserve of the left ventricle** (evaluated by pressure volume relationship = PVR)



European Heart Journal (2007) 28, 1425–1432  
doi:10.1093/eurheartj/ehm082

Clinical research  
Imaging

**Assessment of the contractile reserve in patients with intermediate coronary lesions: a strain rate imaging study validated by invasive myocardial fractional flow reserve**

Frank Weidemann\*, Philip Jung, Caroline Hoyer, Jens Broscheit, Wolfram Voelker, Georg Ertl, Stefan Störk, Christiane E. Angermann, and Joerg M. Strotmann

Medical Clinic II/Center of Cardiovascular Disease, University of Würzburg, Josef-Schneider Str. 2, D 20, 97080 Würzburg, Germany

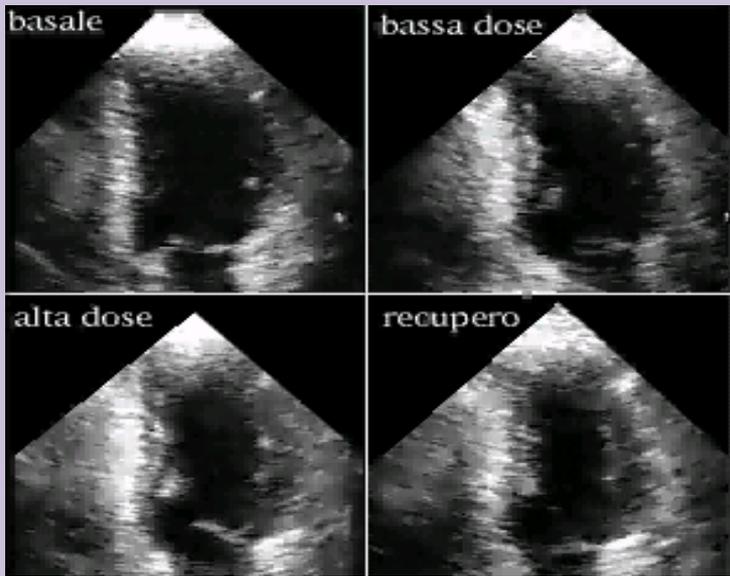
J Am Soc Echocardiogr  
2011; 24: 363-6

Editorial Comment

**Pharmacologic Stress Echocardiography for the Assessment of Organ Suitability for Heart Transplantation: Casting a Broader Net in Search of Donors**

Nowell M. Fine, MD, and Patricia A. Pellikka, MD, FASE, Rochester, Minnesota

# ADONHERS



NO INDUCIBLE ISCHEMIA: WMSI = 1



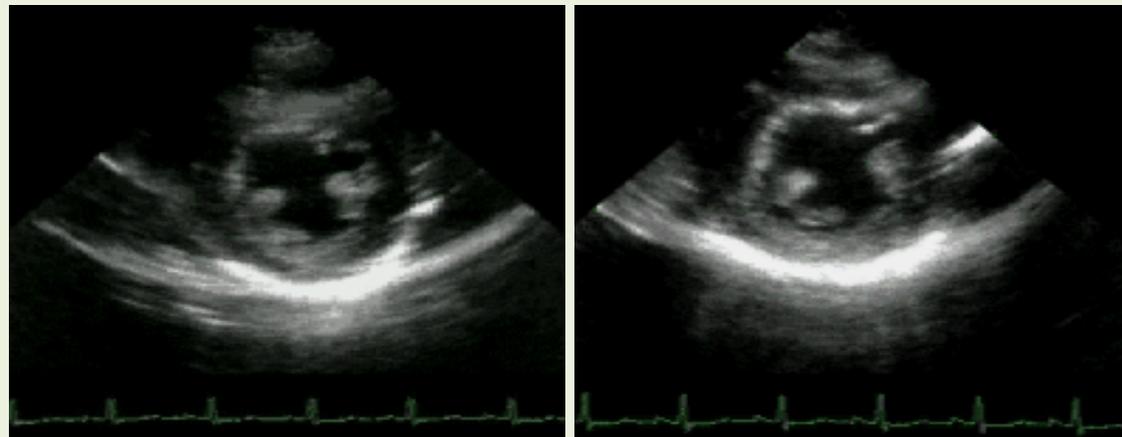
*Heart accepted*

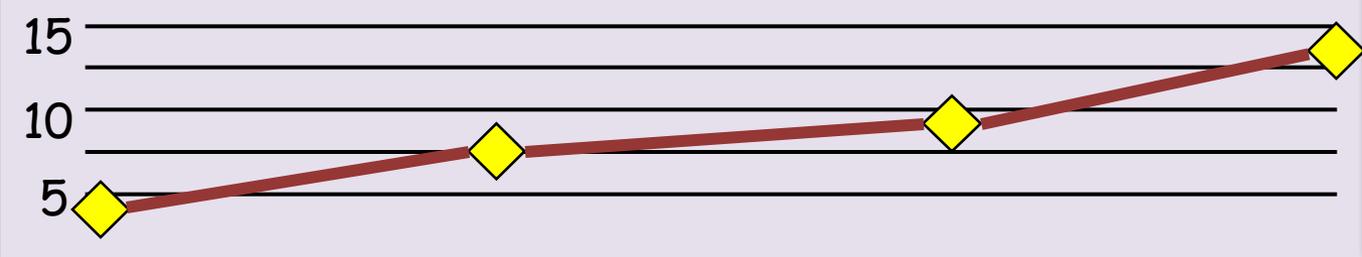
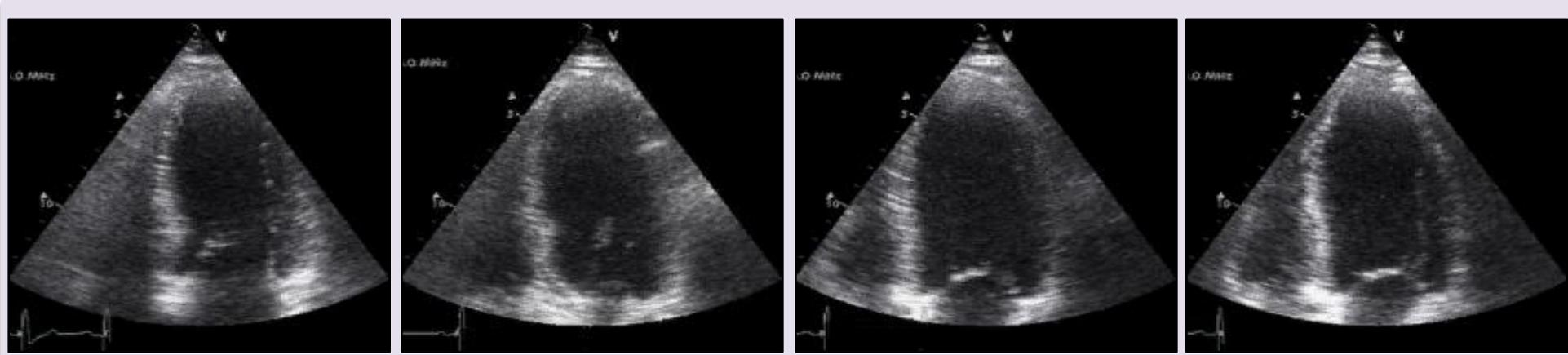
INDUCIBLE ISCHEMIA:  
WMSI > 1

*Heart excluded*

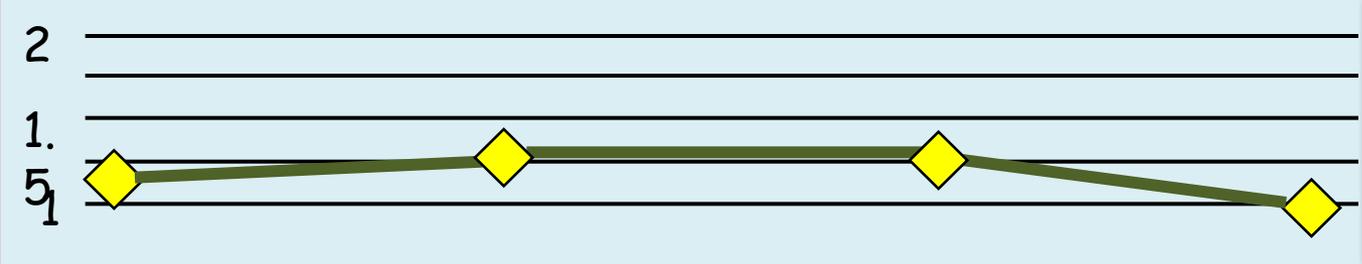
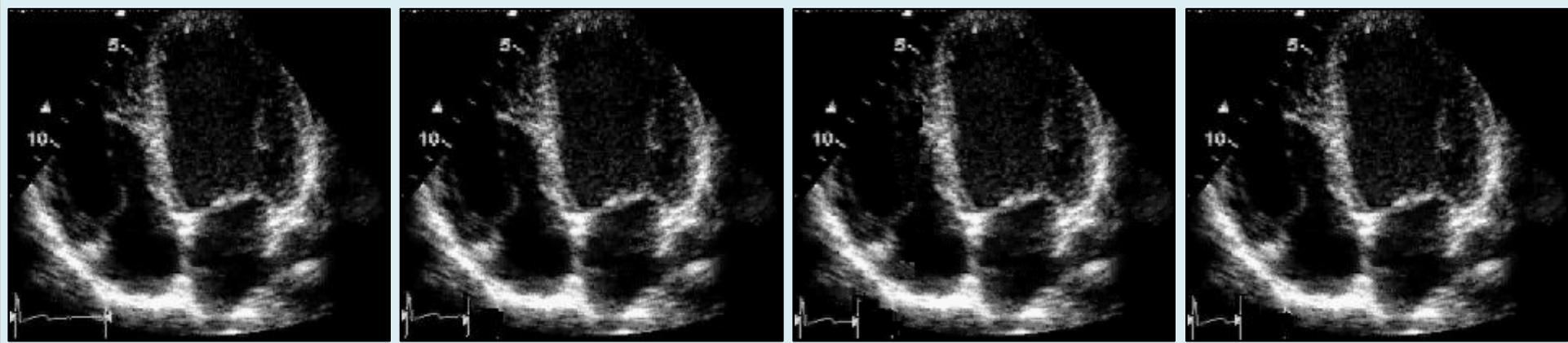
rest

peak





Normal contractile reserve (up-sloping PVR): **HEART ACCEPTED**



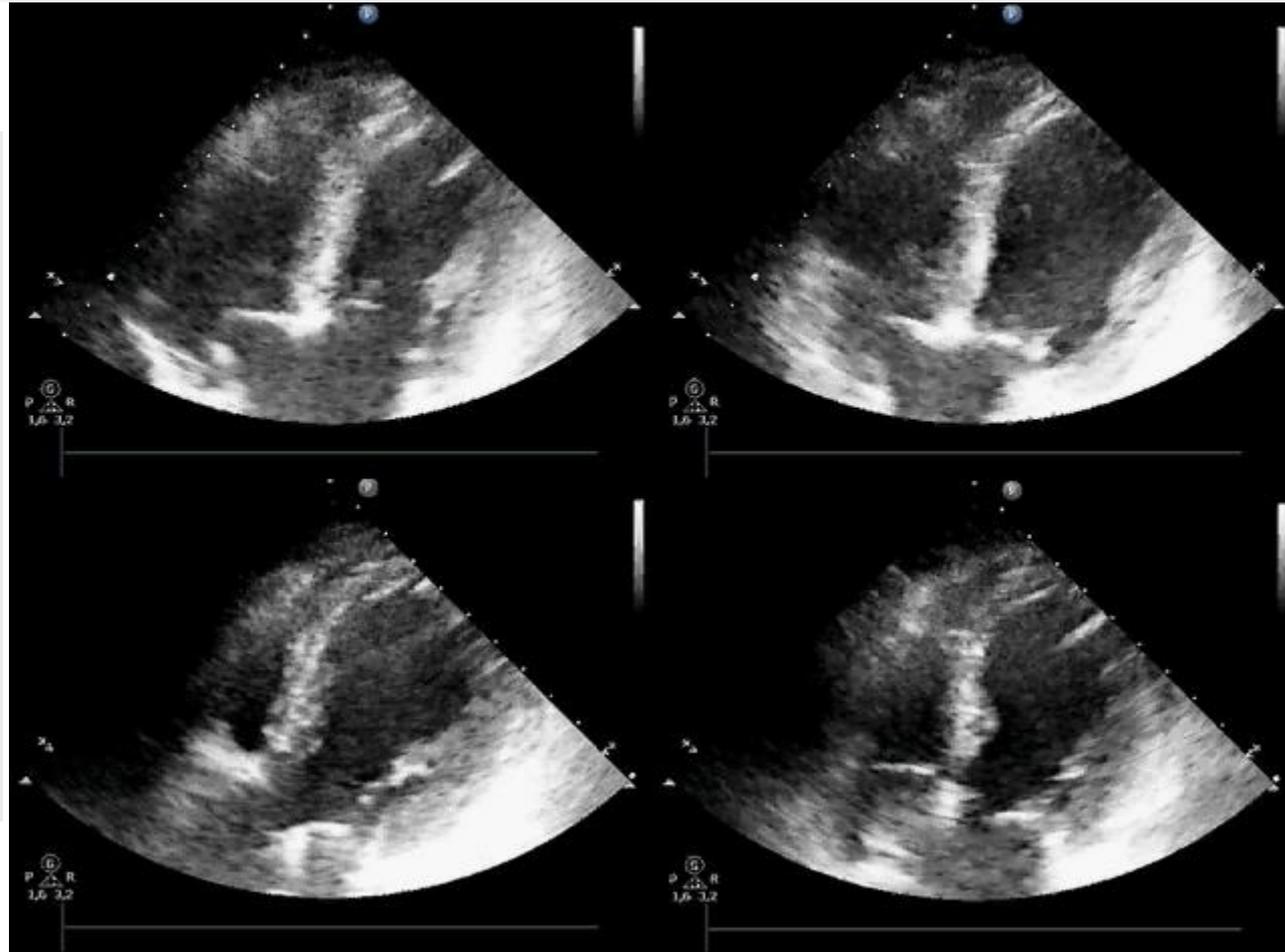
Abnormal contractile reserve (flat-negative PVR): **HEART EXCLUDED**

# Patient

Female donor  
of 50 years

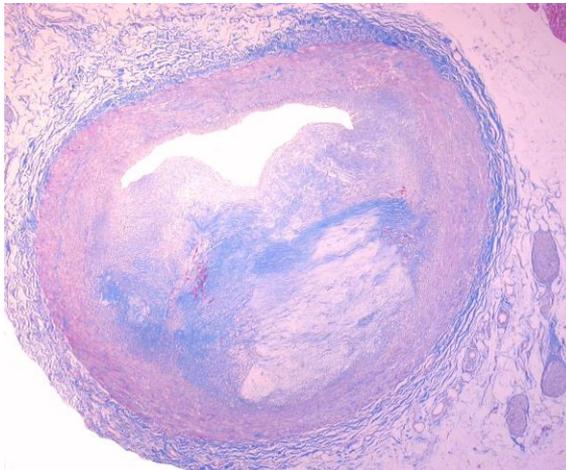
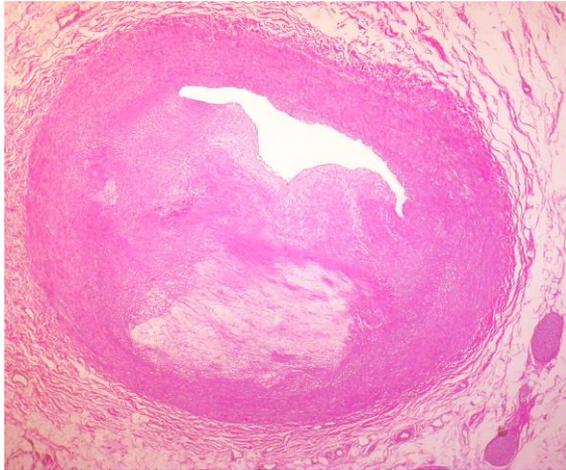
# Stress-echo

hypo-akinesia  
of the left ventricle mid-apical portion



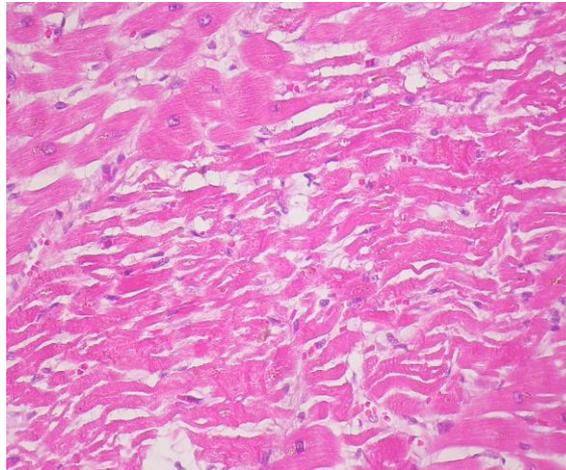
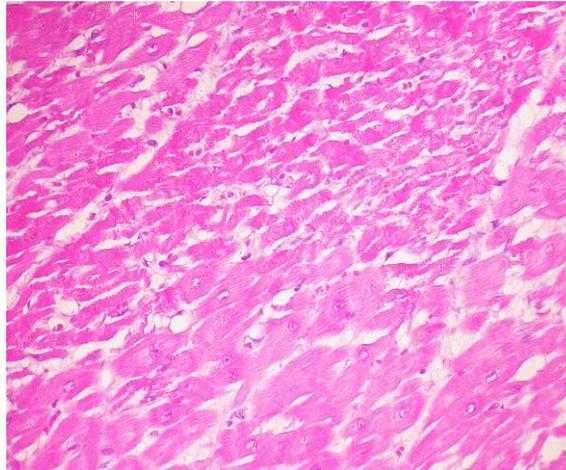
## Coronary atherosclerosis

Fibro-lipidic plaque narrowing around 90% of LAD lumen



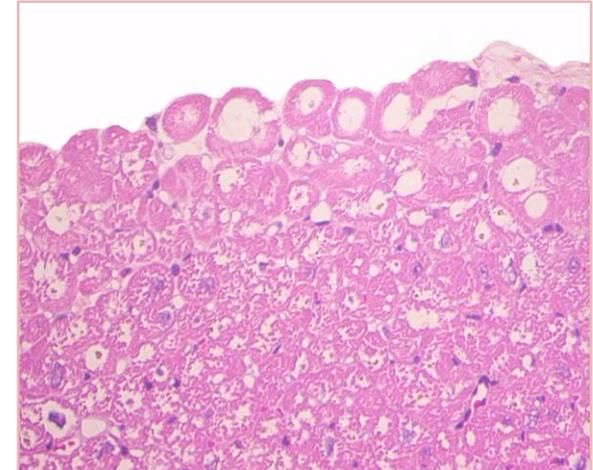
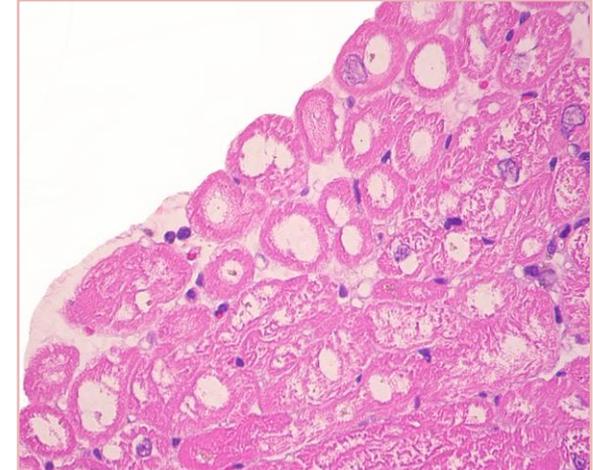
## Myocardial coagulative necrosis

Multifocal myocardial coagulative necrosis irregularly distributed in LV and IVS



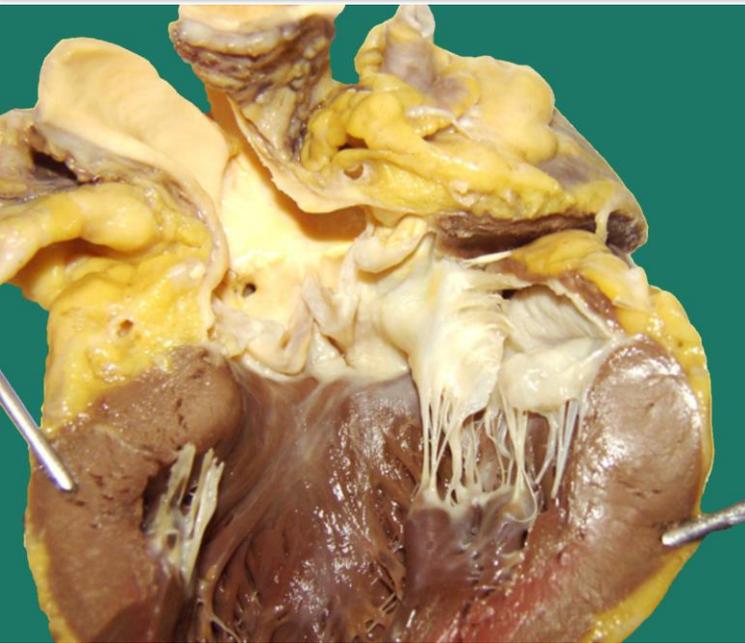
## Other histopathologic lesions

Diffuse coagulative subendocardial myocytolysis



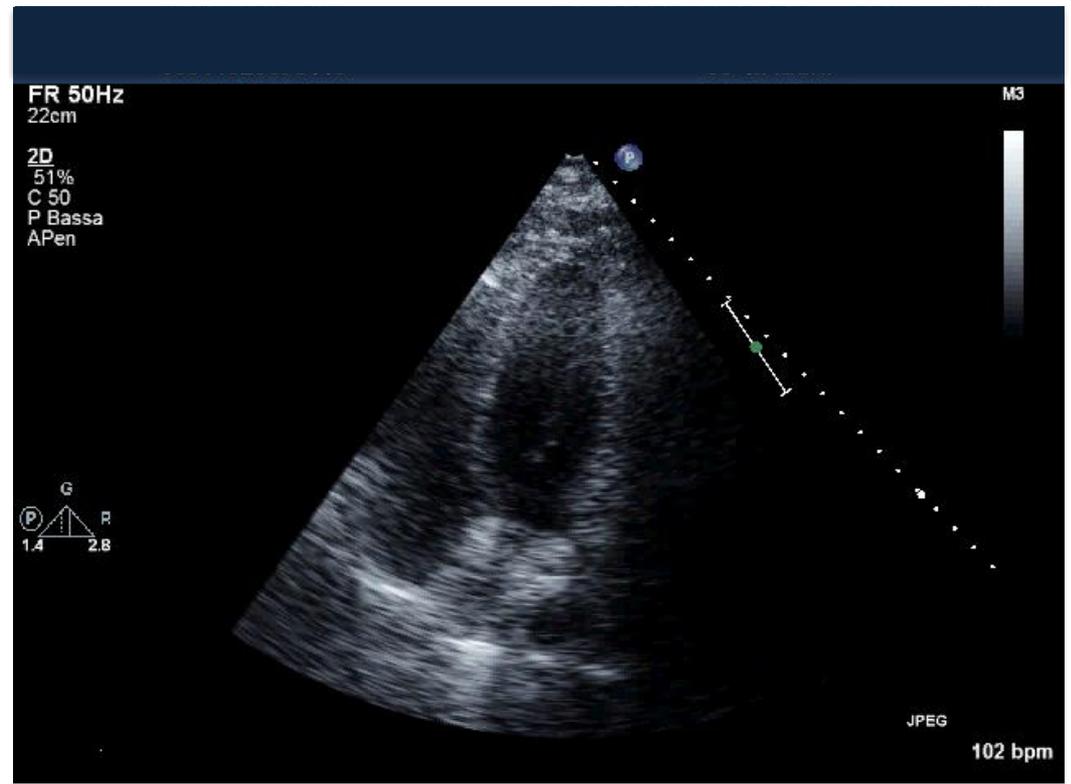
# Patient

Male donor of 59 years



# Stress-echo

Stress-induced inferior wall motion



## Coronary atherosclerosis

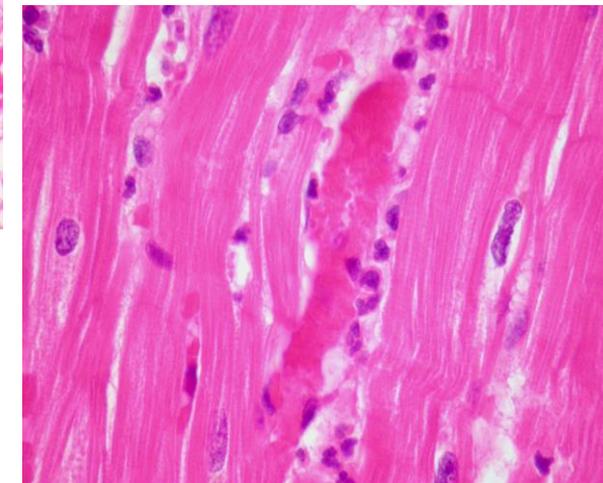
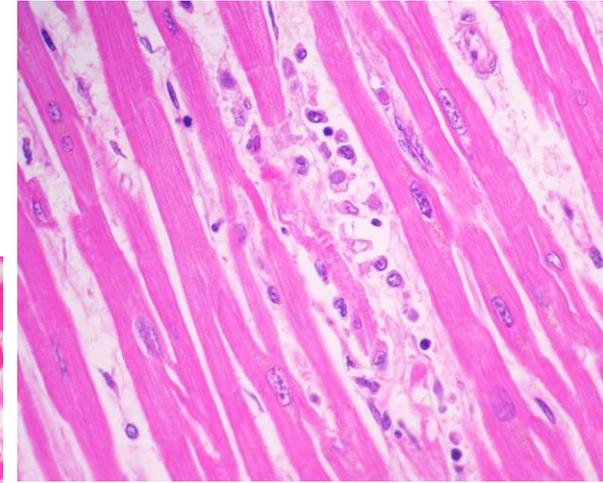
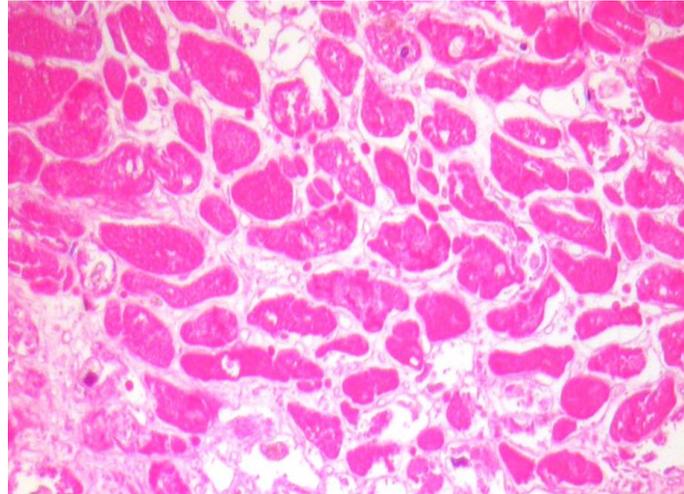
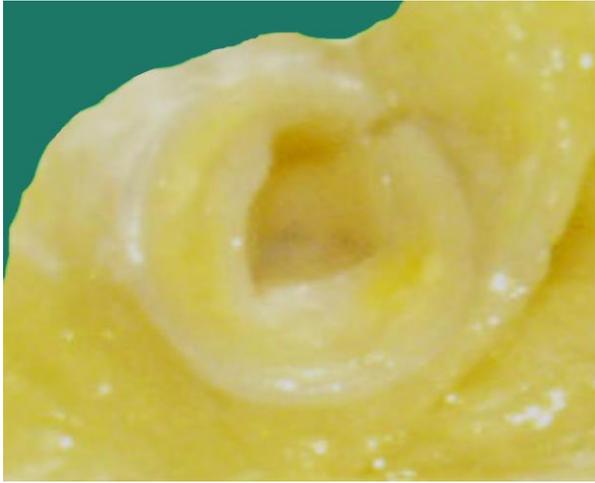
60% right coronary artery stenosis

## Myocardial ischemic necrosis

inferior LV papillary muscle

## Other histopathologic lesions

diffuse catecholamine necrosis



## Stress Echocardiography as a Gatekeeper to Donation in Aged Marginal Donor Hearts: Anatomic and Pathologic Correlations of Abnormal Stress Echocardiography Results

Ornella Leone, MD,<sup>a</sup> Sonia Gherardi, MD,<sup>b</sup> Luigi Targa, MD,<sup>c</sup> Emilio Pasanisi, MD,<sup>d</sup> Piero Mikus, MD,<sup>c</sup> Piero Tanganelli, MD,<sup>f</sup> Massimo Maccherini, MD,<sup>g</sup> Giorgio Arpesella, MD,<sup>c</sup> Eugenio Picano, MD,<sup>d</sup> and Tonino Bombardini, MD, PhD<sup>d</sup>

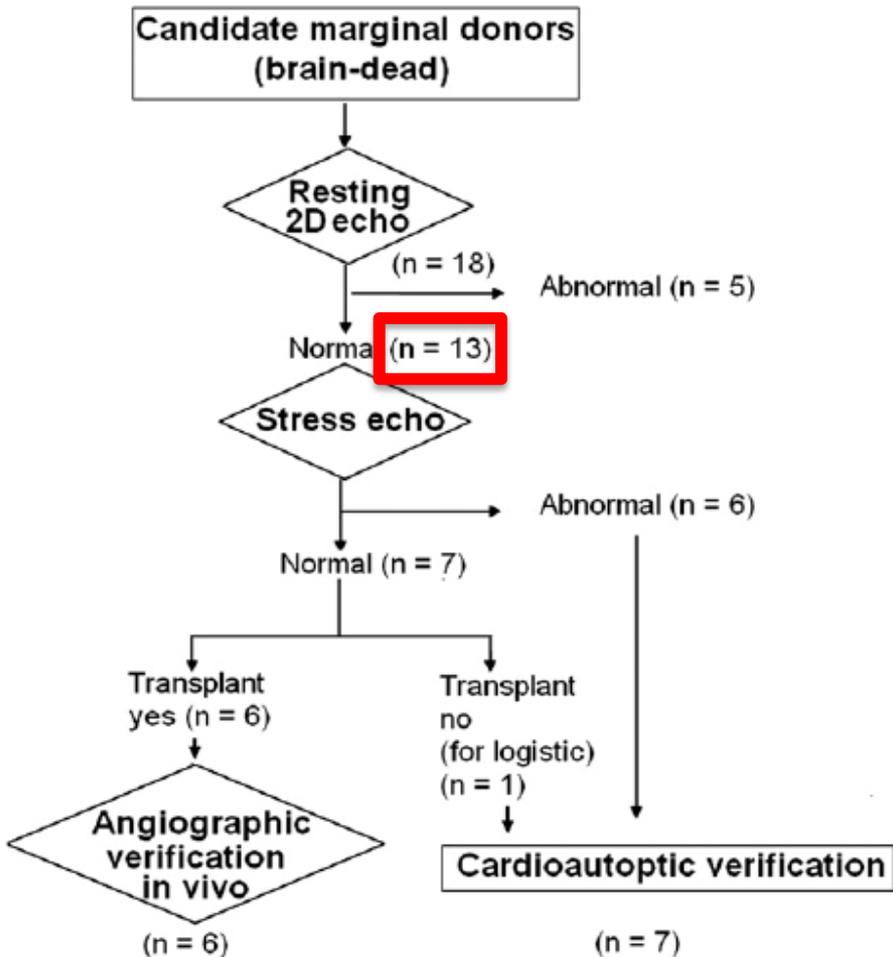


Figure 1. Study flow chart.

6 hearts excluded from donation  
due to positive stress-echo

N. 5  
moderate to severe  
CAD

N. 1  
possible idiopathic  
dilated  
cardiomyopathy

N. 6  
successfully transplanted

Subsequent studies on short and medium-term outcome of recipients of marginal donor hearts selected with pharmacological stress-echocardiography showed favourable results with survival rates similar to that of recipients of standard donor hearts

## Bologna Heart Transplant Centre

### CLINICAL INVESTIGATIONS STRESS ECHOCARDIOGRAPHY

#### Favorable Short-Term Outcome of Transplanted Hearts Selected from Marginal Donors by Pharmacological Stress Echocardiography

Tonino Bombardini, MD, PhD, Sonia Gherardi, MD, Giorgio Arpesella, MD, Massimo Maccherini, MD, Walter Serra, MD, Gaia Magnani, MD, PhD, Riccarda Del Bene, MD, and Eugenio Picano, MD, PhD,  
*Pisa, Cesena, Bologna, Siena, and Florence, Italy*

Bombardini *et al. Cardiovascular Ultrasound* 2014, **12**:20  
<http://www.cardiovascularultrasound.com/content/12/1/20>



### RESEARCH

Open Access

#### Medium-term outcome of recipients of marginal donor hearts selected with new stress-echocardiographic techniques over standard criteria

Tonino Bombardini<sup>1\*</sup>, Giorgio Arpesella<sup>2</sup>, Massimo Maccherini<sup>3</sup>, Francesco Procaccio<sup>4,5</sup>, Luciano Potena<sup>6</sup>, Sonia Bernazzali<sup>3</sup>, Ornella Leone<sup>7</sup> and Eugenio Picano<sup>1</sup>

Pathology data  
from 66  
discarded hearts

Donor scoring system  
assessed by the  
Eurotransplant International  
Foundation



J Heart Lung Transplant 2012;  
31: 387–97

The Journal of  
Heart and Lung  
Transplantation  
<http://www.jhltonline.org>

**Donor scoring system for heart transplantation and the  
impact on patient survival**

Jacqueline M. Smits, MD, PhD,<sup>a</sup> Michel De Pauw, MD, PhD,<sup>b</sup> Erwin de Vries, MSc,<sup>a</sup>  
Axel Rahmel, MD,<sup>a</sup> Bruno Meiser, MD, PhD,<sup>c</sup> Guenther Laufer, MD, PhD,<sup>d</sup> and  
Andreas Zuckermann, MD, PhD<sup>d</sup>

*From the <sup>a</sup>Eurotransplant International Foundation Leiden, Leiden, The Netherlands; <sup>b</sup>Department of Cardiology, University Hospital Ghent, Ghent, Belgium; <sup>c</sup>Department of Thoracic Surgery, Hospital Grosshadem Ludwig-Maximilian University, Munich, Germany; and <sup>d</sup>Department of Thoracic Surgery, University Hospital, Vienna, Austria.*

## Donor scoring system

10 pre-procurement variables:

- age
- cause of death
- donor history of either malignancy, sepsis, drug abuse, meningitis or positive virology
- status (HBsAg, HBcAb, anti-cytomegalovirus)
- donor history of hypertension
- cardiac arrest
- echocardiographic and coronary angiogram findings
- serum sodium value
- doses of noradrenaline
- combined dose of dopamine and dobutamine

## Donor classification

- low-risk donors (LRDs:  $<17$  points)
- high-risk donors (HRDs:  $\geq 17$  points)

# PATHOLOGY EXAMINATION

majority of the unused hearts

a subset of the unused hearts

significant heart disease: 81%

no significant pathological features:  
**19%**

- CAD: 44%
- myocardial injury of variable etiology: 37%

Acceptability criteria for heart donation  
could be improved

in order to identify a subgroup of potentially healthy useable hearts

# CONCLUSION

Routine pathology evaluation of discarded hearts and correlation of pathology findings with clinical data could be one relatively simple means to improve current criteria for accepting hearts

Sharing protocols within single transplant centers could provide additional information with little effort

Sant'Orsola Academica Hospital



Cardio-Thoraco-Vascular Department



## Heart transplant team

### **Cardiac Surgery**

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Emanuele Pilato  
Davide Pacini  
Sofia Martin Suarez  
Antonio Loforte

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Luciano Potena  
Gaia Magnani  
Antonio Russo  
Marco Masetti  
Valentina  
Manfredini

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Barbara Corti  
Valentina Agostini

### **Immunogenetics**

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Fiorenza Fruet  
Sandra Iannelli