

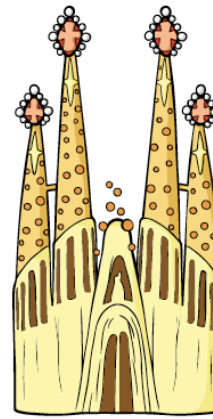
THE CATALAN
TRANSPLANTATION
SOCIETY



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

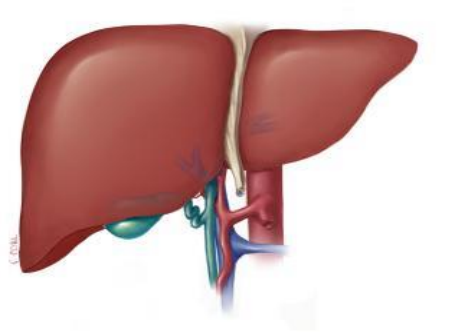
histologic scoring to evaluate the sum of

- 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

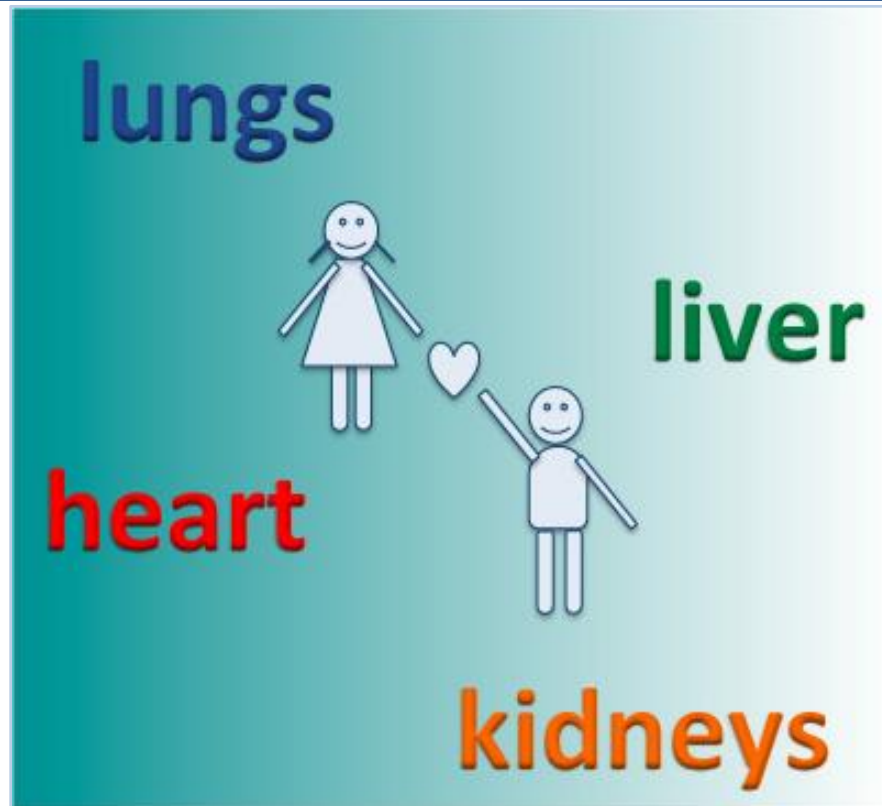
D'Alessandro AM 1991
Markin RS 1993



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

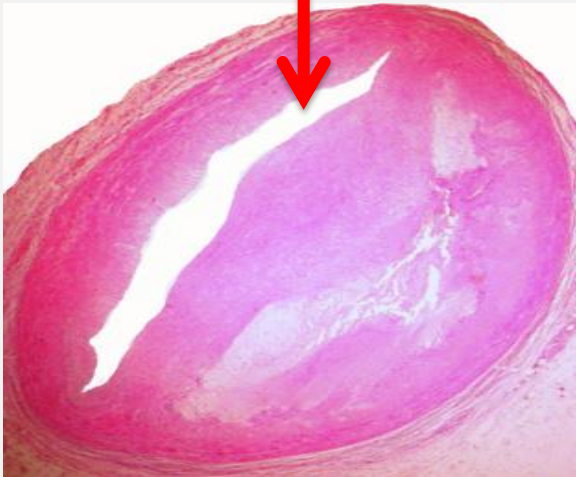


HEART TRANSPLANTATION

two additional aspects

DONOR AGE

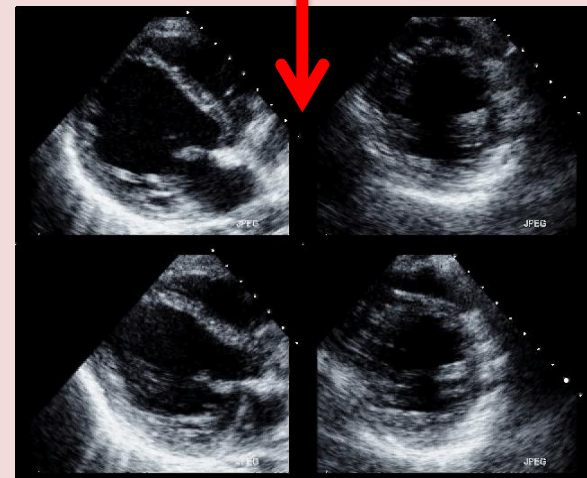
closely related to
age-dependent risk of
transmission of donor
subclinical diseases



coronary artery atherosclerosis

EFFECTS

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



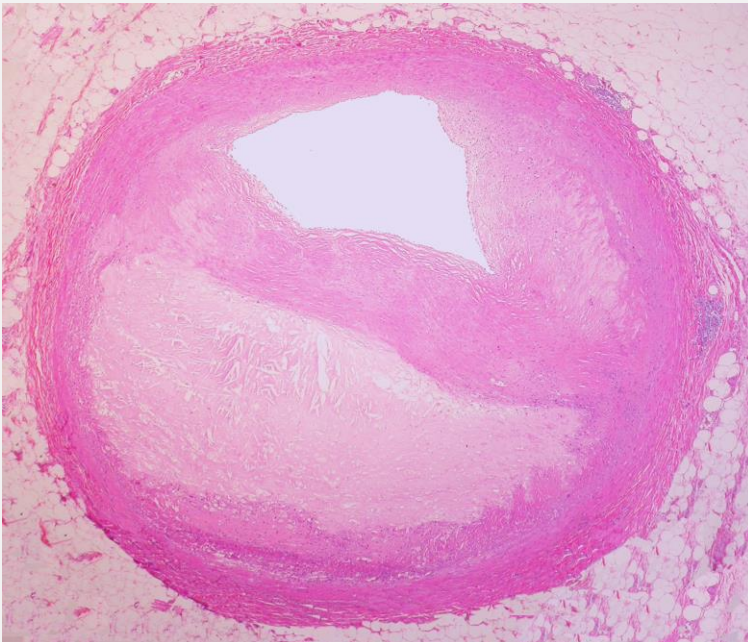
with largely mechanical properties

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

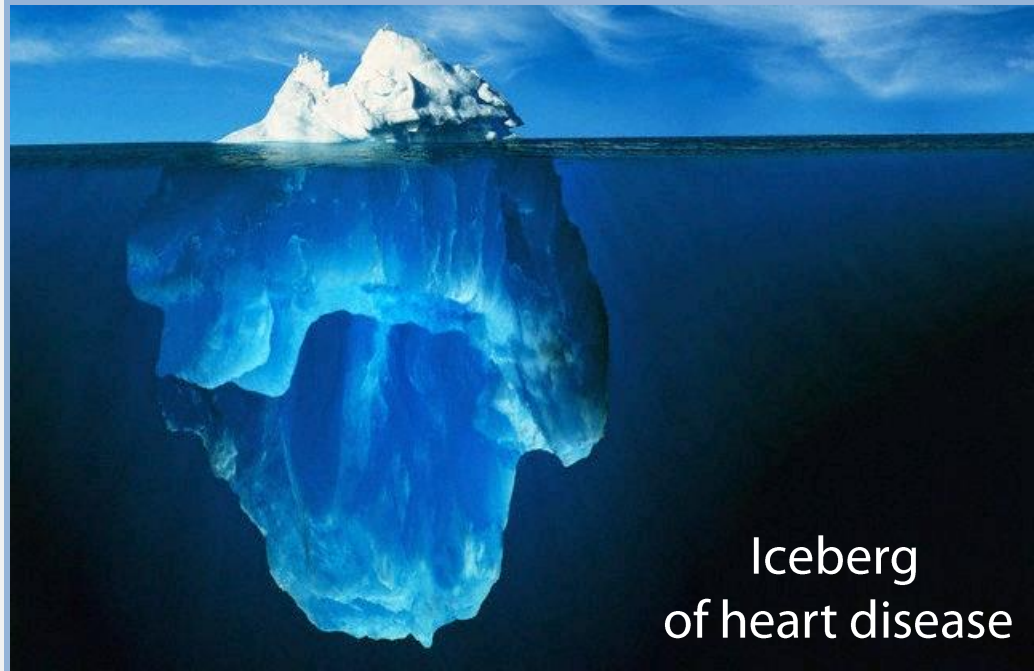
Potential heart donor candidates	36.9%
Hearts ultimately used for transplantation	64.6%

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



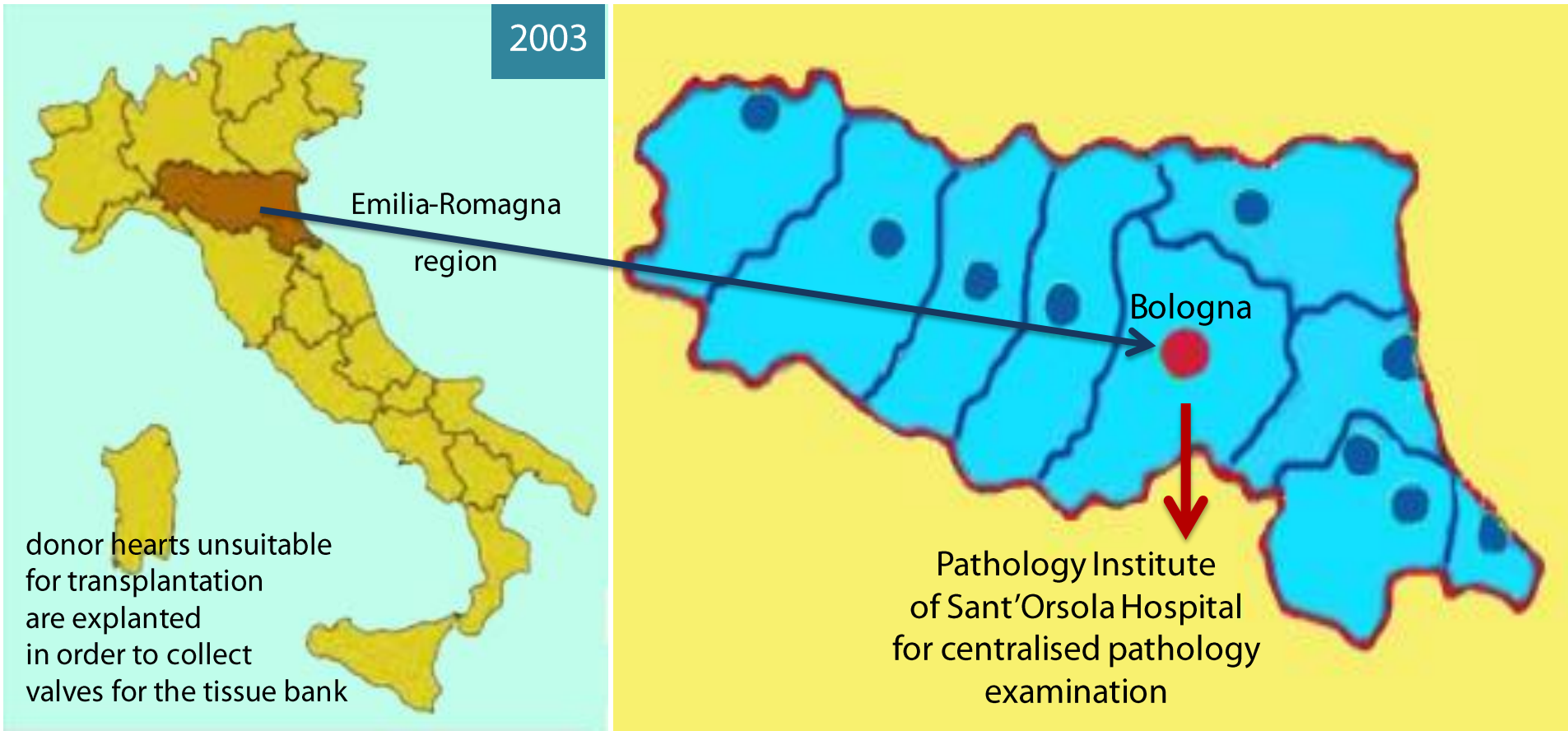
Doroshow RW et al. Availability and selection of donors for pediatric heart transplantation.
J Heart Lung Transplant 1995; 14 : 52-8

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

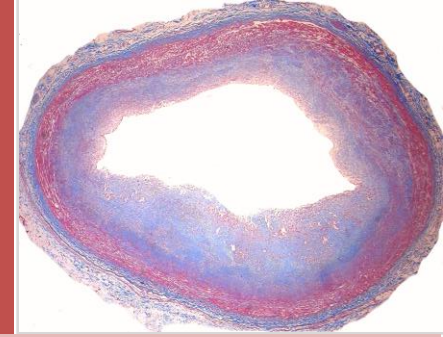
- multi-tissue donors: 35.5%
- multi-organ donors (at least one organ offered or transplanted): 64.7%



the heart was judged unsuitable for transplantation

- anamnesis results
- after clinical-instrumental evaluation

Protocols for pathology examination of hearts unsuitable for transplantation



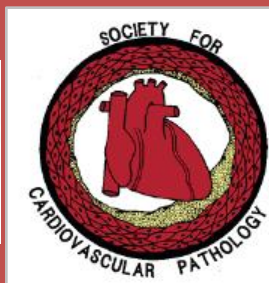
Cardiovasc Pathol 2012; 21: 2-16

CARDIOVASCULAR
PATHOLOGY

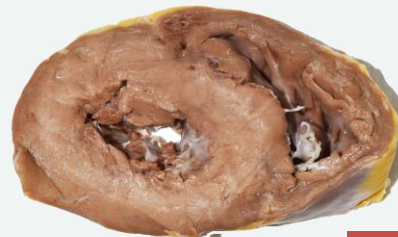
Original Article

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^{a,*}, Cristina Basso^{b,**}, Ulrik T. Baandrup^c, Patrick Bruneval^d, Jagdish Butany^e, Patrick J. Gallagher^f, Marc K. Halushka^g, Dylan V. Miller^h, Robert F. Paderaⁱ, Stanley J. Radio^j, Mary N. Sheppard^k, Kim Suvanna^l, Carmela D. Tan^m, Gaetano Thieneⁿ, Allard C. van der Wal^o, John P. Veinot^o



incomplete



fragmented



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

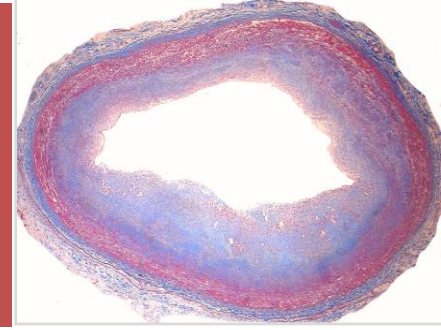
REVIEW AND PERSPECTIVE

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*



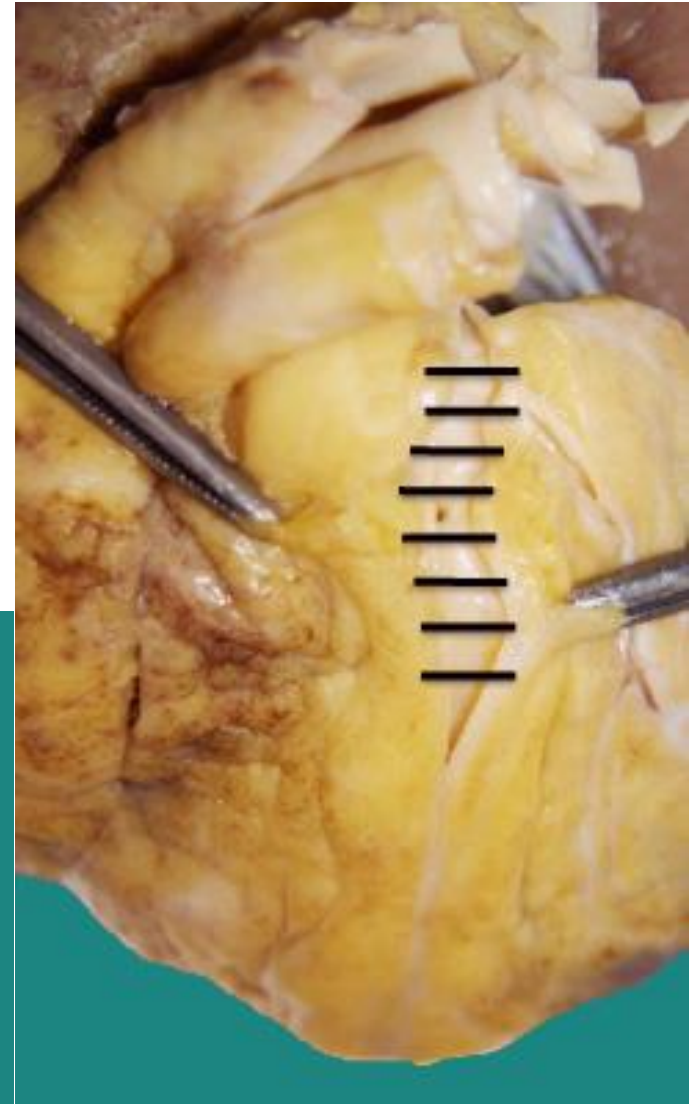
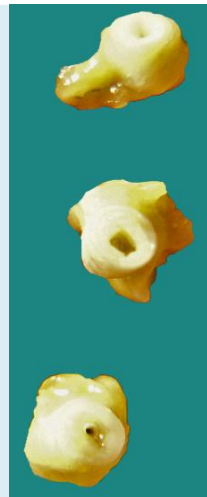
Protocols for pathology examination of hearts unsuitable for transplantation



Non-pressure-fixed
main subepicardial coronary arteries

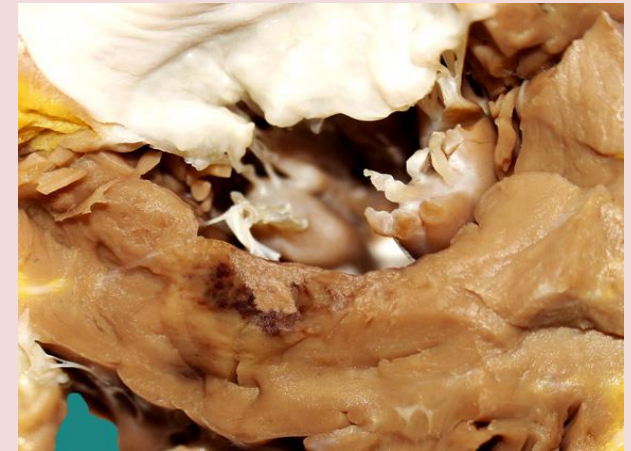
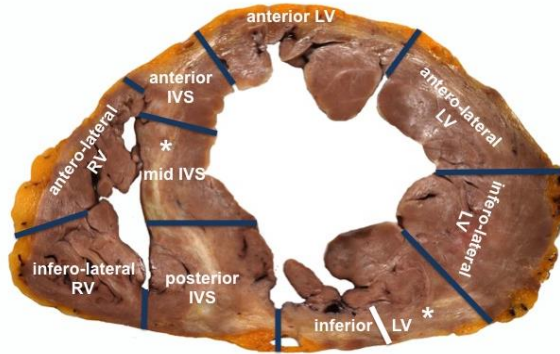
- left main
- left anterior descending
- left obtuse marginal and circumflex branches
- right coronary

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



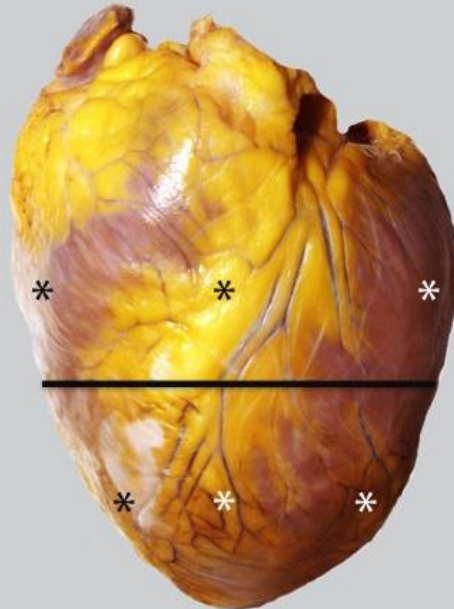
Pathology examination of hearts unsuitable for transplantation SAMPLING

entire
representative
transverse slice
of the heart

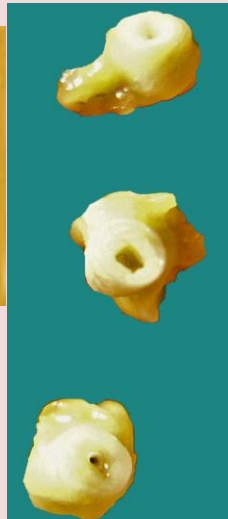


all macroscopically
altered areas

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)	
<ul style="list-style-type: none">65% males; 35% femalesmedian 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%

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

Age: 17.8%

Haemodynamic instability/hypotension:
16.8%

Surgical examination: 13.1%

Lack of recipients: 3.7 %

② Hearts excluded after Intensive Care Unit screening: 61.7%

Cardiac arrest mainly following road accident:
50%

Cardiac arrest due to sudden death: 15.8%

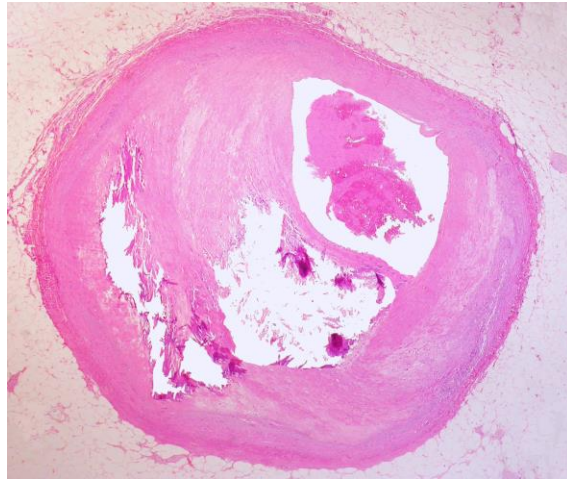
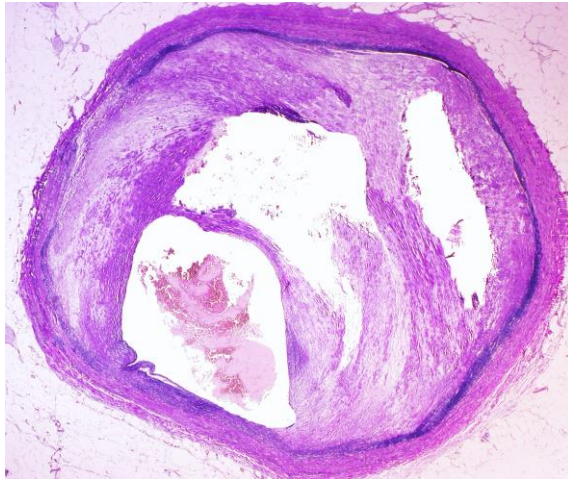
Heart pathology known on the basis of
anamnestic data: 28%

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

Pathology abnormalities

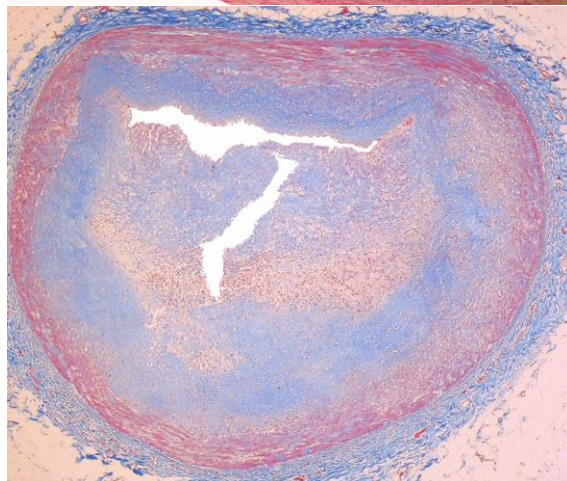
Bologna Heart Transplant Centre

- **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%)

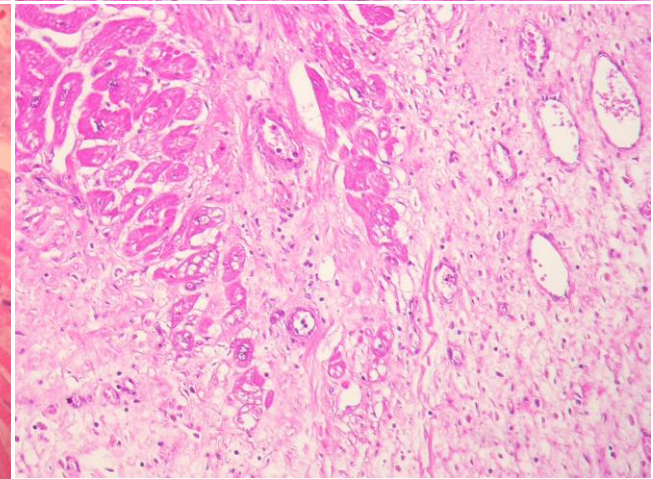
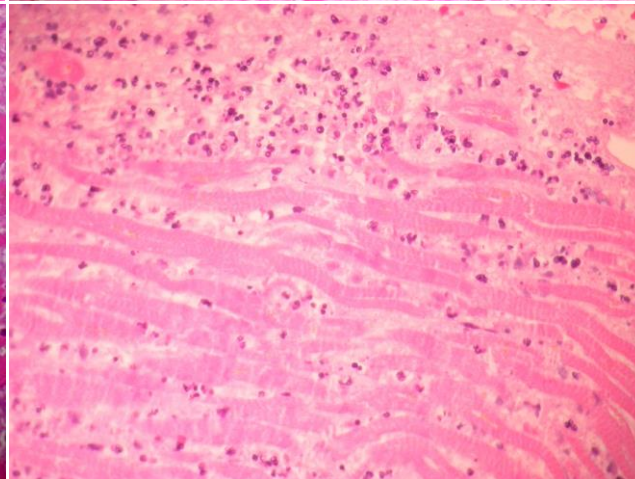
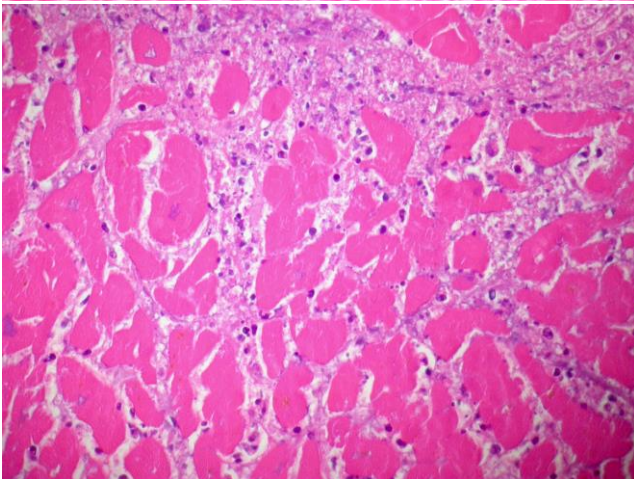
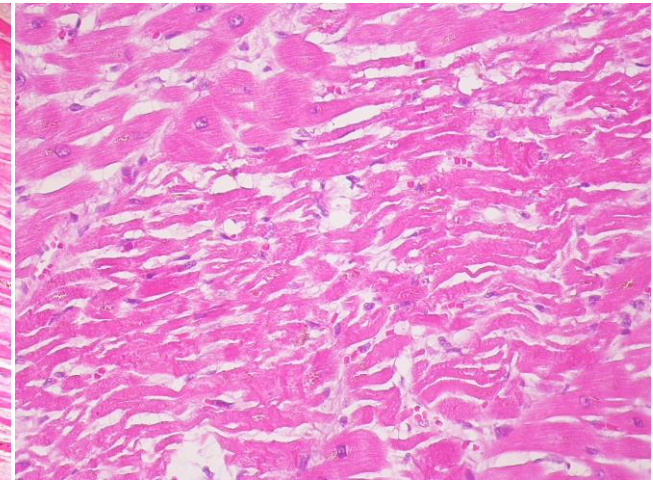
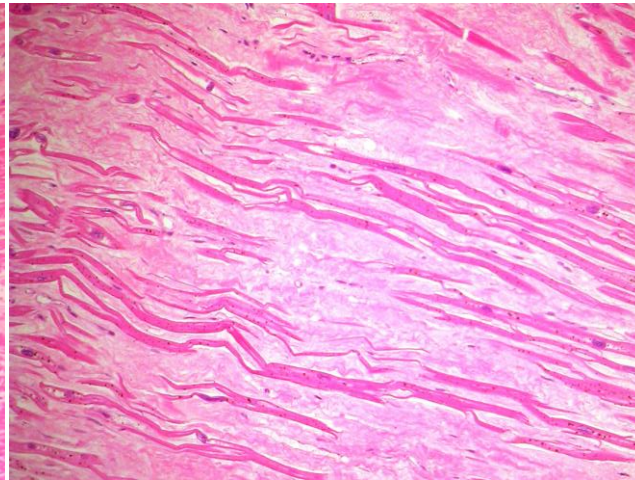
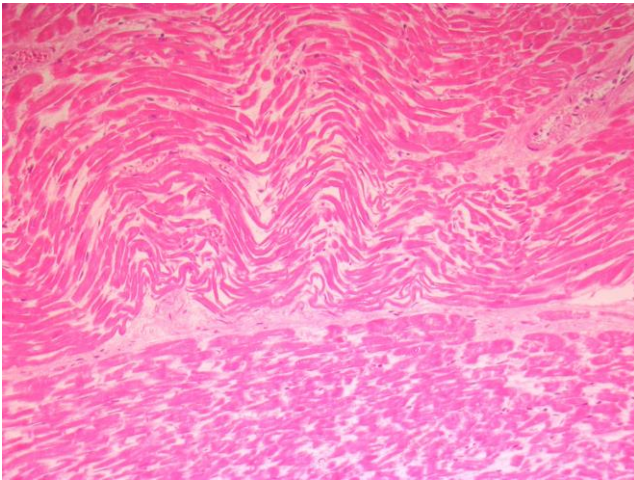


Major pre-existing
disease:

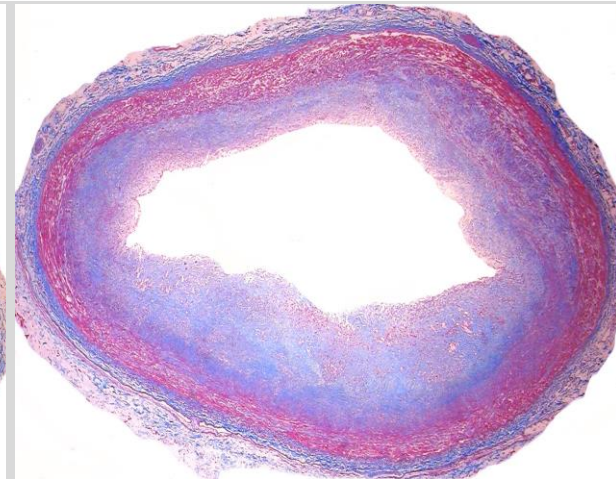
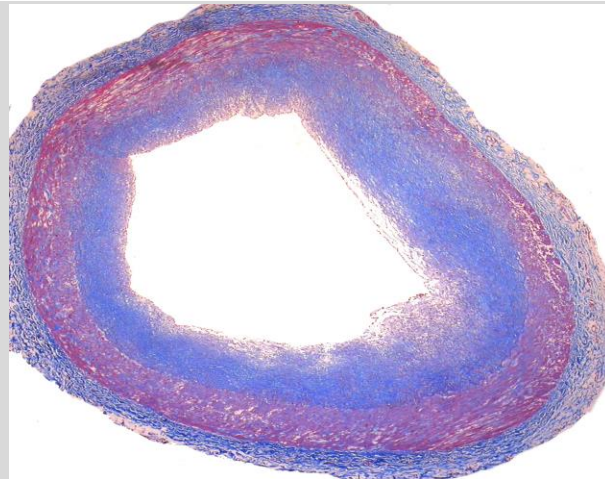
coronary artery
atherosclerosis



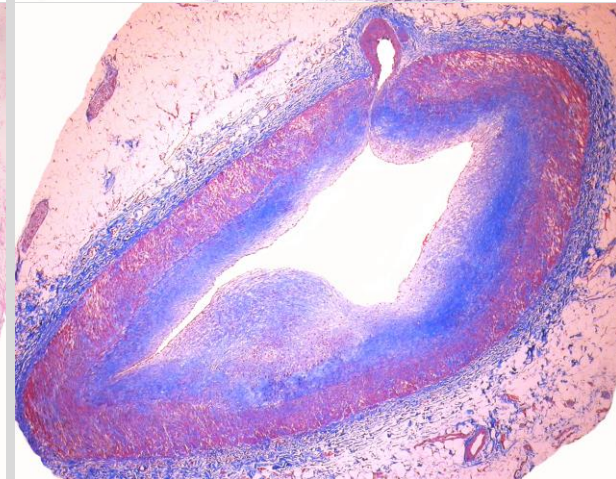
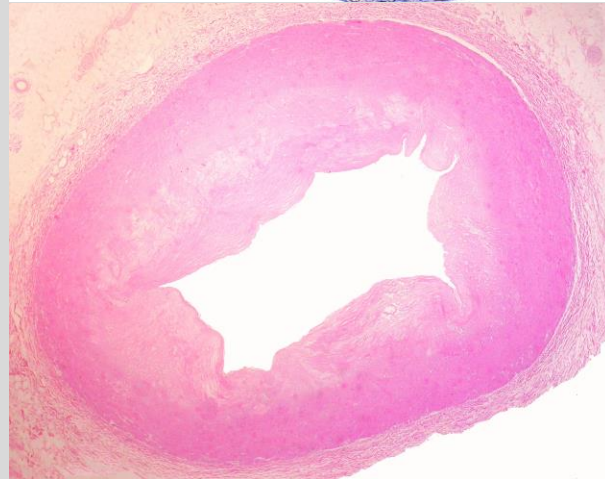
myocardial signs of ischemia/hypoperfusion in varying degrees and stages of evolution



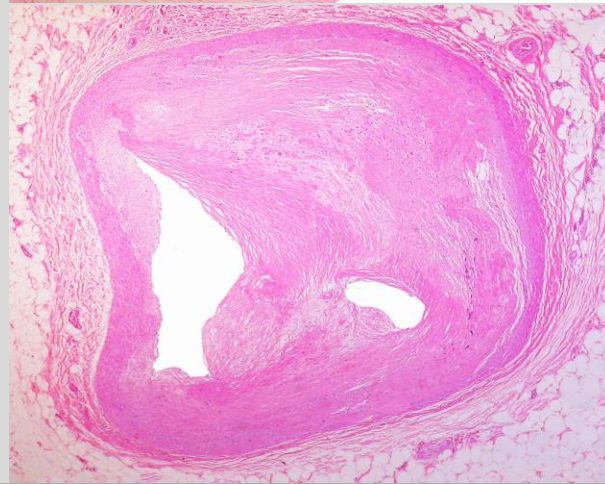
Mild: stenosis < 50%



Subcritical: stenosis 50-75%



Critical/significant:
stenosis 75-100%





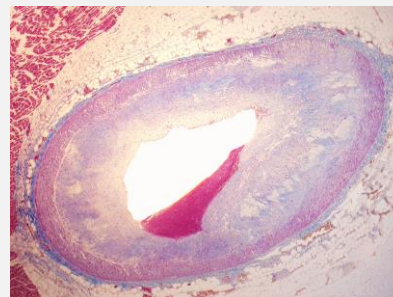
Limitations of pathology examination of coronary atherosclerosis

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

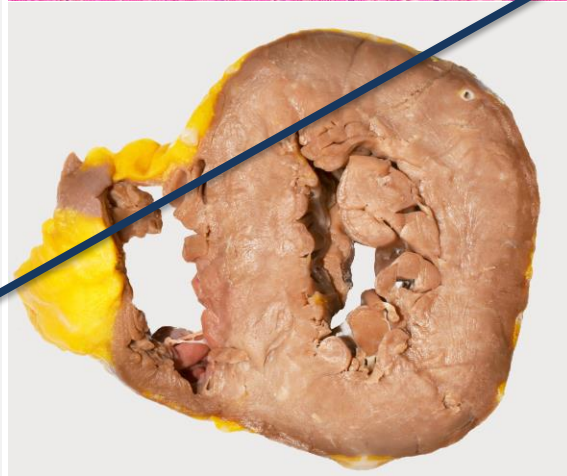
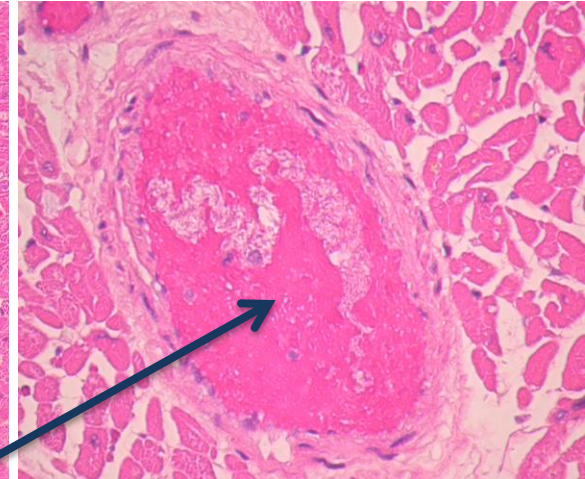
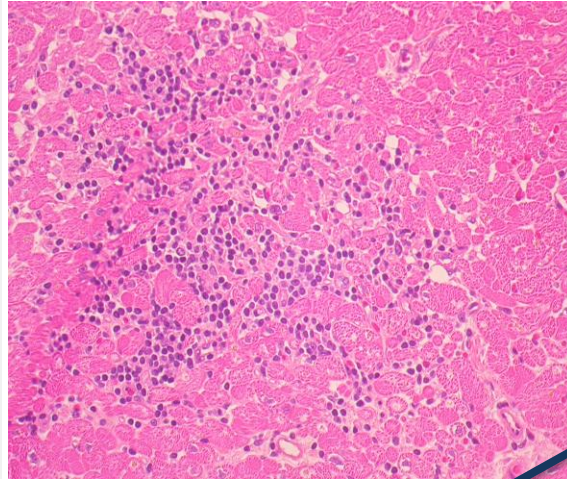
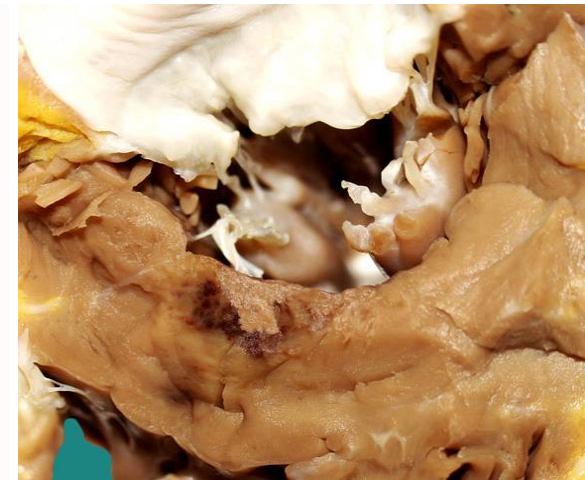
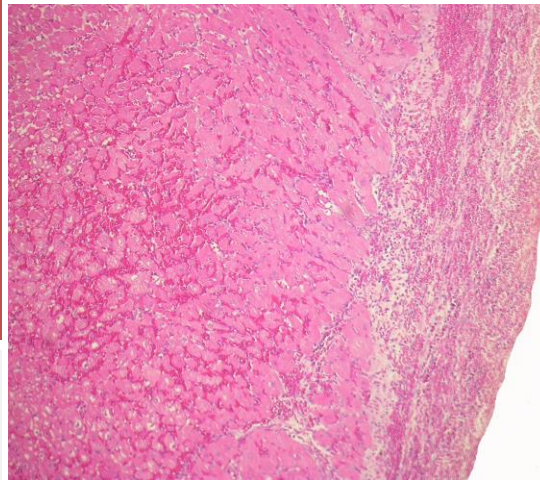
- 22.5% bivasal
- 7.5% trivasal

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



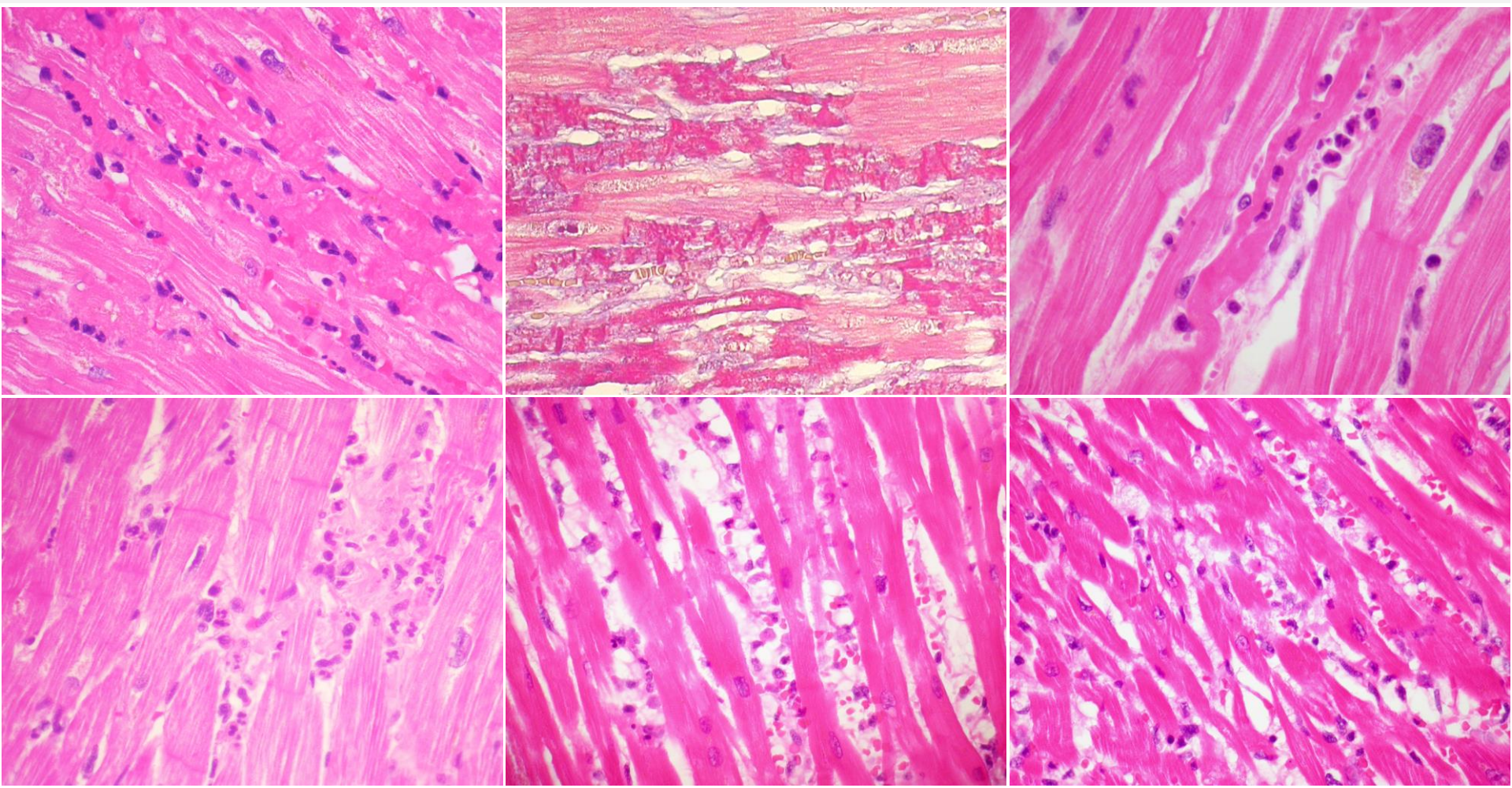
neurogenic stunned
myocardium

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,^a Ayyaz Ali, MRCS,^a Euan Ashley, PhD, MD, FRCP,^b
Darren Freed, PhD, MD,^c Kieran Clarke, PhD,^d Steven Tsui, MD, FRCS,^a
Jayan Parameshwar, FRCP,^a and Stephen Large, FRCP, FRCS^a

- 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

Donor hearts

abnormal

excluded

Pathology examination



dipyridamole
dobutamine

stress echo

normal

abnormal

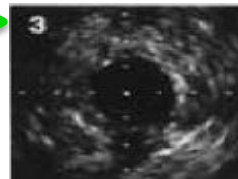
excluded

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

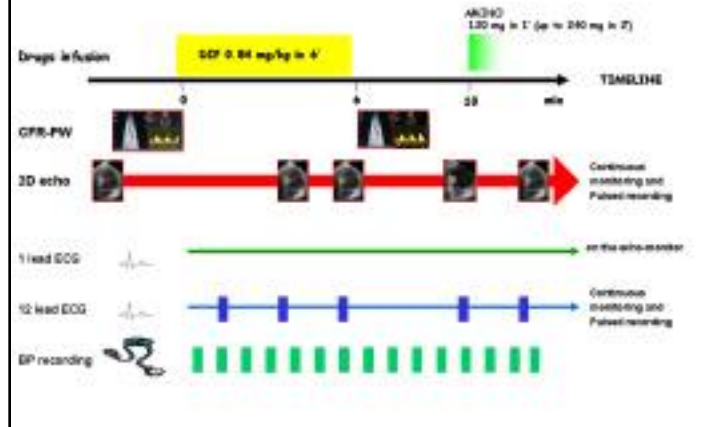


CANDIDATE DONORS



Normal
baseline echo

Study Protocol



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

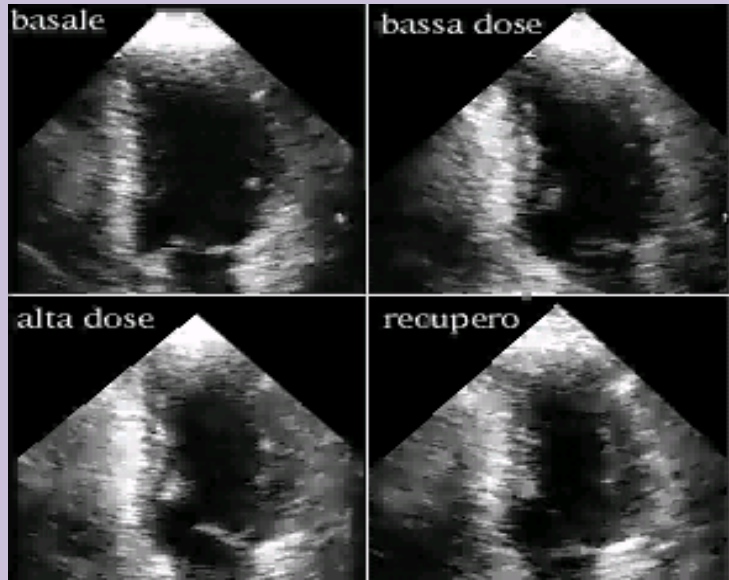
J Am Soc Echocardiogr
2011; 24: 363-6

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



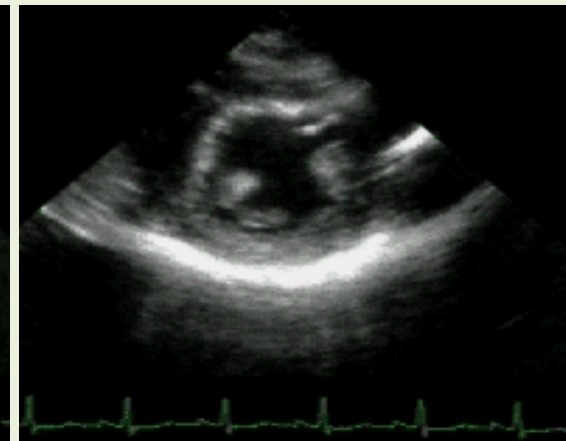
Heart accepted

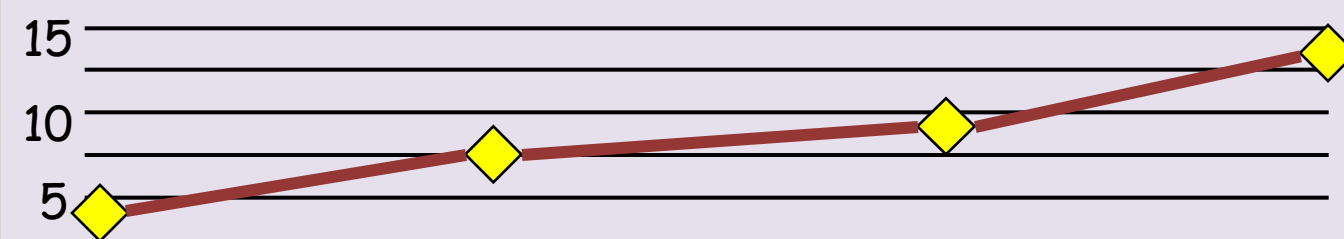
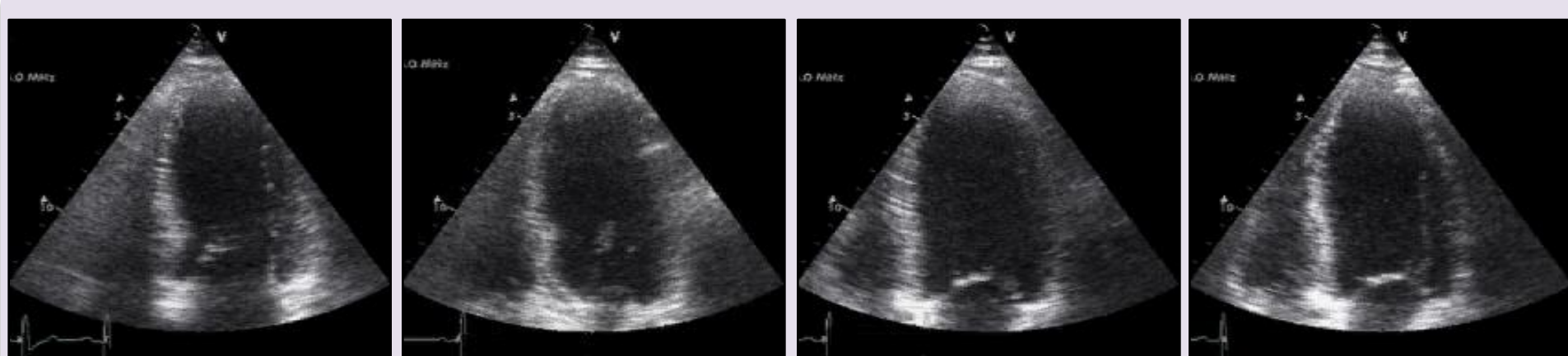
INDUCIBLE ISCHEMIA:
WMSI > 1

Heart excluded

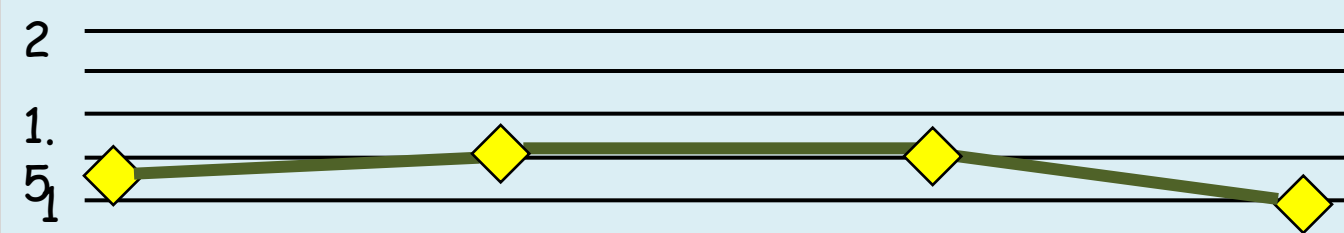
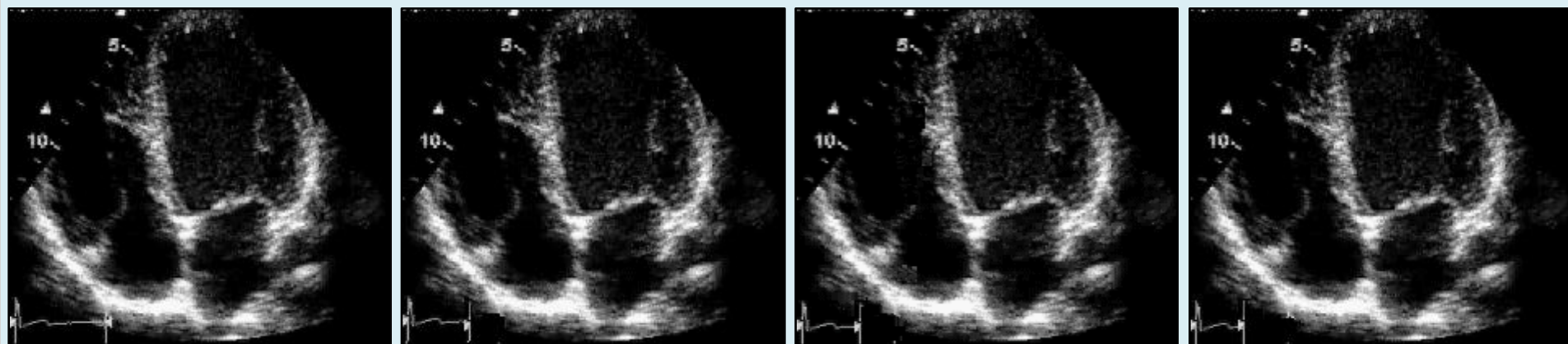
rest

peak





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



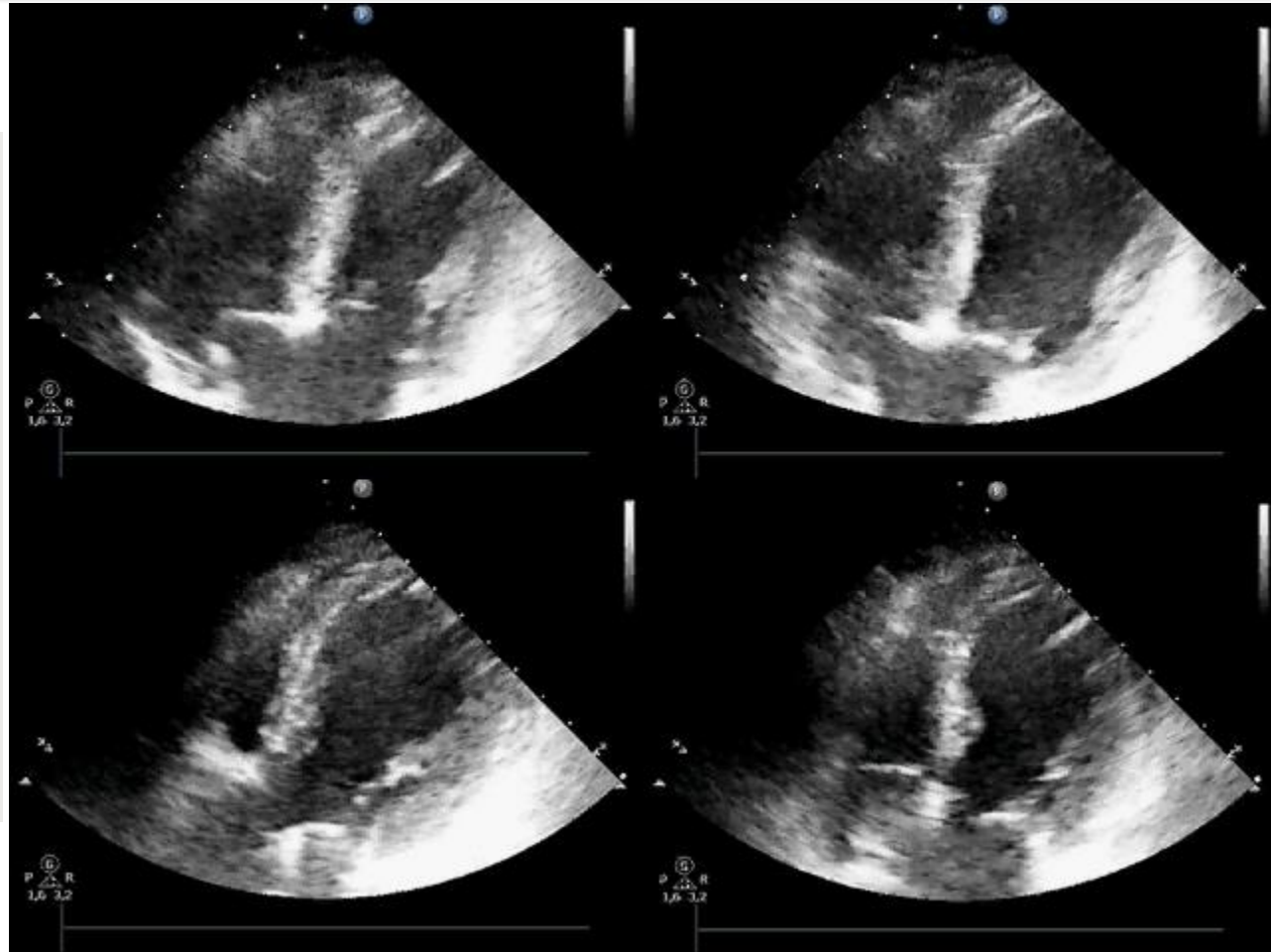
Abnormal contractile
reserve
(flat-negative PVR):
HEART EXCLUDED

Patient

Female donor
of 50 years

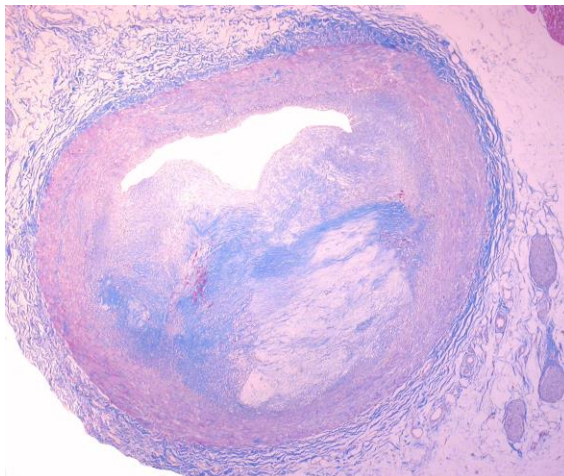
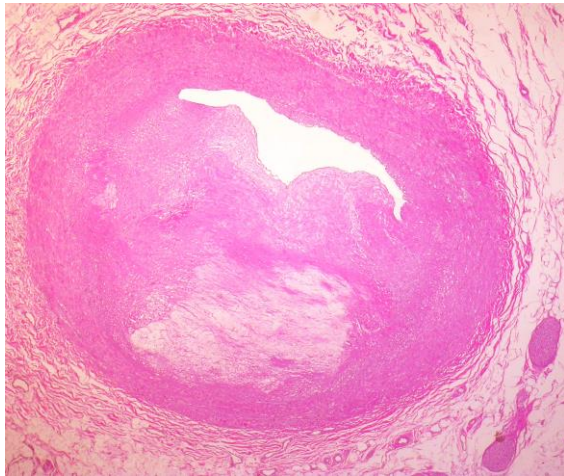
Stress-echo

hypo-akinesia
of the left ventricle mid-apical portion



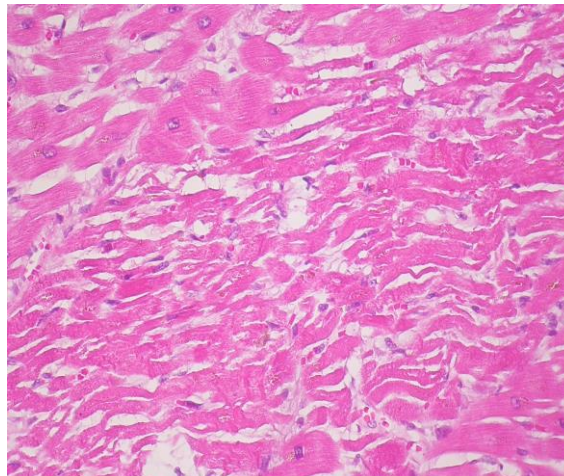
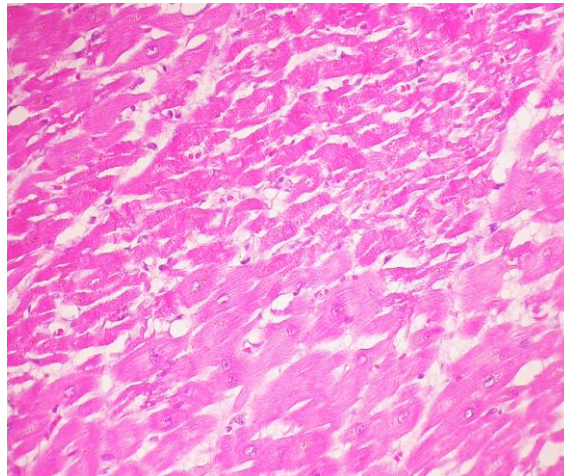
Coronary atherosclerosis

Fibro-lipidic plaque narrowing around 90% of LAD lumen



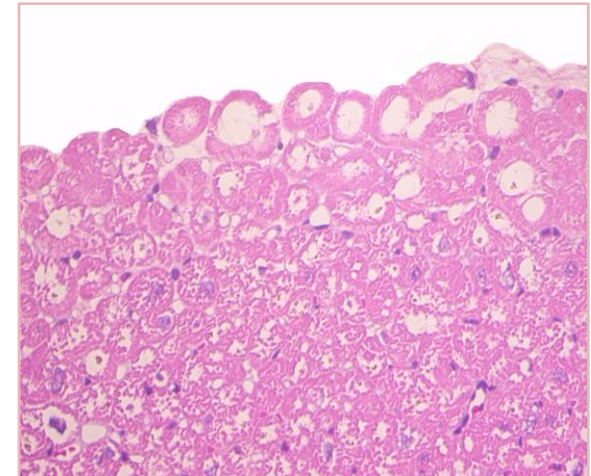
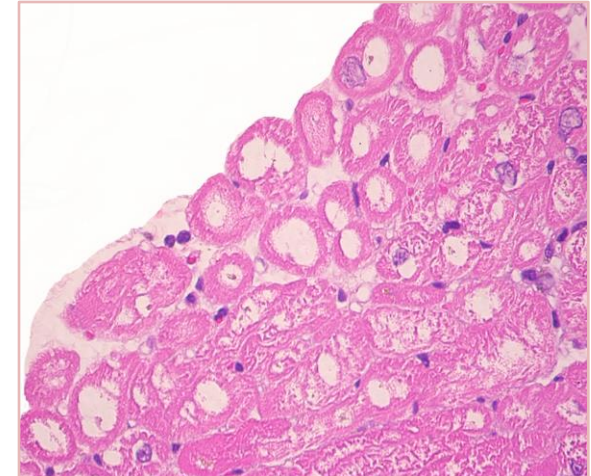
Myocardial coagulative necrosis

Multifocal myocardial coagulative necrosis irregularly distributed in LV and IVS



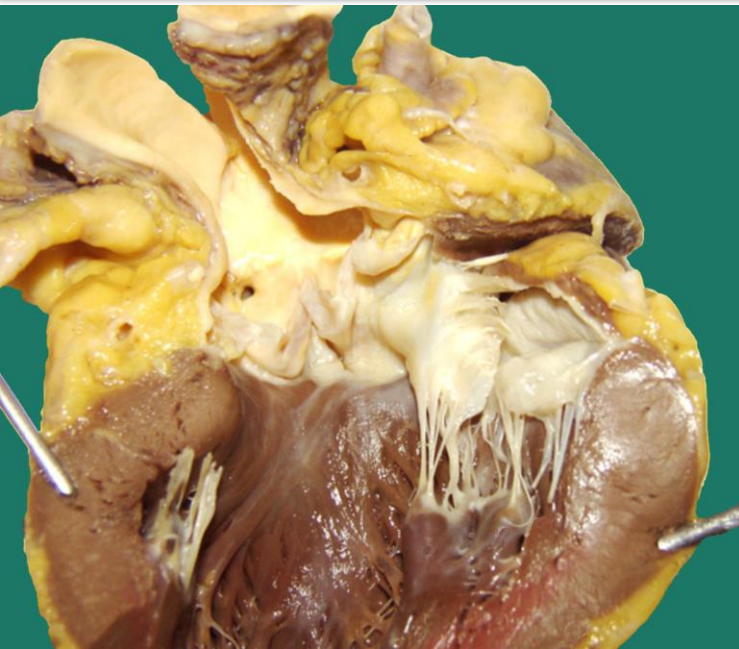
Other histopathologic lesions

Diffuse coagulative subendocardial myocytolysis



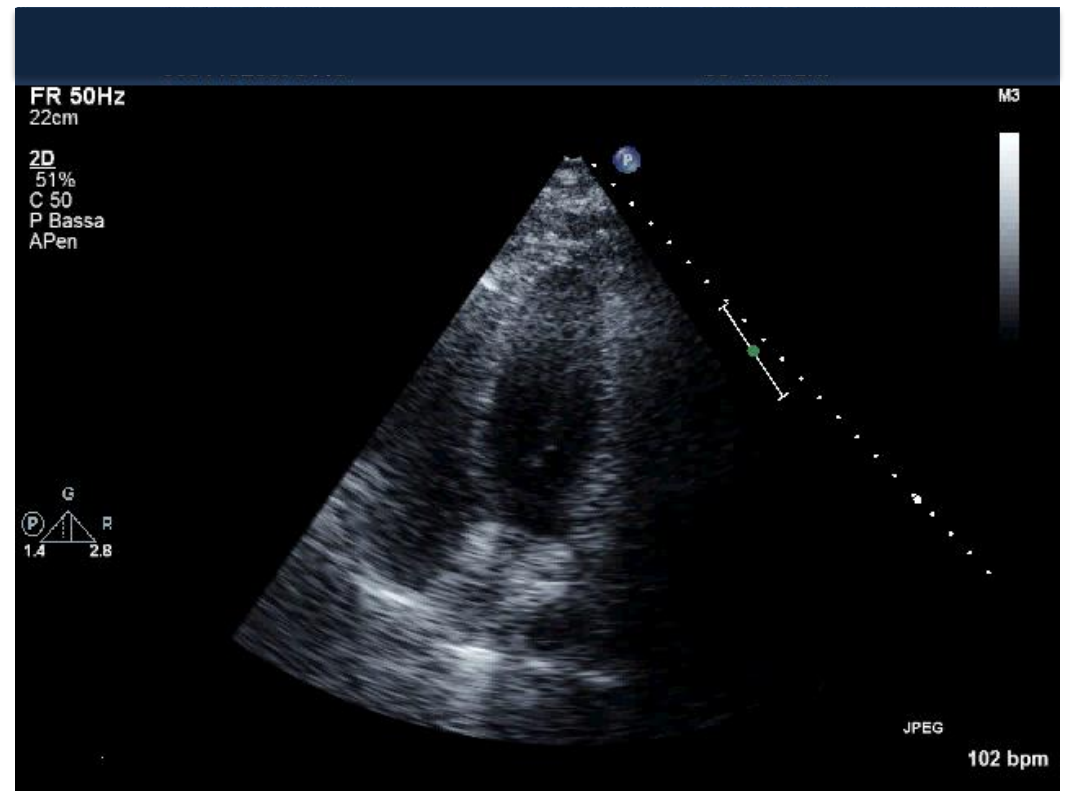
Patient

Male donor of 59 years



Stress-echo

Stress-induced inferior wall motion



Coronary atherosclerosis

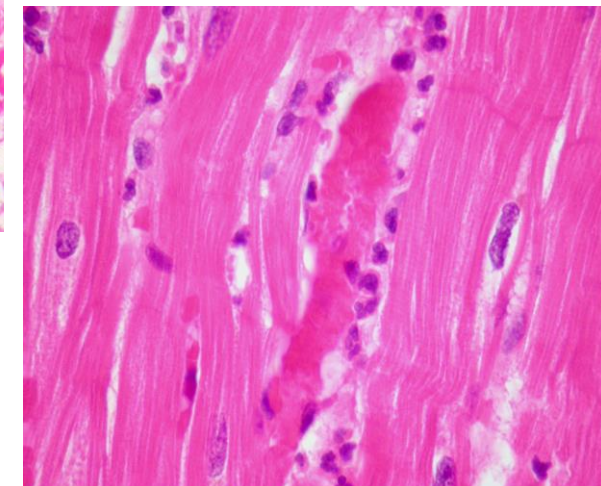
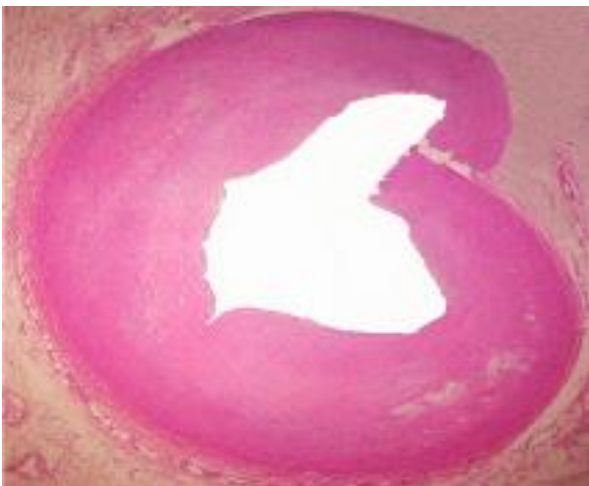
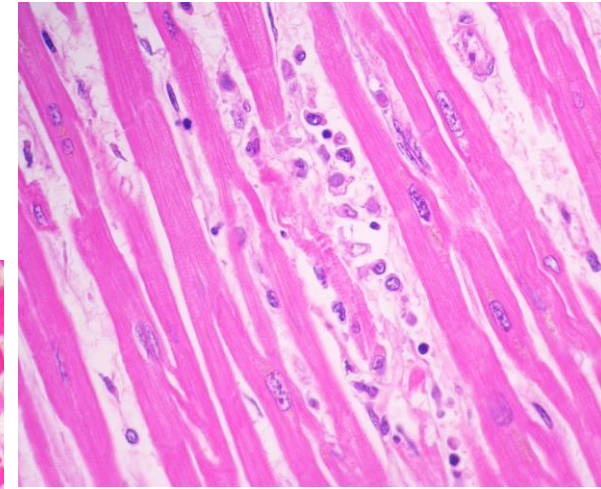
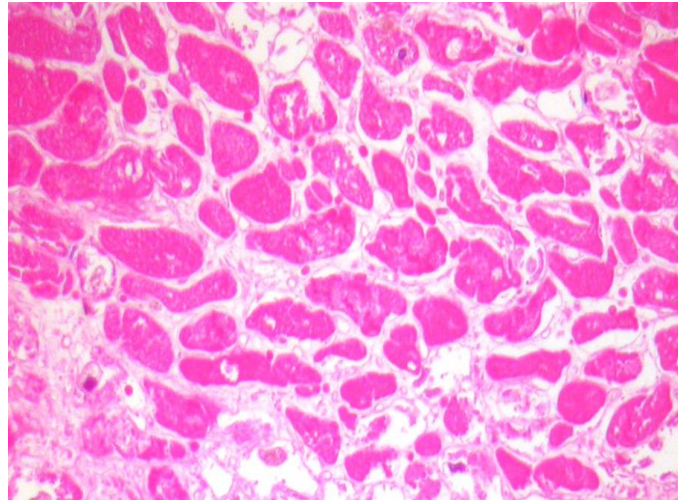
60% right coronary artery stenosis

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,^a Sonia Gherardi, MD,^b Luigi Targa, MD,^c Emilio Pasanisi, MD,^d Piero Mikus, MD,^c Piero Tanganelli, MD,^f Massimo Maccherini, MD,^g Giorgio Arpesella, MD,^c Eugenio Picano, MD,^d and Tonino Bombardini, MD, PhD^d

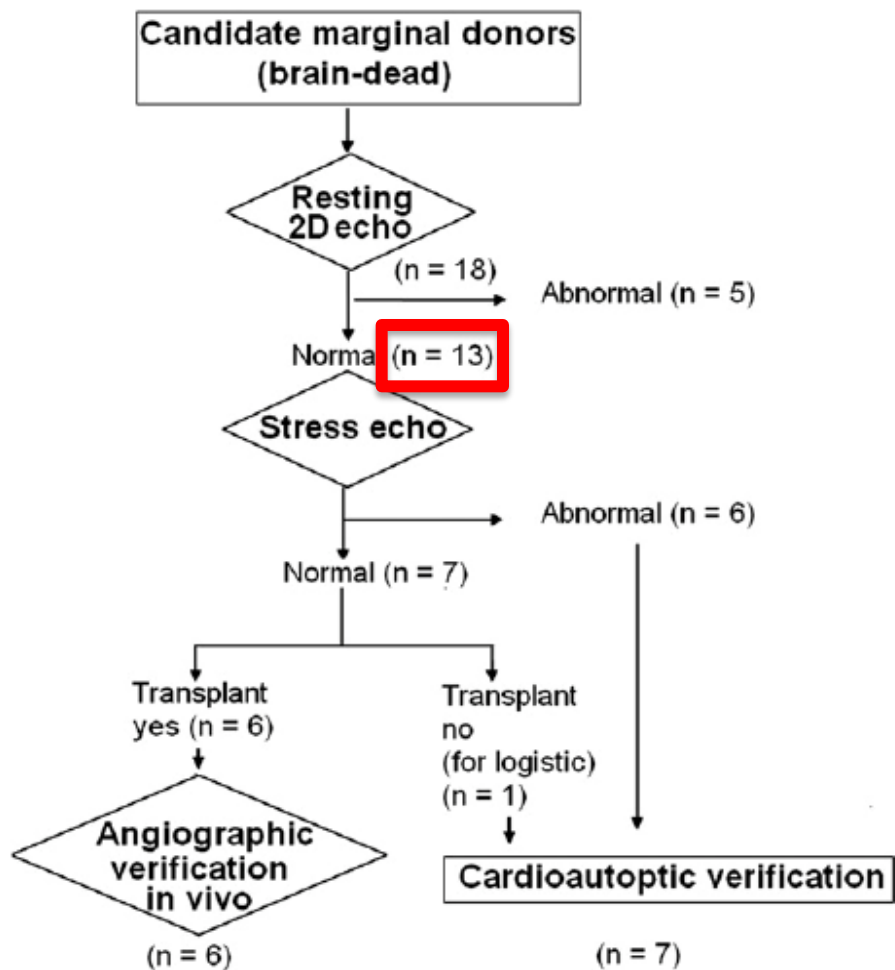


Figure 1. Study flow chart.

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,
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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^{1*}, Giorgio Arpesella², Massimo Maccherini³, Francesco Procaccio^{4,5}, Luciano Potena⁶,
Sonia Bernazzali³, Ornella Leone⁷ and Eugenio Picano¹

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**

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Axel Rahmel, MD,^a Bruno Meiser, MD, PhD,^c Guenther Laufer, MD, PhD,^d and
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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: ≥ 17 points)

PATHOLOGY EXAMINATION

majority of the unused hearts

significant heart disease: 81%

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

a subset of the unused hearts

no significant pathological features:
19%

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

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