# Value of Rubidium-82-PET-CT in the assessment of Patients with Heart Transplant


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# Declaration of
# Financial Interests or Relationships

Pietro Muto:

- **NO** financial interests or relationships to disclose with regard to the subject matter of this presentation

- **NO** conflict of interest

# Talking Points

- **Notes on technical aspects of CardioGen-82®**
- **Outline of the advantages of cardiac PET perfusion imaging and quantitative cardiac PET**
- **Role in Heart Transplant Recipients**

# CardioGen-82® (Rubidium-82 Generator)

**FDA Approval for MPI: 1989**

- $^{82}Rb$ is produced by decay of Strontium-82 ($^{82}Sr$)
- 75 sec. T½
- Stress / Rest: Same sized dose due to short T½
- Kinetics
  - Potassium analogous
  - High extraction fraction at high flow rates
- Perfusion Defects visualized 2-7 min after injection
- New generator every 28 days
- Fixed price, not unit dose
- Dose available 24h/day; 7 days/week; 28 days/month
- Note: Only Pharmacologic stress studies

| PET Tracer | Physical Half-life (min’) | Extraction | Production | Mean Positron Range | Dose (MBq) | Effective dose (mSv) | Clinical Applications |
|---|---|---|---|---|---|---|---|
| $^{13}NH3$ | 9.96 | 80% | Onsite/ nearby cyclotron | 0.7 | 370 - 740 | 0.7-1.5 | **Perfusion/ MBF** |
| $H_2{}^{15}O$ | 2.05 | Diffusible | On-site cyclotron | 1.1 | 700 - 1500 | 0.7-1.4 | **MBF** |
| $^{82}Rb$ | 1.16 | 50-60% | **Generator** | 2.6 | 1100 - 1500 | 1.8-3.5 * 1.26 | **Perfusion/ MBF** |

* The use of 3D PET scanners and software allowing to inject half activity of $^{82}Rb$ with a preserved image quality, the calculated effective dose has been estimated 1.26 mSv for rest and stress scans

**Radiopharmaceuticals. Metabolic Pathways for PET/CT and PET/MRI Molecular Imaging**
Servizi Scientifici Ed. ML De Rimini Chapter 9: $^{82}$Rubidium

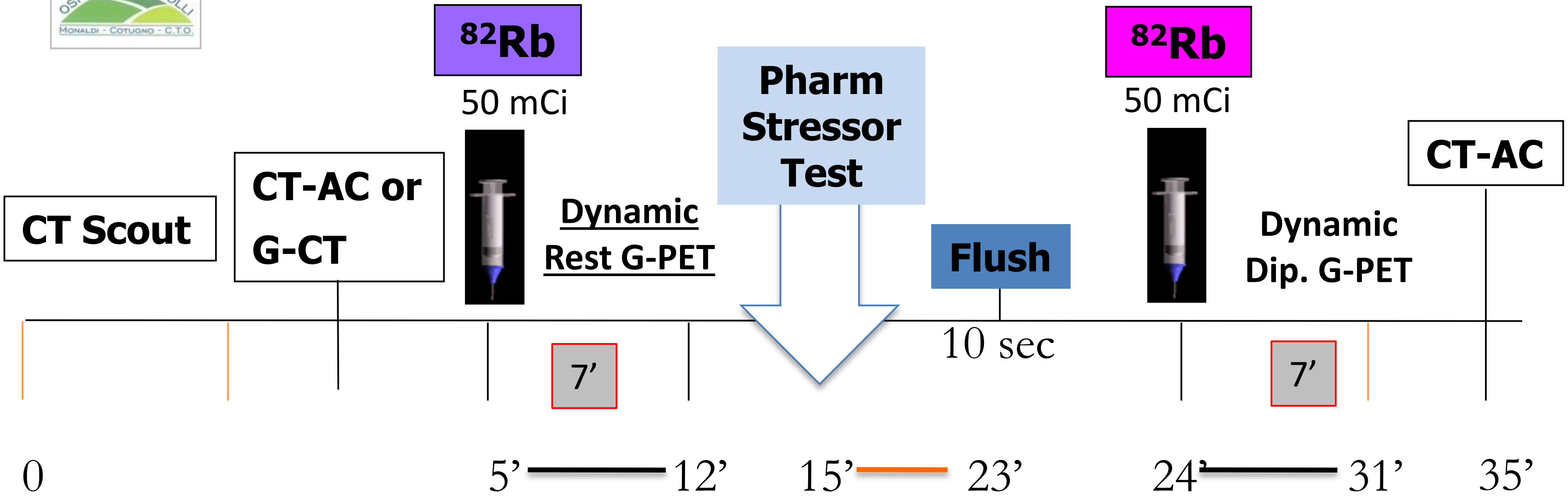
# Sensitivity - Specificity

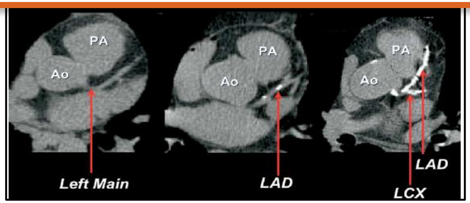
**$^{13}NH_3$ and $^{82}Rb$**

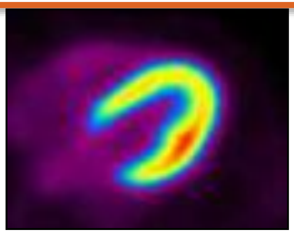
| Author | Sensitivity | Specificity | # Patients |
|---|---|---|---|
| Gould | 95% | 100% | 50 |
| Demer | 94% | 95% | 193 |
| Go | 93% | 78% | 202 |
| Schelbert | 97% | 100% | 45 |
| Yonekura | 93% | 100% | 49 |
| Williams | 98% | 93% | 146 |
| Stewart | 84% | 88% | 319 |
| **Weighted Avg.** | **93% +/- 8** | **92% +/- 5** | **766** |

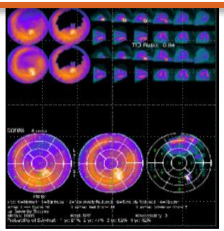
Nuclear Medicine Self-Study Program III: Nuclear Medicine Cardiology. Botvinik, EH, Ed. 1998: Society of Nuclear Medicine, Reston, VA.

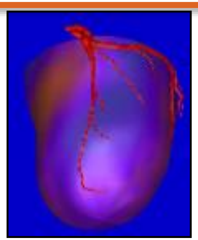
# $^{82}$Rb Acquisition Protocol 35’ (List Mode): Rest/Stressor (Dipyridamole)



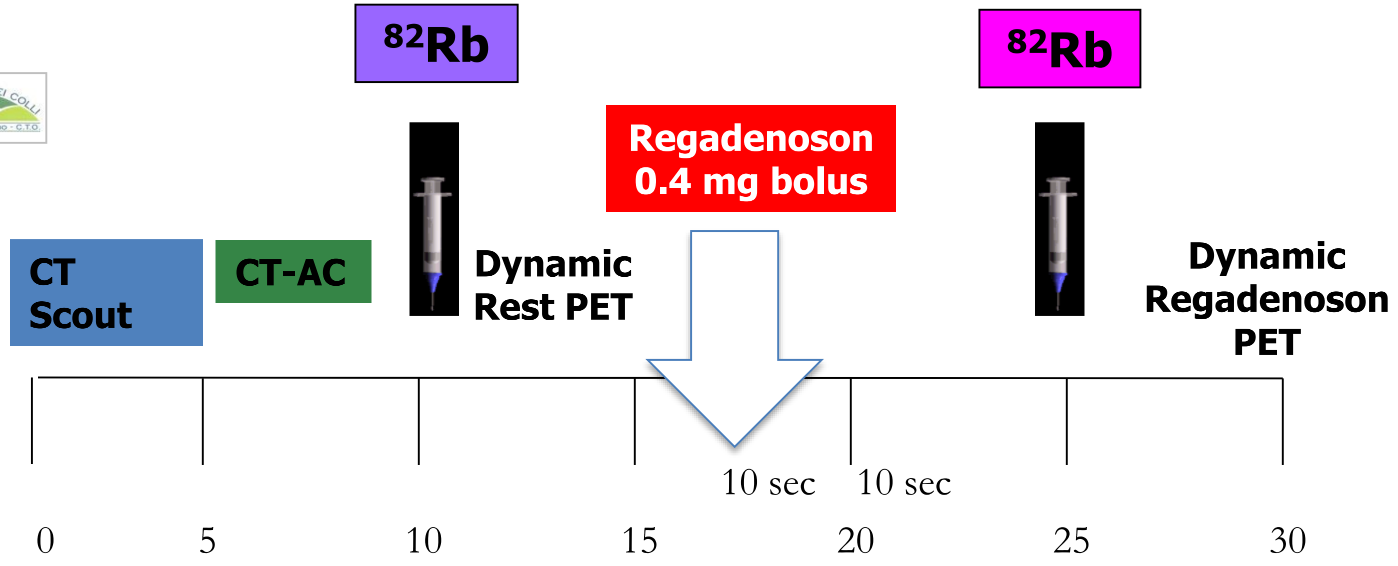





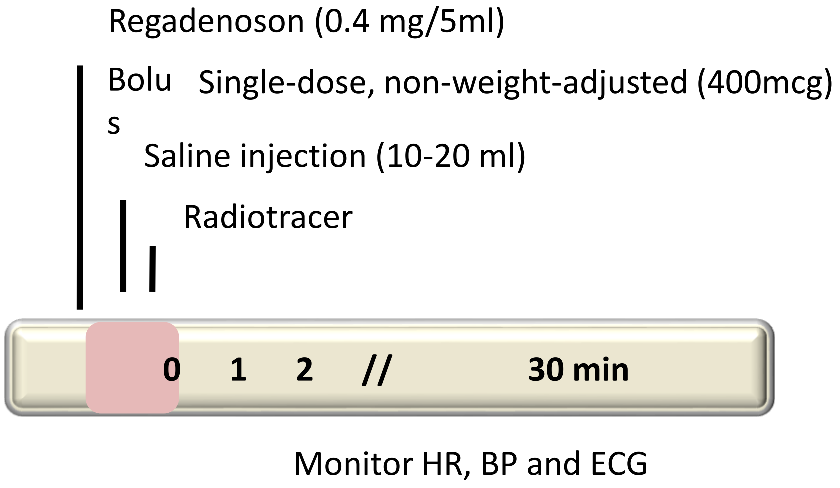


# $^{82}Rb$ Acquisition Protocol 35' (List Mode): Rest/Stressor (Regadenoson)



# Pharmacological Stressor Agent: Regadenoson

## Selective adenosine A2A receptor agonist




**Radiopharmaceutical myocardial extraction directly proportional to CBF**

**Onset of action within 30 sec**

**Similar side effect profile to adenosine but better tolerability**

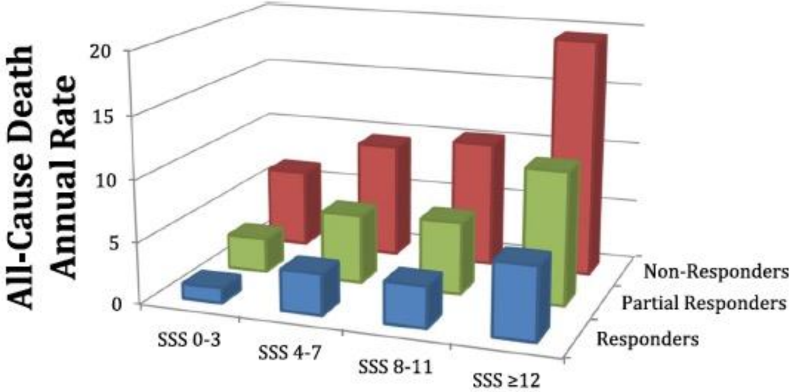
European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:538–548
https://doi.org/10.1007/s00259-017-3878-y

ORIGINAL ARTICLE

CrossMark

# Prognostic value of vasodilator response using rubidium-82 positron emission tomography myocardial perfusion imaging in patients with coronary artery disease

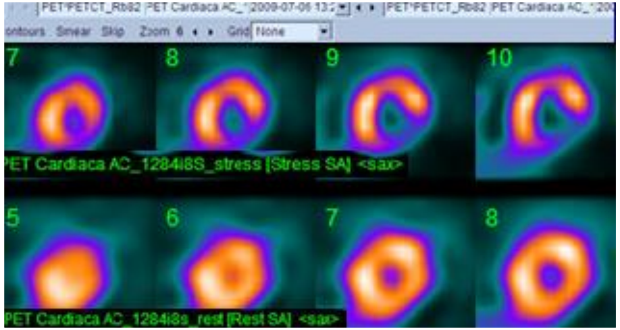
Punitha Arasaratnam[1] · Masoud Sadreddini[1] · Yeung Ya
Sharmila Dorbala[2] · Marcelo F. Di Carli[2] · Rob S. Beanla
Brent A. Williams[4] · Emir Veledar[5] · James K. Min[6] · Li C
Guido Germano[9] · Daniel S. Berman[9] · Leslee J. Shaw[5] ·

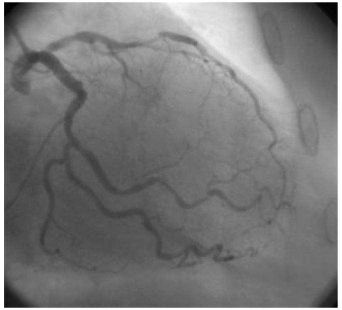


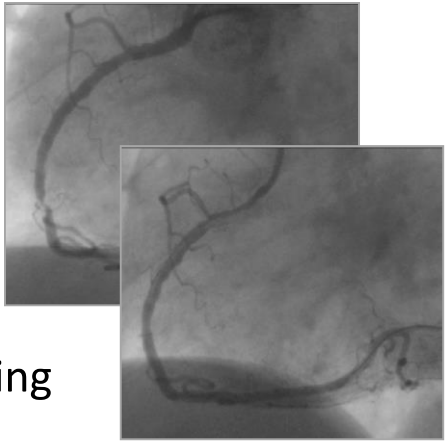

**Conclusion** Hemodynamic response during a vasodilator Rb-82 PET MPI is predictive of ACD. Partial and non-responders may require additional risk stratification leading to altered patient management.

# RUBIDIUM 82 CARDIAC PET/CT:
# The first Italian experience

| Coronary Angiography (CA) | CT -CA) |
|---|---|
| 39 / 80 pts | 5 / 80 pts |



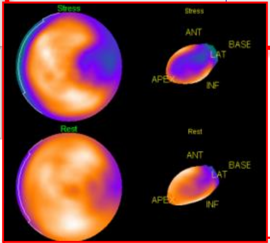



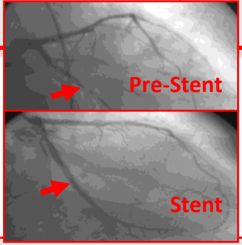


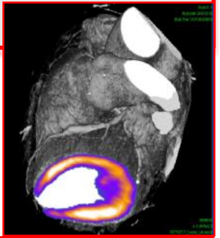
M. L. De Rimini et al. Eur J Nucl Med Mol Imaging (2010) 37

| | Pts Population | 82Rb SDS<2 | 82Rb SDS>4 | CA: Stenosis | CA-CT: Stenosis |
|---|---|---|---|---|---|
| SCA | 8 | / | 8 | 8 (5/8 MVD) | / |
| Stent | 39 | 18 | 21 | 16 | 5 |
| Obese | 14 | 9 | 5 | 5 | / |
| Women | 19 | 14 | 5 | 5 | / |
| Tot. Pts | 80 | 41 (no events) | 39 | 34 | 5 |

EJNMMI (2010) 37



# $^{82}$Rb vs CAD

**Evaluation of ischemic burden (SSS)**

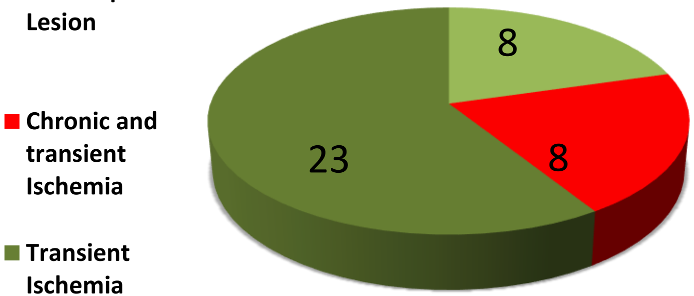
**High Accuracy *in Multi Vessel Disease***

**Fast Protocol**

**Lowering of exposure level**

**Hybrid Scan Advanteges**
**(*Shortage of $^{99}$mTc*)**

**39 pts: $^{82}$Rb SDS>4**



# Role of Cardiac $^{82}Rb$ PET/CT in Heart Transplant Recipients Follow-Up

**To evaluate diagnostic efficacy of cardiac $^{82}Rb$ PET/CT, as possible alternative option versus conventional Coronary Angiography (CCA) and intravascular ultrasound (IVUS) in predicting CAV development in HTx recipients**

ML De Rimini et al. Eur J Nucl Med Mol Imaging (2010) 37

# Heart Transplant (*HTx) Pts*

HTx > 5 yrs → Biopsy: No Myocite damage → CA 1-5 yrs post HTx → IVUS 1-5 yrs post HTx: LAD; Cx

**1/10 pt LDA stenting 1yr after Htx / 1/10 LV dysfunction/CMD 2 yrs after HTx**

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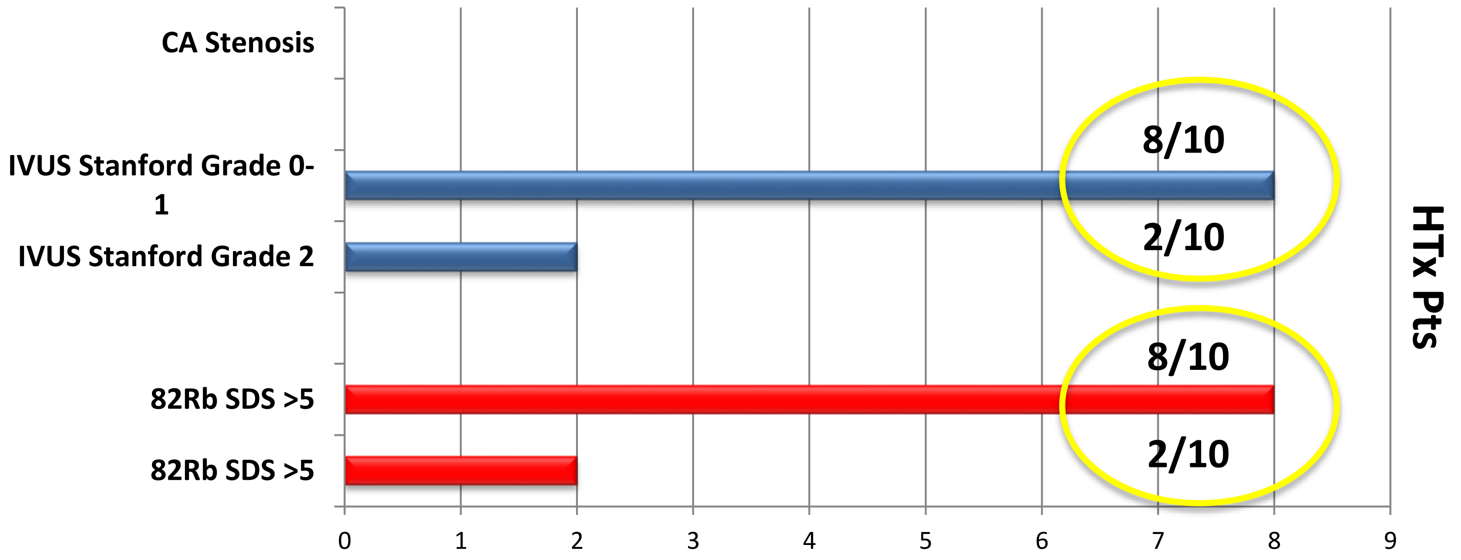
**Analisys:**

- IVUS: Stanford classes and intimal thickening indices (0 as normal - 4 as severe)
- CA: qualitative (obstructive CAD if >70% diameter stenosis)
- $^{82}$Rb PET/CT Basal/Dipyridamole: QPS

EJNMMI (2010) 37




**$^{82}$Rb PET/CT can be suggested to improve HTx pts management for reducing invasive techniques and to establish the functional significance of CAV involvement**

EJNMMI 2010; 37

# Speckle Tracking Echocardiography (STE) in Heart Transplant Recipients (Htx) Follow-Up

REVIEW ARTICLE

## Non-Doppler Two-dimensional Strain Imaging by Echocardiography–From Technical Considerations to Clinical Applications

Gila Perk, MD, Paul A. Tunick, MD, FACC, and Itzhak Kronzon, MD, FACC,
*New York, New York*

Echocardiography
Vol. 20 N. 3 March 2007

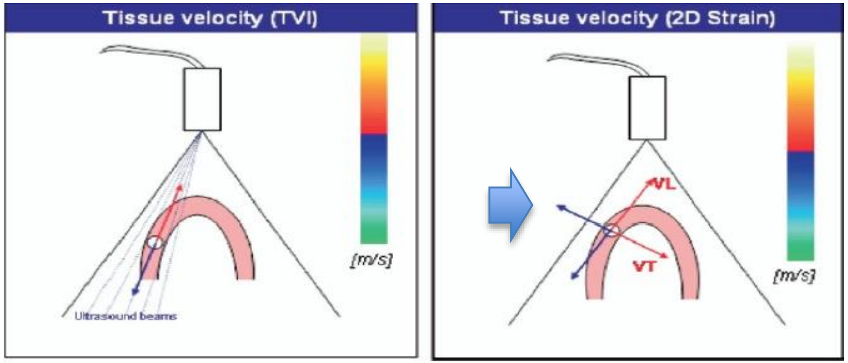
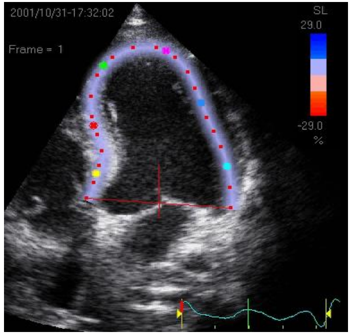



**Figure 3** Angle independency of non-Doppler 2-dimensional (2D) strain imaging. Tissue Doppler measures longitudinal velocity (*VL*) components toward or away from transducer. Non-Doppler 2D strain measures vector velocities in plane of imaging relative to direction of muscle contraction. *VT*, Transverse velocity.



## $^{82}$Rb PET/CT and Speckle Tracking Echocardiography (STE) in Htx Follow-Up

- The reduction of longitudinal strain can be influenced by a progressive chronic phenomenon, strongly associated with the transplant period and the increase in mean arterial pressure secondary to immunosuppressive therapies

- Normoperfusion at $^{82}$RB PET/CT is effective in defining the functional status of CAV (High NPV vs STE) and can improve the management of HTx pts allowing to reduce and/or better select the need for invasive techniques

- The associated impairment of myocardial perfusion and Strain can modify the management of HTx pt and/or suggest the choice of immunosuppressive therapeutic shift

De Rimini ML et al. Clin Transl Imaging 2013

Echocardiography
A Journal of Cardiovascular Ultrasound and Allied Techniques

IMAGES Section Editor – Brian D. Hoit, MD   First published: 3 July 2017 | https://doi.org/10.1111/echo.13596

## Association between left ventricular perfusion defects and myocardial deformation indexes in heart transplantation recipients

Antonello D'Andrea MD, PhD, Maria Luisa De Rimini MD, Raffaella America MD, Chiara Cirillo
Lucia Riegler MD, Giuseppe Limongelli MD, PhD, Michele D'Alto MD, PhD, Gemma Salerno MD,
Ciro Maiello MD, Pietro Muto MD, Maria Giovanna Russo MD, Raffaele Calabrò MD,

**Tot 115 adult HTx**
**(58.3±5.8 years; 69 males)**

### Cardiopulmonary test and Echo analysis

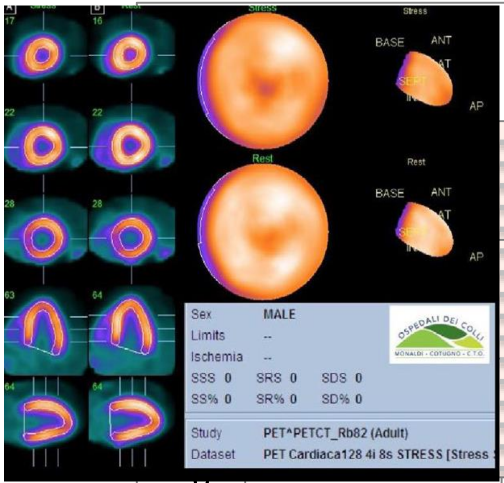
| Variable | Cardiac transplant | Controls | P-value |
|---|---|---|---|
| $VO_2$ max (mL/kg/min) | 24.2±5.32 | | |
| Septal wall thickness (mm) | 11.1±2.4 | 8.9±1.1 | <.01 |
| Posterior wall thickness (mm) | 10.8±1.6 | 8.4±2.1 | <.01 |
| LV end-diastolic volume (mL) | 119.2±13.3 | 113.8±13.7 | NS |
| LV end-systolic volume (ml) | 34.8± 8.1 | 37.1±9.4 | NS |
| Relative diastolic wall thickness | 0.44±0.05 | 0.34±0.04 | <.01 |
| LV mass index ($g/m^{2.7}$) | 62.5±8.7 | 48.4±5.9 | <.001 |
| 2D LV ejection fraction (%) | 57.1±3.8 | 58.9±4.3 | NS |
| LV GLS (%) | −13.7±2.3 | −18.4±3.3 | <.001 |
| Transmitral E-wave (cm/sec) | 62.1±14.3 | 59.3±11.3 | NS |
| Transmitral A-wave (cm/sec) | 37.1±12.1 | 35.1±12.1 | NS |
| Transmitral E/A ratio | 1.7±1.3 | 1.8±1.4 | NS |
| Deceleration time (ms) | 158.2±33.1 | 162.3±28.1 | NS |
| Mitral E/Ea ratio | 8.5±2.1 | 6.9±3.1 | NS |
| LA volume index ($mL/m^2$) | 43.6±12.2 | 30.8±9.4 | <.00001 |
| RV diameter (basal) (mm) | 38.4 ±6.3 | 33.1±5.3 | <.01 |
| PASP (mm Hg) | 37.5±6.6 | 18.7±8.1 | <.0001 |

LV=left ventricle; LA=left atrial; GLS=global longitudinal strain; RV=right ventricle.

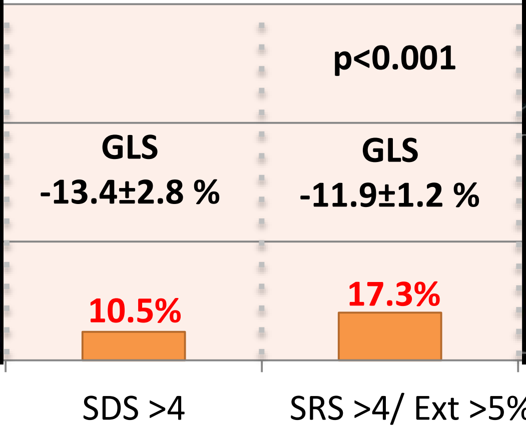
| $^{82}$Rb Gated-PET LVEF | | | |
|---|---|---|---|
| Rest | **58.4±4.4%** | **55.5±3.9 %** | 48.**5±2.9 %** |
| Dipyridamole | **60.5±4.8 %** | **53.1±4.5 %** | 49.2**±1.9 %** |

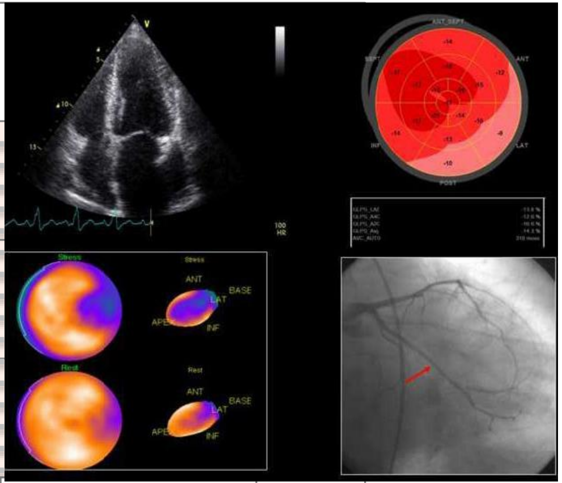
**LV GLS (Global Longitudinal Strain):** a strong MACE and mortality predictor in pts with and without CAV

J Heart Lung Transplant. 2017;36:567–576




## $^{82}$ Rb PET/CT



Echocardiography 2017

**CA: 10 pts**
**Cor. stenosis**

**Therapeuthic shift**

It is known that subendocardial myocardium layers are very sensitive not only to ischemia, but also to edema and fibrosis

In HTx, CAV affects both **epicardial vessels and the microvascular function** and the impairment of both vascular compartments leads to

- Perfusion abnormalities (at $^{82}Rb$)
- subsequently to potentially reduced LV GLS (at Strain)

due to immunologic (acute rejection and anti-HLA antibodies) and nonimmunologic mechanisms (donor age, hypertension, hyperlipidemia, inflammation, and fibrosis)

Echocardiography 2017

# Beyond the Tip of the Iceberg

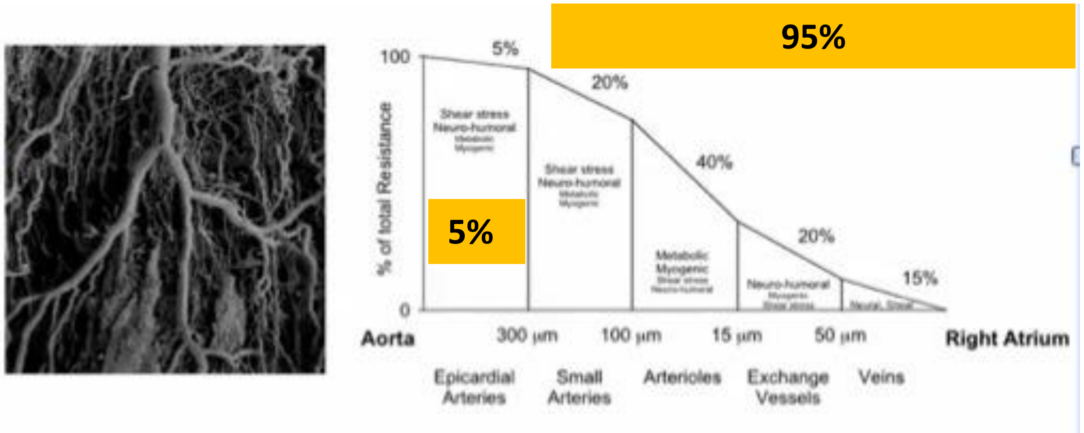
Only 5% of CBF is under control of the Epicardial Arteries

The tip of the iceberg
Resolution >500 µm

The hidden side of the iceberg
Resolution <500 µm

**N Engl J Med. Feb. 2007**

# The microcirculation controls Coronary Resistance and MBF




Toyota et al. *J Nucl Cardiol* 2001

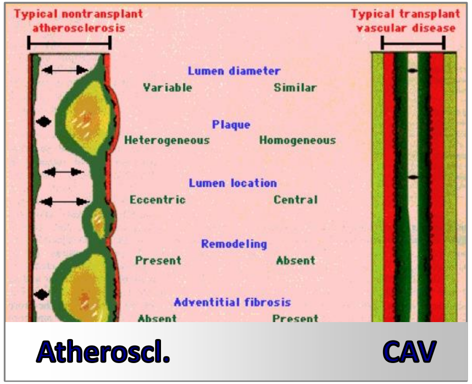
## PET: MBF (ml/m)

***…. it can expand the range of the image, from the organ damage …. to the knowledge of biochemical and molecular mechanisms in order to preventing it ……to Molecular Imaging***

# Heart Transplant (HTx) Recipients

## Chronic Immunologic Response:

- **Afflicts small vessels firstly vs the main epicardial ones**
- **Appears to be the cause of the occlusive long term Cardiac Allograft Vasculopathy (CAV), sharing chronic rejection lesions**
- **Is one of the leading causes of late mortality after HTx**




**Wu YW et al. J Nucl Med 2010; 51:906–912**

| 5 yrs after HTx | |
|---|---|
| Angiographic Vasculopathy | 40-70% |
| Coronary Disease | 42% |
| Severe CAD | 7% |
| Cardiac Death | 7% |

**Cardiac Transplant Research Database 2004 (2609 pts)**

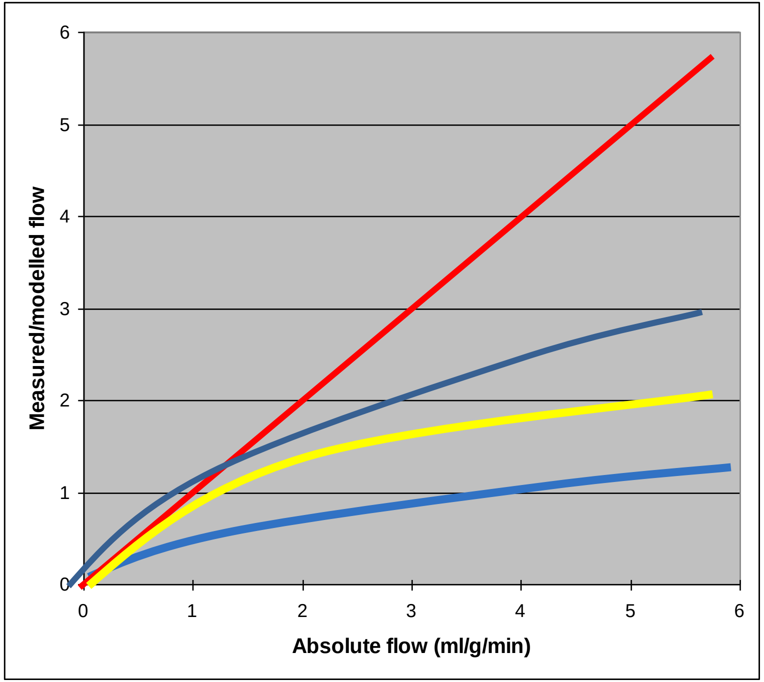
# MBF

Net Extraction Fraction

non-linear

at MBF

(linear relation for flow values > 2.5 ml/min/g)




$^{15}$O-water

$^{13}$NH

$^{18}$F-Flurpiridaz

**$^{82}$Rb**

$^{99m}$Tc-MIBI

MRI/CT contrast

*$^{18}$F-FBnTP*

Prior JO et al. Eur J Nucl Med Mol Imaging 2012, 39:1037–1047

Hsu B et al. JBR 2013, 27(6):452-459

SPECIAL CONTRIBUTION

# Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC

Murthy et al. The Journal of Nuclear Medicine • Vol. 59 • No. 2 • February 2018

ASNC

ASNC/SNMMI POSITION STATEMENT

Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC

Murthy et al. Journal of Nuclear Cardiology®
December 2017

- A growing role of **Quantitative Cardiac PET** in clinical use and in the algorithms of management of Coronary Artery Disease (CAD) has been demonstrated

- The evaluation of Myocardial Blood Flow (MBF) and Flow Reserve (MFR) allows the diagnosis of Microvascular Dysfunction, which is associated to several cardiac diseases

Clinical and Translational Imaging (2018) 6:47–60
https://doi.org/10.1007/s40336-018-0263-1

EXPERT REVIEW

# PET myocardial perfusion quantification: anatomy of a spreading functional technique

L. E. Juarez-Orozco[1,2] · J. R. Cruz-Mendoza[3] · G. Y. Guinto-Nishimura[3] · L. Walls-Laguarda[3] · L. J. Casares-Echeverría[3] · A. Meave-Gonzalez[4] · J. Knuuti[1] · E. Alexanderson[3]

The contribution of MBF and MPR beyond traditional semiquantitative evaluation of perfusion abnormalities improves diagnostic and prognostic performance in patients with CAD.

Quantification of MBF with PET allows detection of early vasomotor abnormalities linked to subclinical disease; it permits treatment evaluation and it offers accurate diagnostic evaluation of patients with known or suspected atherosclerosis

# Diabetes Mellitus

**Diabetes induces dysfunction of the microcirculation and non-obstructive vascular atherosclerosis before than epicardial main vessels involvement**

**Reduced Coronary Flow Reserve (CFR) can be mainly associated with diabetes, both in presence and in absence of epicardial main coronary artery stenosis**

Hagemann CE et al. Review Article $^{82}$Rb PET, Am J Nucl Med Mol Imaging 2015;5(5):457-468

# 20 HTx Pts: 11 No Diabetes (ND) – 9 Diabetes (D)

**Dynamic Images (tot. 7min) Re-framing into:**
**- 12 frames (fr): 5 sec/each;**
- **6 fr: 10 sec/each;**
- **5/20 sec /each;**
- **4/50 sec /each**

## Reconstruction from List Mode

**MPI (Perfusion phase) evaluated at: 90-120 sec.**

**Siemens Healthcare Workstation**

## 3D Reconstruction

checked for Biograph Siemens scanner; oxyorthosilicate (LSO) crystals 13x13x2

**-matrix 128;**
**-2i; 24s;**
**-FWHM 10**
**-OSEM IR with Gaussian post-processing filter 6 mm**

**Re-alignment** PET/CT images (software Siemens)

**ML De Rimini Eur J Nucl Med Mol Imaging (2017) 44**

# Methods

Siemens Healthcare Workstation: Transverse Reconstruction

## *Analysis*

CSI Software Cedars-Sinai
- Quantitative PET (**QPET**)
$^{82}$Rb database

Slomka PJ et al. JNM 2012; 53:171–181

- **MBF / MFR**
- **Summed Perfusion Scores**
  3 regions at polar map (LDA; Cx; RCA)
  17 segment LV (AHA model)
- **LV Function**

*Statistical analysis was performed using the SPSS software*
*Paired t tests were used to compare differences in paired continuous data (P <0.05)*

## *Analysis*

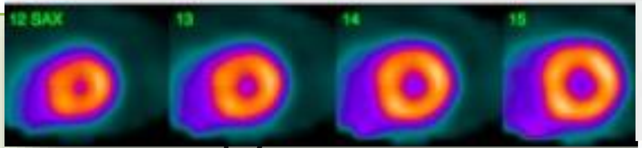
| Perfusion | | |
|---|---|---|
| Normal (SSS≤3; SDS≤2) | Mild to Moderate Ischemia (SDS 2-8) | Severe Ischemia SDS≥8 |

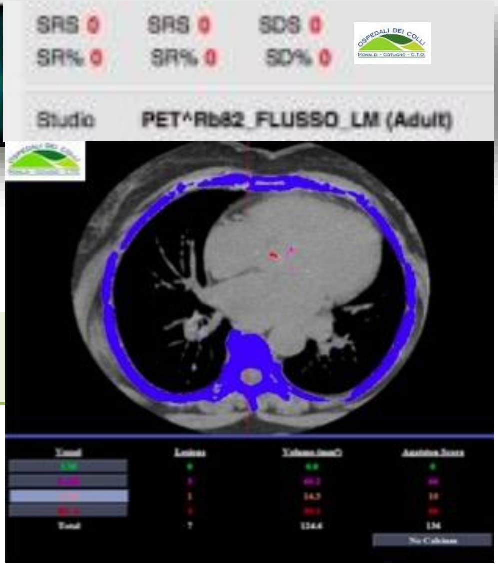
- **MBF** (mL/min/g) from the dynamic imaging (Basal-Hyperemic)
- MFR (hyperemic MBF/baseline MBF): reduced if <2

Camici GP et al. NEJM 2007

# 20 HTx Recipients
# in all Pts:

| | |
|---|---|
| EKG | Hyperemic test: No ischemia |
| MPI | |
| LV Function | Basal LVEF >55%<br>Hyper. LVEF ≥2% vs Basal |
| CAC | 124-300 |



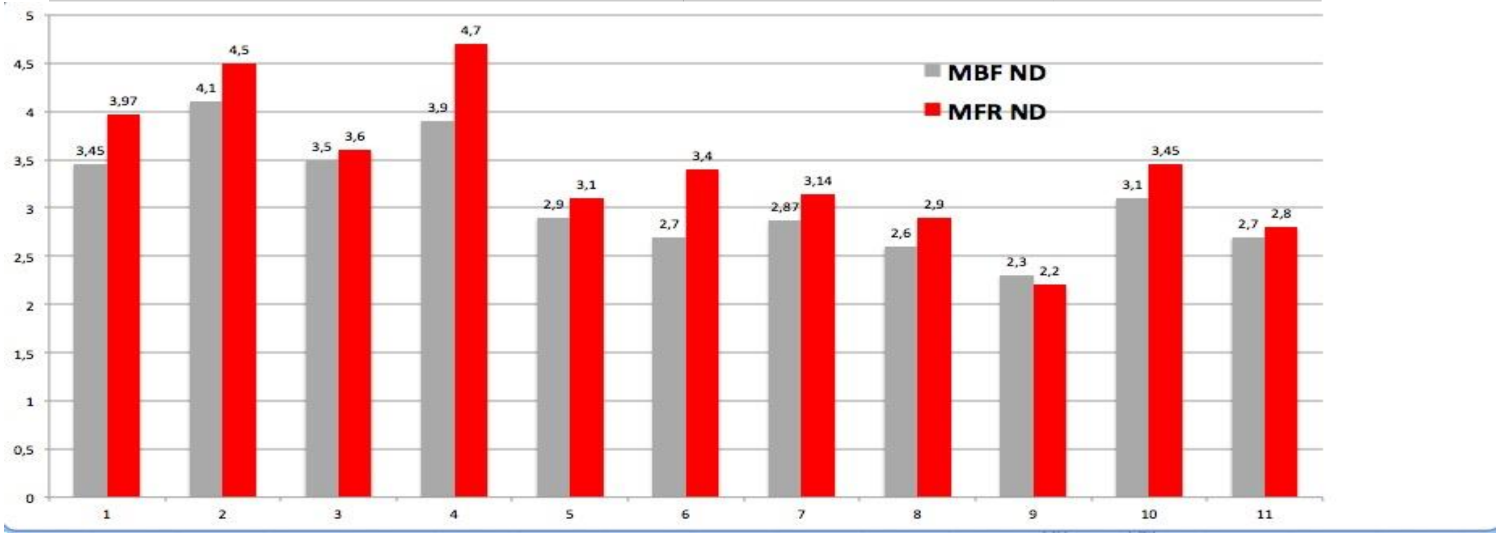




CSI Software Cedars-Sinai-Quantitative PET (**QPET**)
$^{82}$Rb database

EJNMMI (2017) 44

# Non Diabetic Htx patients

| HTx Pts | Hyperemic Flow (ml/m'/g) | Baseline Flow (ml/m'/g) | MFR |
|---|---|---|---|
| 11 ND | 3.45±0.41 | 0.91±0.31 | 3.97±1.15 |

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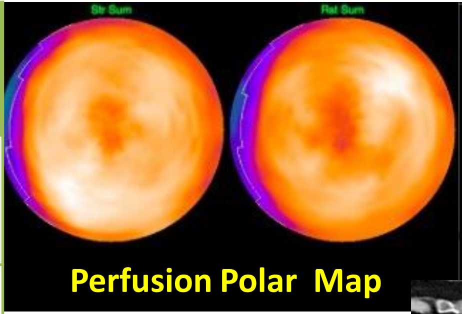
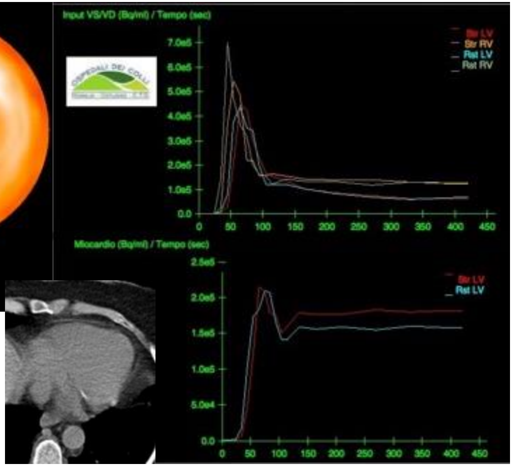
| HTx Pts | Hyperemic Flow (ml/m'/g') | Baseline Flow ml/m'/g') | MFR | |
|---|---|---|---|---|
| 11 ND | 3.45±0.41 | 0.91±0.31 | 3.97±1.15 | |
| 9 D | 2.03±0.66 | 0.89±0.91 | 1.87±0.75 | *P <0.05* |

| | |
|---|---|
| Hyperemic Flow | 1.57 mL/m/g |
| Baseline Flow | 0.96 mL/g/s |
| MFR | 1.65 |

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$^{82}Rb$ with quantitative PET/CT can be clinically feasible for the early detection of CAV and can be used as a reliable marker of disease progression for clinical management of HTx pts

In our selected population of HTx pts, diabetes can be confirmed as a factor influencing MFR

It could be a strong and independent predictor of outcome in diabetic HTx pts without evidence of CAD and normal MPI