Thesis Defense
Doctorate in Electrical Engineering
University of Ottawa

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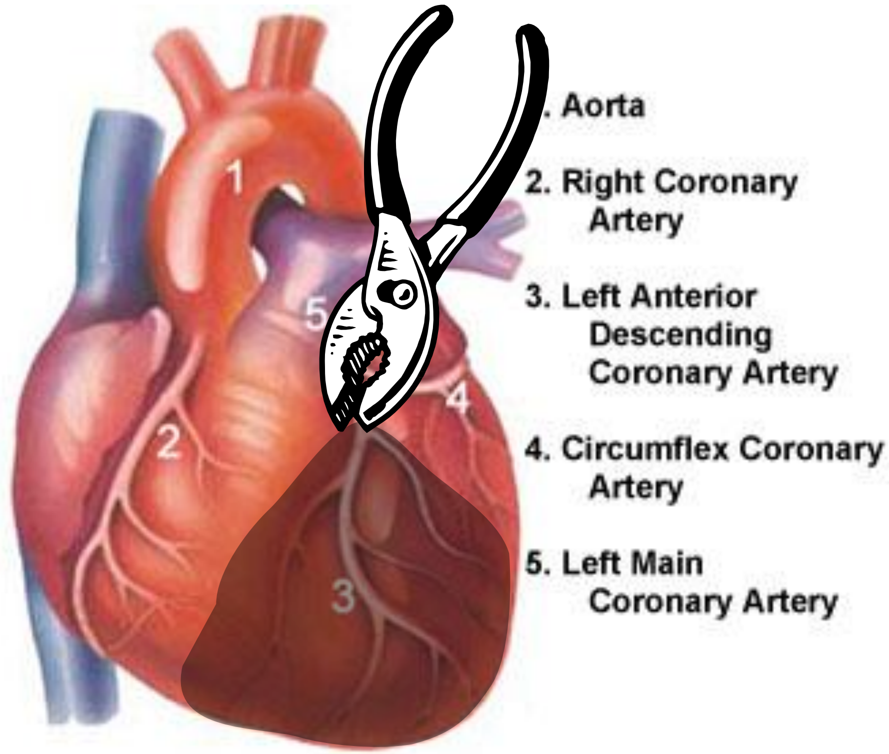
Kinetic Model Based Factor Analysis of Cardiac ^{82}Rb PET Images for Improved Accuracy of Quantitative Myocardial Blood Flow Measurement

Prologue

It wasn't always like this. There were times when Jack's heart was content. It was only in recent weeks that he started to sense that yurning - that desire. At first it was distant. It left him breathless. As the weeks rolled by the sensation became stronger and more frequent. Now it was impossible to ignore. Jack's heart was not getting enough…blood.

- Coronary arteries deliver blood to the myocardium (heart muscle).
- Stenosis can lead to reduced blood supply, reduced heart function, damaging of heart muscle, and death.
- Coronary artery disease is the largest single cause of death in western society.

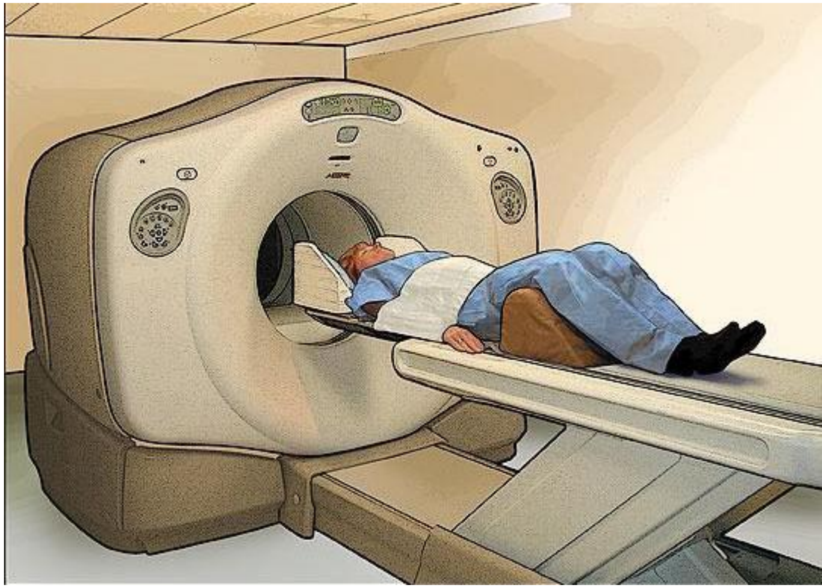


www.daviddarling.info/images

Prologue

Jack is referred for a myocardial perfusion imaging (MPI) exam:

- Radioactive labeled material (tracer) is injected intravenously (e.g. ^{82}Rb PET).
- After several minutes an image of the tracer distribution is acquired.
- Jack's heart is then stressed (exercise / drug) and imaging is repeated.
- The images are then interpreted by a specialist doctor.



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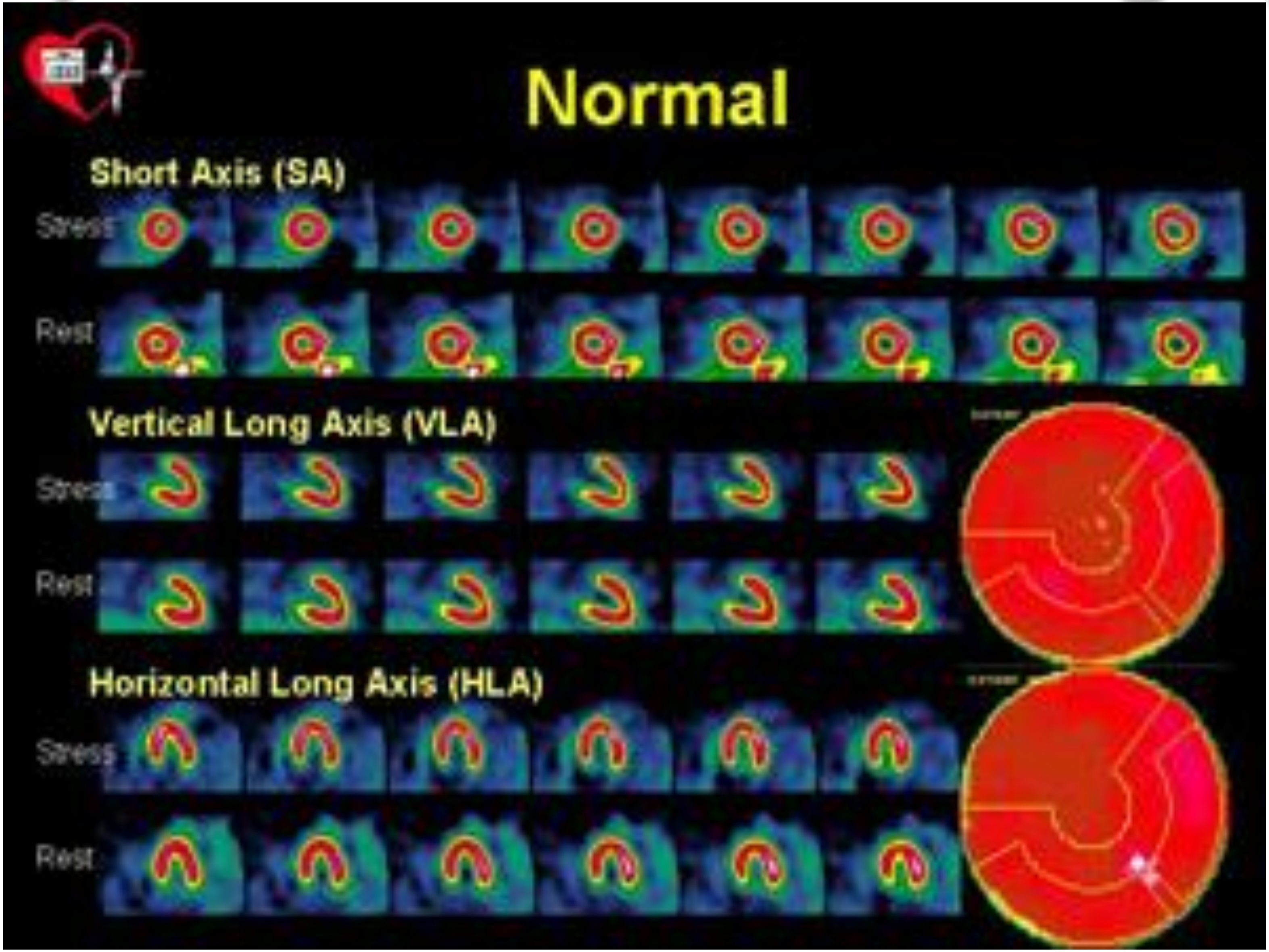
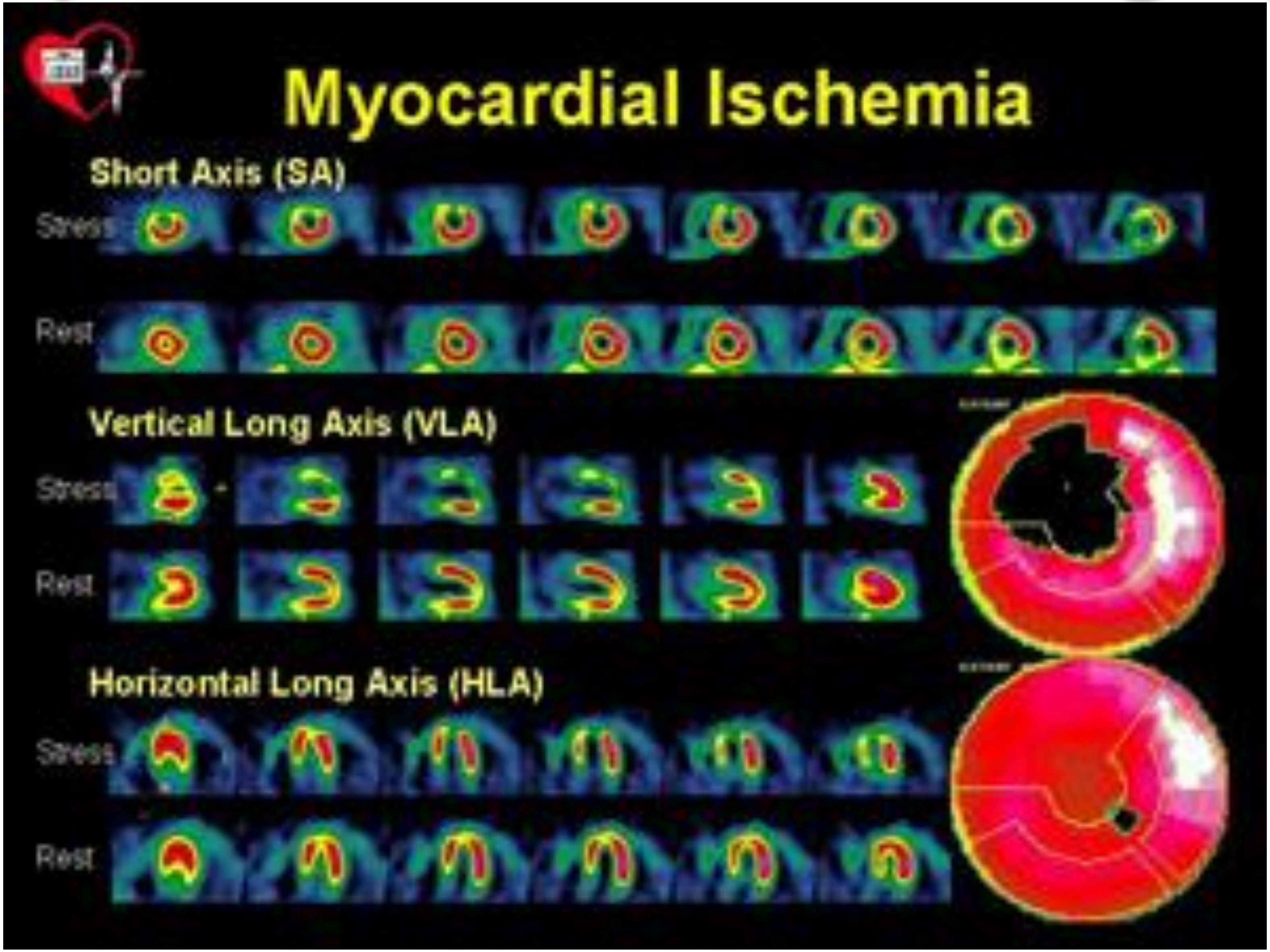
MPI Interpretation

- Dr. Heart receives Jack's MPI data for interpretation. He follows a well rehearsed method:
  - Reorient images to a standard left ventricle (LV) reference frame.
  - Locate brightest region (highest uptake) and assume normal perfusion.
  - Identify regions with reduced stress uptake as ischemic (reduced blood supply).
  - Compare rest and stress images to interpret severity of stenoses.

Myocardial Perfusion Imaging

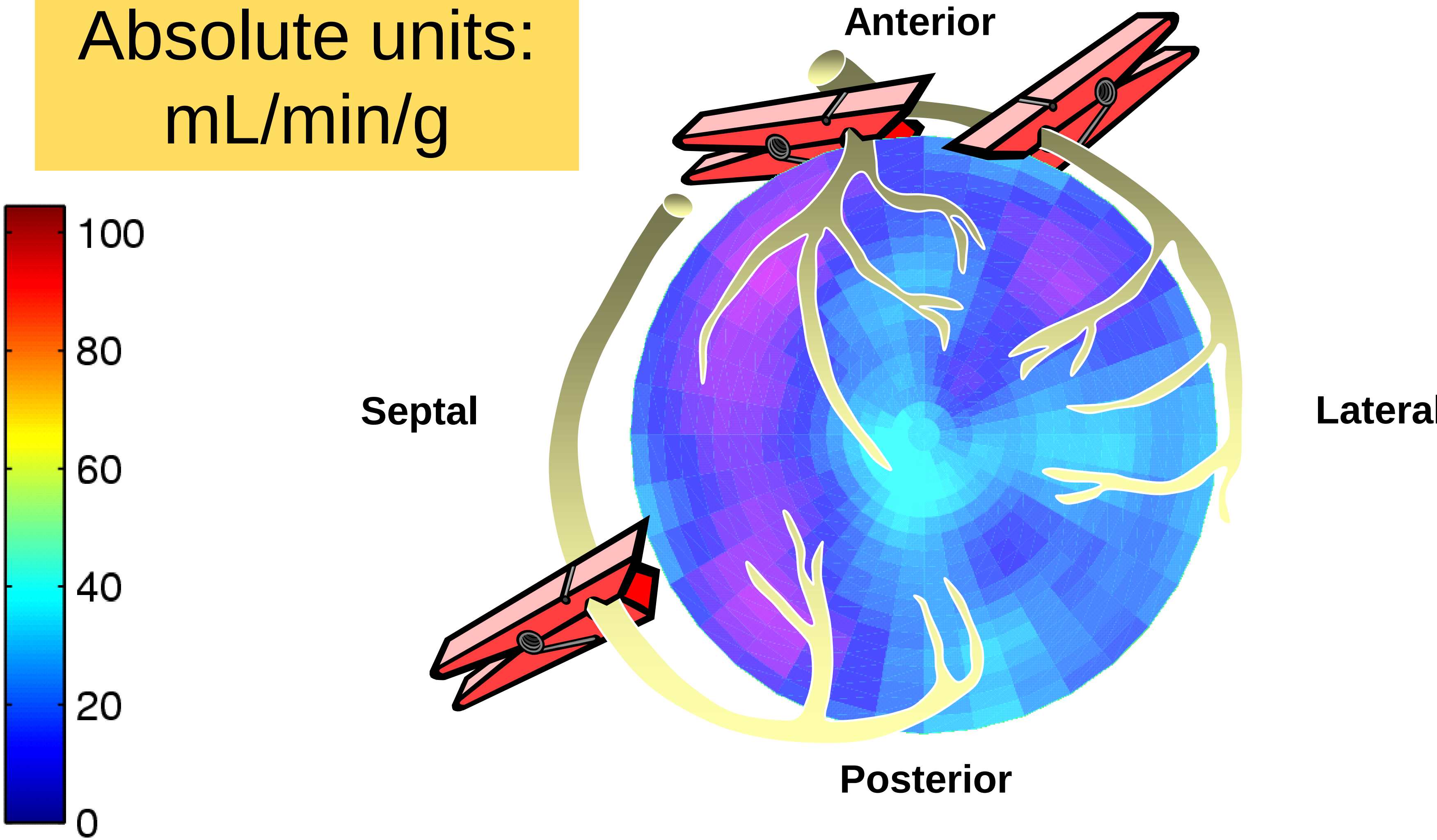


Myocardial Perfusion Imaging



Quantitative Myocardial Blood Flow

Absolute units: mL/min/g



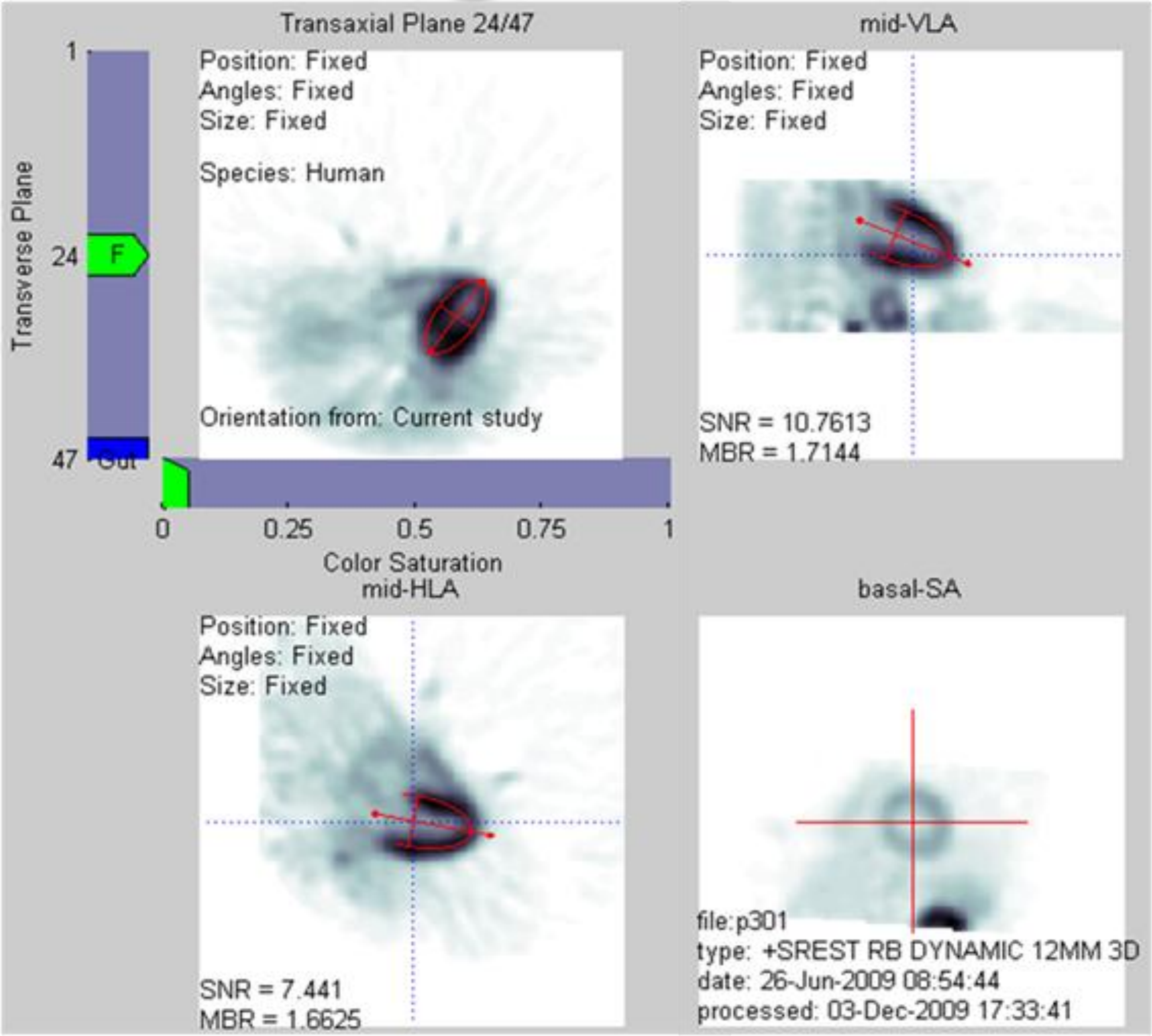
Quantitative MBF can detect multi-vessel disease and distributed disease of the micro-vasculature

Operator Dependent Variability (Chapter 2)

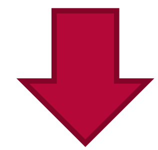
Klein R., Renaud J. M., Ziadi M. C., Thorn S. L., Adler A., Beanlands R. S., deKemp R. A.m "*Intra- and inter-operator repeatability of myocardial blood flow and myocardial flow reserve measurements using Rubdium-82 PET and a highly automated analysis program.*", J. Nucl. Cardiol. (in press)

- Description of highly automated MPI and MBF processing software.
- Assessment of operator dependent variability for MPI, MBF, and flow reserve.

Image Reorientation

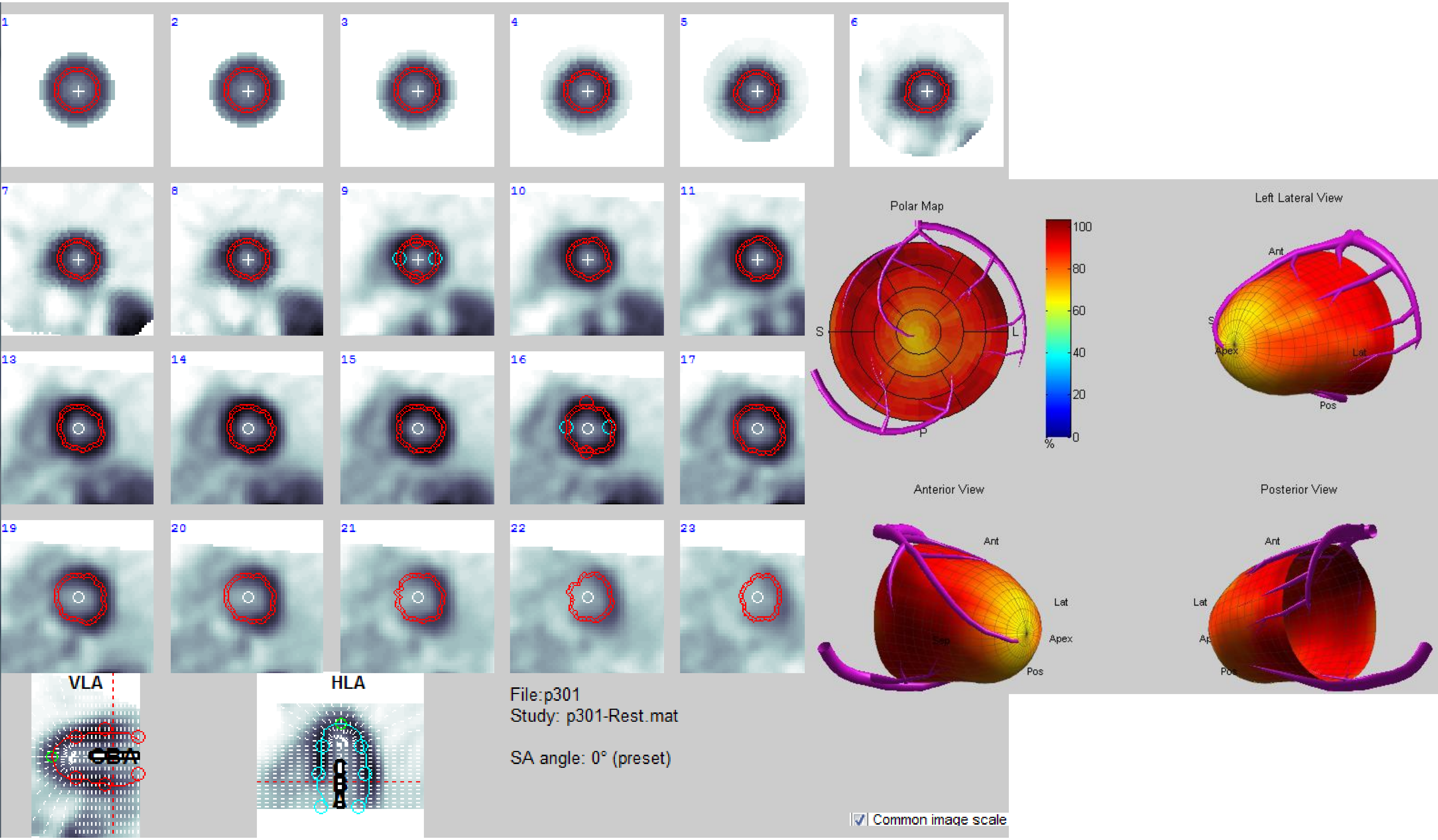


Camera reference frame

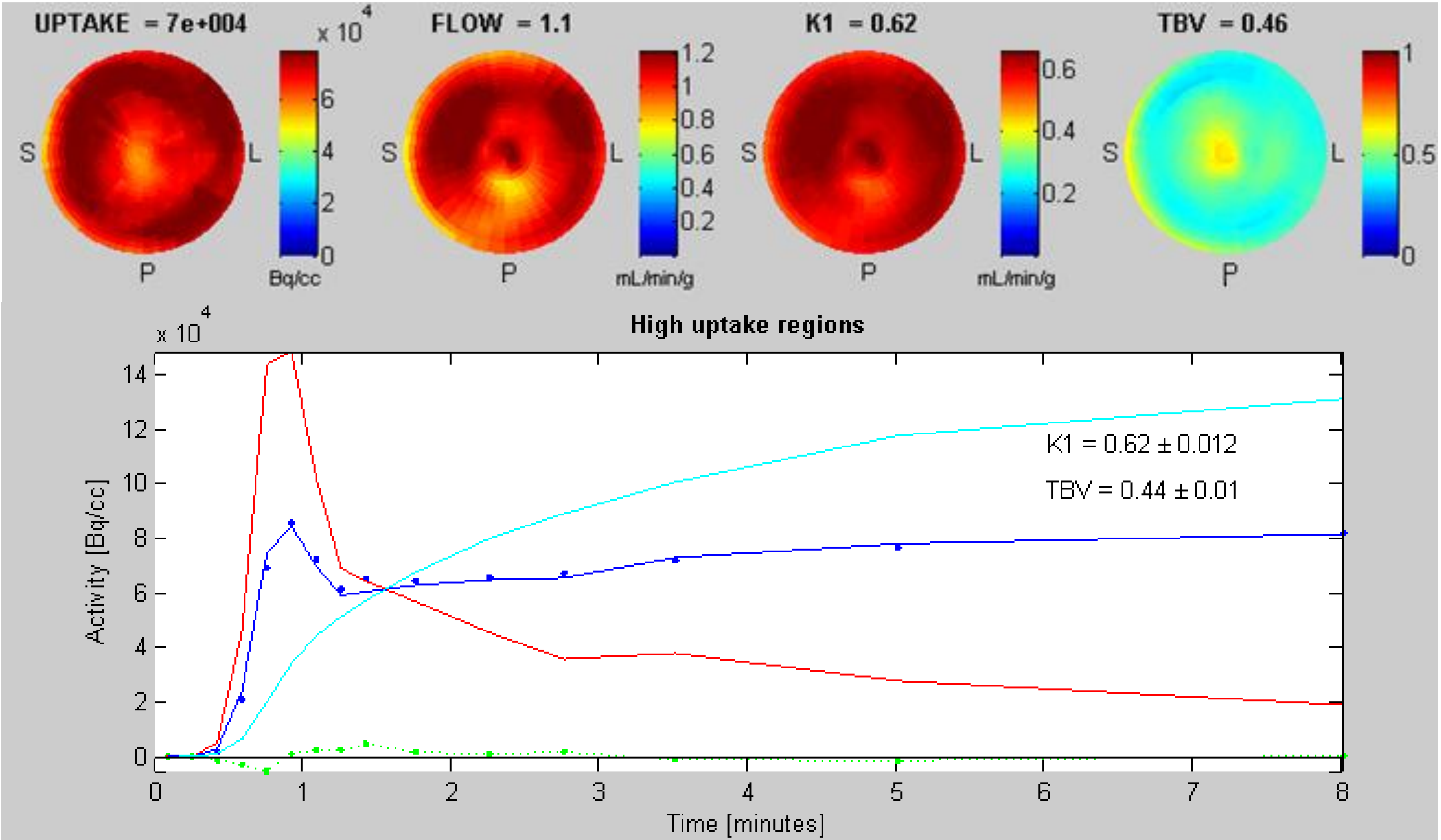


LV reference frame

LV + Blood Pool Segmentation



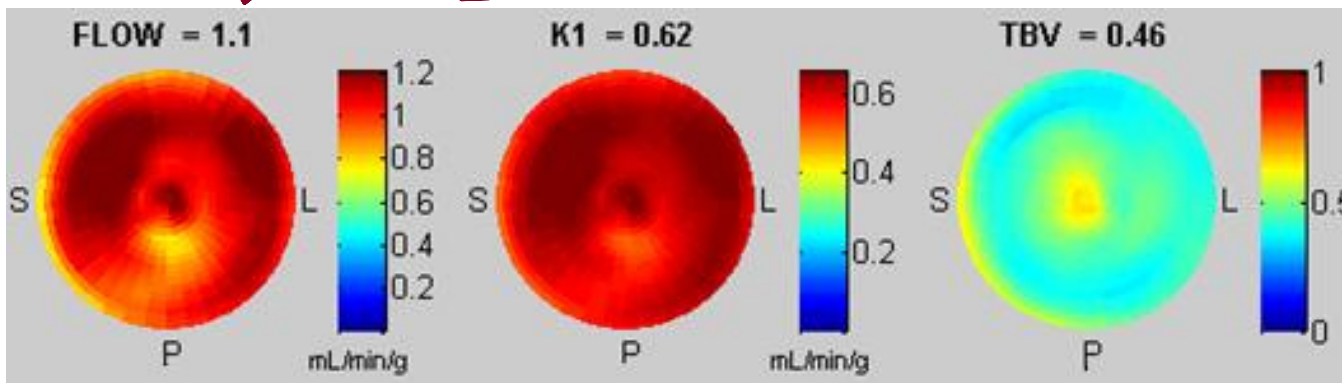
Kinetic Modelling



1-Compartment Kinetic Model

Renkin-Crone

$$\boxed{K_1 = (1 - a \cdot e^{-b/MBF})MBF}$$

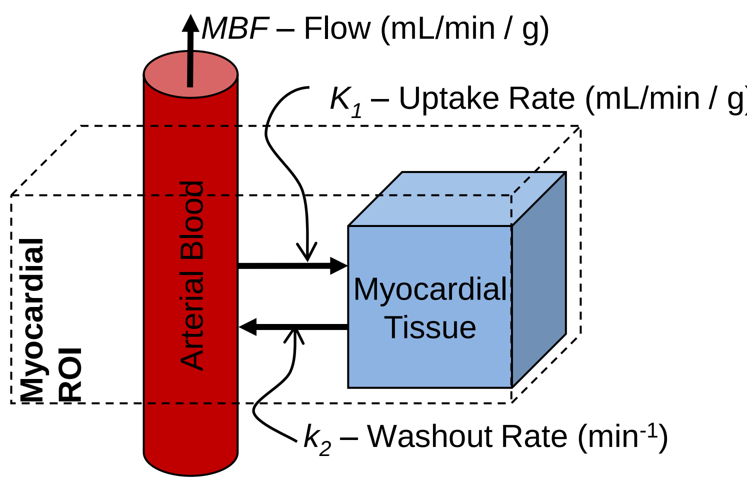


$$C_m(t) = (1 - TBV)C_t(t) + TBV \cdot C_a(t)$$

$$\frac{dC_t(t)}{dt} = K_1 \cdot C_a(t) - k_2 \cdot C_t(t)$$

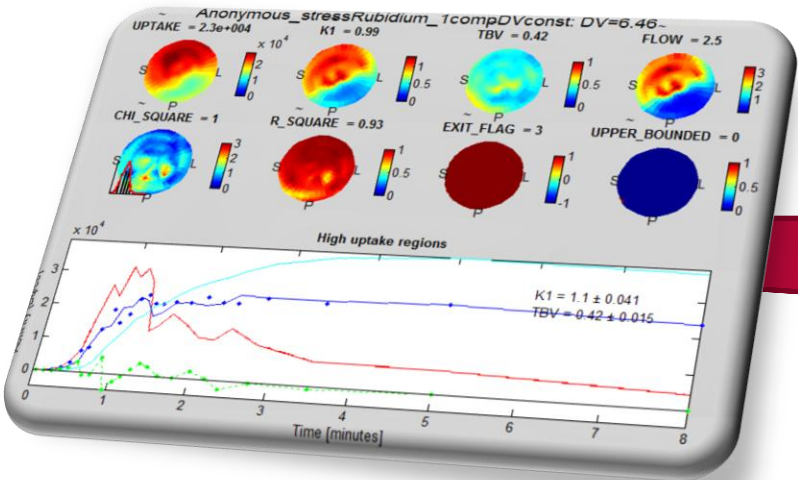
$$C_t(t) = C_a(t) \otimes m(t)$$

$$m(t) = K_1 e^{-k_2 t}$$

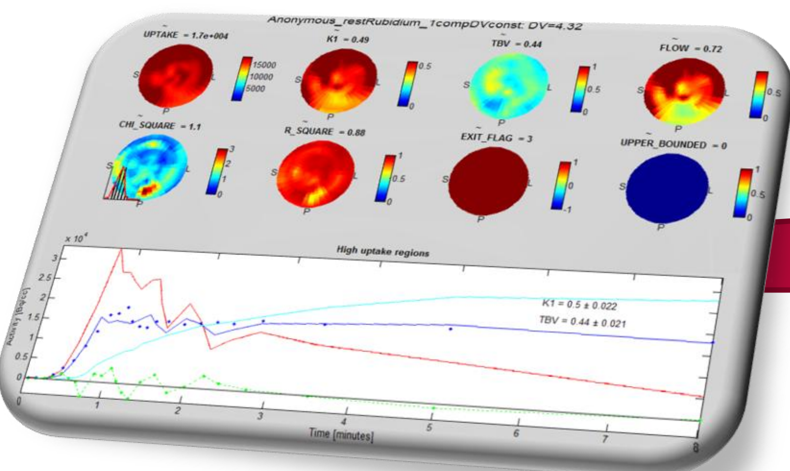


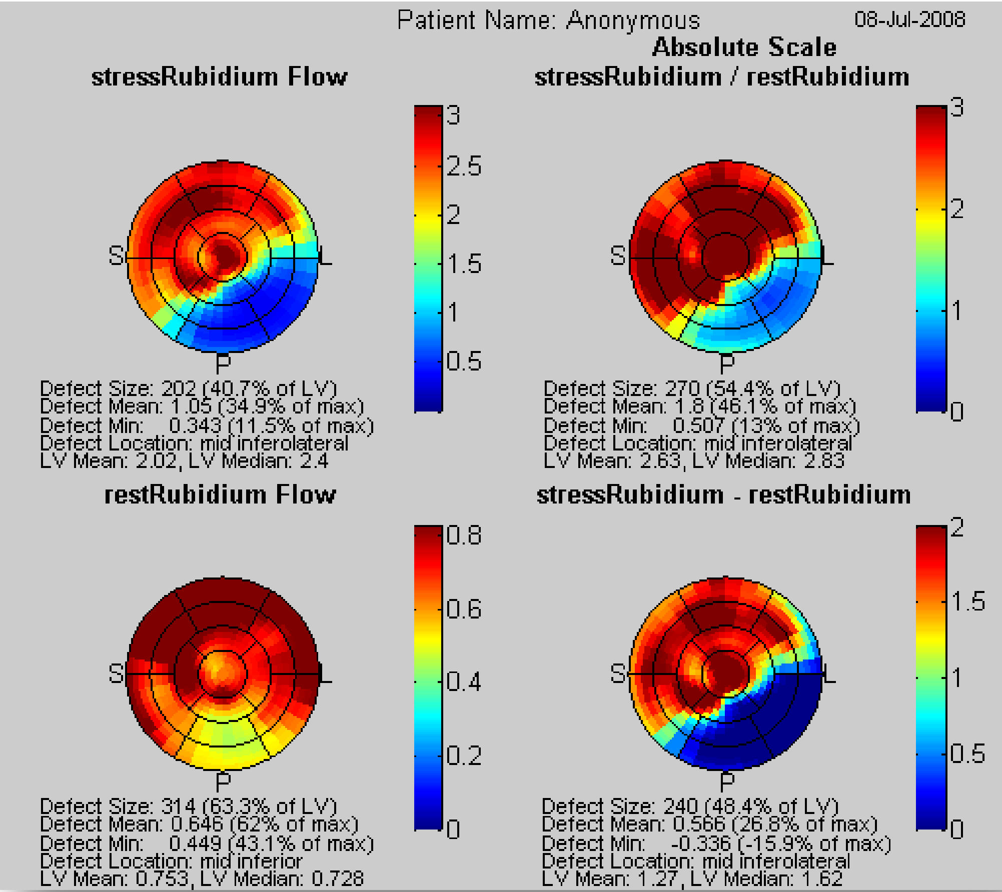
Coronary Flow Reserve

Stress

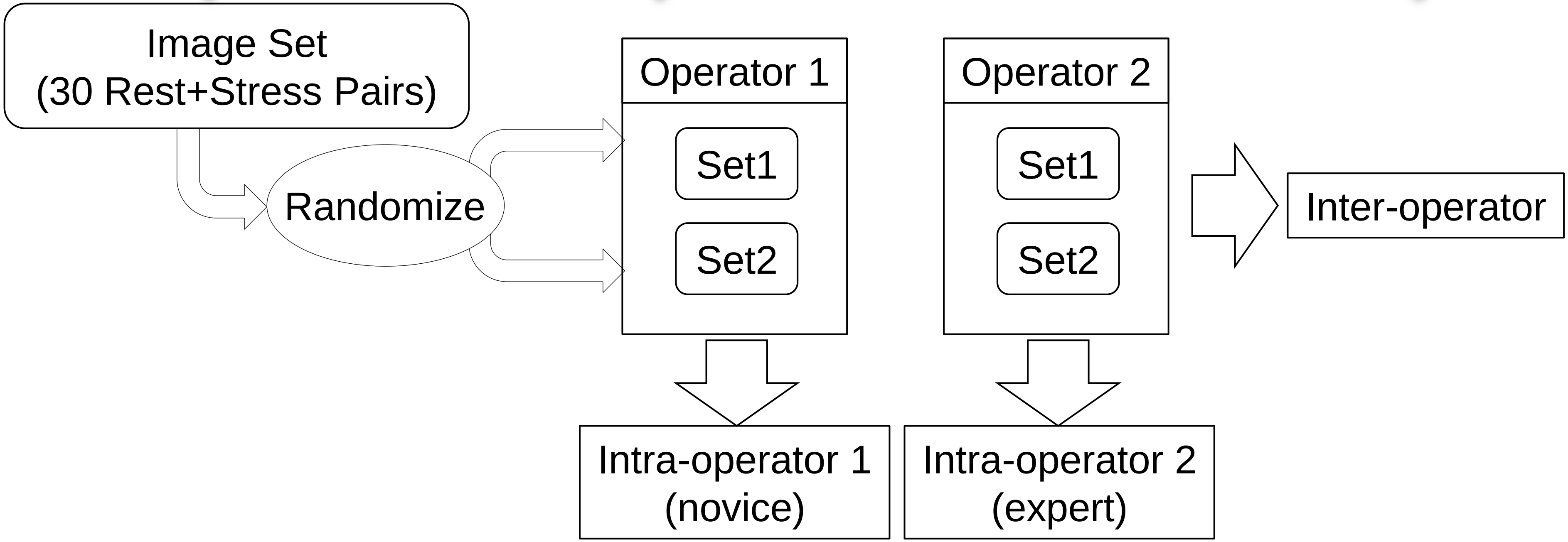


Rest

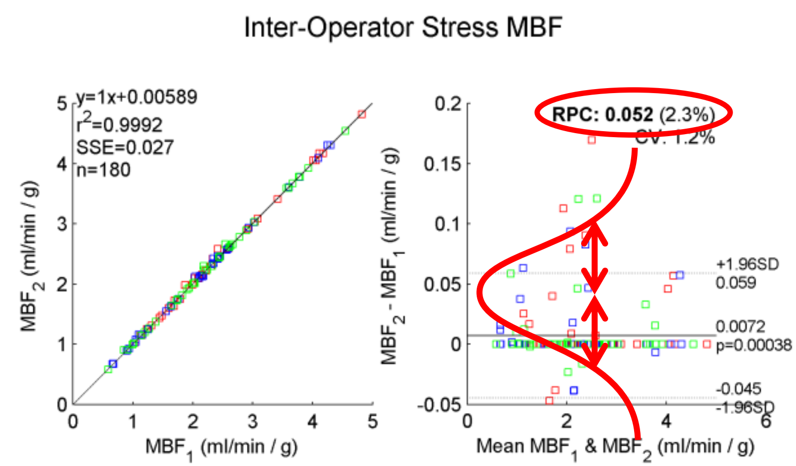




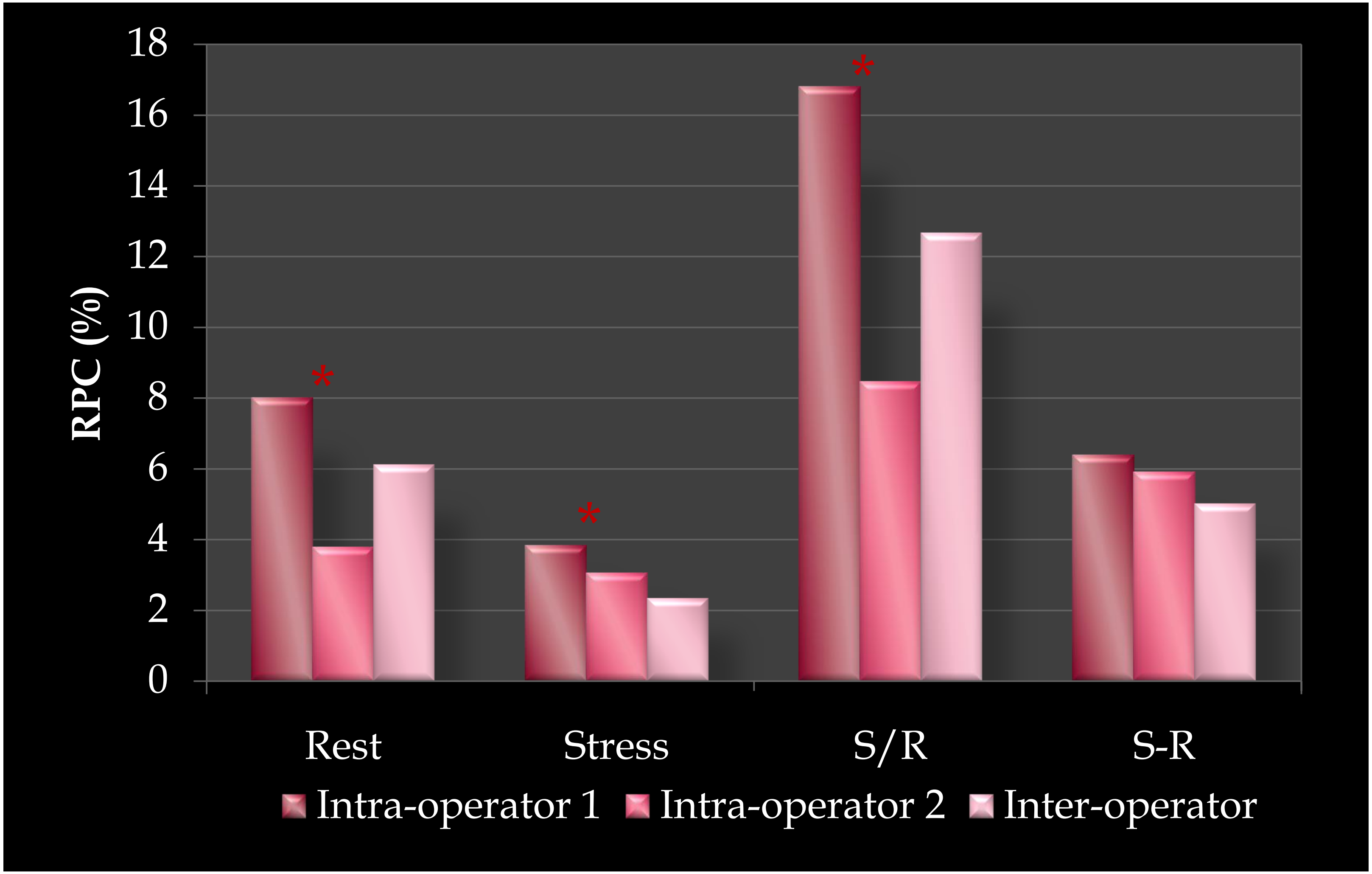
Operator Dependent Variability



- Rest MBF
- Stress MBF
- Stress MBF / Rest MBF
- Stress MBF- Rest MBF



MBF operator Variability

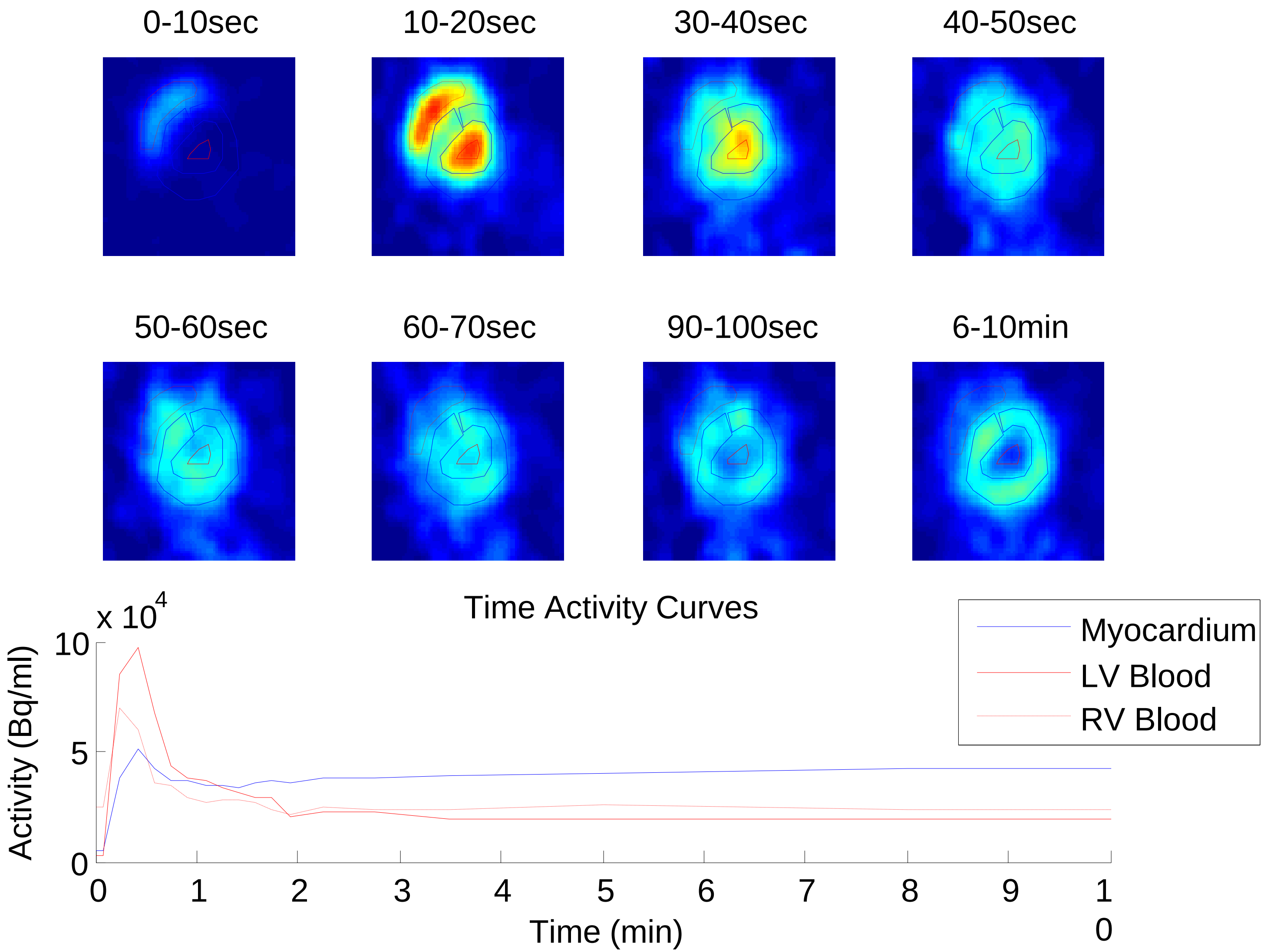


- Experienced operator had less variability than novice operator.
- Stress-Rest less variable than stress/rest.

Conclusion

- Excellent operator dependent variability.
  - Comparison with reported results using other software programs
- Reduced variability with experience.
  - Need to train users, but fast learning curve.
- Importance of reports for quality assurance.
  - Ensuring that results are reliable.
- To Jack:
  - MBF quantification can detect multi-vessel disease + microvascular disease.
  - Diagnosis is not sensitive to operator variability.

Spillover Signal Contamination

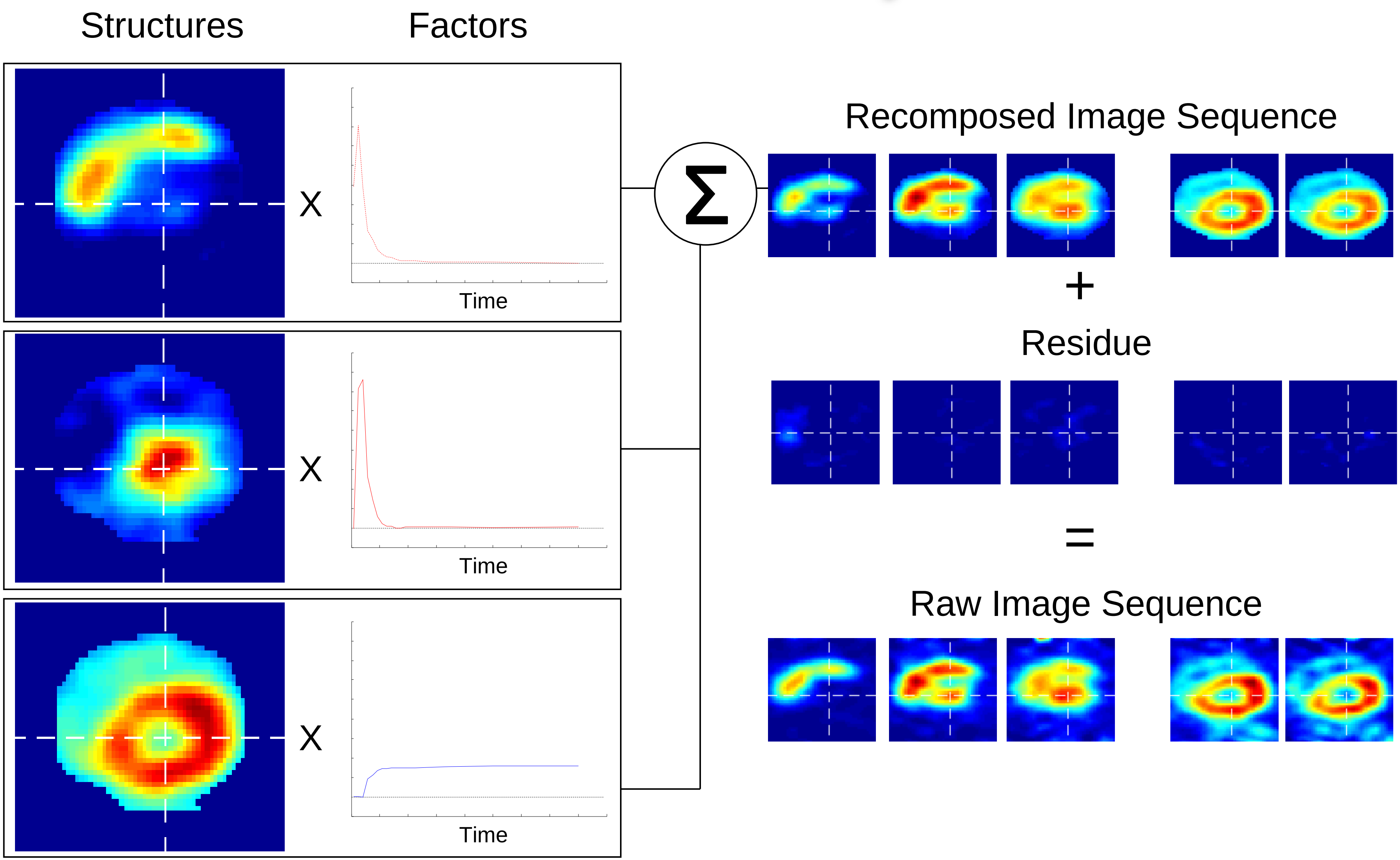


Constrained Factor Analysis (Chapter 3)

Klein R., Bentourkia M., Beanlands R.S., Adler A., deKemp R.A., "*A Minimal Factor Overlap Method for Resolving Ambiguity in Factor Analysis of Dynamic Cardiac PET*", IEEE-Med. Imag. Conf Record 2007;5(10):3268-72.

- Description of new Minimal Factor Overlap factor analysis (MFO).
- Comparison of MFO to previously published Minimal Spatial Overlap factor analysis (MSO)

Factor Analysis



Dynamic Image Decomposition

- Image decomposition is not unique!
  - Additional constraints must be imposed.
    - Constraints should be representative of physical and physiological processes to ensure accurate solution.
- Typical Constraints include:
  - Non-negative factors and structures
  - Minimal Structure Overlap (MSO)
    - Overlooks existence of arterial blood in the myocardium (tissue blood volume) and spillover due to limited spatial resolution.
- Proposed Minimal Factor Overlap (MFO)
    - No strict physiologic evidence to support assumption of maximally different temporal responses.
- Physiologically accurate constraints still needed.

Kinetic Model Based Factor Analysis (Chapter 4)

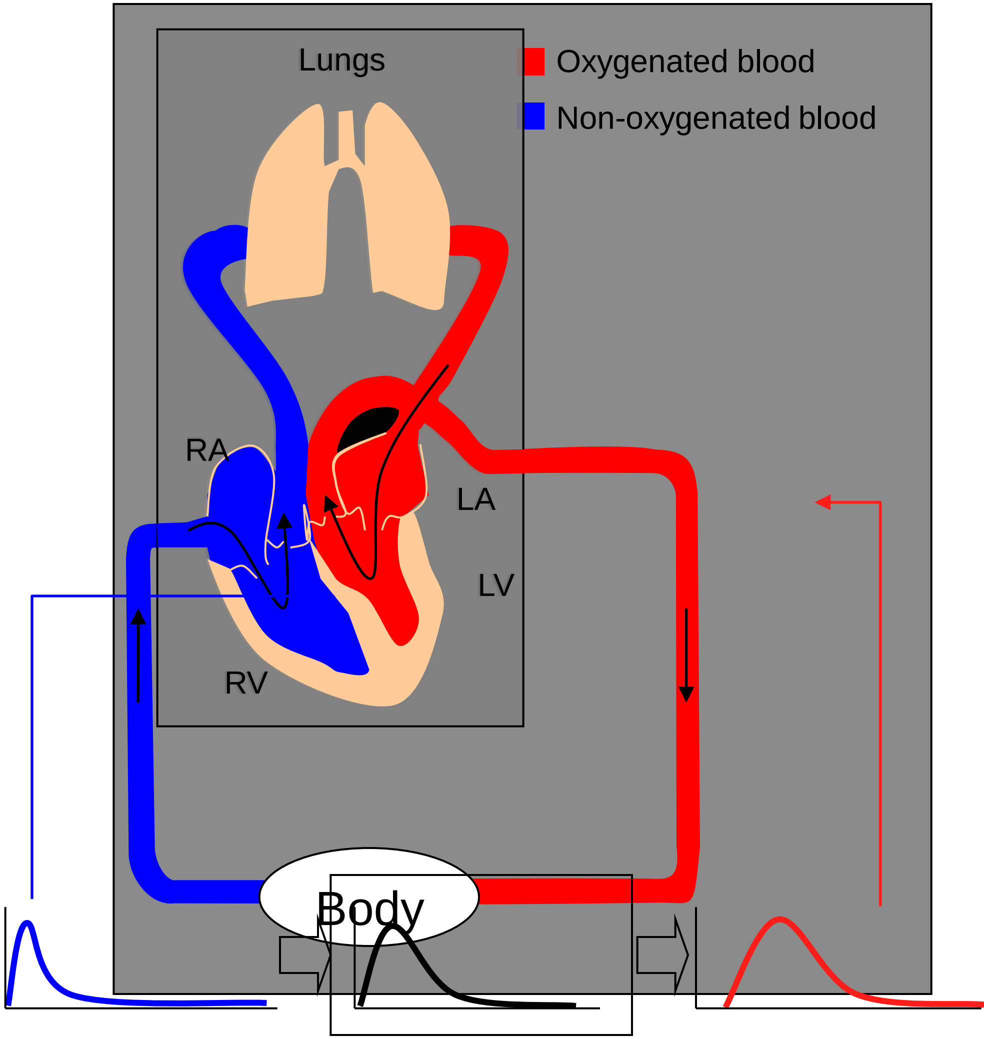
Klein, R., Beanlands, R. S., Wassenaar, R. W., Thorn, S., Lamoureux, M., DaSilva, J. N., Adler, A., deKemp, R. A., "*Model Based Factor Analysis of Dynamic Sequences of Cardiac Positron Emission Tomography*", Med. Phys. (In Press).

- Description of new kinetic model-based factor analysis (MB).
- Comparison of MB to previously published minimal spatial overlap factor analysis (MSO)

Modeling LV blood Factor

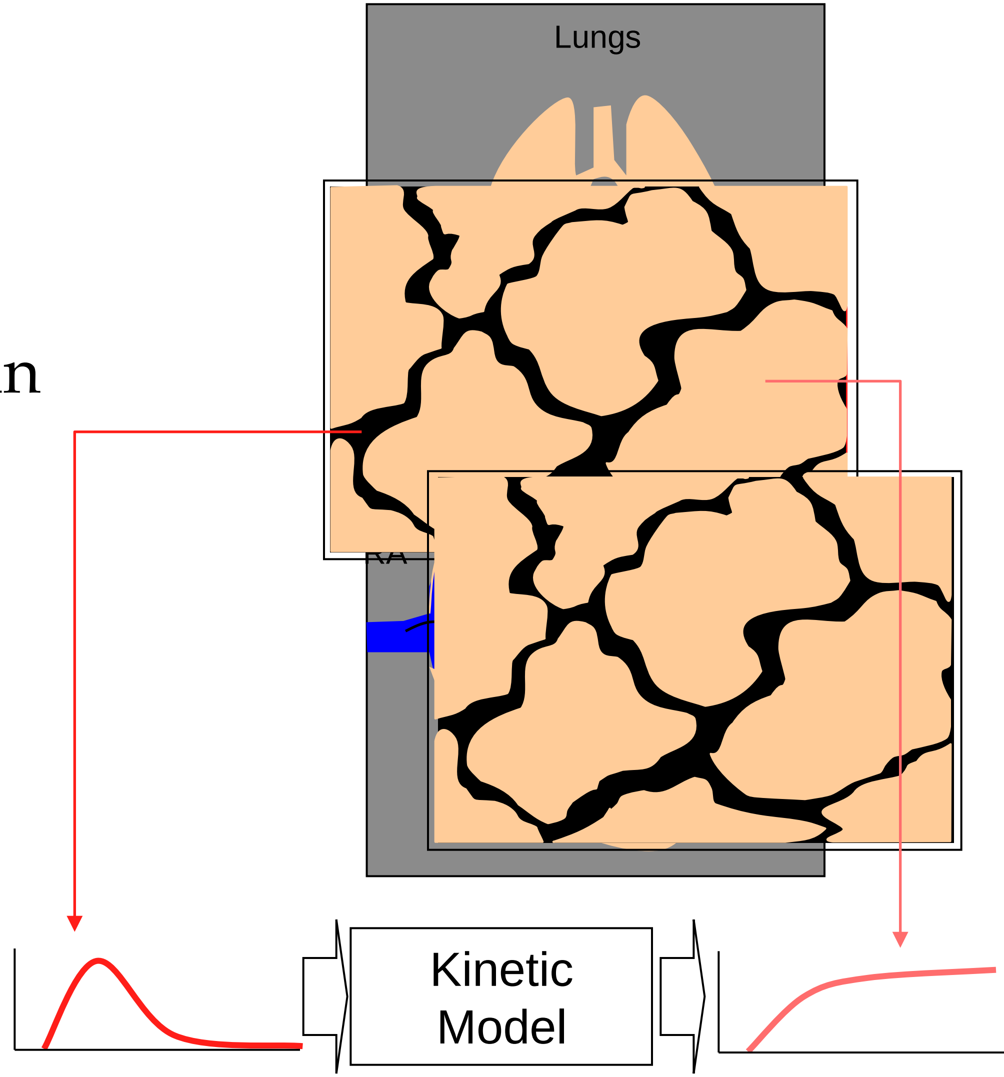
- RA+RV blood flows through the lungs en route the LA+LV resulting in a delay and mixing.
  - Can be described by a Shifted – Gamma Variate Response Function *

* K. Iwata, JNM, 1988 and
M. T. Madsen, PMB, 1992



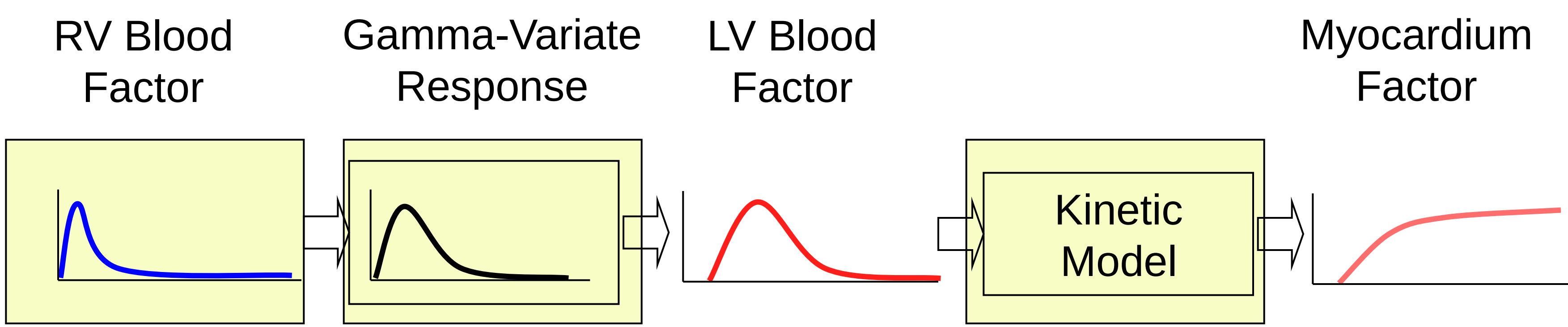
Modeling Tissue Factors

- Blood from the LV flows to the myocardium (and other tissues)
  - Can be described by an appropriate kinetic model



Model Based Factor Analysis

- Instead of resolving 3 factors
  - 3 X (17 time frames – 1)= 48 parameters
- We can resolve
  - 1 X (17 time frames – 1)
    - + 2 parameters (gamma-variate function)
    - + 1 parameter (1 compartment model)
  - Factors are tightly coupled.
  - More control over which factors are resolved.



MSO and MB Factor Analysis

MSO

Step 1 – Decomposition

$$C_{MSO} = W_E\,|\boldsymbol{\varepsilon}| + W_{NF}\,f_{neg}(\boldsymbol{F'}) + W_{NS}\,f_{neg}(\boldsymbol{S'})$$

Step 2 – Rotation (MSO constraint)

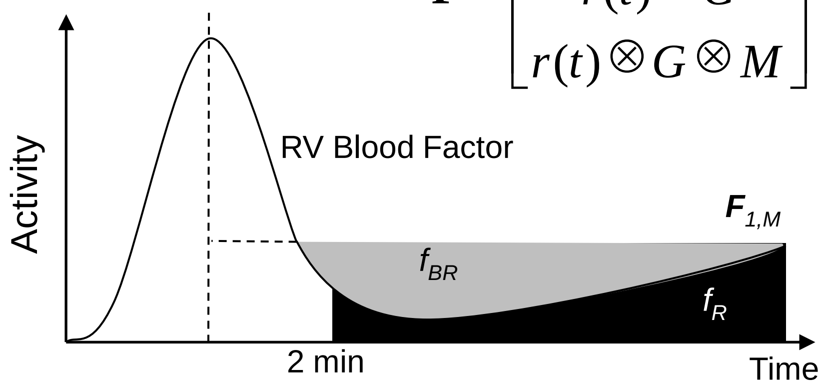
$$f_{tot}^{MSO} = f_{neg}(\mathbf{F'R}) + f_{neg}(\mathbf{R}^{-1}\mathbf{S'}) + b f_{ovl}(\mathbf{R}^{-1}\mathbf{S'})$$

$$f_{ovl}(\mathbf{X}) = \sum_{p=1}^{P}\sum_{q=p+1}^{P}\sum_{i=1}^{N} \frac{|x_{ip}|}{\sqrt{\sum_{j=1}^{N} x_{jp}^2}} \frac{|x_{iq}|}{\sqrt{\sum_{j=1}^{N} x_{jq}^2}}$$

MB

$$C_{MB} = W_E\,|\boldsymbol{\varepsilon}| + W_{NF}\,f_{neg}(\mathbf{F}) + W_{NS}\,f_{neg}(\mathbf{S}) + W_{BR}\,f_{BR} + W_R f_R$$

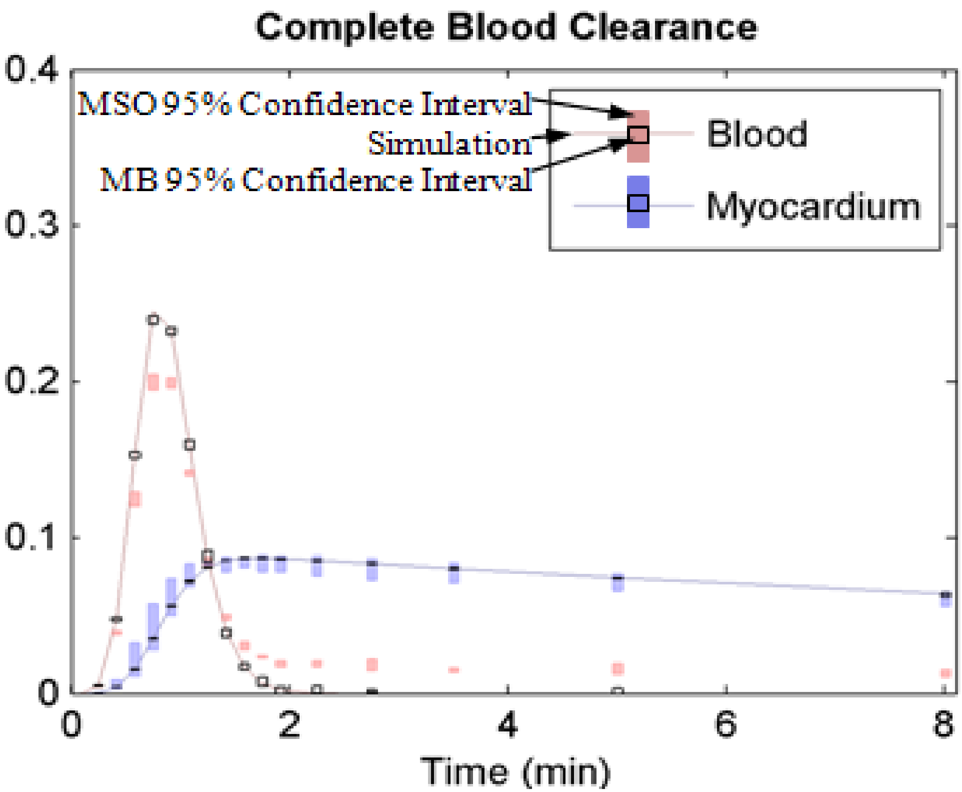
$$\mathbf{F} = \begin{bmatrix} r(t) \\ r(t)\otimes G \\ r(t)\otimes G \otimes M \end{bmatrix}^T$$

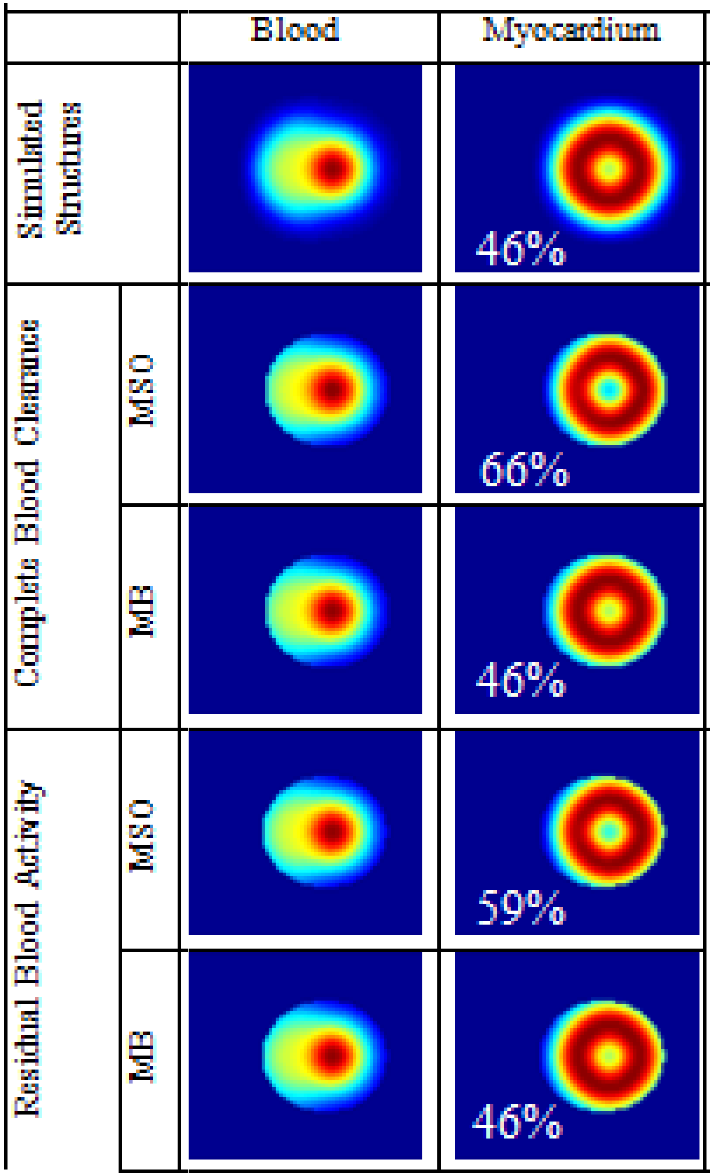


- Error Weight: $W_E = 1/|\boldsymbol{\varepsilon}|$
- Non-negative Factor Weight: $W_{NF} = 100$
- Non-negative Structure Weight: $W_{NS} = 1$

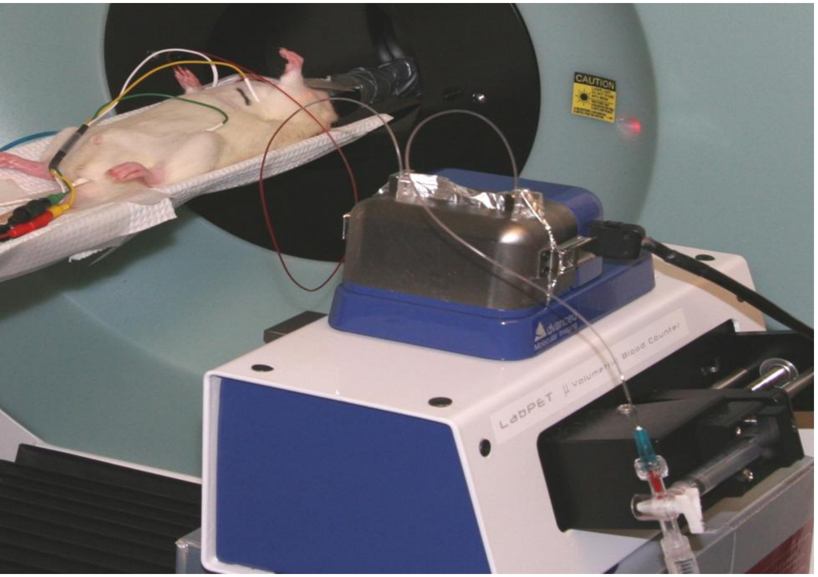
Simulation Results

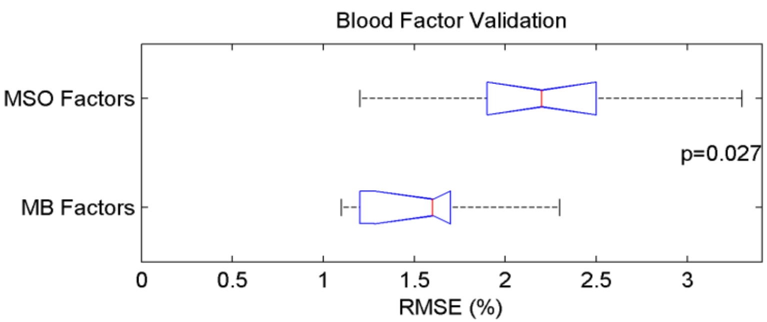
	Specie	MSO	MB	p-value
Factor	Canine	0.5%	0.2%	<0.001
	Rat	0.9%	0.2%	<0.001
Structure	Canine	4.7%	3.0%	<0.001
	Rat	6.7%	3.0%	<0.001

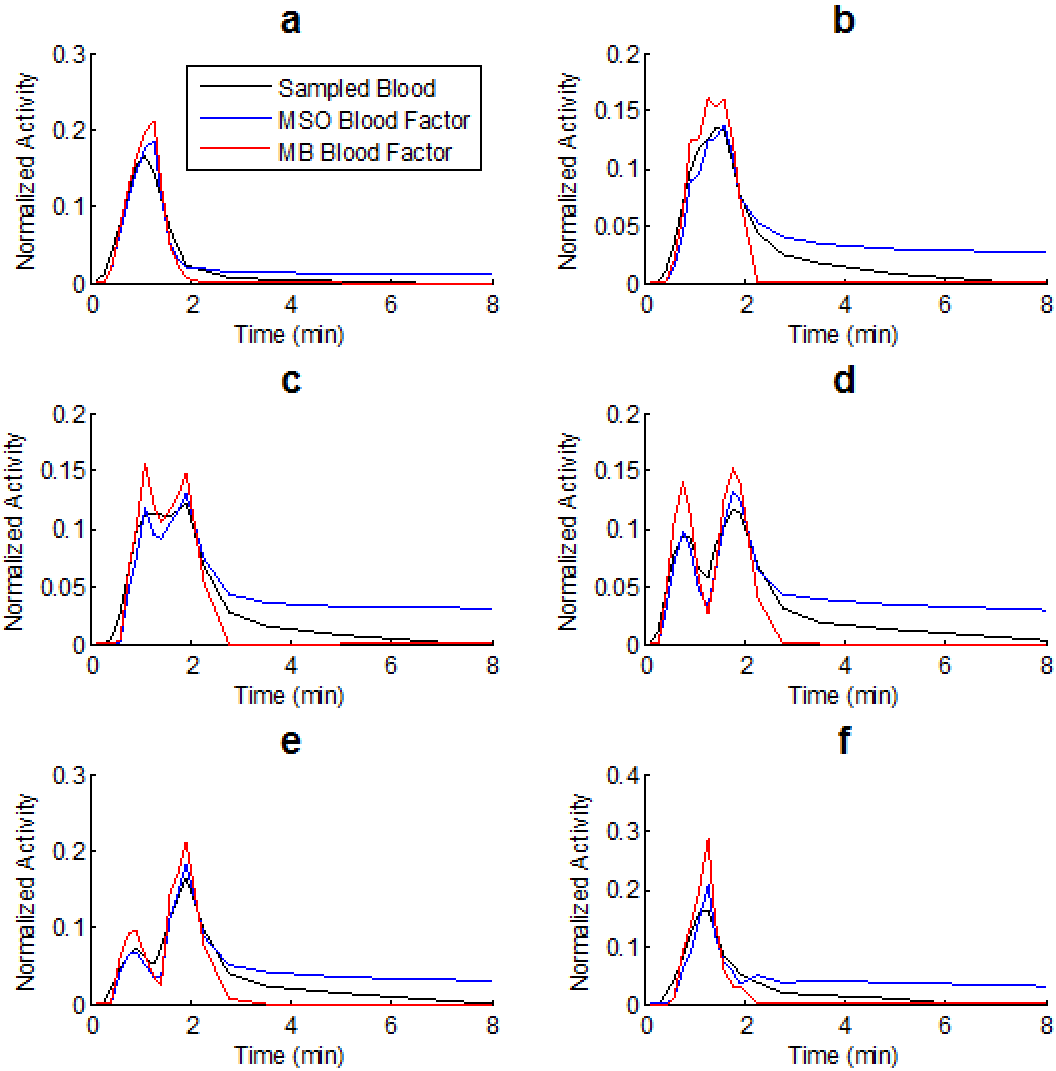




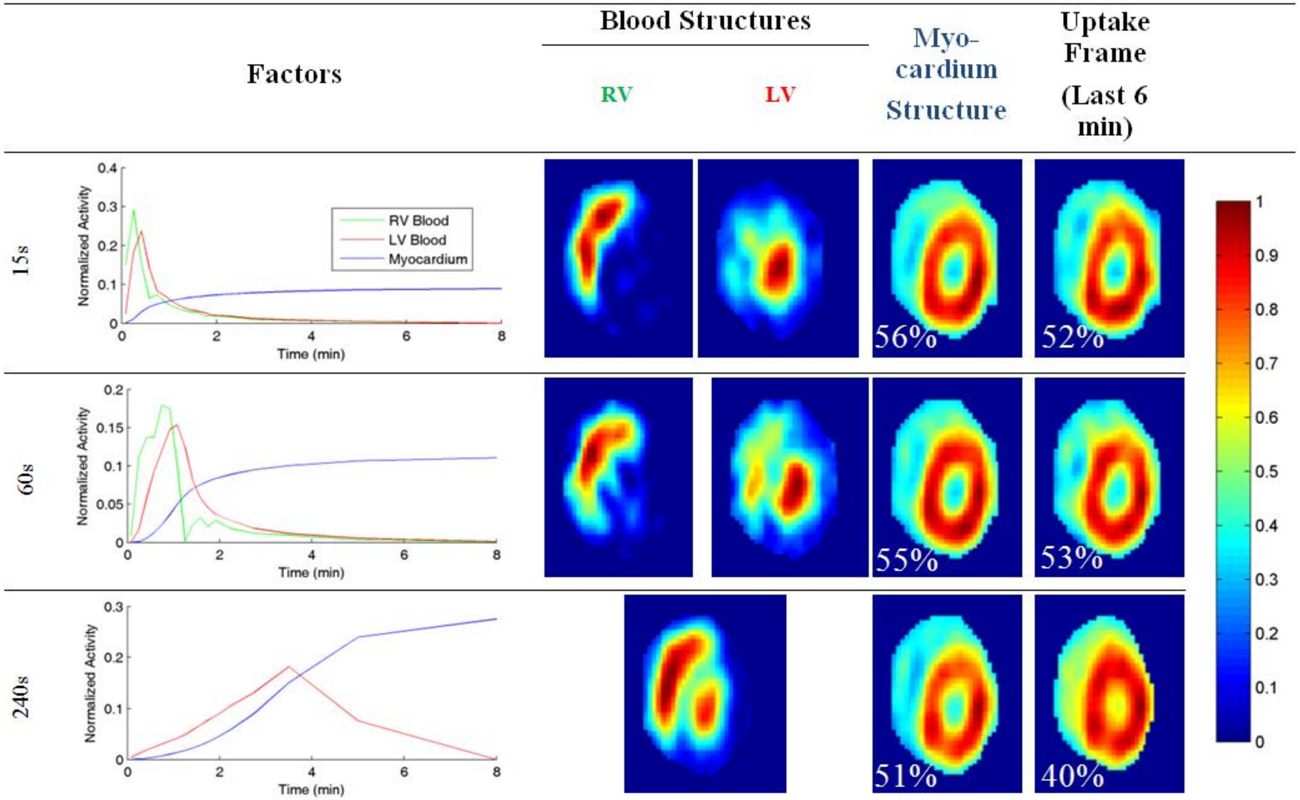
Arterial Blood Sampling



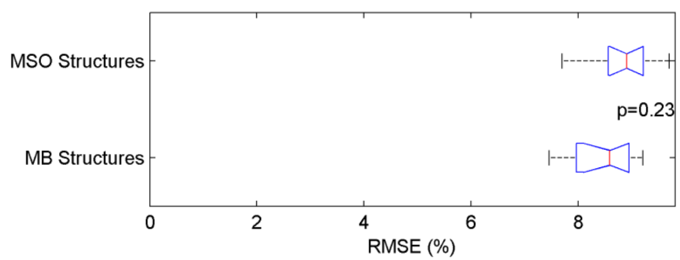




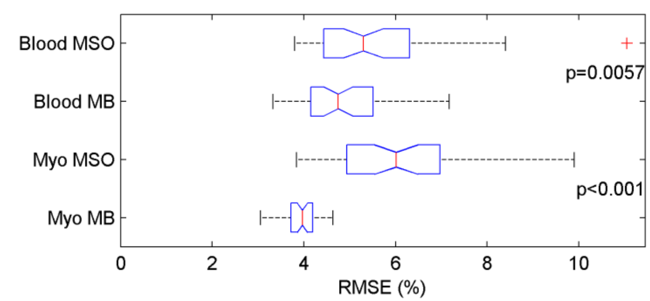
Variable Infusion Durations



Blood structure agreement with CO image



Structure Reproducibility



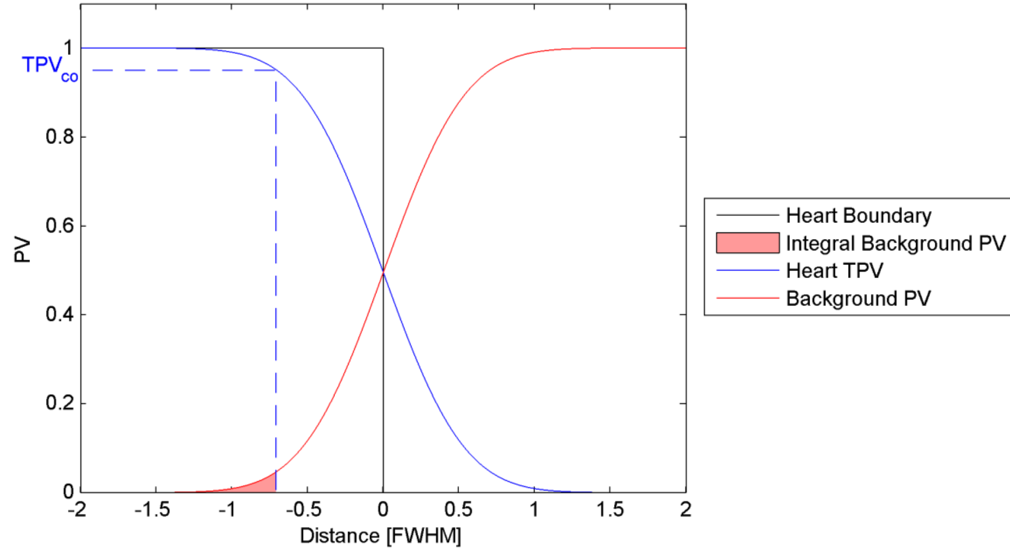
MBF Quantification (Chapter 5)

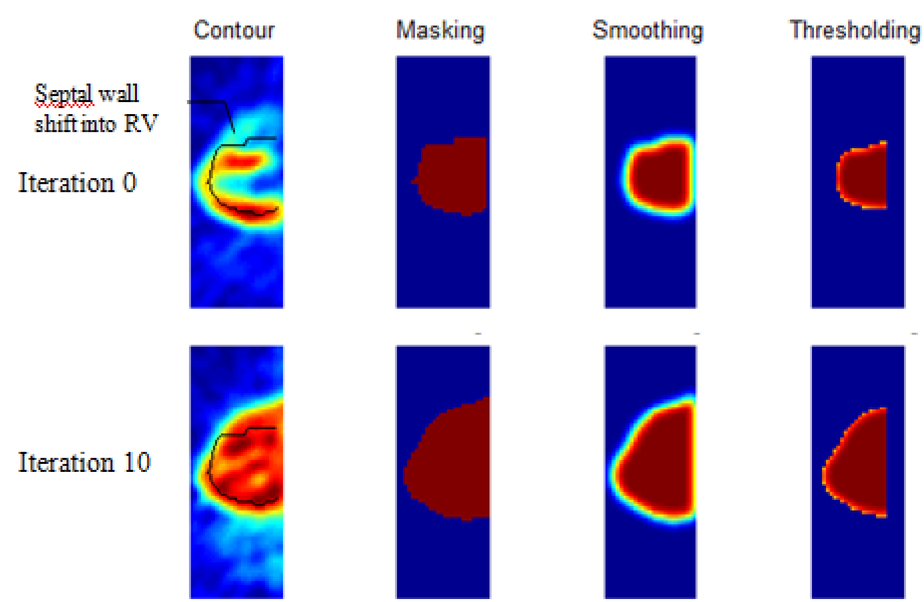
Klein R., Yoshinaga K., Katoh C., Adler A., Beanlands R.S., Tamaki N., deKemp R.A., "*Improved Homogeneity of Normal MBF Using Factor-Analysis with ^{82}Rb PET", S. Nucl. Med. Annual Meeting 2010 (Accepted)*

- Scaling of factors.
- MBF quantification using scaled blood factors.
- Evaluation of MBF accuracy and polarmap uniformity.

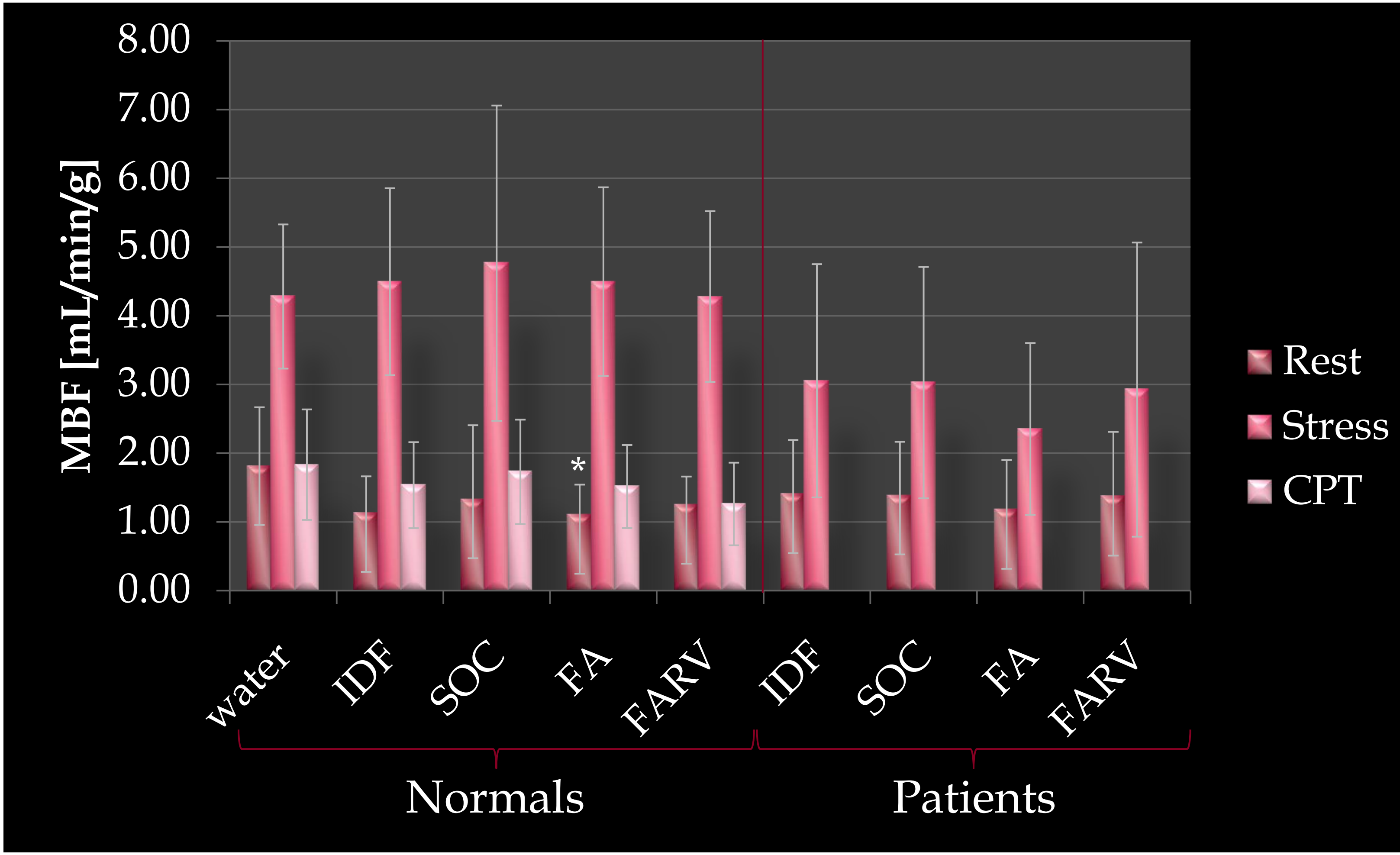
Scaling of Factors and Structures

- Structure scaling based on total partial volume (TPV) = 1 inside heart region.
- Iteratively estimates the heart region and TPV.

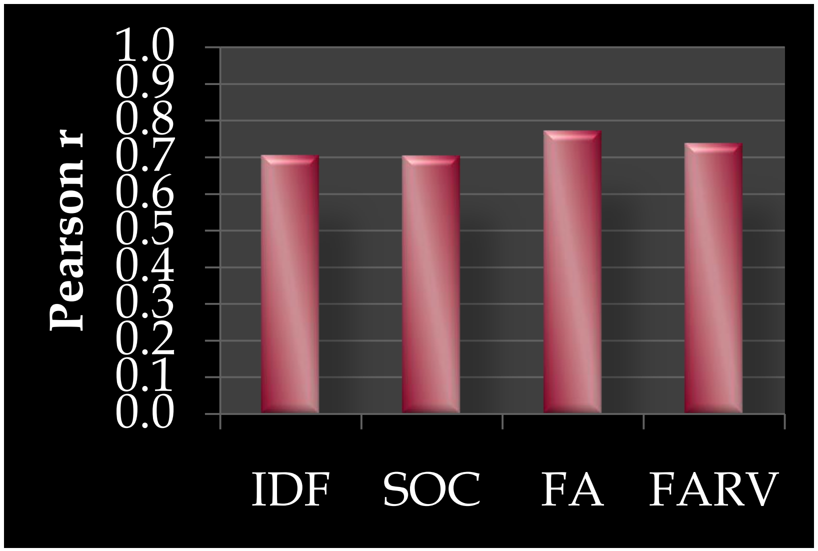


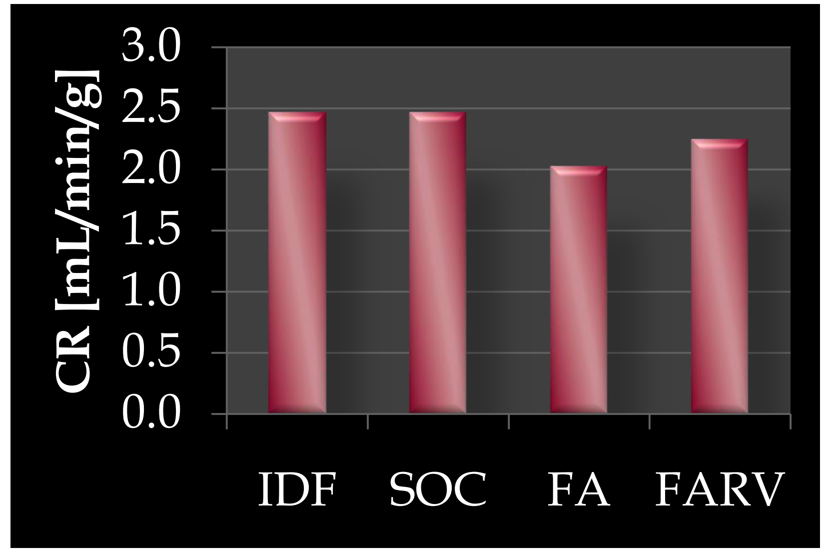


MBF in Normals and Patients



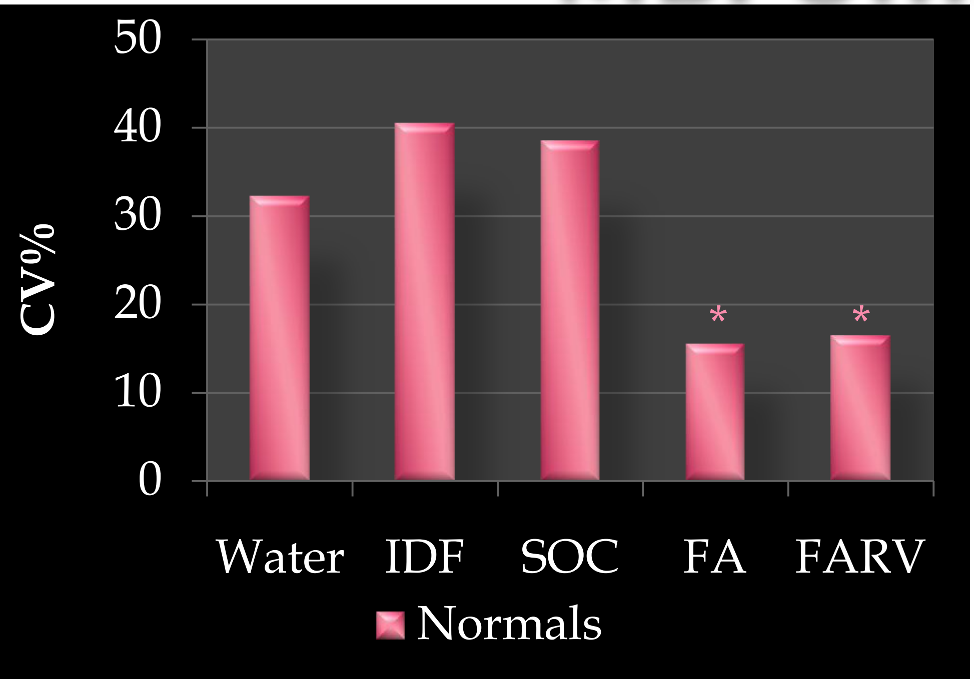
MBF Accuracy



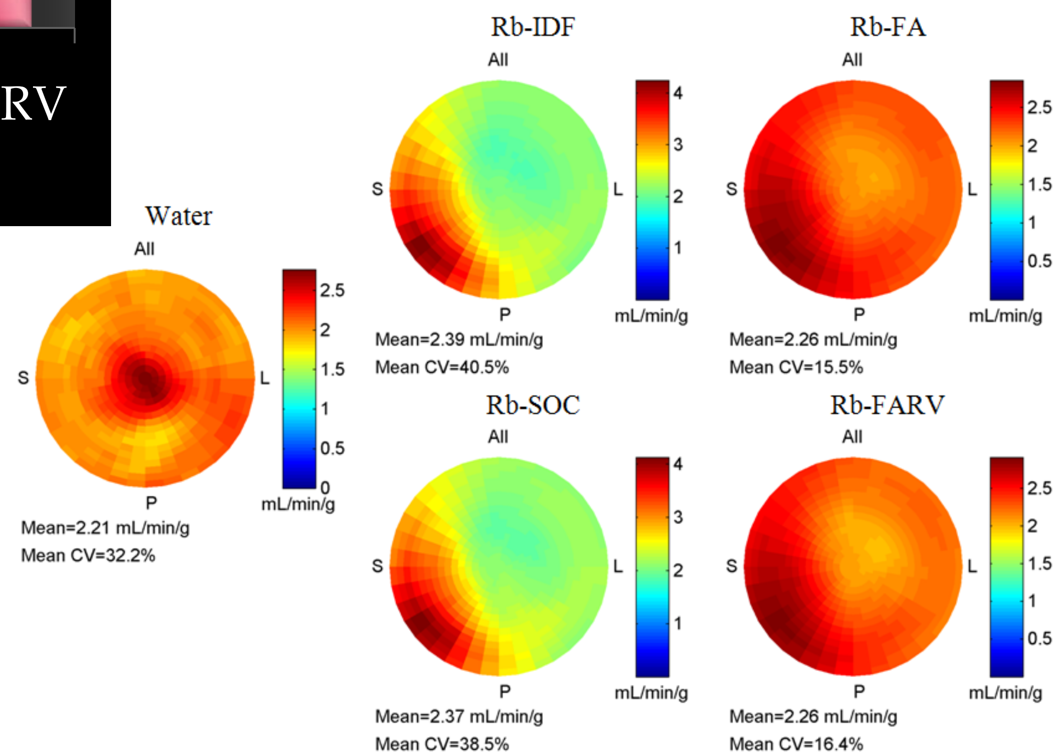


- Bland-Altman analysis with water imaging as a standard.
- No significant difference in accuracy between methods.

MBF Uniformity



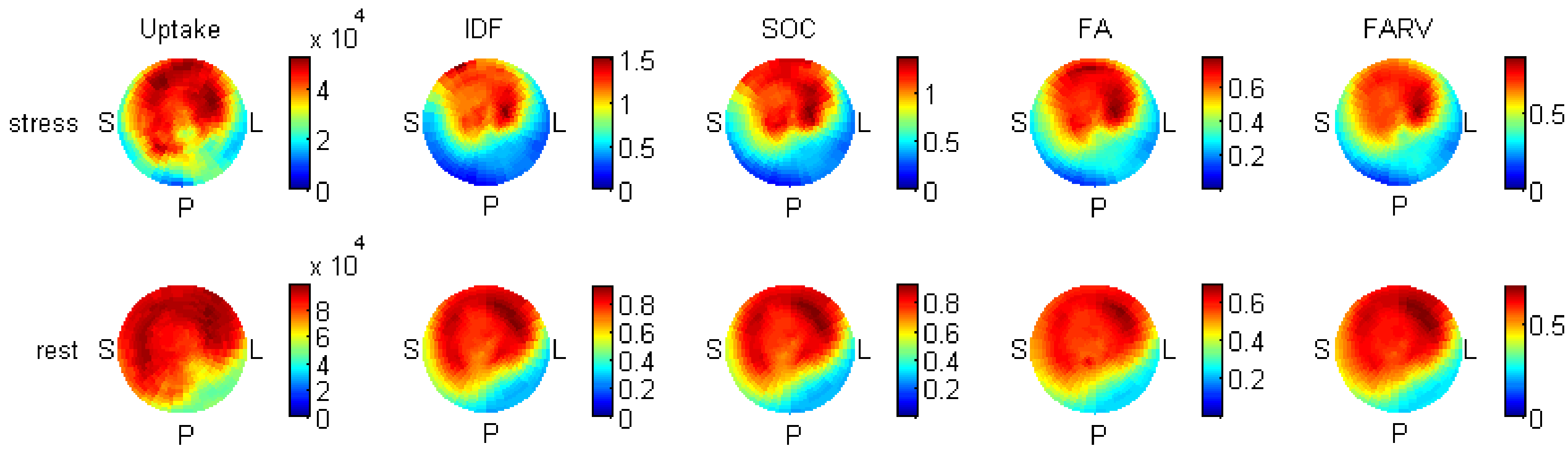
Greater uniformity in normal population



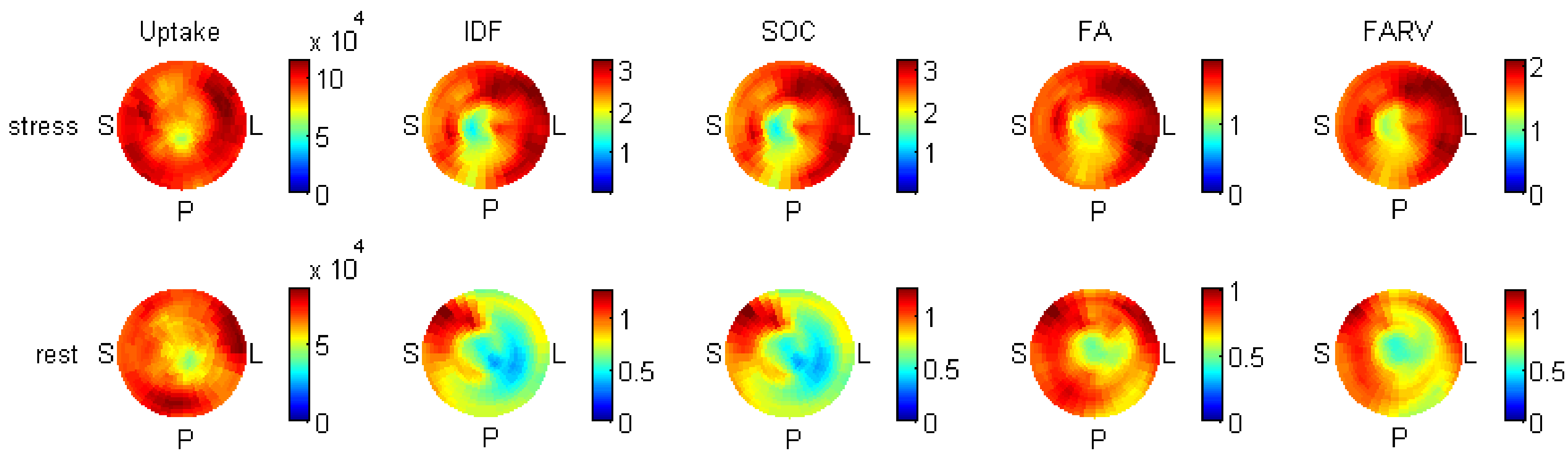
- Lateral region most uniform
- IDF and SOC have higher MBF in septum due to RV spillover.

MBF in Patients

Example case with good PM correspondence



Example case with poor PM correspondence



Discussion and Future Direction (Chapter 6)

- Benefit to Jack:
  - More reliable diagnosis (comparison to databases)
  - Ability to detect smaller changes in longitudinal studies (follow up studies)
  - Detection of smaller regional variations (localization of stenoses)
- Further Validation:
  - Animal Studies:
    - Validation using invasive blood flow measurements (microspheres)
    - Blood sampling in larger animals (dogs, pigs)
  - Human studies
    - Various population cohorts
    - Application to other tracers (other physiologic functions)

THANK YOU FOR YOUR ATTENTION

Other Relevant Publications

- Yoshinaga K., **Klein R.**, Tamaki N., "*Generator Produced Rubidium-82 Positron Emission Tomography Myocardial Perfusion Imaging – From Basic Aspects to Clinical Applications*", J. Of Cardiol. 2010;55(2):163-173.
- Lekx K. S., deKemp R. A., Beanlands R. S. B., Wisenberg G., Wells R. G., Stodilka R. Z., Lortie M., **Klein R.,** Zabel P., Kovacs M. S., Sykes J., Prato F. S., "*Quantification of regional myocardial blood flow in a canine model of stunned and infarcted myocardium: comparison of rubidium-82 positron emission tomography with microspheres*", Nucl. Med. Commun., 2010;31(1):67-74.
- Lekx K. S., deKemp R. A., Beanlands R. S. B., Wisenberg G., Wells G., Stodilka R. Z., Lortie M., **Klein R.**, Zabel P., Kovacs M. S., Sykes J., Prato F. S., "*3D versus 2D dynamic ^{82}Rb myocardial blood flow imaging in a canine model of stunned and infarcted* myocardium", Nucl. Med. Commun., 2010;31(1):75-81.
- Lortie, M., Beanlands, R. S., Yoshinaga, K., **Klein, R.**, DaSilva, J. N., deKemp, R. A., "*Quantification of myocardial blood flow with ^{82}Rb dynamic PET imaging*", Eur. J. Nucl. Med. and Mol. Imaging., 2007;34(11):1765-74.