Accuracy and Precision of PET-derived Absolute Myocardial Blood Flow

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Disclosures

- Bracco – consultant and physician educator
- CDL – consultant and physician educator

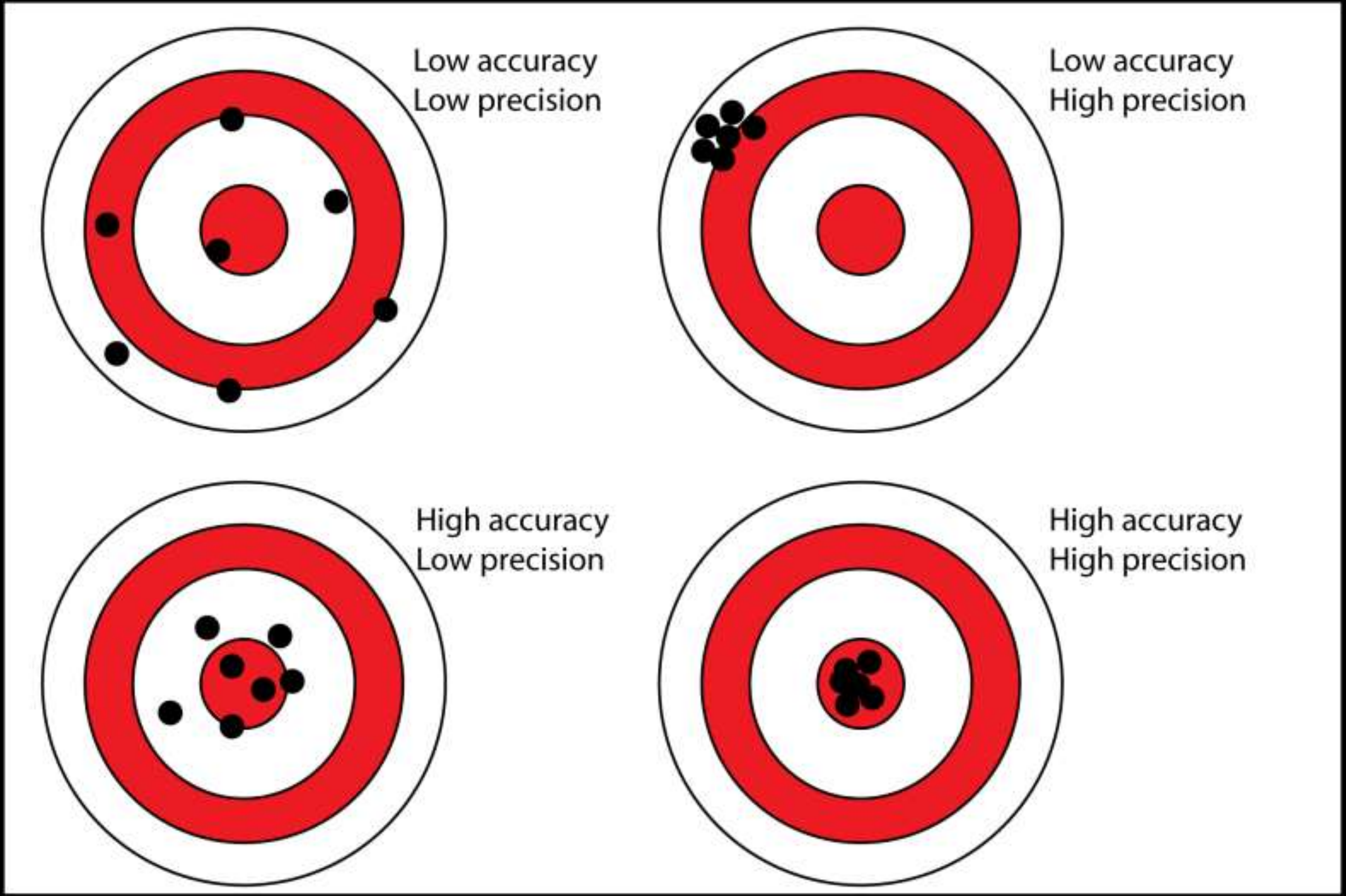
Objectives

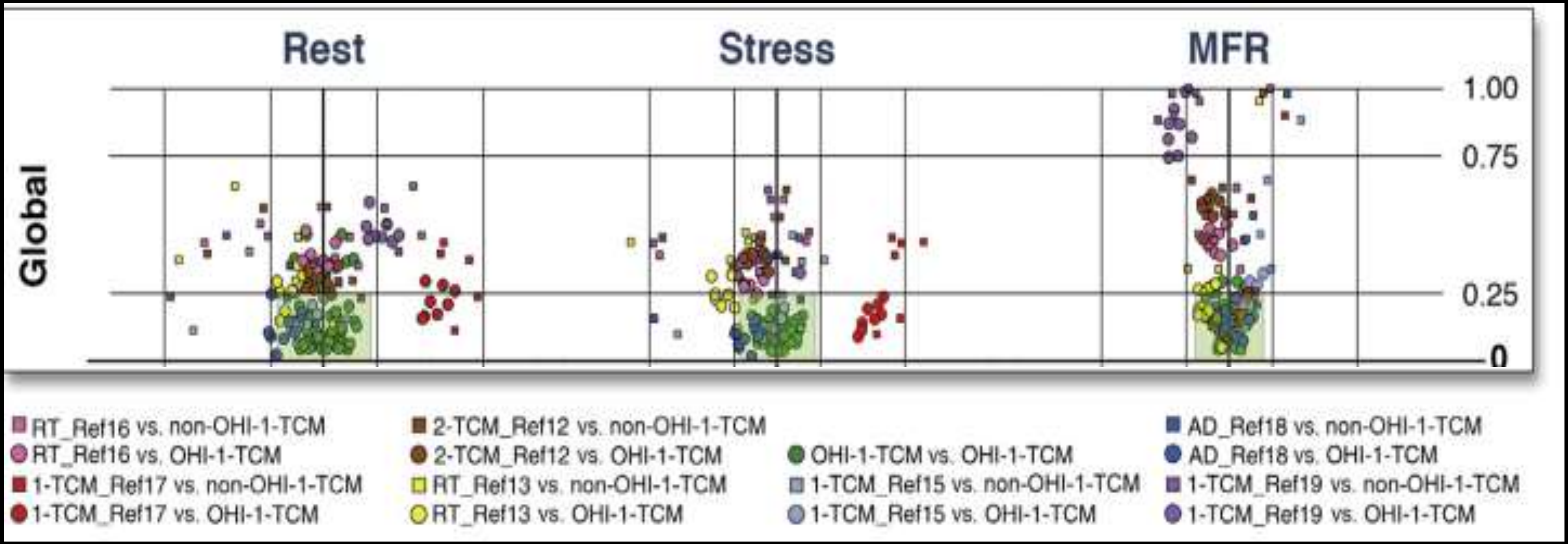
- Define camera performance requirements (such as decay correction) for MBF studies.
- Describe how MBF software derives MBF values.
- Recognize that resting myocardial blood flow values in transmural scar can be used to determine accuracy of software packages.
- Discuss the reasons why MBF software may be inaccurate.
- Analyze and preview existing literature where MBF values are likely to be inaccurate.
- Examine how technique and software impacts precision.

Overview

- Camera
  - Decay
  - Randoms
  - Dead Time
- Software
  - PV correction
  - Arterial Input
- Technique
  - Rb infusion and camera start time
  - IV/Venous anomalies

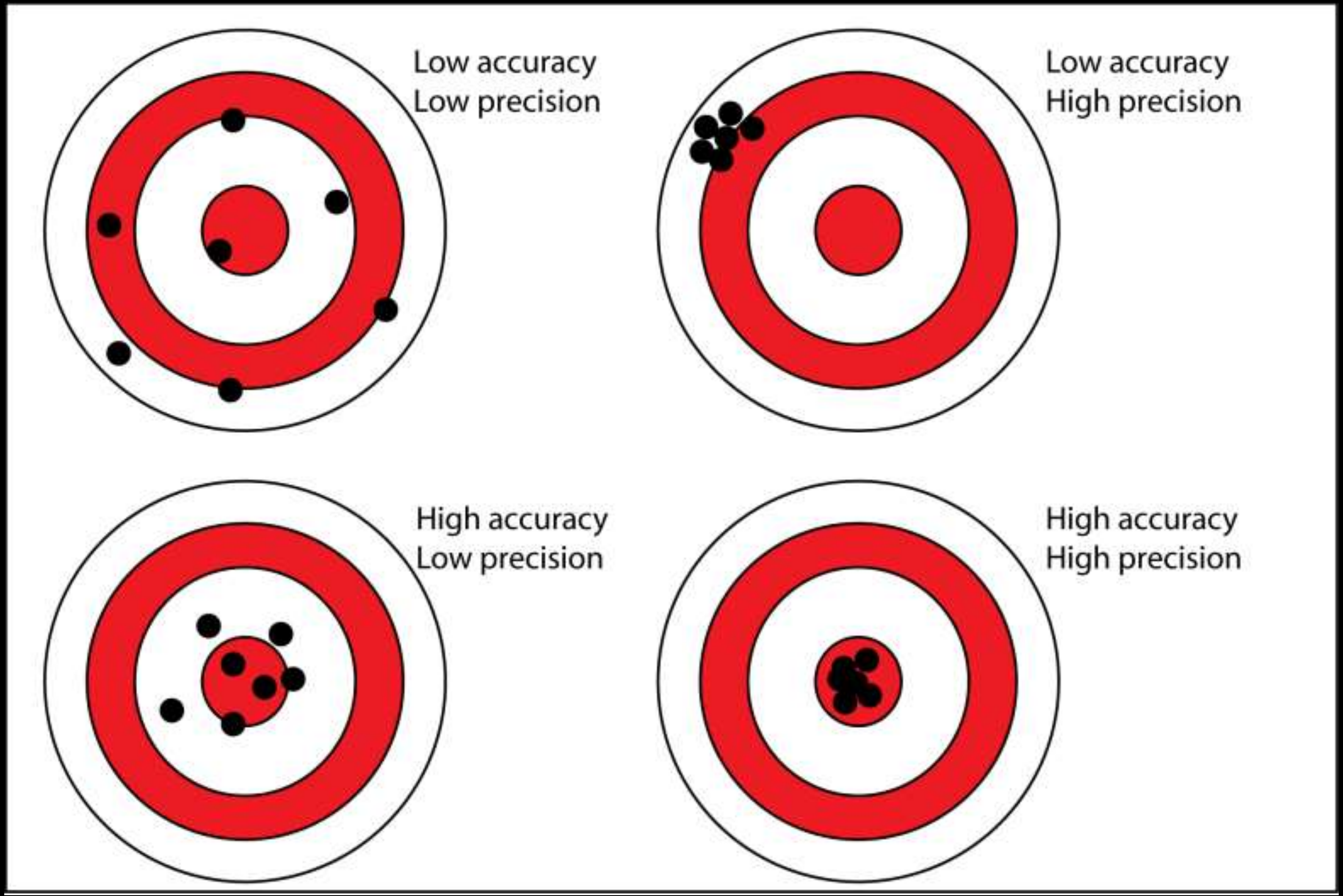
Accuracy and Precision





Nesterov et al, JACC Cardiovasc Imaging. 2014 Nov;7(11):1119-1127.

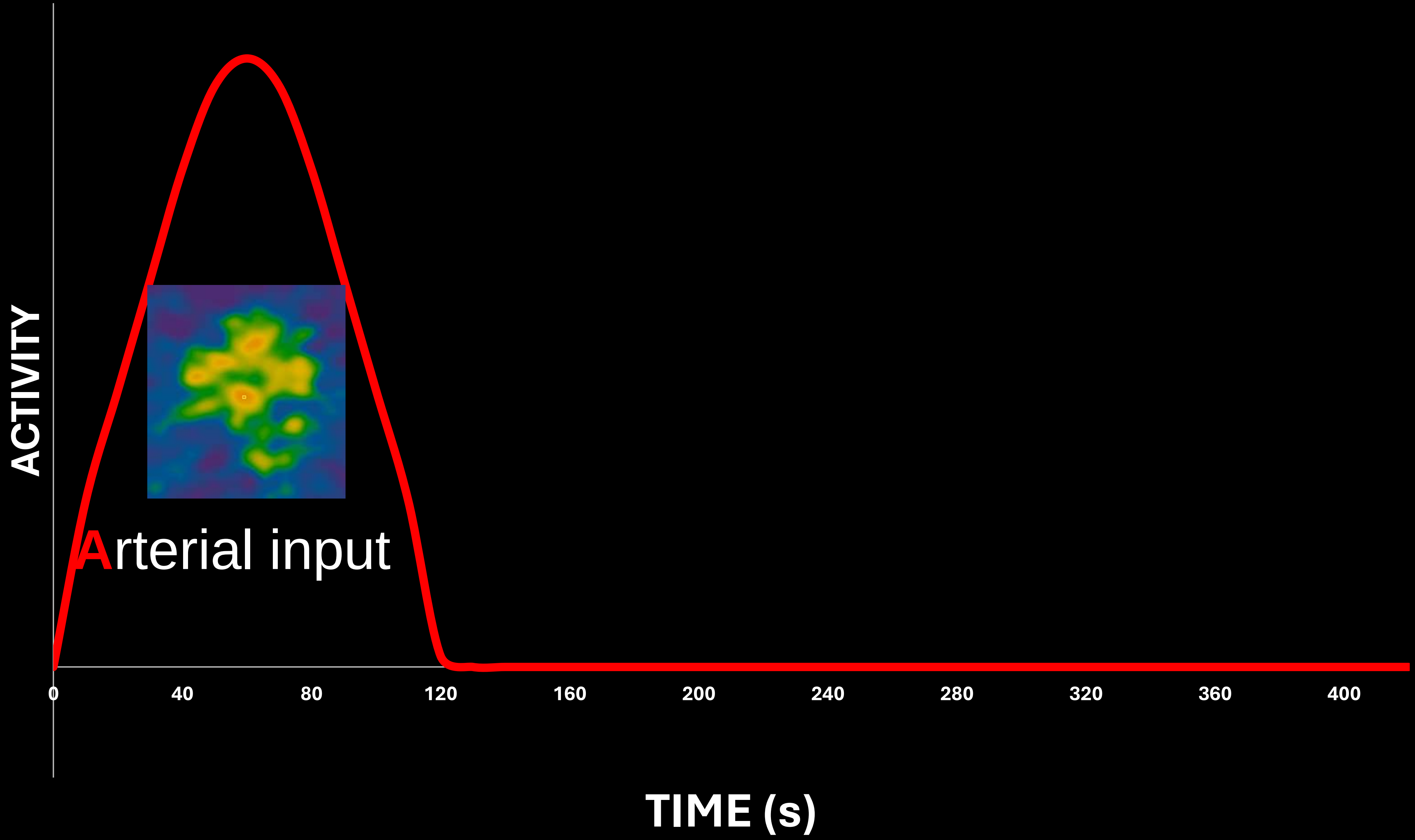
Accuracy and Precision

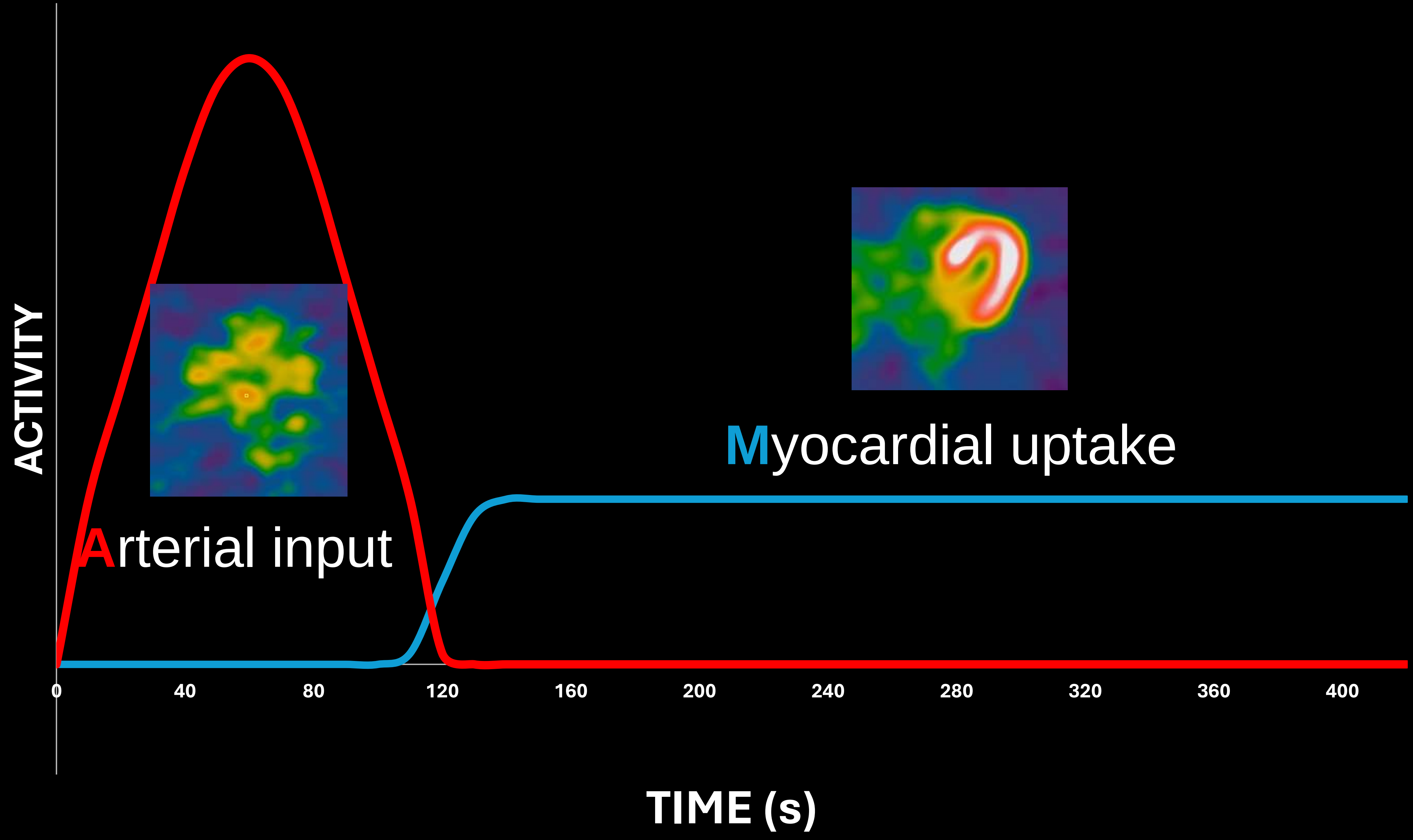


First Attendance Verification Code
4167

$$\text{FLOW} = \frac{\text{Myocardial uptake}}{\text{Arterial input}} \times (\text{PV})(\text{EF})$$

PV= Partial Volume corrections
EF= Extraction Fraction

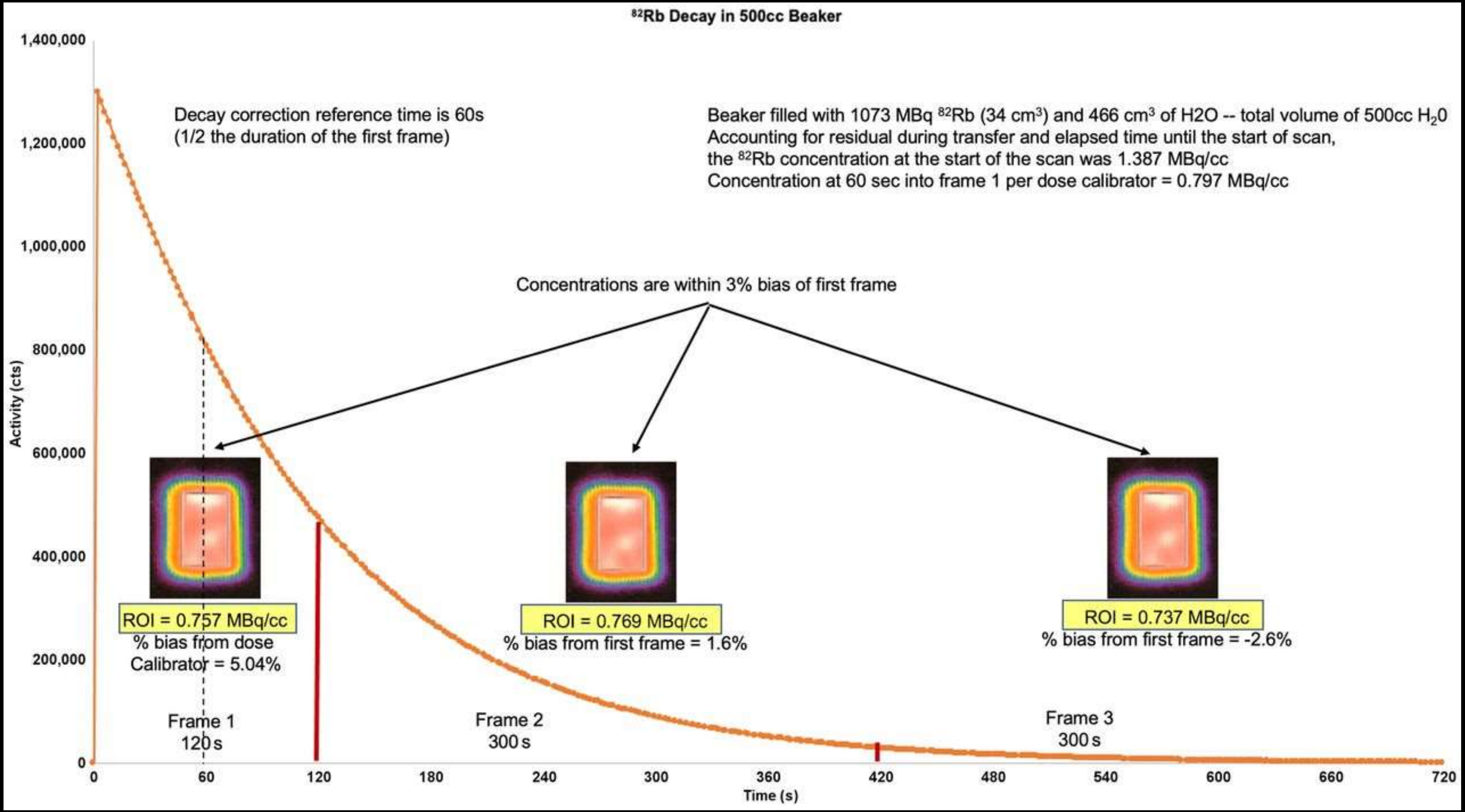

ACTIVITY
Arterial input
0
40
80
120
160
200
240
280
320
360
400
TIME (s)



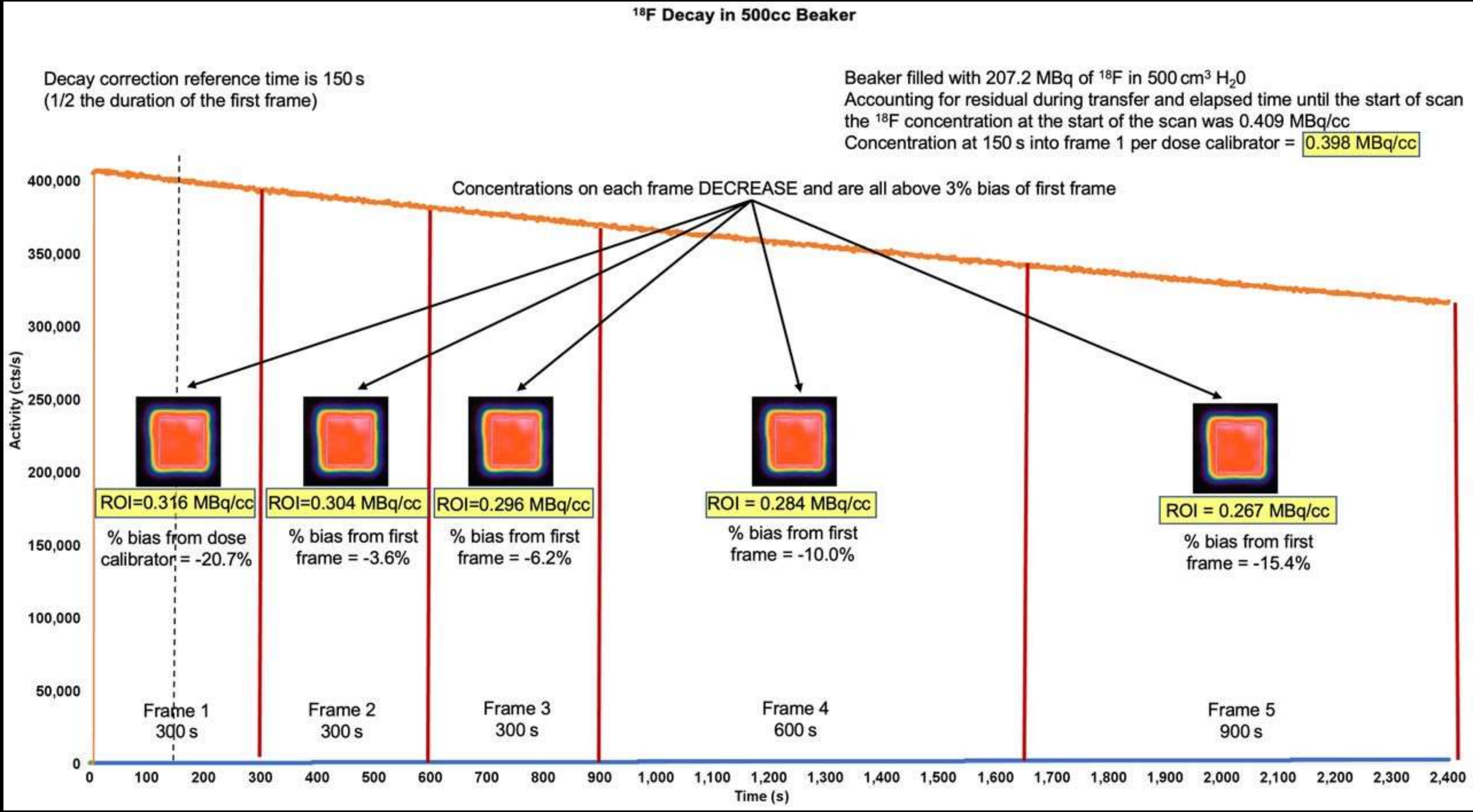
ACTIVITY
Arterial input
Myocardial uptake
0
40
80
120
160
200
240
280
320
360
400
TIME (s)

CAMERA

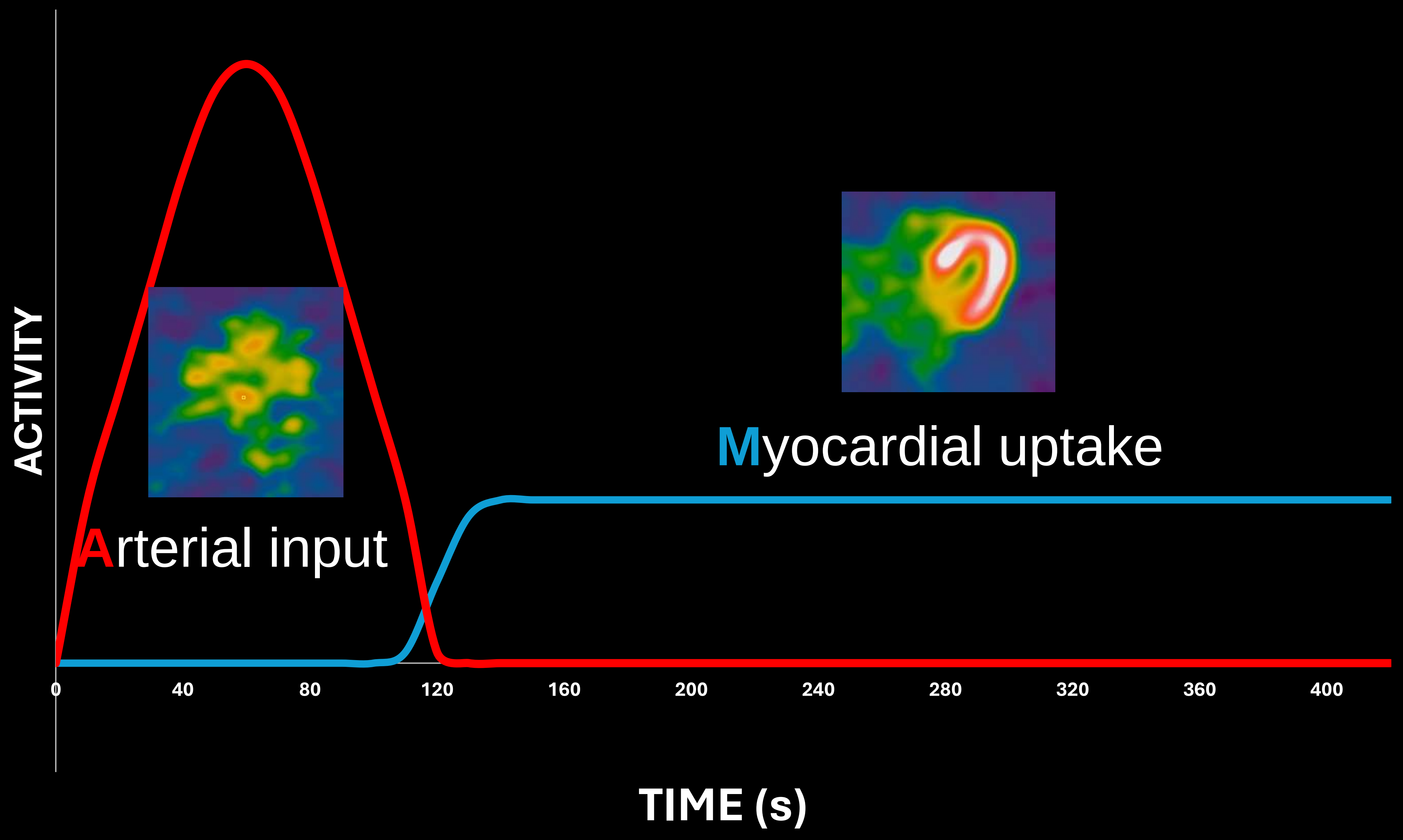
Decay Correction



Bober, RM J Nucl Med Technol. 2021 Dec;49(4):344-349.

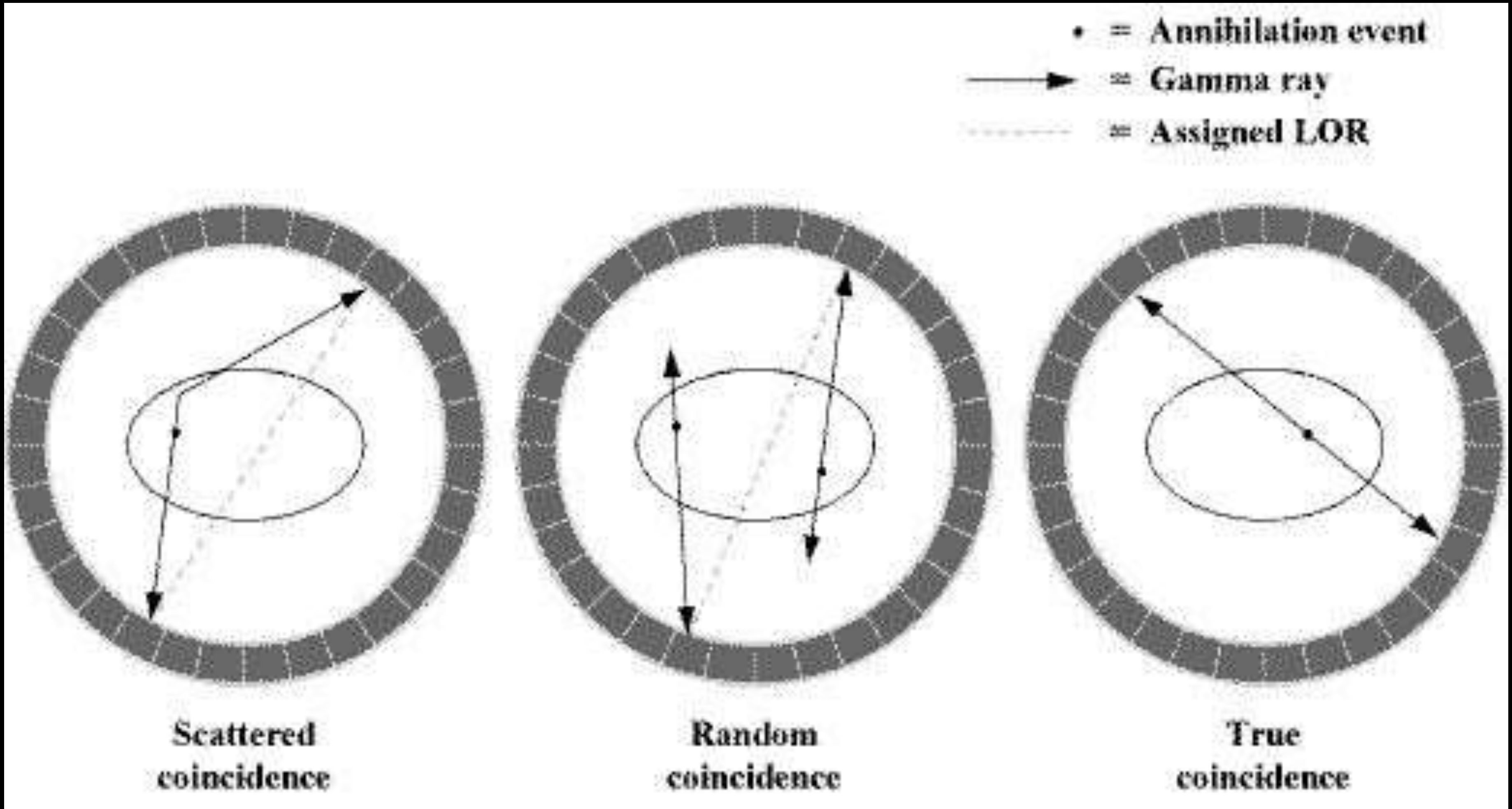


Bober, RM J Nucl Med Technol. 2021 Dec;49(4):344-349.



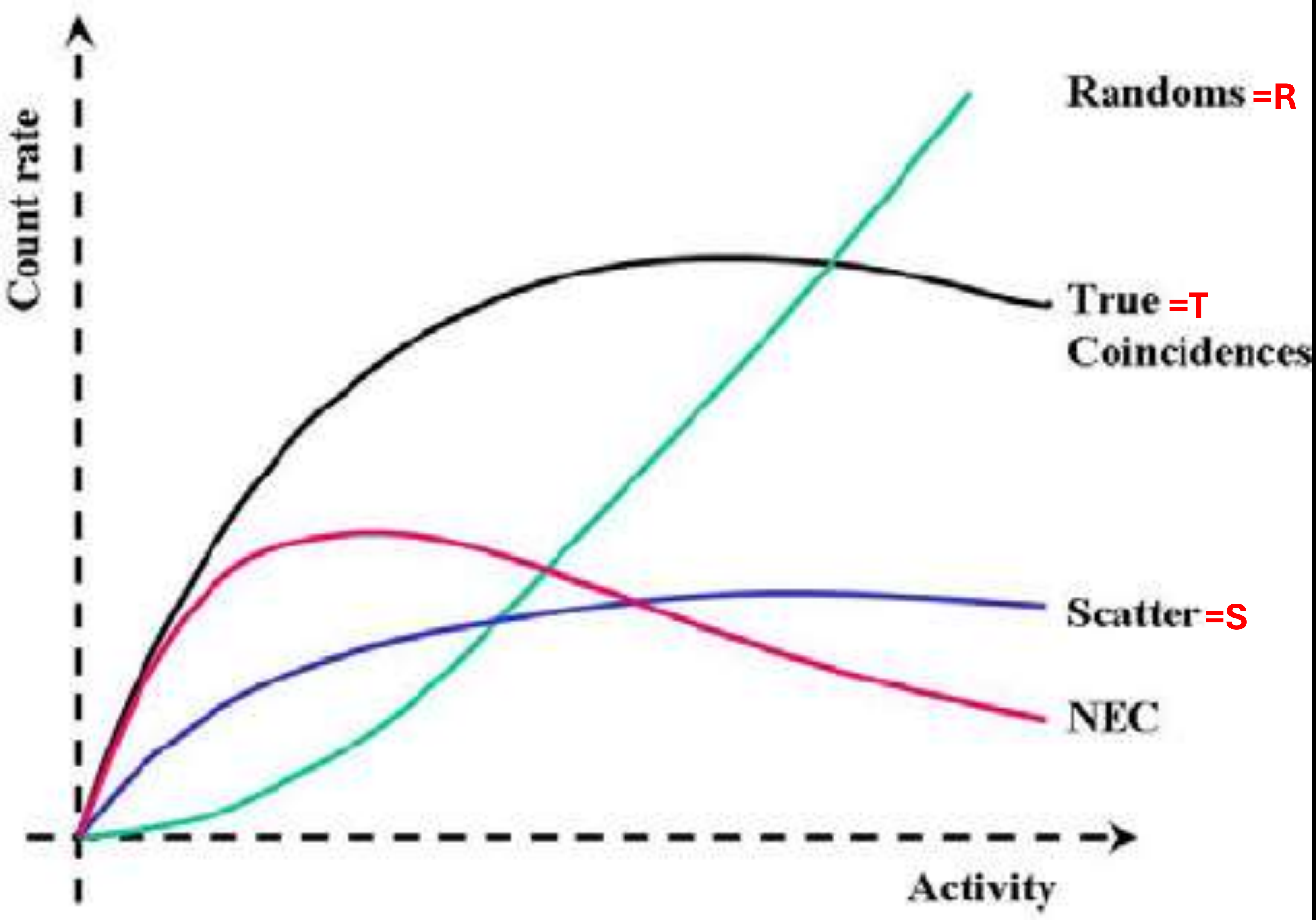
ACTIVITY
Arterial input
Myocardial uptake
0
40
80
120
160
200
240
280
320
360
400
TIME (s)

Types of Detections

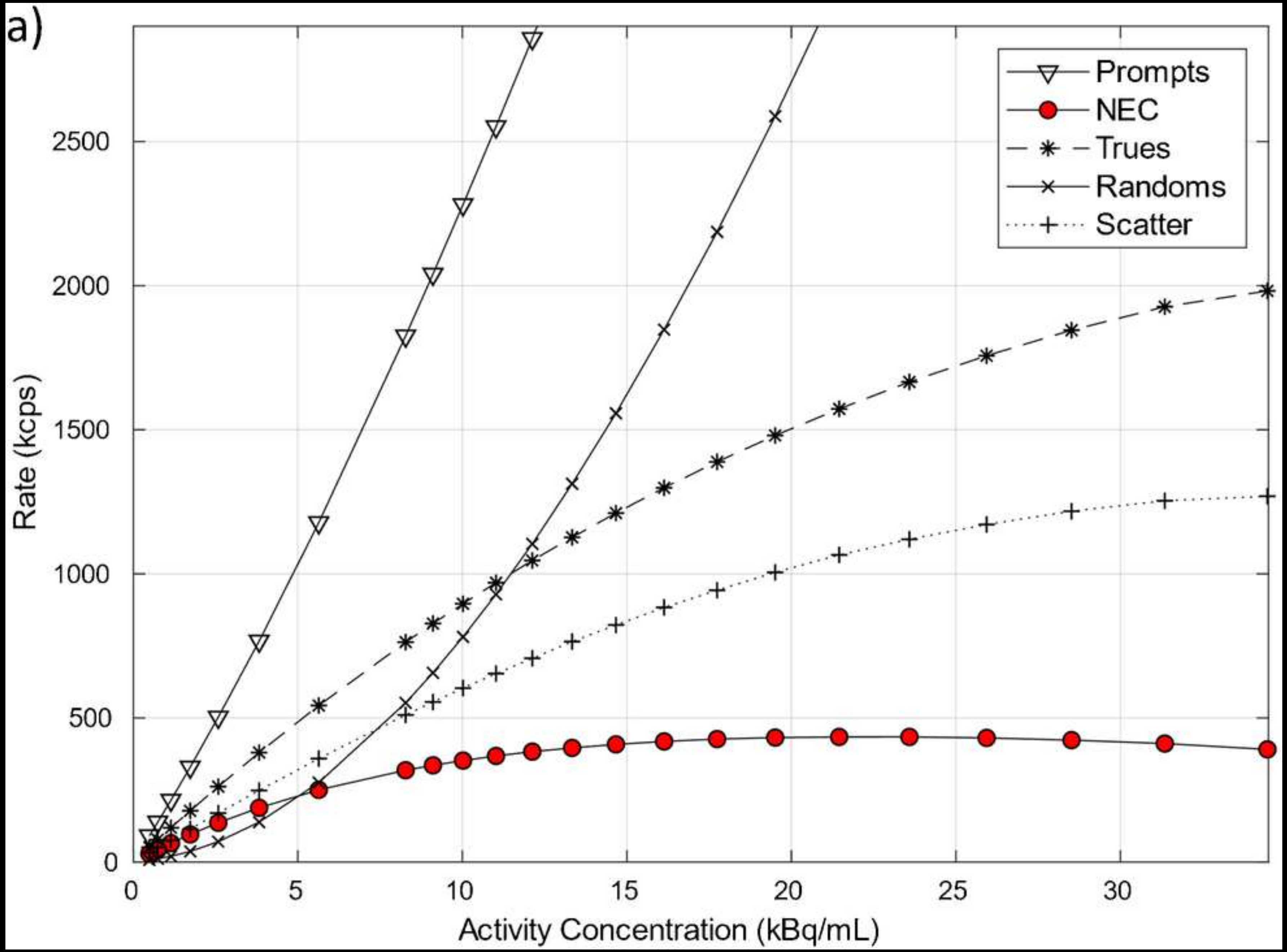


http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html

NECR - Noise Equivalent Count Rate



$$NECR = \frac{T^2}{T+S+R}$$

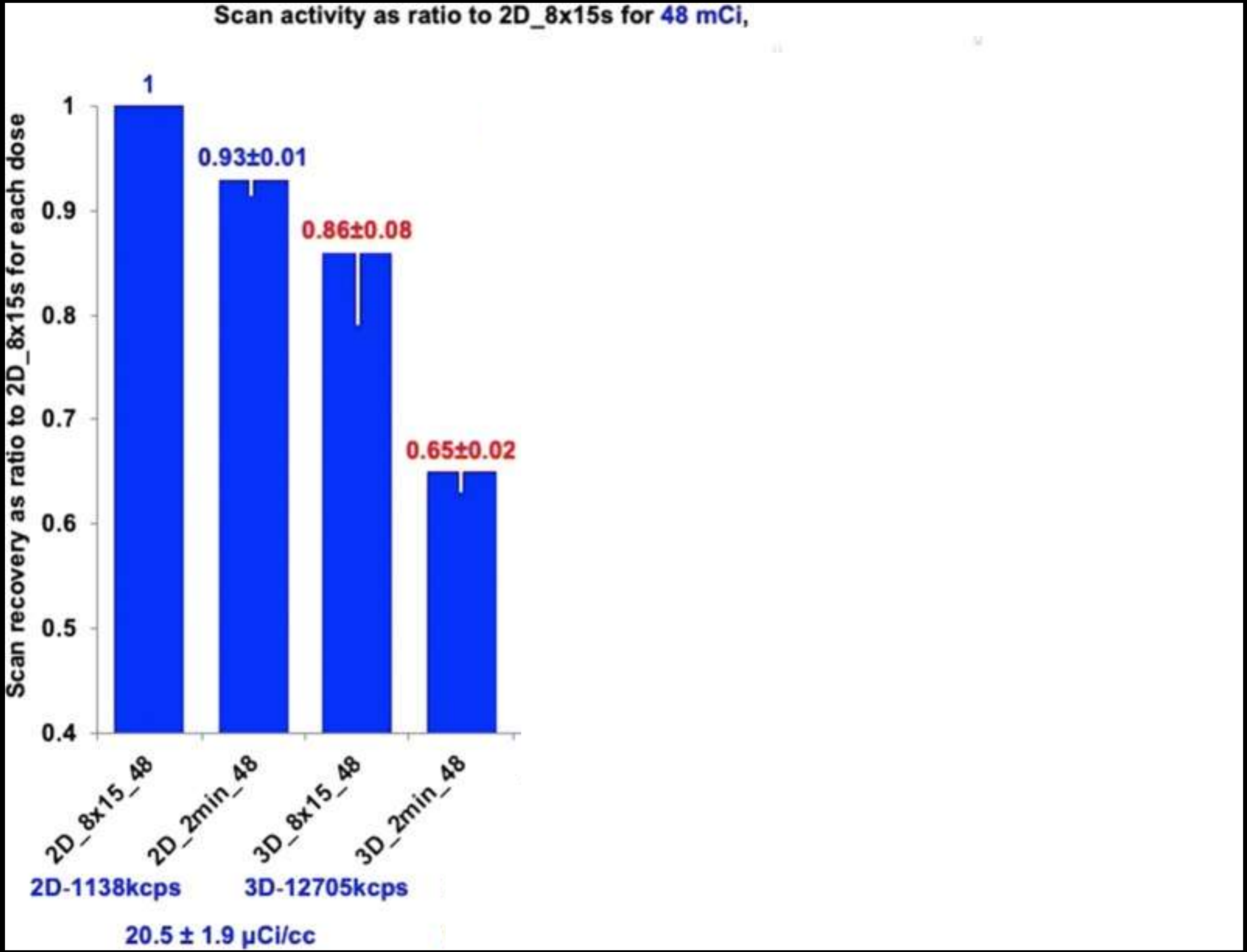


$$NECR = \frac{T^2}{T+S+R}$$

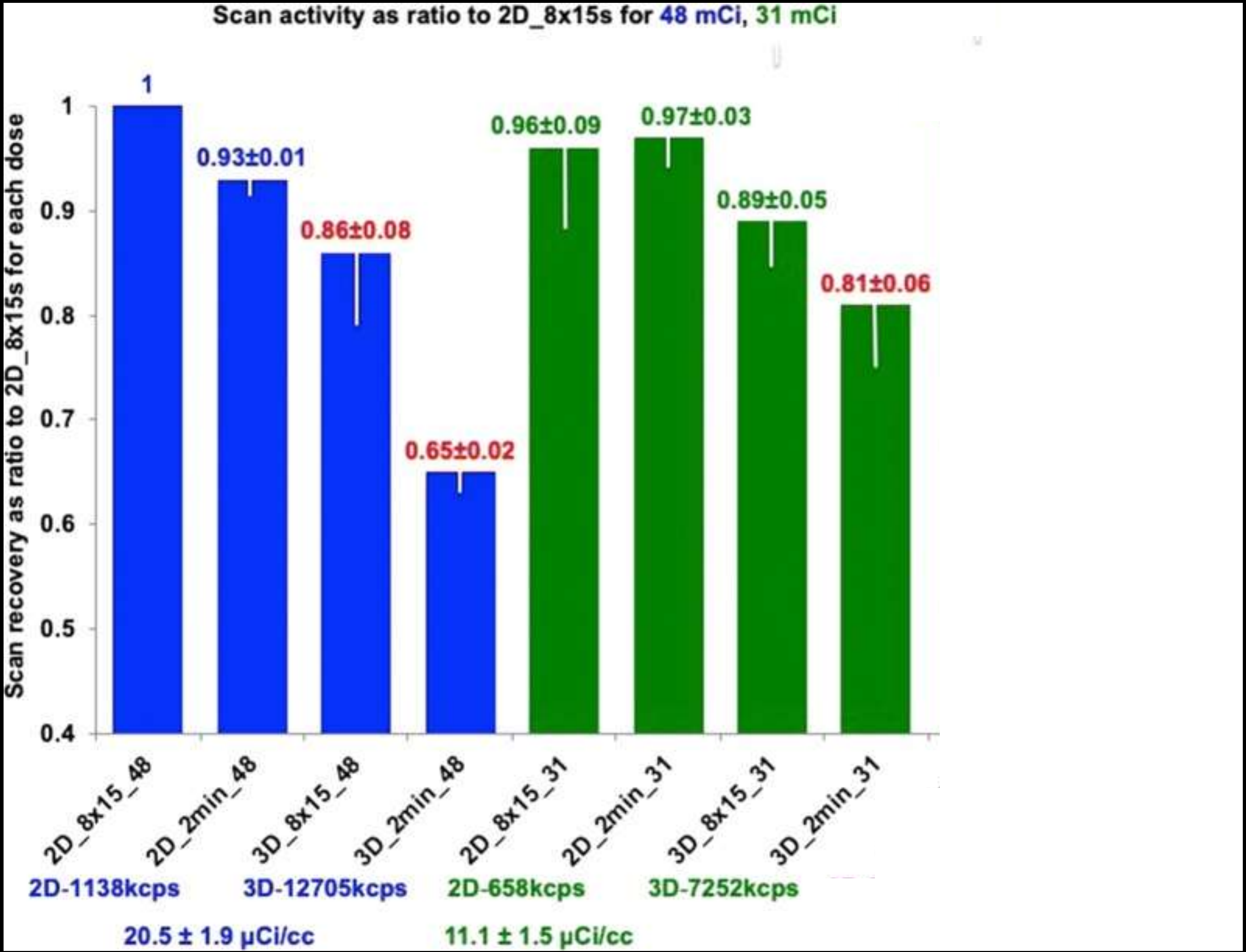
Zeimpekis et al. *Eur J Nucl Med Mol Imaging* 49, 3023–3032 (2022).

Random and scatter correction

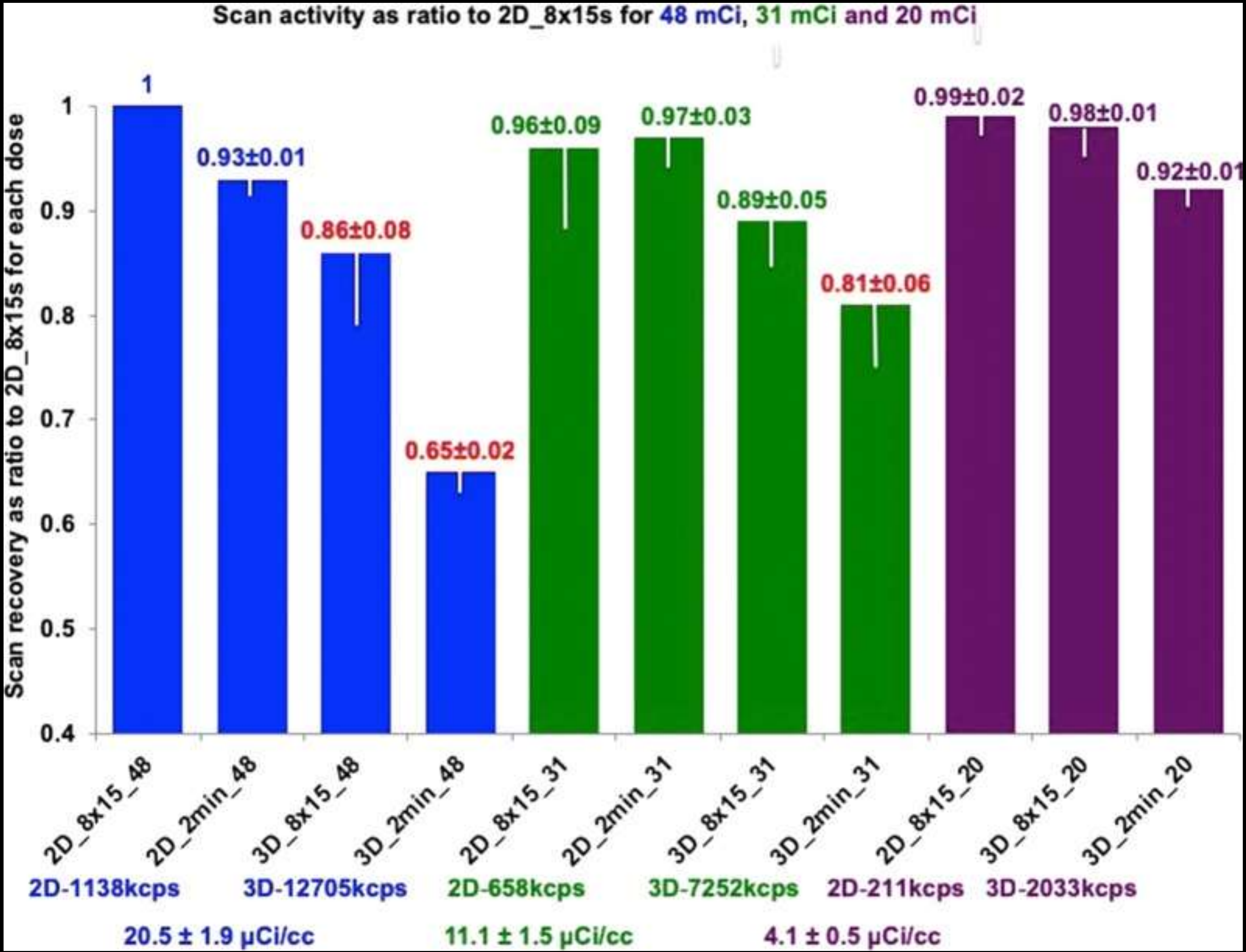
- Corrects the image by “subtracting” random and scatter coincidences
- Random curve is quadratic and exponential
- 0-120s random correction ≠ 5s correction x 24
- Requires processing power
- Scatter correction is more uniform and calculated as as single scatter model



Bui et al. J Nucl Cadiol. 2020; 27(2): 397–409.



Bui et al. J Nucl Cadiol. 2020; 27(2): 397–409.

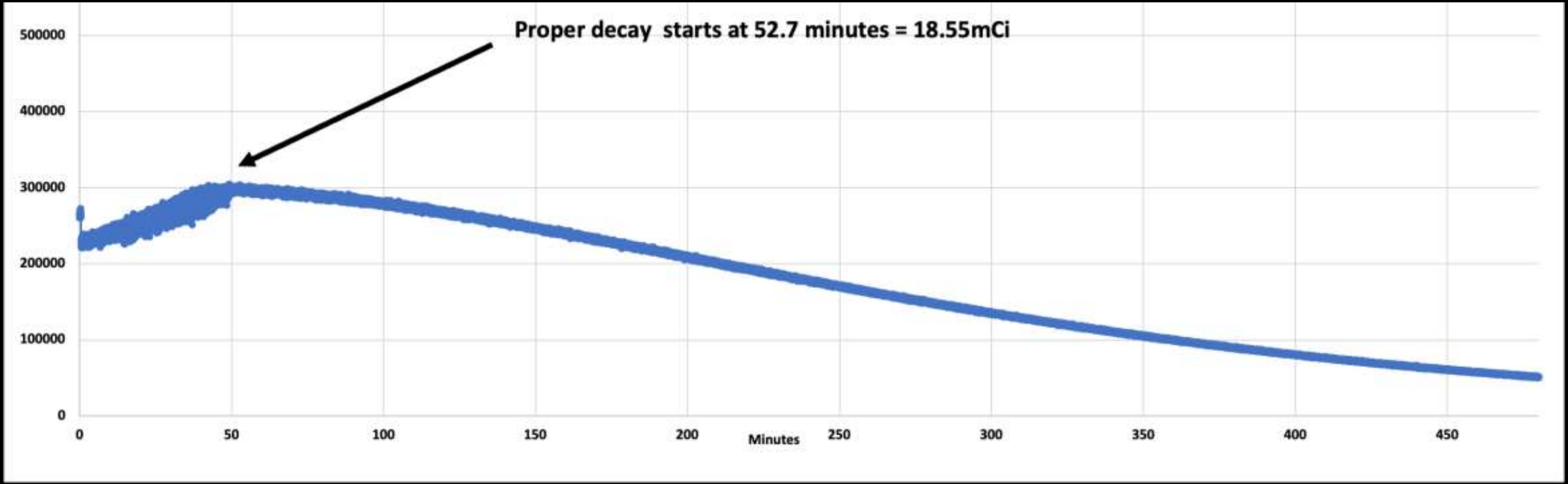


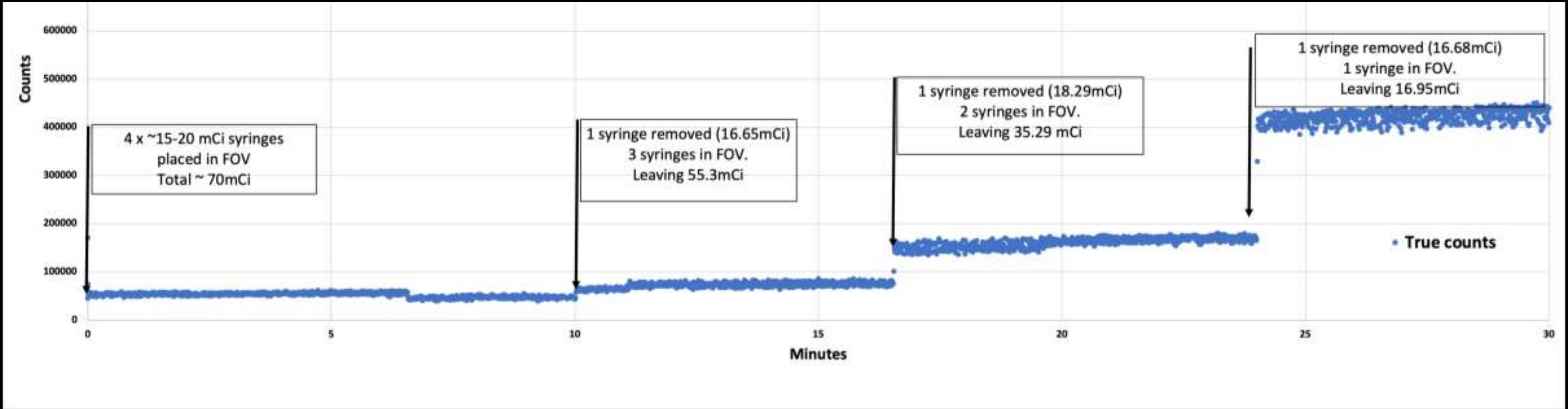
Bui et al. J Nucl Cadiol. 2020; 27(2): 397–409.

Dead Time

- Time after a coincidence detection where the system can not record another event.
- Too much activity causes system “paralysis”
- Some dead time can be measured and counts estimated (dead time correction factors-DTF)
- Too much dead time—information is lost

Decay of 27mCi of F-18





Counts
600000
500000
400000
300000
200000
100000
0
0
5
10
15
20
25
30
Minutes
4 x ~15-20 mCi syringes
placed in FOV
Total ~ 70mCi
1 syringe removed (16.65mCi)
3 syringes in FOV.
Leaving 55.3mCi
1 syringe removed (18.29mCi)
2 syringes in FOV.
Leaving 35.29 mCi
1 syringe removed (16.68mCi)
1 syringe in FOV.
Leaving 16.95mCi
True counts

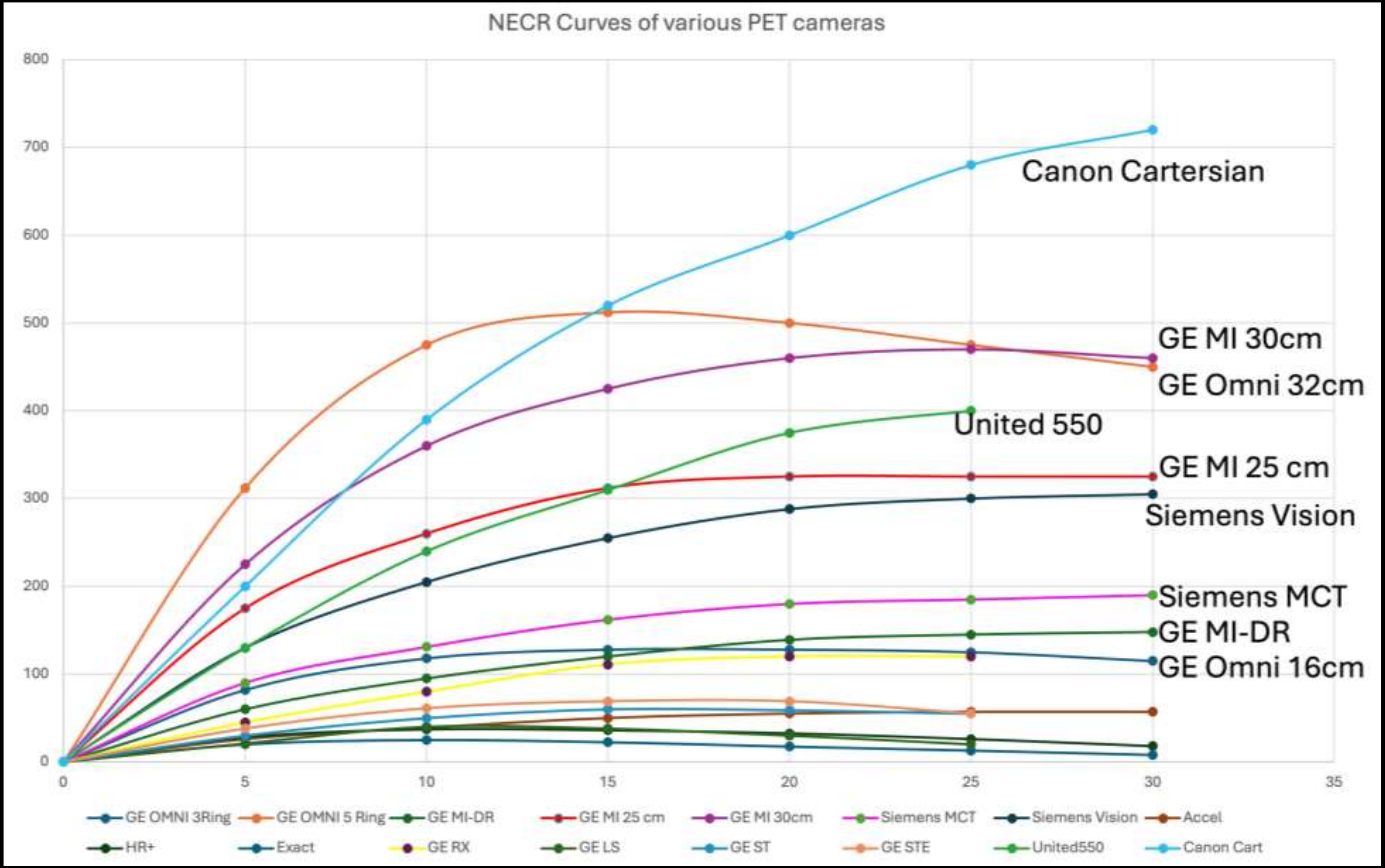
Camera Accuracy

- Decay correction
- Random and scatter correction
  - Framing implications
- Dead time losses
- Each scanner has its own capabilities
- General concept - Newer scanners better capabilities (NOT ALWAYS)

TABLE 1
Recommended Maximum Injected Activity and Performance Metrics

PET system	Patient A_{max}/weight (MBq/kg)	Peak prompts (Mcps)	Peak singles (Mcps)	Peak DTF	Scatter bias(t) (%)	$C_{myo}(t)_{COV}$ (%)
Biograph mCT PET/CT-40	14.4	6.3	64	—	5.2 ± 0.2	12.4 ± 2.1
ECAT Accel Scintron PET 2D	11.4	1.6	26	1.7	8.3 ± 0.6	6.5 ± 0.2
Discovery 690 PET/VCT-64	11.4	5.9	45	1.5	2.4 ± 0.3	11.0 ± 4.8
Discovery IQ (5 ring) PET/CT-16	11.3	14.1	84	3.9	2.7 ± 1.1	2.9 ± 0.2
Biograph TruePoint PET/CT-16	8.0	—	—	—	9.9 ± 0.4	8.0 ± 0.3
Discovery 600 PET/CT-16	6.5	4.1	29	2.0	2.1 ± 0.3	12.1 ± 1.1
Biograph PET/CT-16	5.5	—	22	—	8.6 ± 0.2	16.4 ± 1.3
Discovery RX PET/CT-16	5.1	4.5	—	1.7	3.1 ± 0.3	10.6 ± 0.8
Gemini TF PET/CT-16	4.6	—	—	—	2.5 ± 0.5	7.8 ± 0.9
Discovery STE/VCT-16	3.9	3.5	—	2.1	2.5 ± 0.4	4.3 ± 3.3
ECAT Accel Scintron PET 3D	2.7	1.6	22	1.7	7.4 ± 0.2	6.5 ± 0.3

— = Not available in image header files. t = T_{max} to 7 min.



NECR Curves of various PET cameras
800
700
600
500
400
300
200
100
0
0
5
10
15
20
25
30
35
Canon Cartersian
GE MI 30cm
GE Omni 32cm
United 550
GE MI 25 cm
Siemens Vision
Siemens MCT
GE MI-DR
GE Omni 16cm
GE OMNI 3Ring
GE OMNI 5 Ring
GE MI-DR
GE MI 25 cm
GE MI 30cm
Siemens MCT
Siemens Vision
Accel
HR+
Exact
GE RX
GE LS
GE ST
GE STE
United550
Canon Cart

SOFTWARE

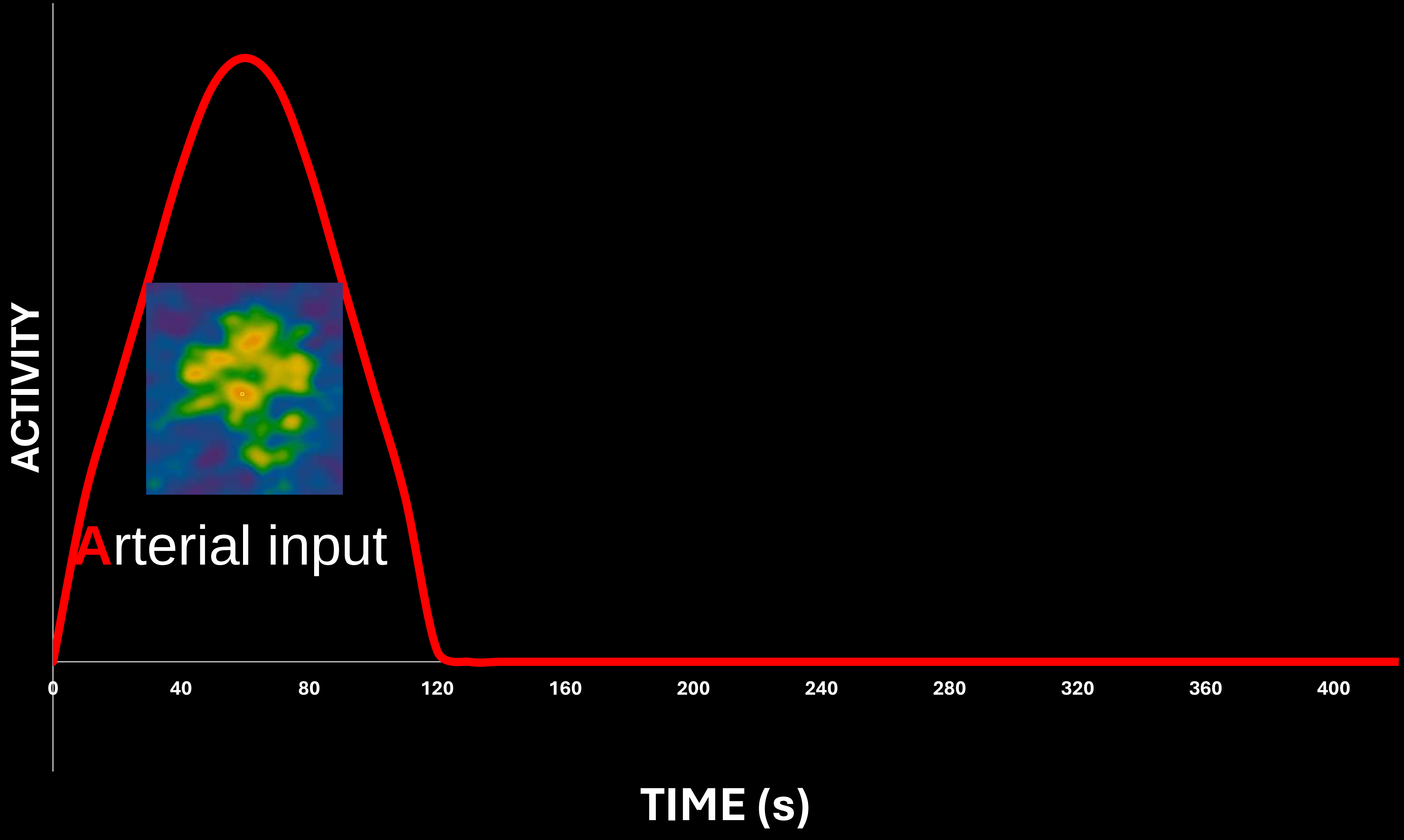
$$\text{FLOW} = \frac{\text{Myocardial uptake}}{\text{Arterial input}} \times (\text{PV})(\text{EF})$$

PV= Partial Volume corrections
EF= Extraction Fraction

$$\text{FLOW} = \frac{}{\text{Arterial input}} \times (\text{PV})$$

PV= Partial Volume corrections

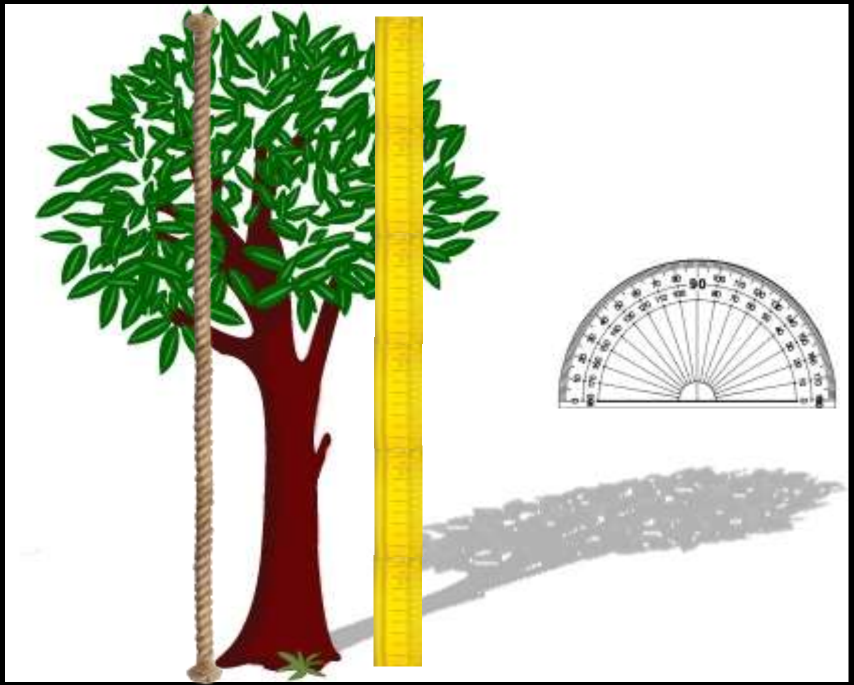
EF= Extraction Fraction



ACTIVITY
Arterial input
0
40
80
120
160
200
240
280
320
360
400
TIME (s)

Arterial Input Determination

- No concensus
- Disagreements are common
- External testing challenging
  - Phantom pumps
  - Tests method but not implementation of software
- 2 general methods
  - Time activity curves
  - Retention

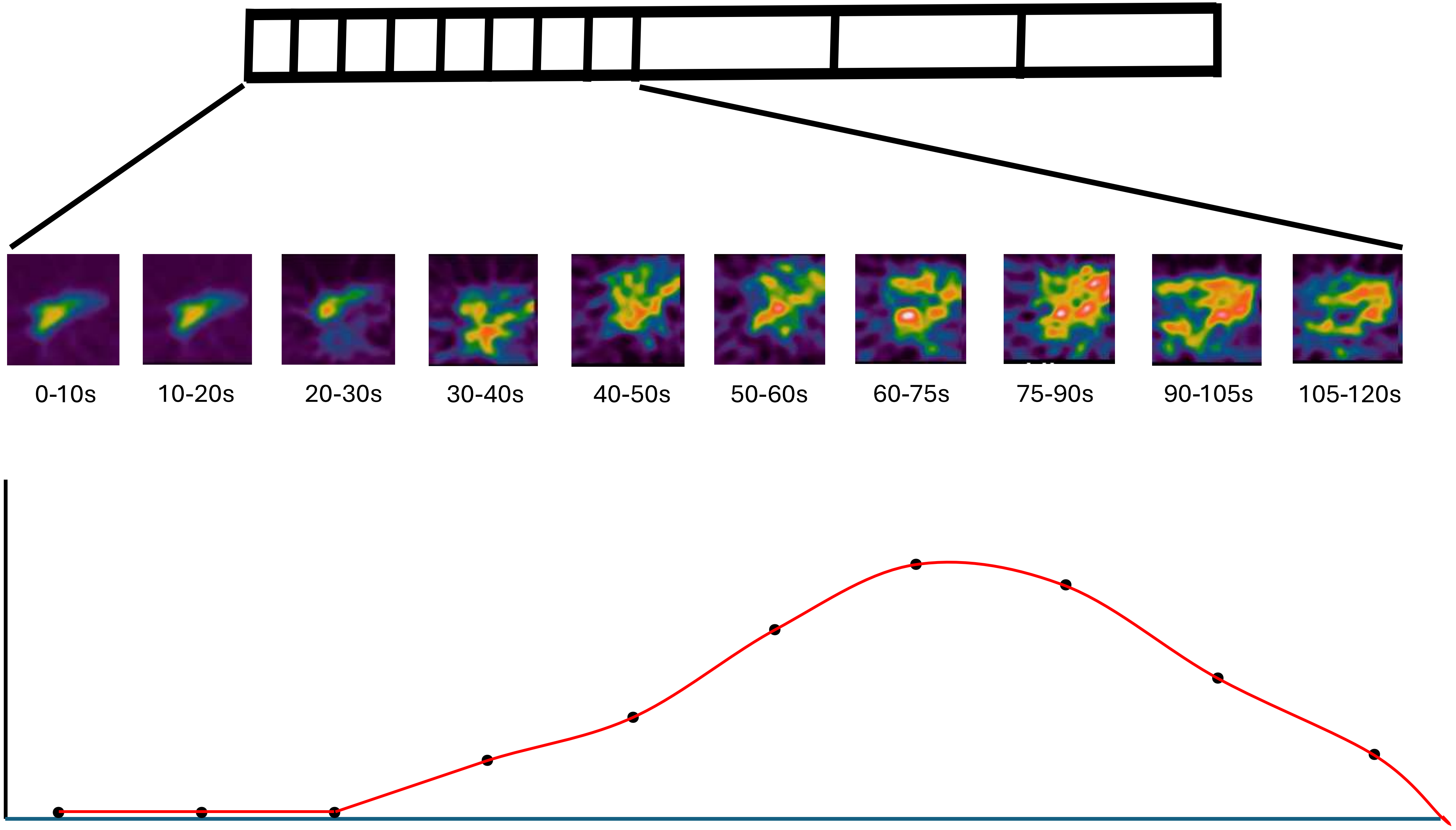


- Multiple methods/solutions
  ALL ARE VALID and ACCURATE

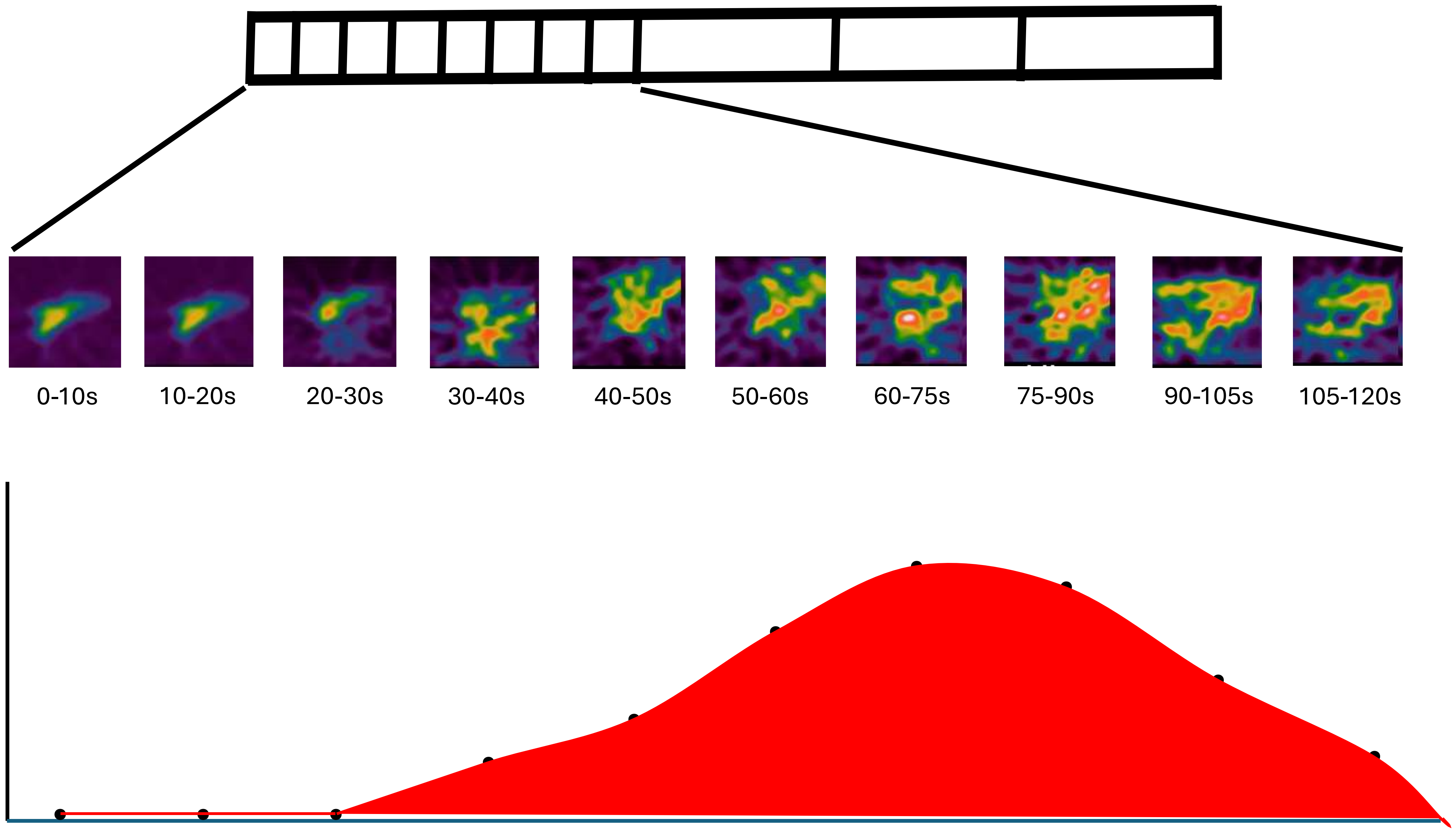
- Practicality
  - Easier
  - More steps
  - Different equipment
  - Accuracy?
  - Precision?

- Potential sources of error

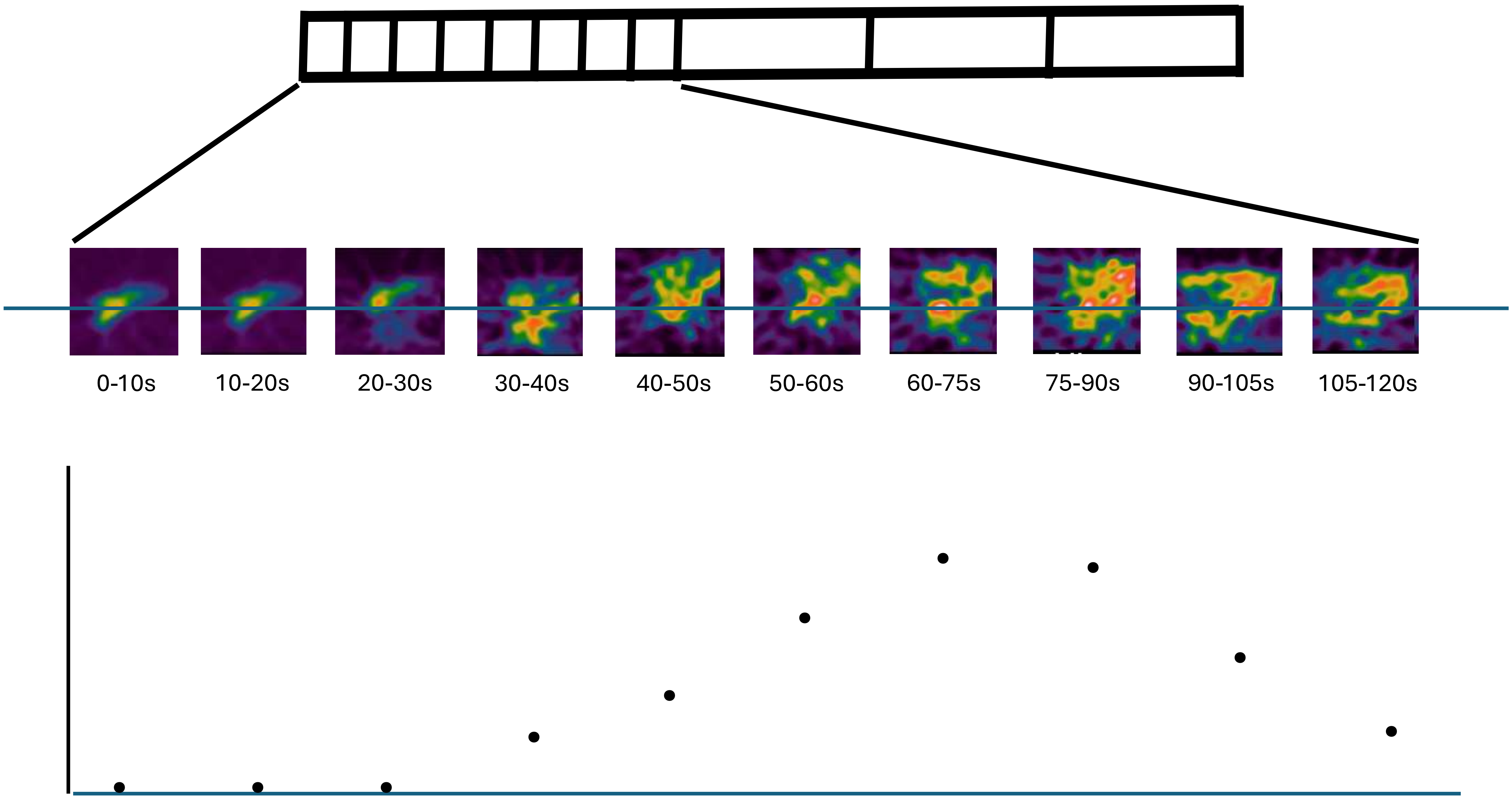
Serial Arterial Input Acquisition



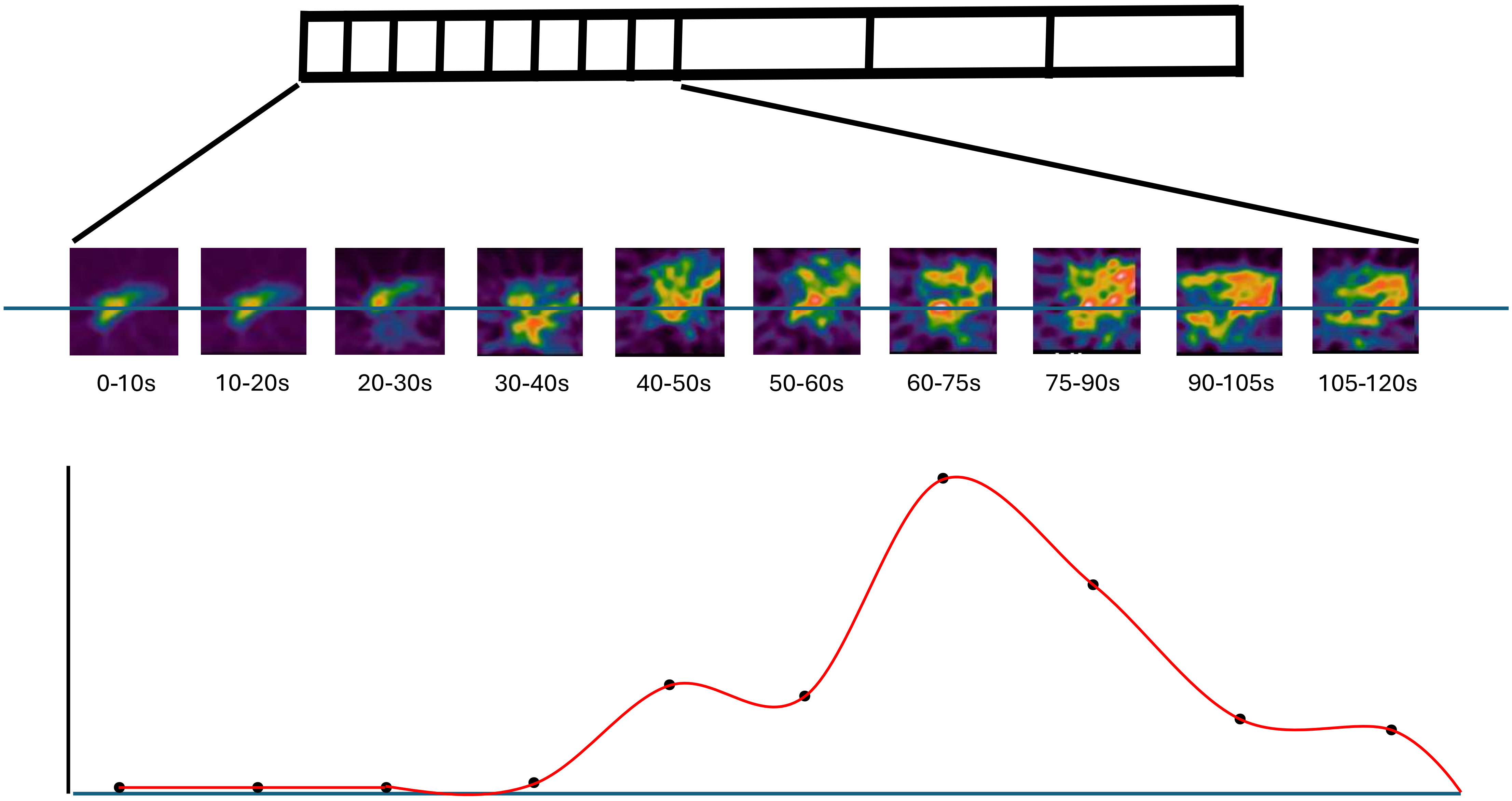
Serial Arterial Input Acquisition



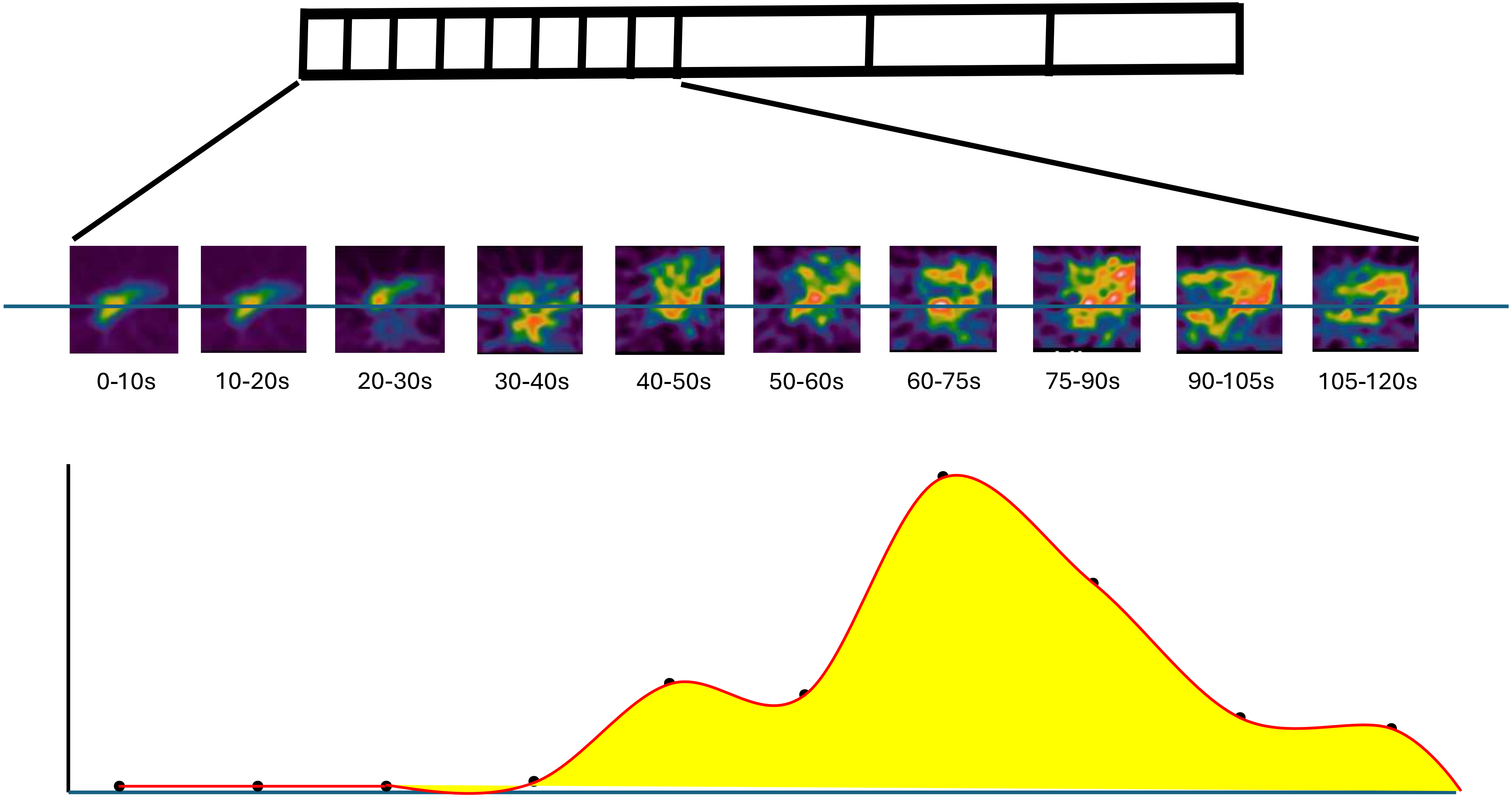
Serial Arterial Input Acquisition

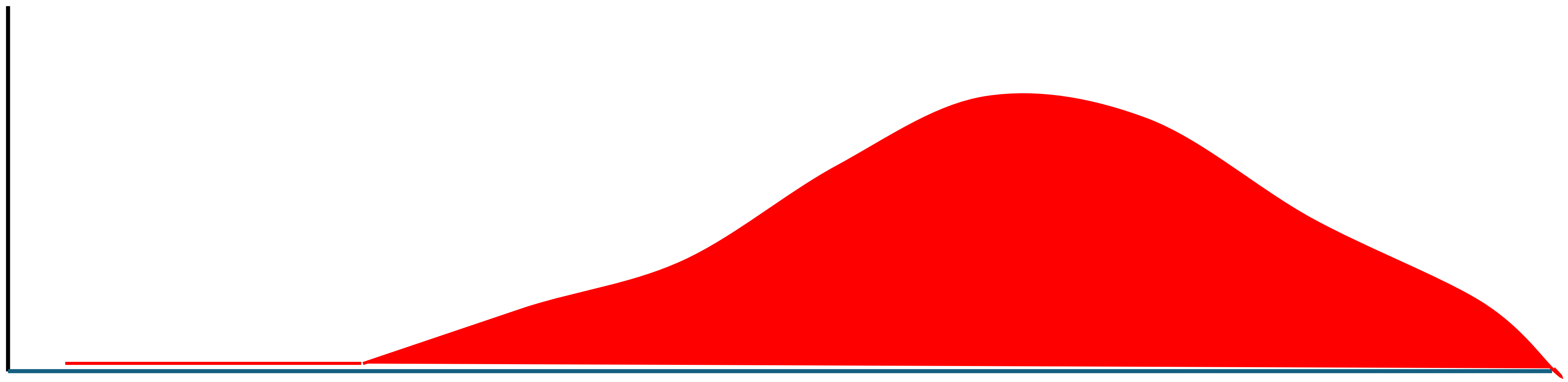


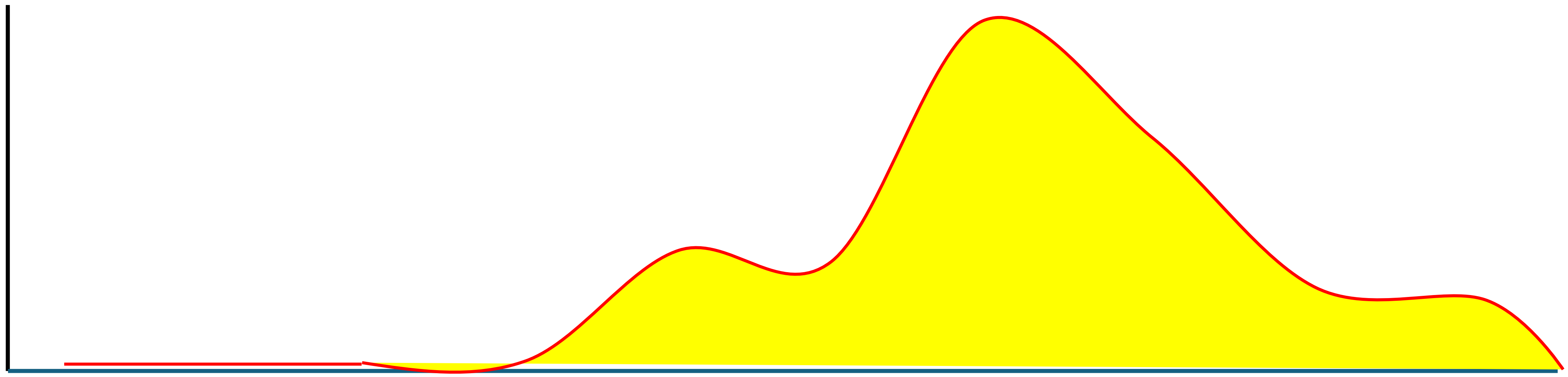
Serial Arterial Input Acquisition

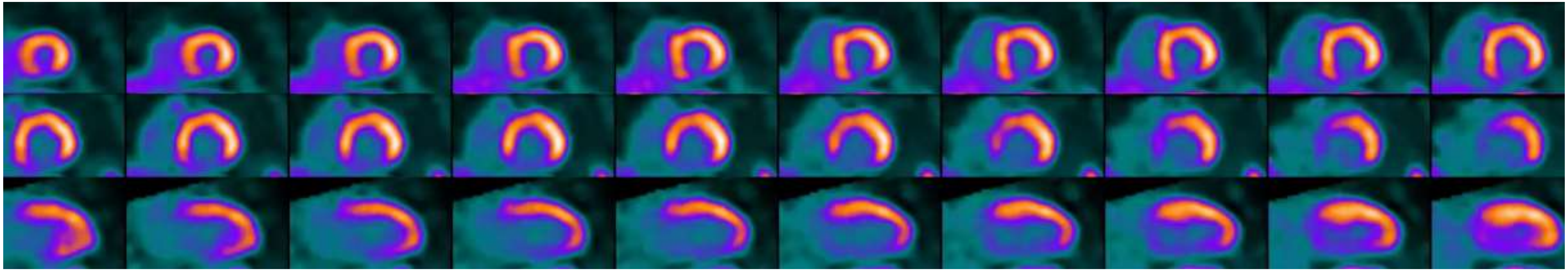


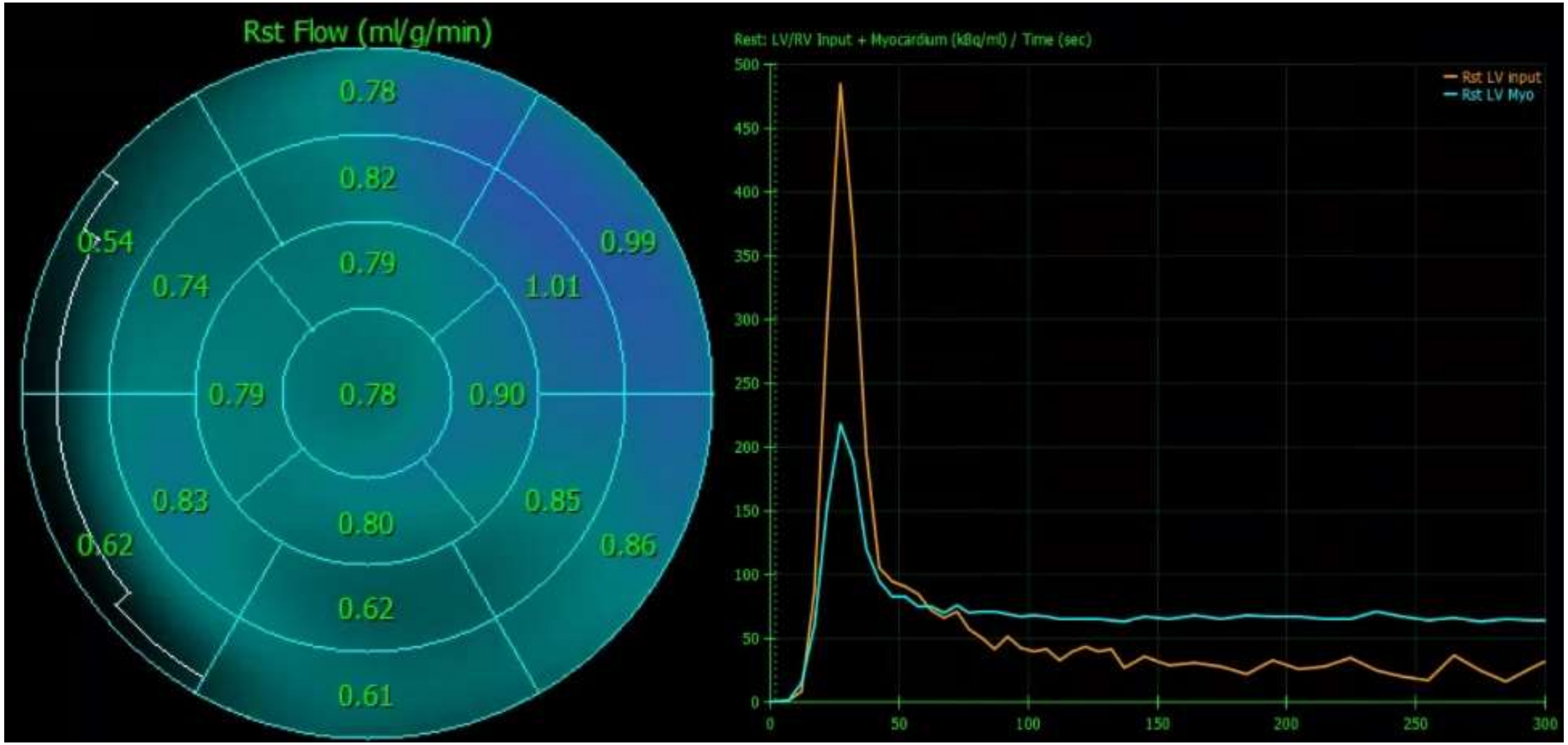
Serial Arterial Input Acquisition



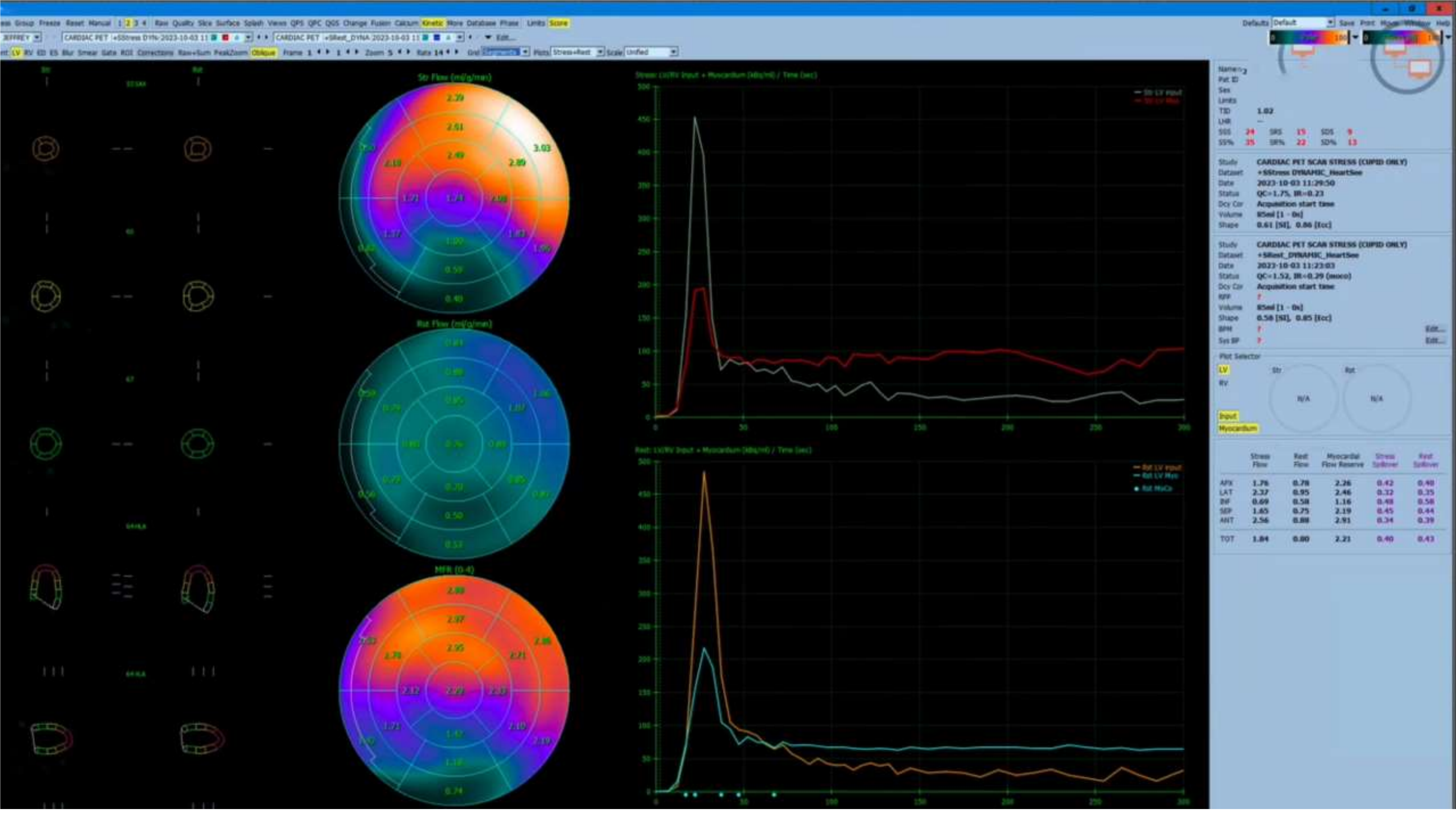








Rst Flow (ml/g/min)
0.78
0.82
0.54
0.74
0.79
1.01
0.99
0.79
0.78
0.90
0.83
0.80
0.85
0.62
0.86
0.62
0.61
Rest: LV/RV Input + Myocardium (kBq/ml) / Time (sec)
Rst LV input
Rst LV Myo
500
450
400
350
300
250
200
150
100
50
0
0
50
100
150
200
250
300

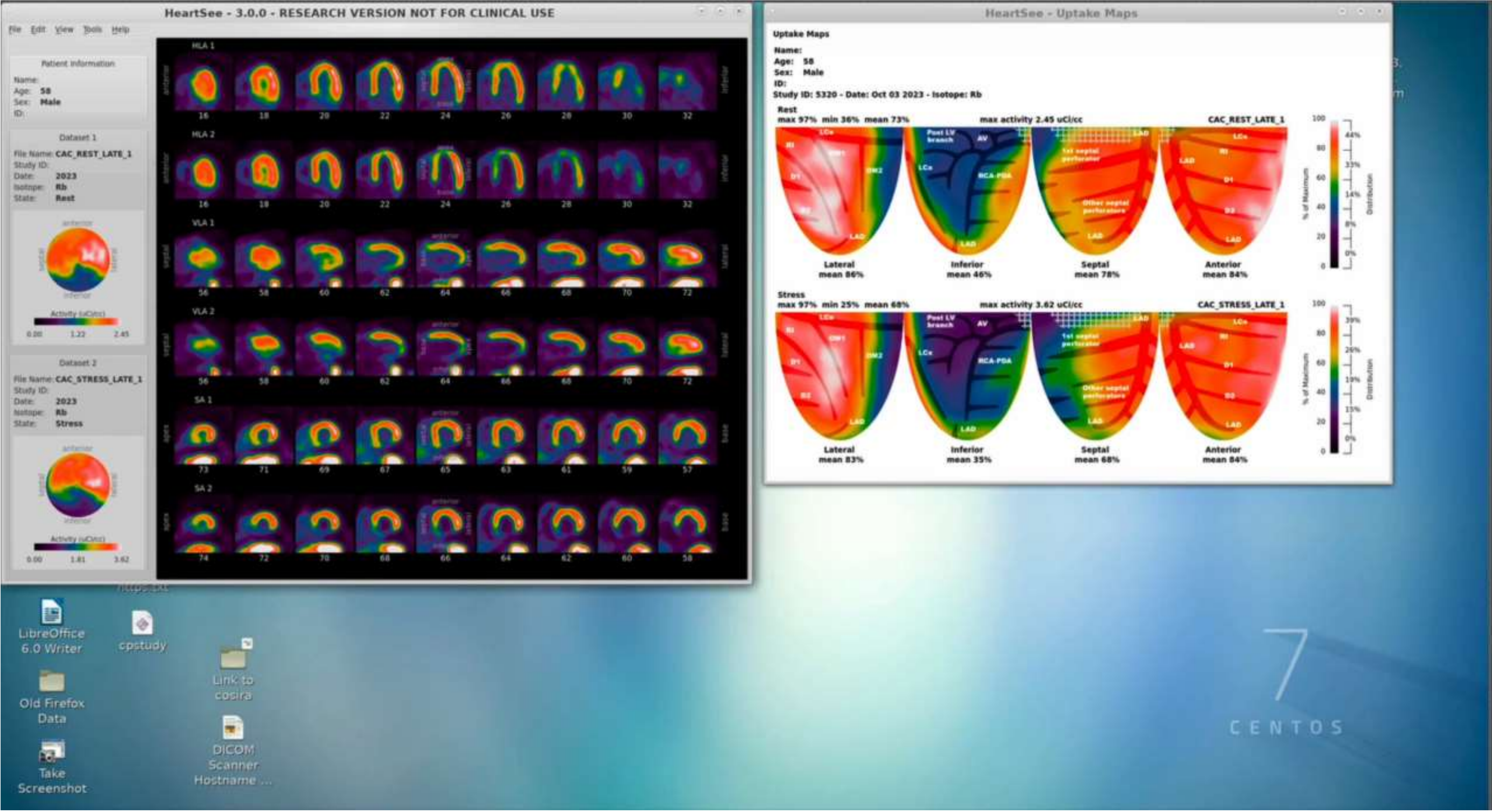

Str Flow (ml/g/min)
Rst Flow (ml/g/min)
MFR (0-4)
Stress: LV/RV Input + Myocardium (kBq/ml) / Time (sec)
Rest: LV/RV Input + Myocardium (kBq/ml) / Time (sec)
Str LV Input
Str LV Myo
Rst LV Input
Rst LV Myo
Rst MoCo
TID 1.02
SSS 24 SRS 15 SDS 9
SS% 35 SR% 22 SD% 13
Study CARDIAC PET SCAN STRESS (CUPID ONLY)
Dataset +SStress DYNAMIC_HeartSee
Date 2023-10-03 11:29:50
Status QC=1.75, IR=0.23
Dcy Cor Acquisition start time
Volume 85ml [1 - 0s]
Shape 0.61 [SI], 0.86 [Ecc]
Study CARDIAC PET SCAN STRESS (CUPID ONLY)
Dataset +SRest_DYNAMIC_HeartSee
Date 2023-10-03 11:23:03
Status QC=1.52, IR=0.29 (moco)
Dcy Cor Acquisition start time
Volume 85ml [1 - 0s]
Shape 0.58 [SI], 0.85 [Ecc]
Plot Selector
LV
RV
Input
Myocardium
	Stress Flow	Rest Flow	Myocardial Flow Reserve	Stress Spillover	Rest Spillover
APX	1.76	0.78	2.26	0.42	0.40
LAT	2.37	0.95	2.46	0.32	0.35
INF	0.69	0.58	1.16	0.48	0.58
SEP	1.65	0.75	2.19	0.45	0.44
ANT	2.56	0.88	2.91	0.34	0.39
TOT	1.84	0.80	2.21	0.40	0.43

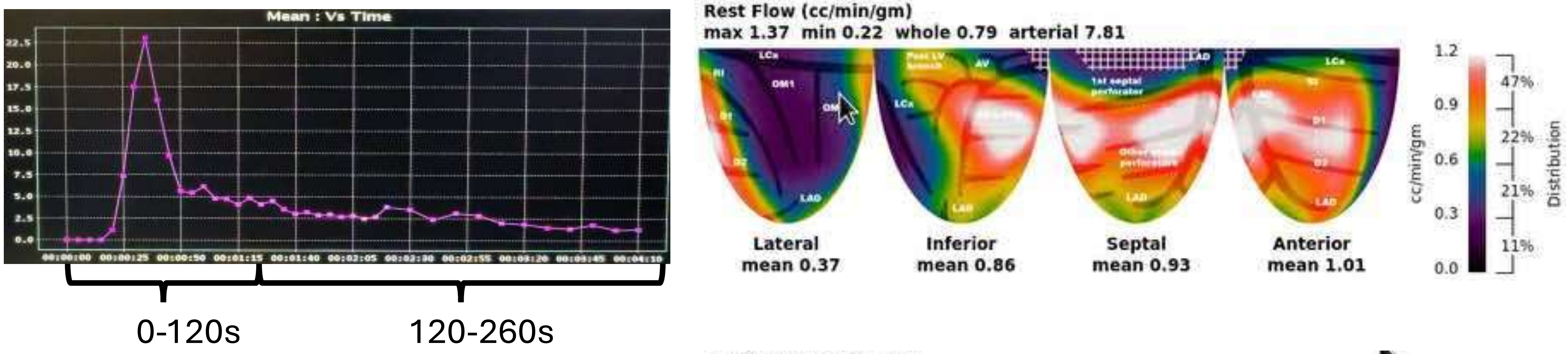
Time activity curve models

- Motion correction necessary for EACH frame
- Frames must be short (5-10s) to account for random corrections
- ~12-24 frames for each dataset MUST be motion corrected
- First introduced commercially ~2018
- Some software – automated, still needs manual correction
- Time consuming and difficult
- Any bias in TAC→bias in MBF estimates
- More complex than retention

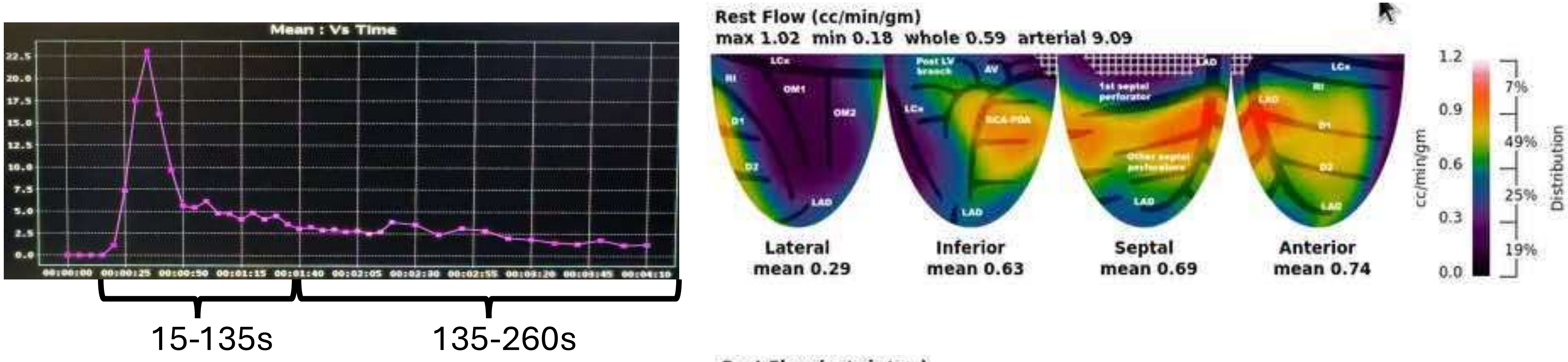
Retention

- Different approach than TAC
- Summation of 0-120s frames (after decay, scatter, random correction)
- Summation IS the integral = area under the curve
- Tolerates mild motion
- Customize location of ROI
- 2-minute image is of high quality
- Shape of the TAC less important

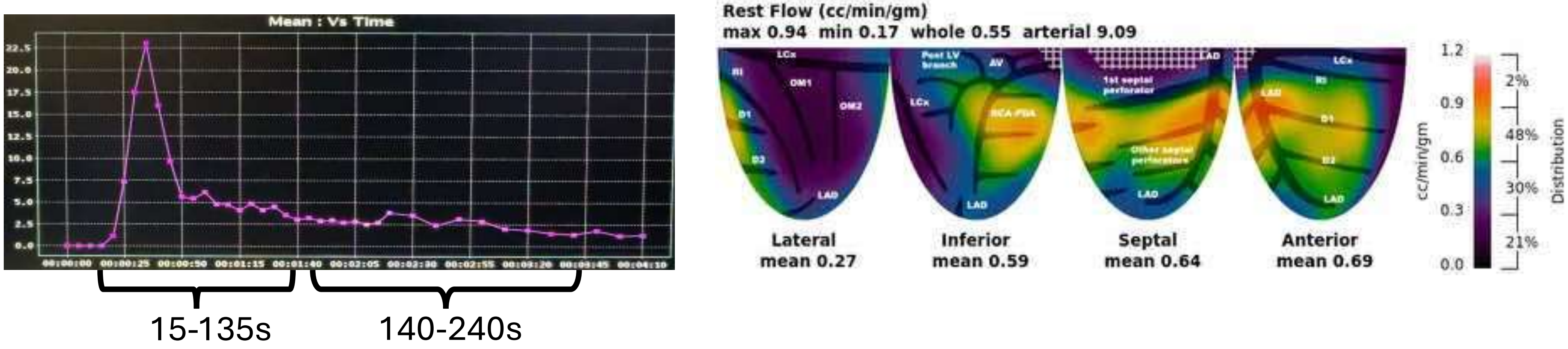

HeartSee - 3.0.0 - RESEARCH VERSION NOT FOR CLINICAL USE
HeartSee - Uptake Maps
Uptake Maps
Name:
Age: 58
Sex: Male
ID:
Study ID: 5320 - Date: Oct 03 2023 - Isotope: Rb
Rest
max 97% min 36% mean 73%
max activity 2.45 uCi/cc
CAC_REST_LATE_1
Lateral mean 86%
Inferior mean 46%
Septal mean 78%
Anterior mean 84%
Stress
max 97% min 25% mean 68%
max activity 3.62 uCi/cc
CAC_STRESS_LATE_1
Lateral mean 83%
Inferior mean 35%
Septal mean 68%
Anterior mean 84%
Patient Information
Dataset 1
File Name: CAC_REST_LATE_1
Date: 2023
Isotope: Rb
State: Rest
Dataset 2
File Name: CAC_STRESS_LATE_1
Date: 2023
Isotope: Rb
State: Stress
LibreOffice 6.0 Writer
cpstudy
Old Firefox Data
Link to cosira
Take Screenshot
DICOM Scanner Hostname ...
CENTOS



Camera started too early.

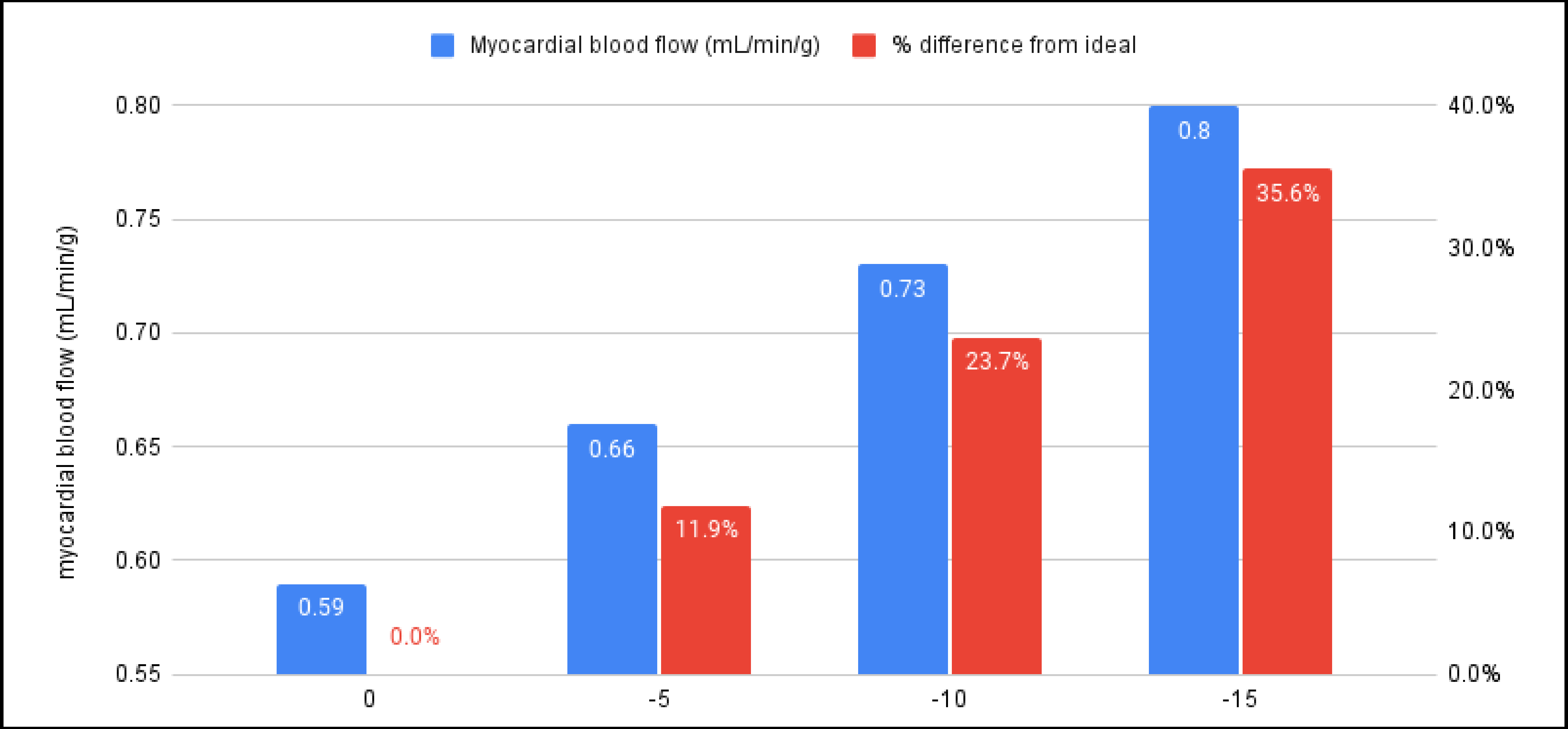


Frames shifted to create the early image starting from frame 3 (15s-135s)

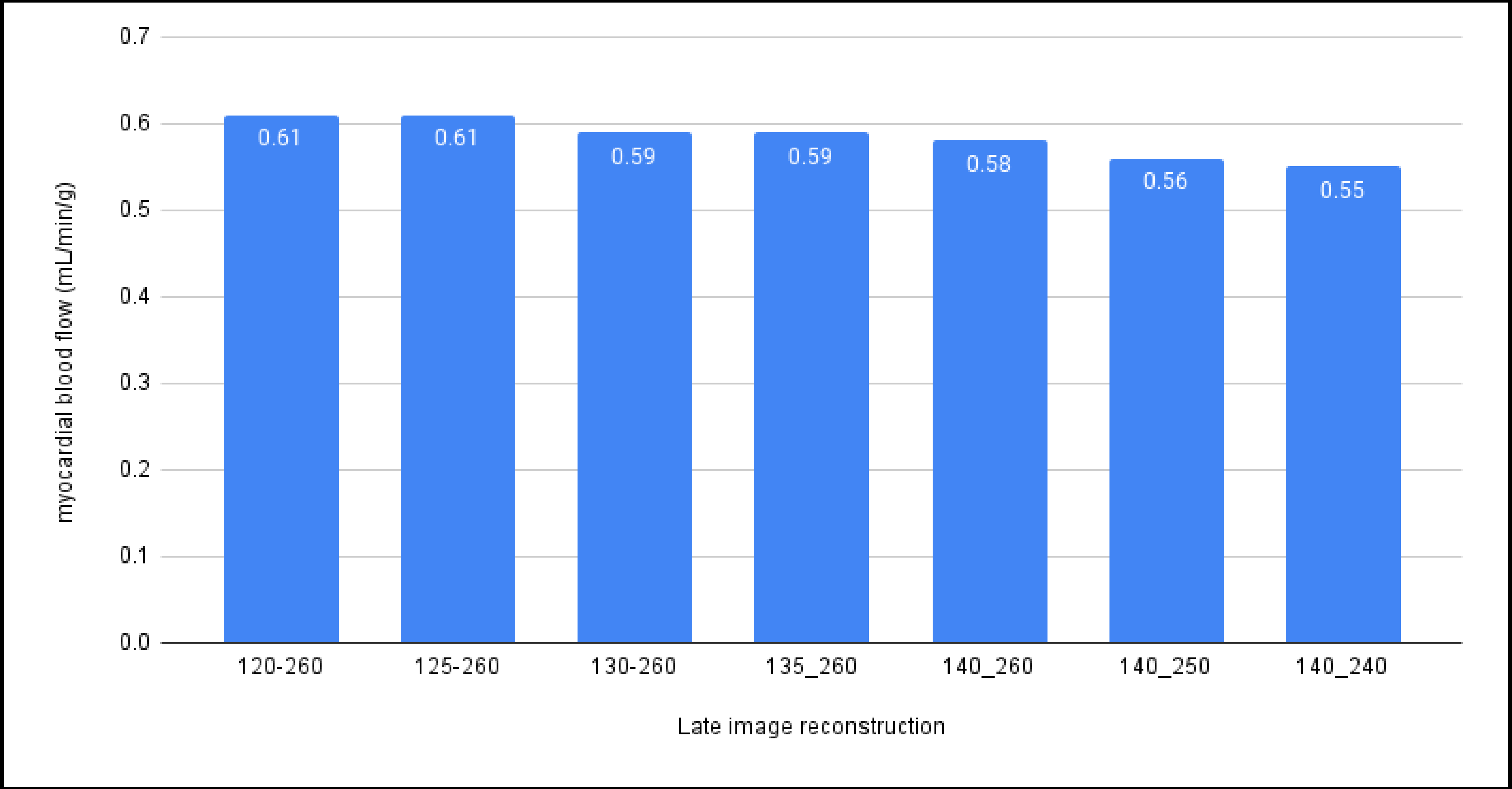


The framing of late images minimally impact MBF

Effect of dilution of arterial input function on MBF

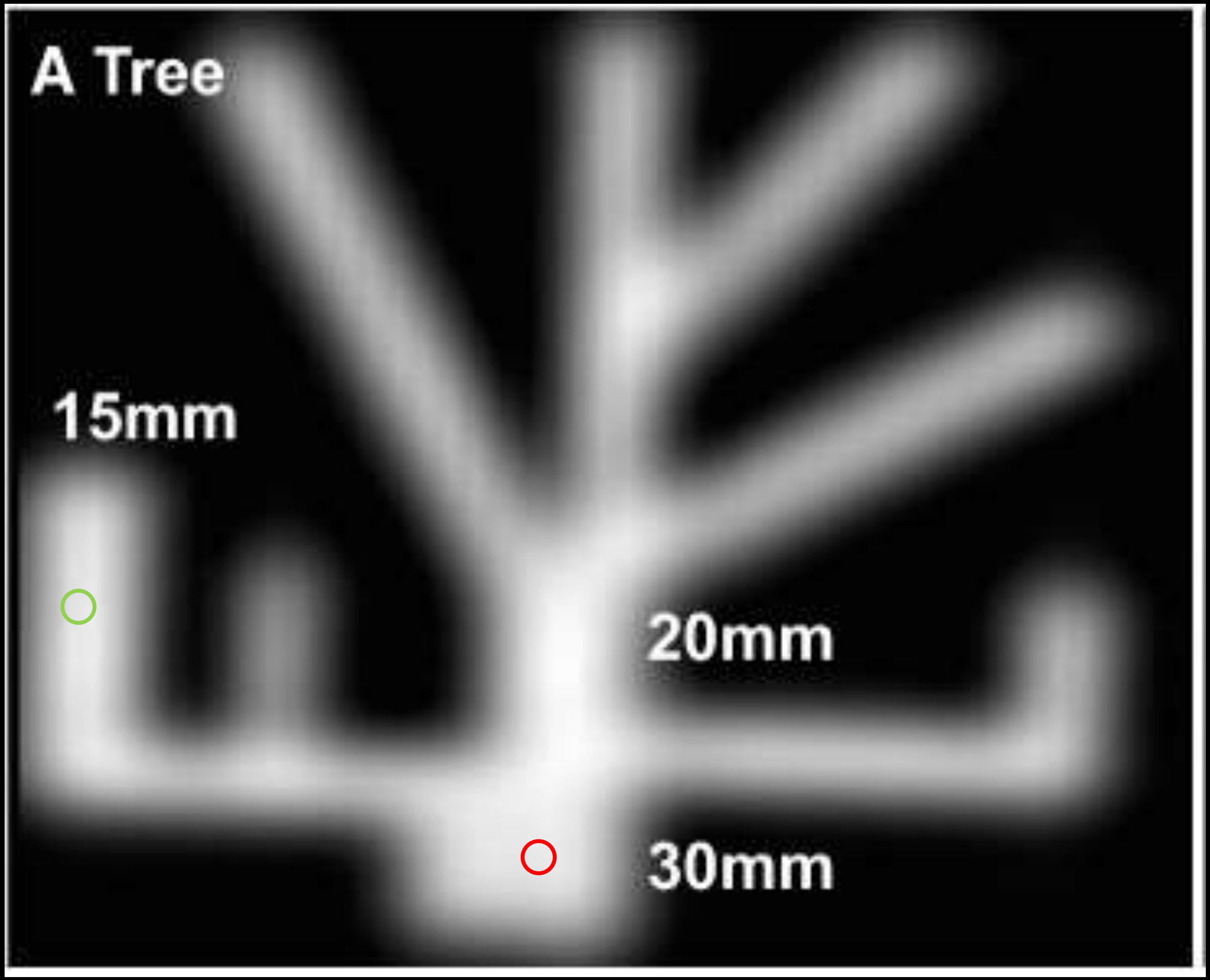


Effect of late image reconstruction timing on MBF



Partial volume loss

- The loss of count recovery due scanner resolution
- Longitudinal and LV circumference - large and not impacted by PV loss
- One dimensional LV wall thickness varies in systole vs. diastole - impacted by PV loss
- Model must account for 1D PV loss
- Dependent on scanner AND recon settings (one size doesn’t fit all)
  - Filter type and cutoff
  - TOF
  - Point spread function
  - FBP vs Iterative



101896 Bq/ml

113429 Bq/ml

101896/113429=**0.898**

Table 2. Rest and stress perfusion, CFR with partial volume corrections based on 1D, 2D, and 3D phantoms (N = 186) using Rb-82

PET Metric	Tree 1D stand PVC 0.9	ACR 2D PVC 0.73	NEMA 3D PVC 0.59
Rest cc/min/g	0.78±0.07	1.20±0.16	1.81±0.33
Stress cc/min/g	1.35±0.22	2.00±0.42	2.89±0.76
CFR	1.82±0.46	1.78±0.43	1.70±0.36

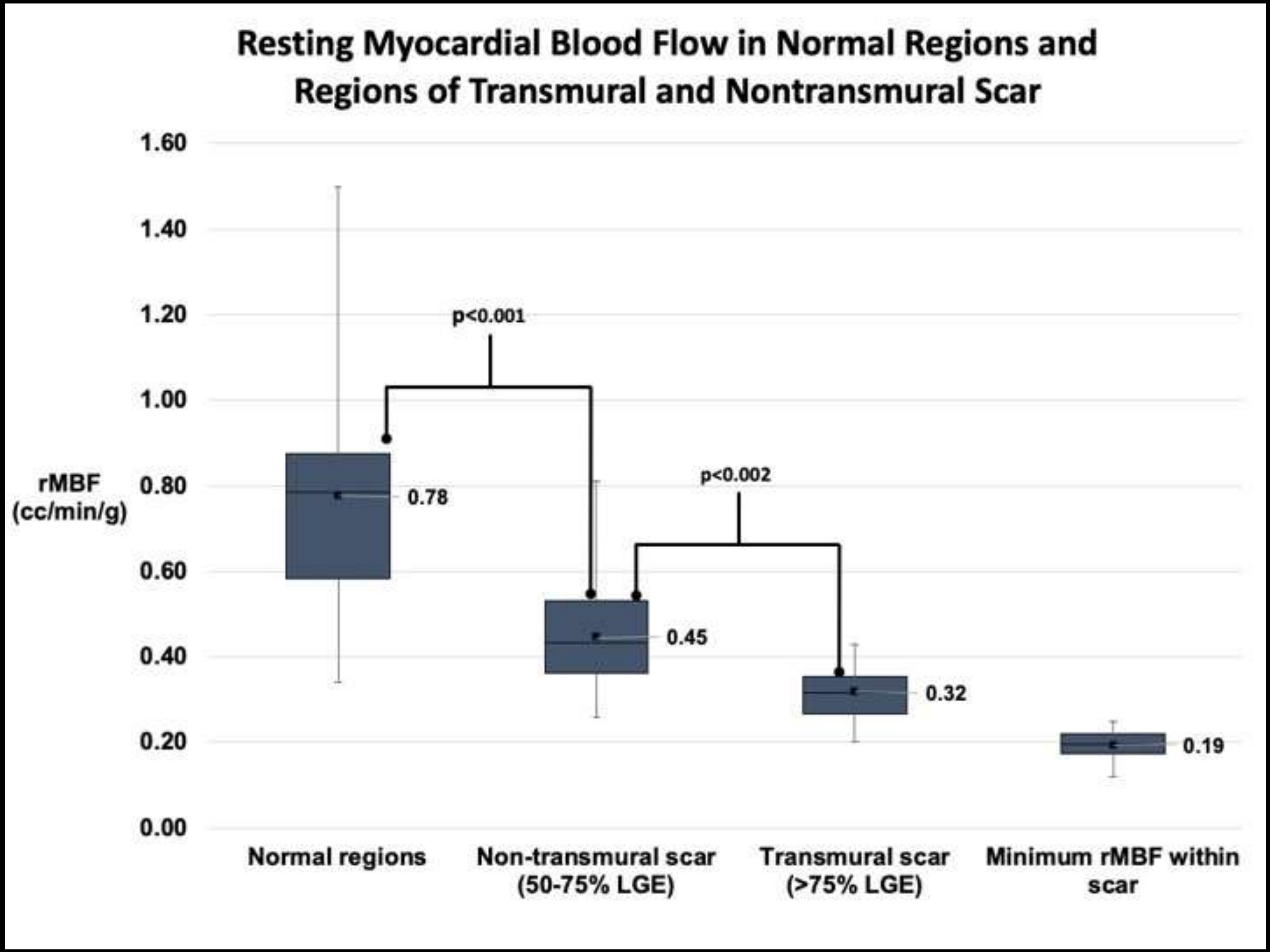
Paired T test between all columns for each row $P < 0.000001$
PVC, Partial volume correction; *CFR*, coronary flow reserve

Gould et al. Journal of Nucl Cardiol, volume 27, Issue 2 April 2020, Pages 386-396

$$\text{FLOW} = \frac{\qquad\qquad}{\text{Arterial input}} \times (\text{PV})$$

PV= Partial Volume corrections
EF= Extraction Fraction

Transmural scar to assess accuracy



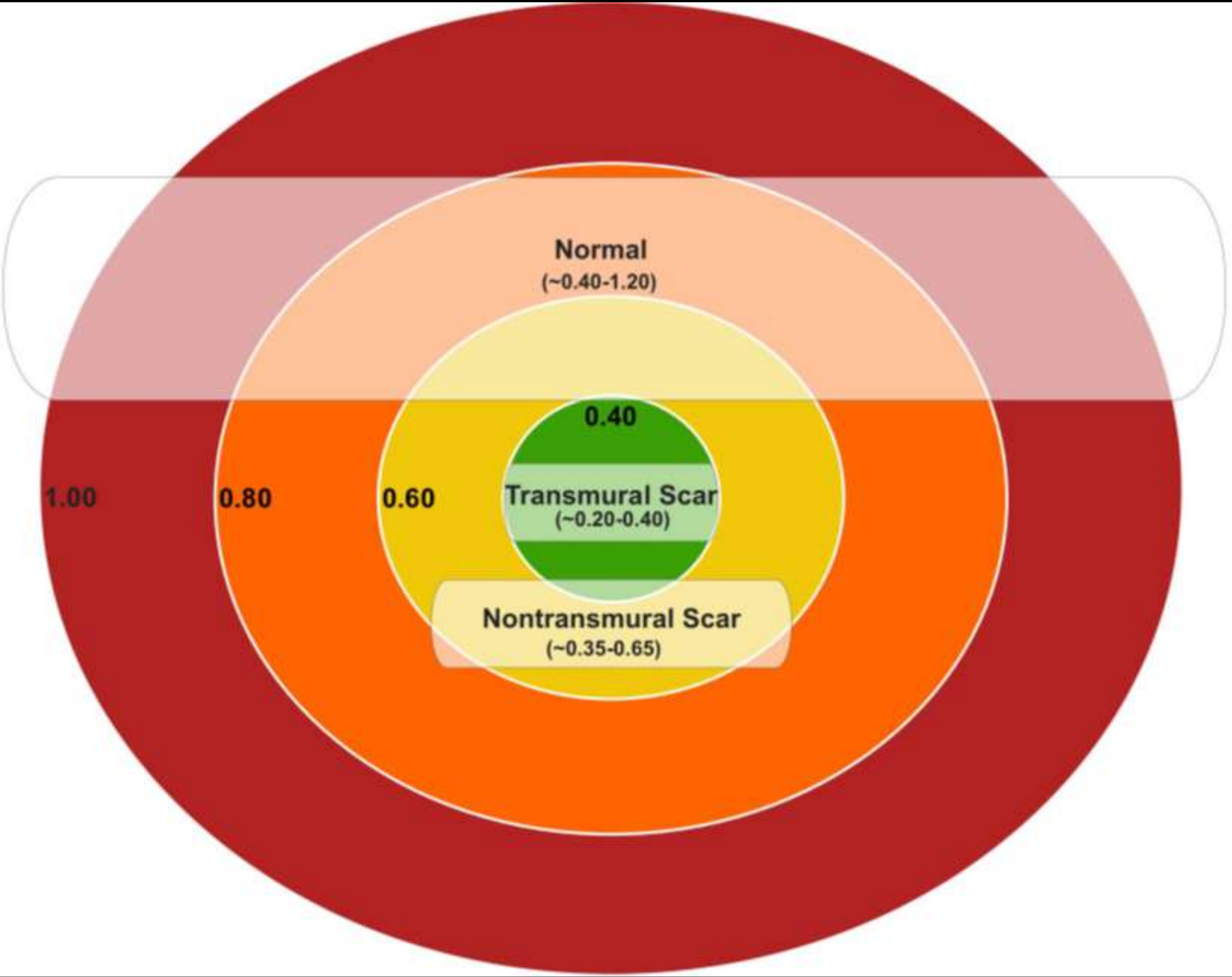
Stewart et al, Ann Nucl Cardiol. 2022; 8(1): 7–13

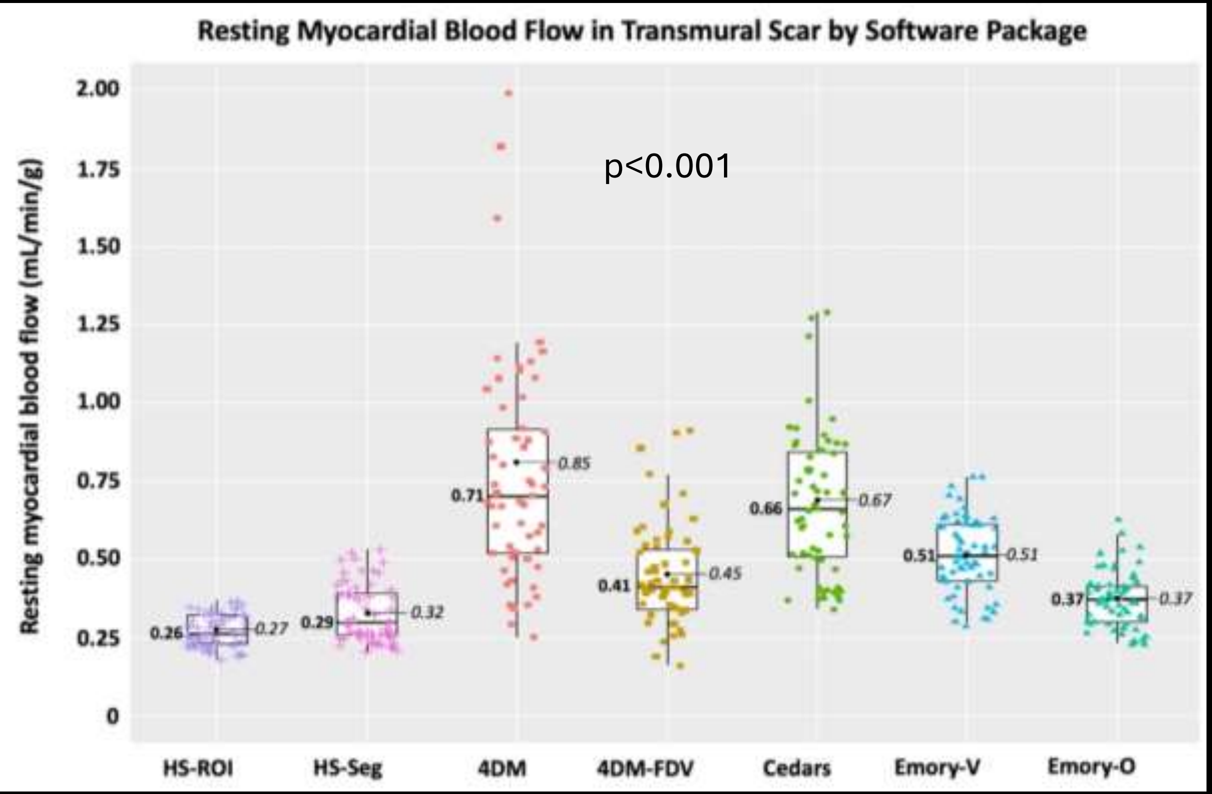
Author	Radiotracer or method	Mean rMBF in transmural scar (mL/min/g)
Rivas [3]	Microspheres	Infarcted layers with rMBF ranging 0.00–0.35
Savage [4]	Microspheres	Infarcted layers with rMBF ranging 0.06–0.25
de Silva [5][§]	[O-15]H_2O	0.28 ± 0.07
Czernin [6]	N-13	0.32 ± 0.12
Bol [7]	microspheres, N-13 and [O-15]H_2O	0.26–0.35
Gewirtz [8]	N-13	0.27 ± 0.17
Sun [9]	N-13	0.28 ± 0.09
Beanlands[*] [10]	N-13	0.30 ± 0.06
Iida [11]	Microspheres, [O-15]H_2O	0.19 ± 0.14
Zhang [12]	N-13	0.32 ± 0.09
Wang [2]	N-13	0.27 ± 0.06
Stewart [1]	Rb-82	0.32 ± 0.07
Bober	Rb-82	0.27 ± 0.05

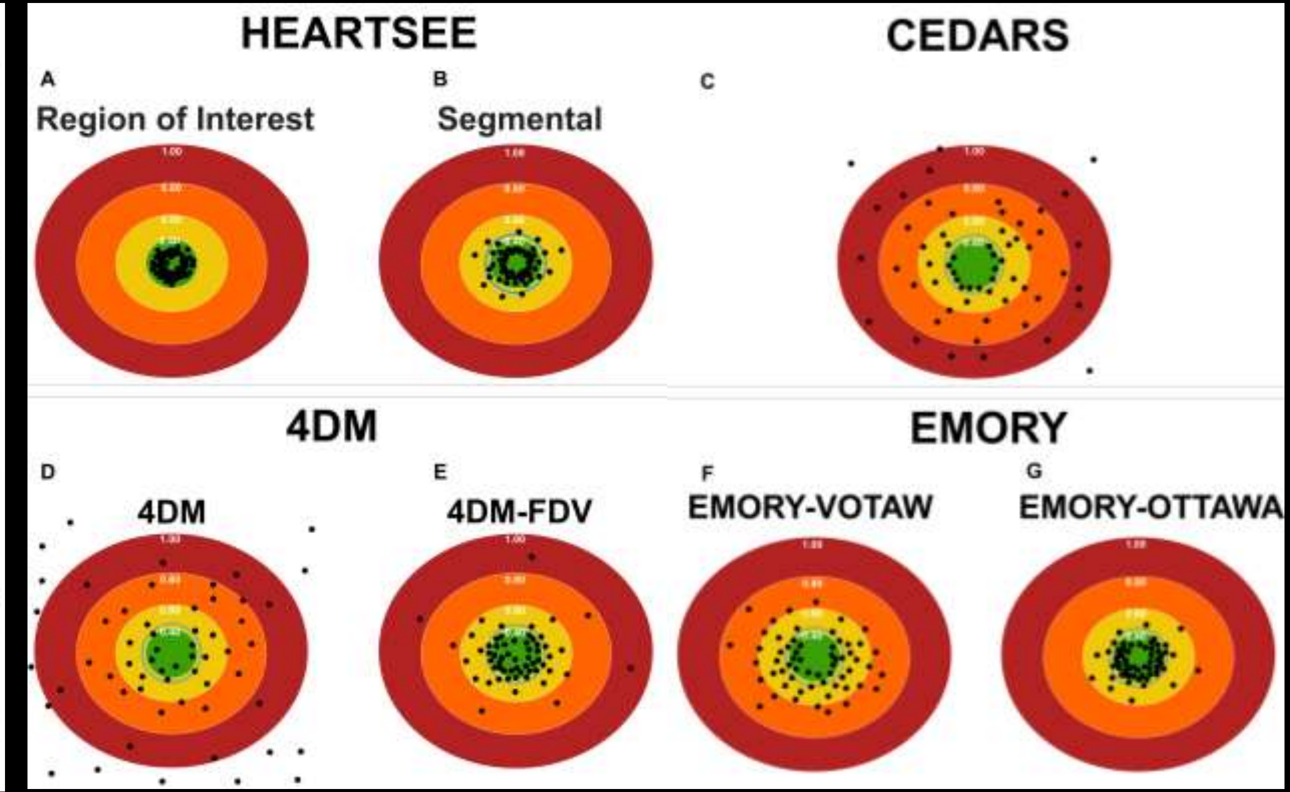
*Two data points excluded due to residual viability

§ Reported resting myocardial blood flow in perfusable tissue value perfusable tissue index (PTI) to the reported values in the conclusio

Bober et al. EJNMMI Res. 2023 Sep 27;13(1):87.


Normal
(~0.40-1.20)
0.40
1.00
0.80
0.60
Transmural Scar
(~0.20-0.40)
Nontransmural Scar
(~0.35-0.65)

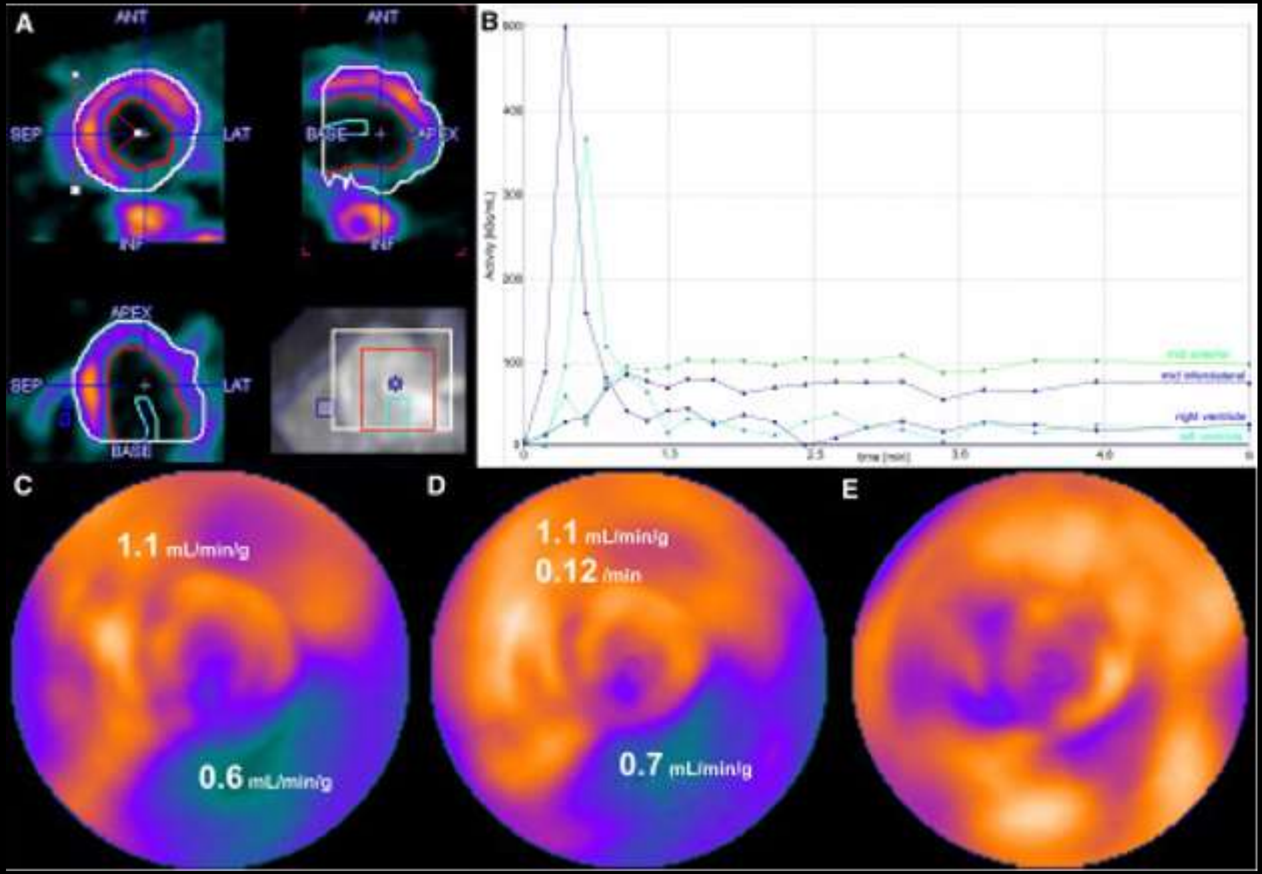




Bober et al. EJNMMI Res. 2023 Sep 27;13(1):87.

PMOD scar= 0.68

Bober et al, Cedars scar = 0.67



Benz et al, February 2021, Journal of Nuclear Cardiology Volume 28, Issue 1 263-273

Rest MBF in normal regions

Author	4DM	Cedars	HeartSee
Oliveira et al	1.1 ± 0.3	1.0 ± 0.2	NA
Bober et al	1.09 ± 0.3	1.03 ± 0.3	0.78 ± 0.27

Oliveira et al, J Nucl Cardiol. 2019 Dec;26(6):2007-2012
Bober et al. EJNMMI Res. 2023 Sep 27;13(1):87.

Whole Heart Resting MBF

Rb-82	0.75	0.75	0.75	0.75	**1.00**	**1.00**
N13	0.75	0.75	0.75	0.75	0.75	0.75

Commercialization

1990 1995 2000 2005 2010 2015 2020

- Pre ~2009
  - MBF mostly restricted to researchers
  - Manual – labor intensive
  - Attention to detail
  - rMBF ~ 0.75-0.80 cc/min/g
- 2007~2010 homegrown automated softwares
- ~2010 commercialization – rMBF>1.00 cc/min/g

Literature review of adult cardiac PET. Resting flow with N-13 and Rb-82

Normal volunteers

Tracer	Subjects	rMBF
N13	849	0.79±0.06
Rb82	1350	0.73±0.04

CAD

Tracer	Subjects	rMBF
N13	2629	0.75±0.09
Rb82	29	0.85±0.07

Risk factors

Tracer	Subjects	rMBF
N13	2629	0.78±0.05
Rb82	121	1.06±0.16

Mixed

Tracer	Subjects	rMBF
Rb82	4591	0.97±0.10

Gould et al, JACC Volume 62, Issue 18,2013,1639-1653. State-of-the-Art Review

Risk factors

Tracer	Subjects	rMBF
N13	2629	0.78±0.05
Rb82	121	1.06±0.16

8 – Abandoned technique – too complex and unreliable

73 – Early version of SW – No Motion Correction
Per vendor – "its wrong if you don't do motion correction"

40 – Retention model and ROI for Arterial input was in the LV (ie – input function is incorrect)[1]

Mixed population

Tracer	Subjects	rMBF
Rb82	4591	0.97±0.10

Gould et al, JACC Volume 62, Issue 18,2013,1639-1653. State-of-the-Art Review

433 – Abandoned technique – too complex and unreliable

2783 – Early version of SW – No Motion Correction
Per vendor – "its wrong if you don't do motion correction"

677 – "Patients were positioned in a 3-dimensional PET system (Discovery Rx/VCT, GE Healthcare, Milwaukee, Wisconsin). 10 MBq/kg of ^{82}Rb was administered intravenously"[1]

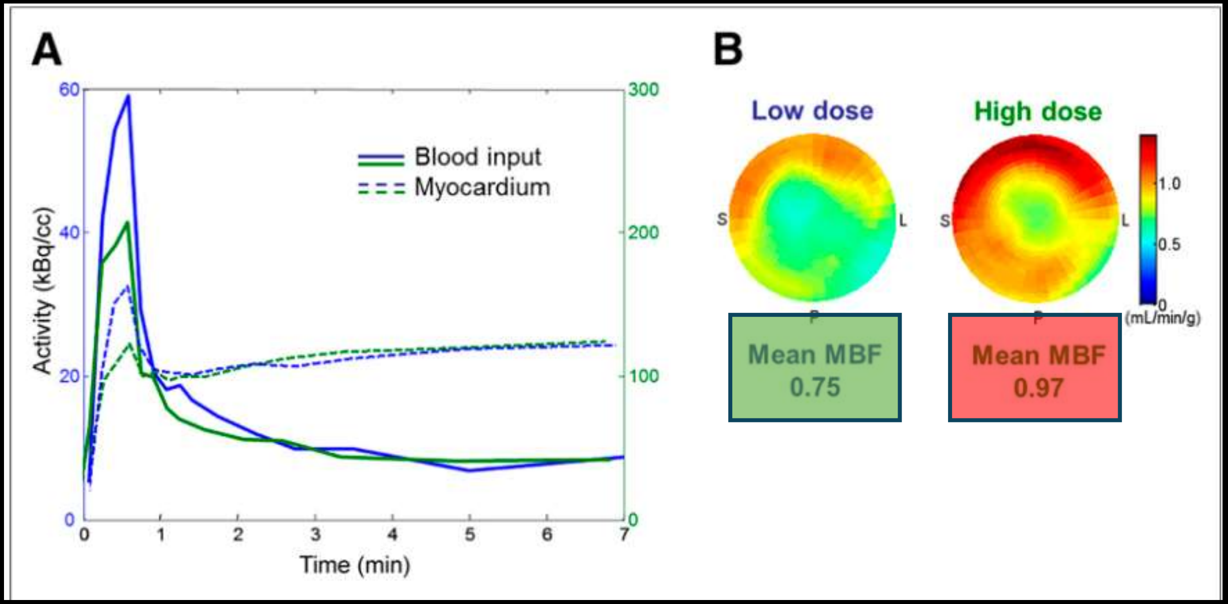
Ziadi, et al. JACC 2011 Aug 9;58(7):740-8

Gould et al, JACC Volume 62, Issue 18,2013,1639-1653. State-of-the-Art Review

Vasquez, Johnson, Gould. J Am Coll Cardiol CV Imag 2013;6:559

Recommended Maximum Injected Activity and Performance Metrics

PET system	Patient A_{max}/weight (MBq/kg)	Peak prompts (Mcps)	Peak singles (Mcps)	Peak DTF	Scatter bias(t) (%)	C_{myo}(t)cov (%)
Biograph mCT PET/CT-40	14.4	6.3	64	—	5.2 ± 0.2	12.4 ± 2.1
ECAT Accel Scintron PET 2D	11.4	1.6	26	1.7	8.3 ± 0.6	6.5 ± 0.2
Discovery 690 PET/VCT-64	11.4	5.9	45	1.5	2.4 ± 0.3	11.0 ± 4.8
Discovery IQ (5 ring) PET/CT-16	11.3	14.1	84	3.9	2.7 ± 1.1	2.9 ± 0.2
Biograph TruePoint PET/CT-16	8.0	—	—	—	9.9 ± 0.4	8.0 ± 0.3
Discovery 600 PET/CT-16	6.5	4.1	29	2.0	2.1 ± 0.3	12.1 ± 1.1
Biograph PET/CT-16	5.5	—	22	—	8.6 ± 0.2	16.4 ± 1.3
Discovery RX PET/CT-16	5.1	4.5	—	1.7	3.1 ± 0.3	10.6 ± 0.8
Gemini TF PET/CT-16	4.6	—	—	—	2.5 ± 0.5	7.8 ± 0.9
Discovery STE/VCT-16	3.9	3.5	—	2.1	2.5 ± 0.4	4.3 ± 3.3
ECAT Accel Scintron PET 3D	2.7	1.6	22	1.7	7.4 ± 0.2	6.5 ± 0.3



Renaud, et al. JNM, January 2017, 58 (1) 103-109

Mixed population

Tracer	Subjects	rMBF
Rb82	4591	0.97±0.10

Mixed – erroneous data excluded

Tracer	Subjects	rMBF
Rb82	698	0.74±0.21

Reproducibility Between SW

JACC Cardiovasc Imaging. 2014 Nov;7(11):1119-1127.

Second Attendance Verification Code
4115

TECHNIQUE
&
PRECISION

How to measure precision

- COV – coefficient of variation
  - Dispersion around the mean
  - Stdev of differences/mean
  - Different conditions can apply
- RPc – repeatability coefficient
  - maximum difference between repeated measurements made **under the same conditions** in 95% of cases
  - 1.96 x SD

Measurement	Coefficient of Variation
Fasting Glucose	9%
SBP reading	11%
LDL	6-14%
EF - ECHO	12%
% stenosis QCA	17%
CRP	46%
Invasive FFR	10%*
FFR-CT	36%**
PET MBF	9.6-10.8%***

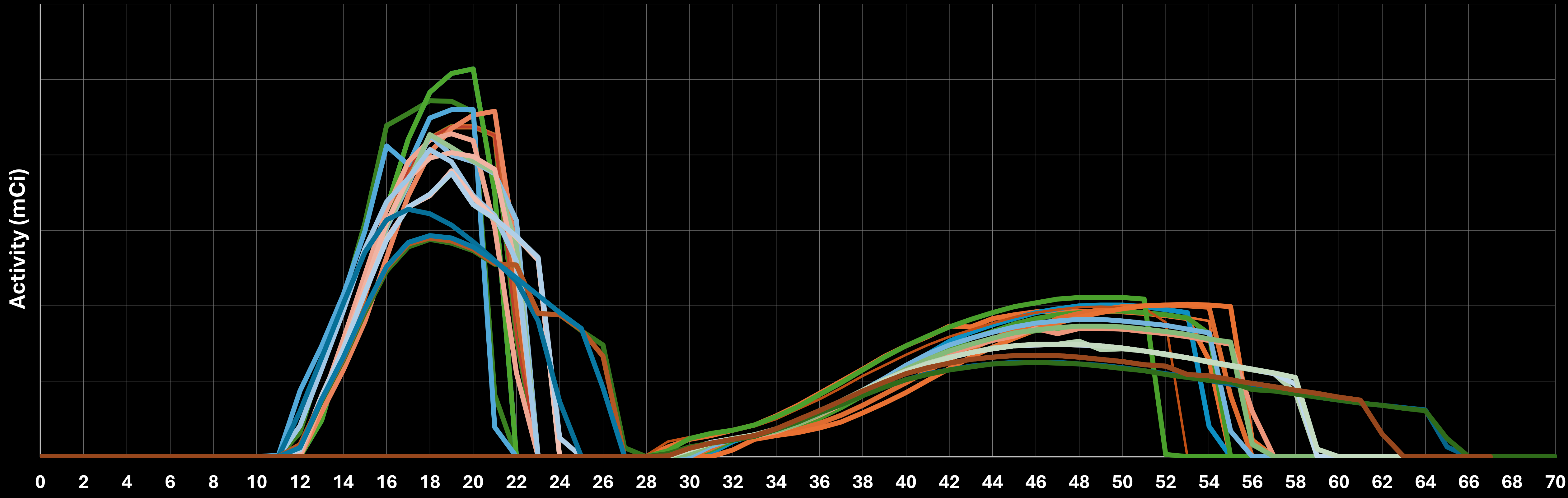
SWP	COV Scar
HeartSee	0.07
4DM	0.16
4DM-FDV	0.11
Cedars	0.11
Emory-V	0.09
Emory-O	0.08
p-value	<0.001

Table from Johnson, NP, JACC Cardiovasc Inter. 2014 Feb;7(2):227-8

* Johnson et al., Curt Cardiol Rep, 2020, 22:20
** Cook, CM, JAMA Cardiol. 2017 Jul 1;2(7):803-810
*** Kitkungvan D et al. JACC Imaging 2017 2017;10:565-77

Bober et al. EJNMMI Res. 2023 Sep 27;13(1):87.

Time activity curves of Rb-82 for fast (50mL/min) and slow (20mL/min) repeated infusions over 5 weeks



Fast vs. Slow infusion?

- Limited camera capabilities
  - Give slower – minimizes dead time
  - Give slower – allows for better myocardial uptake = better image quality
- 22 pts (normal or CAD suspicion) with same day repeat testing
  - CA-CF or CA-CA
  - CA-CA (RC=**21%** more precise than CA-CF)
  - No difference in image quality

CA= constant activity
CF = constant flow

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Fast vs. Slow infusion?

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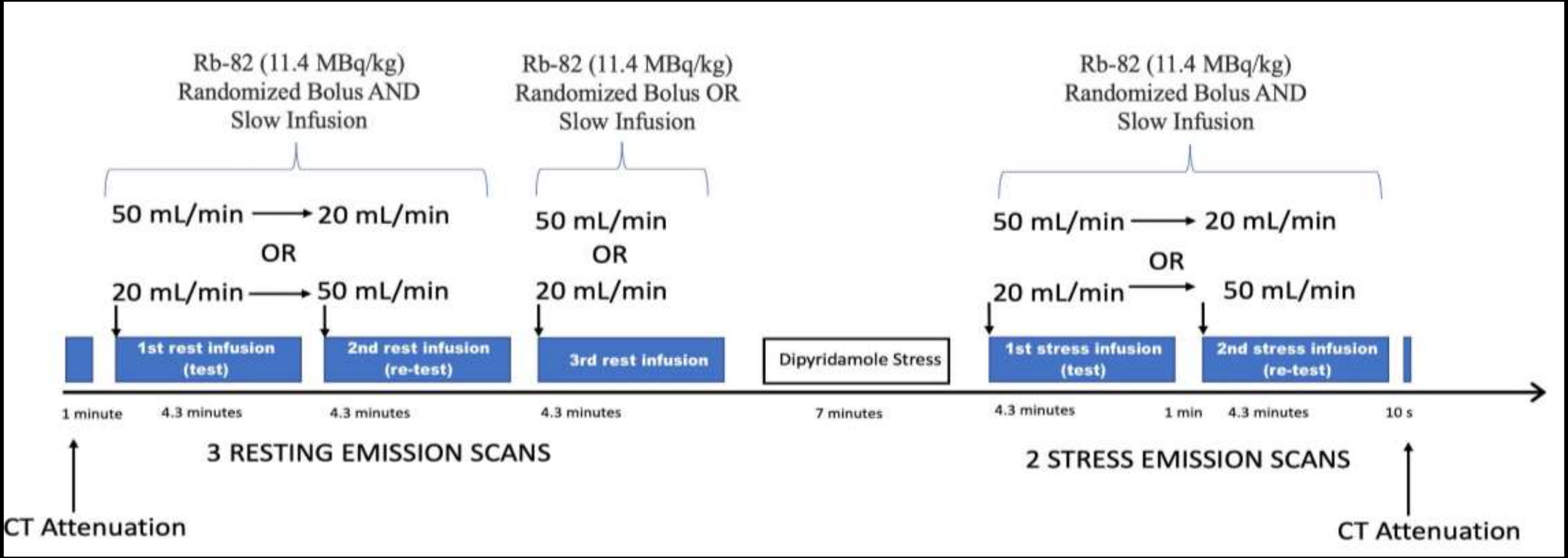
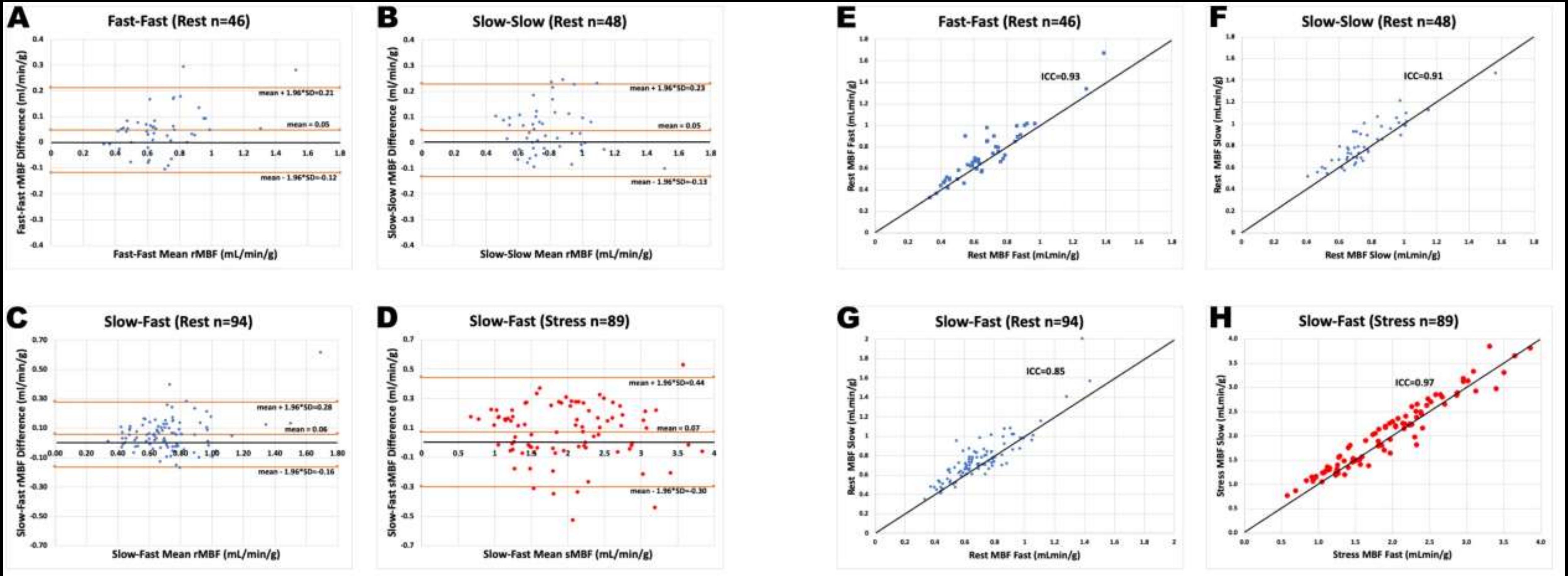
- 22 pts (normal or CAD suspicion) with same day repeat testing
  - CA-CF or CA-CA
  - CA-CA (RC=**21%** more precise than CA-CF)
  - No difference in image quality
- Did not evaluate CF-CF or low EF
- Questionable statistics (repeatability coefficient – CA-CF)
- Did not test standard 50mL/min
- Several non-physiologic values

CA= constant activity
CF = constant flow

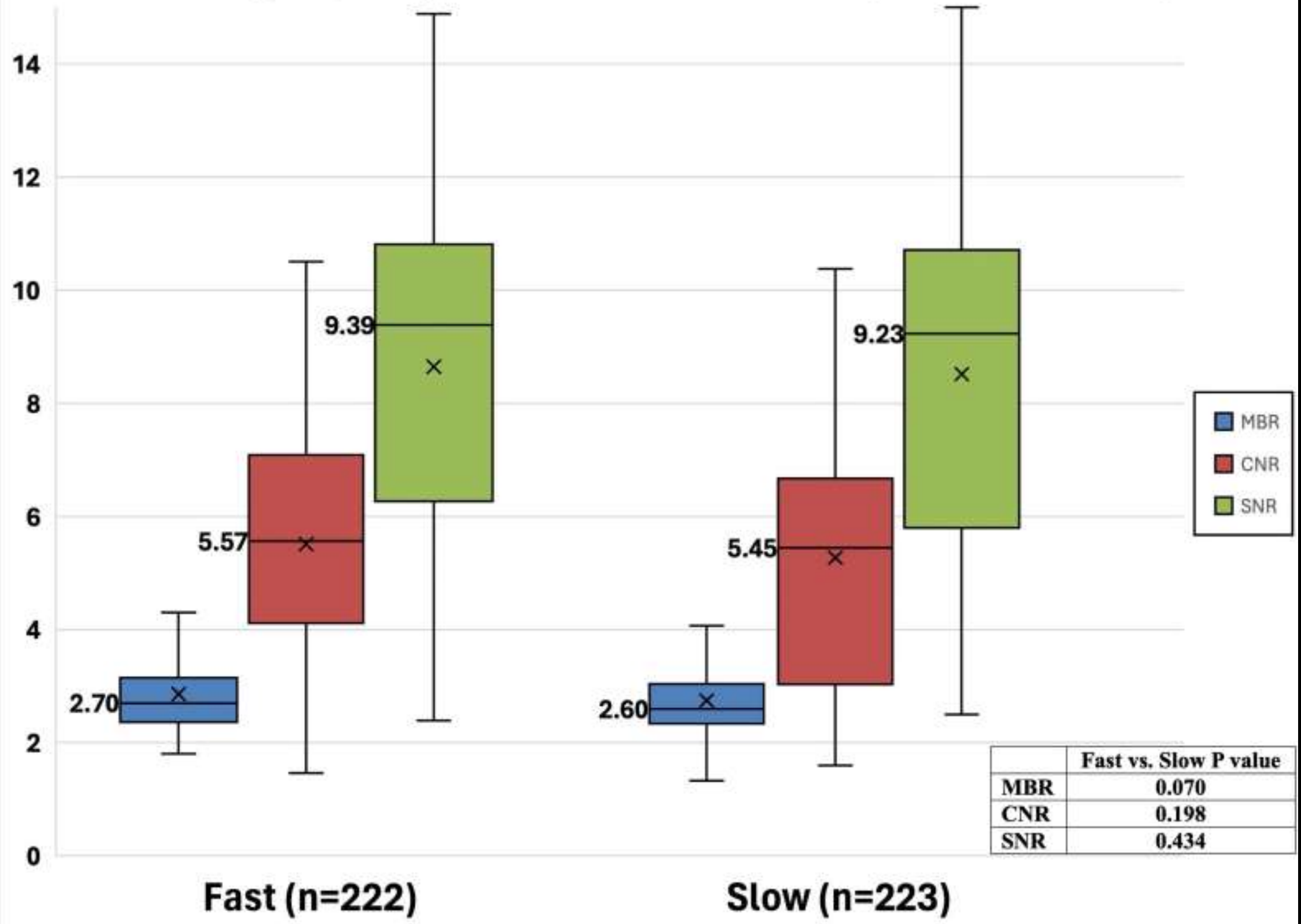

Rb-82 (11.4 MBq/kg)
Randomized Bolus AND
Slow Infusion
Rb-82 (11.4 MBq/kg)
Randomized Bolus OR
Slow Infusion
Rb-82 (11.4 MBq/kg)
Randomized Bolus AND
Slow Infusion
50 mL/min → 20 mL/min
OR
20 mL/min → 50 mL/min
50 mL/min
OR
20 mL/min
50 mL/min → 20 mL/min
OR
20 mL/min → 50 mL/min
1st rest infusion (test)
2nd rest infusion (re-test)
3rd rest infusion
Dipyridamole Stress
1st stress infusion (test)
2nd stress infusion (re-test)
1 minute
4.3 minutes
4.3 minutes
4.3 minutes
7 minutes
4.3 minutes
1 min
4.3 minutes
10 s
3 RESTING EMISSION SCANS
2 STRESS EMISSION SCANS
CT Attenuation
CT Attenuation

	Rest B-B (n=46)	Rest S-S (n=48)	p-value	Stress S-B (n=89)
COV	12.2%	11.6%	0.77	10.0%
RC	16.5%	18.0%	0.77	NA
ICC	0.93	0.91	NA	0.97

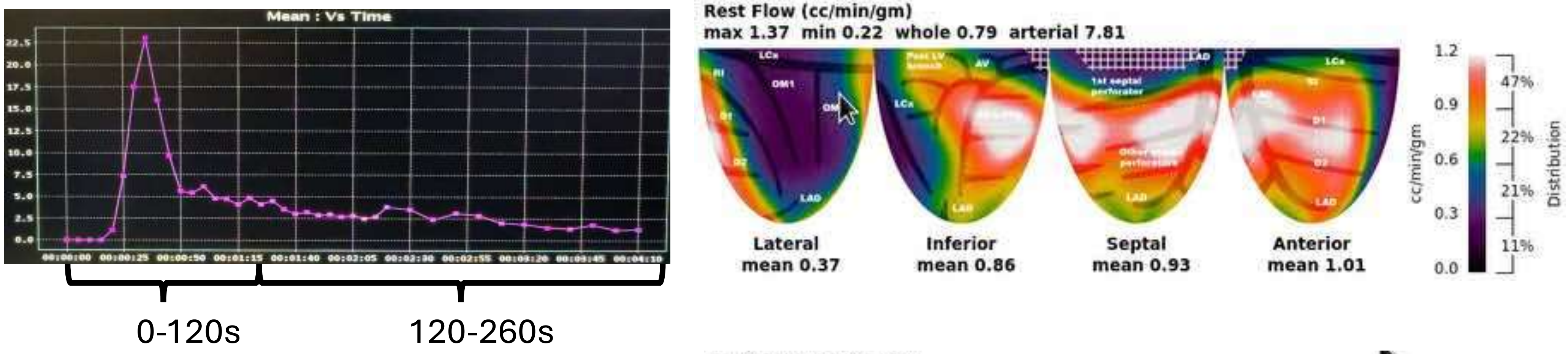


Bober et al, Under Review

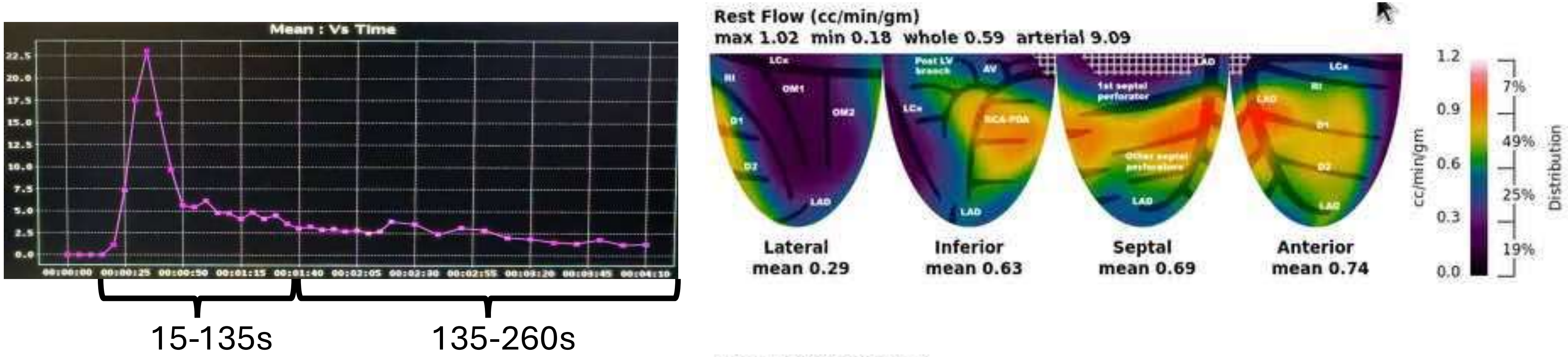
Image Quality Metrics Fast vs. Slow (rest and stress)



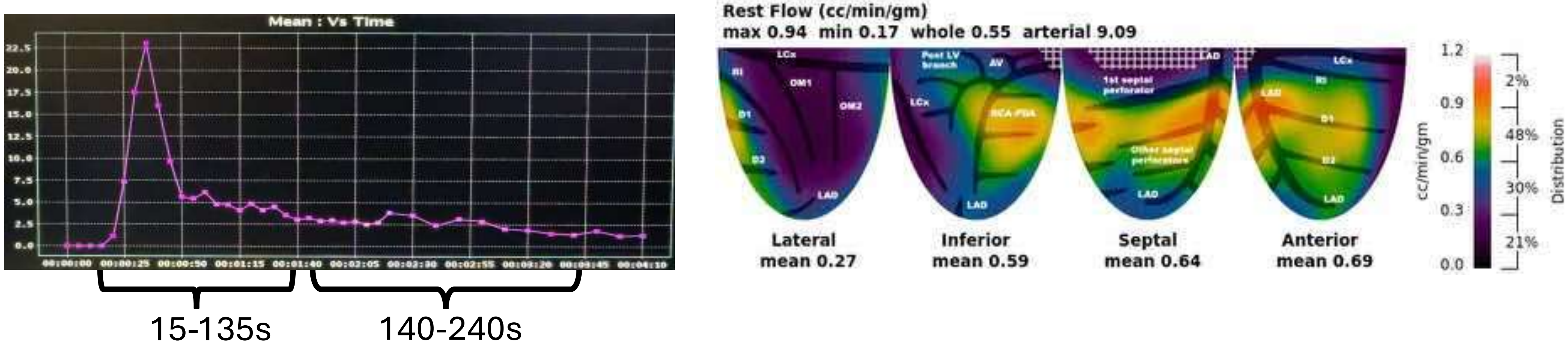
	Fast vs. Slow P value
MBR	0.070
CNR	0.198
SNR	0.434



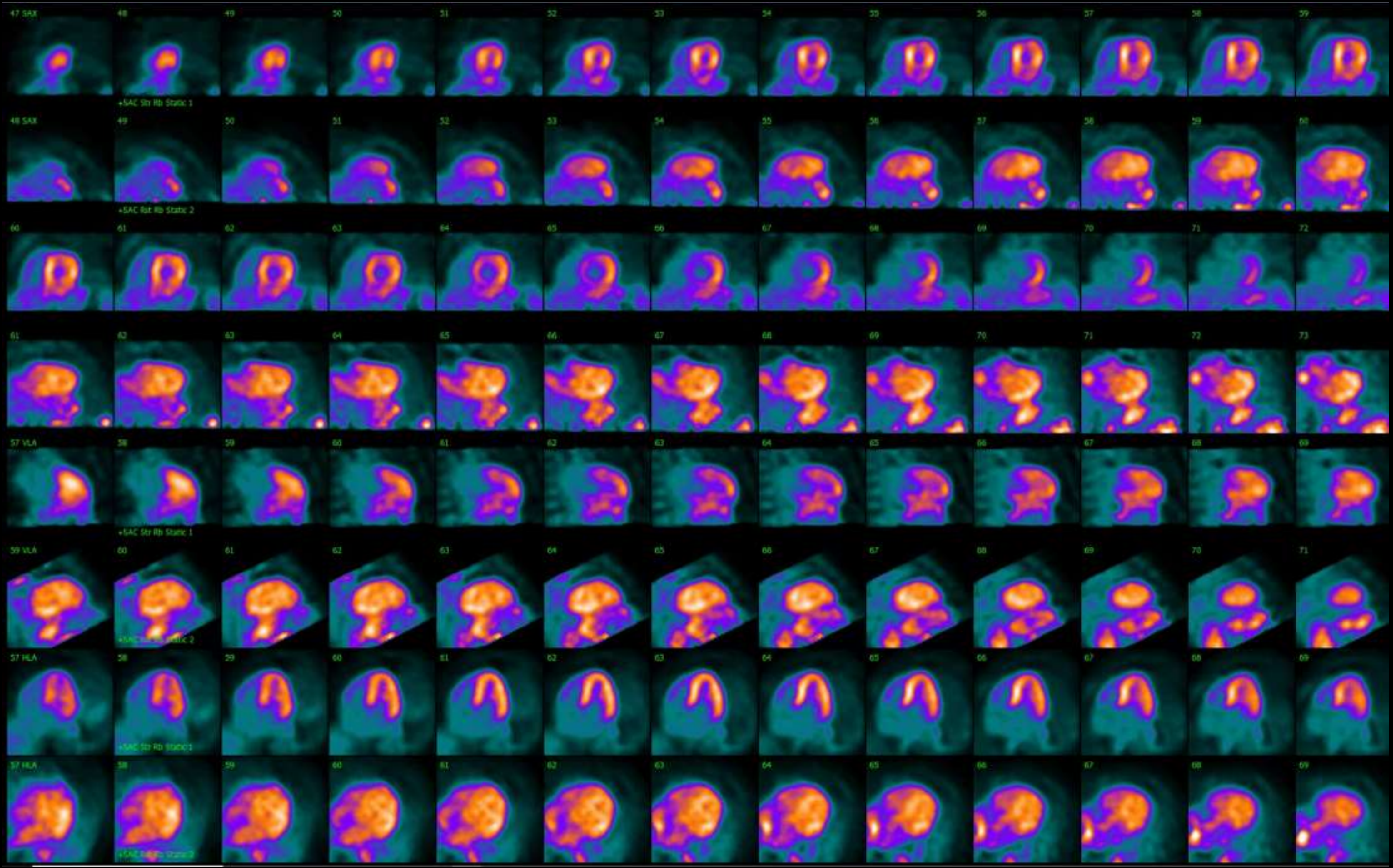
Camera started too early.

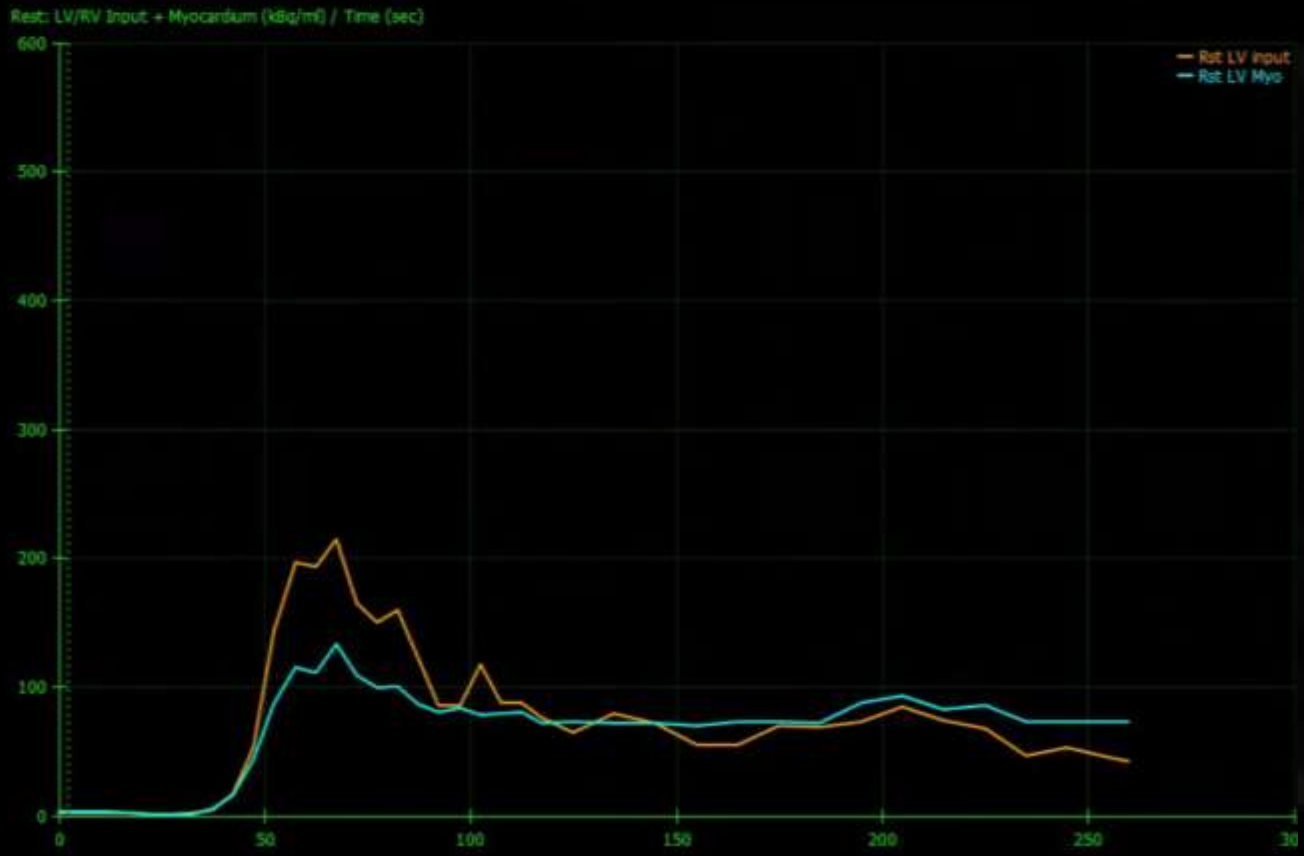


Frames shifted to create the early image starting from frame 3 (15s-135s)



The framing of late images minimally impact MBF


47 SAX
+SAC Str Rb Static 1
48 SAX
+SAC Rst Rb Static 2
57 VLA
+SAC Str Rb Static 1
59 VLA
57 HLA
+SAC Str Rb Static 1
57 HLA



Rest: LV/RV Input + Myocardium (kBq/ml) / Time (sec)
Rst LV input
Rst LV Myo
600
500
400
300
200
100
0
0
50
100
150
200
250

Summary

- Numerous causes of decreased accuracy and/or precision
- Camera, software and technique require understanding
- Check rMBF in transmural scar
  - Assess for accuracy
  - Doesn’t answer why
- Repeat testing
  - Assess for precision