Cardiovascular Disease: Applying MRI to study atherosclerosis, the aortic arch and endothelial permeability in small animal models

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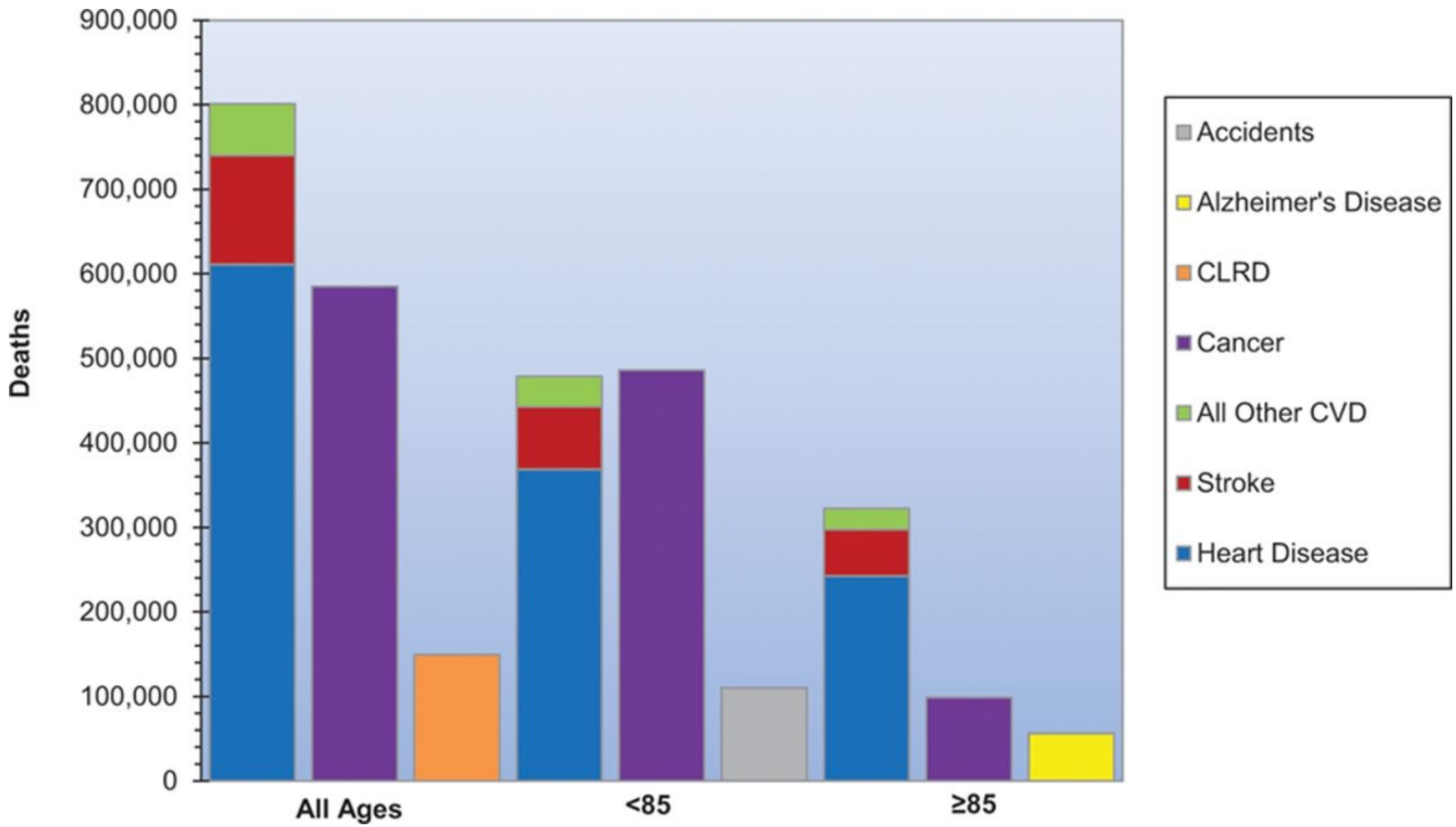
Mount Sinai

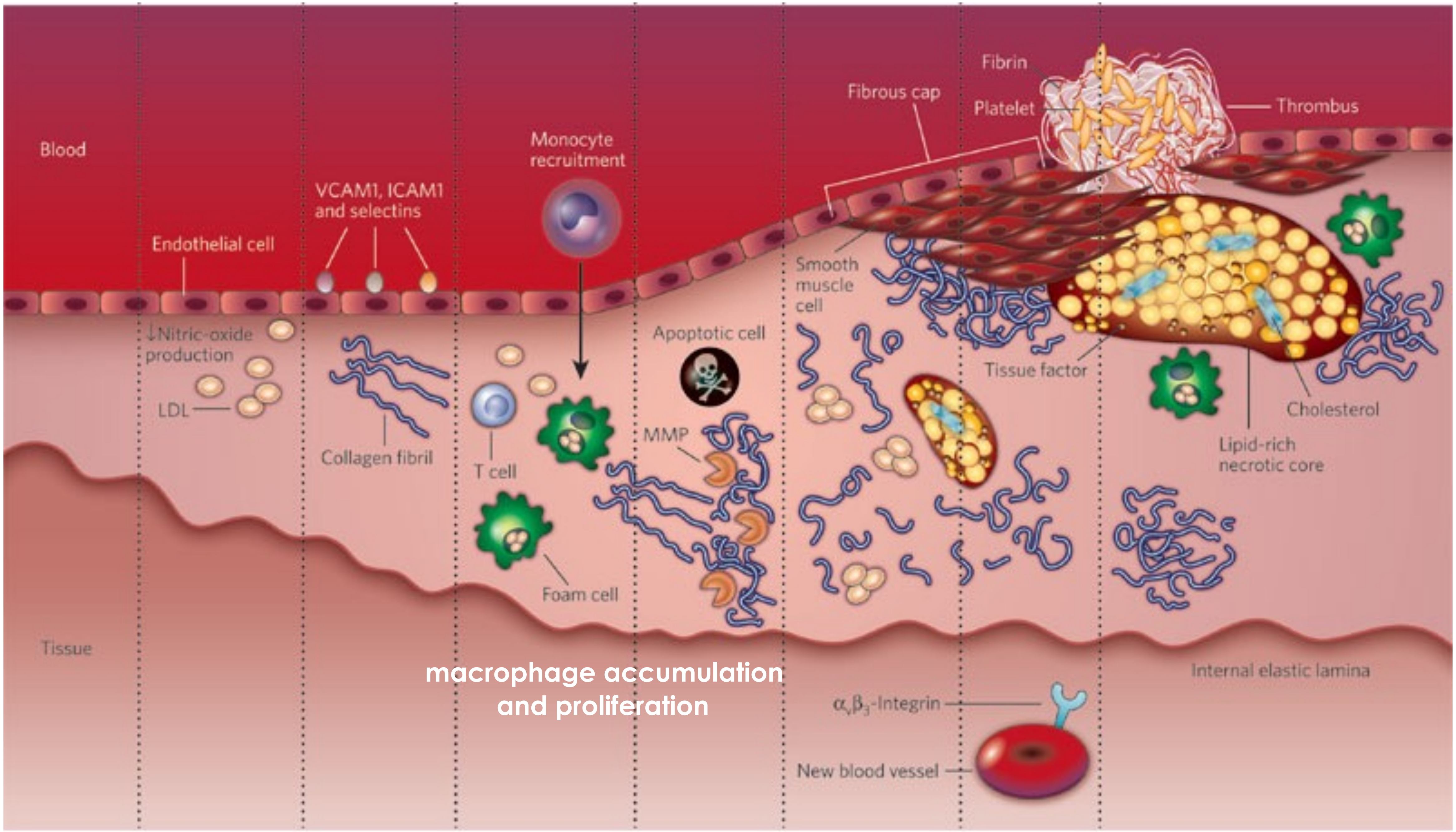
Cardiovascular disease due to atherosclerosis is the main cause of morbidity and mortality world-wide



Heart Disease and Stroke Statistics—2016 Update, A Report From the American Heart Association, 2016

Even in individuals treated with optimal lipid lowering strategies, residual cardiovascular risk is still high

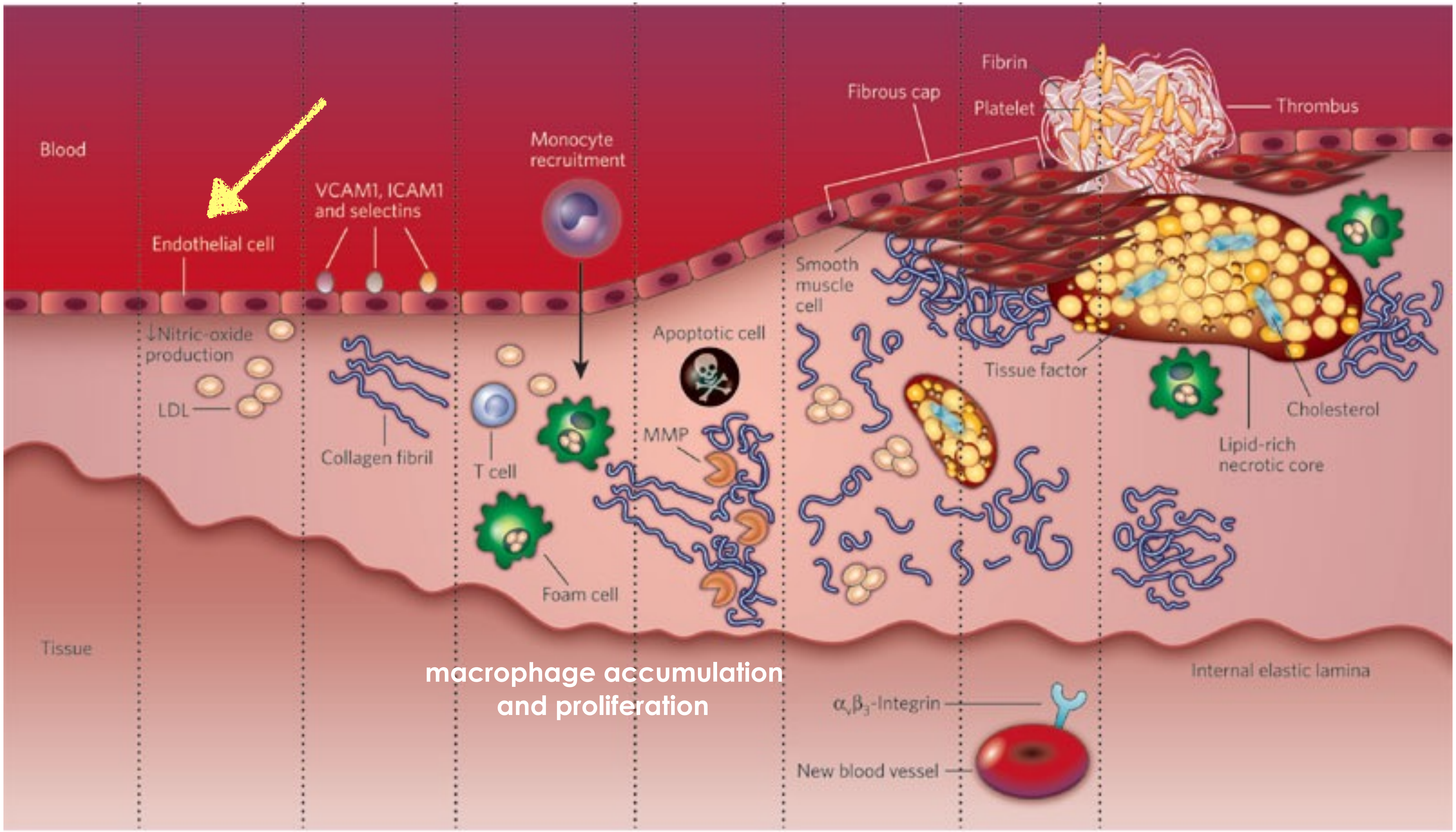
Endothelial permeability and vulnerable atherosclerotic plaques



Sanz J and Fayad Z, Nature 2008

Vulnerable plaques at high-risk for causing clinical events are rich in inflammatory cells and leaky neovessels

Endothelial permeability and vulnerable atherosclerotic plaques



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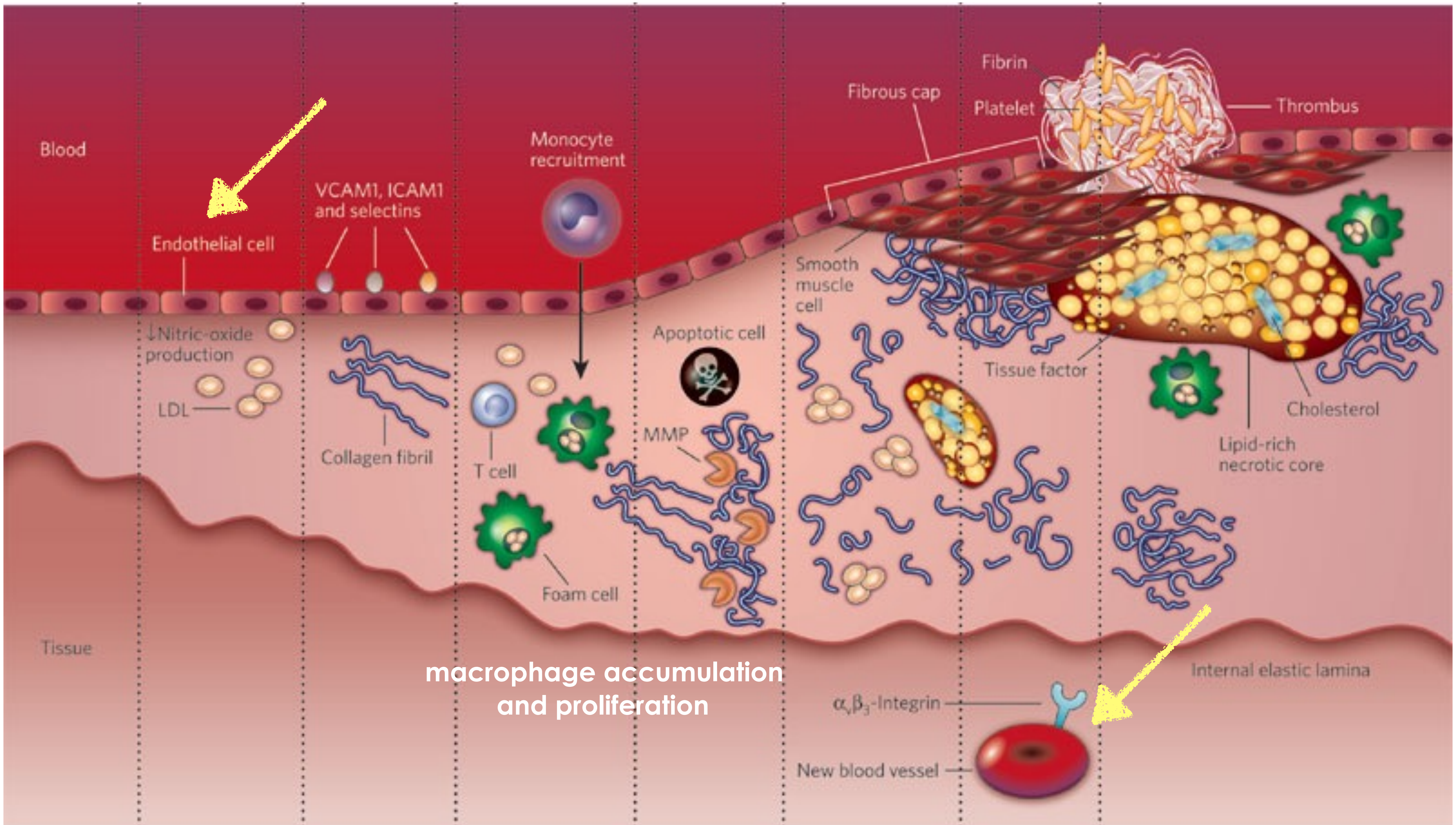
Endothelial permeability and vulnerable atherosclerotic plaques

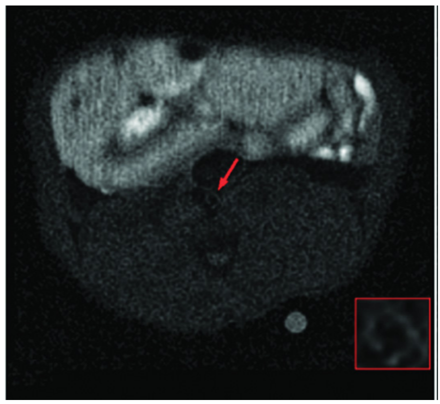


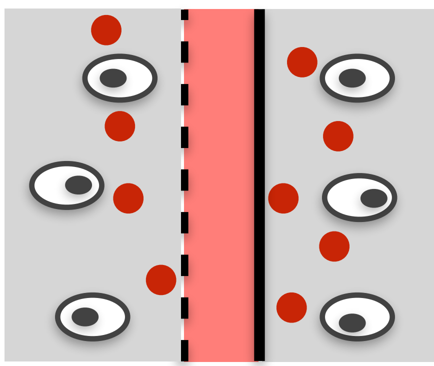
Sanz J and Fayad Z, Nature 2008

Vulnerable plaques at high-risk for causing clinical events are rich in inflammatory cells and leaky neovessels

Endothelial permeability can be investigated using contrast enhanced MRI

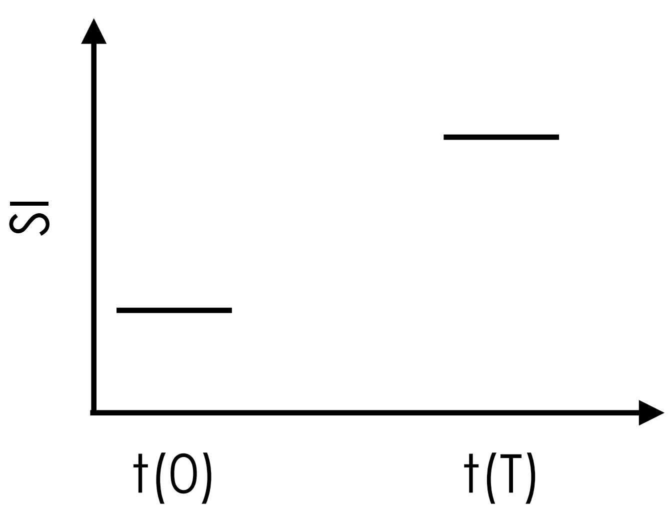
t(0) — injection of T1 shortening, Gd-based contrast agent — t(T)





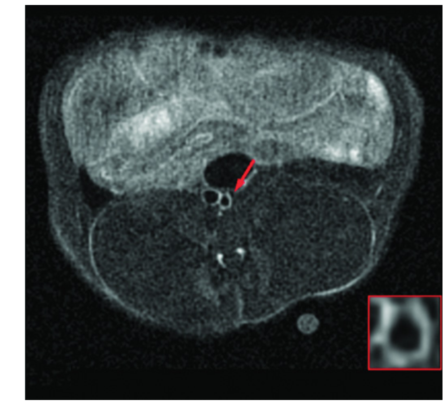
pre-contrast

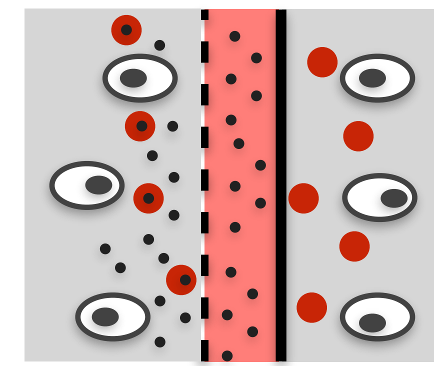
<u>delayed enhancement (DE) imaging</u>: measure change in MR signal intensity after injection



wait ....

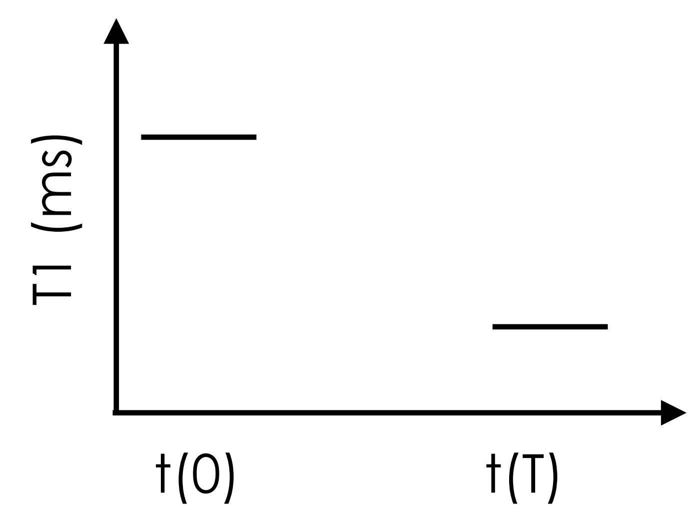
extra-vascular
extra-cellular
non specific





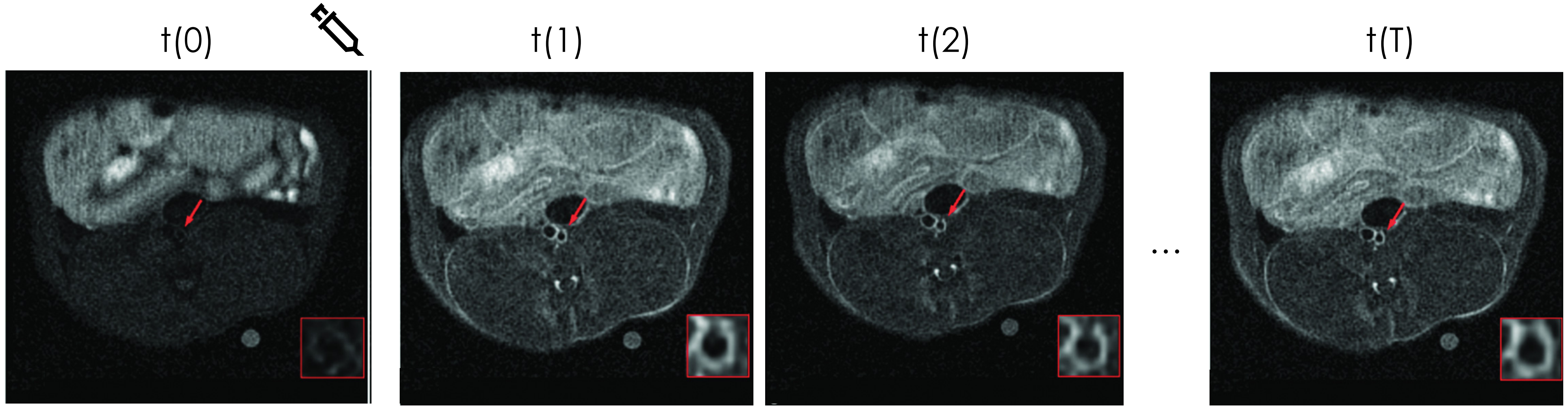
post-contrast

<u>T1 mapping:</u> measurement of shortening of T1 relaxation time after contrast injection



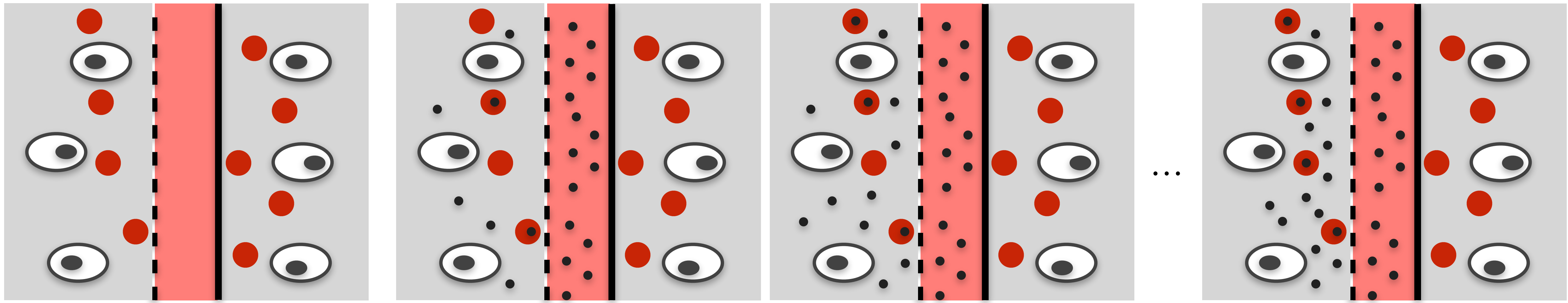
Endothelial permeability can be investigated using contrast enhanced MRI

injection of T1 shortening, Gd-based contrast agent



pre-contrast post-contrast …

dynamic contrast enhanced (DCE) MRI: measure uptake curve of contrast agent in tissue of interest



Endothelial permeability can be investigated using contrast enhanced MRI

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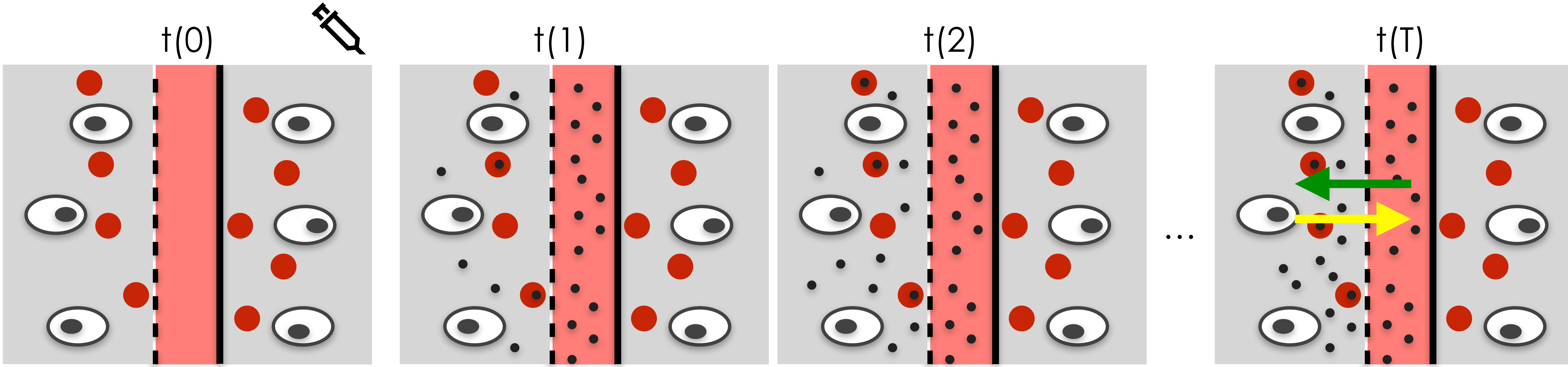
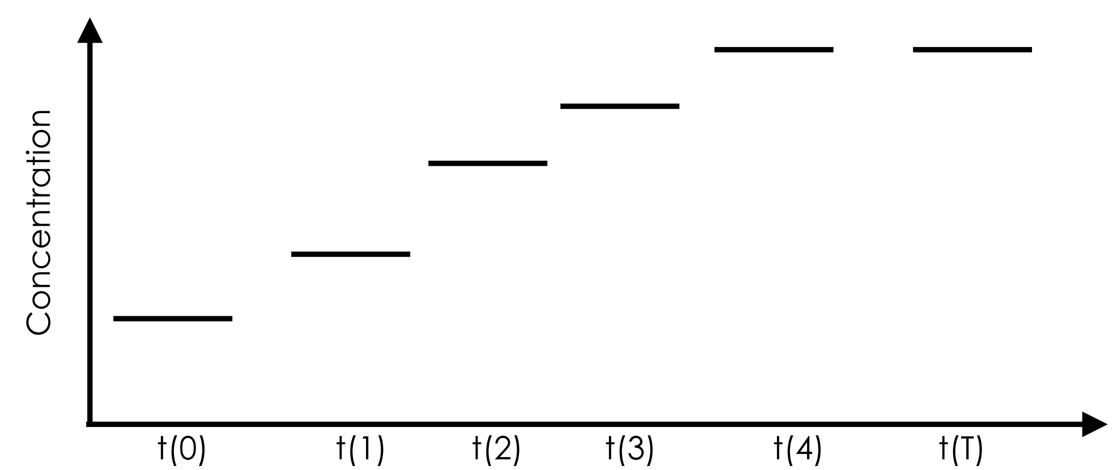


$$C_t(T) = v_p \cdot C_p(t) + K^{trans} \int_0^T C_p(t) \cdot \exp\left(K_{ep} \cdot (T - t)\right) dt$$

modified Tofts model
(Tofts P, J Magn Reson Imaging, 1999)



C_p, contrast agent plasma concentration
C_t, contrast agent tissue concentration
v_p, fractional plasma volume
K^{trans}, flow/permeability
K_{ep} = K^{trans}/v_e = backflow from tissue to plasma compartment

Non model based parameters

AUC, area under the curve
uptake slope
TTP, time to peak
…

Quantitative MRI of endothelial permeability in atherosclerosis: reviews

Angiogenesis. 2010 Jun;13(2):87-99. doi: 10.1007/s10456-010-9172-2. Epub 2010 Jun 6.

Dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) of atherosclerotic plaque angiogenesis.

Calcagno C[1], Mani V, Ramachandran S, Fayad ZA.

Curr Atheroscler Rep. 2016 Jun;18(6):33. doi: 10.1007/s11883-016-0583-4.

Dynamic Contrast-Enhanced MRI to Study Atherosclerotic Plaque Microvasculature.

van Hoof RH[1,2], Heeneman S[2,3], Wildberger JE[1,2], Kooi ME[4,5].

MAGMA. 2018 Feb;31(1):201-222. doi: 10.1007/s10334-017-0644-x. Epub 2017 Aug 14.

Vessel wall characterization using quantitative MRI: what's in a number?

Coolen BF[1,2], Calcagno C[3,4], van Ooij P[5], Fayad ZA[3,4], Strijkers GJ[6], Nederveen AJ[5].

Many studies in humans and animals models (rabbits, mice)

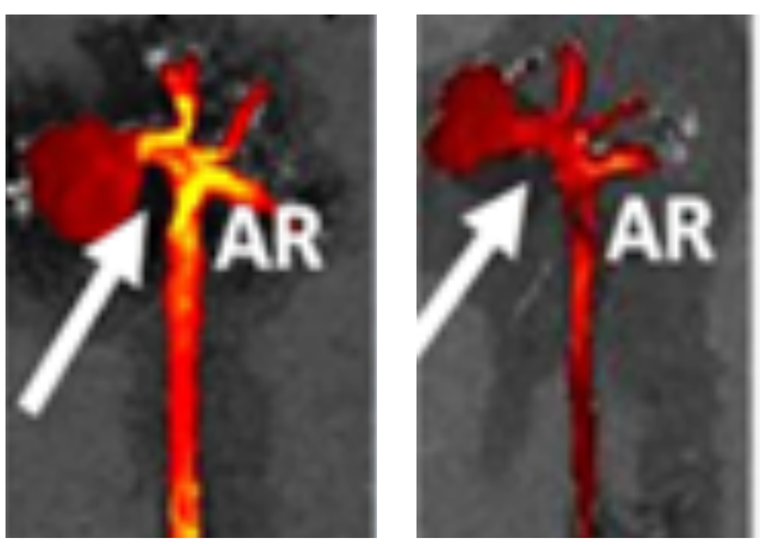
Aortic root endothelial permeability imaging in mice

Why mice?

1. … can be genetically manipulated to create disease models
2. … are a well characterized model of atherosclerosis
3. … can be used in large scale studies
4. … can be investigated using more sophisticated genetic, cellular and molecular assays
5. … to complement *in vivo* imaging

Why the aortic root?

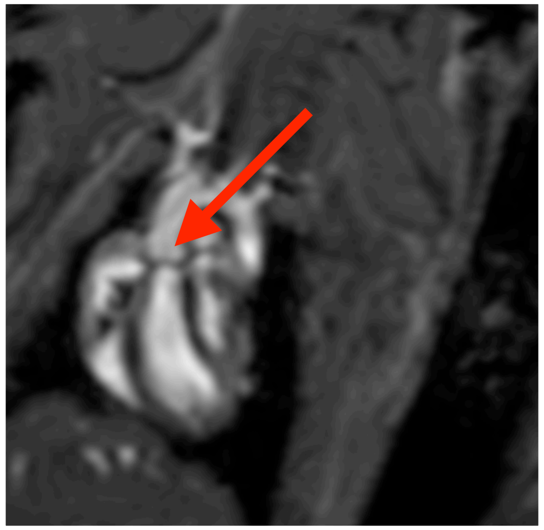
ApoE-/- WT



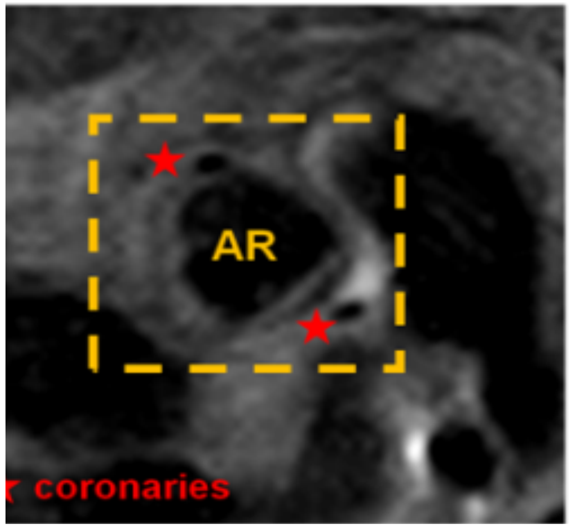
A vascular territory where permeable, inflamed plaques develop consistently and abundantly

Challenges in imaging the mouse aortic root

motion



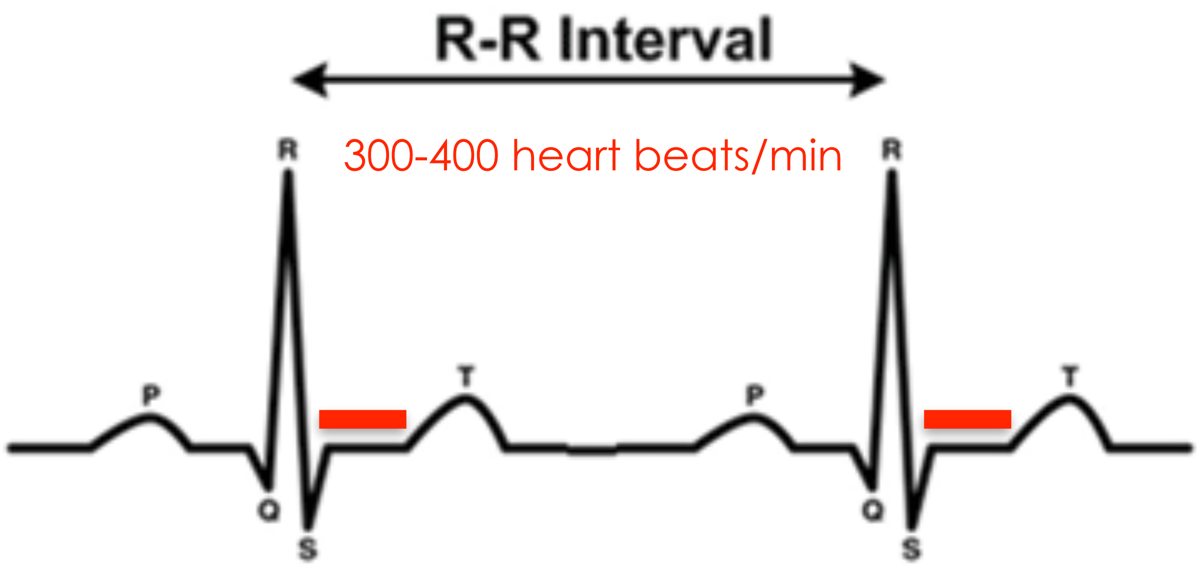
size



constant motion during the rapid cardiac and respiratory cycle

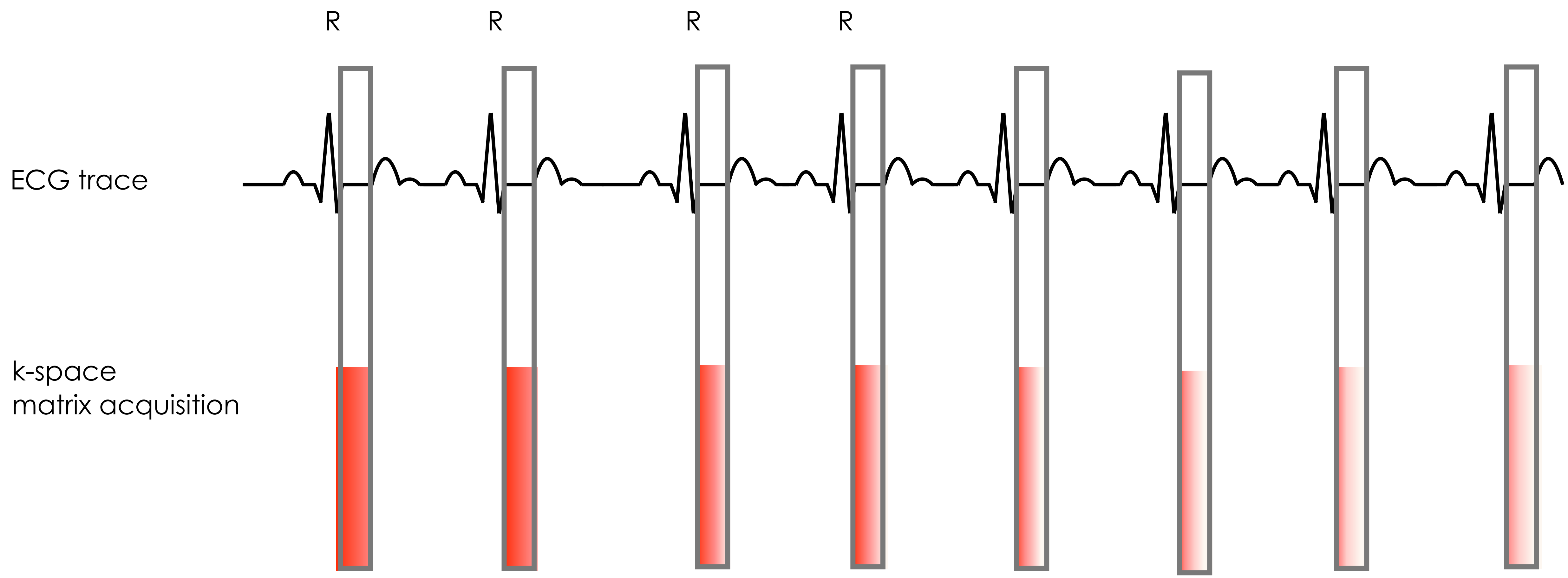
very small size of the vessel wall

it requires synchronization of imaging with the cardiac and respiratory cycle



using conventional techniques imaging is very slow: not suitable to capture fast contrast agent uptake in tissues

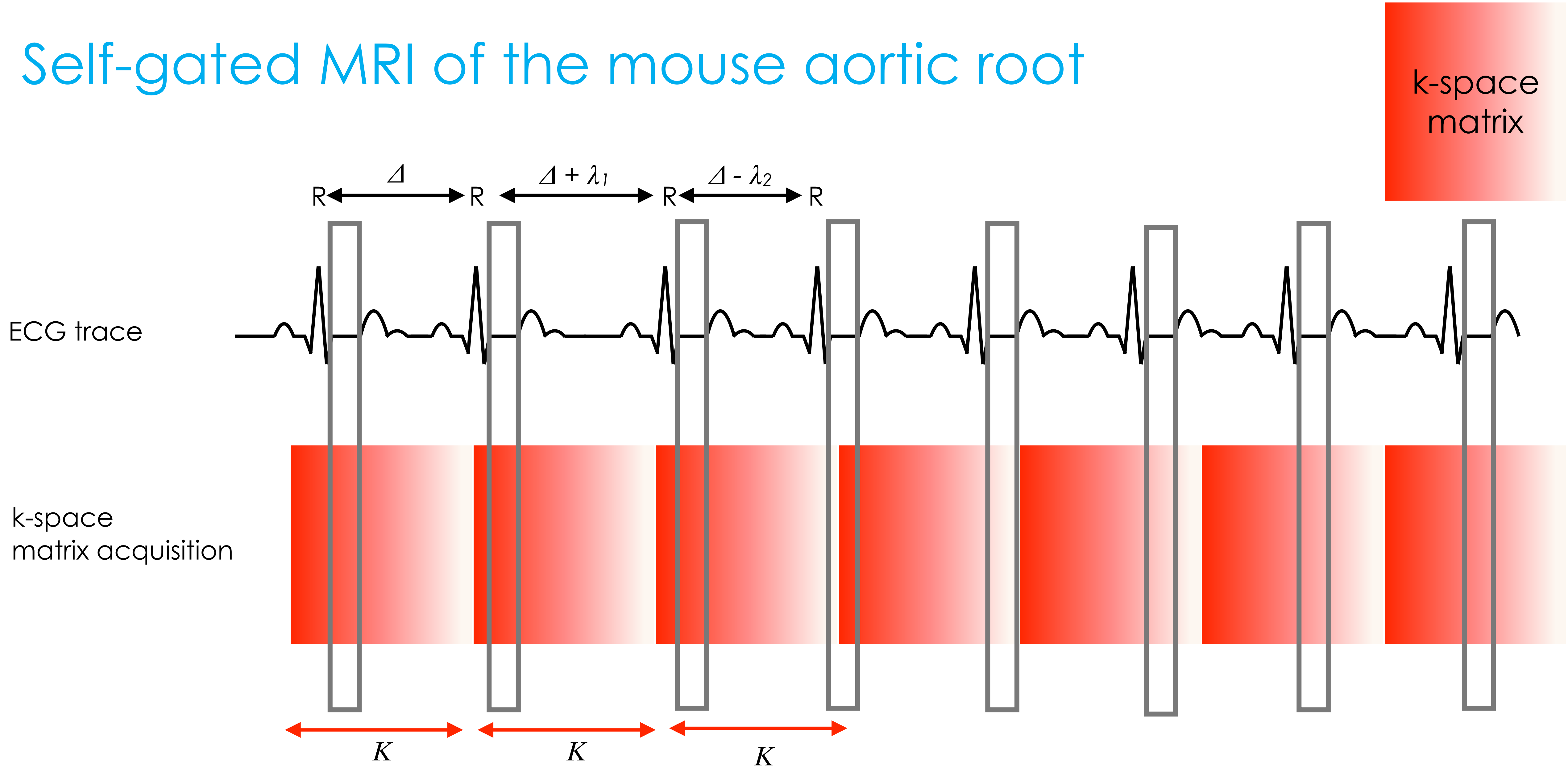
ECG triggered MRI of the mouse aortic root



requires acquiring over many heartbeats to obtain full image of 1 cardiac phase

Coolen et al, MRM 2013
Mootal et al, NMR in Biomed 2013

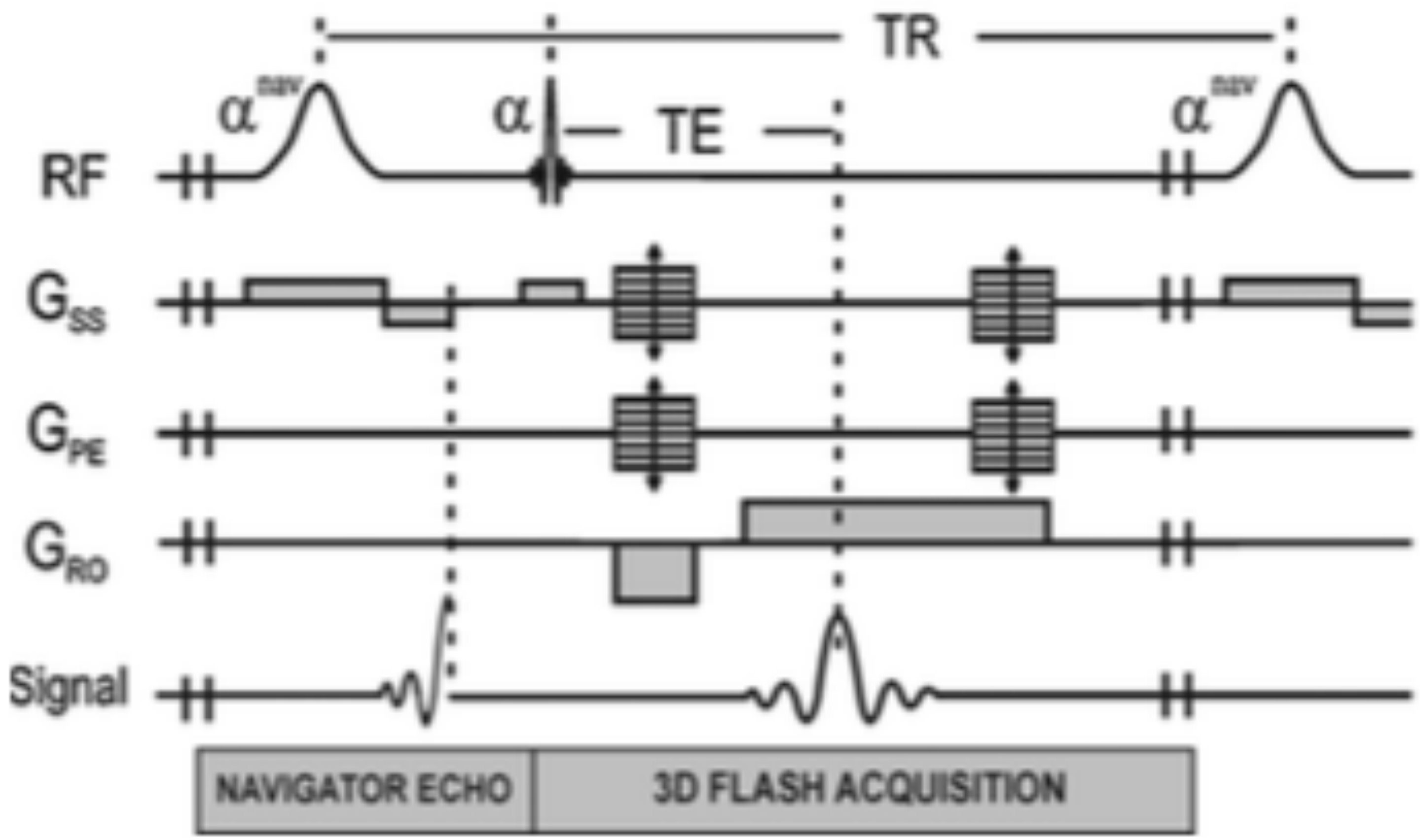
Self-gated MRI of the mouse aortic root

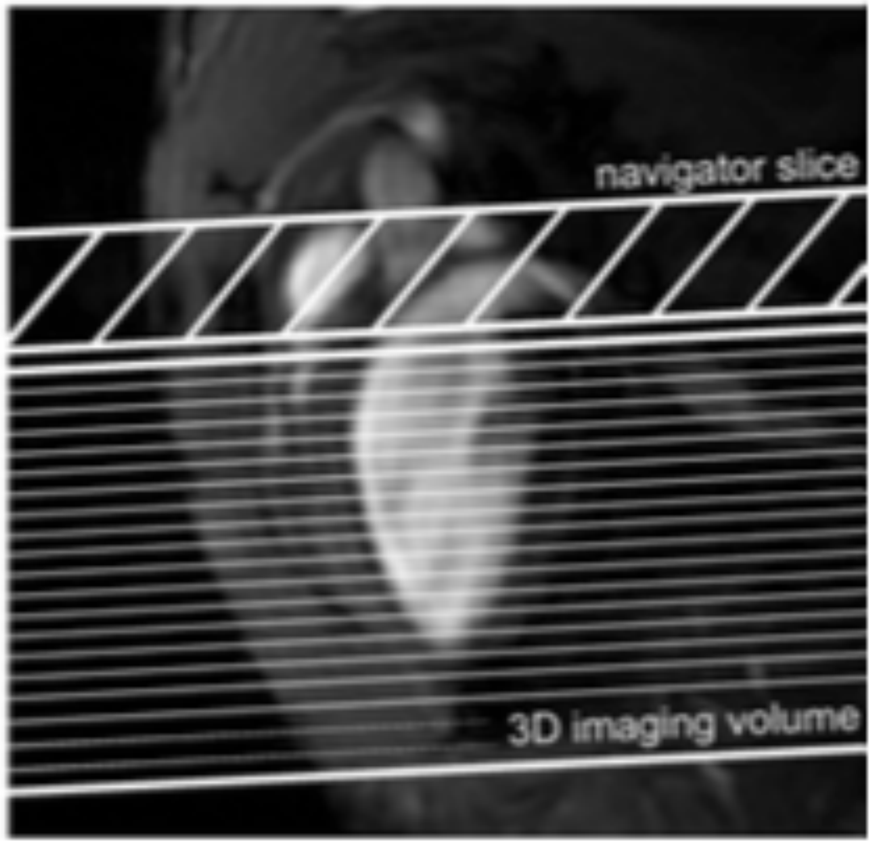


- Acquires data continuously, asynchronously with the beating heart
- Data are binned after acquisition in the desired number of cardiac phases
- These aspects are similar to retrospectively gated imaging with ECG
- However, in this case inning is based on a navigator signal that captures the cardiac and respiratory cycle

Coolen et al, MRM 2013
Mootal et al, NMR in Biomed 2013

Self-gated MRI of the mouse aortic root





Dr. Gustav Strijkers, PhD
Amsterdam Medical Center
Department of Radiology, Mount Sinai

Coolen et al, NMR in Biomed 2011
Heijman et al, NMR in Biomed 2007

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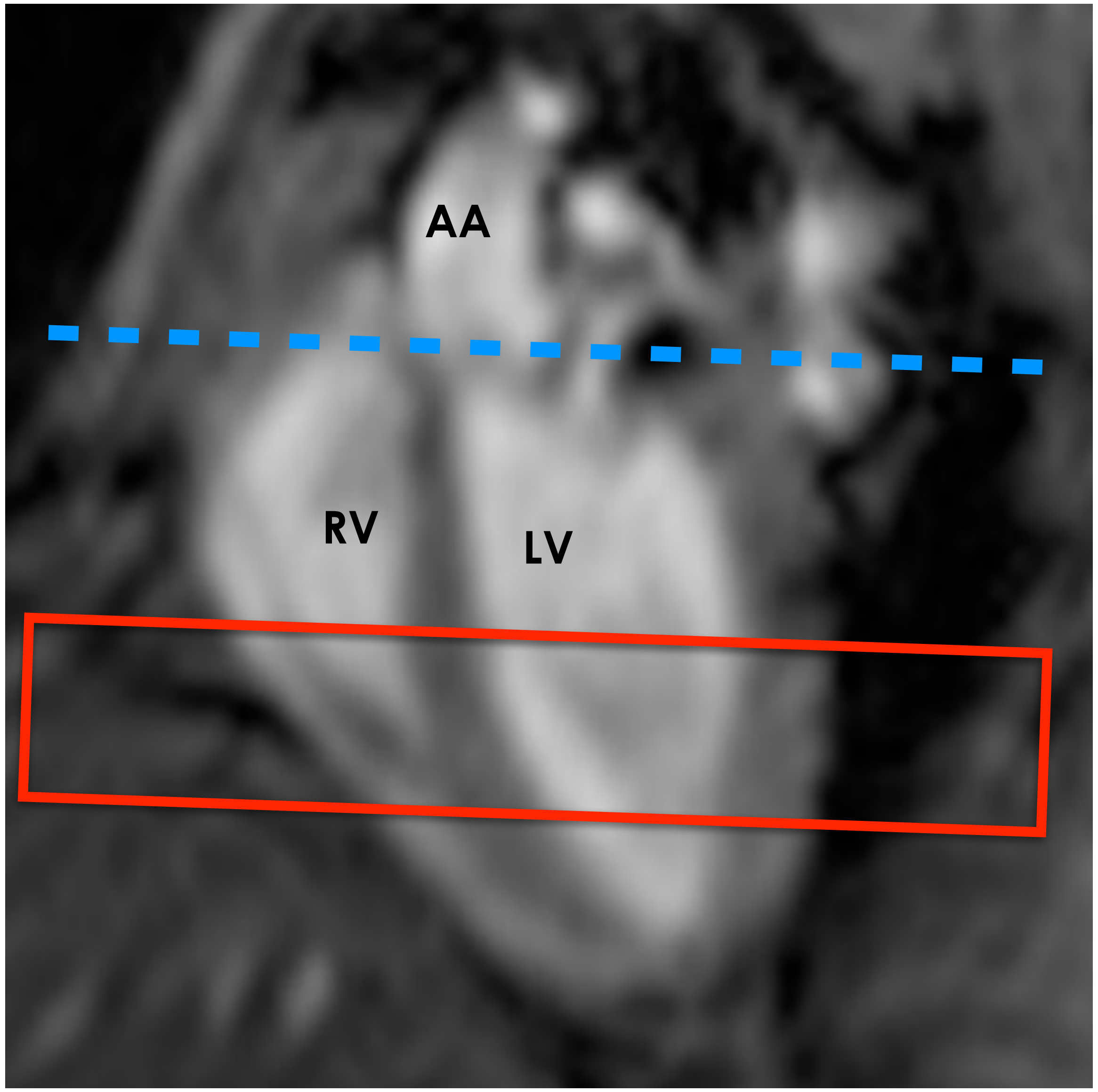

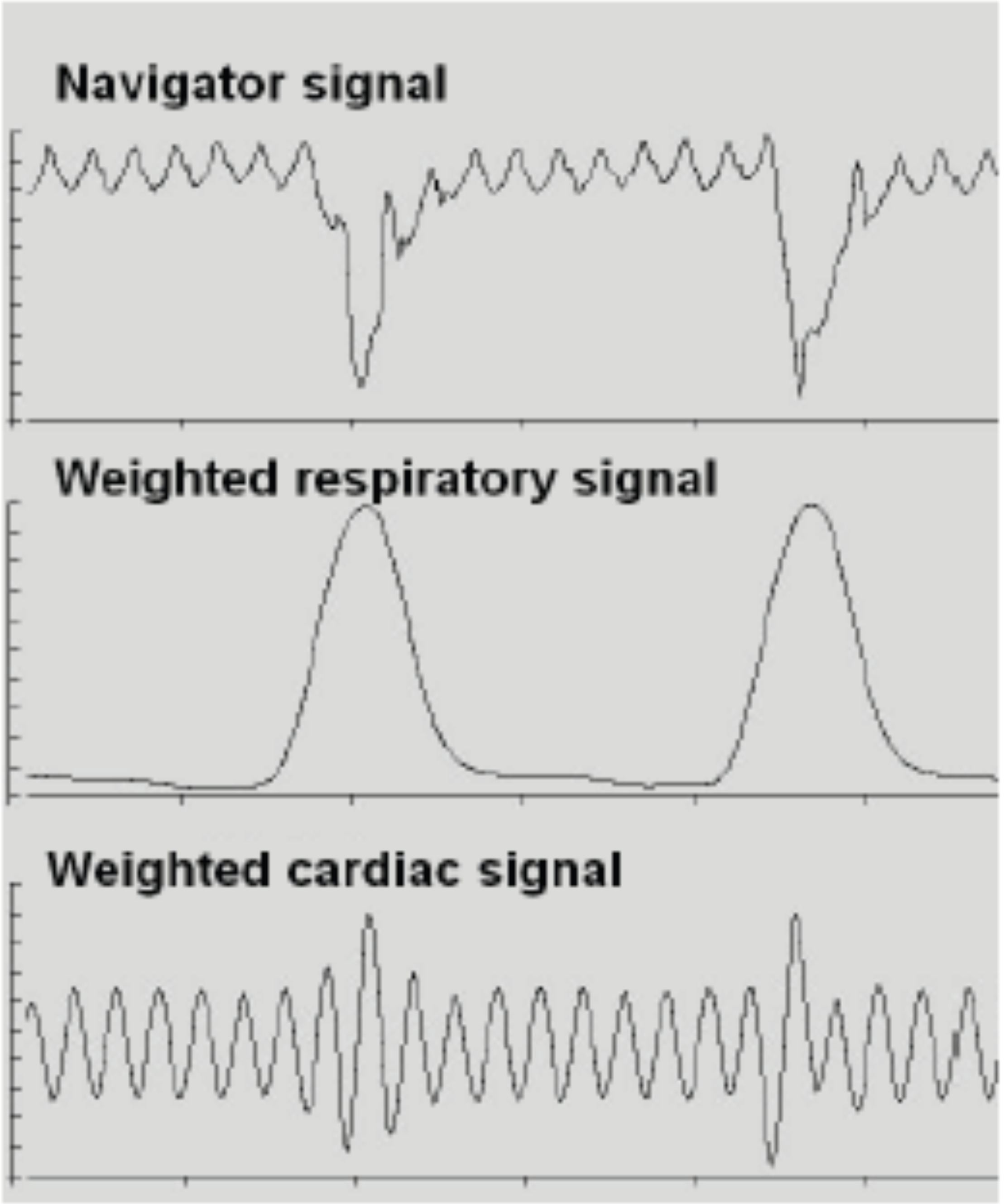

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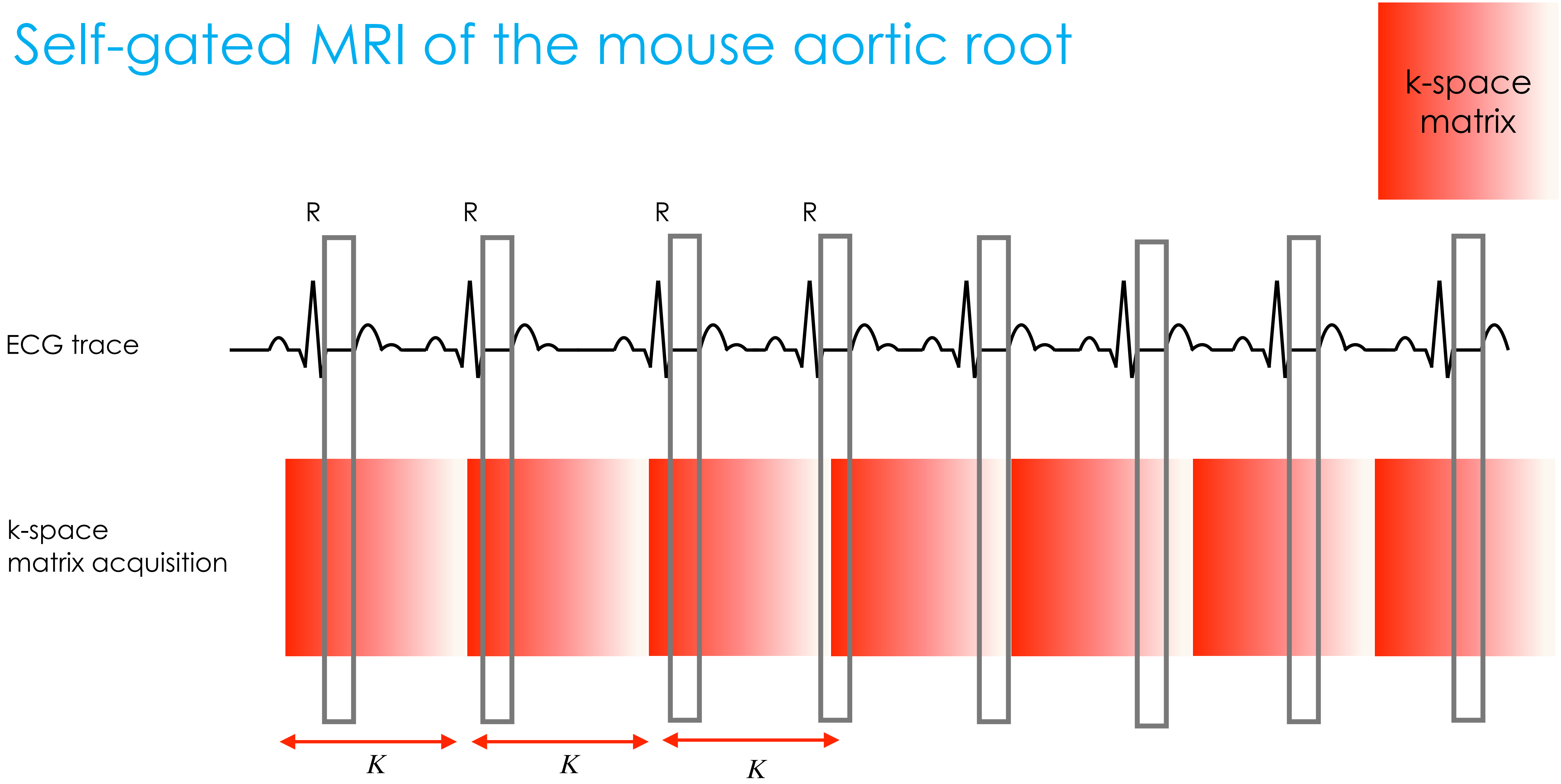
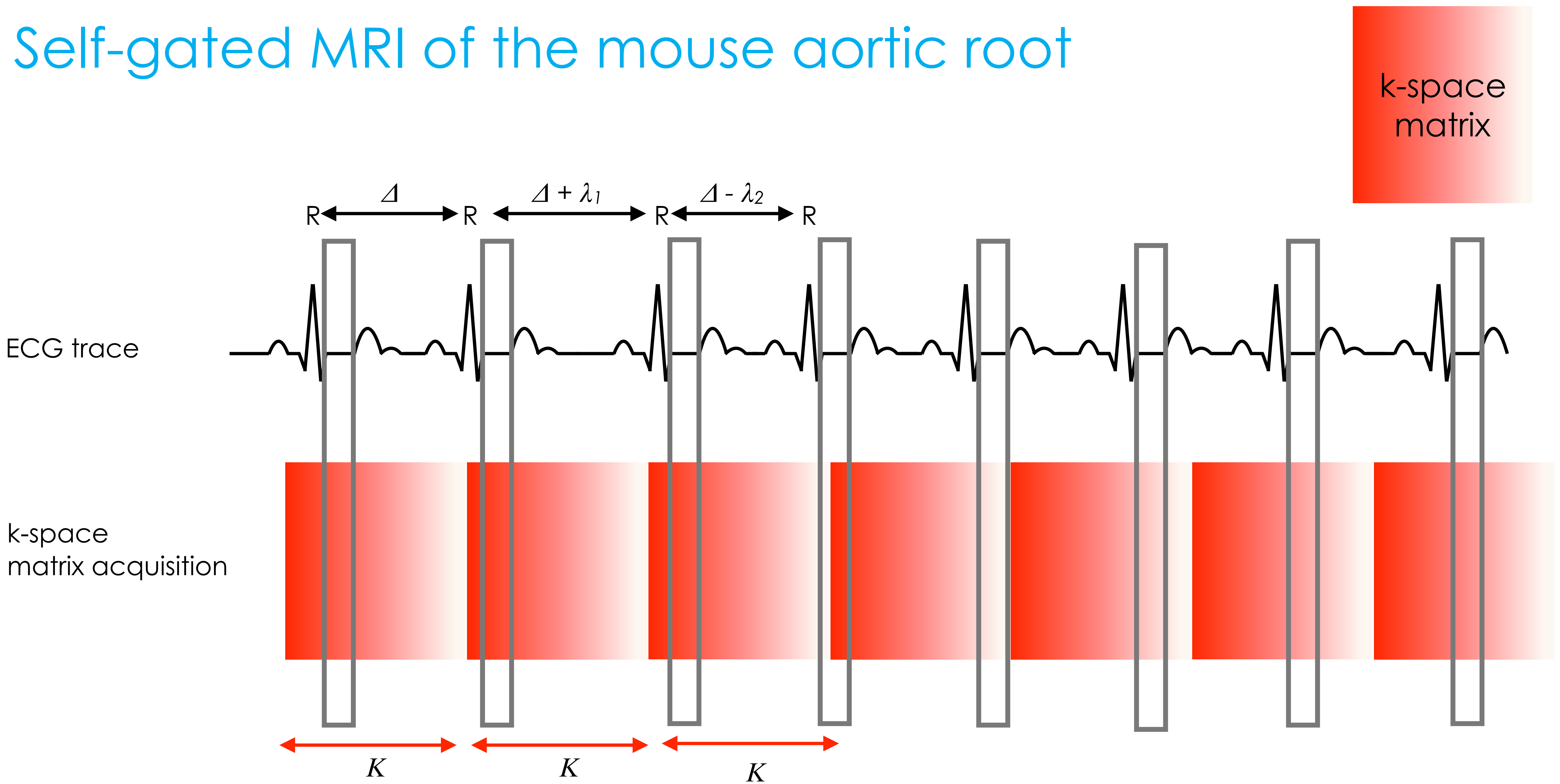


- To acquire full images, many repetitions of the full k-space are acquired, until a sufficient number of k lines for each cardiac phase has been acquired

Coolen et al, MRM 2013
Mootal et al, NMR in Biomed 2013

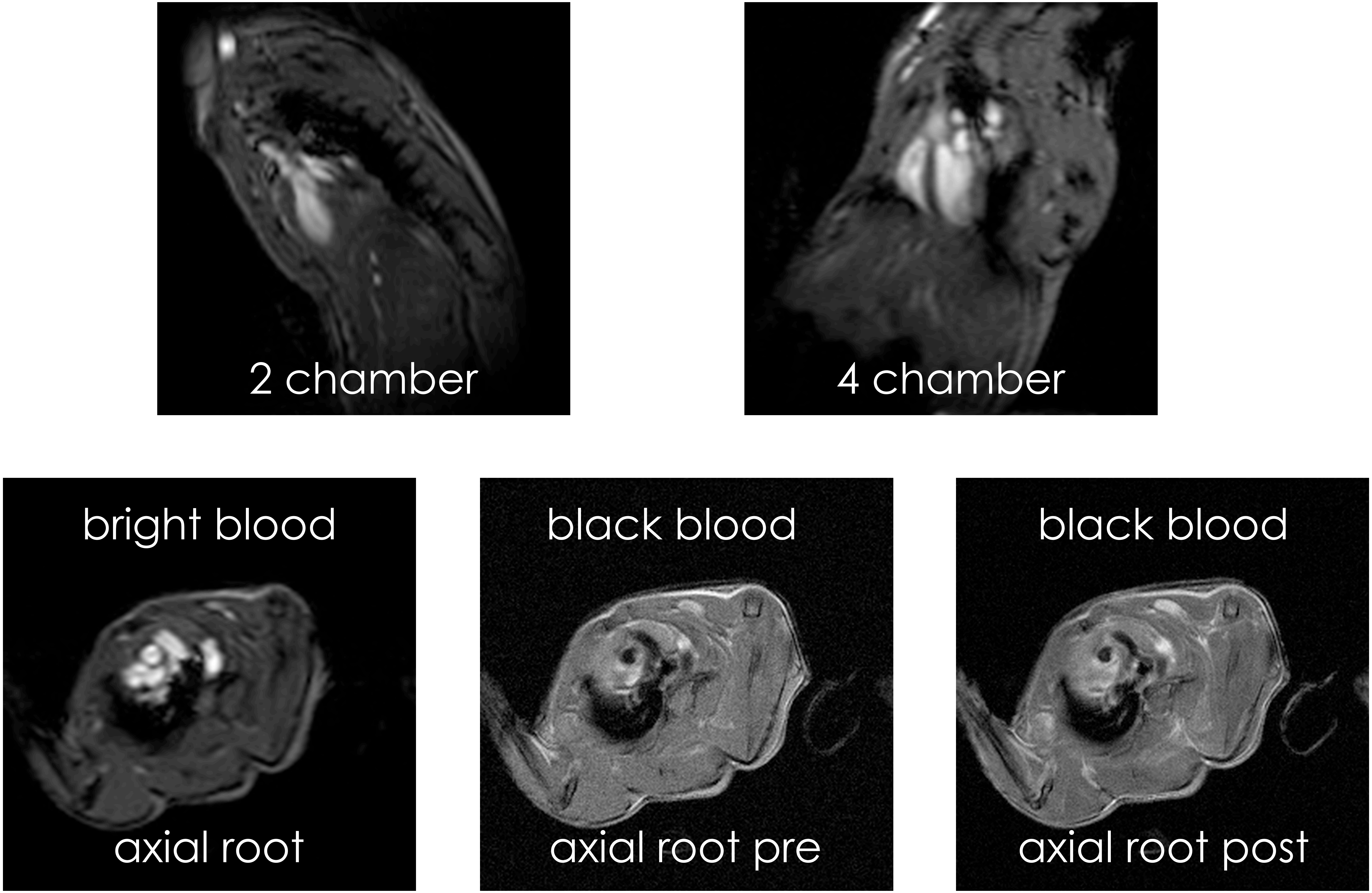
Self-gated MRI of the mouse aortic root



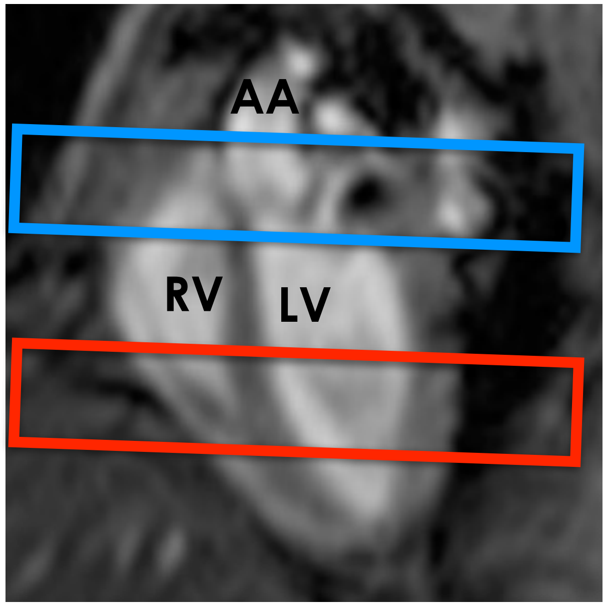
- To acquire full images, many repetitions of the full k-space are acquired, until a sufficient number of k lines for each cardiac phase has been acquired
- Small differences in length among cardiac cycles (Δ) ensure time-shifted acquisition of k-lines intrinsic pseudo-random filling

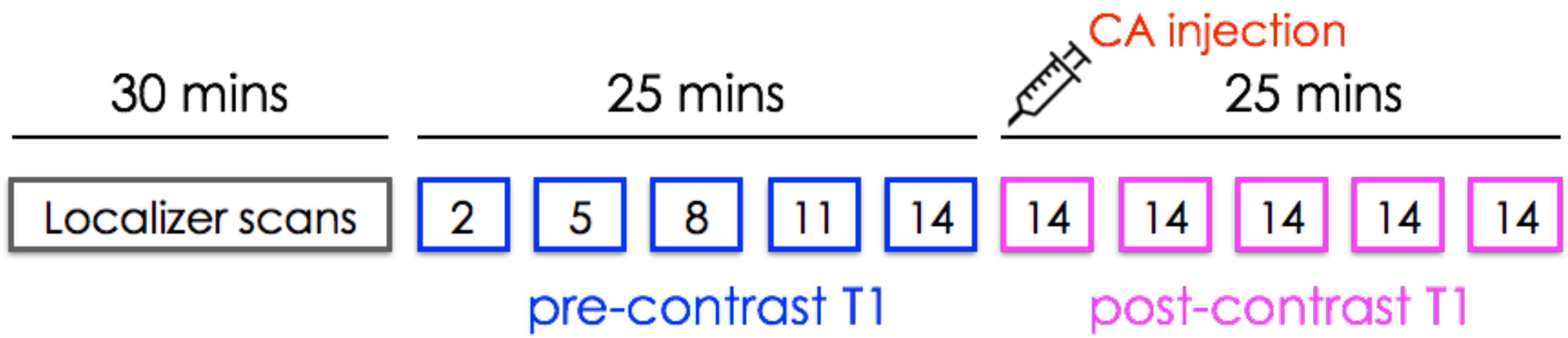
Coolen et al, MRM 2013
Mootal et al, NMR in Biomed 2013

Self-gated MRI of the mouse aortic root



Self-gated post contrast T1 mapping of the mouse aortic root





3D T1 mapping with variable flip angles

pre-contrast T1 calculation

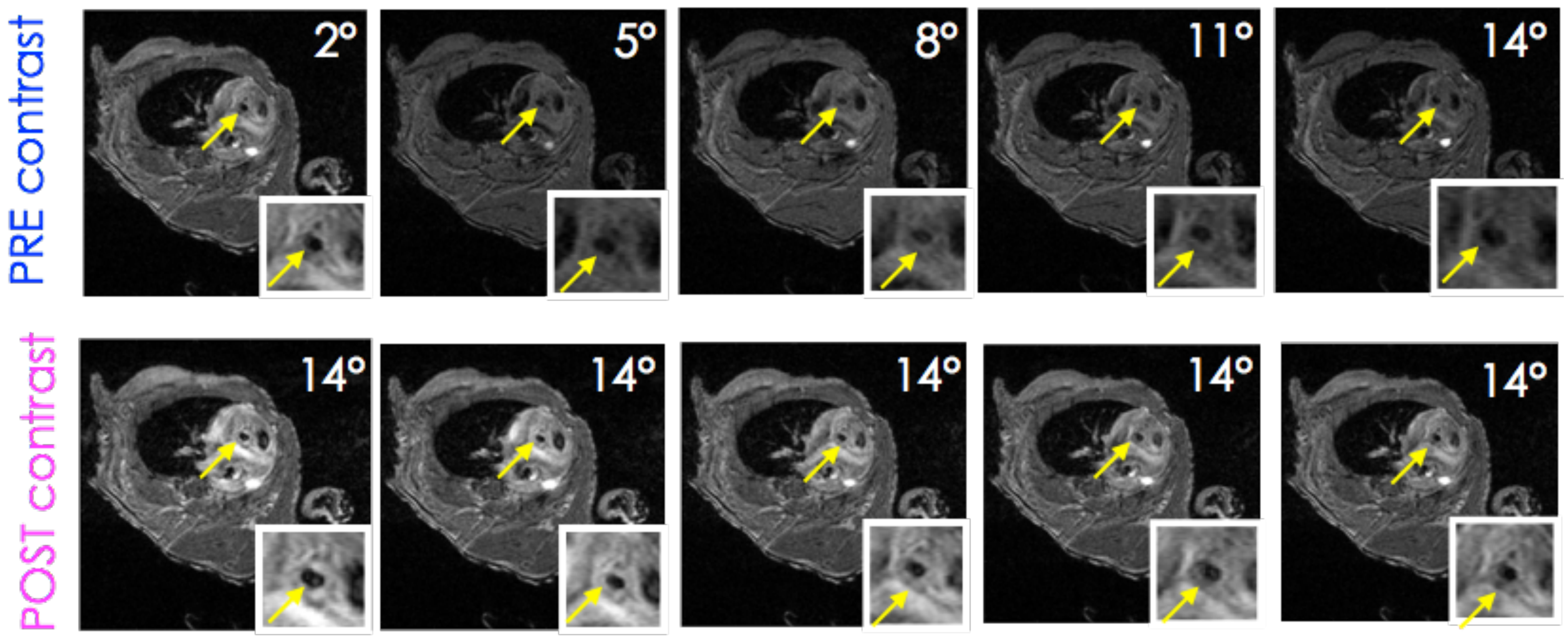
$$I = \frac{M_0 \sin\alpha\left(1-e^{-TR\times R_{1pre}}\right)}{1-\cos\alpha\times e^{-TR\times R_{1pre}}}$$

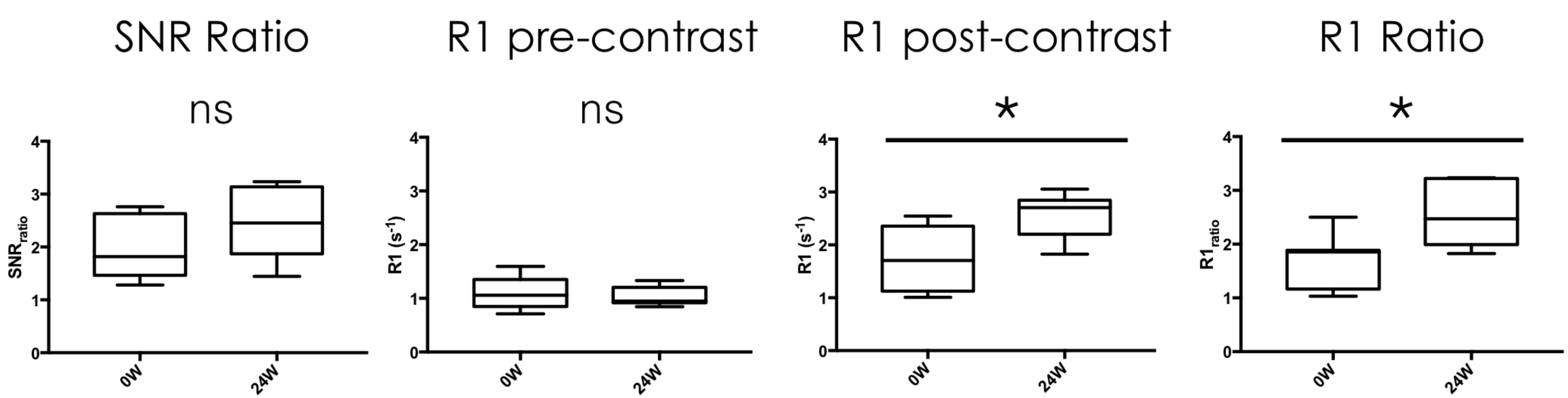
post-contrast T1 calculation

$$I = \frac{M_0 \sin\alpha\left(1-e^{-TR\times R_{1pre}}\right)/1-\cos\alpha\times e^{-TR\times R_{1pre}}}{M_0 \sin\alpha\left(1-e^{-TR\times R_{1post}}\right)/1-\cos\alpha\times e^{-TR\times R_{1post}}}$$

Vandoorne K, NMR in Biomedicine, 2016

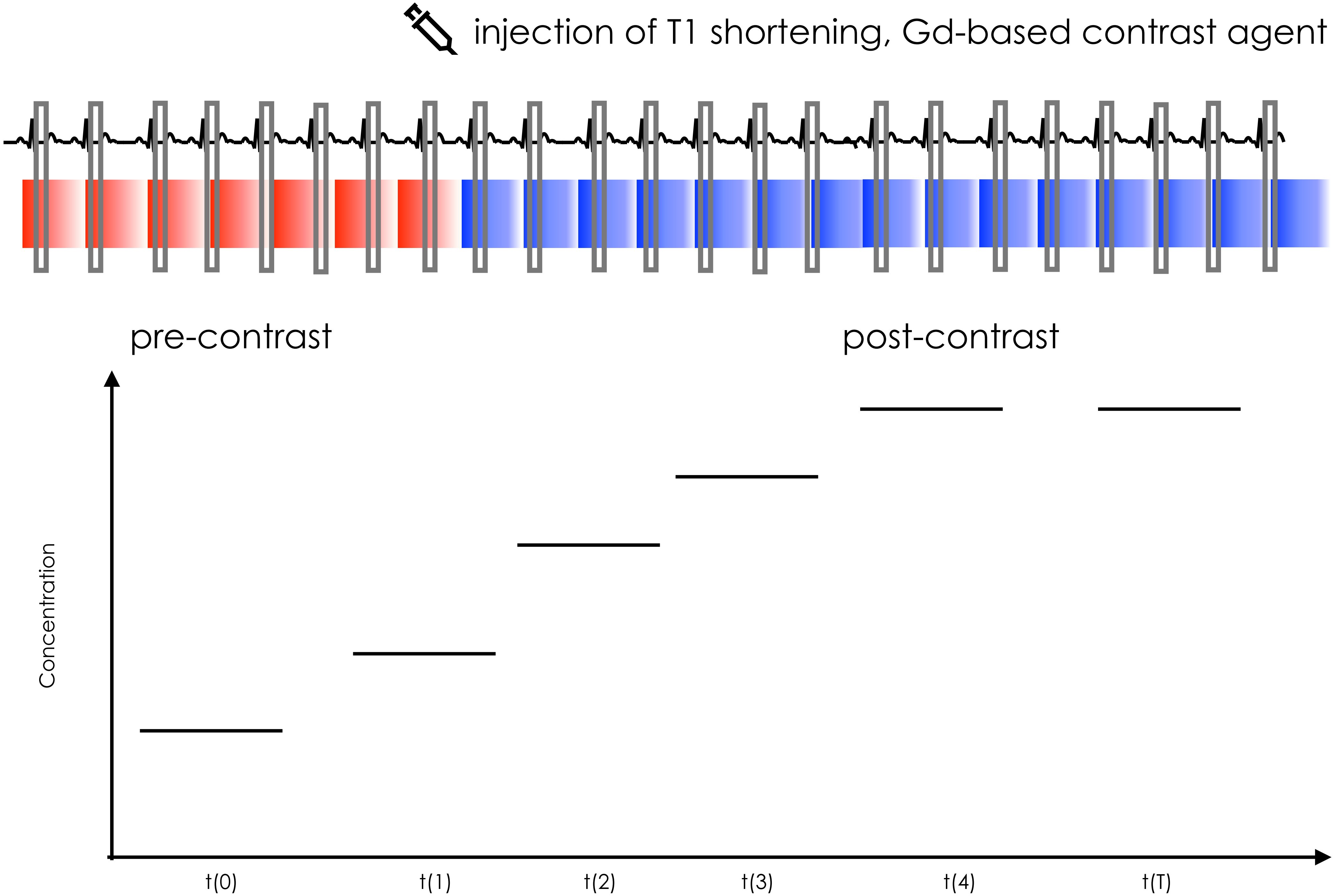
Self-gated post contrast T1 mapping of the mouse aortic root





Soler R, Scientific Sessions of the International Society for Magnetic Resonance in Medicine, 2018

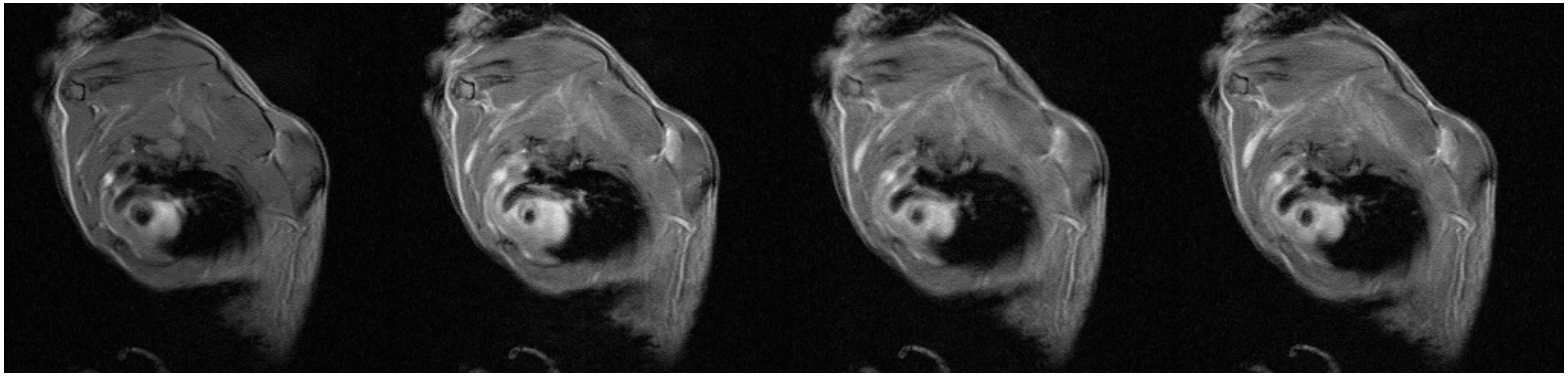
Self-gated DCE-MRI of the mouse aortic root



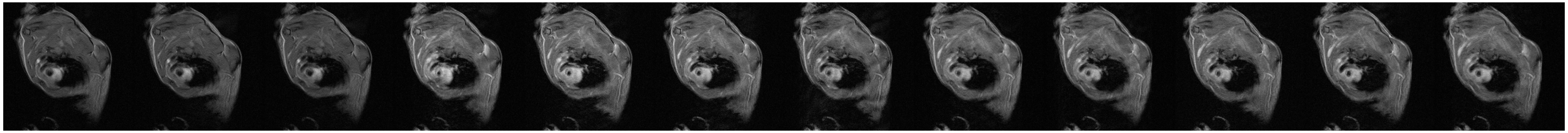
bin into different cardiac phases, but also different temporal dynamic frames

Self-gated DCE-MRI of the mouse aortic root

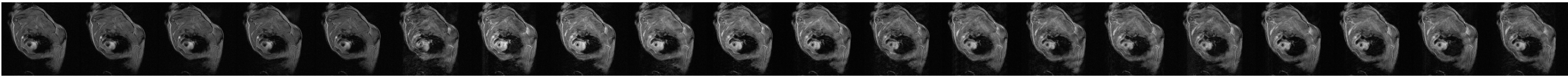
8 cardiac phases, 4 temporal dynamic frames



8 cardiac phases, 12 temporal dynamic frames



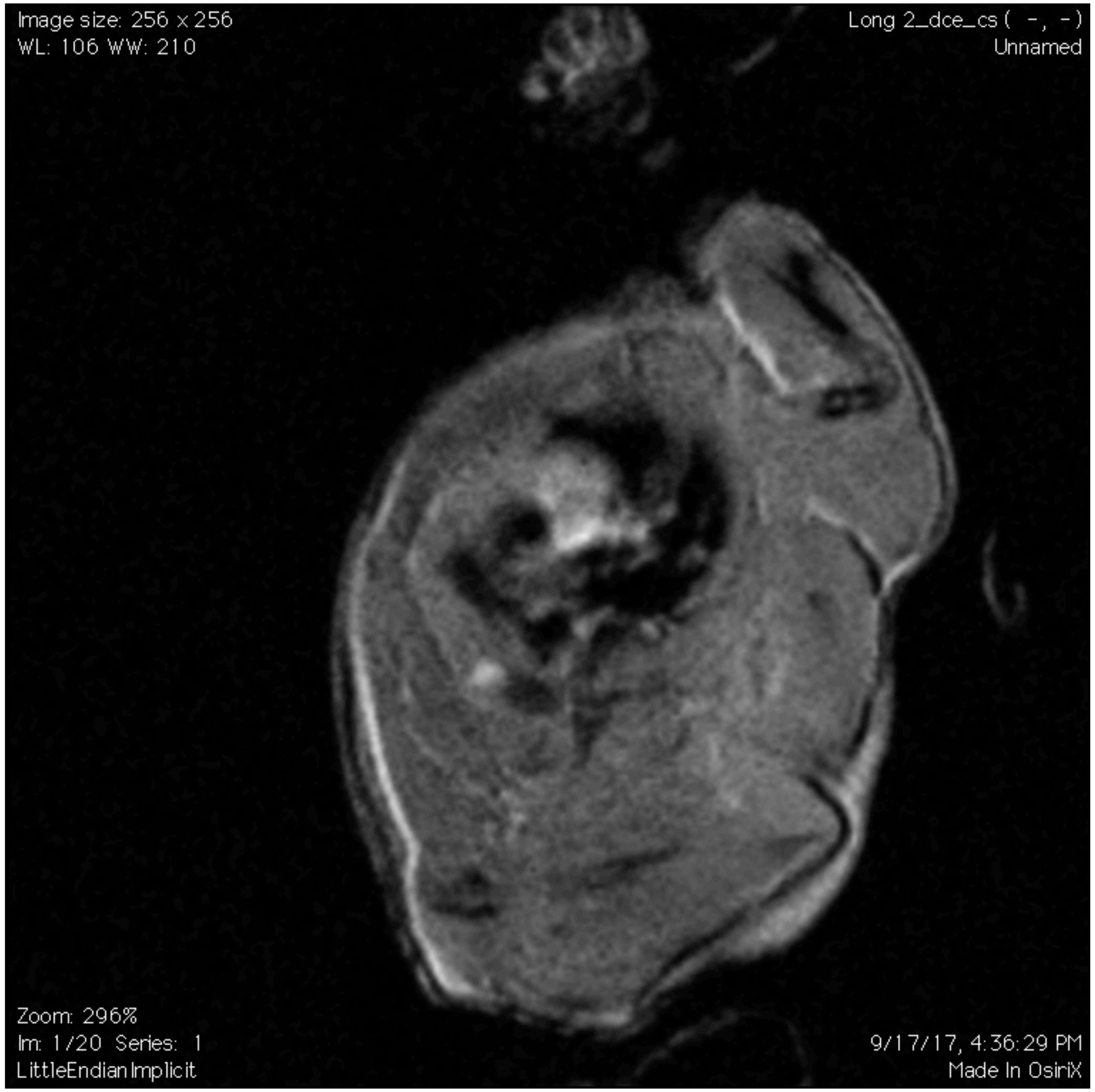
8 cardiac phases, 20 temporal dynamic frames



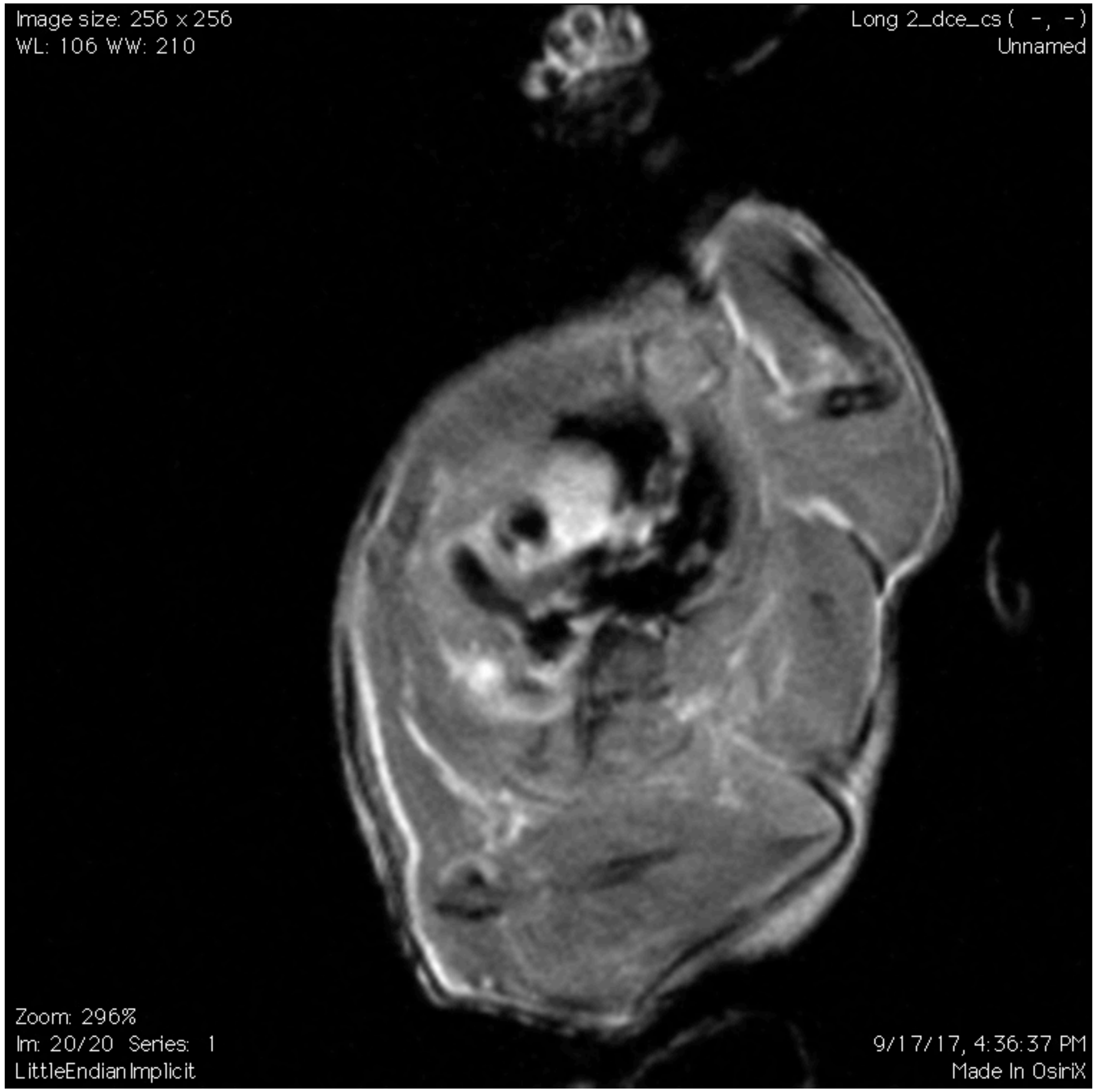
Calcagno C, Scientific Sessions of the International Society for Magnetic Resonance in Medicine, 2015

Self-gated DCE-MRI of the mouse aortic root

Frame #1, 20 dynamics



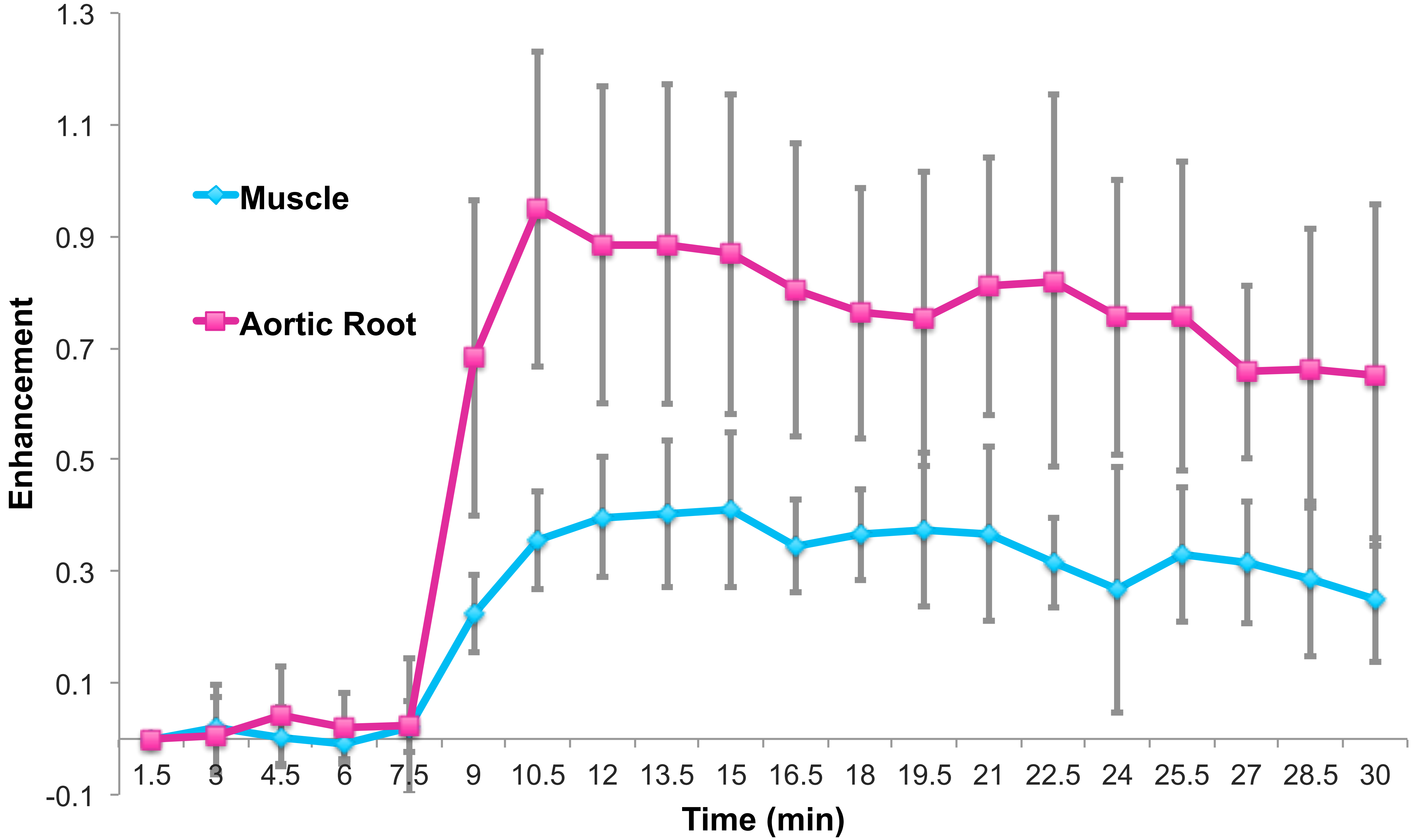
6 cardiac frames, after contrast



~1.5 min per temporal dynamic

Self-gated DCE-MRI of the mouse aortic root

15 cardiac phases, 20 temporal dynamic frames



Thank you!

Mount Sinai