Cardiac Neurotransmission Imaging

For assessment of myocardial sympathetic innervation

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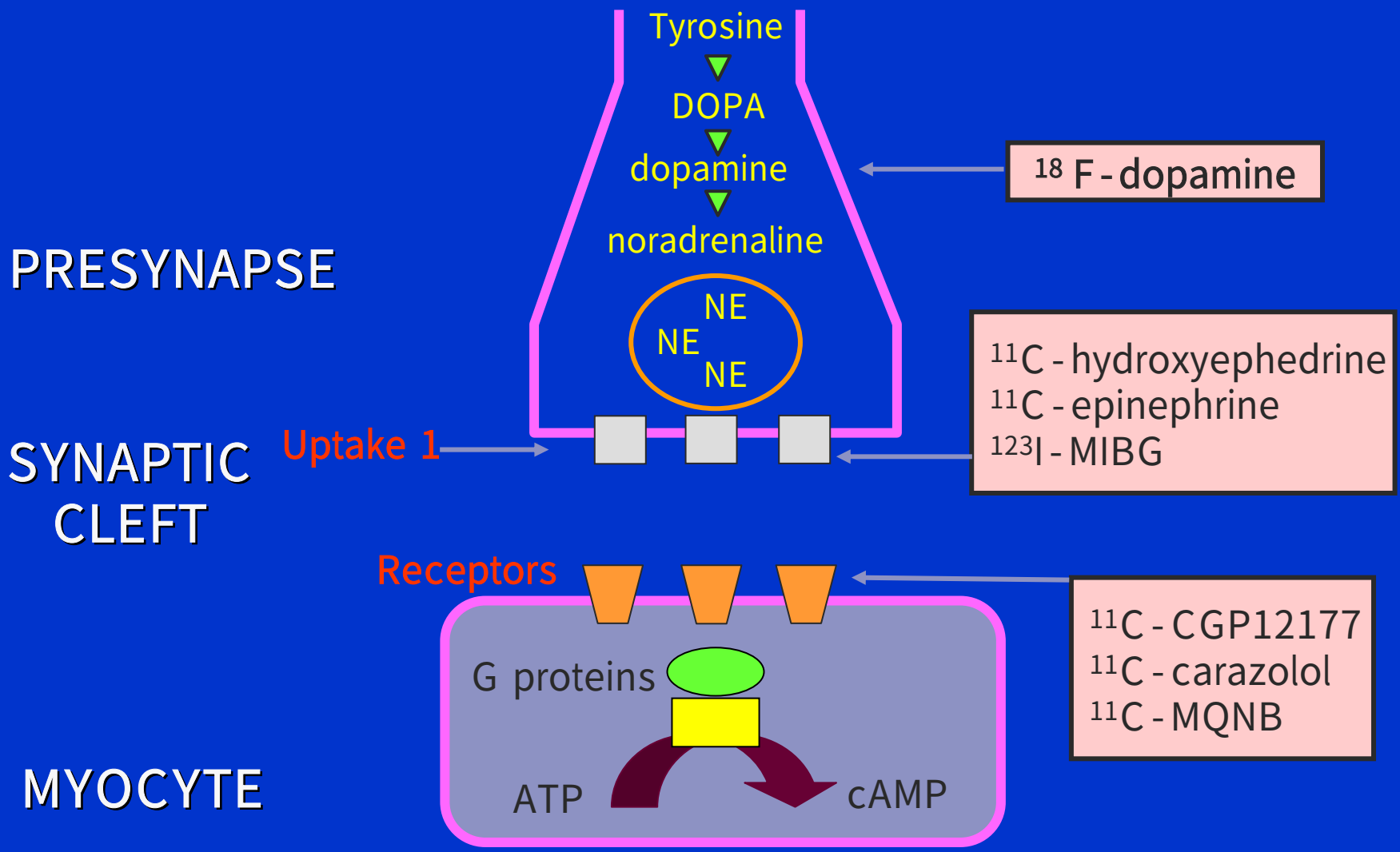
Cardiac neurotransmission imaging

- Visualization and quantitation with SPECT and PET of pathophysiologic processes
  - nerve terminals
  - synaptic clefts
  - postsynaptic sites

EM of cardiac synapse

PET
in vivo visualization of cardiac muscarinic receptors

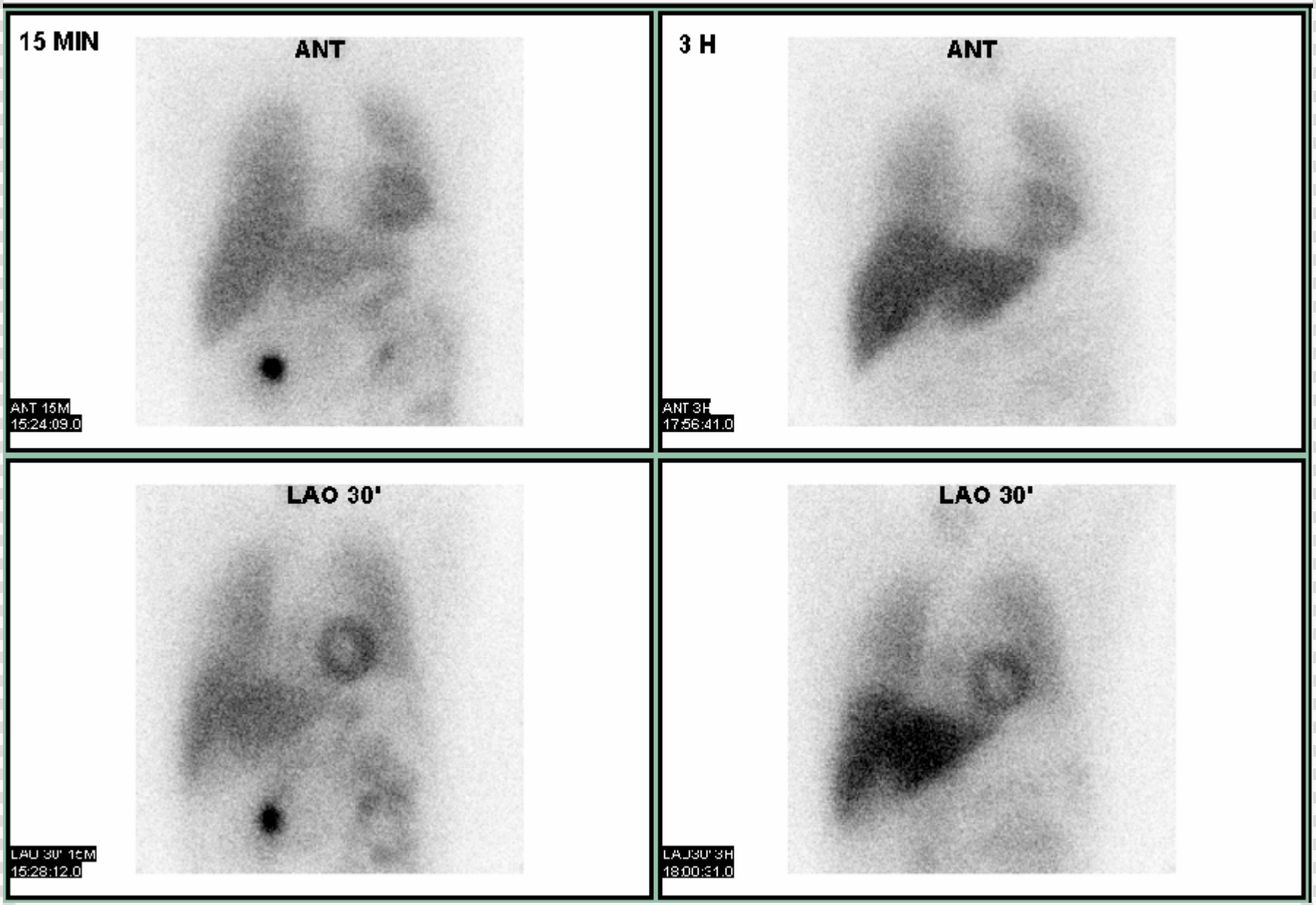

PRESYNAPSE
SYNAPTIC CLEFT
MYOCYTE
Tyrosine
DOPA
dopamine
noradrenaline
NE
NE
NE
Uptake 1
Receptors
G proteins
ATP
cAMP
18 F - dopamine
11C - hydroxyephedrine
11C - epinephrine
123I - MIBG
11C - CGP12177
11C - carazolol
11C - MQNB

Radiopharmaceuticals

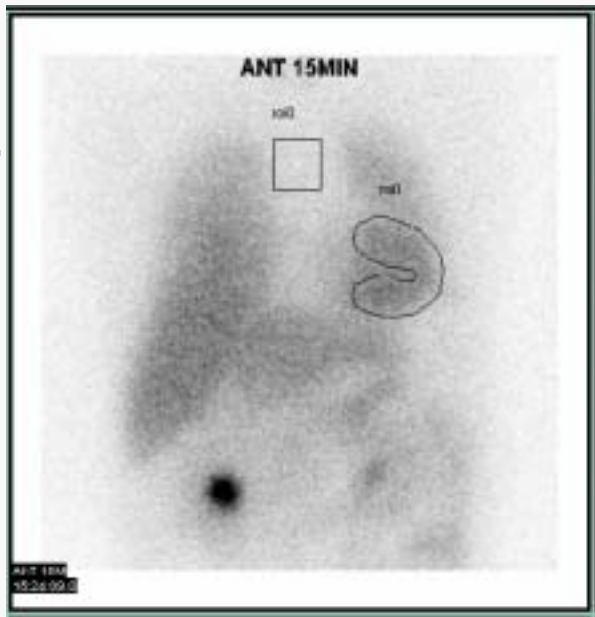
Targeted process	Radiopharmaceutical Imaging / parameters
Transport and storage into axoplasmic vesicles	^{18}F-fluorodopamine PET, - Peak myocardial concentration
Presynaptic uptake-1 and storage	^{123}I-MIBG Planar/SPECT - Heart-to-mediastinum ratio, Wash-out rate
Presynaptic uptake-1 and storage	^{11}C-HED (hydroxyephedrine) PET - Retention fraction, Volume distribution
Presynaptic uptake-1 and storage and metabolism	^{11}C-EPI (epinephrine) PET - Retention fraction, Volume distribution
Postsynaptic adrenoceptor density	^{11}C-CGP (4-(3-*t*-butylamino-2-hydroxypropoxy)-benzimidazol-1) PET - Cardiac Bmax
Postsynaptic adrenoceptor density	^{18}F-fluorocarazolol PET - Cardiac Bmax
Postsynaptic muscarinic receptor density	^{11}C-MQNB (methylquinuclidinyl benzylate) PET, - Cardiac Bmax

MIBG

- MIBG labeled with ^{123}I
  - visualization of the sympathetic nervous system
  - Gamma camera : Planar or SPECT.
- Take up by sympathetic nerve endings
  - sodium- and energy-dependent uptake-1 mechanism
  - similar molecular structures with noradrenaline
  - same uptake and storage mechanisms with noradrenaline



^{123}I - MIBG myocardial scan (normal)



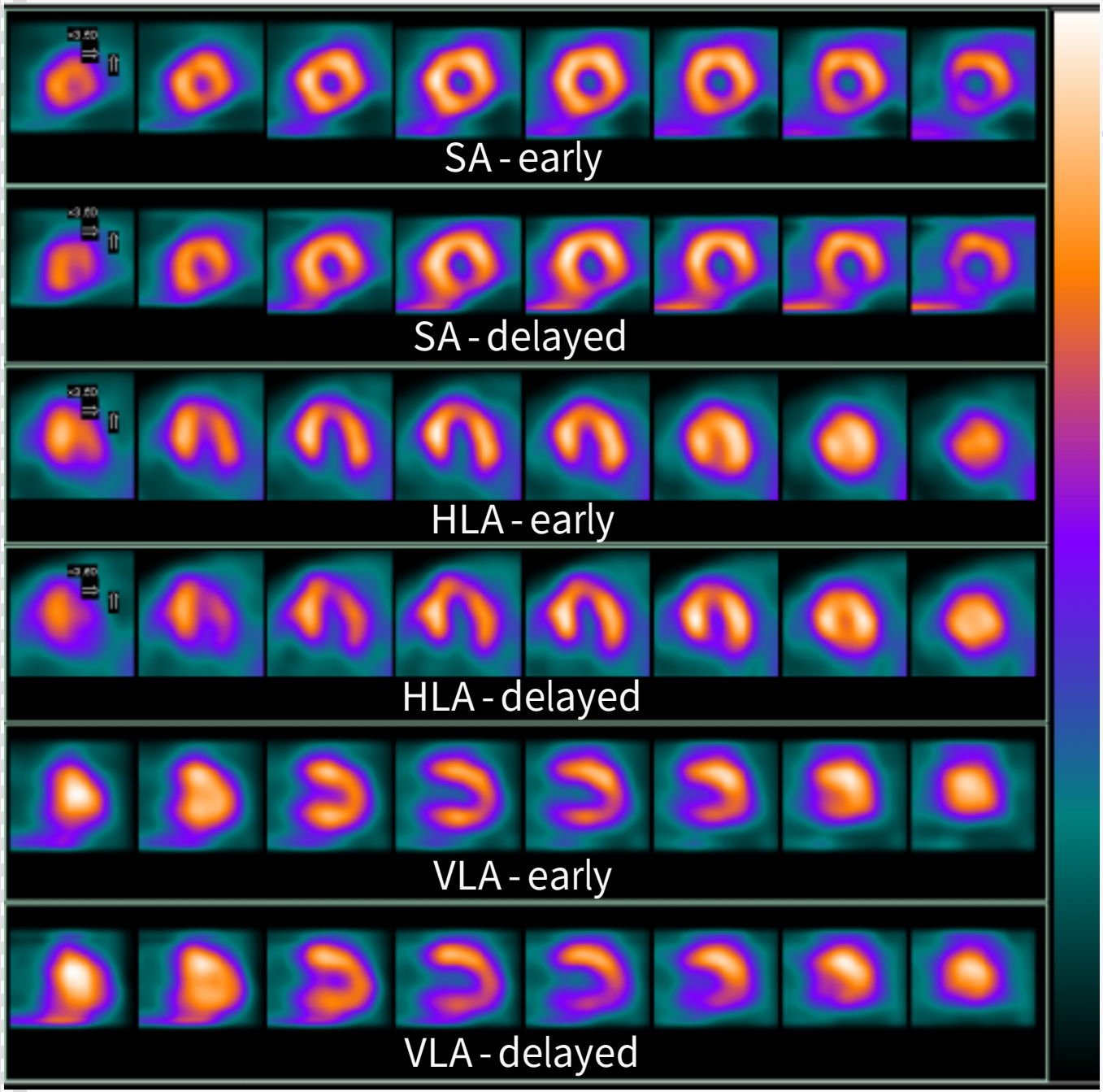
	MEDIASTINUM	HEART
TOTAL	7667	57163
MIN	5	15
MAX	28	71
AVERAGE	15	39
STD	3.9	8.6
PIXEL	506	1450

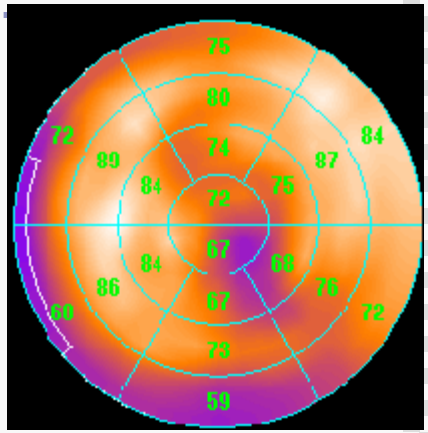
H / M = 2.6%

	MEDIASTINUM	HEART
TOTAL	6863	55426
MIN	3	9
MAX	26	52
AVERAGE	14	37
STD	3.09	8.2
PIXEL	484	1478

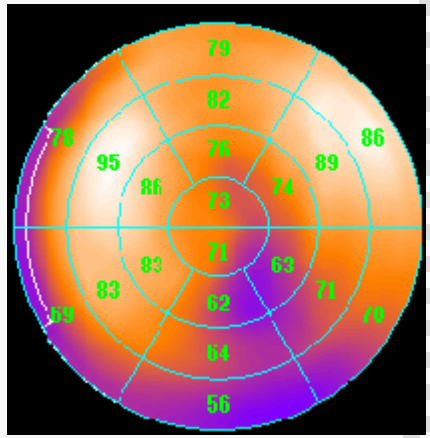
H / M = 2.64%

^{123}I - MIBG myocardial SPECT (normal)





early



Delayed

Clinical application

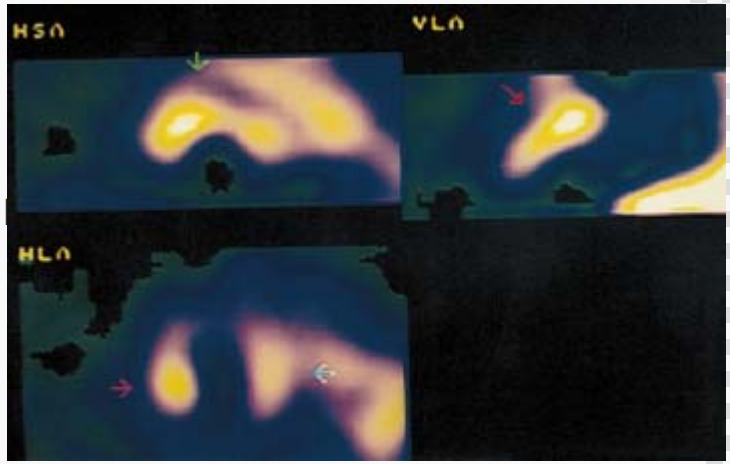
- Primary cardiomyopathy
  - Dysautonomias
  - Heart transplantation
  - Idiopathic ventricular tachycardia and fibrillation
- Secondary cardiomyopathy
  - Dilated cardiomyopathy
  - Coronary artery disease
  - Hypertrophic cardiomyopathy
  - Diabetes mellitus
  - Hypertension
  - Drug-induced cardiotoxicity

Heart Transplantation

- Allograft ; completely denervated
  - Lack of autonomic nerve supply
- Physiologic limitations
  - Inability to perceive pain
    - no symptomatic recognition
    - accelerated allograft vasculopathy
    - acute ischemic events/ LV dysfunction /sudden death
  - Denervation of sinus node
    - no adequate acceleration of heart rate
    - altered hemodynamic performance
    - ↓ exercise capacity

Cardiac neurotransmission imaging

- Slow reinnervation
  - only after 1 y after transplantation
- Myocardial MIBG uptake
  - Increases with time after transplantatio
  - positive correlation
    - heart-to-mediastinum rates
    - time after transplantation
- Serial MIBG studies
  - Reinnervation from the base to the apex
  - primarily in the anterior, anterolateral, and septal regions
  - usually not apparent in the posterior or inferior regions,
  - no Complete reinnervation even up to 12 y after transplantation.



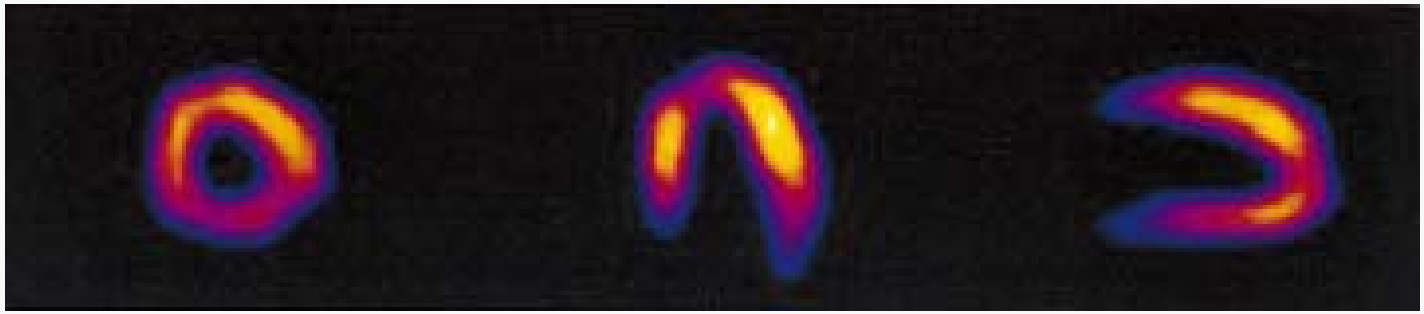
Idiopathic Ventricular Tachycardia and Fibrillation

- The most common arrhythmia of sudden death
- No structural or functional abnormalities of myocardium

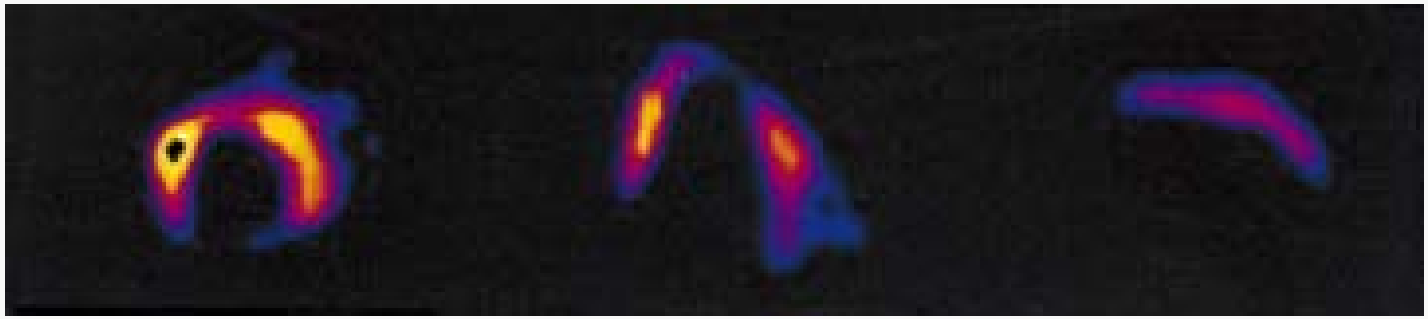
- ^{123}I-MIBG, ^{11}C-hydroxyephedrine, and ^{11}C-CGP,
  - idiopathic right ventricular outflow tract tachycardia
  - ↓ presynaptic myocardial catecholamine reuptake
  - ↓ postsynaptic myocardial β-adrenoceptor density
  - Normal blood catecholamine levels
- ↓ maximal binding capacity ; β-adrenoceptor antagonist
  - impaired catecholamine reuptake
  - ↑ local synaptic catecholamine levels
  - myocardial β -adrenoceptor downregulation

Idiopathic Ventricular Tachycardia

^{201}Tl myocardial SPECT



^{123}I MIBG SPECT

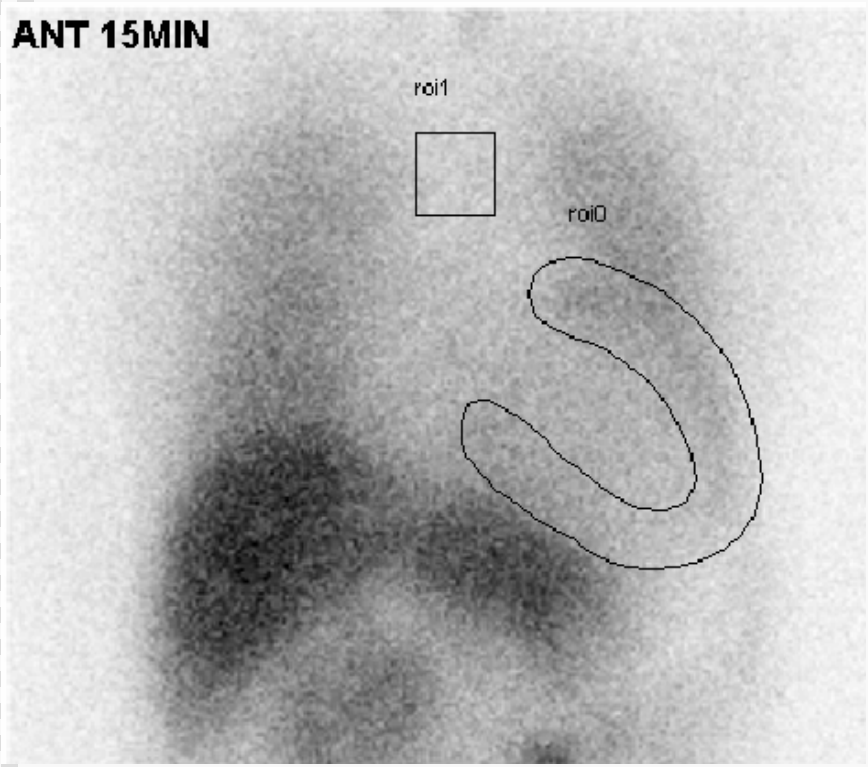


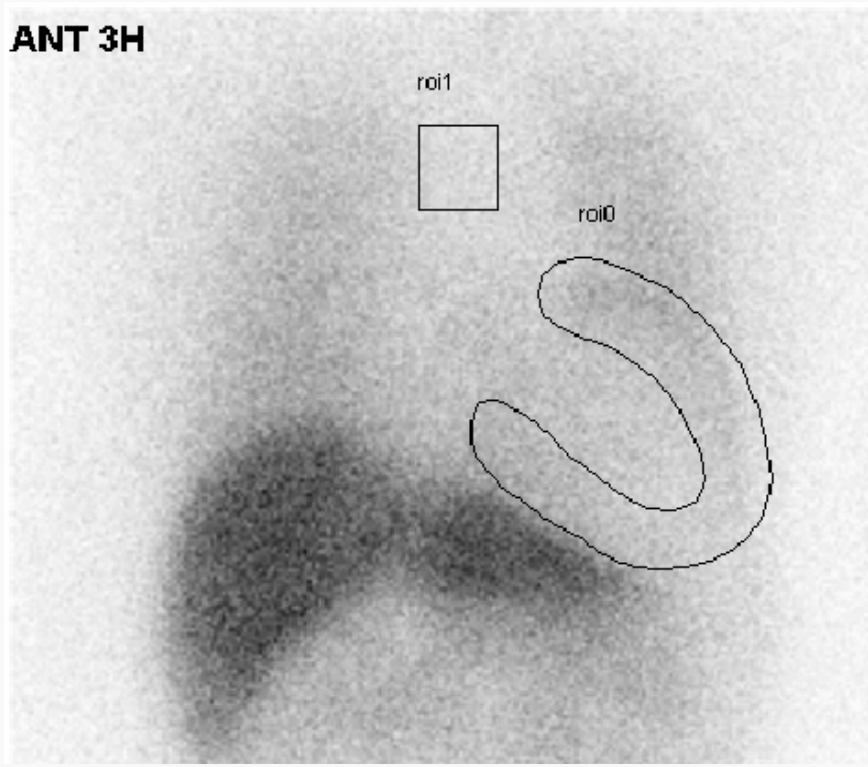
Dilated Cardiomyopathies

- Sympathetic nervous system activity ↑
  - Deleterious effects
    - Vascular constriction and ↑salt and water retention
      - ↑ energy requirement of myocardial wall
    - Altered sympathetic cardiac adrenergic function
      - Arrhythmias
      - desensitization of postsynaptic β-adrenoceptors
      - activation of other neurohumoral systems
  - progression of myocardial dysfunction
- prolonged exposure to norepinephrine
  - modify cellular phenotype / result in myocyte death

- ↑ concentration of circulating catecholamines
  - blunted responsiveness to β-adrenoceptor agonists
  - alterations of sympathetic innervation → fatal outcomes
- Only independent predictors of mortality
  - low MIBG uptake & LVEF
    - Merlet et al. *J Nucl Med.* 1999;40:917–923.
- Most powerful independent predictor of prognosis
    - Washout Rate of MIBG
  - cardiomyopathy : washout rates (>25% from 15 to 85 min)
  - Healthy volunteers (<10%)
    - Momose et al. *Nucl Med Commun.* 1999;20:529 –535

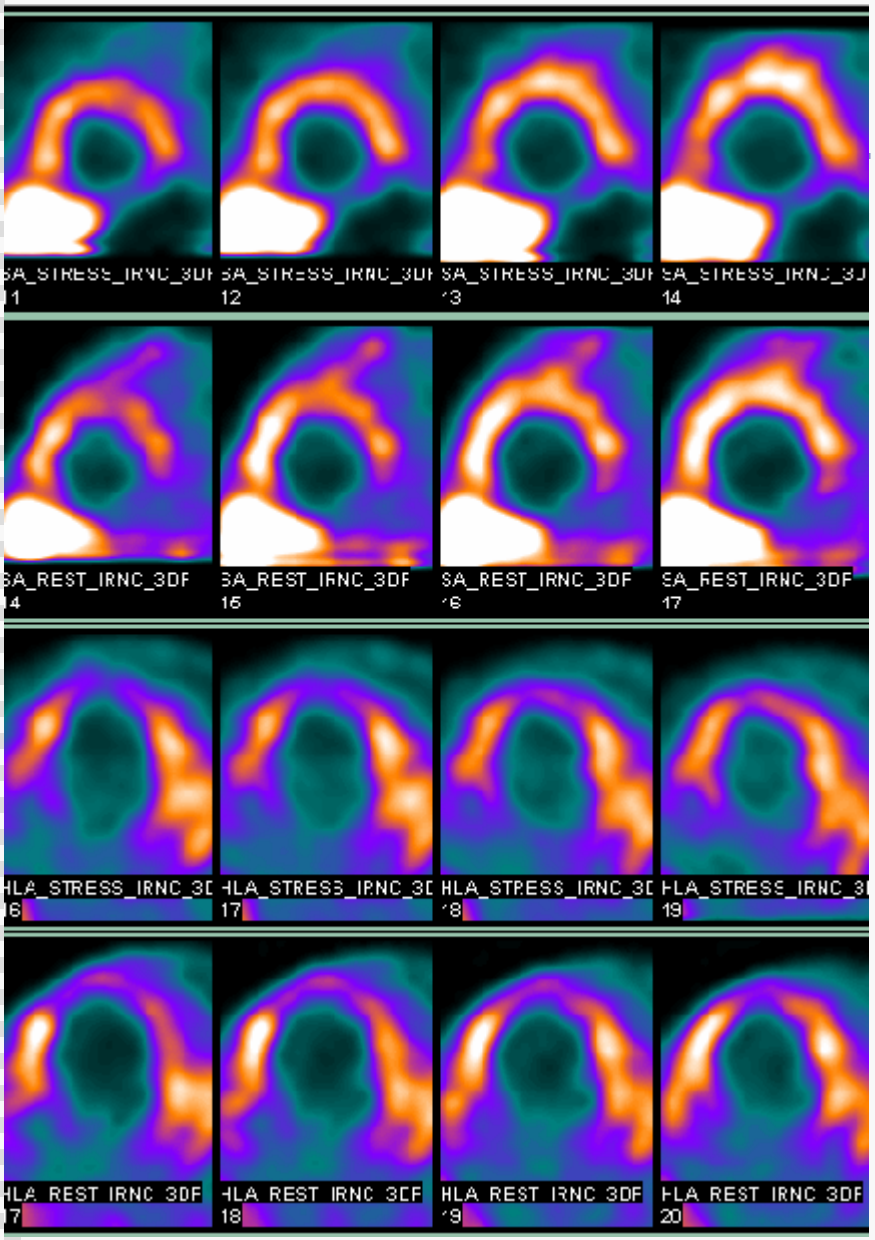
M/61, DCM





H/M ration : 1.57

H/M ration : 1.57


SA_STRESS_IRNC_3DF
11
SA_STRESS_IRNC_3DF
12
SA_STRESS_IRNC_3DF
13
SA_STRESS_IRNC_3DF
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SA_REST_IRNC_3DF
14
SA_REST_IRNC_3DF
15
SA_REST_IRNC_3DF
16
SA_REST_IRNC_3DF
17
HLA_STRESS_IRNC_3DF
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HLA_STRESS_IRNC_3DF
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HLA_STRESS_IRNC_3DF
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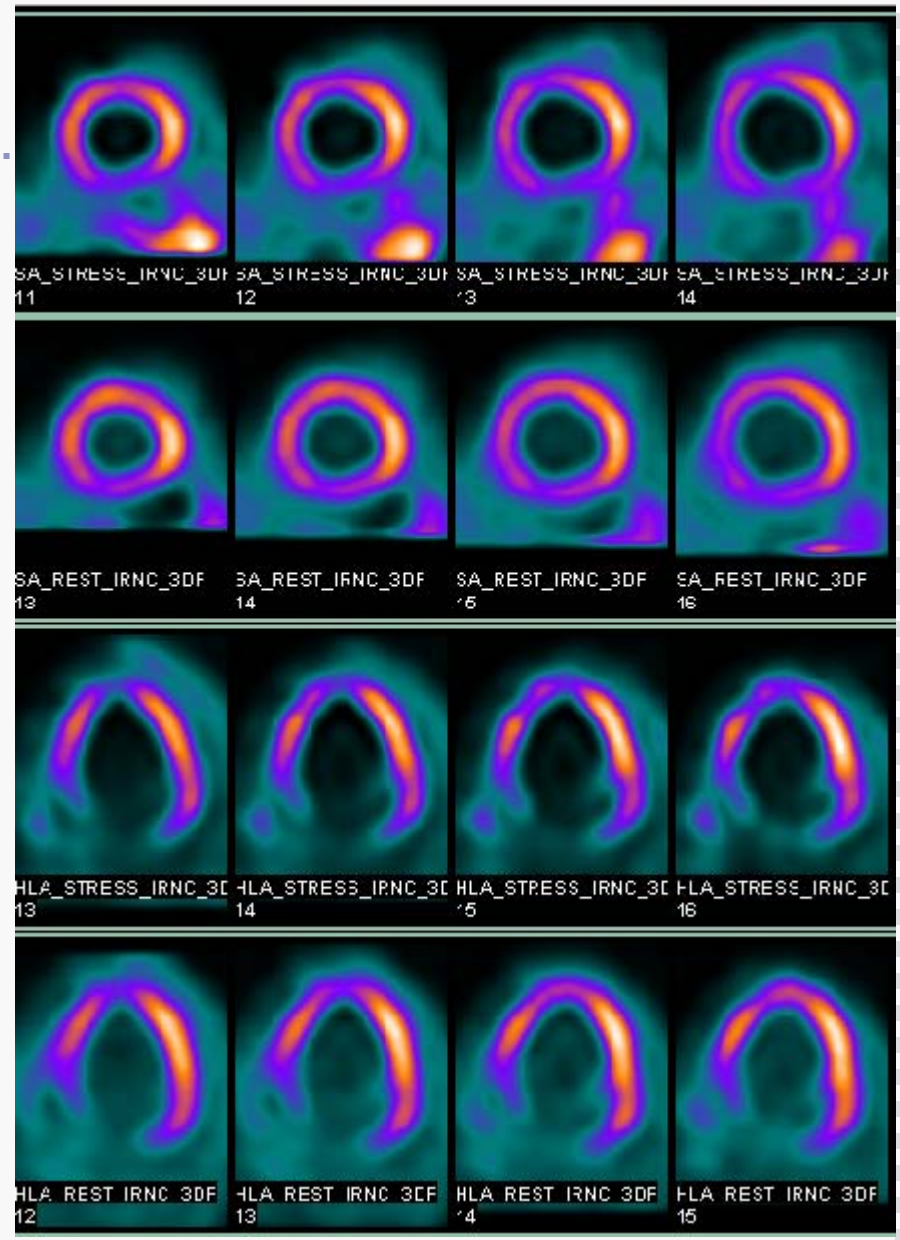
SA_STRESS_IRNC_3DF
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HLA_STRESS_IRNC_3DF
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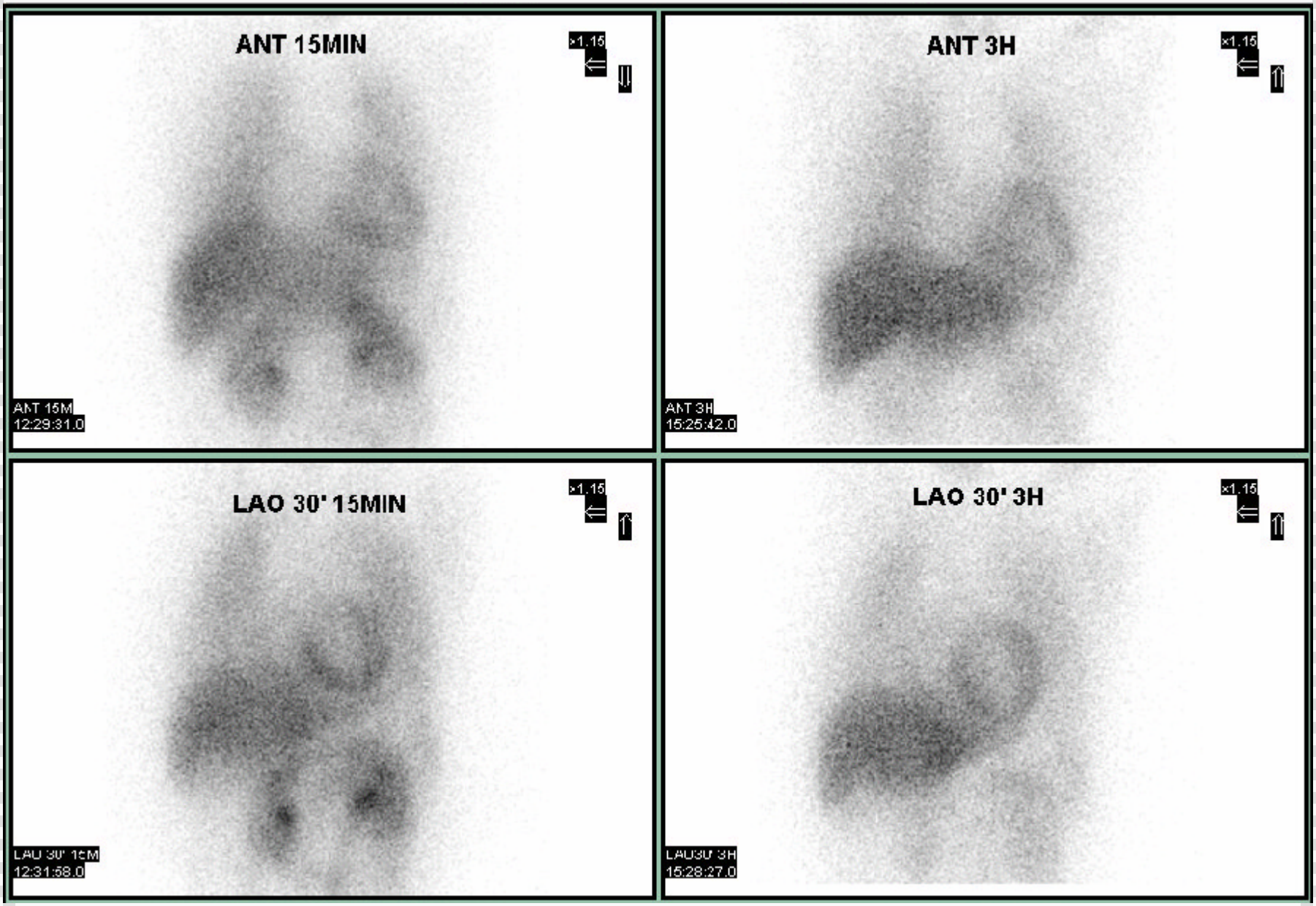
15

F/49, DCM

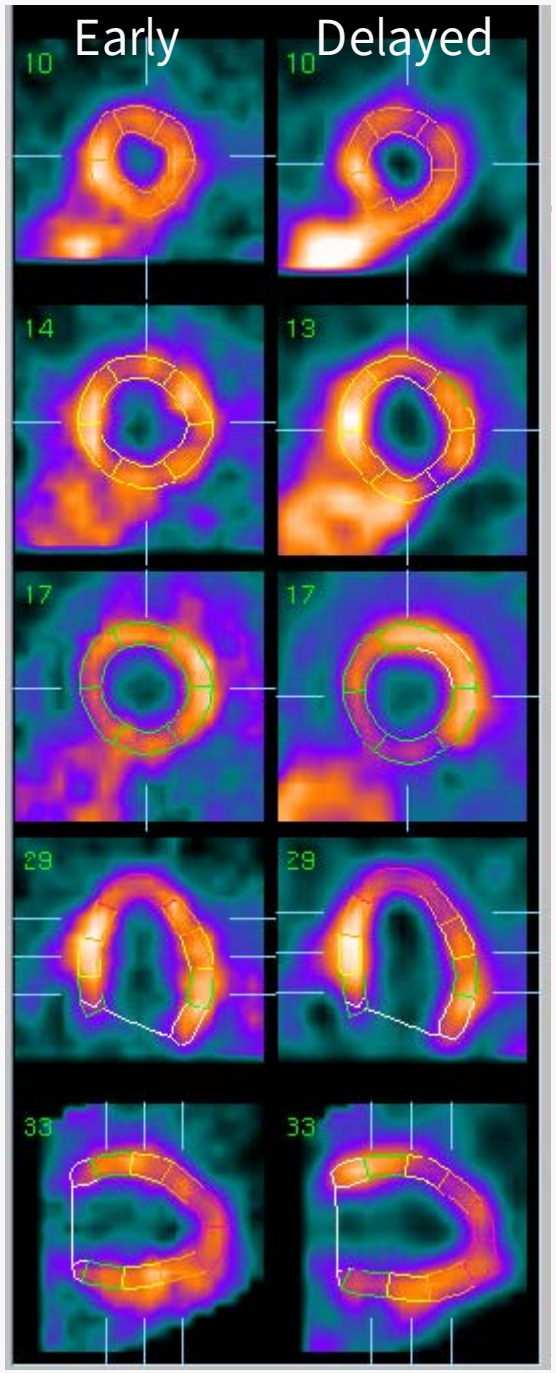


H/M ratio : 2.2

SA

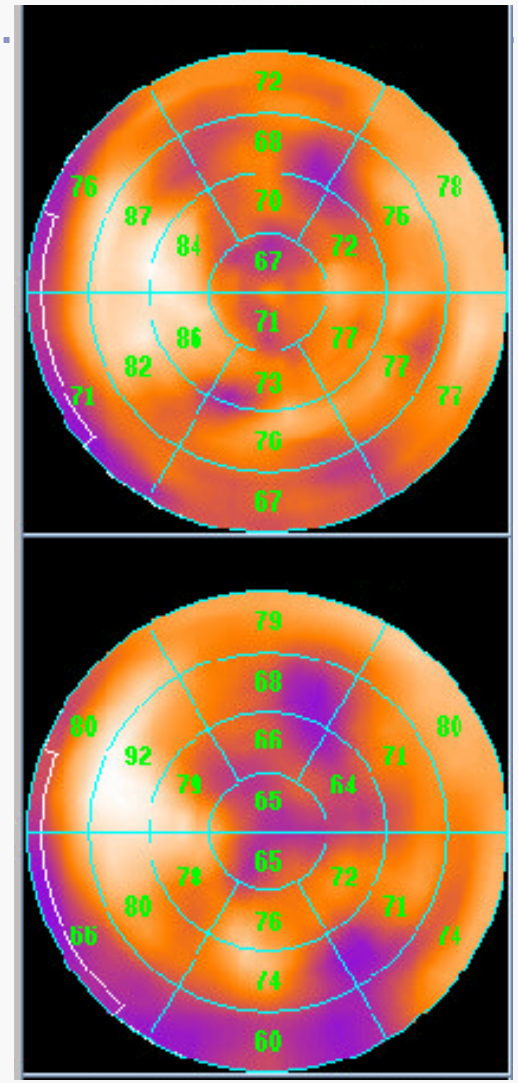
HLA

VLA

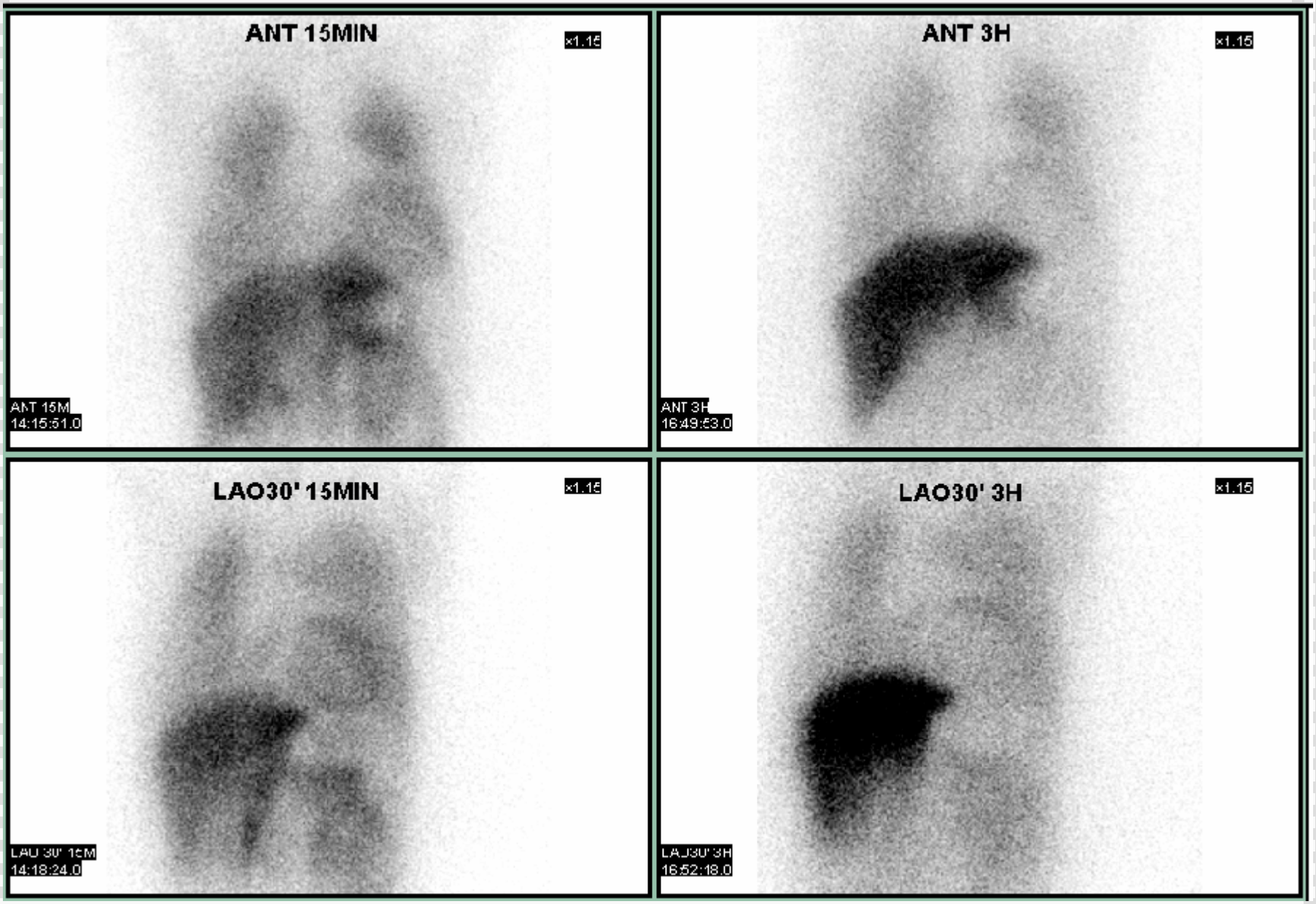


Early

Delayed



F/69, DCM



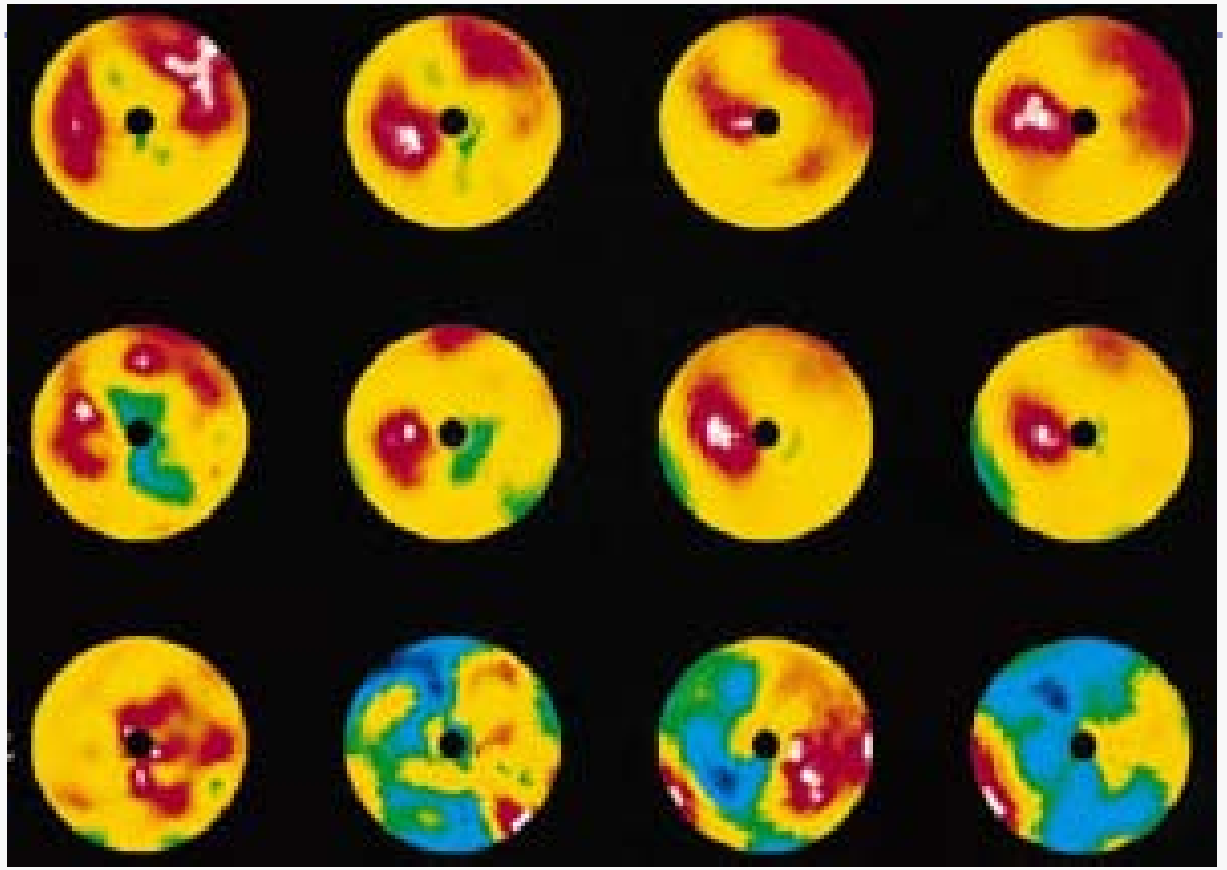
H/M ratio : 1.9

H/M ratio : 1.5

Assess New Forms of Medical Therapy

- Enalapril treatment
  - restoration of neuronal uptake of noradrenaline
    - Somsen et al. *Eur J Nucl Med.* 1995;22:1149 –1154.
- ^{123}I-MIBG myocardial imaging
  - Heart/mediastinum ratio on delayed images
    - good predictor of the response to α-blocker therapy
  - Threshold 1.7 identifying responders to bisoprolol
    - sensitivity : 91%, specificity : 92%.
      - Suwa et al. *Am Heart J.* 1997;133:353–358.

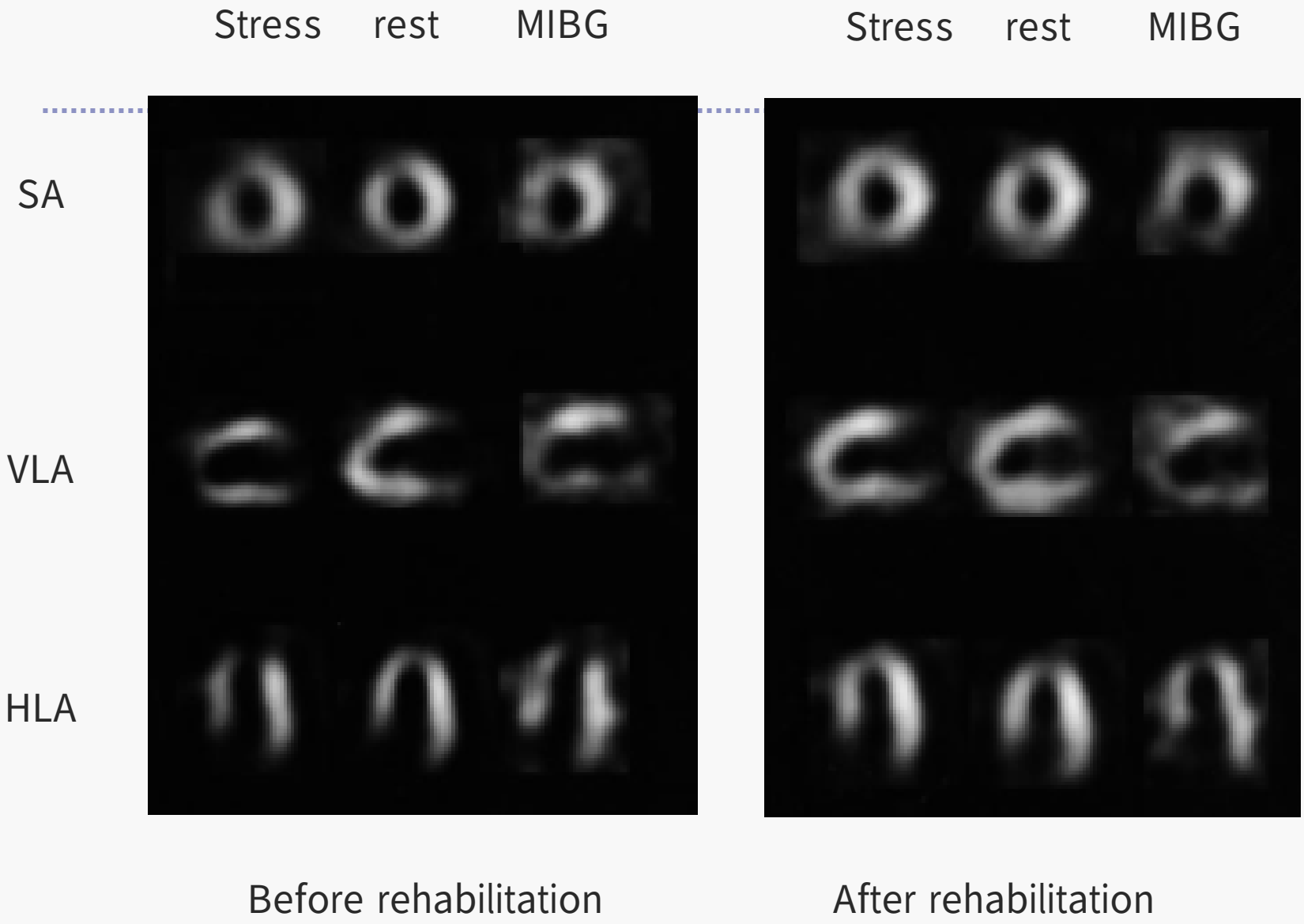
Sequential MIBG studies for monitoring of α-blocker therapy.



	Before	0.4 yrs.	3.3 yrs.	6.9 yrs.
Washout rate	56%	24%	19%	18%
LVEF	28%	59%	65%	62%

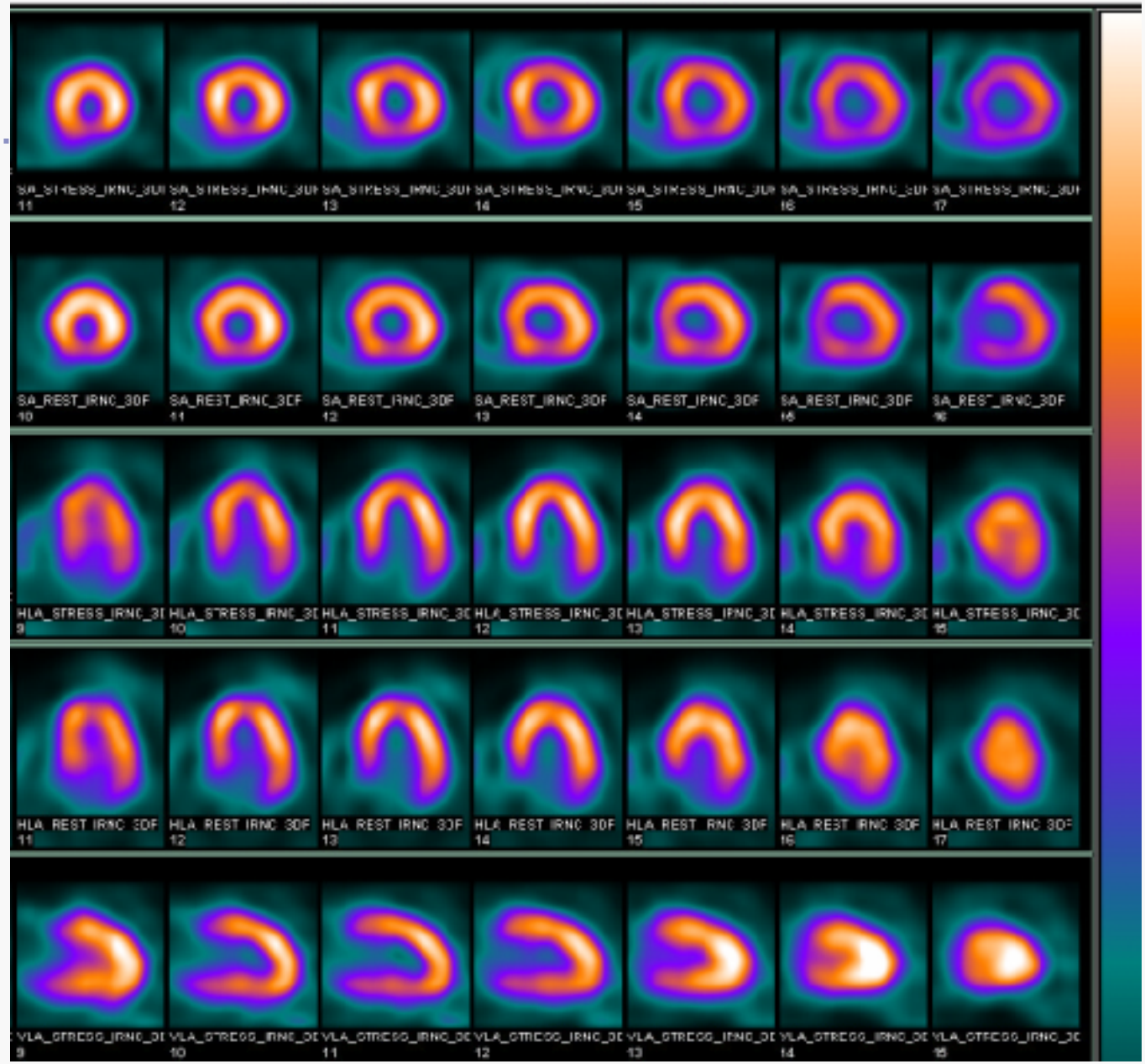
Coronary Artery Disease

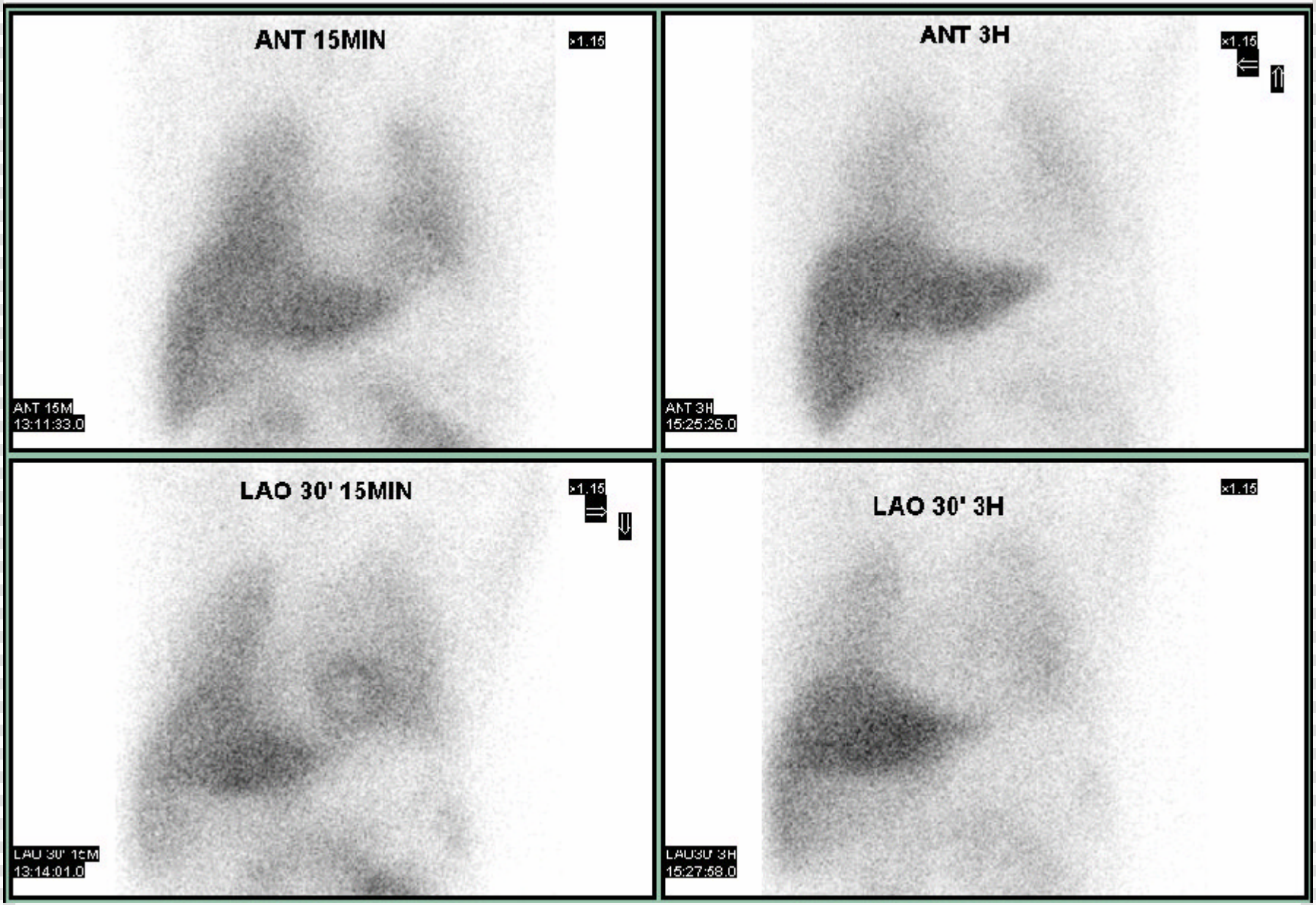
- Sympathetic nervous tissue
  - more sensitive than myocardial tissue in ischemia
- Ischemia
  - damage to sympathetic neurons
    - long time to regenerate
  - repetitive episodes of ischemia
    - permanent loss of MIBG uptake


Stress
rest
MIBG
Stress
rest
MIBG
SA
VLA
HLA
Before rehabilitation
After rehabilitation

M/59

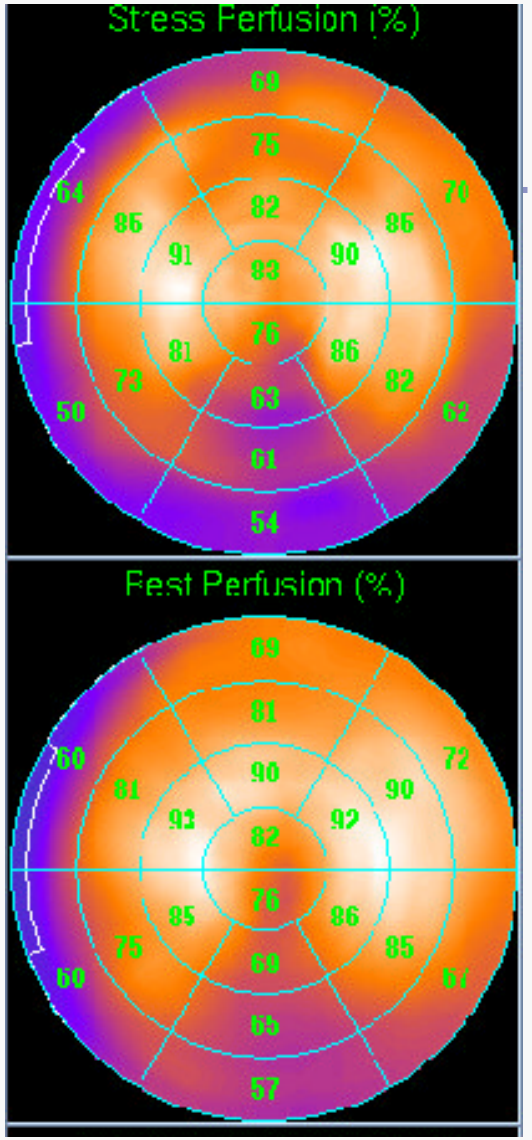
^{99m}Tc - MIBI Myocardial Perfusion SPECT



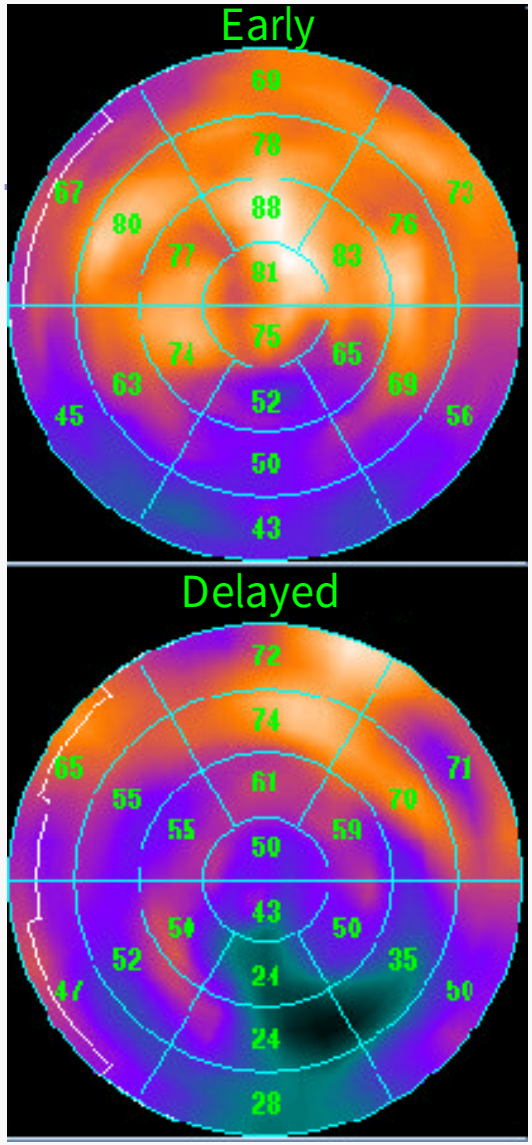


H/M ratio : 2.4

H/M ratio : 1.7



^{99m}Tc-MIBI Myocardial Perfusion SPECT



^{123}I-MIBG Myocardial SPECT

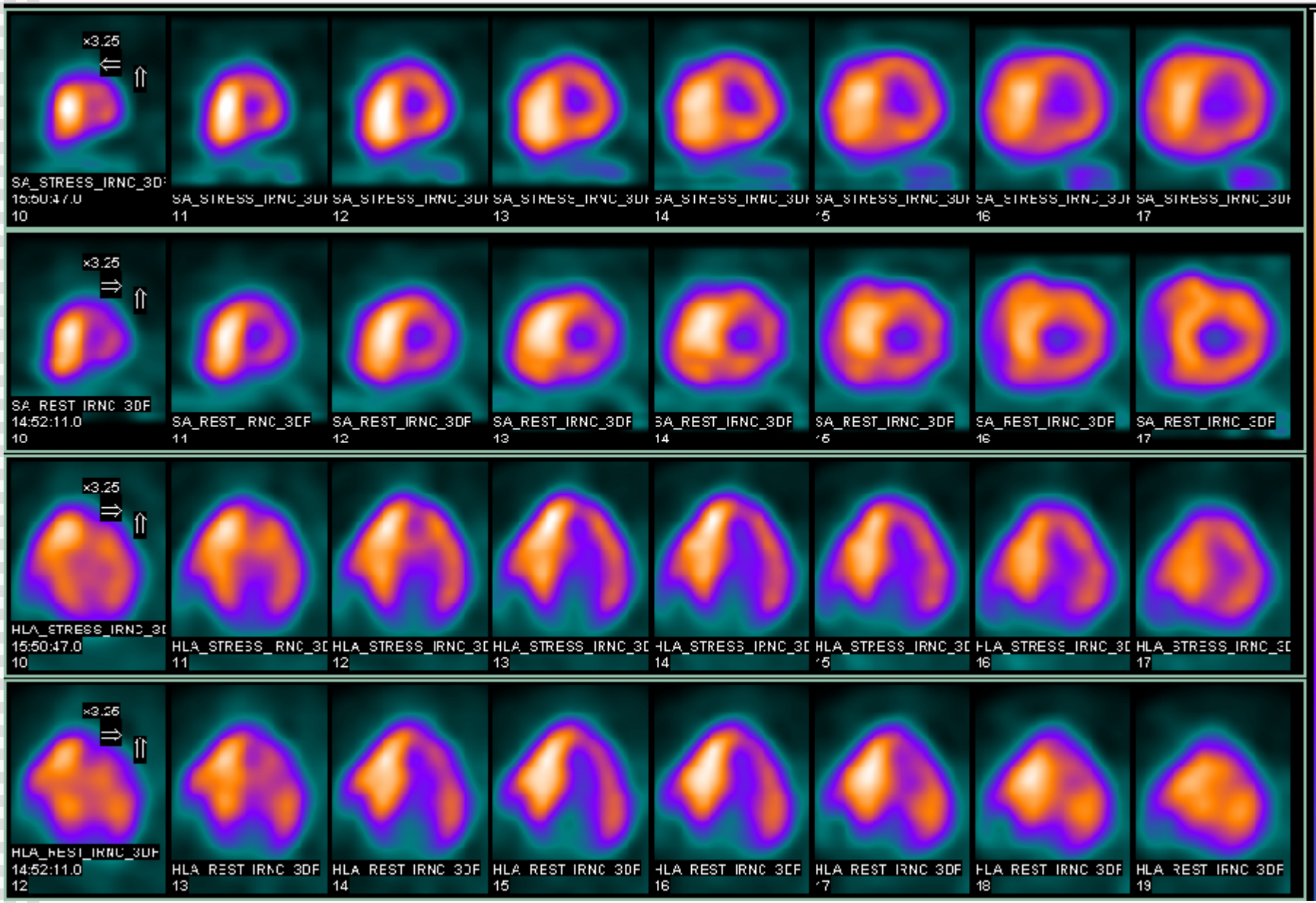
^{123}I-MIBG in Myocardial infarciton

- ^{123}I-MIBG scan on day 10 after acute MI
  - Area of reduced uptake more extensive than thallium perfusion defect
    - McGhie et al. *Am J Cardiol.* 1991;67:236 –242.
- Adrenergic denervation of viable myocardium
  - denervation supersensitivity,
    - exaggerated response of myocardium to sympathetic stimulation.
    - vulnerability to ventricular arrhythmias.
- ^{123}I-MIBG uptake at 3 - 13 mo after infarction
  - no difference in MIBG activity within the infarcted zone
  - increase in activity in the periinfarcted region
  - without a change in perfusion.
    - Hartikainen et al. *Am J Cardiol.* 1996;77:5–9.

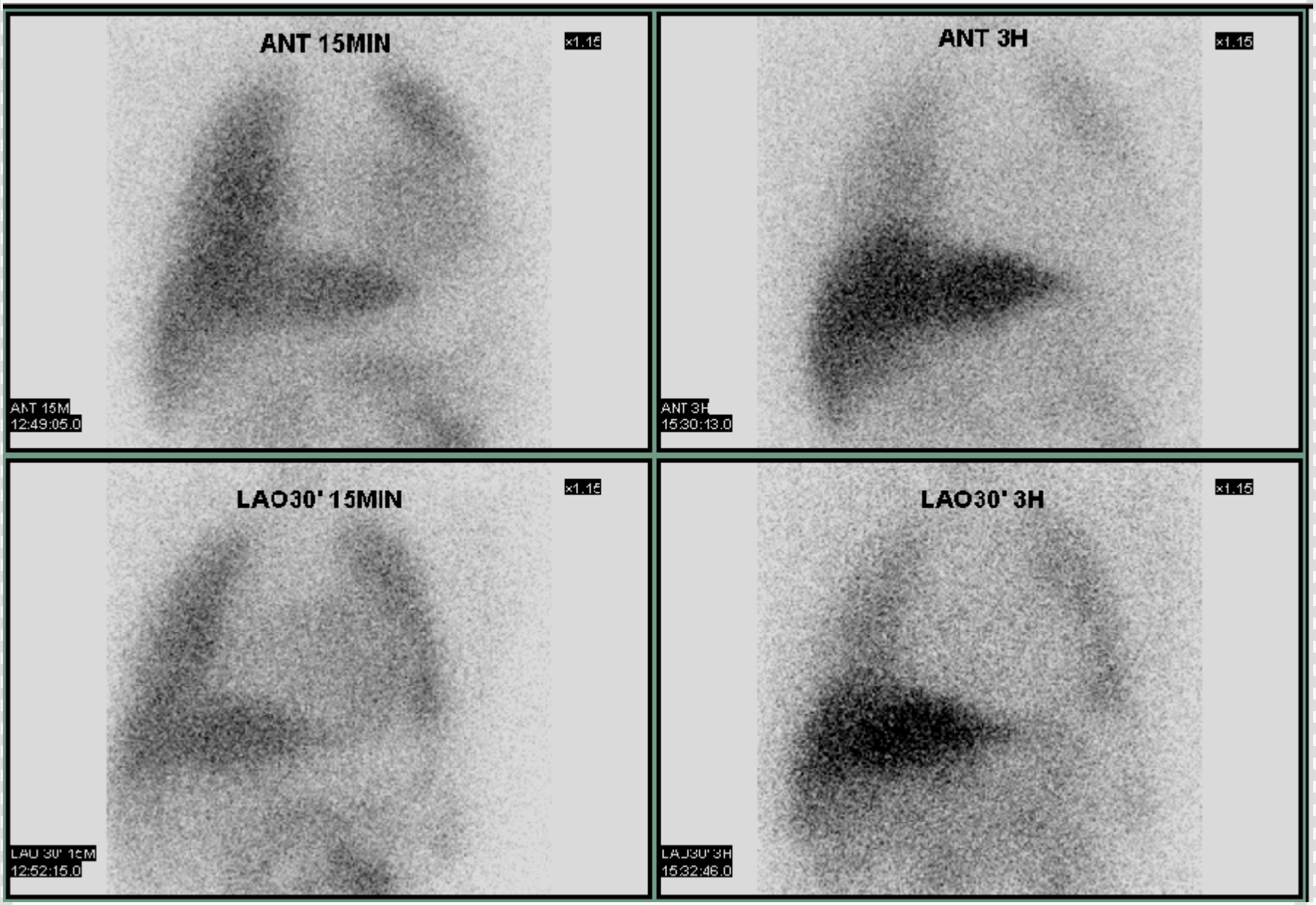
Hypertrophic Cardiomyopathy

- autonomic dysfunction : phenotypic expression
- Impaired Cardiac presynaptic catecholamine reuptake
  - ↑ neurotransmitter concentration in synaptic cleft
  - ↓ postsynaptic β-adrenoceptor density
- Quantitative ^{11}C-hydroxyephedrine and ^{11}C-CGP PET
  - increased washout rate (.25%)
- ^{13}N-ammonia and ^{18}F-fluorodopamine PET
  - ↓ ^{18}F:^{13}N ratio in hypertrophied myocardium
  - ↓ neuronal uptake of catecholamines in hypertrophied myocardium

M/30, HCM



Tc-99m MIBI Myocardial perfusion SPECT



^{123}I MIBG scan

Conclusion

- Cardiac neurotransmission imaging
  - Pathophysiology of disease
  - Selection of patient for various treatment
  - Assessment of results of therapy
- Future direction
  - New tracers
  - Clinical practice
  - Assessment and prediction of therapy