CARDIOVASCULAR
Academic Clinical Program

National Heart Centre Singapore

Academic Medicine
improving patients' lives

HYPERTENSIVE HEART DISEASE

Changing Treatment Paradigm

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Partners in Academic Medicine

SingHealth DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

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National Heart Centre Singapore
National Neuroscience Institute
Singapore National Eye Centre
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Bright Vision Hospital

Academic Medicine
improving patients' lives

No Disclosures

Partners in Academic Medicine

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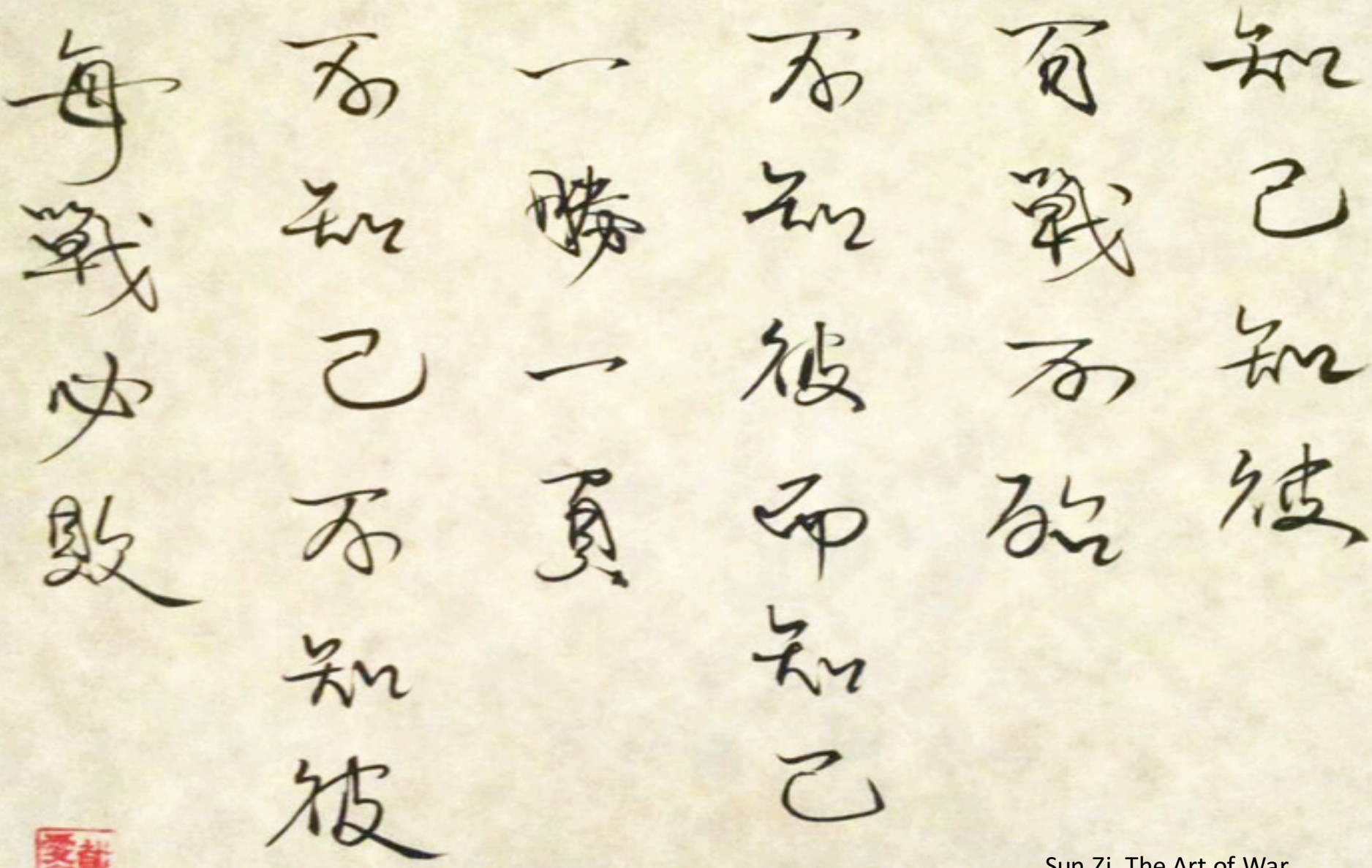
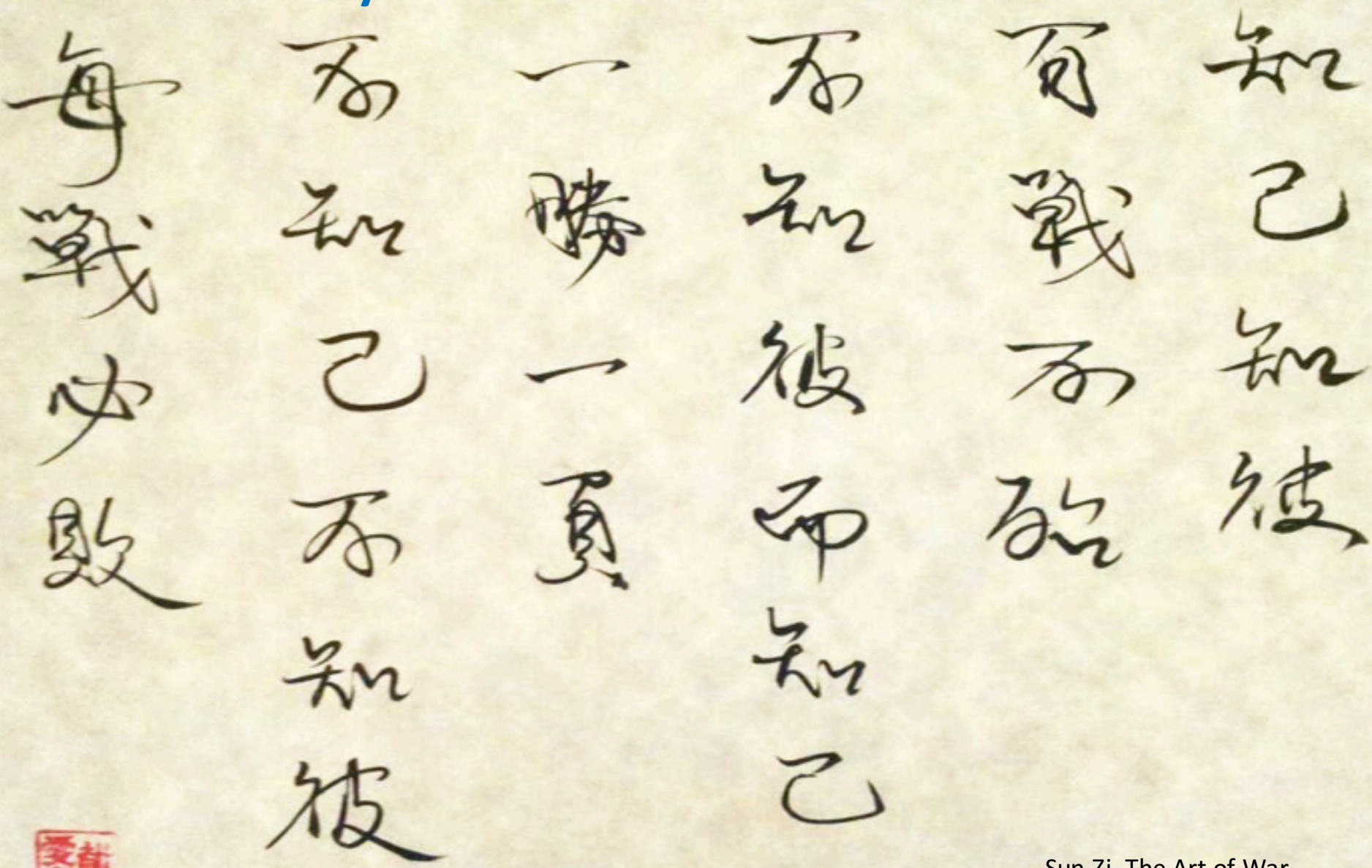
If you know your enemy and yourself , you will not fail in a hundred battles



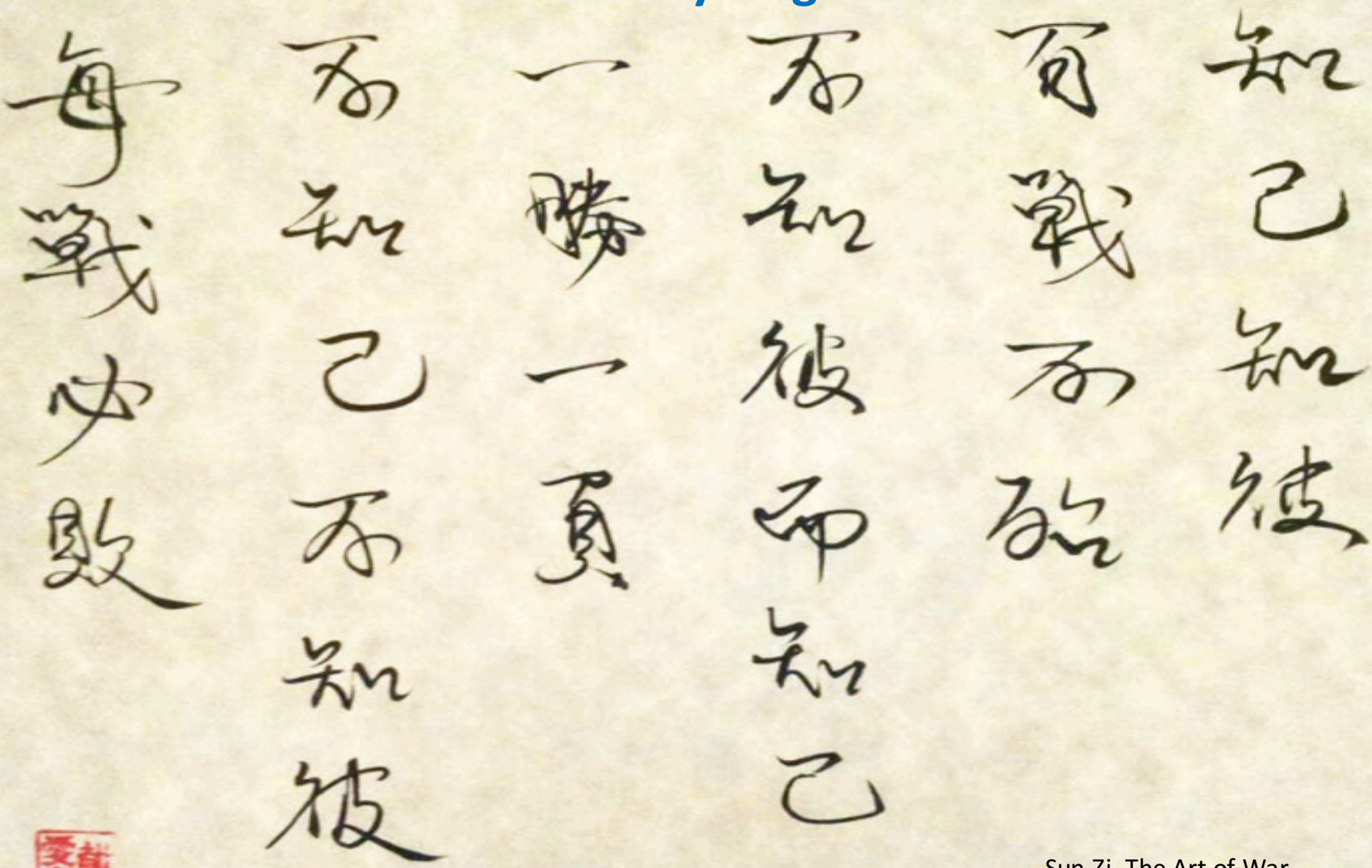
Sun Zi, The Art of War

If you do not know your enemies but do know yourself, you will win one and lose one



Sun Zi, The Art of War

If you do not know your enemies nor yourself, you will succumb in every single battle

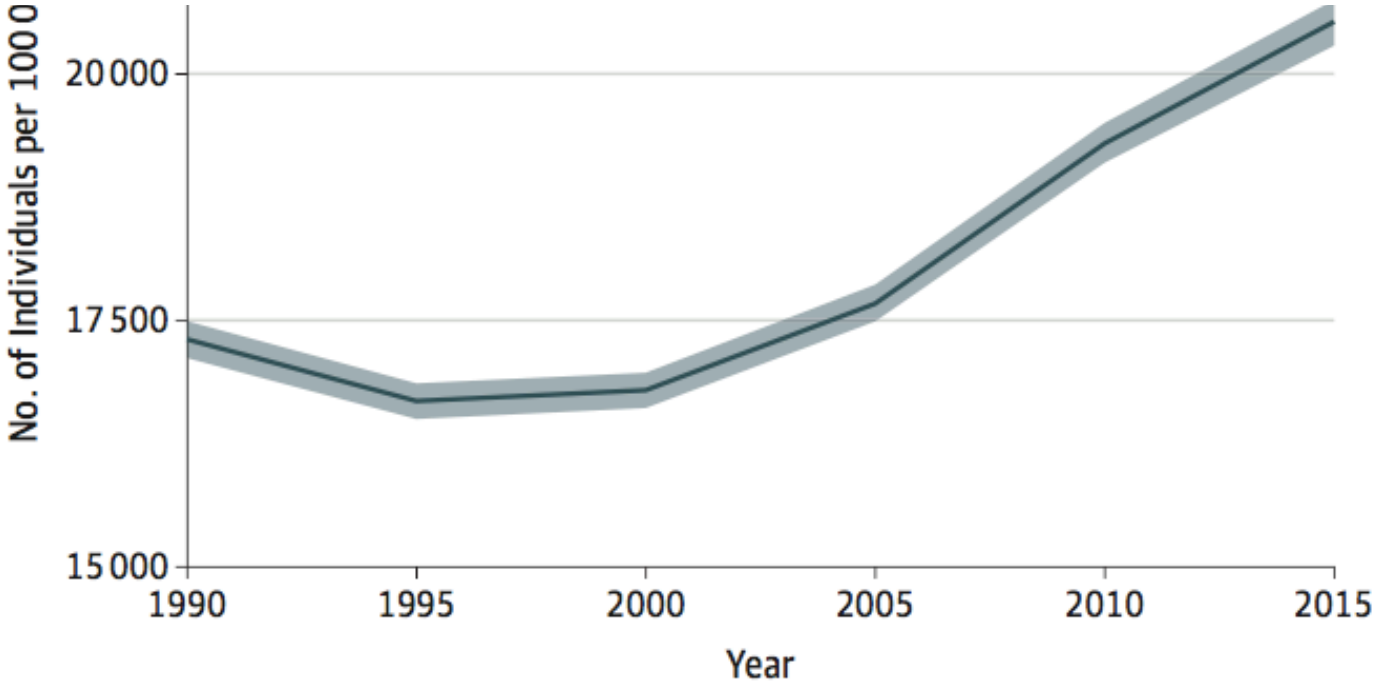


Sun Zi, The Art of War

Global Trend of Hypertension

Enemy of Cardiovascular Health

Projected Estimate (2015): 874 million adults had SBP >140mmHg



Forouzanfar et. al. JAMA 2017;317:165

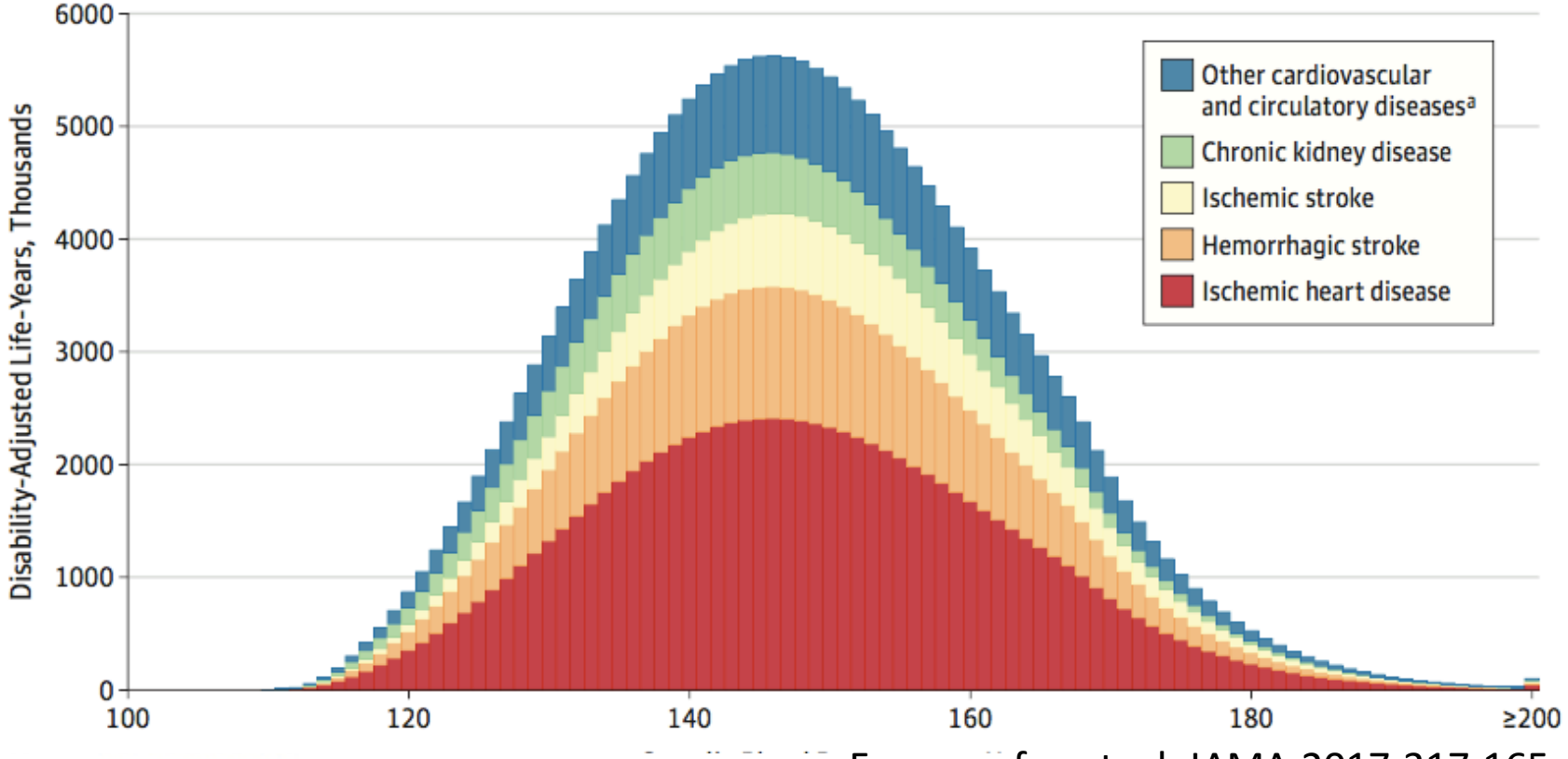
Global Trend of Hypertension

Enemy of Cardiovascular Health

Annual Estimated Death Rate:

1990: 98/100,000

2015: 106/100,000



Forouzanfar et. al. JAMA 2017;317:165

Prevalence of Hypertension in Singapore

National Health Survey 2010

	1992	1998	2004	2010
Hypertension, crude prevalence (age-standardized)	22.2% (27.7%)	27.3% (32.5%)	24.9% (26.8%)	23.5%

Age (years)	Males	Females	Total
30 - 39	10.9	4.5	7.6
40 - 49	21.9	11.5	16.7
50 - 59	33.1	30.8	31.9
60 - 69	53.8	53.0	53.4
30 - 69	**26.4**	**20.7**	**23.5**

Prevalence of Hypertension in Singapore

Singapore Burden of Disease Study 2010

Cardiovascular diseases is THE major contributor of total disease/injury burden in adults >65 years old

Specific Cause	Disability adjusted life years	Years of life lost	Years lived with disability
Ischemic heart disease	41,656	36,453	5,203
Strokes	27,208	17,042	10,166
Hypertensive heart disease	3,788	3,704	84

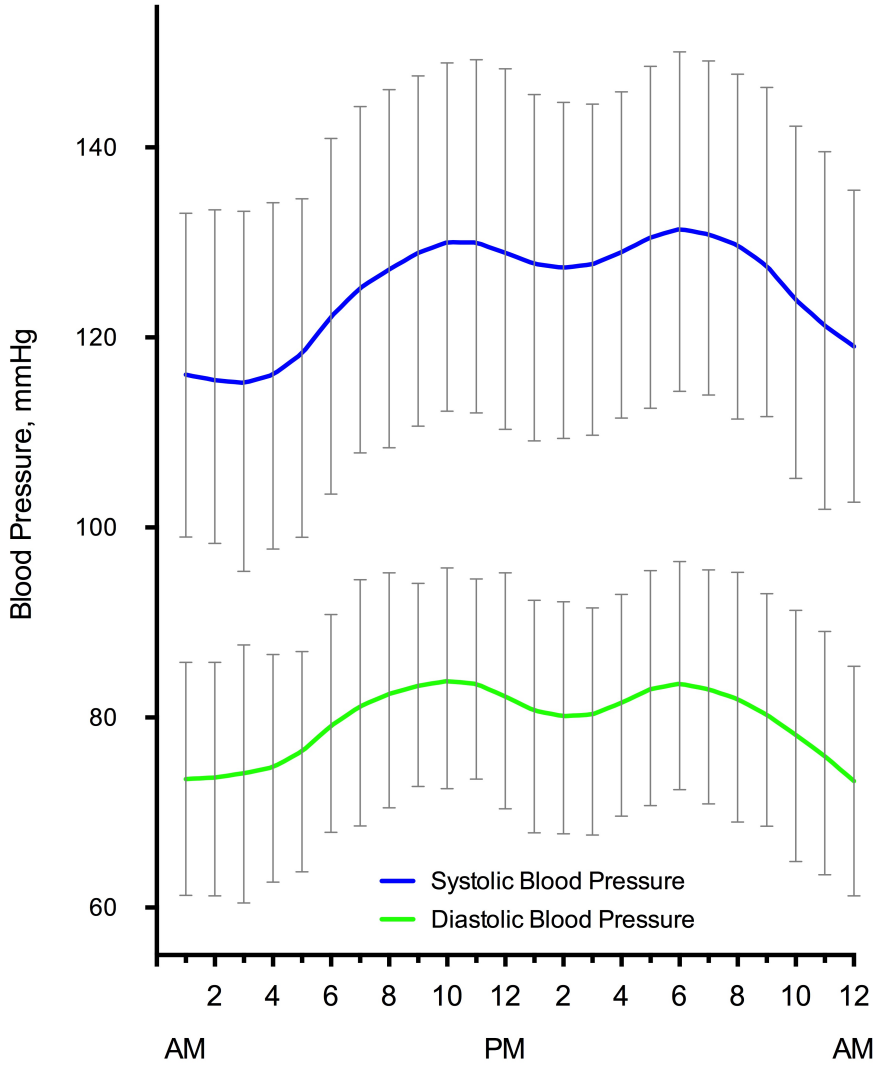
Diagnosis and Management

Sphygmomanometer – 1896

Scipion Riva-Rocci
Italian internist, pathologist, pediatrician

Diagnosis and Management

Limitations: Blood Pressure Variation



- Biological variation
- Measurement variation

Diagnosis and Management

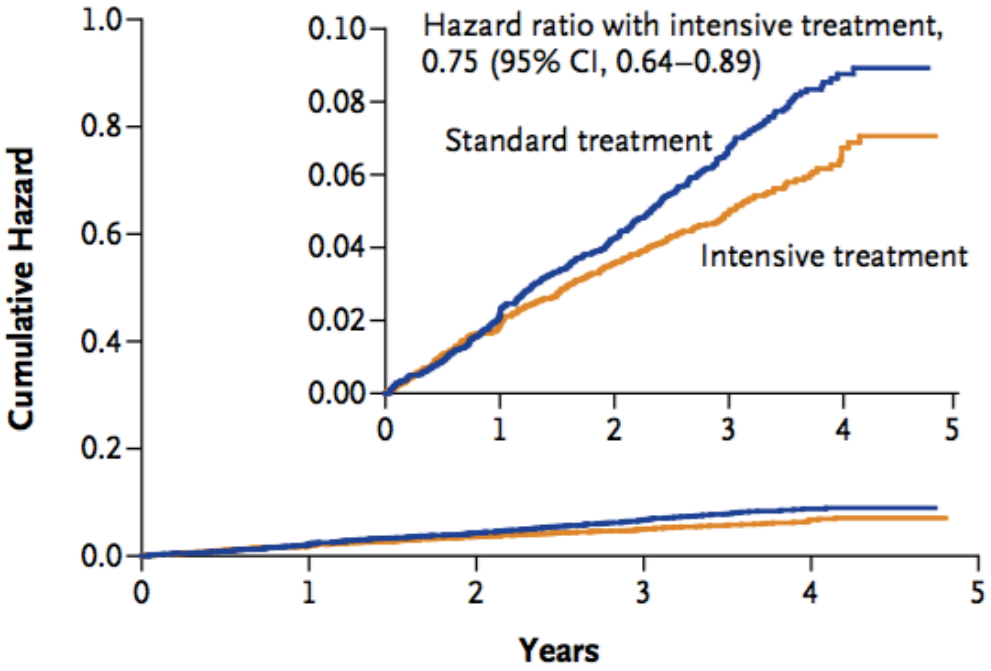
Limitations: Blood Pressure Targets

Society/Organisation	Systolic Blood Pressure Targets	Population
European Society of Hypertension/European Society of Cardiology (2013)	<140mmHg	Patients with low-moderate cardiovascular risk and in patients with diabetes, previous strokes, coronary artery disease or chronic kidney disease
	140-150mmHg	Elderly hypertensive patients **< 80 years**
	140-150mmHg	Elderly hypertensive patients **> 80 years** provided they are in good physical and mental conditions
JNC 8, United States (2014)	<140mmHg	General population < 60 years, individuals with diabetes or chronic kidney disease
	<150mmHg	Elderly hypertensive patients ≥ **60 years**
American Society of Hypertension/International Society of Hypertension (2014)	<140mmHg	General population; individuals with diabetes, chronic kidney disease and coronary artery disease
	<150mmHg	Elderly hypertensive patients **> 80 years**

Diagnosis and Management

The Lower The Better?

A Primary Outcome



No. at Risk

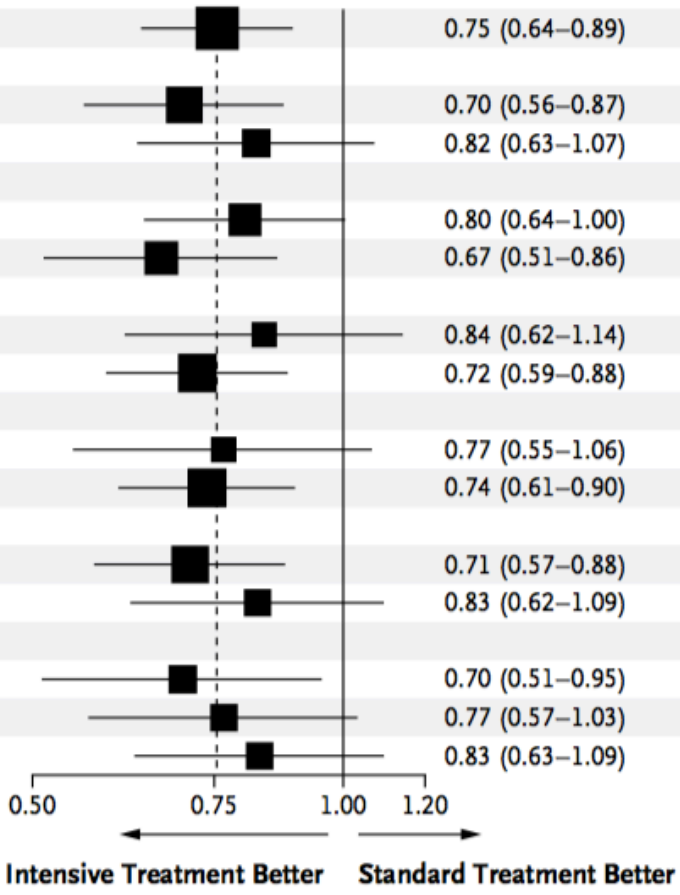
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

The SPRINT Research Group NEJM 2015;373:2130

Diagnosis and Management

The Lower The Better?

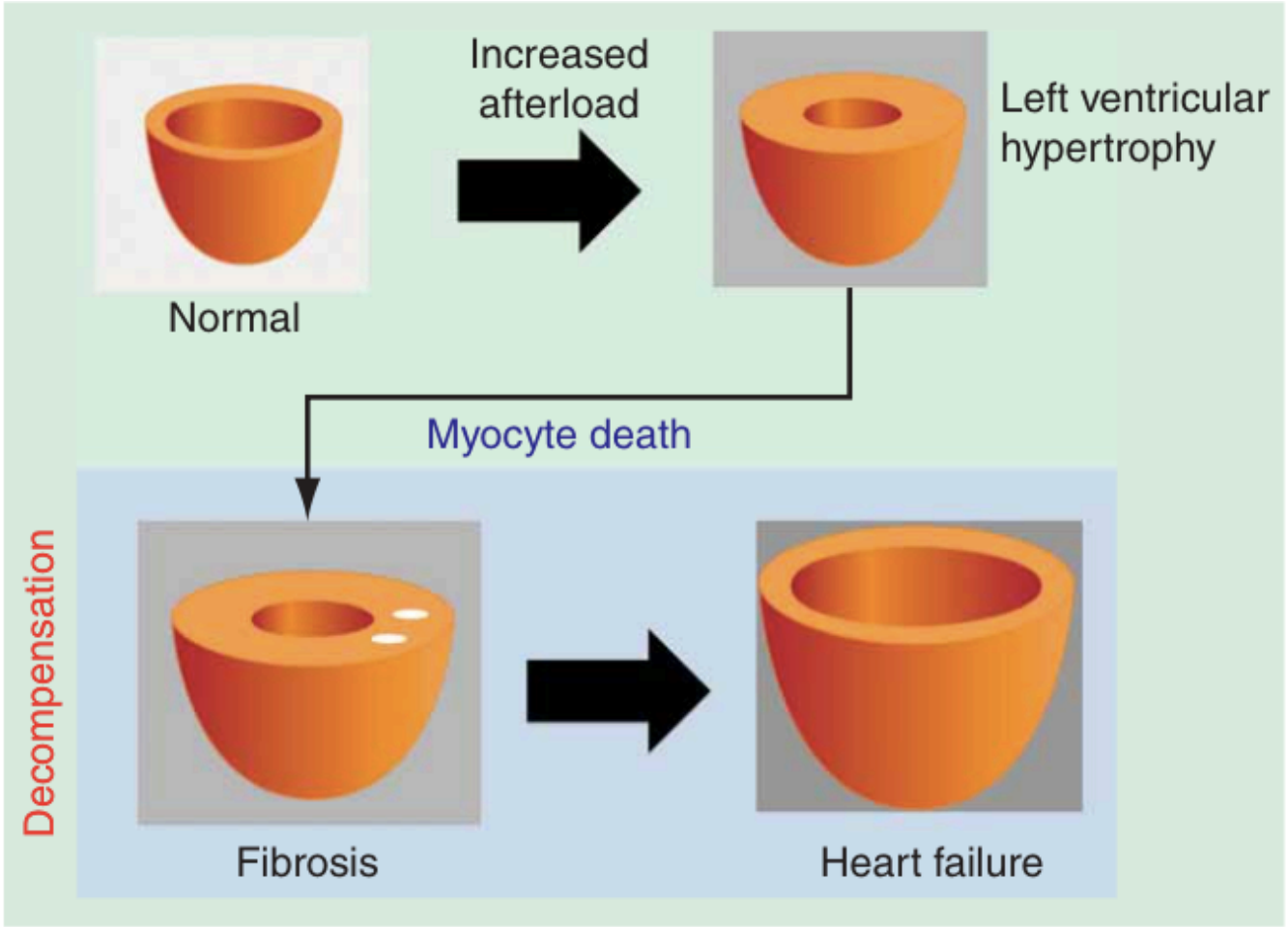
Subgroup	Intensive Treatment	Standard Treatment	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with primary outcome/total no. (%)			
Overall	243/4678 (5.2)	319/4683 (6.8)	0.75 (0.64–0.89)	
Previous CKD				0.36
No	135/3348 (4.0)	193/3367 (5.7)	0.70 (0.56–0.87)	
Yes	108/1330 (8.1)	126/1316 (9.6)	0.82 (0.63–1.07)	
Age				0.32
<75 yr	142/3361 (4.2)	175/3364 (5.2)	0.80 (0.64–1.00)	
≥75 yr	101/1317 (7.7)	144/1319 (10.9)	0.67 (0.51–0.86)	
Sex				0.45
Female	77/1684 (4.6)	89/1648 (5.4)	0.84 (0.62–1.14)	
Male	166/2994 (5.5)	230/3035 (7.6)	0.72 (0.59–0.88)	
Race				0.83
Black	62/1454 (4.3)	85/1493 (5.7)	0.77 (0.55–1.06)	
Nonblack	181/3224 (5.6)	234/3190 (7.3)	0.74 (0.61–0.90)	
Previous cardiovascular disease				0.39
No	149/3738 (4.0)	208/3746 (5.6)	0.71 (0.57–0.88)	
Yes	94/940 (10.0)	111/937 (11.8)	0.83 (0.62–1.09)	
Systolic blood pressure				0.77
≤132 mm Hg	71/1583 (4.5)	98/1553 (6.3)	0.70 (0.51–0.95)	
>132 to <145 mm Hg	77/1489 (5.2)	106/1549 (6.8)	0.77 (0.57–1.03)	
≥145 mm Hg	95/1606 (5.9)	115/1581 (7.3)	0.83 (0.63–1.09)	



The SPRINT Research Group NEJM 2015;373:2130

Hypertension Pathophysiology

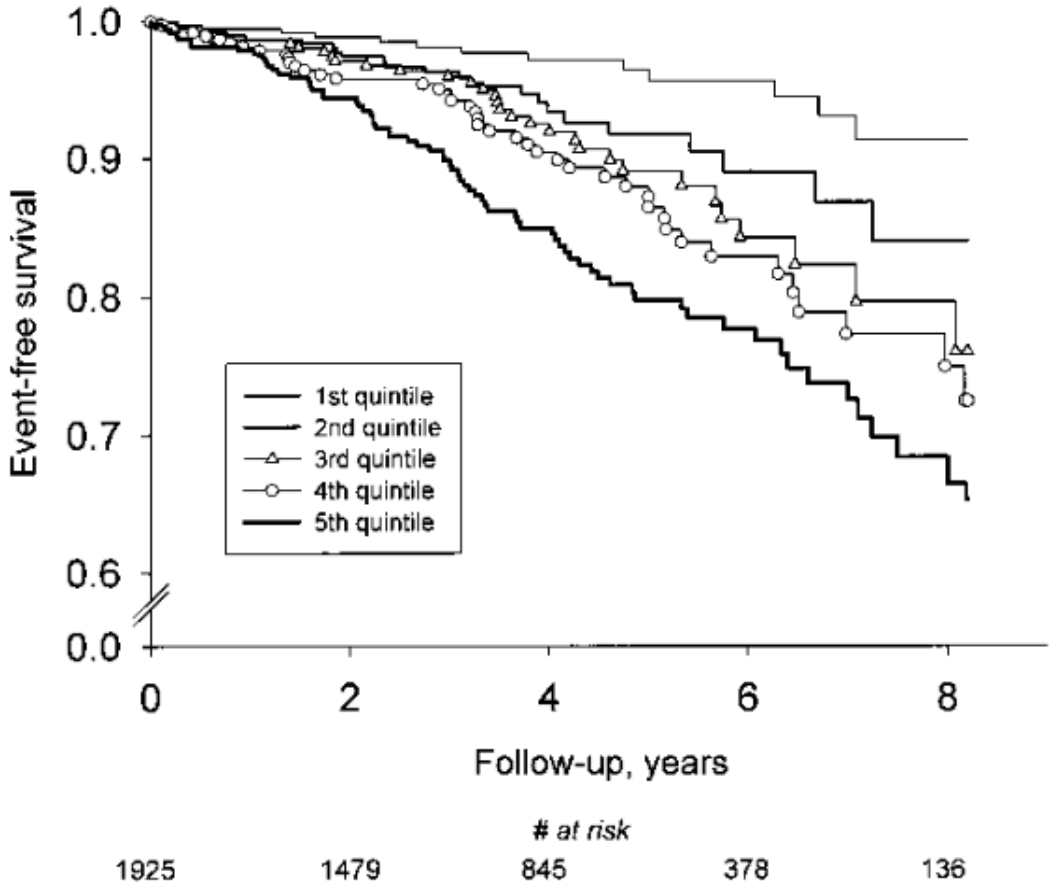
Why Focus on the Myocardium?



Chin et al., Expert Rev Cardiovasc Ther. 2014;12:901

Hypertension Pathophysiology

Prognostic Association with LVH

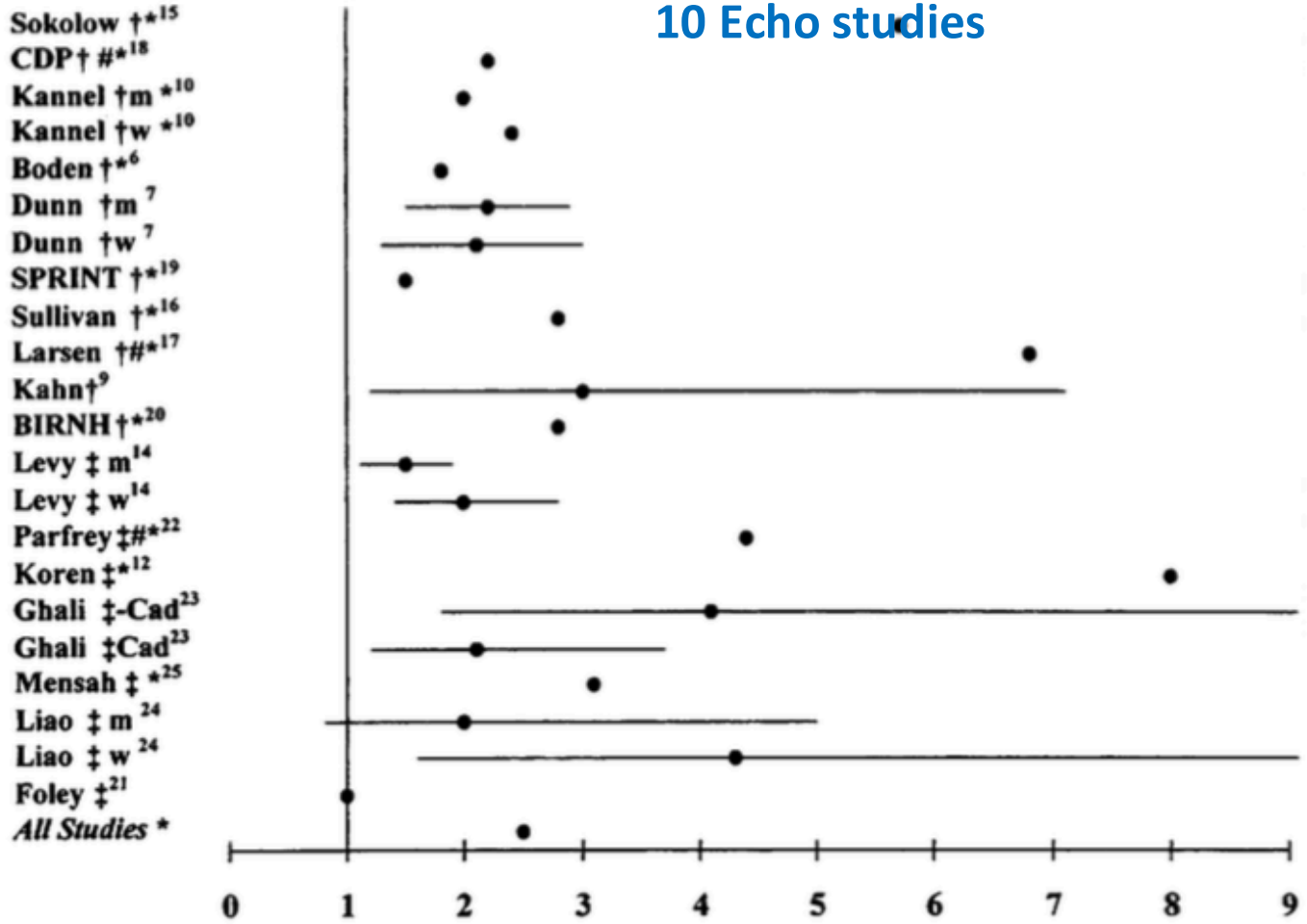


Schillaci et. al. Hypertension 2000;35:580

Hypertension Pathophysiology

Prognostic Association with LVH

12 ECG studies
10 Echo studies



Vakili et al. Am Heart J 2001;141:334

Hypertension Pathophysiology

Prognostic Association with LVH Regression

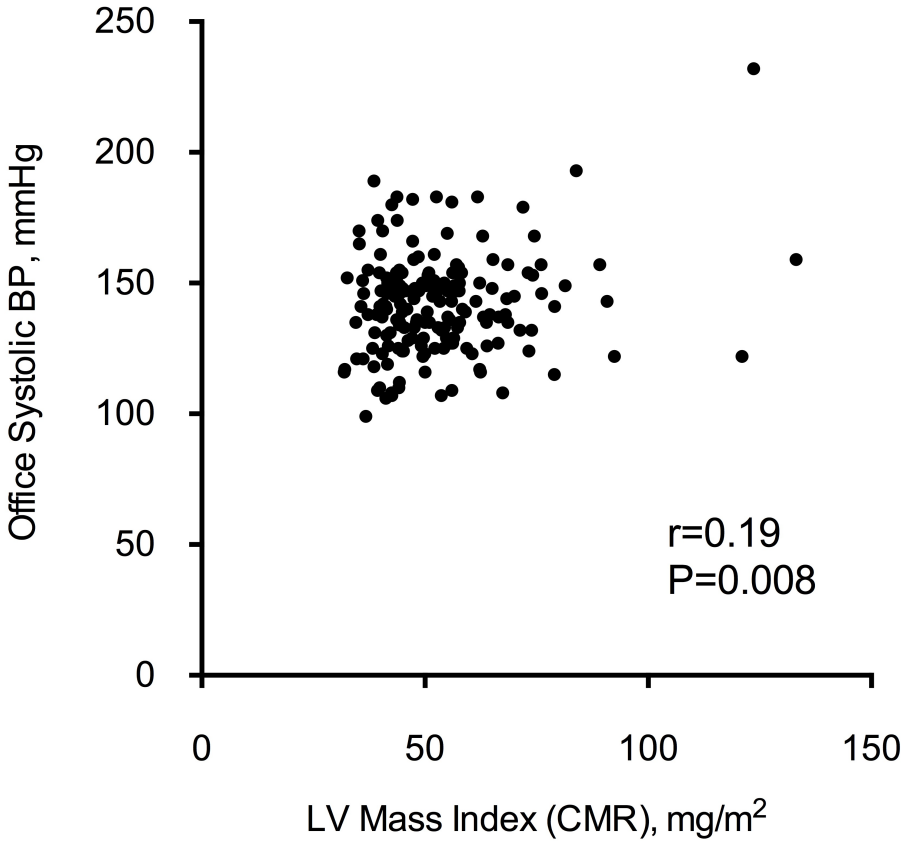
In-Treatment LV Mass Measure and End Point	HR (95% CI)	*P* Value
LVMI decrease of 25.3*†		
Composite	0.78 (0.65-0.94)	.009
CV mortality	0.62 (0.47-0.82)	.001
Myocardial infarction	0.85 (0.62-1.17)	.33
Stroke	0.76 (0.60-0.96)	.02
All-cause mortality	0.72 (0.59-0.88)	.002
LVMI decrease of 25.3*‡		
Composite	0.84 (0.68-1.03)	.10
CV mortality	0.66 (0.49-0.90)	.009
Myocardial infarction	0.91 (0.64-1.32)	.63
Stroke	0.90 (0.67-1.20)	.48
All-cause mortality	0.74 (0.59-0.93)	.008

†Adjusted for baseline LVMI, treatment, and blood pressure lowering.
‡Adjusted for baseline LVMI, treatment, blood pressure lowering, age, smoking, diabetes, prior stroke, prior myocardial infarction, and heart failure.

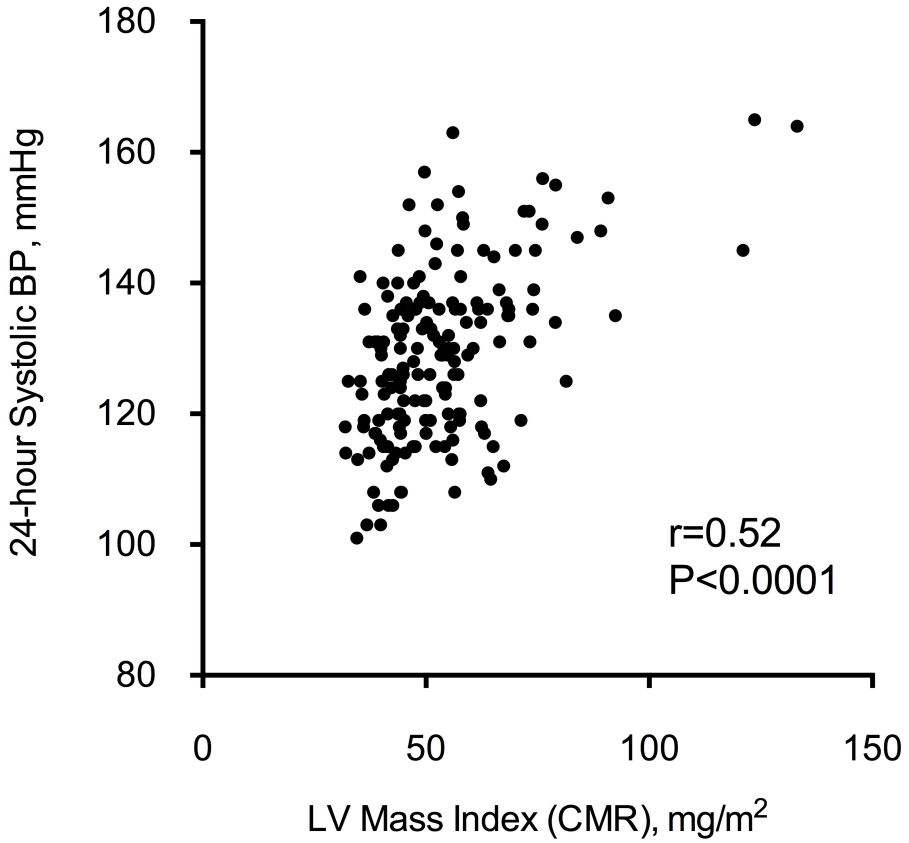
Devereux et. al. JAMA 2004;292:2350

Hypertension Pathophysiology

Association between BP and LVM



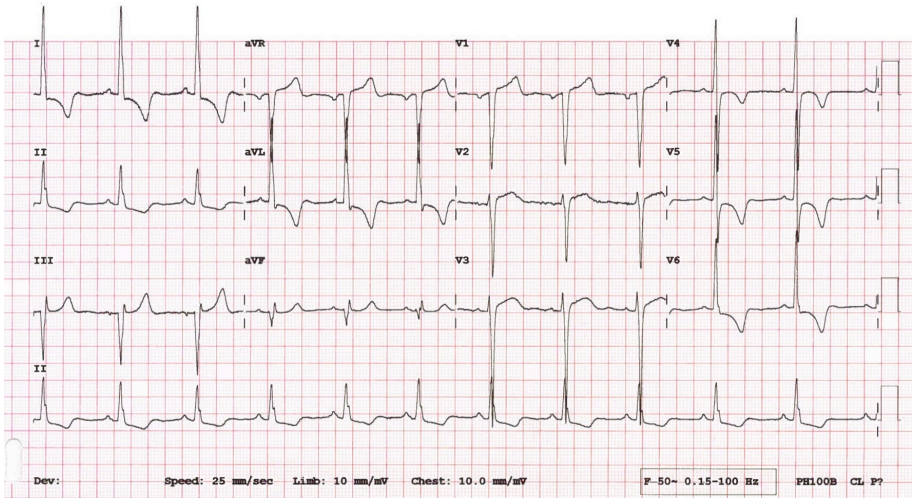
OFFICE BP

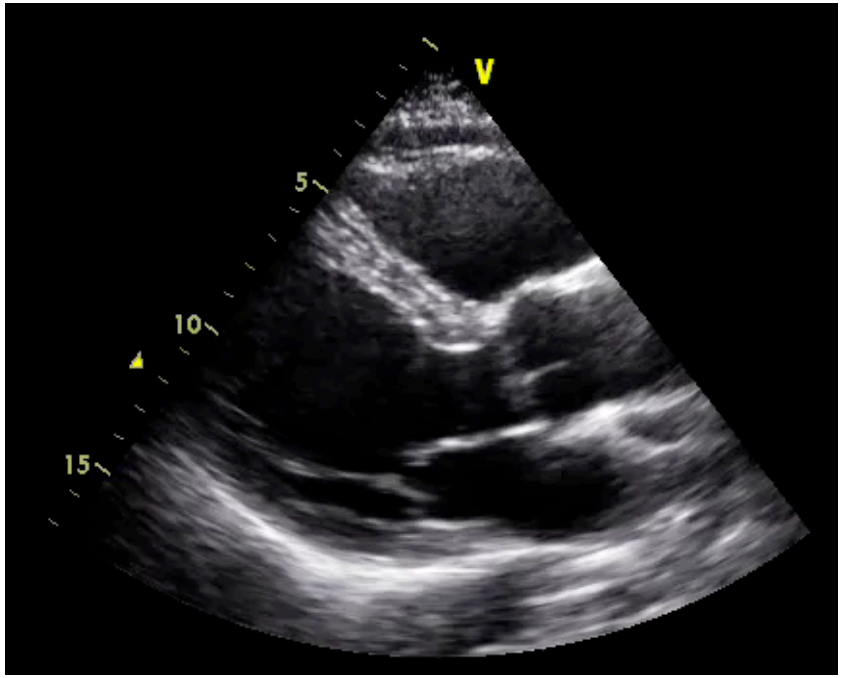


24 Hour BP

Myocardial Response to Hypertension

Conventional Methods of Assessment



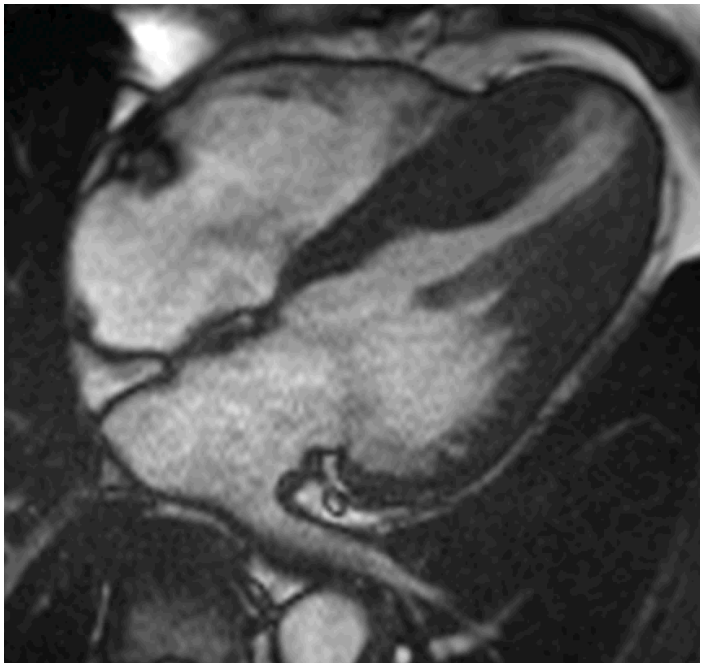


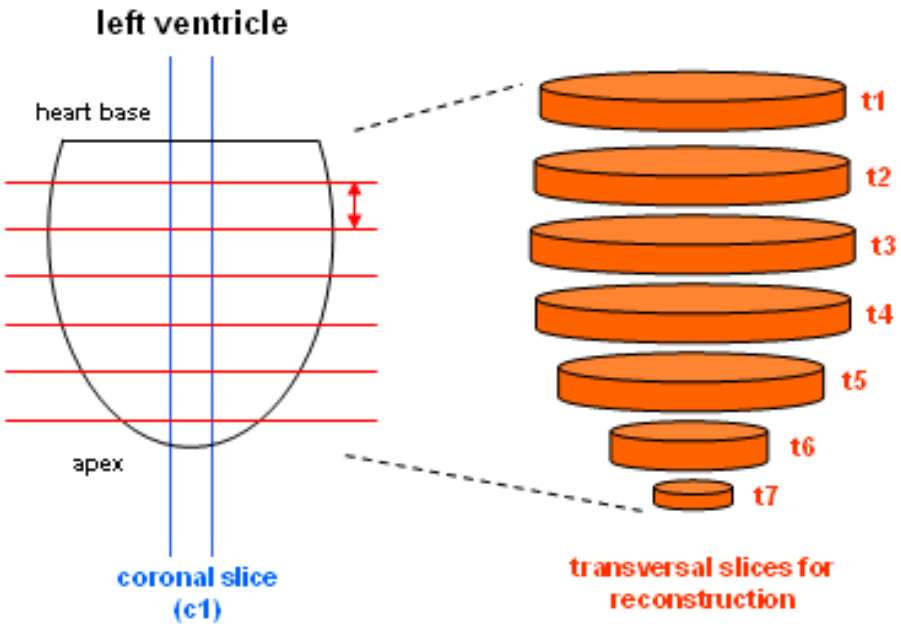
Electrocardiogram

Echocardiogram

Myocardial Response to Hypertension

Why Cardiovascular Magnetic Resonance?





- Highly reproducible
- Avoid any geometric/mathematical assumptions in estimating mass and volumes

Cardiac Assessment with CMR

	Echocardiography		CMR		Reduction in Sample Size by CMR
	SD	Sample Size	SD	Sample Size	
Total study group					
10-ml change in end-diastolic volume	13.5	39	6.7	10	74%
10-ml change in end-systolic volume	14.0	42	5.4	7	83%
10-ml change in stroke volume	13.1	37	5.2	6	84%
3% absolute change in ejection fraction	6.1	87	2.1	11	87%
10-g change in LV mass	25.0	132	7.7	13	90%
Normals					
10-ml change in end-diastolic volume	6.4	9	4.3	4	55%
10-ml change in end-systolic volume	7.0	11	2.8	2	81%
10-ml change in stroke volume	8.0	14	4.0	4	71%
3% absolute change in ejection fraction	5.6	73	1.7	7	90%
10-g change in LV mass	15.9	54	4.2	4	93%
Heart failure					
10-ml change in end-diastolic volume	17.6	66	7.6	13	80%
10-ml change in end-systolic volume	19.7	82	7.4	12	85%
10-ml change in stroke volume	18.0	69	5.9	8	88%
3% absolute change in ejection fraction	7.0	115	2.4	14	88%
10-g change in LV mass	30.4	194	9.6	20	90%
LV hypertrophy					
10-ml change in end-diastolic volume	13.9	41	7.3	12	71%
10-ml change in end-systolic volume	12.2	32	4.6	5	84%
10-ml change in stroke volume	11.5	28	5.5	7	75%
3% absolute change in ejection fraction	5.9	82	2.2	12	85%
10-g change in LV mass	26.9	152	8.4	15	90%

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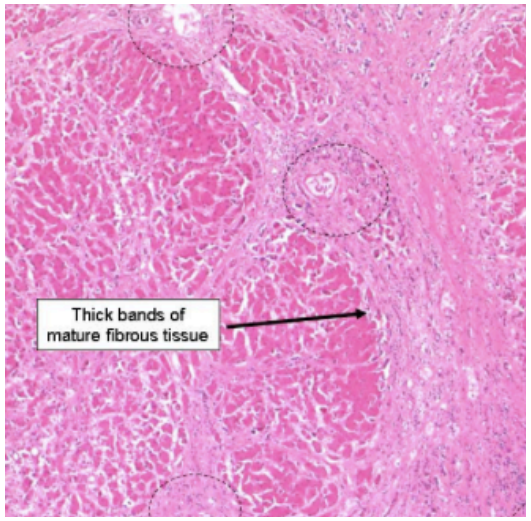
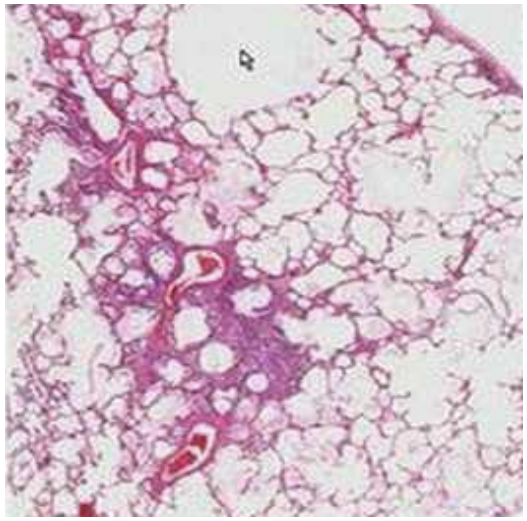
Grothues F, et al Am J Cardiol. 2002;90:29

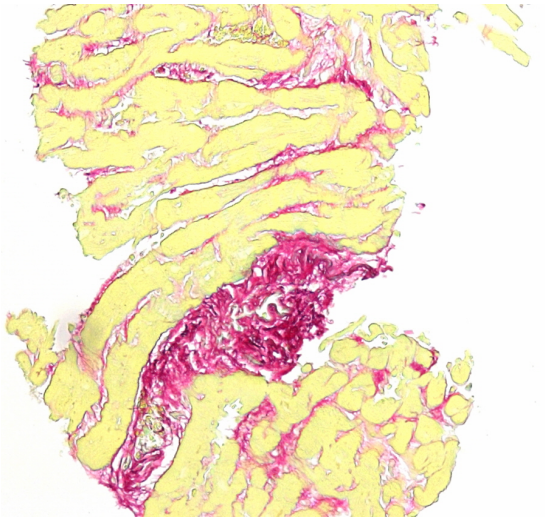
Fibrosis is Bad News!



Liver cirrhosis



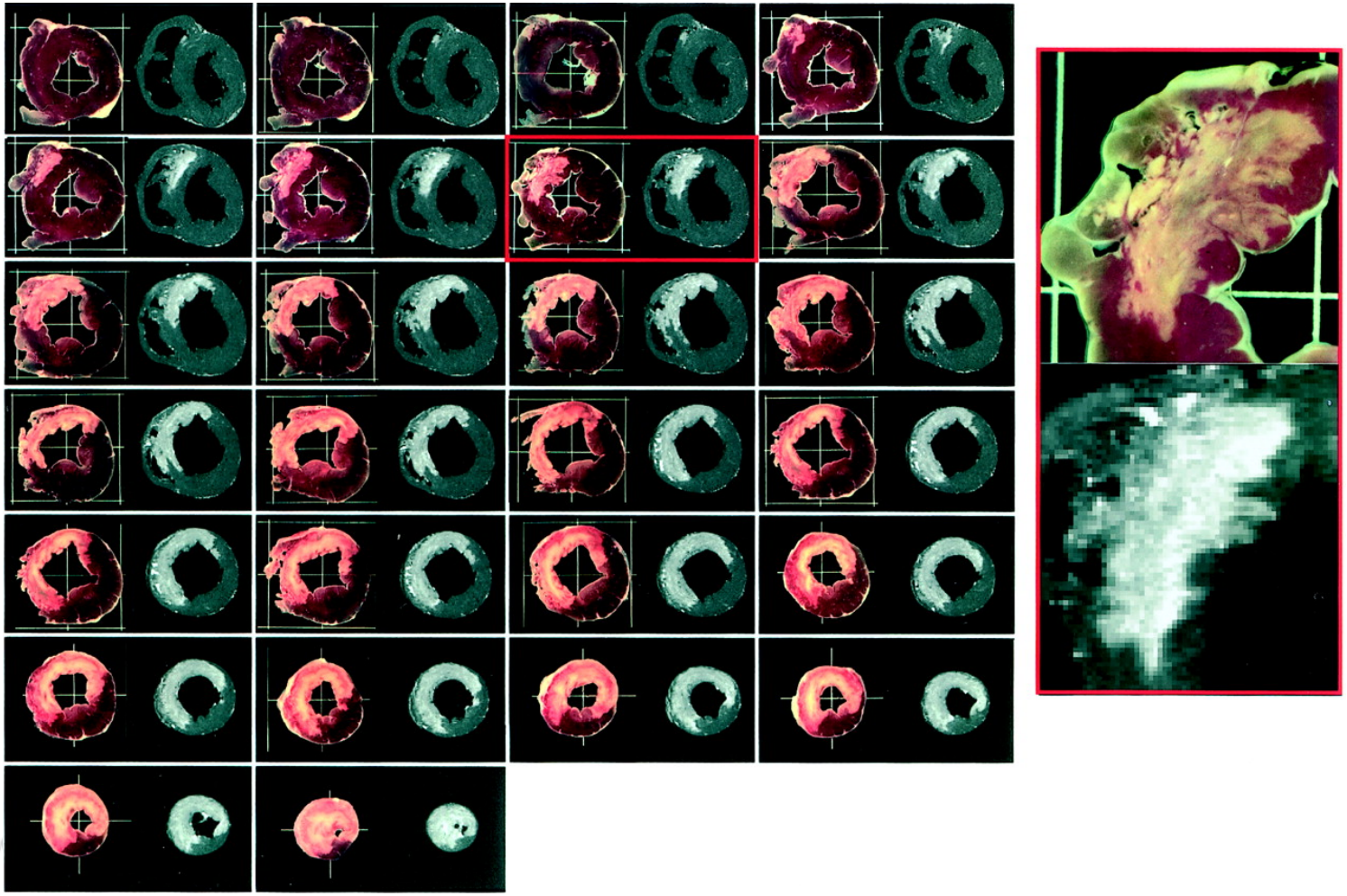
Chronic obstructive pulmonary disease



Cardiac Fibrosis

Gold standard: Invasive Tissue Biopsy

Non-invasive Assessment of Fibrosis

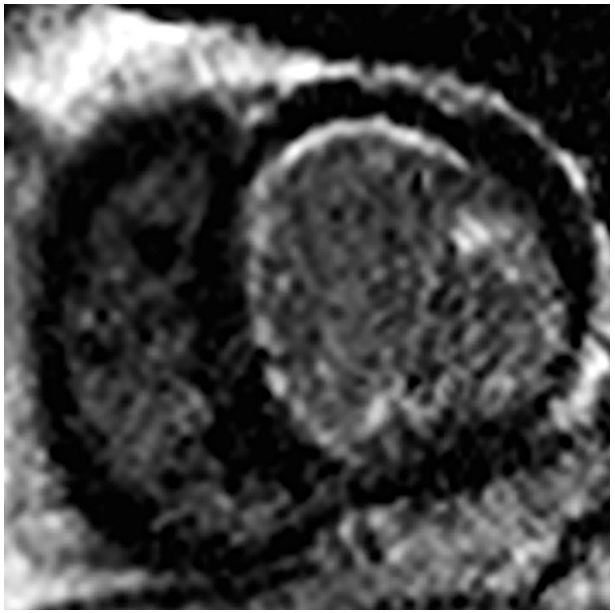


Kim et al. Circulation 1999;100:1992

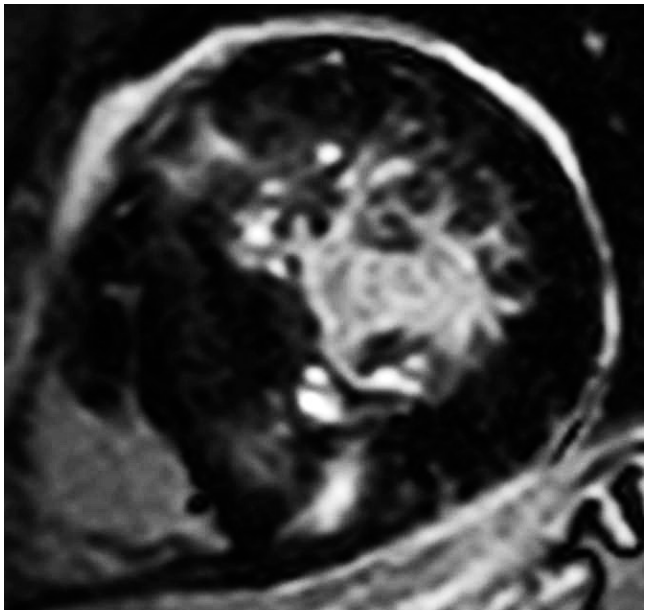
Myocardial Response to Hypertension

Why Cardiovascular Magnetic Resonance?

Myocardial Infarction

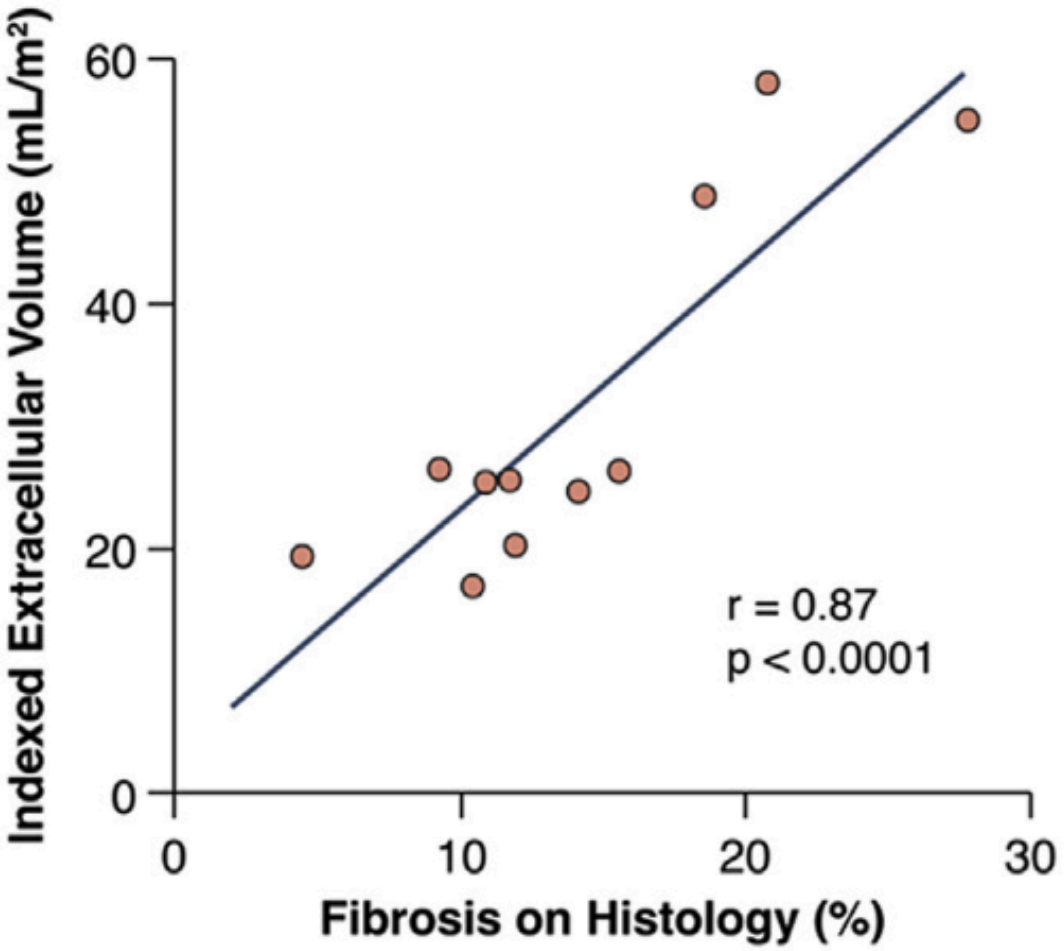


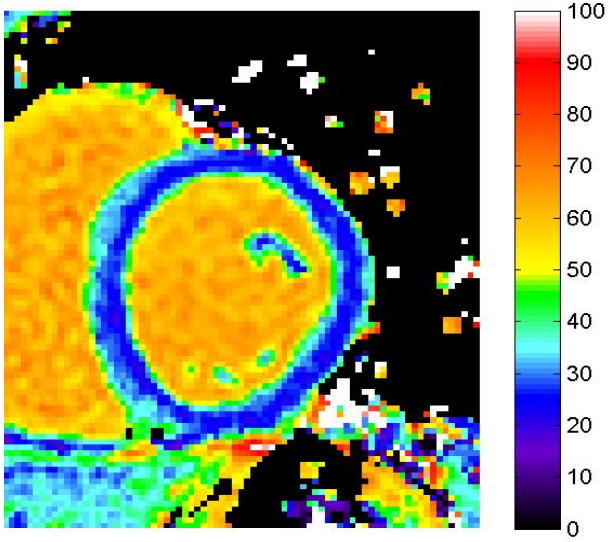
Non ischemic fibrosis



Myocardial Response to Hypertension

Why Cardiovascular Magnetic Resonance?



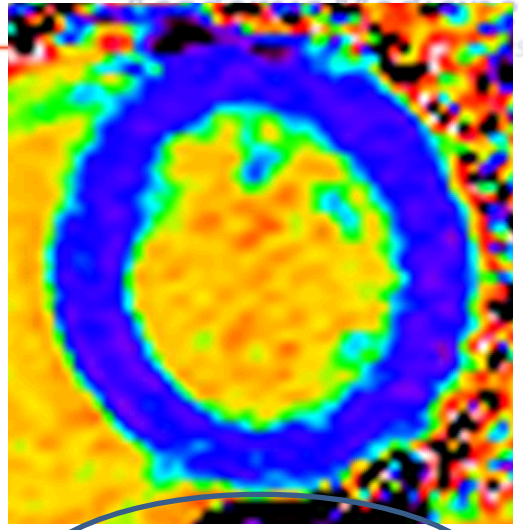


Chin et. al. JACC Imaging 2016 Dec 30 [Epub ahead of print]

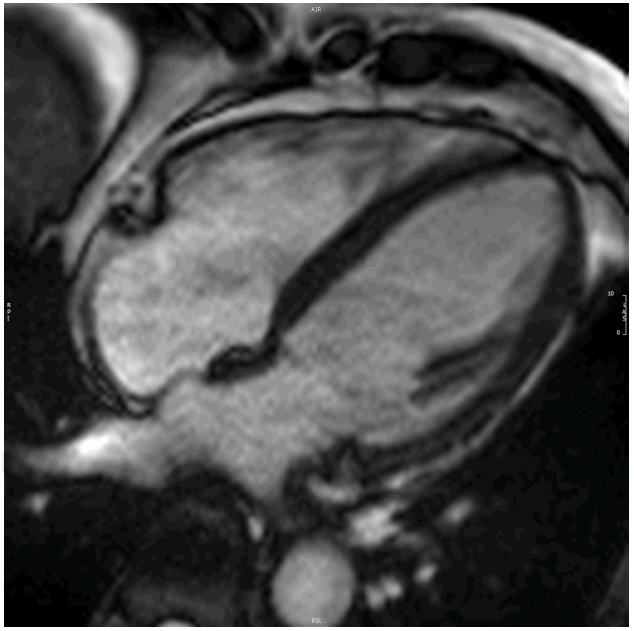
Myocardial Response to Hypertension

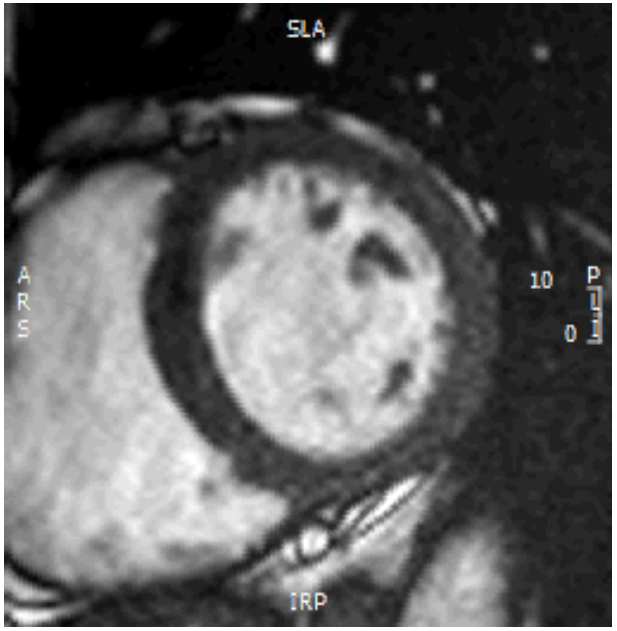
A Heterogeneous Response

74 year old male
Hypertension treated for 15 years
24 hour blood pressure 143/74
Normal LV function
Normal LV mass
No myocardial fibrosis/Normal interstitial volume



Interstitial volume = 12.1mL/m²

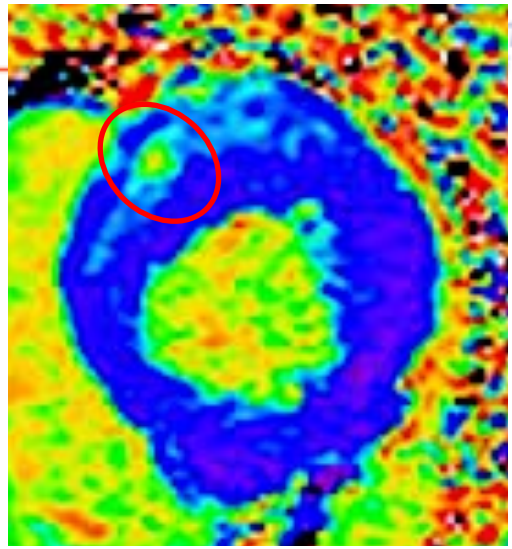




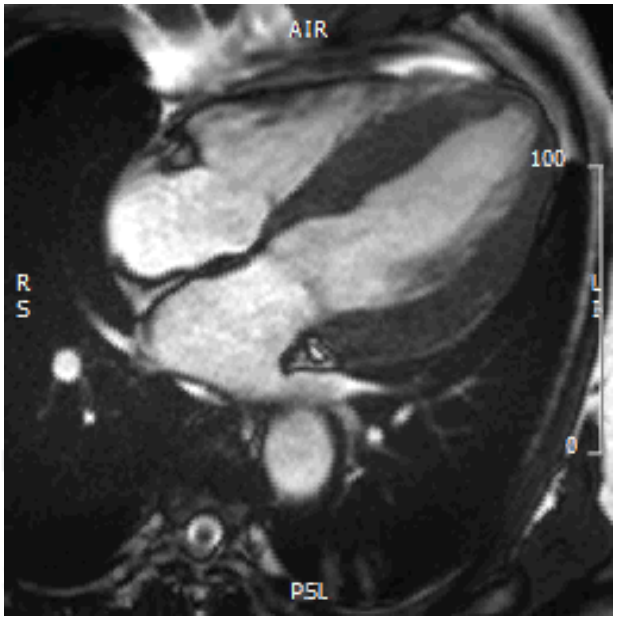
Myocardial Response to Hypertension

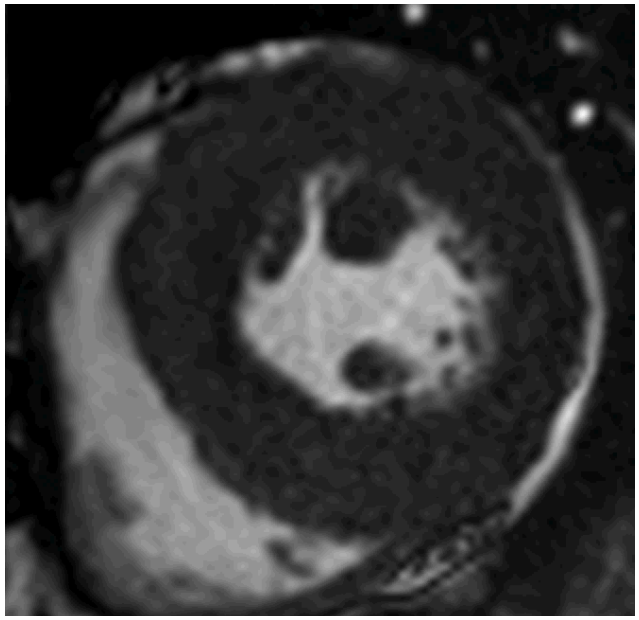
A Heterogeneous Response

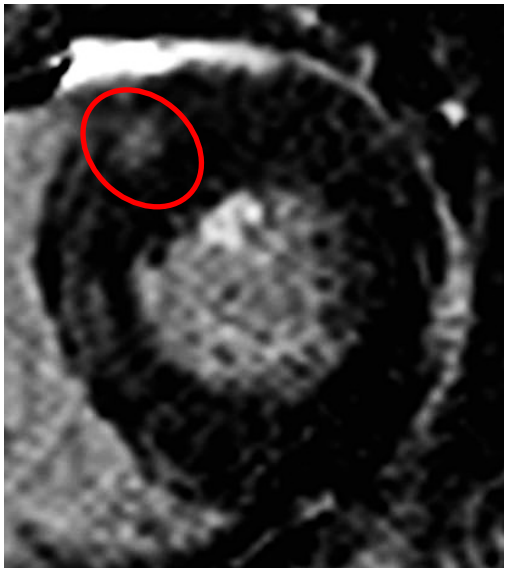
63 years old male
Hypertension treated for 2 years
24 hour blood pressure 145/72
Normal LV function
Left ventricular hypertrophy
Myocardial fibrosis in the basal anterior RV insertion



Interstitial volume = 32.8mL/m²



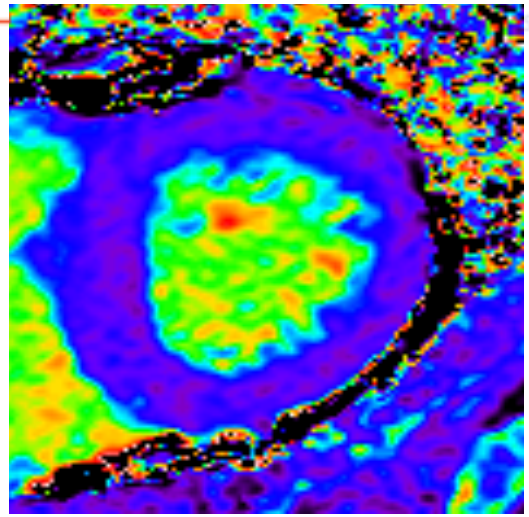




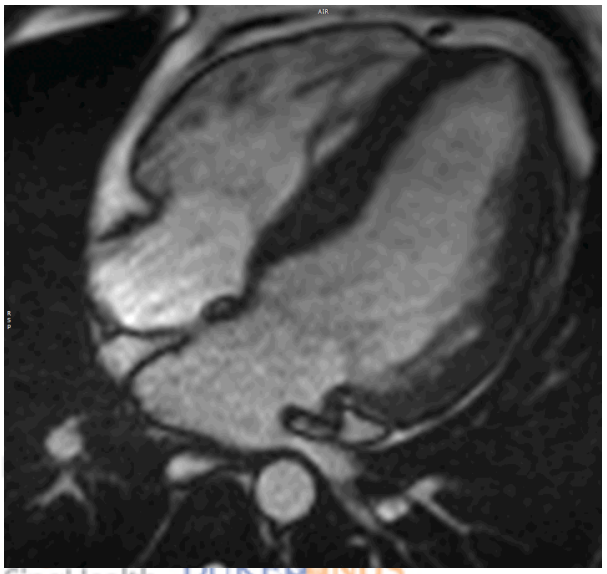
Myocardial Response to Hypertension

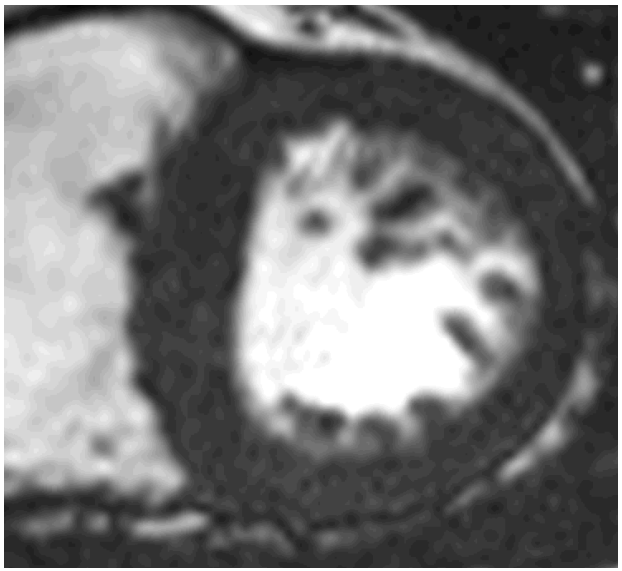
A Heterogeneous Response

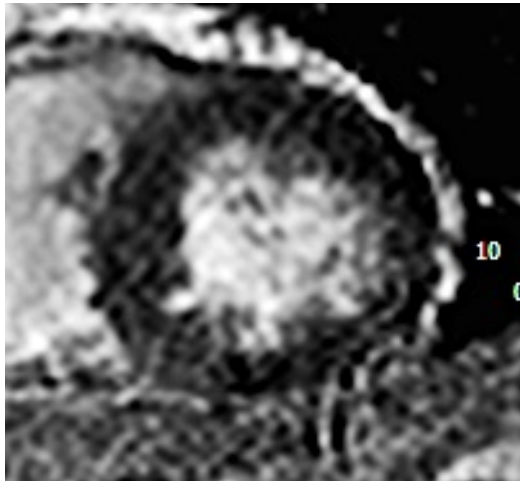
20 years old SAF enlistee
Diagnosed with hypertension at age 19
24 hour blood pressure 155/97
Mildly impaired left ventricular function (LVEF 43%)
Left ventricular hypertrophy
Patchy fibrosis



Interstitial volume = 16.0mL/m²







REMODEL Hypertension Program

Academic Medicine
improving patients' lives

REsponse of the MyOcarDium to HypErtrophic Conditions in the AduLt Population

- Risk stratification and natural history of patients with hypertension
- Identification of novel targeted therapies
- Empowering patients in the management of hypertension

Partners in Academic Medicine

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REMODEL

REMODEL Hypertension Program

Patient Population

Essential hypertension

No cardiovascular events

Newly diagnosed to resistant HTN

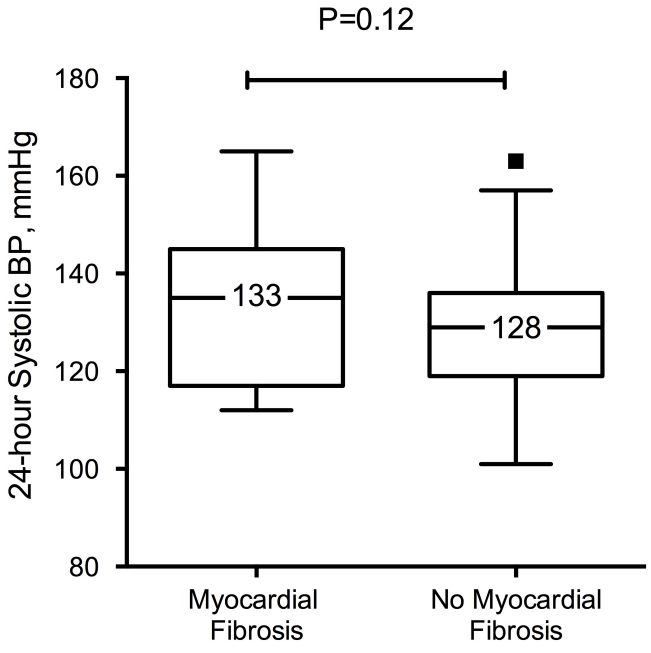
- 24 hour blood pressure monitoring
- Echocardiography/tonometry
- Cardiovascular MRI
- Serum/blood collected and stored
- Urine microalbuminuria
- Retinal imaging

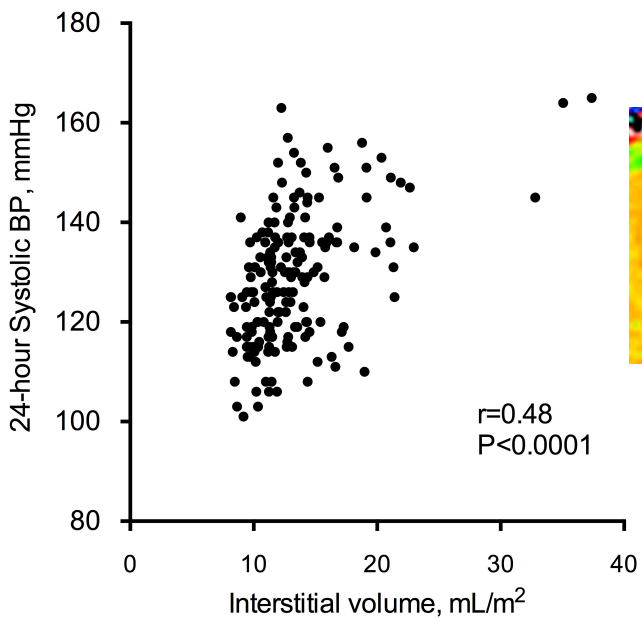
REMODEL Hypertension Program

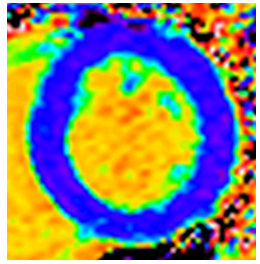
Academic Medicine
improving patients' lives

Myocardial Fibrosis as a Potential Treatment Target

- **27%** had left ventricular hypertrophy defined on cardiovascular magnetic resonance
- **29%** of those with LVH on CMR had myocardial fibrosis







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Myocardial Fibrosis as a Potential Treatment Target

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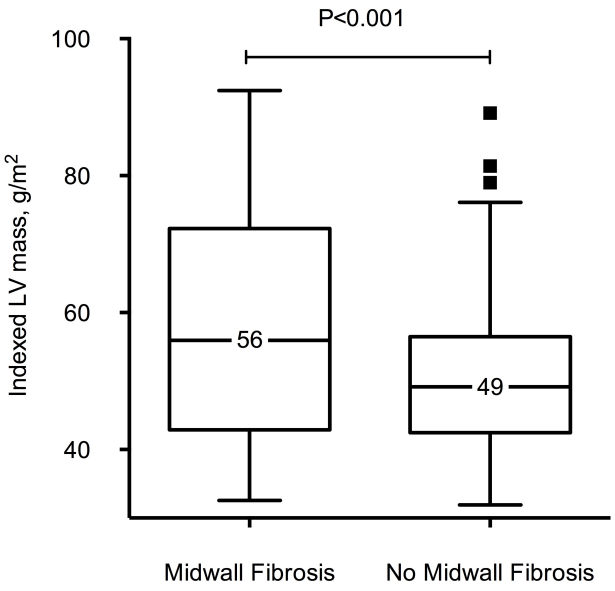

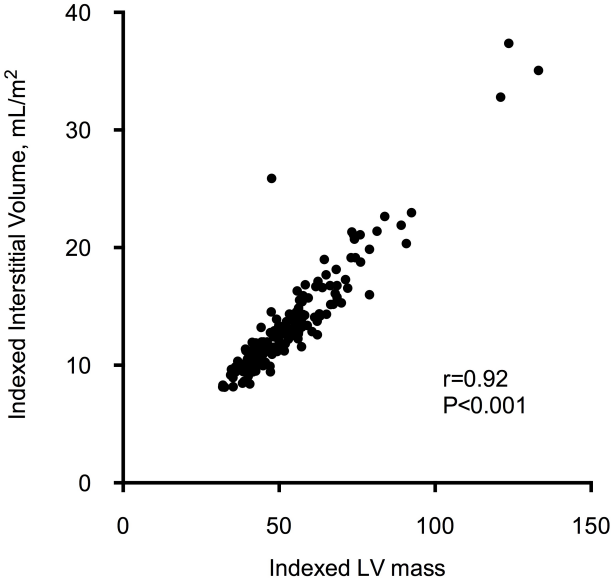

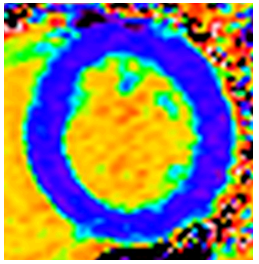

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Key Messages

- Peripheral blood pressure has inherent limitations and does not reflect myocardial response accurately

- Cardiovascular magnetic resonance has increased our knowledge of HHD:
  - Accurate and reproducible measurements
  - Tissue characterization

- Myocardial fibrosis is a potential target for therapies in the management of hypertensive heart disease

Welcome to FIBROTARGETS website

The Fibro-Targets (Targeting cardiac fibrosis for heart failure treatment) project is a multi-disciplinary program involving 11 partners ambitioning "the identification, characterisation and validation of in vitro and in vivo models of novel therapeutically relevant targets" for myocardial interstitial fibrosis (MIF) in heart failure.

Heart failure is a serious disease since it is often irreversible. It is estimated that more than 6.5 million people suffer from heart failure in Europe. It is the leading cause of hospitalization for patients over the age of 65. The incidence is increasing at an alarming rate because of an aging population and the burden of cardiovascular risk factors (diabetes, obesity and high blood pressure). Early interventions targeting key mechanisms, including myocardial interstitial fibrosis, could slow down progression to heart failure.

- **Identification and validation of biomarkers associated with myocardial fibrosis**
- **Developing anti-fibrotic therapies for HF prevention with the aim of regression fibrosis**

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ACKNOWLEDGEMENTS

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National Medical Research Council

- NRF-MOH Healthcare Research Scholarship (MCI) 2008
- NRF-MOH Healthcare Research Scholarship (PhD) 2012
- PhD Seed Funding 2015
- NMRC Transition Award 2016

National Heart Center Singapore

- Professor Stuart Cook
- Professor Carolyn Lam
- Professor Terrance Chua
- Professor Tan Ru San
- Professor Derek Hausenloy
- Dr. Le Thu Thao (Research Fellow)
- Dr. Su Boyang (Research Fellow)
- Dr. Jennifer Bryant (MR Research Fellow)
- Dr. Yiu-Cho Chung (MR Physicist)

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