



1



2

Disclosures



Conflict of Interest - Licensed patents for the use of pacemakers for the prevention and treatment of heart failure with preserved ejection fraction and atrial fibrillation. Medtronic Consultant.

Funding - Heart Rhythm Society, Martin LeWinter Fund, NIH, AHA, Medtronic, Engdahl Family Foundation.

All relevant financial relationships have been mitigated

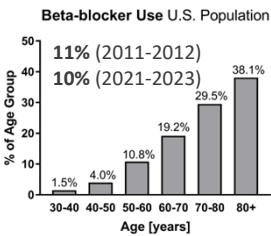
3

The Betablocker Saga

4

Betablocker Cardioprotection Myth

“ low heart rates are better ”



TRUE BUT

Beneficial in HFrEF not HFrEF with AF

Lower Blood Pressure Inferior to Other BP Medications

Less Angina no Mortality Reduction

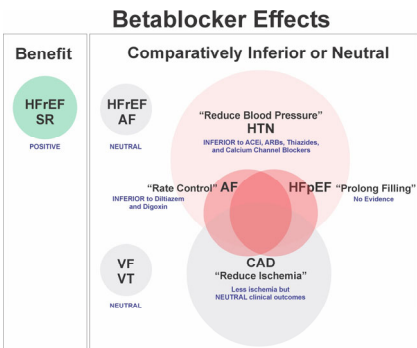
Rate Control in Atrial Fibrillation Inferior to Diltiazem and Digoxin

Prolong Ventricular Filling Higher Filling Pressures

National Center for Health Statistics. National Health and Nutrition Examination Survey: 2011-2012, 2021-2023

5

Betablocker Effects and RCTs



Randomized Betablocker Evidence

	BENEFIT	NEUTRAL	COMPARATIVELY INFERIOR
HTN			
CAD			
HFrEF			
AF			
HFrEF	Sinus Rhythm	Atrial Fibrillation	
VT/VF			

unpublished

6

Contemporary Evidence

ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

M.T. Dransfield, H. Voelker, S.P. Bhatt, K. Brenner, R. Casaburi, C.E. Come, J.A.D. Cooper, G.J. Criner, J.L. Curtis, M.L.K. Han, U. Hatipoğlu, E.S. Helgeson, V.V. Jain, S. Kalhan, D. Kaminsky, S. Kaner, K.M. Kunisaki, A.A. Lambert, M.R. Lammi, S. Lindberg, B.J. Make, F.J. Martinez, C. McEvoy, R.J. Panos, R.M. Reed, P.D. Scanlon, F.C. Sciruba, A. Smith, P.S. Sriram, W.W. Stringer, J.A. Weingarten, J.M. Wells, E. Westfall, S.C. Lazarus, and J.E. Connett, for the BLOCK COPD Trial Group^a

Stopped for futility and safety concerns

➤ Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial

COMMIT (Early Intravenous and Oral Metoprolol in Myocardial Infarction Trial) collaboration group^a

Summary
Background Despite previous randomised trials of early β -blocker therapy in the emergency treatment of myocardial infarction (MI), uncertainty has persisted about the value of adding it to current standard interventions (eg, aspirin and fibrinolytic therapy), and the balance of potential benefits and hazards is still unclear in high-risk patients.

More HF and cardiogenic shock

Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial

POISE Study Group^a

Summary
Background Trials of β blockers in patients undergoing non-cardiac surgery have reported conflicting results. This randomised controlled trial, done in 190 hospitals in 23 countries, was designed to investigate the effects of perioperative β blockers.

More deaths

ORIGINAL ARTICLE

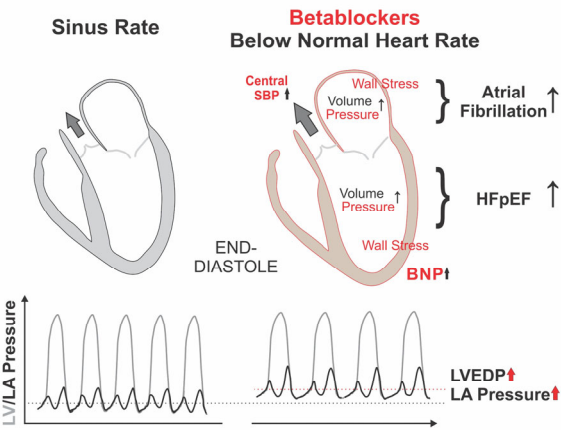
Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction

T. Yndegegn, B. Lindahl, K. Mars, J. Alfredsson, J. Benatar, L. Brandin, D. Erlinge, O. Hallen, C. Held, P. Hjalmarsson, P. Johansson, P. Karlström, T. Kellerth, T. Marandi, A. Ravn-Fischer, J. Sundström, O. Östlund, R. Hofmann, and T. Jernberg, for the REDUCE-AMI Investigators^a

No benefit

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Lower Heart Rate ➔ Higher Filling Pressure



Below Normal Heart Rates

Higher Filling Pressures
Chronotropic Incompetence

➡ Dyspnea on Exertion
Reduced Exercise Capacity
Weight Gain / Diabetes
Higher NT-proBNP levels

Betablocker “HFpEF in a pill”



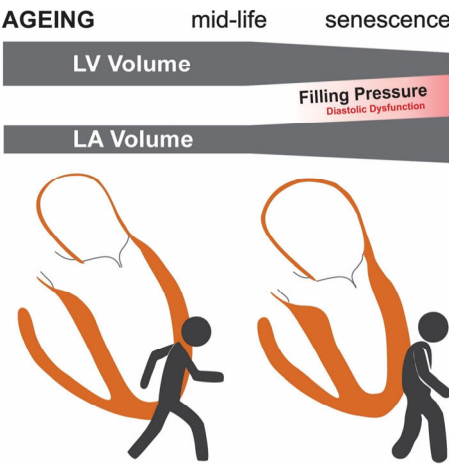
Meyer..LeWinter Circ HF 2019, Habel..Meyer IJCCRP 2023, Meyer..Lustgarten Europace 2023

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What Drives HFpEF and AF ?

9

High Filling Pressures Drive AF and HFpEF

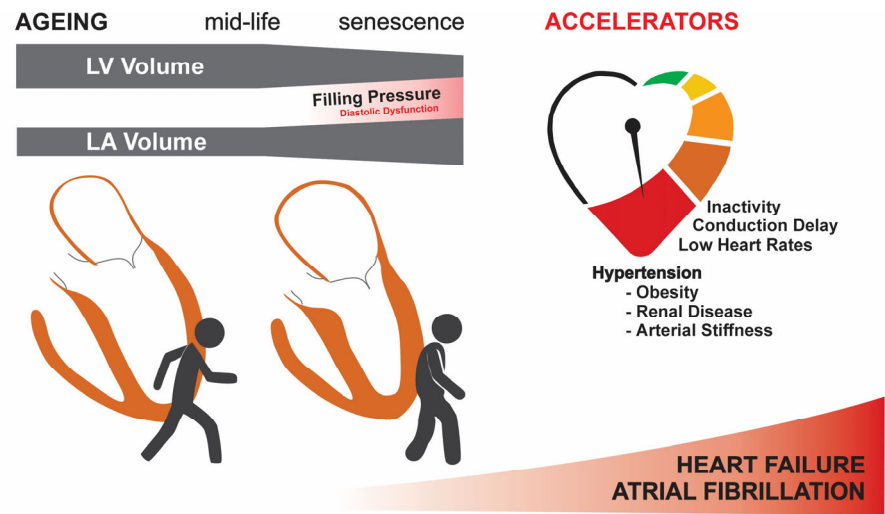


Khan..Meyer JACC HF 2023

Habel..Lustgarten.Meyer Heart Rhythm 2025

10

High Filling Pressures Drive AF and HFpEF



Khan..Meyer JACC HF 2023

Habel..Lustgarten.Meyer Heart Rhythm 2025

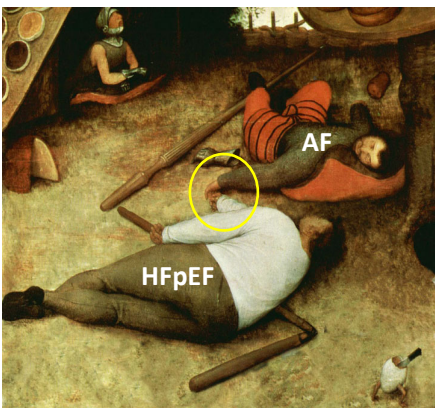
11

AF/HFpEF Twindemic

Two dishes - same ingredients



Pieter Bruegel the Elder The Land of Cockaigne 1567



Habel..Lustgarten.Meyer Heart Rhythm 2025

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Going to the Dark Side of Heart Rate



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Pacing for HFpEF

Contradicting Experts & Guidelines

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Bench - Animal Model - Patients



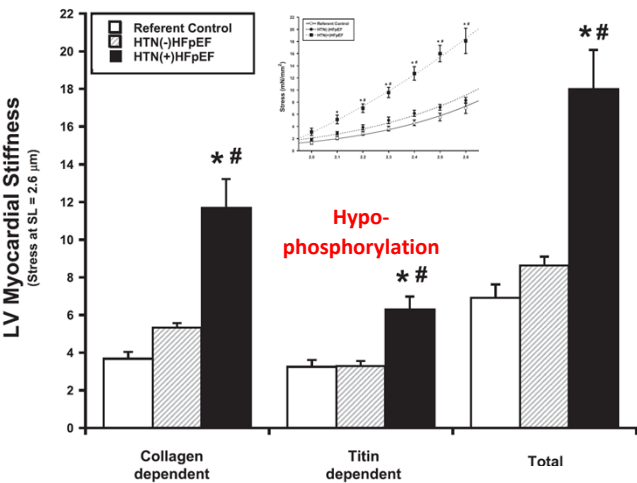
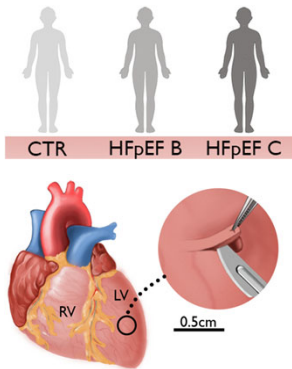
PACEMAKER SYSTEM
Normal Activation Sequence
↓
Accelerated Pacing

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Myocardial Stiffness

Regressive Remodeling + Fibrosis + Titin

Patient Biopsies

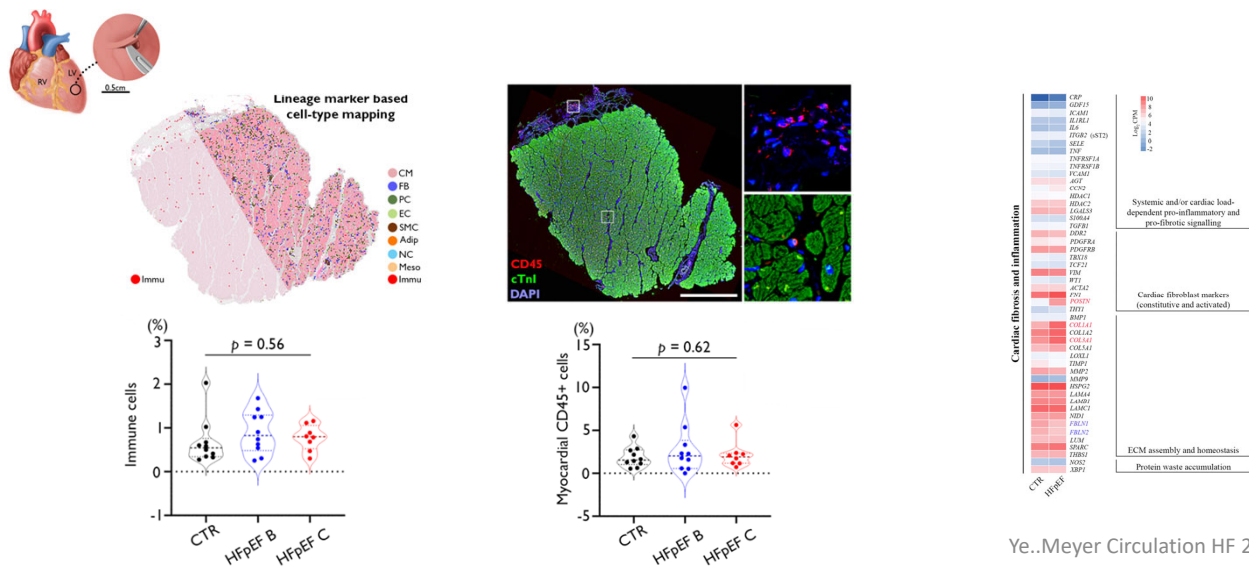


Zile..LeWinter Circulation 2015

18

Normal Abundance of Immune Cells

no pro-inflammatory pathway activation



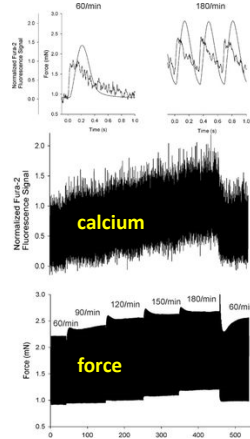
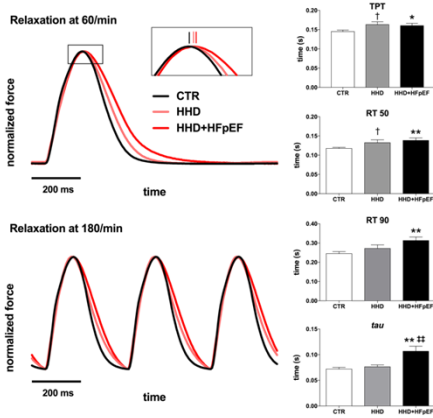
19

Slow Relaxation

[↑ Cellular Calcium]

Patient Biopsies

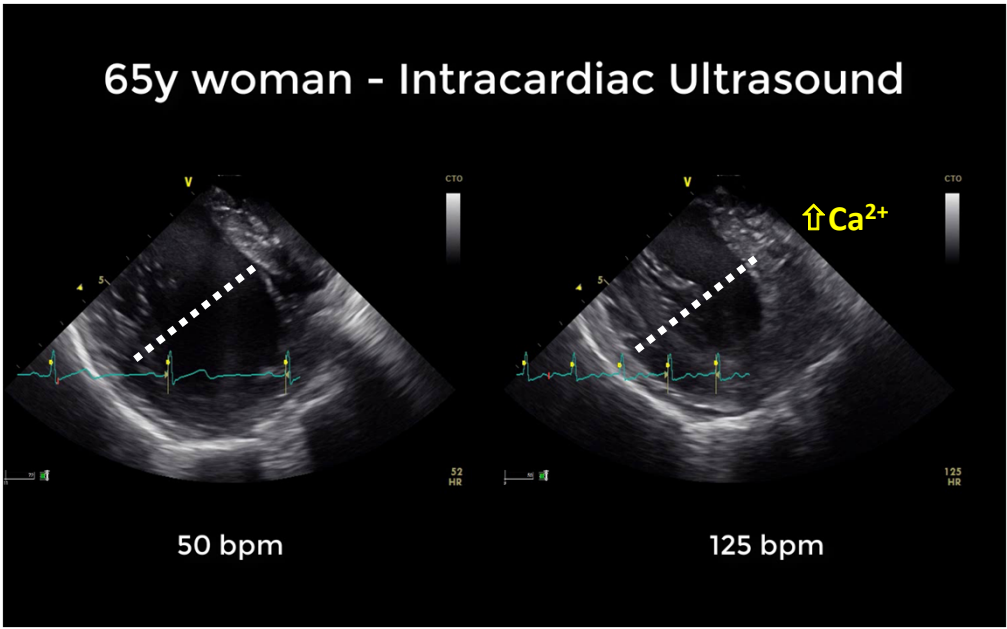
	CTR (n=13), ppm	HHD (n=10), ppm	HHD+HFpEF (n=8), ppm
Ca	188±97	209±139	351±77†
Na	1133±550	1386±556	1020±492
Cu	2.6±0.5	3.1±0.7	3.4±0.6‡
Fe	20.8±7.9	24.3±8.4	21.2±8.8
Mg	89±57	127±44	85±39
P	1084±521	1520±416	1114±396
S	993±426	1259±382	852±357
Zn	13.3±5.3	12.8±4.1	13.6±5.9



Selby..Meyer JACC 2011

Runte..Meyer Circulation HF 2017

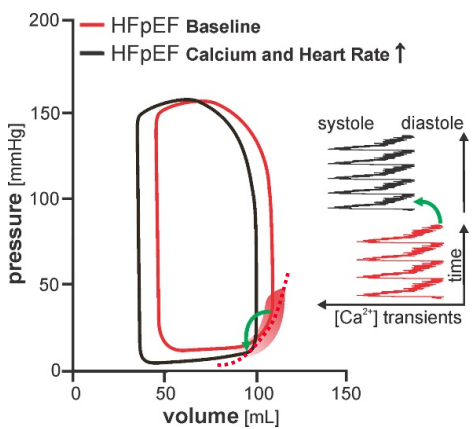
20



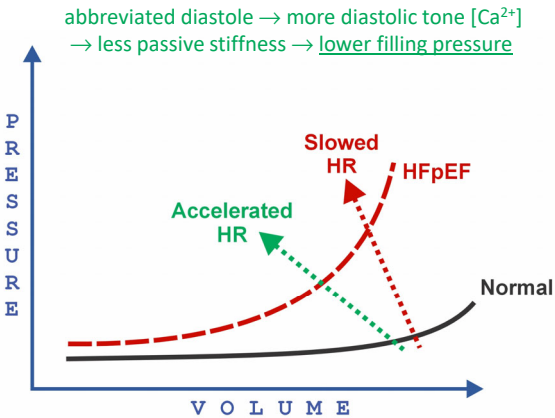
Silverman..Lustgarten.Meyer JAHA 2020

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In-vivo Translation of Augmented Ca^{2+} -Handling



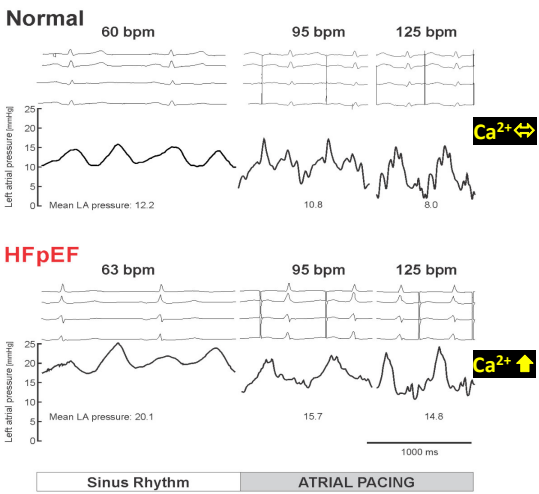
Meyer LeWinter Zile Circulation 2021



Modified from Infeld Heart Rhythm O2 2024

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Accelerated Pacing - HEMODYNAMIC EFFECT



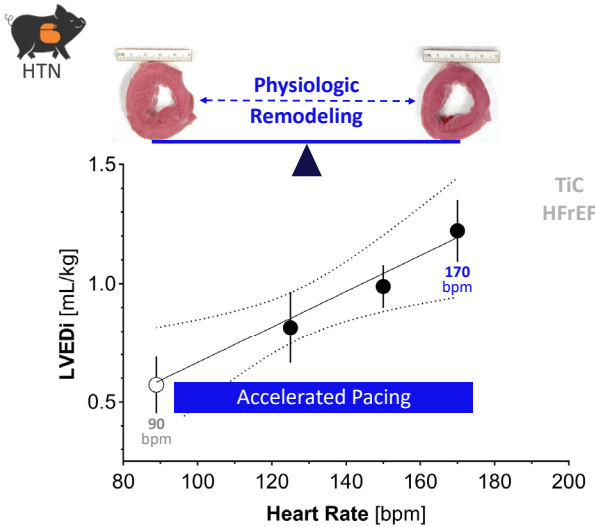
Elevated Resting Heart Rates
→ Lower Filling Pressures

Accelerated Pacing in HFpEF
LVEDP 17±5 mmHg → 9±3 mmHg
Atrial Decongestion

Silverman..Lustgarten.Meyer JAHA 2020

23

Accelerated Pacing - REMODELING EFFECT



PLASTICITY MODULATION
· athletic remodeling ·

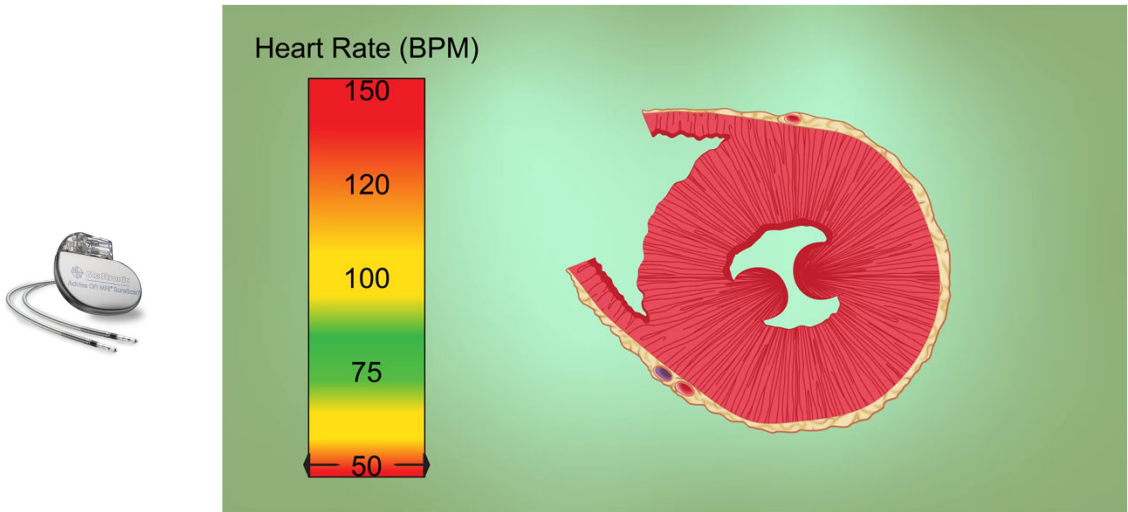
Accelerated Pacing
↑ LV Volume
↓ LV Thickness
↓ EF

Heart Rate = Dose
“rate-shape”

Klein..Meyer AJP 2017

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Accelerated Pacing - REMODELING EFFECT



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Normal Resting Heart Rates

1971-74 NHANES in 28,043 adults

60 - 100 bpm

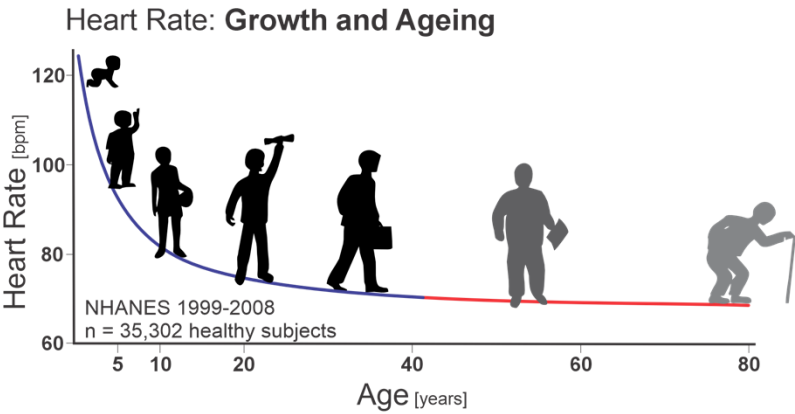
mean 80 bpm

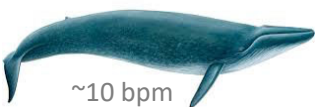
Gillum Public Health Rep 1992

26

Allometric Scaling of Heart Rate

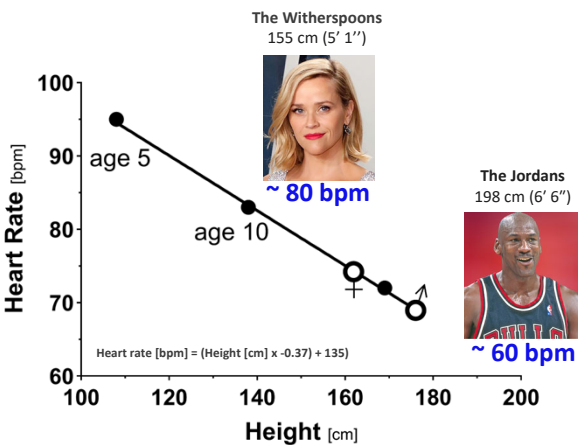

~600 bpm




~10 bpm

27

Heart Rate / Height Relationship



Population Data
60 - 100 bpm
2.5% of adults HR ≤ 60 bpm

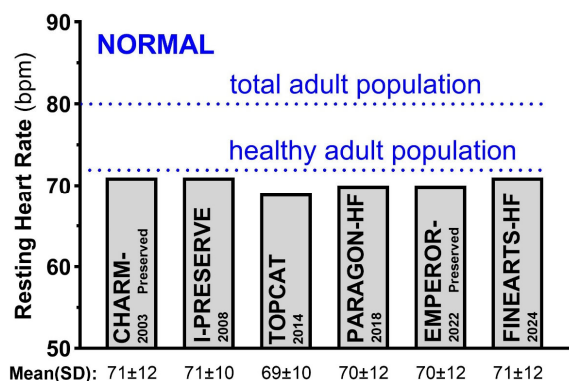


capilar Ar

Infeld..Meyer Heart RhythmO2 2021

28

Mean Heart Rates in HFpEF



Most HFpEF Patients Have Below Normal Heart Rates

⇒ **Less Betablocker** More Room to Breathe

Aiad..Meyer ESC HF 2025

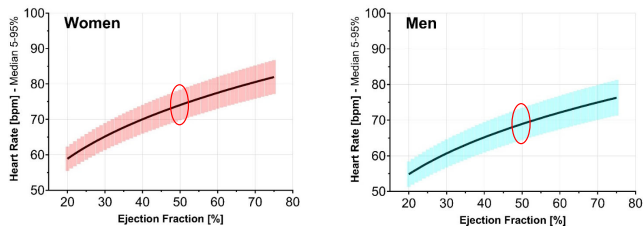
Meyer EHJ 2024

29

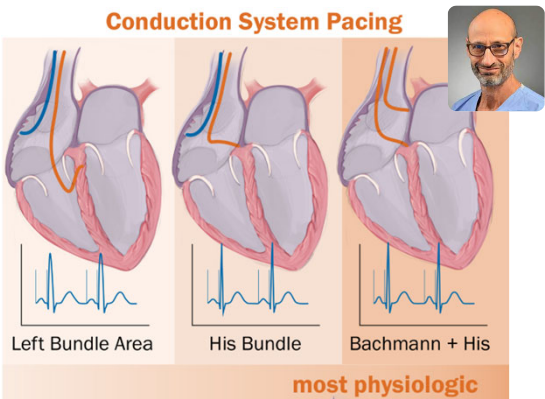
myPACE Algorithm

height-based EF-modified personalized heart rate

Safe and Efficacious Heart Rates Across EF Spectrum



EF change ➔ rate adjustment



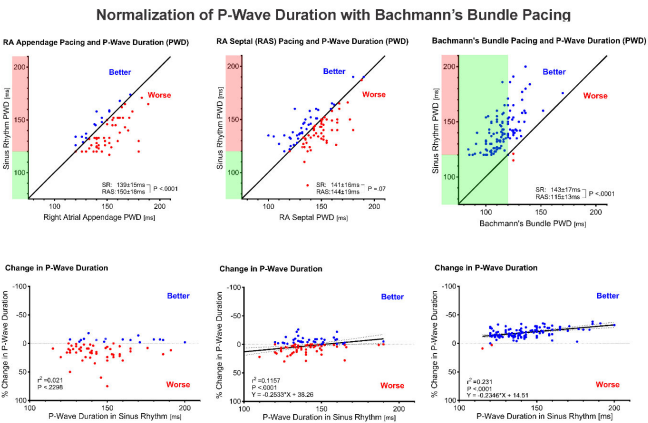
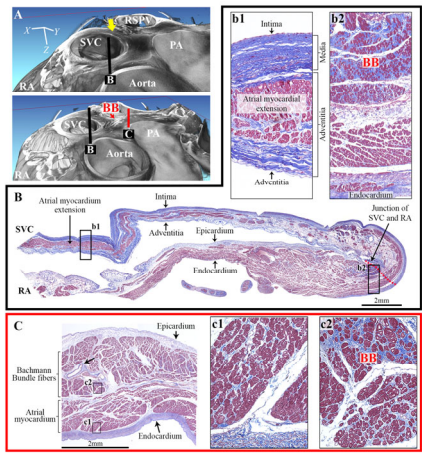
Infeld..Meyer Heart RhythmO₂ 2021

Infeld.Habel..Lustgarten.Meyer Heart RhythmO₂ 2024

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Bachmann Bundle Pacing

faster atrial activation



Heart Rhythm 2025 Lustgarten..Meyer

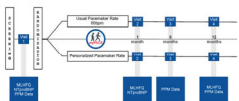
unpublished

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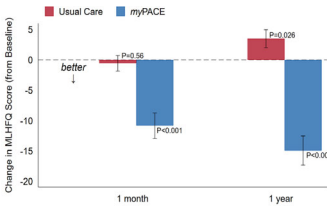
Safety and Feasibility of a Nocturnal Heart Rate Elevation—Exploration of a Novel Treatment Concept
HERNANDEZ C, YESSIRKANT, MICHAEL R, DILL, MICHAEL A, KERN, ROBERTA L, AND MARKUS MEYER
Bachmann's Bundle Pacing
Effects of a Higher Heart Rate on Quality of Life and Functional Capacity in Patients With Left Ventricular Diastolic Dysfunction
Krause-Waldberg, MD¹, Meyer R, MD², Arnold, MD³, David Lustgarten, MD⁴, PhD⁵, and Markus Meyer, MD⁶

myPACE

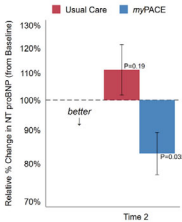
Accelerated Pacing 70-80bpm Usual Care 60bpm



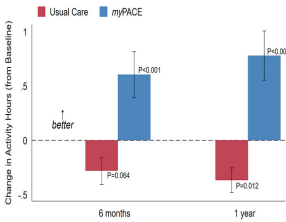
MLHFQ Health Status QoL



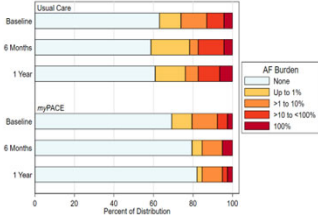
NT-proBNP



Physical Activity Hours



AF Burden



Date: Sat, Jan 18, 2025 at 5:01 AM
Subject: Attn: Dr Markus Meyer --- THANK YOU !!! The MyPACE algorithm has saved my life.

Infeld..Meyer JAMA Card 2023

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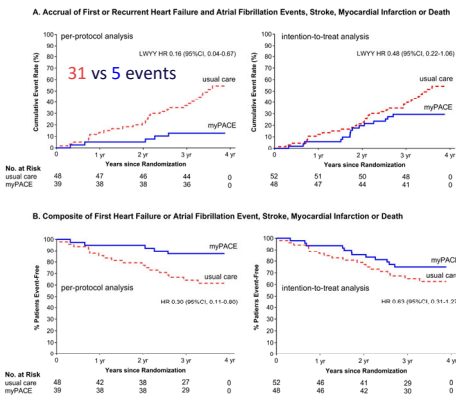
myPACE follow-up >3yr

Cardiac Plasticity

LV septum thinner 🤝
LV volume up 🤝
LA volume down 🤝
LVEF -3% 🤝

Wahlberg..Meyer JAHA 2024

Clinical Outcomes



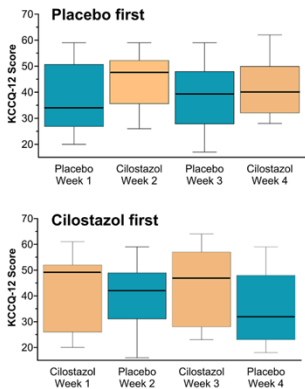
Infeld..Meyer JAMA Card 2025

33

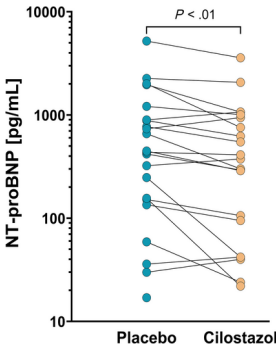
CLIP-HFpEF Cilostazol vs Placebo



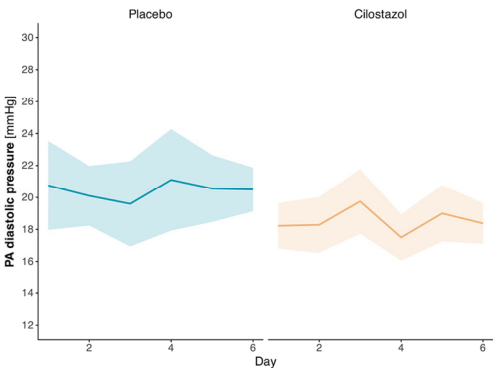
Health Status



NT-proBNP



Pulmonary Artery Pressure

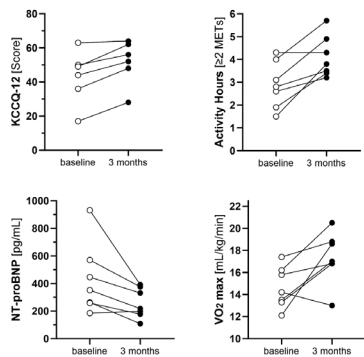


Aiad..Meyer ESC HF 2025

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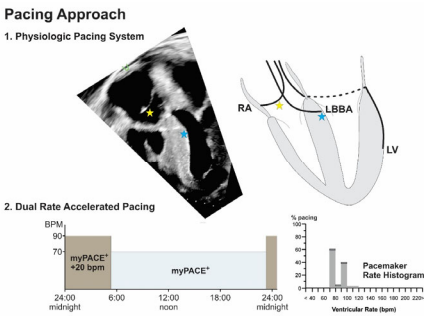
Other Populations to Benefit

Non-obstructive Hypertrophic Cardiomyopathy



Riaz..Weissler-Snir JACC 2024

Cardiac Amyloidosis



Meyer..Roukoz JACC CR 2024

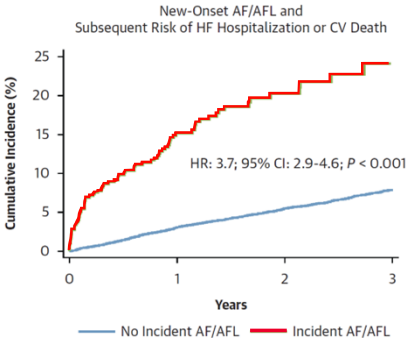
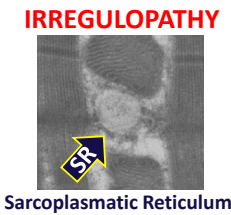
AF

ELEVATED RATE FLOOR
Lower Atrial Pressure
Prevents Pauses

Primary Prevention
Secondary Prevention

Other Populations to Benefit

AF

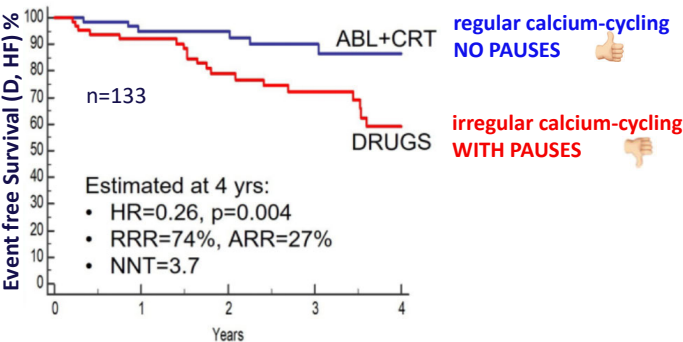


modified from Pabon..Vaduganathan JACC 2025

Pace-and-Ablate in AF

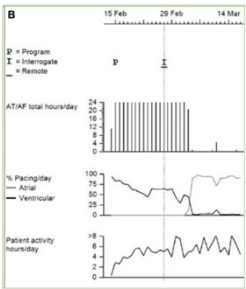
irregular → regular

APAF-CRT



Brignole..Van Gelder EHJ 2021

non-permanent AF accelerated comprehensive CSP



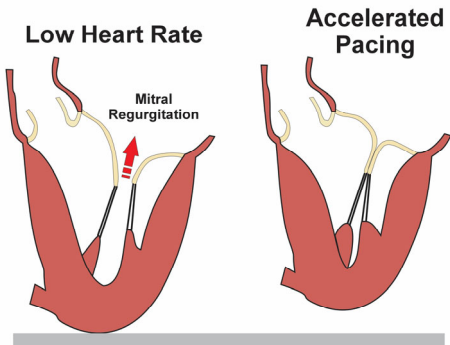
“Pace-and-Wait”

Habel..Lustgarten JACC CR 2025

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Mitral/Tricuspid Valve Regurgitation

closing-the-gap



Higher Heart Rates



Less Chordal Pull



Better Coaptation

unpublished

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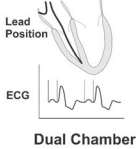


Pacemaker

from back-up to continuous pacing

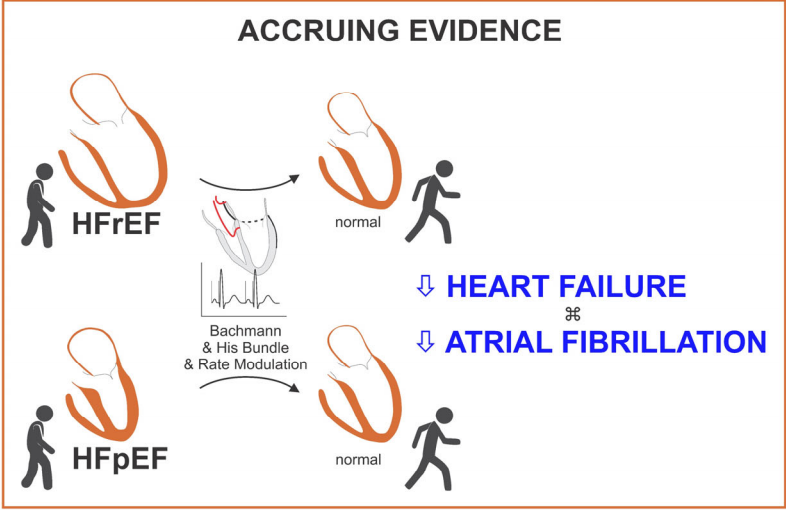


PAST



Lead Position
ECG
Dual Chamber

ACCRUING EVIDENCE



HFrEF normal
HFpEF normal

Bachmann & His Bundle & Rate Modulation

↓ **HEART FAILURE**
⌘
↓ **ATRIAL FIBRILLATION**

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Hemodynamic Booster + Rhythm Manager + FitBit + Plasticity Regulator

Atria

AV Node

Ventricles

Heart Rate Management
Arrhythmia Management
Activity Sensor

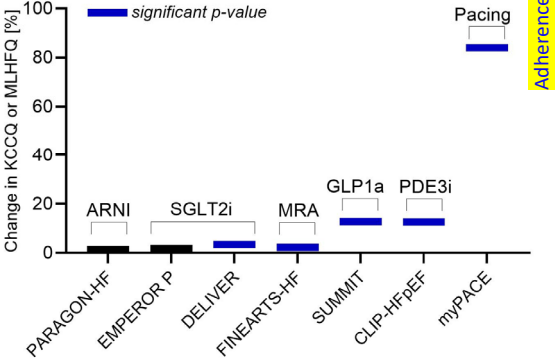
Atrial Synchronization
Atrial Preference Pacing (APP)
Anti-Tachycardia Pacing (ATP)
Atrial Rate Stabilization (ARS)

Rate Adaptive AV Pacing (RAAV)
Adaptive CRT

Ventricular Synchronization
Anti-Tachycardia Pacing (ATP)
Ventricular Rate Stabilization (VRS)

Allosteric Pacing
EF adjusted Pacing

Relative Improvement in Health Status

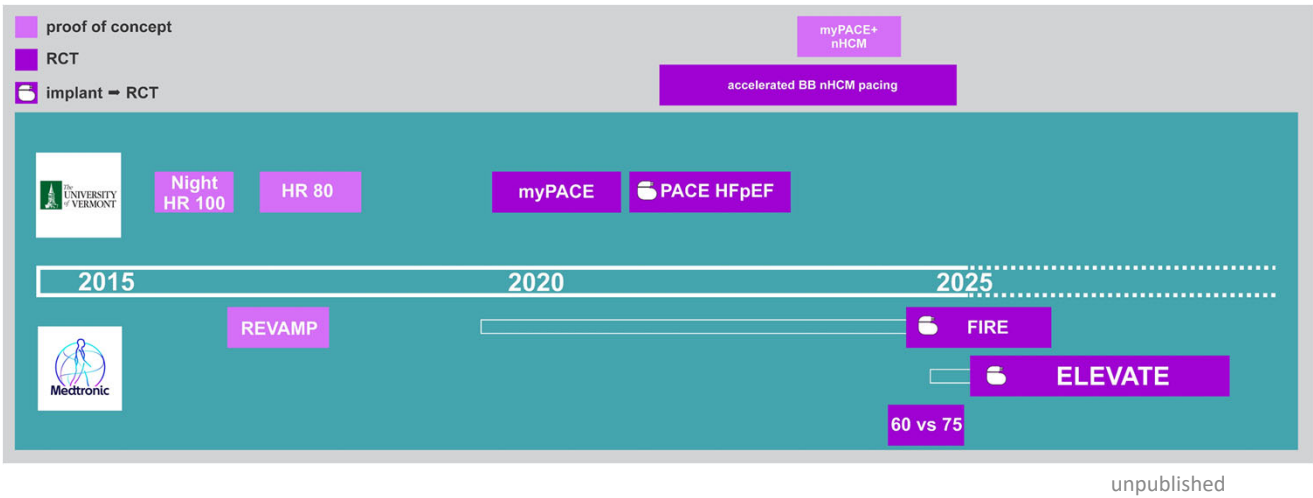


Treatment	Change in KCCQ or MLHFQ [%]	Significant p-value
PARAGON-HF	~5	No
EMPEROR-P	~5	No
DELIVER	~5	No
FINEARTS-HF	~5	No
SUMMIT	~15	Yes
CLIP-HFrEF	~15	Yes
myPACe	~85	Yes

unpublished

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Conduction System Pacing for HFpEF



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CONCLUSIONS



HFpEF/AF Shared Myocardial Substrate

**Personalized Accelerated Conduction System Pacing
Disease/Substrate Modifying Effects**

Prevention and Treatment HFpEF/AF

FIRE-HFpEF

n=50 NCT06678841

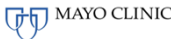
ELEVATE-HFpEF

n=500 NCT06678841

42

Thank You and ELEVATE*

*EF≥50%



Studies

Stephen Bell
Franziska Klein MD PhD
Rich Lachapelle
Betsy Runte MD PhD
Rachel McEntee MD
Lakshmi Nambiar MD
Mehdi Rambod MD
Srinath Yeshwant MD
Maren Arnold MD PhD
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Bo Ye MD PhD
Norman Aiad MD
Elle Nelson BS
Jillian Cicero BS
Neal Duong PhD



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David Schneider MD (UVM)



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Paul Ziegler PhD
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