2023 Howard B. Burchell Memorial Lecture

Dr. Burchell is widely recognized as one of the foremost authorities in cardiology during the 1950s and 1960s. He is considered to have set the stage, with his colleagues, for the ablation of accessory AV connections, which ultimately led to the current era of interventional cardiac electrophysiology. The annual Burchell lecture is a tradition that was created over twenty years ago as a way to honor Dr. Burchell and his contributions to the world of medicine.
Burchell Lecture Past Presentations

- 2022: Clyde Yancy, MD  Heart Failure: a new coming of age for an old disease
- 2021: Mathew Maurer, MD  Cardiac Amyloidosis: Transition from rare, underdiagnosed and untreated to an increasingly and easily recognized and treatable disorder
- 2019: Navin Kapur, MD  Ventricular Unloading: State of the Art and Future Directions
- 2018: Anne Marie Valente, MD  The STORCC Initiative (Standardized Outcomes in Reproductive Cardiovascular Care)
- 2017: Robert Harrington, MD  Rethinking Randomized Clinical Trials
- 2016: Carl Pepine, MD  Emergence of Nonobstructive Coronary Artery Disease in Women
- 2013: Richard Asinger, MD  Stroke Prevention in Atrial Fibrillation: An Overview and Future Directions
- 2012: David Holmes, Jr, MD  Global Cardiovascular Disease
- 2010: Bernie Gersh, MD  Stroke Prevention in Atrial Fibrillation: An Overview and Future Directions

Minneapolis Heart Institute Foundation®
Cardiovascular Grand Rounds

Burchell Lecture: Heart Failure with an Improved Left Ventricular Ejection Fraction: Mechanics, Models and Management

Speaker: Douglas L. Mann
Aida L. Steininger Professor of Cardiology
Professor of Medicine, Cell Biology and Physiology
Washington University School of Medicine
St. Louis, MO

April 17, 2023 | 7:00 – 8:00 AM
Heart Failure with an Improved Left Ventricular Ejection Fraction: Mechanisms, Models and Management

Howard B. Burchell Memorial Lecture
Minneapolis Heart Institute Foundation
April 17th, 2023

Dr. Howard Bertram Burchell

Physician, Scholar, Leader

“In my view, among Howard's many attributes, several are of paramount importance to a successful Editorship—his high professional standing, ceaseless striving for perfection, and compassion…. With a keen mind and persuasive personality, he has continued to use his basic science background, not only in unraveling the complexities of clinical cardiology as they apply to the patient, but also in teaching the developing cardiologist.”

Jesse Edwards, MD
Heart Failure with a Recovered Ejection Fraction

Heart Failure With Recovered Left Ventricular Ejection Fraction
JACC Scientific Expert Panel

Jane E. Wicken, MD,* James C. Fang, MD,* Renuel B. Manguelles, MD,* Douglas L. Mann, MD*ABSTRACT

Reverse left ventricular (LV) remodeling and recovery of LV function are associated with improved clinical outcomes in patients with heart failure with reduced ejection fraction. A growing body of evidence suggests that even among patients who experience a complete normalization of LV ejection fraction, a significant proportion will develop recurrent LV dysfunction accompanied by recurrent heart failure events. This has led to intense interest in understanding how to manage patients with heart failure with recovered ejection fraction (HFRED). Because of the lack of a standard definition for HFRED, and the paucity of clinical data with respect to the natural history of HFRED patients, there are no current guidelines on how these patients should be followed up and managed. Accordingly, this JACC Scientific Expert Panel reviews the biology of reverse LV remodeling and the clinical course of patients with HFRED, as well as provides guidelines for defining, diagnosing, and managing patients with HFRED. (J Am Coll Cardiol 2020;76:719-734) © 2020 by the American College of Cardiology Foundation.

JACC 2020;76: 719-734
Heart Failure with a Recovered Ejection Fraction

- Nomenclature is messy
  - HF improved EF (HFimpEF)
  - HFpEF
  - borderline HFpEF
  - HF recovered EF (HFrecEF)
  - HF midrange EF (HFmrEF)

- The definition is unclear
  - LVEF increase > 5%
  - LVEF increase > 10%
  - LVEF > 50%
  - LVEF > 40%

- Unclear clinical course
- Unclear biological substrate

JACC 2020;76: 719-734

LV Ejection Fraction as a Surrogate Measure of LV Volume

\[ EF = \frac{(EDV-ESV)}{EDV} \]
\[ EF = \frac{SV}{EDV} \]

For a fixed SV a decline in EF reflects an increase in EDV

Epidemiology of Heart Failure with a Recovered LVEF

Modified from Hellawell and Margulies Cardiovasc Ther 2012; 20: 172-181
Epidemiology of Recovery of LVEF

- Improved LV EF > 10%
- Final LV EF > 50%

Effect of FDA Approved Therapies on Reverse LV Remodeling

- Sacubitril/valsartan
  - JAMA 2019; 322:1085-1095
- Empagliflozin
  - Circulation 2021; 143:516-525

Topkara VK, Mann DL. Heart Failure: A Companion to Braunwald’s Heart Disease. 2011
Take Home Message #1
Once the inciting event is removed, recovery of LVEF is the rule rather than the exception.

Take Home Message #2
Although recovery of LVEF occurs frequently, normalization of LVEF (i.e. LVEF > 50%) varies according to the nature and duration of the inciting event.

Durability of Partial Recovery of LV Function (LV EF 40-50%)
Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)

Rastogi et al; Eur J Heart Fail 2017; 19: 1597-1605

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Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)

Rastogi et al; Eur J Heart Fail 2017; 19: 1597-1605

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Proteomic Signatures of Heart Failure in Relation to LVEF

Adamo...Mann, JACC 2020; 76: 1982-1994

Serum Protein Profiling Using DNA Aptamers (SomaLogic 1.3K)
Proteomic Signatures of Heart Failure in Relation to LVEF

Adamo...Mann, JACC 2020; 76: 1982-1994

PCA Analysis Serum Protein Profiles

Adamo...Mann, JACC 2020; 76: 1982-1994
Durability of Complete LVEF Recovery (EF > 50%) in Patients with Heart Failure

Natural History of Heart Failure with a Recovered Ejection Fraction

Basuray et al Circulation 2016; 129:2380-2387
Natural History of Functional Responders with DCM

- LVEF $\geq 50\%$, LVEDDi < 33 mm/m$^2$
- LVEF $\leq 50\%$, LVEDDi $> 33$ mm/m$^2$

100% 15% 50%

The observation that heart failure recurs in patients whose LV structure and function completely normalized, was irreconcilable with everything that I (thought) knew about heart failure biology.
Consensus Statement on Cardiac Remodeling

Cardiac Remodeling—Concepts and Clinical Implications: A Consensus Paper From an International Forum on Cardiac Remodeling
Jay N. Cohn, MD,* Roberto Ferrari, MD,† Norman Sharpe, MD‡ on Behalf of an International Forum on Cardiac Remodeling
Minneapolis, Minnesota; Ferrara, Italy; and Auckland, New Zealand JACC 2000; 35:569-82

Consensus Statement Four

“Although remodeling is generally accepted as a determinant of the clinical course of HF, slowing or reverse remodeling has not, until recently, been a recognized goal of HF therapy. “

Leading Textbooks in the Field Indicated that Reverse LV Remodeling Was Synonymous with Resolution of HF
Take Home Message #3

Try not to avoid drinking too much of your own Kool-Aid, it can leave you confused and hung over.

Clinical Outcomes of Recovery of LV Function

Yes!!

Mann et al. JACC 2012; 60: 2465-2472
So What Are the Biological Determinants of Myocardial Remission?

The Biology of Reverse LV Remodeling and Recovered LVEF

- Myocyte Alterations
- Myocardial Alterations
- Alterations in LV Geometry
The Slinky Hypothesis™

Transcriptional Profiling of Human DCM pre- and post-VAD

Topkara et al JCI Insight 2016; 1:e86038
Transcriptional Profiling of Human DCM pre- and post-VAD

Topkara et al JCI Insight 2016; 1:e86038

Incomplete Recovery of Myocyte Function Following LVAD Support

Ambardekar et al Circ Heart Fail 2011:4; 425-432
Persistent Ultrastructural Changes Following Reverse Remodeling

Diakos et al. JACC Basic Transl Sci 2016; 1: 432-444

Changes in Myocardial Metabolism Following LVAD support

Diakos et al. JACC Basic Transl Sci 2016; 1: 432-444
The Biology of Reverse Cardiac Remodeling

Myocyte Alterations

Myocardial Alterations

Alterations in LV Geometry

Persistent Changes in ECM Following Reverse Remodeling

Madigan et al J Thorac Cardiovasc Surg. 2001 May;121:902-8
The Biology of Adverse Cardiac Remodeling

Myocyte Alterations

Myocardial Alterations

Alterations in LV Geometry

Reverse LV Remodeling Leads to Unloading of the Heart

D/L > 0.75  
Dilated LV: Spherical

D/L < 0.75  
Normal LV: Prolate Ellipse
Abnormal LV Structure Following Reverse Remodeling

From Barbone Circ 2001: 101[Suppl I]; I-229-I232

Take Home Message # 4

Reverse LV remodeling is not a mirror image of the molecular and cellular pathways that become dysregulated during adverse LV remodeling, but rather reverse LV remodeling represents a coordinated multilevel process that allows the heart to adopt a new, less pathologic steady state that is associated with improved pump function and improved clinical prognosis.

Many of the multilevel molecular changes that occur during forward LV remodeling remain dysregulated in reverse remodeled hearts, despite improvements in structural and functional abnormalities.
Biological Robustness

- A perturbation may drive the state of the system toward the boundary of its steady state.
- When the state of the system returns to its original state, it is called ‘stability’ and ‘homeostasis’. When it transits to steady state 2, the system regains its stability in a new steady state.
- If the system’s functions are still intact, such a transition is considered to be a biologically robust response regardless of whether it is in steady state 1 or 2.

Kitano Mol Syst Biol 2007: 137; 1-7

Frankly, we also are becoming a little concerned that he has no intention of making this talk clinically relevant.
Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

- Recovered LVEF from < 40% to > 50%
- Normalized LVEDV
- NT-proBNP < 250 mg/ml
- Randomly assigned 1:1 to phased withdrawal of GDMT
- Primary end point relapse of DCM in 6 mos
  - Decrease in LVEF by > 10% and LVEF < 50%
  - Increase in LVEDV by > 10%
  - 2x rise in NT-proBNP

Halliday et al Lancet 2018

TRED-HF: Primary End Point

"This finding suggests that, for many patients, improvement in cardiac function following treatment does not reflect full and sustained recovery but rather reflects remission, which requires at least some treatment to be maintained."

Halliday et al Lancet 2018
Diagnosis and Management of HF Patients with a Recovered Improved LVEF

**CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY**

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary

- **Nomenclature**
  - HF with improved EF (HFimpEF)

- **Working Definition**
  - Documentation of LVEF < 40%
  - Follow-up LVEF > 40%
  - Assessment of LVEF trajectory is important


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Diagnosis and Management of HF Patients with an Improved LVEF

**Initial Classification**

**Serial Assessment and Reclassification**

**Recommendation for HF with Improved EF (HFimpEF)**

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular dysfunction, even in patients who may become asymptomatic. (80).</td>
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</tbody>
</table>
Which of the GDMT Drugs are Important for Treating Patients with HFimpEF?

We don’t really know.....

Vardeny et al, Nat Med 2022; 28: 2504-2511

Halliday et al, JACC: Heart Failure 2022; 9: 509-517

HFimpEF Patients are Extremely Heterogeneous

Janwanishtaporn...Greenberg JACC:Heart Failure 2022; 10:27-37
HFimpEF Patients are Heterogeneous

Probability of maintaining an LVEF > 50% during follow-up

Kaplan Meier Analysis of Mortality Across Clusters

Perry...Mann PLOS ONE 2021 (doi.org/10.1371/journal.pone.o24837)

HFimpEF Patients are Heterogeneous

Effect of Genetic Variations

- Baseline and longitudinal data from 1,005 genotyped DCM probands from 20 centers in Spain
- Patients treated with GDMT (no SGLT2i)
- Median follow-up of 4.04 years
- Reverse LV remodeling occurred in 46.2% genotype negative patients and 39.6% of genotype positive patients

Escobar-Lopez JACC 2021: 78; 1682-1699
Treatment of HFrEF (Stages C and D)

Medical Management of HFimpEF

- HFimpEF patients are very heterogeneous
  - Clinical approach should take into account the etiology of LV dysfunction
- We understand very little about which medications patients are required and which medications can be withdrawn
  - The DELVER trial demonstrated that Dapigliflozin improved outcomes in patients with HFimpEF
- Based on the results of the TRED-HF study (n=51) the 2022 ACC/HFSA/HFSA HF guidelines recommend to continue GDMT in all patients
  - Relapse of HF is associated with recurring myocyte injury
- Cessation of diuretic therapy can be considered
  - If HF recurs after stopping diuretics, uptitrating GDMT should be considered

Wilcox...Mann JACC 2020;76: 719-734
We Have Always Known About Myocardial Remission…

Desai A S, Stevenson L W Circulation 2012;126:501-506

Forward LV Remodeling
Relapse with worsening LVEF
Reverse LV Remodeling and Improved LVEF
Remission

Median Time from hospital discharge

Why We All Need to Care About This Stuff….

“Does it score?”
Thank you for giving me the opportunity to present the 2023 Burchell Lecture!
Unusual Causes of Heart Failure

By M. H. H. McLean, M.D., D.P.H.

A

A unusual incursion into the realm of heart failure and its management is the application of immunological and pathogenetic principles. This field, previously dominated by the study of the various types of heart failure and the various mechanisms by which these types are produced, is now expanding to include the study of the immune system and its role in heart failure.

In this context, heart failure is viewed as a disease of the immune system, with the heart serving as a target organ for immune-mediated damage. This view is supported by the observation that heart failure patients often have an elevated level of systemic inflammation, characterized by the presence of inflammatory markers such as C-reactive protein and tumor necrosis factor-alpha.

One of the key challenges in the management of heart failure is the identification of patients with an immune-mediated form of the disease. This is particularly important in the case of idiopathic dilated cardiomyopathy, where the role of the immune system is increasingly being recognized as a critical factor in the development and progression of the disease.

In summary, the study of the immune system in heart failure has the potential to revolutionize our understanding of this disease and to lead to the development of new therapies aimed at modulating the immune response and alleviating the symptoms of heart failure.

Inflammatory Causes

The subcategory of inflammatory causes are the subcategories: (1) direct infections, (2) hypersensitivity state including possible autoimmune disease, and (3) granulomatous lesions. It is important to emphasize that the

In recent years, there has been an apparent increased incidence of patients who have a relentlessly progressive type of chronic myocarditis, with the total duration of life after onset being some months or years. The clinical picture is often characterized by severe disturbances in rhythm and conduction, with heart block and paroxysms of ventricular tachycardia being characteristic. Late in the disease, the patient often has a persistent pre-stroke gallop rhythm and presents a shock-like picture already mentioned in the introduction as typical of some patients with heart

Circulation 1960; 21:436 - 443