Physiological and clinical consequences of diastolic dysfunction

S Magder
Division of Critical Care,
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Case
Case

• 88 y/o
Case

- 88 y/o
- Fell and contused left lung
Case

- 88 y/o
- Fell and contused left lung
- Unable to wean
Case

- 88 y/o
- Fell and contused left lung
- Unable to wean
- Fluid retention and Serum Creatinine ~ 250 mmol/L
Case

- 88 y/o
- Fell and contused left lung
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- Fluid retention and Serum Creatinine ~ 250 mmol/L
- Edematous
Case

- 88 y/o
- Fell and contused left lung
- Unable to wean
- Fluid retention and Serum Creatinine ~ 250 mmol/L
- Edematous
- Pulmonary edema
+ extensive amyloid
"Scar" tissue + extensive amyloid
Preferred term -

- Meaning of “diastolic dysfunction is ambiguous
  - Affected by systolic function
  - Some have systolic dyssynchrony
  - Dependent upon volume status

Currently preferred term is:

**Heart Failure with preserved ejection fraction**
• Pop: first admission to hospital with CHF and EF measured (n=2450)
• 31% of heart failure pt had EF > 50
• 17% had acute pulmonary edema (cp to 21% in those with EF <40)
• Similar survival to those with < 40%
Patient characteristics (cp to low EF patients)

- Factors:
  - Older - 75 vs 72
  - women - 66 vs 37%
  - AF - 32 vs 24%
  - Hypertension - 55 vs 49

- Less modifiable risks: DM, smoking, lipids
- Less PVD, angina, MI, CABG
- More PND, pulmonary edema, SOA
Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S.,
Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H.,

- Mayo clinic 15 year review – n = 4596 with EF
- 53% reduced EF (defined as < 50%) and 47% normal
Patient characteristics (cp to low EF patients)

- Risk factors:
  - Older
  - BMI higher 29.7 vs 28.6
  - female -64%
  - AF -41 vs 28%
  - DM (no diff)
  - less CAD and less valve disease
Survival again the same
Survival again the same

![Graph showing survival rates for preserved and reduced ejection fraction conditions over years, with a P-value of 0.03.](image)
Diastolic dysfunction increasing over time

![Graph A](image1.png)

- Patients with Preserved Ejection Fraction (%)
- 1986 to 2002
- $r=0.92, P<0.001$

![Graph B](image2.png)

- Preserved ejection fraction
- Reduced ejection fraction
- No. of Admissions
- 1986 to 2002
- $r=0.81, P<0.001$
- $r=-0.33, P=0.23$
Causes of death (taken from I-Preserve) (Zile et al Circl 2010; 121:1393)

• 60% of deaths were cardiovascular
  – SD - 26%
  – CHF – 14%
  – MI – 5%
  – Stroke – 9%
Pathology 1

- **Left ventricular hypertrophy**
  - Early – compensation for hypertension
  - Late – excess LVH - Due to activation of RAS pathway?

- **Myocardial Fibrosis**
  - Collagen accumulation – phenotype switch and enhanced cross-linking
  - Increased fibrillar collagen content and altered geometry

*Net effect is a stiffer myocardium*
Pathology 2

• Vascular endothelial dysfunction
  – Decreased NOS activity

• Titin abnormalities
  – Titin is a large cytoskeletal structural protein
  – Shifts of a shorter N2B isoform in response to increased stiffness (this helps contractility but makes the wall stiffer)
Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., and Agata Ptaszynska, M.D., for the I-PRESERVE Investigators*

Cumulative Incidence of Primary Outcome (%)

Months since Randomization

No. at Risk
Irbesartan 2067 1929 1812 1730 1640 1569 1513 1291 1088 816 497
Placebo 2061 1921 1808 1715 1618 1539 1466 1246 1051 776 446
Hemodynamics
LV ventricular PV loop and EF

Pressure

Volume

ESV/ESP

Passive Filling Curve
LV ventricular PV loop and EF

ESV/ESP “contractility”

Passive Filling Curve
LV ventricular PV loop and EF

- ESV/ESP: "contractility"
- Passive Filling Curve
- EDP
LV ventricular PV loop and EF

ESV/ESP “contractility”

Passive Filling Curve

Pressure

Volume
LV ventricular PV loop and EF

Pressure

Volume

ESV/ESP “contractility”

Passive Filling Curve

EDP
LV ventricular PV loop and EF

Pressure

Volume

ESV/ESP “contractility”

Passive Filling Curve

SV

EDP
LV ventricular PV loop and EF

Pressure

Volume

ESV/ESP “contractility”

Passive Filling Curve

EDV-ESV

PV loop

SV

EDP

Ef

Initial Volume
LV ventricular PV loop and EF

ESV/ESP “contractility”

EDV-ESV

Passive Filling Curve

Pressure

EDV

Volume

SV

EDP
LV ventricular PV loop and EF

ESV/ESP “contractility”

Passive Filling Curve

\[ EF = \frac{EDV - ESV}{EDV} \]
LV ventricular PV loop and EF

- ESV/ESP “contractility”
- Passive Filling Curve
- EF = \( \frac{EDV-ESV}{EDV} \)
LV ventricular PV loop and EF

Pressure

Volume

EDV

EDP

SV

EDV-ESV

ESV/ESP “contractility”

Passive Filling Curve

EF = \frac{EDV-ESV}{EDV}
LV ventricular PV loop and EF

Pressure

Volume

SV

EDV-ESV

ESV/ESP “contractility”

Passive Filling Curve

EF = \frac{EDV-ESV}{EDV}

~ 55 %
**Pressure**

**Volume**

**Systolic dysfunction and EF**

\[ EF = \frac{EDV - ESV}{EDV} \]

56 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

EF = \frac{EDV-ESV}{EDV}

56 %
Systolic dysfunction and EF

ESP/ESV "decrease contractility"

\[ EF = \frac{EDV - ESV}{EDV} \]

56 %
Systolic dysfunction and EF

- **ESP/ESV** “decrease contractility”
- EF = \( \frac{EDV-ESV}{EDV} \)
- EF = 56%
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

$\text{EF} = \frac{\text{EDV-ESV}}{\text{EDV}}$

56 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

\[ EF = \frac{EDV - ESV}{EDV} \]

56 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

$EF = \frac{EDV - ESV}{EDV}$

56 %
Systolic dysfunction and EF

Pressure

ESP/ESV “decrease contractility”

Volume

EF = \frac{EDV-ESV}{EDV}

56 %

25 %
Systolic dysfunction and EF

Systolic dysfunction can lead to a decrease in contractility.

\[
EF = \frac{EDV - ESV}{EDV}
\]

- ESP/ESV
- "decrease contractility"
- EF = \frac{EDV - ESV}{EDV}
- 56%
- 25%
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

EF = \frac{EDV-ESV}{EDV}

Pressure

Volume

56 %

25 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

EF = \frac{EDV-ESV}{EDV}

EDV

Pressure

Volume

56 %

25 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

\[ EF = \frac{EDV - ESV}{EDV} \]

56%

25%
Systolic dysfunction and EF

EF = \frac{EDV - ESV}{EDV}

56%

25%

ESP/ESV “decrease contractility”
Systolic dysfunction and EF

EF = \frac{EDV - ESV}{EDV}

ESP/ESV "decrease contractility"

EDV

56 %

25 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

$EF = \frac{EDV-ESV}{EDV}$

56 %

25 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

\[ EF = \frac{EDV - ESV}{EDV} \]

EDV: 56 %

ESP/ESV: 25 %
Systolic dysfunction and EF

ESP/ESV “decrease contractility”

EF = \frac{EDV-ESV}{EDV}

EF = 56% 25% 40%
Ventricular pressure-time curve

Aorta

Ventricle

A-V Closure
∴ “preload”

Atrium
Ventricular pressure-time curve

Aorta

Ventricle

A-V Closure
\[ \therefore \text{“preload”} \]

Atrium
Ventricular pressure-time curve

Isovolumetric relaxation

Aorta

A-V Closure :: “preload”

Atrium

Ventricle

A

C

V
Ventricular pressure-time curve

Aorta

Ventricle

Atrium

A-V Closure

∴ “preload”

Isovolumetric relaxation
Ventricular pressure-time curve

Aorta

Ventricle

Atrium

A-V Closure \( \therefore \) “preload”

Isovolumetric relaxation

Prolonged relaxation
- Increase in time constant

V

A
Diastolic dysfunction

ESP/ESV “contractility”

$$\text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}}$$

SV

EDP

\(~ 56 \% \)
Diastolic dysfunction

ESP/ESV "contractility"

Decrease diastolic compliance

\[ \text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \]

~ 56 %
Diastolic dysfunction

ESP/ESV "contractility"

Decrease diastolic compliance

\[ EF = \frac{EDV-ESV}{EDV} \]

~ 56 %
Diastolic dysfunction

ESP/ESV "contractility"

Decrease diastolic compliance

\[ EF = \frac{EDV-ESV}{EDV} \]

~ 56 %

SV

EDP
Diastolic dysfunction

ESP/ESV “contractility”

Decrease diastolic compliance

\[ EF = \frac{EDV-ESV}{EDV} \]

~ 56 %
Diastolic dysfunction

ESP/ESV “contractility”

Decrease diastolic compliance

EF = \frac{EDV-ESV}{EDV}

\approx 56\%
Diastolic dysfunction

ESP/ESV “contractility”

Decrease diastolic compliance

\[ EF = \frac{EDV - ESV}{EDV} \]

\(~ 56 \% \)
Diastolic dysfunction

ESP/ESV “contractility”

Decrease diastolic compliance

EF = \frac{EDV - ESV}{EDV}

~ 56 %

No change
Diastolic dysfunction

ESP/ESV “contractility”

Pressure

Volume

SV

EDP
Diastolic dysfunction

Pressure

Volume

ESP/ESV “contractility”

Increase BP

SV

EDP

SV
Diastolic dysfunction

ESP/ESV "contractility"

Increase BP

SV

EDP

Pressure

Volume
Diastolic dysfunction

Pressure

Volume

ESP/ESV “contractility”

Increase BP

SV

EDP
Diastolic dysfunction

ESP/ESV “contractility”

Increase BP

SV

EDP
Diastolic dysfunction

ESP/ESV “contractility”

Increase BP

SV

EDP

Pressure

Volume
Diastolic dysfunction

- ESP/ESV 
- "contractility"

Increase BP

SV

EDP

Pressure

Volume
Diastolic dysfunction

ESP/ESV "contractility"

Increase BP

SV

EDP
Diastolic dysfunction

ESP/ESV “contractility”

Increase BP
Diastolic dysfunction

Pressure

Volume

ESP/ESV “contractility”

Increase BP

SV

EDP

SV
Diastolic dysfunction

- ESP/ESV “contractility”
- Increase BP
- SV
- EDP
“Diastolic + systolic” dysfunction

\[ EF = \frac{EDV - ESV}{EDV} \]

\~ 56%
“Diastolic + systolic” dysfunction

\[ \text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \]

\(~ 56\% ~\)
“Diastolic + systolic” dysfunction

ESP/ESV

Passive filling curve

\[ EF = \frac{EDV - ESV}{EDV} \]

~ 56 %
“Diastolic + systolic” dysfunction

ESP/ESV

Passive filling curve

EF = \frac{EDV-ESV}{EDV}

\sim 56\%
"Diastolic + systolic" dysfunction

\[ EF = \frac{EDV - ESV}{EDV} \approx 56\% \]
“Diastolic + systolic” dysfunction

$EF = \frac{EDV - ESV}{EDV}$

$\sim 56\%$
“Diastolic + systolic” dysfunction

\[ EF = \frac{EDV - ESV}{EDV} \]

\(~ 56\%\)
"Diastolic + systolic" dysfunction

Pressure

Volume

\[ \text{EF} = \frac{\text{EDV-ESV}}{\text{EDV}} \]

\(~ 56\% ~\)
“Diastolic + systolic” dysfunction

\[ \text{EF} = \frac{\text{EDV}-\text{ESV}}{\text{EDV}} \]

\[ \sim 56\% \]
"Diastolic + systolic" dysfunction

Pressure

Volume

$EF = \frac{EDV - ESV}{EDV}$

$\sim 56\%$

ESP/ESV

Passive filling curve

EDP
“Diastolic + systolic” dysfunction

\[ EF = \frac{EDV - ESV}{EDV} \]

\( \sim 56\% \)
“Diastolic + systolic” dysfunction

\[ \text{ESP/ESV} \]

\[ \text{EF} = \frac{\text{EDV-ESV}}{\text{EDV}} \]

\( \sim 56\% \)

Passive filling curve
"Diastolic + systolic" dysfunction

\[ \text{ESP/ESV} \]

\[ \text{EF} = \frac{\text{EDV-ESV}}{\text{EDV}} \]

\[ \approx 56\% \]
"Diastolic + systolic" dysfunction

\[ \text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \]

\( \sim 56\% \)
“Diastolic + systolic” dysfunction

\[ EF = \frac{EDV - ESV}{EDV} \]

\( \approx 56\% \)

\( \approx 40\% \)

Pressure

Volume

ESP/ESV

Passive filling curve

EDP
"Diastolic + systolic” dysfunction

\[ \text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \]

\(~ 56 \% ~\)

\(~ 40 \% ~\)
Effect of HR change on ventricular PV loop

Pressure vs. Volume diagram showing:
- ESV/ESP
- SV
- (EDV-ESV)
- EDV
- EDV_{post}
Effect of HR change on ventricular PV loop

$\text{EF} = \frac{\text{EDV-ESV}}{\text{EDV}}$

$\text{SV} = (\text{EDV-ESV})$

$\text{EDV}_{\text{post}}$
Effect of HR change on ventricular PV loop

$$EF = \frac{EDV - ESV}{EDV}$$
Effect of HR change on ventricular PV loop

\[
\text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}}
\]

HR (same Q)
Effect of HR change on ventricular PV loop

$\text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}}$

HR (same Q)
Effect of HR change on ventricular PV loop

\[
EF = \frac{EDV - ESV}{EDV}
\]

HR (same Q)
Effect of HR change on ventricular PV loop

\[ EF = \frac{EDV - ESV}{EDV} \]

HR (same Q)

Pressure

Volume
Effect of HR change on ventricular PV loop

\[ EF = \frac{EDV - ESV}{EDV} \]

HR (same Q)
Effect of HR change on ventricular PV loop

$$\text{EF} = \frac{\text{EDV}-\text{ESV}}{\text{EDV}}$$

Same ↓ in top and bottom

HR (same Q)
Effect of HR change on ventricular PV loop

\[
EF = \frac{EDV - ESV}{EDV}
\]

Same ↓ in top and bottom

HR (same Q)

EF goes ↓

Pressure

EDV

Volume

EDV_{pre}
Effect of HR change on ventricular PV loop

ESV/ESP

EF = \frac{EDV-ESV}{EDV}

Same ↓ in top and bottom

HR (same Q)

EF goes ↓

But contractility did not change
Importance of chronotropic response in exercise
Importance of chronotropic response in exercise

$\uparrow$ Eeslv

$F$ vs $V$

SVrest, SVex, SVmax

EDP & EDV
Importance of chronotropic response in exercise

- SVrest
- SVex
- SVmax
- Eeslv
- EDP
- EDV
Importance of chronotropic response in exercise
Importance of chronotropic response in exercise

Diagram showing the relationship between Eeslv, SVrest, SVex, SVmax, EDP, and EDV.
Importance of chronotropic response in exercise

Eeslv

SVrest

SVmax

SVex

EDP & EDV
Importance of chronotropic response in exercise

Even a large rise in EDP would not be sufficient to compensate for lack of HR increase.

$\uparrow$ Eeslv

SVrest

SVex

SVmax

EDP & EDV

F

V
Importance of chronotropic response in exercise

Even a large rise in EDP would not be sufficient to compensate for lack of HR increase.
Even a large rise in EDP would not be sufficient to compensate for lack of HR increase.
Importance of chronotropic response in exercise

Even a large rise in EDP would not be sufficient to compensate for lack of HR increase.

SVrest, SVex, SVmax, Eeslv, F, V, EDP, EDV
A greater % of stressed volume in the pulmonary compartment.
A greater % of stressed volume in the pulmonary compartment
A greater % of stressed volume in the pulmonary compartment

Unless volume increases
Diagnosis

• Clinical suspicion
  – Dyspnea
  – Decreased exercise capacity
  – Right “phenotype”

• Echocardiography
  – However ----
  • Not precise
  • Dependent on volume status
  • Dynamic tests likely better than rest
Normal  Abnormal relaxation  Pseudonormal  Restriction [reversible]  Restriction [irreversible]

\[ E \quad A \]

\[ e' \quad a' \]

Mean LAP  

Diastolic dysfunction grade 1 2 3 4
Treatment

- Limited options
- Control blood pressure
  - Lowering afterload lowers the ESV and therefore EDV and pressure
  - Reduces a key factor driving ventricular hypertrophy
  - Reduce aortic elastance
- Diuretic therapy for symptoms
  - However, must balance this with renal function
Practical Approach to Grade Diastolic Dysfunction

Septal e'
Lateral e'
LA volume

Septal e' ≥ 8
Lateral e' ≥ 10
LA < 34 ml/m²
- Normal function

Septal e' ≥ 8
Lateral e' ≥ 10
LA ≥ 34 ml/m²
- Normal function, Athlete's heart, or constriction

Septal e' < 8
Lateral e' < 10
LA ≥ 34 ml/m²

E/A < 0.8
DT > 200 ms
Av. E/e' ≤ 8
Ar-A < 0 ms
Val ΔE/A < 0.5
- Grade I

E/A 0.8-1.5
DT 160-200 ms
Av. E/e' 9-12
Ar-A ≥ 30 ms
Val ΔE/A ≥ 0.5
- Grade II

E/A ≥ 2
DT < 160 ms
Av. E/e' ≥ 13
Ar-A ≥ 30 ms
Val ΔE/A ≥ 0.5
- Grade III
Pathophysiology of HfPEF

- Fluid overload = ↑ preload
- Chronotropic incompetence
- Co-morbidities: Renal Dysfunction, Anemia, Infection, Obesity
- Atrial dysfunction + Atrial Failure
- Exertional blood pressure ↓ After Load = Diastolic Dysfunction + ↓ Systolic Reserve
- LV Stiffness ↓ Relaxation
  - LVH, Fibrosis, AGE, Titin, Myocyte Δs
- Vascular stiffness ↓ Vasodilation
  - Systemic + Pulmonary
- Cardiac energetics ↓