Diastole - Summary

• Relaxation
  – Active process
  – Measurable during isovolumic relaxation
  – Heart rate effects

• Passive ventricular properties
  – Geometry: wall thickness and radius
  – Histology: cellular composition, collagen
  – Extrinsic factors

• (Atrial systole – atrial transport – stepchild)
Diastolic function - Suction

Diastolic function (Suction)

Pressure (mmHg) vs. Volume (ml)

- Purely elastic pressure-volume curve of the myocardial shell in the absence of the component due to active relaxation
- Elastic Properties, Geometry (size & wall thickness)
- Extent of Relaxation
- Pericardium
- Ventricular Interaction (adaptation)
- Viscoelasticity (atrial kick)
- Coronary Vascular Engorgement

Physiology of Diastole

• Diastole: traditionally, from S2 to S1
  – More specifically, onset is at maximal elastance, slightly before aortic valve closure (protodiastole)
Physiology of Diastole

- Diastole: traditionally, from S2 to S1
  - More specifically, onset is at maximal elastance, slightly before aortic valve closure (protodiastole)
Physiology of Diastole

• Diastole: traditionally, from S2 to S1
  – More specifically, onset is at maximal elastance, slightly before aortic valve closure (protodiastole)

• Normal function: LV accepts adequate filling volume to maintain cardiac output at normal operating pressure

• Active diastole: Lusitropic function

• Passive diastole: mechanical properties
Relaxation Factors

- Cytosolic Ca++ must fall
- Viscoelastic properties of myocardium
- Phosphorylation of troponin I accelerates relaxation
- Systolic load accelerates relaxation
Relaxation Factors – (1)

• Cytosolic Ca++ must fall – (1)
  – 10-fold, from 100 nM to 10 nM*
  – Requires ATP used by SERCA2a (sarcoendoplasmic reticulum Ca2+-adenosine triphosphatase), the dominant cardiac isoform using 1 ATP for 2 Ca++ ions
  – SERCA2a constitutes ~90% of SR protein

Relaxation Factors – (2)

• Cytosolic Ca++ must fall – (2)
  – SERCA2a is regulated by phosphorylation of phospholamban for reuptake of Ca++ into SR (dephosphorylated phospholamban is inhibitory**)
  – Phospholamban is phosphorylated at at least 2 sites
    • Ser-10 by PKC** (in vitro only)
    • Ser-16 β-adrenergic stimulation to cAMP to PKA**
    • Thr-17 Calcium ions and calmodulin-dependent protein kinase**

**Zhao W et al. J Mol Cell Cardiol. 2004;37:607
Braunwald’s Heart Disease, 7th Ed. Opie LH. Ch 19, p. 464, 481.
Relaxation Factors – (3)

• Viscoelastic properties of myocardium
• Phosphorylation of troponin I accelerates relaxation
• Systolic load accelerates relaxation

**Zhao W et al. J Mol Cell Cardiol. 2004;37:607
Braunwald’s Heart Disease, 7th Ed. Opie LH. Ch 19, p. 464, 481.
Triad Junction of T-tubule and Sarcoplasmic Reticulum

Junction foot structures; cytoplasmic domains of RyR

Calsequestrin strands in sarcoplasmic reticulum terminal cisternae

T-tubule (DHPR, voltage-dependent Large Ca^{++} channel)

Calsequestrin and the RyR


Active diastole: Lusitropic function

- Myocyte relaxation
  - kinetics of crossbridge cycling (slower cycling slows relaxation, such as high afterload in early systole)
  - affinity of Ca++ for TnC (higher affinity slows relaxation)
  - activity of Ca++ reuptake and extrusion (lower activity of SERCA2 or Na-Ca exchanger slows relaxation, such as ischemia)
Active diastole: Lusitropic function

• Restorative forces (titin compression? Probably not)
  – End-systolic LV volume < equilibrium LV volume
  – Leads to suction
  – Negative pressure reached rarely in MS, otherwise not seen due to LV filling, also damped by viscous forces
  – Pressures below 0 seen in the cath lab are not real, but are due to underdamped waveforms
Passive (Fully Relaxed) Diastole

- Compliance = \( \Delta \text{volume}/\Delta \text{pressure}, \ (\Delta V/\Delta P) \)
- End-diastolic pressure-volume relation (EDPVR)
- Factors:
  - Ratio of volume to wall thickness
  - Intrinsic stiffness of myocardial tissue
    - At low volumes largely due to properties of titin
    - At high volumes largely due to properties of connective tissue
  - Stiffness is change in stress (force/cross sectional area) related to change in strain (change from initial length or area)
- External constraints: parietal pericardium, myocardial vascular blood volume (turgor), atrial function
Titin in Diastolic Function

Titin’s behavior itself is viscoelastic

Mechanism of passive and restoring force generation. Titin’s extensible region is in a shortened state in slack sarcomeres (B) and extends on sarcomere stretch (C and D), lowering conformational entropy and giving rise to an entropic force, known as passive force. When slack sarcomeres shorten to below the slack length (A), the thick filament moves into titin’s incompressible near Z-disc region (in gray) and the extensible region now extends in a direction opposite of that during stretch, developing restoring force. Figure not to scale.
Titin in Diastolic Function

The Z-Disk of the Sarcomere

Hoshijima, M. AJP-Heart Circ Physiol • 2006;290:1313
Spectrum of Dystrophic Syndromes

Fibrillin-1 in Fibrosis

A J Physiol Heart Circul 2005
Diastolic Phases

Diastolic Pressure and Flow

Canine model with ultra-sonic crystals and micro-manometer pressures

From Ohno M et al. Circulation 1994;89:2241
Diastolic Pressure and Flow

High fidelity LA and LV pressure and Doppler transmitral

Closed chest canine

Courtois M et al. Circulation 1988;78:661
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Delayed relaxation, prolonged tau

Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.

\[ P = \alpha e^{\beta v} + C \]
<table>
<thead>
<tr>
<th><strong>TABLE 20–3</strong></th>
<th>Two Pathways of Ventricular Dilation and Increased Filling Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic (Acute)</strong></td>
<td>Dilation and increased end-diastolic pressure caused when increased venous return or decreased ejection increases end-diastolic volume. This form of dilation occurs when physiological (functional) signaling increases sarcomere length, which increases the heart’s ability to perform work (Starling law of the heart)</td>
</tr>
<tr>
<td><strong>Architectural (Chronic)</strong></td>
<td>Dilation and increased filling pressures caused when hypertrophy increases cardiac myocyte length and alters passive muscle properties. By increasing wall stress, this growth response increases the energy demands of the heart and decreases cardiac efficiency, initiating a vicious circle that worsens heart failure. This form of dilation occurs when abnormal transcriptional (proliferative) signaling causes eccentric hypertrophy (systolic dysfunction), and it tends to progress (remodeling)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adults &lt;41 yr</th>
<th>Adults &gt;55 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak mitral flow velocity (E) (cm/sec)</td>
<td>76 ± 13</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Peak mitral filling rate (A) (cm/sec)</td>
<td>38 ± 8</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Mitral E/A</td>
<td>2.1 ± 0.6</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Mitral E deceleration time</td>
<td>184 ± 24</td>
<td>—</td>
</tr>
<tr>
<td>Mitral E deceleration rate (m/sec²)</td>
<td>5.6 ± 2.7</td>
<td>—</td>
</tr>
<tr>
<td>Isovolumetric relaxation time (msec)</td>
<td>74 ± 26</td>
<td>—</td>
</tr>
<tr>
<td>Peak pulmonary venous AR wave (cm/sec)</td>
<td>18 ± 3</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Peak pulmonary venous S wave (cm/sec)</td>
<td>41 ± 10</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Peak pulmonary venous D wave (cm/sec)</td>
<td>53 ± 10</td>
<td>38 ± 10</td>
</tr>
</tbody>
</table>

E/A = E wave/A wave ratio.

<table>
<thead>
<tr>
<th>Pulmonary Venous Wave</th>
<th>Left Atrial Function</th>
<th>LV Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>First systolic wave</td>
<td>Atrial relaxation</td>
<td></td>
</tr>
<tr>
<td>Second systolic wave</td>
<td>Reservoir function</td>
<td>LV contraction</td>
</tr>
<tr>
<td></td>
<td>Atrial compliance</td>
<td>RV contraction</td>
</tr>
<tr>
<td>Early diastolic wave</td>
<td>Conduit function</td>
<td>Ventricular relaxation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular chamber stiffness</td>
</tr>
<tr>
<td>Atrial reversal wave</td>
<td>Booster pump function</td>
<td>Ventricular chamber stiffness</td>
</tr>
<tr>
<td></td>
<td>Atrial compliance</td>
<td></td>
</tr>
</tbody>
</table>

LV = left ventricular; RV = right ventricular.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young Patients &lt;35 yr</th>
<th>Intermediate-Aged Patients 35-50 yr</th>
<th>Older Patients &gt;50 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum + dP/dt (mm Hg/sec)</td>
<td>1011 ± 160</td>
<td>1170 ± 159</td>
<td>1147 ± 374</td>
</tr>
<tr>
<td>Stroke work (g-m/m²)</td>
<td>19 ± 10</td>
<td>20 ± 10</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>26 ± 8</td>
<td>30 ± 11</td>
<td>38 ± 10</td>
</tr>
<tr>
<td>Pulse wave velocity (m/sec)</td>
<td>4.7 ± 0.4</td>
<td>6.5 ± 0.9</td>
<td>7.9 ± 0.6</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn-sec · cm⁻⁵)</td>
<td>1872 ± 789</td>
<td>2373 ± 762</td>
<td>2440 ± 770</td>
</tr>
<tr>
<td>Arterial compliance (ml/mm Hg)</td>
<td>1.33 ± 0.63</td>
<td>0.72 ± 0.40</td>
<td>0.51 ± 0.17</td>
</tr>
</tbody>
</table>

LV = left ventricular.  
### TABLE 19-5  Some Indices of Diastolic Function

<table>
<thead>
<tr>
<th>Isovolumic Relaxation</th>
<th>Early Diastolic Filling</th>
<th>Diastasis</th>
<th>Atrial Contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(-)dP/dt_{max}$ (Fig. 19–28)</td>
<td>Relaxation kinetics on ERNA (rate of volume increase)</td>
<td>Pressure-volume relation indicates compliance</td>
<td>Invasive measurement of atrial and ventricular pressures</td>
</tr>
<tr>
<td>Aortic closing–mitral opening interval</td>
<td>Early filling phase (E phase) on Doppler transmirtal velocity trace</td>
<td></td>
<td>Doppler transmitral pattern (E to A ratio)</td>
</tr>
<tr>
<td>Peak rate of LV wall thinning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time constant of relaxation ($\tau$)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$A =$ atrial contraction phase; $E =$ early filling phase; $ERNA =$ equilibrated radionuclide angiography; $LV =$ left ventricular.
Assessment of Diastolic Function

- **M-mode Echo:**
  - chamber sizes
  - mitral and LV motion
  - aortic root motion

- **2-D (B-mode) Echo:**
  - chamber sizes and wall thickness
  - mitral and LV motion
  - aortic root motion
  - atrial volume change
  - interatrial septal shape and motion

- **Doppler assessment**
Doppler Assessment of Diastole

- Transmitral flow assessment
- Isovolumic relaxation time
- Pulmonary venous flow assessment
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
Normal LVIT Pattern

Decreased Operative Compliance (increase E and short E-deceleration)

Diastolic Pressure-Volume Relation and LVIT Pattern

Normal diastolic pressure-volume relation with increased volume

Abnormal diastolic pressure-volume relation with no change in volume

Nishimura, JACC 1997; 30:8
Diastolic Patterns of Pressure, Volume, and Flow

Smith, Mikel, in Otto, 1997
LVIT Velocity Measurements

- **E** - peak E velocity
- **A** - peak A velocity
- **DT** - time from peak E to zero
- **Decel slope** – more dependent on peak E height
- **Adur** - duration of A wave

Nishimura, JACC 1997; 30:8
Technical Aspects of LVIT Pattern

- Pulsed wave preferred
- Apical 4 (or 2 or LA)
- Sample volume at mitral leaflet tips
- Modal (darkest) velocity

Smith, Mikel, in Otto, 1997
LVIT Flow Pattern

- **Normal**: E 70-100 cm/s, A 45-70 cm/s, E/A 1.0-1.5, DT 160-220 msec
- **Older**: lower E, higher A, lower E/A, longer DT
- **Arrhythmia**: Faster HR and longer PR interval- lower E, higher A, merge at >100; afib - no A, variable E
- **Preload**: decrease causes decrease in E wave and no change of A wave
- **Systolic function**: increase in end-systolic volume (systolic dysfunction or high afterload) lowers E and slows DT
- **Atrial function**: atrial systolic dysfunction gives low A wave
- **Respiration**: inspiration reduces E by 5-10%, no change in A
## Factors Affecting Mitral E/A Ratio

**Increased:**
- Slow heart rate
- Elevated LA pressure
- High LV elastic recoil
- Young age (phys S3)
- Restrictive hemodyln
- Severe AR
- Atrial mechanical fail
- Small LVESV

**Decreased**
- Abnormal LV relaxation
- Increased aortic pressure
- Increased PR interval
- Tachycardia
- Asynchronous LV relaxation

---
Pai RG. **Clin Cardiol** 1996;19:277
Limitation of LVIT Doppler pattern in diastolic function

Deterioration of diastolic function with benign-appearing LVIT flow

Nishimura, JACC 1997; 30:8
Abnormal Transmirtal (LVIT) Filling Patterns

Abnormal Relaxation
- advanced age
- low preload
- systolic dysfunction
- tachycardia
- long PR
- ischemia
- pulmonary htn

Restrictive Filling
patient with dilated cardiomyopathy

Nishimura, JACC 1997; 30:8
62 year-old man, dilated Cardiomyopathy:

Prolonged LV relaxation, tau = 68 msec

Elevated LA pressure 32mmHg

Nishimura, JACC 1997; 30:8
CW Doppler of MR

PW Doppler LVIT (not simultaneous)

PR interval and Diastole

Baseline:
- first degree AV block
- diastolic MR and
- E-A superimposition

AV sequential pacing:
- PR interval normal
- no diastolic MR
- forward SV increase 40%

Nishimura, JACC 1997; 30:8
Doppler Assessment of Diastole

- Transmitral flow assessment
- **Isovolumic relaxation time**
- Pulmonary venous flow assessment
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
Isovolumic Relaxation Time

Isovolumic Relaxation Time

Time from aortic closure to mitral opening

From phono S2 to mitral opening on M-mode

Doppler method: Apical five-chamber view
CW Doppler Directed between aortic outflow and mitral inflow

Normal 65 msec +/- 20

Short IVRT: restrictive cardiomyopathy restrictive filling pattern
Long IVRT: advanced age, impaired relaxation

Smith, Mikel, in Otto, 1997
Isovolumic Relaxation Time

- **Increased** by
  - Abnormal LV relaxation (2)
    - Ischemia, infarction, hypertrophy, DM
  - Elevated aortic pressure (1)
  - Asynchrony of LV relaxation (LBBB, Paced, HCM) (2)
  - Aging (1,2)

- **Decreased** by
  - Elevated LA pressure (3)
  - Tachycardia (2)
  - Elevated sympathetic tone, catecholamines (2)
  - Smaller LV end-systolic volume (1)

Pai RG. *Clin Cardiol* 1996;19:277
Intraventricular flow during Isovolumic Relaxation

Abnormal flow from apex to base during IVRT in patient with anterior MI and apical wall motion abnormality.

Normally flow is from base to apex.

Edvardsen et al, JASE 1999; 12:801
Doppler Assessment of Diastole

- Transmitral flow assessment
- Isovolumic relaxation time
- **Pulmonary venous flow assessment**
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
Pulmonary Venous Flow

- **Technique**: TTE – right upper pulmonary vein, 5-10 mm from orifice

- **Waves**:
  - **systolic** usually dominant (S, 40-60 cm/s)
  1. early – atrial relaxation
  2. late – descent of MV annulus
  - **diastolic** (D, 35-45 cm/s, coincides with MV E wave but 50 msec later, from ventricular relaxation)
  - **atrial reversal** (Ar, 22-32 cm/s, duration 137msec, larger with high atrial afterload and preserved atrial systolic function)

- **Tachycardia** - S and D waves may merge
Pulmonary Venous Flow

From Rossvoll O et al. (Hatle) J Am Coll Cardiol 1993:21:1687
Pulmonary Venous Flow Pattern

• LV preload and systolic and diastolic function
  – Increased LA pressure - lower S if LV systolic dysfunction, (more S if LV systolic function is preserved)
  – Impaired relaxation – larger S and lower D, corresponding to lower MV E
  – Pseudonormal – lower S and dominant D wave and larger Ar wave (lower LV compliance)
  – Restrictive – low S and large D and rapid D deceleration, Ar is variable

• Age increases systolic dominance and maybe Ar
• Mitral regurgitation* reduces S wave, reverses if severe MR
• Large ASD causes single continuous antegrade wave and diminished AR wave**

Normal Pulmonary Vein PW Doppler Patterns

S - systolic
D - diastolic
SE - early systolic atrial relaxation
SL - late systolic descent of MV annulus
Ar - atrial reversal
Si - systolic integral
Di - diastolic integral

Smith, Mikel, in Otto, 1997
Pulmonary Venous Flow and LA pressure

With higher LA pressure, the S wave is lower

Mean LA = 9 mmHg
Mean LA = 15 mmHg

Kuecherer HR et al. Circulation 1990;82:1127
Pulmonary Venous Doppler and LV Diastolic Pressure

- 78 patients with chronic atrial fibrillation
  - 35 study group
  - 23 test group
- Wedge pressure simultaneous or very close in time to echo-Doppler
- Mitral and pulmonary vein flow patterns
  - Pulmonary venous diastolic measurements
  - Transmitral E wave measurements

Chirillo F et al. J Am Coll Cardiol 1997;30:19
Pulmonary Venous Doppler and LV Diastolic Pressure

Chirillo F et al.
J Am Coll Cardiol 1997;30:19
Pulmonary Venous Doppler and LV Diastolic Pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV MAX</td>
<td>57.0 CM/S</td>
</tr>
<tr>
<td>TEMPO</td>
<td>0.170 SEC</td>
</tr>
<tr>
<td>INCLIN.</td>
<td>332. CM/S2</td>
</tr>
<tr>
<td>IPG MAX</td>
<td>1.30 mmHg</td>
</tr>
<tr>
<td>P1/2t</td>
<td>50.3 mSEC</td>
</tr>
<tr>
<td>BV MAX</td>
<td>62.4 CM/S</td>
</tr>
<tr>
<td>TEMPO</td>
<td>0.175 SEC</td>
</tr>
<tr>
<td>INCLIN.</td>
<td>354. CM/S2</td>
</tr>
<tr>
<td>PG MAX</td>
<td>1.56 mmHg</td>
</tr>
<tr>
<td>P1/2t</td>
<td>51.6 mSEC</td>
</tr>
</tbody>
</table>
Pulmonary Venous Doppler and LV Diastolic Pressure
Pulmonary Venous Doppler and LV Diastolic Pressure

Chirillo F et al.
J Am Coll Cardiol
1997;30:19
Pulmonary Venous Doppler and Wedge Pressure

- 141 patients with acute first MI and sinus rhythm
- Time since MI 2.1 days, <7 da
- Exclusions: merging of LVIT E and A waves, valvular disease
- Simultaneous PCWP
- E deceleration – negative correlation with PCWP
- PV deceleration – strong negative correlation with PCWP

Yamamuro A et al. J Am Coll Cardiol 1999;34:90
Pulmonary Venous Doppler and Wedge Pressure

Yamamuro A et al. J Am Coll Cardiol 1999;34:90
Pulmonary Venous Doppler and Wedge Pressure

Yamamuro A et al. J Am Coll Cardiol 1999;34:90
Pulmonary Venous Doppler and LV Diastolic Pressure

- 93 patients undergoing surgery (CABG or AVR), intraoperative TEE, S-G cath and LA cath
- End-expiration (positive pressure)
- PV Doppler 10 mm from orifice of a superior pulmonary vein
- If PV-D deceleration was bimodal, the first and steeper portion was extrapolated to zero to obtain deceleration time ($DT_D$)
- $DT_D < 175$ msec implies LA pressure > 17 mmHg

Kinnaird TD et al. J Am Coll Cardiol 2001;37:2025
Pulmonary Venous Doppler and LA Pressure
Pulmonary Venous Doppler and LV Diastolic Pressure

Bland-Altman plot variation up to 6 mmHg

Similar results in 2 other studies, one in atrial fibrillation and one in recent MI

Kinnaird TD et al. J Am Coll Cardiol 2001;37:2025
PV Deceleration and LA Pressure

Abscissa and Ordinate Inverted

TEE

TTE

PV-DT (ms)

PCWP (mmHg)

r = -0.89

PVF Deceleration time (ms)

MPWP (mm Hg)

n = 35

y = -0.1224x + 40.504

r = -0.91

SEE = 2.94
PV Deceleration and LA Pressure

Abscissa and Ordinate Inverted

IntraOp

Acute MI

A Fib

n = 35
y = -0.1224x + 40.504
r = -0.91
SEE = 2.94
PV Deceleration and LA Pressure

![Graph showing the relationship between DT_D (msec) and P_LA (mmHg). The correlation coefficient r is -0.92.](image)
Impaired LV Relaxation

Transmitral flow:
- Small E, slow E decel,
- Large A

Pulmonary venous flow:
- Smaller D wave,
- Larger S wave, variable Ar

2 hypertensive patients with impaired relaxation

Smith, Mikel, in Otto, 1997
Pseudonormal Diastolic Pattern

Transmitral flow:
Normal E and A pattern

Pulmonary vein flow:
Reduced S wave from decreased atrial relaxation, possibly large Ar wave from reduced ventricular compliance

Smith, Mikel, in Otto, 1997
Pseudonormal Diastolic Pattern

Transmitral flow: Normal E and A pattern

Pulmonary vein flow: reduced S wave from decreased atrial relaxation, possibly large Ar wave from reduced ventricular compliance

Smith, Mikel, in Otto, 1997
Transmitral flow restrictive pattern
large E, short decel time, small A

Pulmonary vein flow
small S wave, large D wave, rapid D descent, no Ar (atrial failure)

Smith, Mikel, in Otto, 1997
Assessing LVIT and PV flows: Comparing LVIT-A with PV-Ar

Rossvoll O et al. J Am Coll Cardiol 1993;21:1687
Doppler Assessment of Diastole

- Transmitral flow assessment
- Isovolumic relaxation time
- Pulmonary venous flow assessment
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
Color M-Mode Propagation Velocity

Garcia et al. JASE 1999; 12:129
Color M-Mode Propagation Velocity

Measure slope:
• First aliasing velocity
• Begin at mitral tips
• to 4 cm distally
• May be curvilinear
• End-expiration
• Average several measures
• Adjust scale or baseline to produce aliasing (50-75% of peak E transmural PW Doppler)

Garcia, JACC 1998; 32:865
Color M-Mode Propagation Velocity

Garcia, JACC 1998; 32:865
Normal     Delayed Relaxation     Restrictive

LVIT-E normal     LVIT-E reduced     LVIT-E augmented
Vp normal         Vp reduced         Vp reduced

Garcia, JACC 1998; 32:865
Color Flow Propagation Velocity

Resting Normal
LAD balloon occlusion Delay filling
Balloon down Normal

Stugaard M. Circulation 1993;88:2708
Color Flow Propagation Velocity

Stugaard M. Circulation 1993;88:2708
Prognostic Value of LVIT Pattern and Flow Propagation Velocity

• 125 pts with first MI
  – If DT>140 and <240ms and VP>45 cm/s = normal (38 pts)
  – DT>240 = impaired relaxation (38 pts)
  – DT nl and VP<45 cm/s = pseudonormal (26 pts)
  – DT<140 = restrictive (23 pts)

• Progressive higher age, admission HR, peak CK, Killip class, and lower BP
• Progressive larger ventricles, lower EF, worse wall motion score, shorter IVRT, and MR regurgitation
• Restrictive or pseudonormal filling pattern was risk for death, relative risk 4 to 6, more than Killip class, age, wall motion, or peak CK

Doppler Assessment of Diastole

- Transmitral flow assessment
- Isovolumic relaxation time
- Pulmonary venous flow assessment
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
LV transit time in Early Diastole in Normal and Hypertrophic Cardiomyopathy

Pai, R, JASE 1999; 10:532
Transit time from LVIT to LVOT During early and late diastole

Te/Ta = 1.05
Te/Ta = 3.0
Te/Ta = 3.23

Doppler Assessment of Diastole

- Transmitral flow assessment
- Isovolumic relaxation time
- Pulmonary venous flow assessment
- Flow propagation velocity
- Pulse transit time
- Tissue Doppler imaging
Tissue Doppler Echocardiography in Diastolic Function

Garcia, JACC 1998; 32:865
Pulsed Doppler
A-4C
LVIT

Tissue Doppler
Echocardiography
A-4C
MV annulus

Normal Healthy Volunteer
Pseudonormalization Severe Aortic Stenosis

Garcia, JACC 1998; 32:865
Normal

Restriction

Constriction

M-mode
Mitral
Annulus

PW Doppler
LVIT

Tissue
Doppler
Axial
Velocity

Garcia, JACC 1998; 32:865
Measures of Elevated LV Filling Pressure

- LVIT E/A > 2
- LVIT Edceltime < 150 ms
- Short IVRT
- PV S/D << 1
- PVAr > MVAdur
- LAE, low LA EF, atrial septum bulge to right in systole
- LVE

- Caveats: Better if LV EF is low; none is truly reliable; correlation with which measure – LVEDP-Z, PCWP, LV preA, mean LA
Estimating LV Filling Pressure

34 patients with DCM

Tissue Doppler Imaging (Doppler myocardial imaging, DMI) of AV Ring

- Differentiating constriction from restriction
  - 2D echo informs on ventricular function and pericardial calcification
  - PW Doppler of ventricular filling usually differentiates
  - TDI is reported to differentiate, but exceptions are reported now (2 patients with constriction and low early TDI movement and hyperdynamic movement of the apex, a structure that usually is stationary)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normal (young)</th>
<th>Normal (adult)</th>
<th>Delayed Relaxation</th>
<th>Pseudonormal Filling</th>
<th>Restrictive Filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A (cm/s)</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&lt;1</td>
<td>1-2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>&lt;220</td>
<td>&lt;220</td>
<td>&gt;220</td>
<td>150-200</td>
<td>&lt;150</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>60-100</td>
<td>&lt;60</td>
</tr>
<tr>
<td>S/D</td>
<td>&lt;1</td>
<td>≥1</td>
<td>≥1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>AR (cm/s)</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>≥35</td>
<td>≥25</td>
</tr>
<tr>
<td>Vp (cm/s)</td>
<td>&gt;55</td>
<td>&gt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Em (cm/s)</td>
<td>&gt;10</td>
<td>&gt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

Garcia, JACC 1998; 32:865
### Stages of Diastolic Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Normal (young)</th>
<th>Normal (adult)</th>
<th>Delayed Relaxation</th>
<th>Pseudonormal Filling</th>
<th>Restrictive Filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A (cm/s)</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&lt;1</td>
<td>1-2</td>
<td>&gt;2</td>
</tr>
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<td>DT (ms)</td>
<td>&lt;220</td>
<td>&lt;220</td>
<td>&gt;220</td>
<td>150-200</td>
<td>&lt;150</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>60-100</td>
<td>&lt;60</td>
</tr>
<tr>
<td>S/D</td>
<td>&lt;1</td>
<td>≥1</td>
<td>≥1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>AR (cm/s)</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>≥35</td>
<td>≥25</td>
</tr>
<tr>
<td>Vp (cm/s)</td>
<td>&gt;55</td>
<td>&gt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Em (cm/s)</td>
<td>&gt;10</td>
<td>&gt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

Garcia, JACC 1998; 32:865
# Differentiation of Diastolic Problems

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Restrictive Cardiomyopathy</th>
<th>Constrictive Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td><img src="image" alt="ECG waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resp</strong></td>
<td><img src="image" alt="Resp waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MV flow</strong></td>
<td><img src="image" alt="MV flow waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TV flow</strong></td>
<td><img src="image" alt="TV flow waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PV flow</strong></td>
<td><img src="image" alt="PV flow waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HV flow</strong></td>
<td><img src="image" alt="HV flow waveform" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DT image</strong></td>
<td><img src="image" alt="DT image waveform" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hoit, Fig 68-2, From Hurst, 2001
COPD and Diastole: RV and LV

• 48 patients with severe COPD
  – Group 1: 25 pulmonary hypertension
  – Group 2: 23 normal PA pressure
  – Group 3: 59 normal controls

• Pulmonary hypertension:
  – Lower TV and MV E, Higher TV and MV A, longer IVRT and slower propagation velocity than Groups 2 or 3, and no difference between group 2 and 3.

Mitral Regurgitation to estimate tau (relaxation constant)

Digitized LV pressure estimate from MR Doppler

Review References

- Smith MD. Left ventricular diastolic function: clinical utility of Doppler echocardiography. Ch. 3 in Otto CM. *The Practice of Clinical Echocardiography* WB Saunders, 1997
- Pai RG. Newer Doppler measures of left ventricular diastolic function. *Clin Cardiol* 1996;19:277
Pulmonary Venous Flow Pattern

- LV preload and systolic and diastolic function
  - Increased LA pressure - more S dominance if LV systolic function is preserved, lower S if LV systolic dysfunction
  - Impaired relaxation - lower D wave and more S, corresponding to lower MV E
  - Pseudonormal - dominant D wave and larger Ar wave (lower LV compliance)
  - Restrictive has large D and rapid D deceleration, Ar is variable

- RV systolic function

- SBP and peripheral vascular resistance

- Age increases systolic dominance and maybe Ar

- Mitral regurgitation* reduces S wave, reverses if severe MR

- Large ASD causes single continuous antegrade wave and diminished AR wave**

Titin in Diastolic Function

• Also called connectin, after actin and myosin the third most abundant muscle protein, about 10% of muscle protein
• Molecular scaffolding for thick filament formation (highly ordered and tightly attached to thick filament in the A band)
• Giant protein (3,000 kD) providing most of the elasticity of resting striated muscle, especially the I-band region (with thin filament)
• Resting length 1 micrometer spanning from Z to M lines
• Structure: 300 Ig and related FNIII repeats (account for almost 90% of its mass), and PEVK domain (Pro-Glu-Val-Lys) that makes a polyproline helix (PPII)
• Abnormality in titin gene has been implicated in familial hypertrophic cardiomyopathy*

Labeit S et al. Circulation Research 1997;80:290
Titin in Diastolic Function

Erickson HP.
Science 1997;276:1090
Domain architecture and sarcomeric layout of the titin filament. The domain structure of the human soleus titin, as predicted by its 100-kb mRNA, is shown. The 3.7-MD soleus titin peptide contains 297 copies of 100-residue repeats, which are members of the Ig and FN3 superfamilies. Each of these domains folds into a 10- to 12-kD small globular subunit, as shown by structural studies. Specific for the I-band segment of titin are strings of tandemly repeated Ig domains (tandem-Ig titin) and the "PEVK domain," rich in proline, glutamate, valine, and lysine residues. The tandem-Ig and the PEVK region of titin represent those parts of the titin filament that extend during physiological amounts of stretch. Specific for the A-band titin are regular patterns of Ig and FN3 domains, referred to as "super repeats." These super repeats provide multiple and structurally ordered binding sites for myosin and C protein. In addition to the Ig/FN3 repeats and the PEVK region of titin, 8% to 10% of titin's mass is formed by unique sequence insertions. Among the encoded peptides are phosphorylation motifs (P_i) and a serine/threonine kinase. The mapped calpain p94-binding sites are shown. Arrows above the domain pattern indicate the sites at which muscle type-specific alternative splicing occurs. Labeit S et al. Circ Res. 1997.
Current model of titin extension with sarcomere stretch in psoas muscle. The inset shows a typical passive length-tension curve of single psoas myofibrils, with the letters A through D referring to the sarcomere lengths depicted in the main figure. It should be pointed out that this model proposed for psoas titin extension may not adequately address the situation in cardiac muscle, where the contribution of the short PEVK segment to I-band titin extensibility is very small. In cardiac sarcomeres, a significant passive tension increase appears shortly above slack length and seems to be correlated with extension of the tandem-Ig region. The precise mechanism of titin elasticity remains to be elucidated. Color codes are as follows: blue, actin; green, myosin; yellow, PEVK region of titin; and red, non-PEVK domains. The filled circles represent the I-band tandem-Ig modules. T12, N2-A, MIR, and BD6 are known binding sites of titin antibodies used to measure the extension properties of I-band titin in single isolated myofibrils. 

Model for titin in the sarcomere. The titin filament is shown in black, the thin filament (actin) in yellow, and the thick filament (myosin) in red. The epitopes of the titin antibodies T12 and antibodies to the MIR have been mapped in the sarcomere by immunoelectron microscopy; the positions of their epitopes in the titin sequence are known. Antibodies to the titin kinase domain react with the periphery of the M line. Therefore, it can be estimated which sections of the titin sequence are in the Z disc, I band, A band, and the M line. For the I band, the range of variation as predicted by the observed splice variants is indicated. The presumed extensible element of the I band, the PEVK element, is located between the N2 line titin and the second tandem Ig block (zig-zag pattern). Within the thick filament in the central C zone (green stripes), titin binds to both the C protein and myosin and is likely to specify the presence of 11 copies of the 430 Angstrom thick filament repeat in vertebrate striated muscles. Phosphorylation of tandemly arranged Ser-Pro repeats in the Z disc and the M line titin (red P) may control integration of the titin filament into Z discs and M lines during myogenesis.

Labeit M et al. Science 1995;270:293
Domain structure of the cardiac titin filament. The modular architecture of cardiac titin as predicted by its full-length cDNA is shown. A total of 244 copies of 100-residue repeats (indicated by vertical rectangles) are contained, of which 112 belong to the Ig (red) domain and 132 to the FN3 (white) superfamily. The 100-residue repeats are indicated by region and position regardless of whether they are Ig or FN3 domains. The titin kinase domain is shown in black, the PEVK element (N2-B 163-residue variant; see Figure 3 in yellow. Sequences with no homology to database entries comprise 10% of the titin primary structure (blue). The epitope positions of T12 and MIR are indicated. The change in motif organization NH \(_{2}\)-terminal of T12 is proposed to be the Z disc-I band junction; the start of super-repeats COOH-terminal of MIR is proposed to be the beginning of the A band region of titin. Within the A band region, the D zone contains six copies of the seven-module super-repeat (A1 through A42); the C zone contains 11 copies of the 11-module super-repeat (A43 through A163). The positions of the tandemly repeated RMSP and VKSP motifs in the Z disc and M line region of titin are shown [29].

Labett M et al. Science 1995;270:293
Titin in Diastolic Function

Nonfailing

β3 → NOS

β1 > β2

R-AC-cAMP

Contractility

β3

Failing

β3

β2 > β1

Opie LH. Ch 19, “Mechanisms of Cardiac Contraction and Relaxation”
Braunwald’s Heart Disease, 7th ed. 2004.
Acetylcholine
Bradykinin
Opioid

Adenosine
A₁ A₃

PKC

ROS

Mito

KATP

Ca²⁺

ATP↑

Early protection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ventricular Myocyte*</th>
<th>Atrial Myocyte</th>
<th>Purkinje Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Long and narrow</td>
<td>Elliptical</td>
<td>Long and broad</td>
</tr>
<tr>
<td>Length, ( \mu m )</td>
<td>60-140</td>
<td>About 20</td>
<td>150-200</td>
</tr>
<tr>
<td>Diameter, ( \mu m )</td>
<td>About 20</td>
<td>5-6</td>
<td>35-40</td>
</tr>
<tr>
<td>Volume, ( \mu m^3 )</td>
<td>15,000-45,000</td>
<td>About 500</td>
<td>135,000-250,000</td>
</tr>
<tr>
<td>T-tubules</td>
<td>Plentiful</td>
<td>Rare or none</td>
<td>Absent</td>
</tr>
<tr>
<td>Intercalated disc</td>
<td>Prominent end-to-end transmission</td>
<td>Side-to-side as well as end-to-end transmission</td>
<td>Very prominent abundant gap junctions. Fast; end-to-end transmission</td>
</tr>
<tr>
<td>General appearance</td>
<td>Mitochondria and sarcomeres very abundant. Rectangular branching bundles with little interstitial collagen</td>
<td>Bundles of atrial tissue separated by wide areas of collagen</td>
<td>Fewer sarcomeres, paler</td>
</tr>
</tbody>
</table>

### Composition and Function of Ventricular Cell

<table>
<thead>
<tr>
<th>Organelle</th>
<th>% of Cell Volume</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myofibril</td>
<td>About 50-60</td>
<td>Interaction of thick and thin filaments during contraction cycle</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>16 in neonate; 33 in adult rat; 23 in adult human</td>
<td>Provide adenosine triphosphate chiefly for contraction</td>
</tr>
<tr>
<td>T system</td>
<td>About 1</td>
<td>Transmission of electrical signal from sarcolemma to cell interior</td>
</tr>
<tr>
<td>Sarcoplasmic reticulum (SR)</td>
<td>33 in neonate; 2 in adult</td>
<td>Takes up and releases Ca(^{2+}) during contraction cycle</td>
</tr>
<tr>
<td>Terminal cisternae of SR</td>
<td>0.33 in adult</td>
<td>Site of calcium storage and release</td>
</tr>
<tr>
<td>Rest of network of SR</td>
<td>Rest of volume</td>
<td>Site of calcium uptake en route to cisternae</td>
</tr>
<tr>
<td>Sarcolemma</td>
<td>Very low</td>
<td>Control of ionic gradients; channels for ions (action potential); maintenance of cell integrity; receptors for drugs and hormones</td>
</tr>
<tr>
<td>Nucleus</td>
<td>About 5</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Lysosomes</td>
<td>Very low</td>
<td>Intracellular digestion and proteolysis</td>
</tr>
<tr>
<td>Sarcoplasm (+ cytoplasm) (+ nuclei + other structures)</td>
<td>About 12 in adult rat; 18 in humans</td>
<td>Provides cytosol in which rise and fall of ionized calcium occur; contains other ions and small molecules</td>
</tr>
<tr>
<td>Agonist</td>
<td>Ionic Current</td>
<td>Effect</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Beta-adrenergic stimulation</strong></td>
<td>$I_{\text{Ca}}$ increased</td>
<td>+Inotropic</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{K}}$ increased</td>
<td>↓APD, ↑filling time</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{Na}}$ increased</td>
<td>↓APD, ↑filling time</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{to}}$ increased</td>
<td>↓APD, ↑filling time</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{f}}$ increased</td>
<td>↑Heart rate</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{Na}}$ increased</td>
<td>↑Contraction, ↑conduction</td>
</tr>
<tr>
<td><strong>Acetylcholine (ACh) during beta stimulation</strong></td>
<td>$I_{\text{Ca}}$ decreased</td>
<td>–Inotropic</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{Na}}$ decreased</td>
<td>–Dromotropic</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{f}}$ decreased</td>
<td>–Chronotropic</td>
</tr>
<tr>
<td><strong>ACh direct effect on K$^+$ currents</strong></td>
<td>$I_{\text{kACH}}$ and $I_{\text{kATP}}$ increased</td>
<td>Heart rate ↓</td>
</tr>
<tr>
<td><strong>Alpha-adrenergic stimulation</strong></td>
<td>$I_{\text{to}}$ decreased</td>
<td>+Inotropic</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{k}}$ decreased</td>
<td>+Inotropic</td>
</tr>
<tr>
<td></td>
<td>$I_{\text{kACH}}$ decreased</td>
<td>Atrial current, effects not clear</td>
</tr>
</tbody>
</table>

*Data from Matsuda et al.\textsuperscript{130}  
\textsuperscript{1}Data from Matsuda et al.\textsuperscript{131}  
\textsuperscript{2}Data from Volders et al.\textsuperscript{135}  
\textsuperscript{3}Data from Chang and Cohen\textsuperscript{132}  
\textsuperscript{4}Data from Kurachi.\textsuperscript{133}  
\textsuperscript{5}Data from Fedida.\textsuperscript{134}  
– = negative; + = positive; ↑ = increased; ↓ = decreased; APD = action potential duration; ATP = adenosine triphosphate.
<table>
<thead>
<tr>
<th>TABLE 19–3 The Cardiac Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Ventricular Contraction</strong></td>
</tr>
<tr>
<td>Isovolumic contraction (b)</td>
</tr>
<tr>
<td>Maximal ejection (c)</td>
</tr>
<tr>
<td><strong>Left Ventricular Relaxation</strong></td>
</tr>
<tr>
<td>Start of relaxation and reduced ejection (d)</td>
</tr>
<tr>
<td>Isovolumic relaxation (e)</td>
</tr>
<tr>
<td>LV filling: rapid phase (f)</td>
</tr>
<tr>
<td>Slow LV filling (diastasis) (g)</td>
</tr>
<tr>
<td>Atrial systole or booster (a)</td>
</tr>
</tbody>
</table>

The letters a to g refer to the phases of the cardiac cycle shown in Wiggers’ diagram (Fig. 19–19). These letters are arbitrarily allocated so that atrial systole (a) coincides with the A wave and (c) with the C wave of the jugular venous pressure.

LV = left ventricular.
<table>
<thead>
<tr>
<th>Physiological Systole</th>
<th>Cardiologic Systole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovolumic contraction</td>
<td>From $M_1$ to $A_2$, including:</td>
</tr>
<tr>
<td>Maximal ejection</td>
<td>Major part of isovolumic contraction*</td>
</tr>
<tr>
<td></td>
<td>Maximal ejection</td>
</tr>
<tr>
<td></td>
<td>Reduced ejection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiological Diastole</th>
<th>Cardiologic Diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced ejection</td>
<td>$A_2$-$M_1$ interval (filling phases included)</td>
</tr>
<tr>
<td>Isovolumic relaxation</td>
<td></td>
</tr>
<tr>
<td>Filling phases</td>
<td></td>
</tr>
</tbody>
</table>

*Note that $M_1$ occurs with a definite albeit short delay after the start of LV contraction.
### TABLE 19–6 Characteristics of Stunning, Hibernation, and Ischemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stunning</th>
<th>Hibernation</th>
<th>True Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial mechanical function</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>Postischemic: normal/high</td>
<td>Modestly reduced or low normal; reduced coronary vascular reserve</td>
<td>Most severely reduced</td>
</tr>
<tr>
<td>Myocardial energy metabolism</td>
<td>Harmful effects of fatty acid fuels versus glucose</td>
<td>Reduced or low normal; in steady state with intermittent ischemia-reperfusion</td>
<td>Reduced; increasingly severe as ischemia proceeds</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to days; merges with delayed recovery from ischemia over weeks</td>
<td>Days to hours to months; occasionally longer</td>
<td>Minutes to hours; then lethal</td>
</tr>
<tr>
<td>Outcome</td>
<td>Full spontaneous recovery</td>
<td>Variable recovery if revascularized</td>
<td>Myocyte necrosis if severe ischemia persists</td>
</tr>
<tr>
<td>Proposed change in metabolic regulation of calcium</td>
<td>Cytosolic overload of calcium in early reperfusion with damage to contractile proteins</td>
<td>Hypothetically enough glycolytic ATP to prevent contracture (glucose mismatch)</td>
<td>Insufficient glycolytic ATP to prevent calcium overload and irreversibility</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate.

### TABLE 19–7 Abnormalities of Calcium Cycling in Heart Failure

<table>
<thead>
<tr>
<th>Subcellular</th>
<th>Organelle</th>
<th>Whole Heart</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERCA2a↓</td>
<td>SR Ca depleted</td>
<td>Negative FFR</td>
<td>127</td>
</tr>
<tr>
<td>RyR hyperphosphorylated</td>
<td>SR Ca release↓ Diastolic leak</td>
<td>Rate of contraction↓</td>
<td>126</td>
</tr>
<tr>
<td>Na/Ca exchange ↑</td>
<td>Released Ca extruded</td>
<td>Rate of contraction↓</td>
<td>126</td>
</tr>
<tr>
<td>Prolonged APD and RyR changes</td>
<td>Cytosolic Ca↑ Diastolic tension↑ with pacing</td>
<td>Positive FFR</td>
<td>137</td>
</tr>
</tbody>
</table>

APD = action potential duration; FFR = force-frequency relationship; RyR = ryanodine receptor; SERCA = sarcoplasmic reticulum Ca²⁺-adenosine triphosphatase; SR = sarcoplasmic reticulum.

Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
<table>
<thead>
<tr>
<th>TABLE 20–1</th>
<th>Uses of Cardiac Function Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Prognostication</td>
<td></td>
</tr>
<tr>
<td>Timing of intervention</td>
<td></td>
</tr>
<tr>
<td>Mechanism of therapy</td>
<td></td>
</tr>
<tr>
<td>Assessment of therapy</td>
<td></td>
</tr>
<tr>
<td>Detection of complications</td>
<td></td>
</tr>
<tr>
<td>Surrogate for clinical outcomes</td>
<td></td>
</tr>
</tbody>
</table>

Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
### TABLE 20–2  Definitions of Terms Used to Describe Systolic and Diastolic Function

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload</td>
<td>Distending force of the ventricular wall, which is highest at end-diastole and is responsible for sarcomere length at the beginning of systolic contraction</td>
</tr>
<tr>
<td>Afterload</td>
<td>Resisting force of the ventricular wall during systolic ejection, which is necessary to overcome peripheral vascular resistance or impedance; measures of afterload are peak-systolic, mean-systolic, or end-systolic wall stress</td>
</tr>
<tr>
<td>Contractility</td>
<td>Intrinsic ability of the myocardium to generate force at a certain rate and time (controlled for loading conditions)</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Stroke volume multiplied by heart rate</td>
</tr>
<tr>
<td>Stroke work</td>
<td>Mean systolic blood pressure multiplied by stroke volume</td>
</tr>
<tr>
<td>Stroke force</td>
<td>Stroke work per ejection time</td>
</tr>
<tr>
<td>Stress</td>
<td>Force per area</td>
</tr>
<tr>
<td>Wall stress</td>
<td>Pressure multiplied by radius, divided by wall thickness × 2</td>
</tr>
<tr>
<td>Compliance or distensibility</td>
<td>Change in volume per change in pressure (dV/dP)</td>
</tr>
<tr>
<td>Elastance</td>
<td>Slope of the end-systolic pressure-volume relation</td>
</tr>
<tr>
<td>Elasticity</td>
<td>Property of a material to restore its initial length or geometry after distending force has been removed</td>
</tr>
<tr>
<td>Strain</td>
<td>Length change in percent of initial length; two definitions are used: LaGrangian strain $e = (l - l_0)/l_0$ and natural strain $e = \ln(l/l_0)$</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Pressure per volume change (dP/dV). <em>Ventricular stiffness</em> is a measure for changes of the ventricle as a whole; <em>myocardial stiffness</em> is a measure for changes of the myocardium itself. Ventricular properties are characterized by instantaneous pressure-volume relations, whereas myocardial properties are best described by stress-strain relations.</td>
</tr>
<tr>
<td>Creep</td>
<td>Time-dependent lengthening of a material in the presence of a constant force</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td>Time-dependent decrease of stress in the presence of a constant length</td>
</tr>
<tr>
<td>Viscoelasticity</td>
<td>Resistance of a material to length changes (strain) or the velocity of length changes (strain rate)</td>
</tr>
</tbody>
</table>
Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
Rotation-LV area-loop

C (n = 11)  
R (n = 12)  
AS (n = 11)

Apical rotation (%) vs LV area (%)
<table>
<thead>
<tr>
<th>Index</th>
<th>Sensitive to Inotropic Changes</th>
<th>Dependence On Preload</th>
<th>Dependence On Afterload</th>
<th>Dependence On Ventricular Volume or Mass</th>
<th>Ease of Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction; fractional shortening</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>End-systolic volume or dimension</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>VCF</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Afterload-corrected VCF</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>ESPVR</td>
<td>++++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>End-systolic stiffness</td>
<td>++++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Preload recruitable stroke work</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Left ventricular dP/dt</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

ESPVR = slope of end-systolic pressure-volume relation; VCF = velocity of circumferential fiber shortening; dP/dt = rate of ventricular pressure rise. Adapted from Carabello B: Evolution of the study of left ventricular function: Everything old is new again. Circulation 105:2701, 2002.

Carroll JD and Hess OM. Ch 20, “Assessment of Normal and Abnormal Cardiac Function” Braunwald’s Heart Disease, 7th ed. 2004.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Echo/Doppler</th>
<th>MR imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV volume</td>
<td>Standard 2D views allow measurement of multiple dimensions (Fig. 20-15). The parasternal long-axis view shows the outflow tract diameter</td>
<td>Segmentation of individual slices provides chamber size. Adjacent areas are then summed to provide volume and shape measurements</td>
</tr>
<tr>
<td>Regional wall motion</td>
<td>Free RV wall and interventricular septum are imaged and paradoxical motion can easily be detected</td>
<td>Cine MR imaging provides contrast between the blood pool and the myocardial wall. RV wall motion is assessed using RVOT cines in the sagittal and short-axis cine images</td>
</tr>
<tr>
<td>RV mass</td>
<td>Approximated by wall thickness determinations along with chamber size measurements</td>
<td>Myocardium from the junction between the RV free wall and the interventricular septum can be traced on each slice from the base to the apex, including trabeculations. Myocardial volume computed from summated multiple slices is multiplied by 1.05 to give the mass in grams</td>
</tr>
<tr>
<td>RV wall composition</td>
<td>Not well studied in transthoracic images. Intracardiac ultrasound provides higher resolution data</td>
<td>MR imaging is potentially useful to distinguish fat from muscle</td>
</tr>
<tr>
<td>Regurgitant fraction</td>
<td>Doppler profiles provide semiquantitative approach</td>
<td>True regurgitant volumes can be measured from phase velocity maps in the main pulmonary artery and aortic root</td>
</tr>
</tbody>
</table>

RV = right ventricular; RVOT = RV outflow tract; 2D = two-dimensional.