ESC 2010

“DIABETIC CARDIOMYOPATHY”

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DISCLOSURES

• Consultant/speaker/honoraria: none since 06/31/08

• Editorial Boards: American Heart Journal, American Journal of Cardiology (associate editor); Circulation; Circulation-Heart Failure; Circulation- Quality Outcomes; Congestive Heart Failure

• Guideline writing committees: ACC/AHA, chronic HF; and ACC/AHA Guideline Taskforce

• Federal appointments: FDA: Past Chair, Cardiovascular Device Panel; ad hoc consultant, FDA; member, NIH CICS study section

• Volunteer Appointments: American Heart Association- President, American Heart Association, 2009-2010
Risk factors
- Hyperlipidemia
- Hypertension
- Diabetes
- Insulin resistance

Atherosclerosis
- LVH

Coronary thrombosis
- Myocardial ischemia
- Coronary thrombosis

Myocardial infarction
- Arrhythmia
- Loss of muscle
- Sudden death
- Remodeling
- Ventricular dilation
- Heart failure
- Death

Remodeling

Heart failure
- Death

From Risk Factors to Heart Failure: The Cardiovascular Continuum

Adapted from Dzau and Braunwald. Am Heart J. 1991;131:1244-1263.
At Risk for Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF.

**Stage B**
Structural heart disease but without signs or symptoms of HF.

**STAGE C**
Structural heart disease with prior or current symptoms of HF.

**STAGE D**
Refractory HF requiring specialized interventions.

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**Therapy Goals**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**Drugs**
- ACEI or ARB in appropriate patients for vascular disease or diabetes

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**Therapy Goals**
- All measures under Stage A Drugs
- ACEI or ARB in appropriate patients
- Beta-blockers in appropriate patients

**Development of symptoms of HF**
- E.g. Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**Therapy Goals**
- All measures under Stages A and B
- Dietary salt restriction

**Drugs For Routine Use**
- Diuretics for fluid retention
- ACEI
- Beta-blockers

**Drugs in Selected Patients**
- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates

**Devices In Selected Patients**
- Biventricular pacing
- Implantable defibrillators

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**Therapy Goals**
- Appropriate measures under Stages A, B, C
- Decision re: appropriate level of care

**Options**
- End-of-life care
- Extraordinary measures
  - Heart transplant
  - Chronic inotropes
  - Permanent mechanical support
  - Experimental surgery or drugs
<table>
<thead>
<tr>
<th>Stage</th>
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**e.g. Patients with:**
- hypertension
- atherosclerotic disease
- diabetes
- obesity
- metabolic syndrome *or*

**Patients**
- using cardiotoxins
- with FHx CM

**Therapy Goals**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**Drugs**
- ACEI or ARB in appropriate patients for vascular disease or diabetes

**Heart Failure**
- Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes
  - Obesity
  - Metabolic syndrome
  - Cardiotoxins
  - FHx CM
Diabetic Cardiomyopathy

- Definition: “a distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease”

- Original description: Rubler et al. in 4 diabetic patients with HF but no evidence of CAD by angiography or by pacing [lactate production]

- Phenotype:
  - Increased LVEDP
  - Normal LVEDV
  - Decreased LV compliance

Rubler et al. American Jnl of Cardiology 30. 1972
Diabetic Cardiomyopathy

• Epidemiology
  ▪ Diabetes affects 180 million worldwide
  ▪ 2/3 of patients with established CVD have impaired glucose homeostasis; affects 30% of HF patients
  ▪ Every 1% increase in Hgb A$_{1c}$ leads to an 8% increase in HF; in UKPDS, for Hgb A$_{1c}$ < 6%, 2.3 HF events/100 person-years; but for > 10%, 11.9 HF events/100 person – years
  ▪ Prevalence of HF in general population: 1-4%
  ▪ Prevalence of HF in diabetic population: 15%
Epidemiology of Diabetic CHF

- Framingham Study
  - 2 diabetic males
  - 5 diabetic females
  - 4 young diabetic males
  - 8 young diabetic females

- Nursing home data
  - Initially without CHF
  - Over 43 months, 23% non-diabetic, 39% with diabetes

Diabetic Cardiomyopathy

• Increased risk of HF in diabetic patients with retinopathy c/w a microvascular etiology of diabetic cardiomyopathy [Cheung N, et al. JACC, 2008; 51: 1573 - 1578]

• Retinal arteriolar narrowing associated with LV remodeling [ref. MESA]
Diabetic Cardiomyopathy

- Pathologically characterized by ventricular hypertrophy, myocardial fibrosis and fat droplet deposition
- Other physical characteristics:
  - Early changes in diastolic function — affects up to 75% asymptomatic diabetic patients
  - Collagen deposition
  - Presence of advanced glycosylation end products [AGEs]
  - Late compromise of LV systolic function
    - Earliest evidence is seen in long-axis systolic dysfunction with NL EF

Diabetic Cardiomyopathy

• Diagnosis
  - ECHOCARDIOGRAPHY- diagnosis of LVH and with pulsed wave Doppler, inferences RE: diastolic function; Tissue Doppler aids in the assessment of LV strain
  - CARDIAC MRI- excellent for measuring LV mass
  - CLINICAL! – must rule out CAD, HTN, valvular heart disease and other forms of cardiomyopathy
Diabetic Cardiomyopathy

• Mechanisms/Pathophysiology
  ▪ Hyperglycemia
    • Increased ROS
  ▪ Hyperinsulinemia
    • Activation of SNS & RAAS
  ▪ Advanced Glycation End Products
    • Increased due to oxidative stress
    • RAGE [receptor for AGE] is also increased
    • Collagen Deposition
    • Expression of NF-kB and change in cardiac myosin expression
  ▪ Enhanced Free Fatty Acid Utilization
    • Leads to FFA accumulation & lipotoxicity
PARP- poly ADP-ribose polymerase
PKC- protein kinase C
DAG- diacylglycerol
Diabetes Mellitus

Elevated FFAs
(dominant energy source for myocardium in diabetics)
- Due to increased beta-oxidation

- Ca transporter protein dysfunction
- (-) PDH
- Long chain acyl carnitines (+)
  - Ceramide (+)
  - Glycolytic intermediates (+)
    - Uncoupling of oxidative phosphorylation

- Impaired contraction and relaxation
- Apoptosis

DIABETIC CARDIOMYOPATHY
Hyperglycemia → Cytokine and RAAS Activation → Collagen/Fibrotic Tissue Deposition → Advanced Glycosylation → Stiffened Myocardium → Myocardial Dysfunction
Diabetic Cardiomyopathy

Is diabetic microangiopathy a factor?

• No increase in lactate production with cardiac pacing
• Endothelial dysfunction may lead to repeated vaso-constriction, reperfusion injuries, and myocardial dysfunction
• Increased small vessel permeability leading to interstitial edema, fibrosis, and myocardial dysfunction
• Diabetic subjects have a defect in reactive angiogenesis in response to ischemia that could lead to myocardial dysfunction

HMGB1: the missing link between diabetes mellitus and heart failure

- HMGB1- high mobility group box-1 protein; initiates a robust signal for host defense in response to cell injury or death
- Mouse cardiomyocytes exposed to elevated glucose expressed HMGB1 and increased binding to RAGE; followed by increased NF-kB binding activity and sustained increases in TNF-alpha and IL-6 expression
- **HMGB1 can be inhibited by Box A treatment**

Volz, Seidel, Laohachewin et al. Basic Research in Cardiology July 2010
Diabetic Cardiomyopathy- SUMMARY

- Likely a unique clinical entity but debate remains
- Requires the absence of CAD and the presence of LVH, fibrosis and decreased compliance
- Cause is likely multifactorial but clearly related to hyperglycemia, hyperinsulinemia, enhance FFA utilization, and oxidative stress
- No specific therapies and clearly unaffected by current anti-diabetic agents [esp., TZDs]
- Future considerations involve earlier and more precise diagnosis, identification of the culprit pathophysiology and elucidation of new treatment targets, e.g. HMGB1