Reversing Coronary Artery Disease and Heart Muscle Damage

William T. Abraham, MD, FACP, FACC, FAHA, FESC
Professor of Medicine, Physiology, and Cell Biology
Chair of Excellence in Cardiovascular Medicine
Director, Division of Cardiovascular Medicine
Associate Dean for Clinical Research
Director, Clinical Trials Management Office
Deputy Director, Davis Heart & Lung Research Institute
Coronary Artery Disease (CAD)

Normal Artery

Narrowing of Artery

Lipid deposit of plaque
# Major Risk Factors for CAD

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Non-Modifiable</th>
<th>Emerging Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>Family history</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Abnormal cholesterol levels</td>
<td>Age</td>
<td>Elevated lipoprotein (a) levels</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>High CRP</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>Low HDL</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>High TG</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>Poor diet</td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstructive Sleep Apnea</td>
</tr>
</tbody>
</table>
Major Risk Factors You Can Modify, Treat, or Control by Changing Your Lifestyle or Taking Medicine

- Tobacco smoke — Smokers' risk of developing coronary heart disease is 2-4 times that of nonsmokers. Cigarette smoking is a powerful independent risk factor for sudden cardiac death in patients with coronary heart disease; smokers have about twice the risk of nonsmokers. Cigarette smoking also acts with other risk factors to greatly increase the risk for coronary heart disease. Exposure to other people's smoke increases the risk of heart disease even for nonsmokers.
High blood cholesterol — As blood cholesterol rises, so does the risk of coronary heart disease. When other risk factors (such as high blood pressure and tobacco smoke) are present, this risk increases even more. A person's cholesterol level is also affected by age, sex, heredity, and diet.
Major Risk Factors You Can Modify, Treat, or Control by Changing Your Lifestyle or Taking Medicine

- High blood pressure — High blood pressure increases the heart's workload, causing the heart to thicken and become stiffer. It also increases your risk of stroke, heart attack, kidney failure, and congestive heart failure. When high blood pressure exists with obesity, smoking, high blood cholesterol levels, or diabetes, the risk of heart attack or stroke increases several times.
Physical inactivity — An inactive lifestyle is a risk factor for coronary heart disease. Regular, moderate-to-vigorous physical activity helps prevent heart and blood vessel disease. The more vigorous the activity, the greater your benefits. However, even moderate-intensity activities help if done regularly and long term. Physical activity can help control blood cholesterol, diabetes, and obesity, as well as help lower blood pressure in some people.
Major Risk Factors You Can Modify, Treat, or Control by Changing Your Lifestyle or Taking Medicine

- Obesity and overweight — People who have excess body fat, especially if a lot of it is at the waist, are more likely to develop heart disease and stroke even if they have no other risk factors. Excess weight increases the heart's work. It also raises blood pressure and blood cholesterol and triglyceride levels, and lowers HDL ("good") cholesterol levels. It can also make diabetes more likely to develop. Losing even as few as 10 pounds, you can lower your heart disease risk.
Major Risk Factors You Can Modify, Treat, or Control by Changing Your Lifestyle or Taking Medicine

- Diabetes mellitus — Diabetes seriously increases your risk of developing cardiovascular disease. Even when glucose (blood sugar) levels are under control, diabetes increases the risk of heart disease and stroke, but the risks are even greater if blood sugar is not well controlled. About three-quarters of people with diabetes die from some form of heart or blood vessel disease.
A Heart Attack Waiting to Happen

*This is not a photo of Carl*
## Major Risk Factors for CAD: Carl Then

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Carl Then</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>✔</td>
</tr>
<tr>
<td>Abnormal cholesterol levels</td>
<td>✔</td>
</tr>
<tr>
<td>Diabetes</td>
<td>✔</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>✔</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>✔</td>
</tr>
<tr>
<td>Poor diet</td>
<td>✔</td>
</tr>
</tbody>
</table>

In addition, Carl had obstructive sleep apnea.
Carl Then: Coronary Angiogram

- Occluded LAD
- Narrowed Cx
What Can We Do to Eliminate CAD?

- 80% of heart disease is preventable
- Less than 5% of the U.S. population is doing what they need to do to prevent it
- Lifestyle change is the key
Prevention of CAD

- Quit smoking
- Increase Physical Activity
  - Minimum of 30 minutes of moderate intensity physical activity ≥ 5 days per week
  - For those who need to lose weight or sustain weight loss, 60-90 minutes of moderate intensity physical activity ≥ 5 days per week
- Achieve / Maintain Ideal Weight
  - BMI between 18.5 and 24.9
  - Waist circumference < 35 inches
Prevention of CAD

- Improve Diet
  - Fruits and vegetables
  - Whole grain, high-fiber foods
  - Fish, at least twice a week
  - Saturated fats < 10% of calories, < 300mg cholesterol/d
  - Limit trans fatty acid intake (<1% of calories)
  - Limit salt and sodium intake (<2.4 g/d)
  - Alcohol no more than 1 drink per day
  - Limit portion sizes
Prevention of CAD

- Lower Blood Pressure
  - goal \( \leq 120/80 \) mmHg

- Treat Dyslipidemia (Lower High Cholesterol)
  - Total Cholesterol goal < 200 mg/dL
  - LDL goal < 100 mg/dL (or < 70 for established CAD)
  - Triglycerides goal < 150 mg/dL
  - HDL goal > 50 mg/dL

- Treat Diabetes Mellitus (Lower Blood Sugar)
  - \( \text{HbA}_{1c} < 7\% \)
Key Medications for CAD Treatment

- Angiotensin Converting Enzyme (ACE) Inhibitors
- Beta-Blockers
- Aspirin
- Statins
- Others
## Major Risk Factors for CAD: Carl Now

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Carl Then</th>
<th>Carl Now</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>✔</td>
<td>Blood pressure 110/80</td>
</tr>
<tr>
<td>Abnormal cholesterol levels</td>
<td>✔</td>
<td>Cholesterol 102, LDL 47, Triglycerides 58</td>
</tr>
<tr>
<td>Diabetes</td>
<td>✔</td>
<td>Off of insulin</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>✔</td>
<td>BMI from 28.6 to 24.2</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>✔</td>
<td>Very active</td>
</tr>
<tr>
<td>Poor diet</td>
<td>✔</td>
<td>Better diet</td>
</tr>
</tbody>
</table>

In addition, Carl’s obstructive sleep apnea has completely gone away with weight loss. Carl is taking the essential medications to treat CAD.
Carl Now: Coronary Angiogram

Normal Cx

Patent LAD Graft
Getting Enough Sleep Might Just Save Your Heart

- Sleeping <5 hours of sleep/night is associated with more blockages in heart arteries vs those getting >5 hours of sleep

- Each additional hour of sleep = lowering systolic blood pressure by ~17mm Hg

- Insufficient sleep linked to increased risk for heart disease, colon cancer, breast cancer, and diabetes
In Summary, What Can You Do to Protect Your Heart?

- Don’t Smoke / Quit Smoking
- Know your Blood Pressure / Control your Blood Pressure
- Know your Cholesterol / Control your Cholesterol
- Maintain a Low Fat Diet
- Maintain a Healthy Weight
- Control your Stress / Sleep > 5 hours/night
- Exercise Regularly / Not Optional, Daily Dose
- Prevent or Control diabetes
- Know your Family History
- Be Aware of Chest Pain
- Be Screened for Heart disease
Adverse Changes in Heart Structure and Function After a Heart Attack

1 week

EDV 137 mL ESV 80 mL
EF 41%

3 months

EDV 189 mL ESV 146 mL
EF 23%

Apical 4 Chamber View
This process is reversible!

- Weak hearts can get stronger
- Large hearts can get smaller
- These changes improve quality of life and longevity
Approved Treatments Promoting Reverse Remodeling of the Failing Heart

- ACE Inhibitors/Angiotensin Receptor Blockers*
- Beta-Blockers*
- Aldosterone Antagonists*
- Cardiac Resynchronization Therapy*
- Surgical Approaches/Devices
  - LVADs*
  - Mitral valve repair
  - Others

*These therapies save lives!
Investigational Devices to Improve Heart Function
What is Cardiac Contractility Modulation?

- Non-excitatory electrical signals delivered to the ventricles
- Applied during the absolute refractory period of the heart contraction
- Increases cardiac contractility without an increase in myocardial work (increases efficiency of the heart as a pump)
OPTIMIZER IVs: Delivers CCM Signals to Heart

**IPG**
- Small,
- Rechargeable battery,
- Flexible positioning

**Charger**
- Portable,
- Battery driven,
- Integrity test

**Programmer**
- Intuitive user interface,
- Remote support
Cardiac Contractility Modulation

- Studies show that CCM:
  - Increases heart function and structure
  - Improves quality of life, exercise capacity, and functional status
  - May prolong life
The Baroreflex as a Therapeutic Target

Integrated Autonomic Nervous System Response
Inhibits **Sympathetic** Activity
Enhances **Parasympathetic** Activity

- Carotid Baroreceptor Stimulation
  - ↓ HR
  - ↓ Remodeling
  - ↓ Elevated BP
  - ↑ Vasodilation
  - ↑ Diuresis
  - ↑ Renin secretion
CLINICAL RESEARCH

Baroreflex Activation Therapy for the Treatment of Heart Failure With a Reduced Ejection Fraction

William T. Abraham, MD,* Michael R. Zile, MD,†† Fred A. Weaver, MD,§ Christian Butter, MD,|| Anique Ducharme, MD, MSc,¶ Marcel Halbach, MD,# Didier Klug, MD,** Eric G. Lovett, PhD,†† Jochen Müller-Ehmsen, MD,‡‡ Jill E. Schafer, MS,§§ Michele Senni, MD,|||| Vijay Swarup, MD,¶¶ Rolf Wachter, MD,## William C. Little, MD***
### BAT for HFrEF Trial Results: Summary

<table>
<thead>
<tr>
<th>Measure</th>
<th>Difference</th>
<th>p value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (% improved)</td>
<td>31</td>
<td>&lt;0.01</td>
<td>BAT</td>
</tr>
<tr>
<td>MLWHF QoL Score (points)</td>
<td>20</td>
<td>&lt;0.001</td>
<td>BAT</td>
</tr>
<tr>
<td>6-MHW Distance (m)</td>
<td>58</td>
<td>&lt;0.01</td>
<td>BAT</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)*</td>
<td>342</td>
<td>0.02</td>
<td>BAT</td>
</tr>
<tr>
<td>LVEF (absolute %)</td>
<td>2.5</td>
<td>0.15</td>
<td>BAT</td>
</tr>
<tr>
<td>Hospitalization Days for Worsening HF (days/pt/yr)</td>
<td>6.4</td>
<td>0.05</td>
<td>BAT</td>
</tr>
</tbody>
</table>

* Median
Parachute Ventricular Partitioning Device

**Parachute Implant**

- **Anchor (Laser Cut)**
  Engages LV Wall (2mm)

- **Suture (Polypropylene)**
  Collapses Device. Supports ePTFE at the Edge

- **Membrane (ePTFE)**
  Dual layer occlusive membrane. Allows tissue growth.

- **Frame (Nitinol)**
  16 Arms Laser Cut from a Single Tube

- **Foot (Urethane)**
  Radiopaque. Shock Absorber

<table>
<thead>
<tr>
<th></th>
<th>65mm</th>
<th>75mm</th>
<th>85mm</th>
<th>95mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard (+3mm)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Short</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Guide Catheter**

3 shapes (14 or 16Fr)

**Delivery System**

20cc balloon is inflated to anchor device
Parachute Ventricular Partitioning Device: Mechanism of Action

(1) “RESTORING EFFECT”
Reduces wall stress in the upper chamber by changing LV geometry and reducing volume

(2) “TRAMPOLINE EFFECT”
Replaces the stiff/rigid scar with a more compliant Parachute that provides outward force by the anchors to aid in diastolic filling

Improves diastolic compliance that reduces end diastolic filling pressures
Parachute Clinical Effects in Trials to Date

- Improves in functional status, quality of life, and exercise capacity
- Lower than expected rates of morbidity and mortality suggested by totality of study data
Intra-Atrial Shunt Device

L to R shunting self regulates LAP elevations preventing pulmonary congestion and hospitalization

Leaflets function to improve forward-flow & prevent reverse shunting (oxygen desaturation and paradoxical embolization)

Hourglass shape Nitinol frame for laminar flow & secure septal retention (orifice diameter 5.1mm)

ePTFE skirt

Porcine pericardial leaflets

RA LA
V-Wave Clinical Experience Summary

- More than 25 patients implanted to date
- HF patients with both reduced and preserved EF (75% with reduced-EF)
- Marked improvement in quality of life and exercise capacity
- No worsening in RV function
- No device related adverse events
- No device malfunctions; no migrations or embolization
Bottom Line

- Coronary artery disease and heart muscle damage are potentially reversible
- Lifestyle changes and medications are key
- Future devices may add incremental value to currently available therapies