State-of-the-Art in CVD Risk Assessment
Risk Factors vs. Structural vs. Functional Tests

AUGUST 6, 2015 4:30 PM CDT

Presenter:
Morteza Naghavi, M.D.,
Chairman of Scientific Advisory Board

www.endothelix.com

For follow up and slides, please contact Will Sotka
william.sotka@endothelix.com
Disclaimer:

Opinions presented in this presentation solely reflect my personal views and should not be attributed to Endothelix, SHAPE, or any other individuals or organization.
Let’s Begin with the End in Mind
Screening for Atherosclerosis
Risk Factors vs Disease

**Numerous Risk Factors**
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- Over 200 risk factors have been reported.

**Examples of Arterial Structure Tests**
- Carotid IMT and Plaque Measured by Ultrasound
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- Coronary Calcium Score Measured by CT
- Ankle Brachial Index

**Examples of Arterial Function Tests**
- Brachial Vasoreactivity Measured by Ultrasound
- Vascular Compliance Measured by Radial Tonometry
- Microvascular Reactivity Measured by Fingertip Tonometry
The Problem
The CVD Pandemic: Annual Incidence

> 15 Million Heart Attacks Each Year

Source: World Heart Federation

Incidence rates based on 1995 data
Adapted from American Heart Association: Heart and Stroke Statistical Update, 1998.
Unpredicted
In >50% of victims, the first symptom of asymptomatic atherosclerosis is a sudden cardiac death or acute MI.
The real problem:
Not knowing the risk
Traditional Risk Factors Miss the Majority of High Risk Patients
Akosah et al. JACC 2003:41 1475-9

1998 – 2002. 222 patients with 1st acute MI, no prior CAD, no DM. Men <55 y/o (75%), Women <65. 40% hypertensive

What was NCEP risk before the MI? Would they have received statin therapy or more intensive statin therapy?

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>10 yr risk &gt;20%</th>
<th>Goal LDL&lt;100 mg/dL</th>
<th>(optional &lt; 70 mg/dL)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>6%</td>
<td></td>
<td></td>
<td>6%</td>
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<td></td>
<td>6%</td>
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<td>6%</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td></td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>8%</td>
<td>10%</td>
<td>18%</td>
<td>61%</td>
</tr>
<tr>
<td>Lower / Moderate Risk</td>
<td>9%</td>
<td>70%</td>
<td>10%</td>
<td>18%</td>
</tr>
</tbody>
</table>

> 70% the day before the event would have been classified as low to moderate risk!!!
Of 136,905 patients hospitalized with CAD, 77% had normal LDL levels below 130 mg/dl

Modified from Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009
Of 136,905 patients hospitalized with CAD, 45.4% had normal HDL levels above 40 mg/dl.
Of 136,905 patients hospitalized with CAD, 61.8% had normal triglyceride levels below 150 mg/dl.
Problem 1 – Inaccurate Individualized Assessment of Cardiovascular Risk

Who Has Higher Cardiovascular Risk Based Only on Risk Factors?

Sir Winston Churchill, 91 □
- Overweight
- Not Fit
- Heavy Smoker

Jim Fixx, 53 □
- Not Overweight
- Very Fit
- Non-Smoker
Problem 2 – Inadequate Monitoring of Vascular Response to Treatments

Who is Not Responding to Therapy and Has High Residual Risk?

Tim Russert

Provided with current standard of care

- Statin
- Aspirin
- ACE Inhibitors
- Reached target lipid profile

FAMOUS POLITICAL JOURNALIST
DIED OF SUDDEN HEART ATTACK
AT HIS DESK
In Search of the "Vulnerable Patient"
In Search of Vulnerable Patients

1,400,000 Annual Heart Attacks (ACS + SCD)

~50%
 Apparently Healthy People (New)

~50%
 CHD Patients (Recurring)

140,000,000 Americans over the age of 35
In Search of Vulnerable Patients
1,400,000 Annual Heart Attacks (ACS + SCD)

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CHD Patients (Recurrent)

140,000,000 Americans over the age of 35
Review: Current Perspective

From Vulnerable Plaque to Vulnerable Patient
A Call for New Definitions and Risk Assessment Strategies: Part I

Morteza Naghavi, MD; Peter Libby, MD; Erling Falk, MD, PhD; S. Ward Casscells, MD; Silvio Litovsky, MD; John Rumberger, MD; Juan Jose Badimon, PhD; Christodoulos Stefanadis, MD; Pedro Moreno, MD; Gerard Pasterkamp, MD, PhD; Zahi Fayad, PhD; Peter H. Stone, MD; Sergio Waxman, MD; Paolo Raggi, MD; Mohammad Madjid, MD; Alireza Zarrabi, MD; Allen Burke, MD; Chun Yuan, PhD; Peter J. Fitzgerald, MD, PhD; David S. Siscovick, MD; Chris L. de Korte, PhD; Masanori Aikawa, MD, PhD; K.E. Juhani Airaksinen, MD; Gerd Assmann, MD; Christoph R. Becker, MD; James H. Chesebro, MD; Andrew Farb, MD; Zorina S. Galis, PhD; Chris Jackson, PhD; Il-Kyung Jang, MD, PhD; Wolfgang Koenig, MD, PhD; Robert A. Lodder, PhD; Keith March, MD, PhD; Jasenka Demirovic, MD, PhD; Mohamad Navab, PhD; Silvia G. Priori, MD, PhD; Mark D. Rekhter, PhD; Raymond Bahr, MD; Scott M. Grundy, MD, PhD; Roxana Mehran, MD; Antonio Colombo, MD; Eric Boerwinkle, PhD; Christie Ballantyne, MD; William Insull, Jr, MD; Robert S. Schwartz, MD; Robert Vogel, MD; Patrick W. Serruys, MD, PhD; Goran K. Hansson, MD, PhD; David P. Faxon, MD; Sanjay Kaul, MD; Helmut Drexler, MD; Philip Greenland, MD; James E. Muller, MD; Renu Virmani, MD; Paul M Ridker, MD; Douglas P. Zipes, MD; Prediman K. Shah, MD; James T. Willerson, MD
The Vulnerable Patient Consensus Statement Preceding the SHAPE Initiative

Review: Current Perspective

From Vulnerable Plaque to Vulnerable Patient
A Call for New Definitions and Risk Assessment Strategies: Part II

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First SHAPE Symposium

Association for Eradication of Heart Attack

Towards

The National SHAPE Program
(Screening for Heart Attack Prevention and Education)

IN SEARCH OF THE VULNERABLE PATIENT

1.4 Million Heart Attacks Every Year

Very High Risk

High Risk

At Risk

Periodic Screening

Intravascular Imaging

Step 3

IVUS

CT Imaging (Total Plaque Burden)

Step 2

Noninvasive Imaging

Step 1

CRP Framingham Risk Score

Biomarker(s)

140 Million Americans over the Age of 35
SHAPE Task Force Meeting
From Vulnerable Plaque to Vulnerable Patient—Part III:
Executive Summary of the Screening for Heart Attack Prevention
and Education (SHAPE) Task Force Report

Morteza Naghavi, MD, Erling Falk, MD, PhD, Harvey S. Hecht, MD,
Michael J. Jamieson, MD, Sanjay Kaul, MD, MPH, Daniel Berman, MD,
Zahi Fayad, PhD, Matthew J. Budoff, MD, John Rumberger, MD, PhD,
Tasneem Z. Naqvi, MD, Leslee J. Shaw, PhD, Ole Faergeman, MD, Jay Cohn, MD,
Raymond Bahr, MD, Wolfgang Koenig, MD, PhD, Jasenka Demirovic, MD, PhD,
Dan Arking, PhD, Victoria L. M. Herrera, MD, Juan Badimon, PhD,
James A. Goldstein, MD, Yoram Rudy, PhD, Juhani Airaksinen, MD,
Robert S. Schwartz, MD, Ward A. Riley, PhD, Robert A. Mendes, MD,
Pamela Douglas, MD, and Prediman K. Shah, MD, for the SHAPE Task Force†

Screening for early-stage asymptomatic cancers (eg, cancers of breast and colon) to
prevent late-stage malignancies has been widely accepted. However, although ath-
erosclerotic cardiovascular disease (eg, heart attack and stroke) accounts for more
death and disability than all cancers combined, there are no national screening
guidelines for asymptomatic (subclinical) atherosclerosis, and there is no government-
or healthcare-sponsored reimbursement for atherosclerosis screening. Part I and Part
II of this consensus statement elaborated on new discoveries in the field of athero-
sclerosis and included recommendations for clinical treatment. This Part III
shall cover the guidelines for screening, treatment, and prevention. The

†The authors and Task Force Members have no relevant financial
interests to declare. The opinions expressed are those of the
authors and do not necessarily reflect the views of the
American College of Cardiology, American Heart
Association, or Atherosclerotic Peripheral Vascular Disease
Association.
Step 1
Test for Presence of the Disease
- Atherosclerosis Test
  - Negative
    - No Risk Factors
    - + Risk Factors
  - Positive
    - <75th Percentile
    - 75th-90th Percentile
    - ≥90th Percentile

Step 2
Stratify based on the Severity of the Disease and Presence of Risk Factors

Step 3
Treat based on the Level of Risk
- Lower Risk
- Moderate Risk
- Moderately High Risk
- High Risk
- Very High Risk
**The 1st SHAPE Guidelines**

### Apparently Healthy Population Men >45y Women >55y

**Step 1**
- **Very Low Risk**
  - Exit
  - **All >75y receive unconditional treatment**

**Atherosclerosis Test**

**Step 2**

- **Negative Test**
  - CACS = 0
  - CIMT < 50th percentile
  - No Risk Factors
  - + Risk Factors

- **Positive Test**
  - CACS ≥ 1
  - CIMT ≥ 50th percentile or Carotid Plaque

### Step 3

**Lower Risk**

- LDL Target: < 160 mg/dl
- Re-test Interval: 5-10 years

**Moderate Risk**

- LDL Target: < 130 mg/dl
- Re-test Interval: 5-10 years

**Moderately High Risk**

- ABI < 0.9
- CRP > 4 mg
- Optional
- LDL Target: < 130 mg/dl
- Re-test Interval: Individualized

**High Risk**

- LDL Target: < 100 mg/dl
- Re-test Interval: Individualized

**Very High Risk**

- LDL Target: < 70 mg/dl
- Re-test Interval: Individualized

### LDL Target and Re-test Interval

- **Follow Existing Guidelines**
- **Myocardial Ischemia Test**
  - Yes
  - No

---

1: No history of angina, heart attack, stroke, or peripheral arterial disease.
2: Population over age 75y is considered high risk and must receive therapy without testing for atherosclerosis.
3: Must not have any of the following: Chol > 200 mg/dl, blood pressure > 120/80 mmHg, diabetes, smoking, family history, metabolic syndrome.
4: Pending the development of standard practice guidelines.
5: High cholesterol, high blood pressure, diabetes, smoking, family history, metabolic syndrome.
6: For stroke prevention, follow existing guidelines.
Prevalence, Impact, and Predictive Value of Detecting Subclinical Coronary and Carotid Atherosclerosis in Asymptomatic Adults

The BioImage Study

Usman Baber, MD, MS,* Roxana Mehran, MD,* Samantha Sartori, PhD,* Mikkel Malby Schoos, MD, PhD,† Henrik Sillesen, MD, DMSc,‡ Pieter Muntendam, MD,¶ Mario J. Garcia, MD,§ John Gregson, PhD,∥ Stuart Pocock, PhD,∥ Erling Falk, MD, DMSc,¶ Valentin Fuster, MD, PhD*
Atherosclerosis: A Very Prevalent Silent Disease
About 60% of this asymptomatic study population had “Polyvascular atherosclerosis”
Existing Guidelines (Status Quo):
• Screen for Risk Factors of Atherosclerosis
• Treat Risk Factors of Atherosclerosis

The SHAPE Guidelines:
• Screen for Atherosclerosis (the Disease) Regardless of Risk Factors
• Treat based on the Severity of the Disease and its Risk Factors
The new ACC/AHA Guidelines are still inaccurate because the recommendation is based on epidemiological “normal” cutoff points from a mixed population of different ethnicities not personalized structural and physiological assessment of atherosclerosis.
Natural Course of Atherosclerotic CVD (heart attack, stroke, PAD,....)

Endothelial Dysfunction

Elevated Blood Pressure

Large Artery Wall Thickening

Plaque Formation

Clinical Events

Unlike endothelial dysfunction, structural disorders in arteries occur slowly, appear later in life, and do not respond quickly to treatments.

Undetectable Structural Disorder

Detectable Structural Disorder

Endothelial dysfunction precedes structural disorders, plaque build up, and clinical events.
Screening for Atherosclerosis: Risk Factors vs Disease

Numerous Risk Factors
- High LDL
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- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- Over 200 risk factors have been reported.

Examples of Arterial Structure Tests
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- Microvascular Reactivity Measured at Fingertip
ROC Curve, its AUC and Corresponding Odds Ratio


Risk Factors

hs-CRP, LDL, HDL, Smoking, Hypertension, Diabetes, etc.
Screening for Atherosclerosis
Risk Factors vs Disease

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<table>
<thead>
<tr>
<th>OR</th>
<th>AUC</th>
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<tbody>
<tr>
<td>105</td>
<td>0.95</td>
</tr>
<tr>
<td>38</td>
<td>0.9</td>
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<tr>
<td>11</td>
<td>0.8</td>
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<tr>
<td>4</td>
<td>0.7</td>
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<tr>
<td>2</td>
<td>0.6</td>
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<tr>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Structural

CAC + FRS
IMT + FRS

Risk Factors
hs-CRP, LDL, HDL, Smoking, Hypertension, Diabetes, etc.
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<tr>
<td>Smoking</td>
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<td>0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes etc</td>
<td>1</td>
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Combined structural & functional?
We need more data!
Evidence Based
Screening for Atherosclerosis
Risk Factors vs Disease

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- High BP
- Diabetes
- Smoking
- CRP
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Examples of Arterial Function Tests
- Microvascular Reactivity Measured by Fingertip Tonometry
What is Endothelial Function?

“Endothelial Function” is a misnomer! Endothelial cells serve many functions.
The vascular endothelium serves multiple functions:
1) it regulates fluid and molecule traffic between blood and tissues
2) it is an anti-coagulant surface
3) it contributes to vascular homeostasis and repair
4) it plays a vital role in vascular tone and blood flow regulation

Assessing this function is the most practical way of measuring endothelial function.
Endothelial Dysfunction (Vascular Dysfunction) and Various Diseases

This slide shows the extent of involvement of endothelial dysfunction in various diseases, much like a high blood pressure measurement or fever that is indicative of different problems.

This is why we believe endothelial function monitoring will be adopted as part of routine vital sign monitoring.
Most people don’t realize that our body is a giant network of vessels (OVER 60,000 MILES) and 99.99% of it is microvascular and barely visible.

These microvessels function very similarly and their endothelial function is the most important part of the vascular health.
Approximately 60,000 Miles of Arteries, Veins and Capillaries

Surface area > 3 tennis courts!
View the animated video http://www.endothelix.com/index.php/physicians/youtube-videos
Endothelial and Vascular Dysfunction: A “Barometer of Cardiovascular Risk”

- Marker of the inherent atherosclerotic risk
- An integrated index of both the overall CV risk factor burden and the sum of all vasculoprotective factors in an individual.

Aging  Diet
Smoking  Inactivity
Diabetes  ↑ Cholesterol
↑ Blood Pressure  Oxidative Stress
Genetics  Medications
What causes Endothelial Dysfunction?

Negatively Affect

Smoking
Diabetes
High Blood Pressure
High Cholesterol
Weight Gain
Mental Stress
Excessive Inflammation

Positively Affect

Exercise
Weight Loss
Stress Reduction
Cholesterol-Lowering Drugs
Risk Factors:
- Excessive
- Inflammation
- Mental Stress
- Weight Gain
- High Cholesterol
- High Blood Pressure
- Diabetes
- Smoking

Protective Factors:
- Cholesterol-Lowering Drugs
- Stress Reduction
- Weight Loss
- Exercise
Natural Course of Atherosclerotic CVD (heart attack, stroke, PAD,....)

Unlike endothelial dysfunction, structural disorders in arteries occur slowly, appear later in life, and do not respond quickly to treatments.

Endothelial dysfunction precedes structural disorders, plaque build up, and clinical events.
Endothelial cells, in response to shear stress or other stimuli, release nitric oxide and other compounds that elicit relaxation of nearby smooth muscle cells and result in vasodilation.
PARADOXICAL VASOCONSTRICTION INDUCED BY ACETYLCOLINE IN Atherosclerotic Coronary Arteries

Paul L. Ludmer, M.D., Andrew P. Selwyn, M.D., Thomas L. Shook, M.D., Richard R. Wayne, B.S., Gilbert H. Mudge, M.D., R. Wayne Alexander, M.D., Ph.D., and Peter Ganz, M.D.

Abstract  Acetylcholine is believed to dilate normal blood vessels by promoting the release of a vasorelaxant substance from the endothelium (endothelium-derived relaxing factor). By contrast, if the endothelium is removed experimentally, acetylcholine constricts blood vessels. We tested the hypothesis that muscarinic cholinergic vasodilatation was due to the release of an endothelial factor. Acetylcholine caused a dose-dependent dilation from a control diameter of 1.94±0.16 mm to 2.16±0.15 mm with the maximal acetylcholine dose (P<0.01). In contrast, all eight of the arteries with advanced stenoses showed dose-dependent constriction, from 1.05±0.05 mm to 0.32±0.16 mm at the highest concentration of acetylchol...
CVE’s over 4 Years in 176 Subjects without CAD
According to CVR and CA Diameters Changes with ACh

Cor Vasc Res Change Ach

CA Diameter Change Ach

vasodil or T1 CVR
vasocon or T2,3 CVR
Cardiac Events in 157 CAD Patients over 28 Months Stratified by CBF Responses to ACh
Brachial Artery Ultrasound with FMD

Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery
A Report of the International Brachial Artery Reactivity Task Force

Mary C. Corretti, MD, FACC,* Todd J. Anderson, MD,† Emelia J. Benjamin, MD, MSc,‡
David Celermajer, MD,§ François Charbonneau, MD,¶ Mark A. Creager, MD,¶ John Deanfield, MD,#
Helmut Drexler, MD,∥ Marie Gerhard-Herman, MD,¶ David Herrington, MD, MHS,¶
Patrick Vallance, MD,∥ Joseph Vito, MD,‡ Robert Vogel, MD*  
Baltimore, Maryland; Calgary, Alberta and Montreal, Quebec, Canada; Boston, Massachusetts; Sydney, Australia; London, United Kingdom; Hannover, Germany; and Winston-Salem, North Carolina
Reactive Hyperemia

Reactive hyperemia is the transient increase in organ blood flow that occurs following a brief period of ischemia (e.g., arterial occlusion).

The left panel shows the effects of a 2 min arterial occlusion on blood flow. In this example, blood flow goes to zero during arterial occlusion. When the occlusion is released, blood flow rapidly increases (i.e., hyperemia occurs) that lasts for several minutes. The hyperemia occurs because during the period of occlusion, tissue hypoxia and a build up of vasodilator metabolites (e.g., adenosine) dilate arterioles and decrease vascular resistance. Then when perfusion pressure is restored (i.e., occlusion released), flow becomes elevated because of the reduced vascular resistance. During the hyperemia, the tissue becomes reoxygenated and vasodilator metabolites are washed out of the tissue. This causes the resistance vessels to regain their normal vascular tone, thereby returning flow to control.
Research Method Uses Ultrasound Imaging

Baseline

POST OCCLUSION

increases < 5%

= Endothelial Dysfunction

THE LANCET

Original Articles

Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis

David J. Snapinn, Yoshie Aoki, Peter M. Thrombosis Research Institute, Sydney, Australia

Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis

David J. Snapinn, Yoshie Aoki, Peter M. Thrombosis Research Institute, Sydney, Australia

Buccal Artery Flow-Mediated Vasodilation in a Healthy Individual

Time after cuff release (sec)

Buccal diameter (mm)
Brachial Artery Ultrasound with FMD

BASELINE

5 minute cuff occlusion

The resulting reactive hyperemia creates increased shear stress in the brachial artery, which stimulates the release of NO and causes vasodilation.

POST OCCLUSION
Ultrasound Imaging of the Brachial Artery

Baseline

4-5 mm

45-60 sec after cuff release

5.0 mm, FMD = 11%

Brachial Artery Flow-Mediated Vasodilation in a Healthy Individual
Comparison of Brachial and Coronary Flow-Mediated Vasodilation
Figure 5. Hazard ratio (95% CI) for cardiovascular event for brachial diameter (BD)/unit SD (height adjusted) in univariate and 4 multivariable models. *FRS indicates Framingham Risk Score. **Full model was adjusted for age, sex, diabetes mellitus, cigarette smoking, systolic blood pressure, blood pressure medication use, HDL cholesterol, LDL cholesterol, triglycerides, heart rate, and statin use.

Figure 1 A Kaplan-Meier survival curve showing survival until the first composite adverse CV end point (cardiac mortality, nonfatal myocardial infarction, hospitalization for heart failure or angina pectoris, stroke, coronary artery bypass grafting, and percutaneous coronary interventions) in subjects with FMD above (dashed line) and below (solid line) the median value of 11.3%, after controlling for traditional risk factors (age, gender, lipoproteins, diabetes, hypertension, and BMI). Patients with FMD below the median had lower survival rate compared with those with FMD above the median (p <0.001).

Michael Shechter, Alon Shechter, Nira Koren-Morag, Micha S. Feinberg, Liran Hiersch

Usefulness of Brachial Artery Flow-Mediated Dilation to Predict Long-Term Cardiovascular Events in Subjects Without Heart Disease

The American Journal of Cardiology, Volume 113, Issue 1, 2014, 162 - 167

http://dx.doi.org/10.1016/j.amjcard.2013.08.051
The following slides describe Endothelix’s VENDYS technology for assessment of vascular reactivity and endothelial function.

For more information please contact Mr. William Sotka

william.sotka@endothelix.com
Moving Endothelial Function Testing out of the Research Lab and into Doctors Offices

Brachial Artery Ultrasound FMD

• Ultrasound measurement of brachial artery dilation
• 15-minute test
• Not automated
• Requires skilled operator

VENDYS® - Endothelix, Inc.

• Fingertip temperature changes
• 15-minute test
• Fully automated
• Operator independent
This movie clearly demonstrates the importance of vascular reactivity and endothelial function test as an indicator of vascular health.
What is VENDYS® technology?

VENDYS® is a simple, yet innovative, combination of the two most useful medical tools.
How does VENDYS® measure vascular function?
VENDYS® Vascular Function Monitoring

Fingertip Temperature Sensors on Both Index Fingers

Blood Pressure “Occluding” Cuff on Right Upper Arm
Vascular Function Monitoring

VENDYS® measures vascular function by monitoring fingertip temperature changes during a reactive hyperemia protocol.

The Higher the Temperature Rebound, the Better the Vascular Function

**Step 1:** Baseline Temperature Established (5 min)

**Step 2:** Cuff Inflates, Test Finger Temperature Drops (5 min)

**Step 3:** Cuff Deflates, Temperature Rebounds (5 min)
The Higher the Temperature Rebound, the Better the Vascular Function
Infrared Imaging

Cuff inflated

Post cuff deflation

View Video: http://www.endothelix.com/index.php/component/k2/item/97-vendys_a_novel_biomarker_for_clinical_trials
VENDYS®

- Operator Independent
- Non-invasive
- Easy to use
- Inexpensive

Vascular Reactivity Index = 2.12
VENDYS® Portable

A complete system to perform automated, vascular function studies

- Cuff management module (CMM)
- Digital thermal monitoring (DTM) module
- VENDYS® fingertip probes
- Laptop computer with pre-installed software
  - Data acquisition
  - Report generation and data tabulation
Software Screenshots

Automated BP measurement from patient’s left arm
Software Screenshots

Begin VENDYS® test: 5-5-5 protocol
Software Screenshots

Completion of study (note quality flag indicators on bottom right)
Vascular Function Test

Vascular Reactivity Index
aTR = 3.16

The VENDYS Report
Software Screenshots

Completed Test Viewer

VENDYS Report

- Right Finger (R)
- Left Finger (L)
- Zero Reactivity Curve (ZRC)
- Room Temperature

system Test

Adjusted Reactivity Curve

Vascular Reactivity Index

aTR = 2.12

Endothelix

Date/Time of Test: 5/5/2011

Report Viewer
The VENDYS® Report

Temperature Curves
- Red = right finger
- Blue = left finger

Vascular Reactivity Gauge
- Green = Good
- Yellow = Intermediate
- Red = Poor

Flags help to notify user of conditions that may affect the technical quality of the study.

A summary of VENDYS indices is shown here.

aTR is the primary vascular reactivity index.

Ambient room temperature is recorded throughout the study.
Sample Report Screen:
“Good” Vascular Reactivity

VENDYS Report

Right Finger (R)
Left Finger (L)
Zero Reactivity Curve (ZRC)
Room Temperature

Adjusted Reactivity Curve

Vascular Reactivity Index

Poor (aTR < 1)  Intermediate (1 < aTR < 2)  Good (aTR > 2)

Room Temperature

Blood Pressure and Pulse

Vascular Reactivity Index
aTR = 2.41

Endothelix
Date/Time of Test
6/3/2011

*Note: Cold Finger Flag check was disabled
Sample Report Screen:
“Intermediate” Vascular Reactivity

Vascular Function Test

Fairway Medical Technologies, Inc.
710 N Post Oak Rd STE 204

Vascular Reactivity Index

aTR = 1.41

Endothelix
Date/Time of Test
7/12/2011

*Note: Cold Finger Flag check was disabled.
Sample Report Screen:
“Poor” Vascular Reactivity

Vascular Function Test
Digital Thermal Monitoring of Endothelial Function and Vascular Reactivity

Vascular Reactivity Index (VRI) = 0.72

Test Date:
Thank you for your attention.
We hope you enjoyed this webinar.
Addressing Problem 1:
Inaccurate Individualized Assessment of Cardiovascular Risk
Lower Fingertip Temperature Rebound is Associated with Higher Burden of Cardiovascular Risk Factors Measured by Framingham Risk Score
Lower Fingertip Temperature Rebound is Associated with Higher Coronary Plaque Burden
The Combination of Low Fingertip Temperature Rebound and High Framingham Risk Score is Associated with High Risk Coronary Artery Calcium Score
VENDYS Improves Risk Stratification of High Risk Patients (CAC ≥ 100) over Traditional Risk Factor Assessment

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC ± S.D.</th>
<th>95% CI</th>
<th>P (compared to FRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENDYS + FRS</td>
<td>0.89 (0.02)</td>
<td>0.84 - 0.93</td>
<td>0.001</td>
</tr>
<tr>
<td>VENDYS</td>
<td>0.79 (0.03)</td>
<td>0.72 - 0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>FRS</td>
<td>0.66 (0.04)</td>
<td>0.57 - 0.77</td>
<td>- - -</td>
</tr>
</tbody>
</table>
Lower Fingertip Temperature Rebound is Associated with the Presence of Cardiometabolic Disorders

![Bar graph showing comparison of Fingertip Temperature Rebound (TR) across different conditions: Neither Condition, Metabolic Syndrome, Diabetes Mellitus.](image)
Fingertip Temperature Rebound Decreases as the Number of Cardiometabolic Risk Factors Increases
## Clinical Studies

VENDYS® for Risk Assessment in Asymptomatic Patients

VENDYS Improves Identification of High Risk Diabetic Patients (CAC ≥ 100)

### Table: AUC ± S.D., 95% CI, P

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC ± S.D.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENDYS + DM</td>
<td>0.91 (0.02)</td>
<td>0.87 - 0.95</td>
<td>0.0001</td>
</tr>
<tr>
<td>VENDYS</td>
<td>0.79 (0.03)</td>
<td>0.72 - 0.84</td>
<td>0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>0.70 (0.03)</td>
<td>0.63 - 0.78</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

DM = Diabetes Mellitus
Lower Fingertip Temperature Rebound is Associated with Increased Insulin Resistance, Coronary Calcification, and Framingham Risk Score
In Patients with Chest pain, Lower Fingertip Temperature Rebound is Associated with Myocardial Perfusion Defects
A Combination of VENDYS and Framingham Risk Score May Aid Detection of Vaguely Symptomatic Patients (SSS ≥ 4) with Myocardial Perfusion Defects

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC ± S.D.</th>
<th>95% CI</th>
<th>P</th>
<th>Comparison with FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENDYS + FRS</td>
<td>0.84 (0.03)</td>
<td>0.77 - 0.91</td>
<td>0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>VENDYS</td>
<td>0.75 (0.04)</td>
<td>0.65 - 0.84</td>
<td>0.0001</td>
<td>0.04</td>
</tr>
<tr>
<td>FRS</td>
<td>0.65 (0.05)</td>
<td>0.56 - 0.77</td>
<td>0.004</td>
<td>- - -</td>
</tr>
</tbody>
</table>

SSS – Summed Stress Score

* VENDYS: VENDYS Treatment
  * FRS: Framingham 10 year CHD risk score: <10%, 10-20%, >20%
In Patients with Chest Pain, Lower Fingertip Temperature Rebound is Associated with Coronary Artery Disease
A Combination of Low Fingertip Temperature Rebound and High Framingham Risk Score is Associated with Obstructive Coronary Artery Disease
A Combination of VENDYS and Framingham Risk Score May Aid Clinical Risk Assessment of Vaguely Symptomatic Patients Suspected of having Obstructive Coronary Artery Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC ± S.D.</th>
<th>95% CI</th>
<th>P</th>
<th>Comparison P with FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENDYS + FRS + CAC</td>
<td>0.94 (0.03)</td>
<td>0.88 - 0.97</td>
<td>0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>CAC$^{+}$</td>
<td>0.84 (0.04)</td>
<td>0.76 - 0.90</td>
<td>0.0001</td>
<td>0.003</td>
</tr>
<tr>
<td>VENDYS + FRS</td>
<td>0.79 (0.04)</td>
<td>0.72 - 0.85</td>
<td>0.0001</td>
<td>0.009</td>
</tr>
<tr>
<td>VENDYS$^{+}$</td>
<td>0.74 (0.04)</td>
<td>0.65 - 0.82</td>
<td>0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>FRS$^{+}$</td>
<td>0.63 (0.05)</td>
<td>0.54 - 0.72</td>
<td>0.0001</td>
<td>- -</td>
</tr>
</tbody>
</table>

$^{+}$ Coronary Artery Calcium Score: CAC: 0, 1-99, 100-399, ≥400

$^{+}$ Fingertip Temperature Rebound: Tertiles of VENDYS TR

$^{+}$ Framingham 10 Year CHD Risk Score (FRS): <10%, 10-20%, >20%
Digital Thermal Monitoring of Vascular Function is Reproducible

<table>
<thead>
<tr>
<th>Variable</th>
<th>D</th>
<th>SD_0</th>
<th>CV (%)</th>
<th>CR (%)</th>
<th>ICC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>0.47</td>
<td>0.054</td>
<td>11.4</td>
<td>10.6</td>
<td>0.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>0.44</td>
<td>0.038</td>
<td>8.7</td>
<td>7.5</td>
<td>0.79</td>
<td>0.0005</td>
</tr>
<tr>
<td>Start Temperature</td>
<td>0.51</td>
<td>0.036</td>
<td>7.1</td>
<td>7.1</td>
<td>0.81</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**DTM (VENDYS®) Indices of Vascular Function**

<table>
<thead>
<tr>
<th></th>
<th>D</th>
<th>SD_0</th>
<th>CV (%)</th>
<th>CR (%)</th>
<th>ICC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (°C)</td>
<td>0.209</td>
<td>0.012</td>
<td>5.7</td>
<td>2.4</td>
<td>0.82</td>
<td>0.0001</td>
</tr>
<tr>
<td>AUC</td>
<td>0.292</td>
<td>0.014</td>
<td>4.8</td>
<td>2.8</td>
<td>0.83</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

D: mean absolute difference; SD_0: SD of mean differences; CV: coefficient of variability [(SD_0 / D)*100]; CR: coefficient of repeatability [(SD_0 * 1.96)*100]; ICC: Intra-class Correlation Coefficient.
12-month Treatment with Aged Garlic Extract was Associated with Lower Coronary Calcium Progression and Higher Fingertip Temperature Rebound
Comparison with Competitor

**VENDYS®** - Endothelix, Inc.

- Fingertip **temperature** changes
- 15-minute test
- **Fully automated**

**EndoPAT®** - Itamar Medical Inc.

- Fingertip **pressure** changes
- 15-minute test
- **Not automated**
## VENDYS® Competitive Advantages

<table>
<thead>
<tr>
<th>Feature</th>
<th>VENDYS® by Endothelix</th>
<th>EndoPAT® by Itamar Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room temperature sensor included in device</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Automated blood pressure measurement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Automated cuff inflation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Remote desktop troubleshooting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Controlled room temperature required</td>
<td>Yes (monitored)</td>
<td>Yes (not monitored)</td>
</tr>
<tr>
<td>Minor finger movement can invalidate a test and expire the probe</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Able to detect sympathetic nervous overactivity</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Infrared Imaging

Cuff inflated

Post cuff deflation

VENDYS Digital Thermal monitoring of Neurovascular Reactivity?

NVRI

Ischemia induced contra-lateral neurovascular vasodilation, mediated by nitric oxide?

Good?

Bad?
VENDYS Data Registry

(over 6,000 patients)
VENDYS VRI Distribution, \(n = 5452\)

Data from 15 clinics using VENDYS
VENDYS VRI vs. Age

![Scatter plot showing the relationship between VRI and Age. The data points are distributed across the age range with a trend line indicating a negative correlation.](image-url)
Prevalence of Poor VRI in different age groups

Poor VRI is defined as <1.0
Distribution of Age with Poor VRI scores

- % VRI < 1
- Age distribution for males and females across different age groups: < 30, 30 - 39, 40 - 49, 50 - 59, 60 - 69, >= 70.
This slide clearly shows the value of VRI. As shown above, poor VRI is not strongly dependent on age (unlike Framingham Risk Score, Coronary Calcium Score, or Pulse Wave Velocity, all highly dependent on age). Endothelial function can be very good in an 80 plus individual who survived despite risk factors.
Men (n = 2794)

- 12.46% Poor
- 74.34% Intermediate
- 13.21% Good

Women (n = 2440)

- 14.26% Poor
- 65.29% Intermediate
- 20.45% Good
VRI in measured the right hand vs. NVRI measured in the left hand
### Multiple Linear Regression

#### SUMMARY OUTPUT

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple R</strong></td>
<td>0.225088</td>
</tr>
<tr>
<td><strong>R Square</strong></td>
<td>0.050665</td>
</tr>
<tr>
<td><strong>Adjusted R Square</strong></td>
<td>0.049166</td>
</tr>
<tr>
<td><strong>Standard Error</strong></td>
<td>0.50977</td>
</tr>
<tr>
<td><strong>Observations</strong></td>
<td>3173</td>
</tr>
</tbody>
</table>

#### ANOVA

<table>
<thead>
<tr>
<th></th>
<th>df</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>Significance F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>5</td>
<td>43.92206</td>
<td>8.784412</td>
<td>33.80365</td>
<td>9.66E-34</td>
</tr>
<tr>
<td>Residual</td>
<td>3167</td>
<td>822.995</td>
<td>0.259866</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3172</td>
<td>866.9171</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Coefficients

<table>
<thead>
<tr>
<th></th>
<th>Coefficients</th>
<th>Standard Error</th>
<th>t Stat</th>
<th>P-value</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
<th>Lower 95.0%</th>
<th>Upper 95.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.914831</td>
<td>0.096839</td>
<td>19.77327</td>
<td>3.76E-82</td>
<td>1.724957</td>
<td>2.104706</td>
<td>1.724957</td>
<td>2.104706</td>
</tr>
<tr>
<td>Age</td>
<td>-0.00739</td>
<td>0.000737</td>
<td>-10.0275</td>
<td>-2.56E-23</td>
<td>-0.00884</td>
<td>-0.00595</td>
<td>-0.0084</td>
<td>-0.00595</td>
</tr>
<tr>
<td>SBP</td>
<td>8.81E-06</td>
<td>0.000646</td>
<td>0.013643</td>
<td>0.989115</td>
<td>-0.00126</td>
<td>0.001275</td>
<td>-0.00126</td>
<td>0.001275</td>
</tr>
<tr>
<td>DBP</td>
<td>0.002977</td>
<td>0.001144</td>
<td>2.601336</td>
<td>0.009329</td>
<td>0.000733</td>
<td>0.00522</td>
<td>0.000733</td>
<td>0.00522</td>
</tr>
<tr>
<td>HR</td>
<td>-0.00115</td>
<td>0.000767</td>
<td>-1.49678</td>
<td>0.13455</td>
<td>-0.00265</td>
<td>0.000356</td>
<td>-0.00265</td>
<td>0.000356</td>
</tr>
<tr>
<td>Male</td>
<td>-0.10522</td>
<td>0.018841</td>
<td>-5.58459</td>
<td>2.54E-08</td>
<td>-0.14216</td>
<td>-0.06828</td>
<td>-0.14216</td>
<td>-0.06828</td>
</tr>
</tbody>
</table>
**VENDYS Publications**

**DTM Clinical Papers:**
- Beneficial effects of aged garlic extract and coenzyme Q10 on vascular elasticity and endothelial function: The FAITH randomized clinical trial Nutrition / Elsevier (2013). PDF
- Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: A randomized clinical trial. Preventive Medicine (2009). PDF

- Concomitant insulin resistance and impaired vascular function is associated with increased coronary artery calcification. Int. Journal of Cardiology (2009). PDF
- Vascular dysfunction measured by fingertip thermal monitoring is associated with the extent of myocardial perfusion defect. JNC (2009). PDF
- Relations between digital thermal monitoring of vascular function, the Framingham risk score, and coronary artery calcium score. JCCT (2008). PDF


- Post-Exercise Reactive Hyperemia: A Novel Preoperative Risk Assessment Tool Poster Abstract
- Digital Thermal Monitoring: Non-Invasive Assessment of Perioperative Microvascular Function Poster Abstract
**DTM Technical Papers:**


**Review Articles about Vascular/Endothelial Dysfunction Measurement:**

Endothelial dysfunction over the course of coronary artery disease. Eur Heart J (2013). [PDF](#)


Additional Publications


