Epicardial fat in HIV population
A potential risk biomarker for coronary artery disease

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Objectives of this educational exhibit are to understand:

- Anatomy and physiology of epicardial fat.
- Method of measurement of epicardial fat.
- Relationships of epicardial fat with coronary artery disease in general population and in HIV-infected patients.
Why to study epicardial fat in the HIV population?
Since the introduction of the highly active antiretroviral therapy, life expectancy of HIV individuals has dramatically improved, now, approaching that of the general population (1).

Unfortunately, although HIV patients live longer, they are subject to age-related diseases such as coronary artery disease (2).

Moreover, the risk for coronary artery disease seems to be greater than that of non-infected persons (3).

Figure 1: Causes of death of HIV infected patients (adapted from the D:A:D study)
Risk stratification in the HIV patient population is of great importance. However, scores actually used underestimate cardiovascular disease risk, and probably do not take into account how specific is the HIV population (4,5).

Assessment of novel cardiovascular risk factors specific for this population is needed.

More recently, epicardial fat has emerged as a potential risk biomarker due to the key localization of this fat depot, its metabolic properties and clinical measurability.
What is epicardial fat?
**What is epicardial fat?**

- Epicardial fat is the visceral fat of the heart. It covers 80% of its surface and represent 20% of its weight (6).

- Epicardial fat predominates in the atrioventricular and interventricular grooves around cardiac blood vessels. It can extend to cover the surface of the atria and/or ventricles and in extreme cases may cover the entire epicardial surface (7).

- Epicardial fat is a dynamic fat depot. Its mass increases with age. It can also increase, or remodel, in conditions such as obesity and inflammation (6).

**Figure 1 : Human epicardial fat.** (A) anterior view of a normal heart. (B) anterior view of a hypertrophic heart. In the normal heart, the fat distribution is limited to the atrioventricular and interventricular grooves. In the hypertrophic, the adipose tissue also fills the epicardial spaces between these sites. Iacobellis et al. Reprinted by permission from Macmillan Publishers Ltd: [Nature Clinical Practice Cardiovascular Medicine] (2, 536-543) doi:10.1038/ncpcardio0319, copyright (2005). [http://www.nature.com/ncpcardio/journal/v4/n9/full/ncpcardio0984.html](http://www.nature.com/ncpcardio/journal/v4/n9/full/ncpcardio0984.html)
Epicardial fat is located between the visceral layer of pericardium and myocardium without a structure or fascia separating it from the myocardium and the epicardial vessels.

The coronary arteries are immersed in the epicardial fat allowing them to interact very closely with it.


What is epicardial fat?

- Epicardial fat has to be distinguished from the fat that is situated outside the visceral pericardium, the paracardial fat.

- Both epicardial fat and paracardial fat form the pericardial fat (also called cardiac fat or mediastinal fat).

### Table 1: Differences between epicardial fat and paracardial fat

<table>
<thead>
<tr>
<th></th>
<th>Epicardial fat</th>
<th>Paracardial fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy</td>
<td>Between the myocardium and visceral layer of pericardium</td>
<td>Outside the visceral pericardium</td>
</tr>
<tr>
<td>Embryology</td>
<td>Splanchnopleuric mesoderm</td>
<td>Primitive thoracic mesenchyme</td>
</tr>
<tr>
<td>Vascularization</td>
<td>coronary arteries</td>
<td>Pericardiophrenic branches of the internal mammary artery</td>
</tr>
</tbody>
</table>

**Figure 4:** Removal of paracardial fat allowing to reveal epicardial fat. Nelson et al. Journal of Cardiovascular Magnetic Resonance 2009;11:15. DOI: 10.1186/1532-429X-11-15. (Open access)
What is epicardial fat?

- Epicardial fat is considered as a “beige” or “brite” adipose tissue: it has the phenotype of white adipose tissue but produce “Uncoupling Protein 1” (UCP1), a marker of brown adipocytes.

- Epicardial fat is composed of adipocytes and pre-adipocytes; It contains nervous and nodal tissue, as well as inflammatory, stromal and immune cells within it.

Figure 5: Microscopic appearance of the epicardial fat in the right ventricle. Iacobellis et al. Reprinted by permission from Macmillan Publishers Ltd: [Nature Clinical Practice Cardiovascular Medicine] (2, 536-543 doi:10.1038/ncpcardio0319), copyright (2005).
http://www.nature.com/nccardio/journal/v4/n9/full/ncpcardio0984.html
Epicardial fat, as a beige adipose tissue, combines secretory functions of white adipose tissue and thermogenic functions of brown adipose tissue.

Epicardial fat has the particularity to release and uptake free fatty acids greater than other fat depots and secretes a higher proportion of pro-inflammatory cytokines (8).
How to evaluate epicardial fat?
During the last few years, there was a great interest in imaging epicardial fat as an indicator of the general adiposity or to predict incident cardiovascular events. Imaging epicardial fat has been used also to follow treatment (statins, weight loss....).

Epicardial fat can be measured by a variety of different imaging techniques including:
- Transthoracic echocardiography
- Cardiac CT
- Cardiac MRI

There is no consensus on what quantity of epicardial fat is considered to be “normal“.
Epicardial fat by echocardiography

- Probably the easiest, cheapest and non invasive method for evaluating epicardial fat.
- Epicardial fat is visible as an echo free space between the myocardium and the visceral layer of the pericardium.
- The thickness is measured perpendicularly to the right ventricle free wall in the parasternal long and short axis views where EAT is thought to be thickest at the end of systole in 3 cardiac cycles. Systolic measurement is more accurate, and avoids chances of uneven fat compression which could occur in diastole.

Most of clinical studies using echocardiography have reported excellent interobserver and intraobserver agreement for epicardial fat thickness measurement (9,10).

A main disadvantage of ultrasound is that it does not reflect the asymmetric distribution of fat surrounding the heart, not does it enable to assess total fat volume.

Figure 7: Epicardial fat measurement by echocardiography in the parasternal long and short axis views. Epicardial fat (indicated by arrows) with increased thickness (A and B) and minimum epicardial fat (C and D). Bertaso et al. Arg Bras Cardiol 2013 Jul; 101(1): e18–e28. doi: 10.5935/abc.20130138. (Open access)
Epicardial fat by cardiac CT

- It is possible to measure epicardial fat with CT scanners with 16 or more detectors.

- Cardiac CT for both coronary calcium scoring and coronary CT angiography allows accurate measurement of epicardial fat.

- Cardiac CT allows the measurement of the volume, the area and the thickness of epicardial fat.

- Standard fat attenuation values are used to define fat attenuation by CT; for non-contrast CT typically an attenuation range between -190 and -30 Hounsfield units is used (as shown in figure A).
1. **Epicardial fat volume quantification:**
   - A predefined threshold of -190 to -30 HU is applied to identify voxels consisting of fat.
   
   - The pericardium is then traced of manually or via a semi-automated process to exclude any extra cardiac fat on 6 – 8 axial sections.

   - The superior extent for the epicardial fat measurements is defined as the bifurcation of the pulmonary artery and the inferior extent as the end of the pericardial sac.

   - The fat voxels were then summed to obtain the total epicardial fat volume with a dedicated software.
2. **Epicardial fat area**: measured on the slice where the epicardial fat is the most predominant.

3. **Epicardial fat thickness**: measured at the level of the right coronary artery and the left descending coronary artery.

4. **Pericoronary epicardial fat volume**: can also be measured.
CT disadvantages include exposure to ionizing radiation and a relatively high cost.

Interscan reproducibility for measurement of epicardial fat is high, with correlation coefficients $\geq 0.98$ for the same multidetector CT scanner (11).

Figure 7: Epicardial fat measurement by cardiac CT. Epicardial fat (indicated in green) with increased volume (A and B) and minimum epicardial fat (C and D).
MRI is considered the gold standard for the evaluation of the adipose tissue. It provides the most specific and precise measurements of epicardial fat volume (12-14).

Quantification of epicardial fat volume is similar to cardiac CT, by tracing the pericardium and epicardial fat voxels are added in each slice.

While the image resolution and accuracy of CMR is greater than CT, it is also far more costly and less accessible.

Epicardial fat and coronary artery disease (CAD)
Epicardial fat and CAD in the general population

- A significant amount of research has investigated the link between increased Epicardial fat and CAD (15-18).

- Overall, most observational studies identified a direct association between the amount of EF and the presence/severity of coronary artery disease (CAD) as well with MACE (Major adverse cardiac events).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Imaging technique</th>
<th>N</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Measure of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mustelier et al. 2011</td>
<td>echocardiography</td>
<td>250</td>
<td>Thickness EF ≥ 5.2 mm in systole</td>
<td>CAD(sténose ≥50%)</td>
<td>OR: 1.27 (95% CI: 1.1 - 1.5)</td>
</tr>
<tr>
<td>Yerramasu et al. 2012</td>
<td>CT</td>
<td>333</td>
<td>EF Volume</td>
<td>CAC score</td>
<td>OR: 1.13 (95% CI: 1.04 - 1.22)</td>
</tr>
<tr>
<td>Cheng et al.2010</td>
<td>CT</td>
<td>223</td>
<td>EF Volume &gt; 125cm3</td>
<td>MACE in 4 years</td>
<td>OR: 1.74 (95% CI:1.03 – 2.95)</td>
</tr>
<tr>
<td>Shmilovich et al.53, 2011</td>
<td>CT</td>
<td>232</td>
<td>EF volume indexed for total body surface &gt; 68.1cm3/m2</td>
<td>MACE in 4 years</td>
<td>OR: 2.8 (95% CI: 1.3 - 6.4)*</td>
</tr>
</tbody>
</table>
Studies that evaluate epicardial fat in the HIV population are few. Most of them found that quantity of epicardial fat is higher than in the non infected population (19,21). Epicardial fat seems to be associated to HIV related factors (HIV infection duration, HAART, CD4...) (19,20).

Epicardial fat is also associated to coronary artery disease (18-23).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Imaging technique</th>
<th>N</th>
<th>Exposure</th>
<th>Clinical variables/outcome</th>
<th>Measure of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaraldi et al., 2011</td>
<td>Cardiac CT</td>
<td>876 HIV +</td>
<td>Epicardial fat volume</td>
<td>CAC &gt; 100</td>
<td>OR = 1.10, p= 0.011</td>
</tr>
<tr>
<td>Zona et al., 2012</td>
<td>Cardiac CT</td>
<td>240 HIV +</td>
<td>Progression of epicardial fat volume</td>
<td>Progression of CAC</td>
<td>OR= 1.04, p=0.03</td>
</tr>
<tr>
<td>Longenecker et al., 2013</td>
<td>Cardiac CT</td>
<td>100 HIV +</td>
<td>Epicardial fat volume</td>
<td>CAC &gt; 0</td>
<td>Spearman’s p = 0.228, p=0.024</td>
</tr>
<tr>
<td>Brener et al., 2014</td>
<td>Cardiac CT</td>
<td>706 HIV +</td>
<td>Epicardial fat volume</td>
<td>Presence of plaque</td>
<td>OR : 1.1, p=0.02</td>
</tr>
</tbody>
</table>
Epicardial fat as a therapeutic target

- Epicardial quantification has been used in multiple studies as a marker of the effectiveness of weight loss interventions, exercise and pharmaceutical treatments (24-27).

- Epicardial fat can serve as a target for pharmaceutical agents targeting the adipose tissue, such as statins or ant-diabetes medications.
Conclusion
Epicardial fat is a unique fat depot with anatomical and functional characteristics different from other fat depots.

Epicardial fat can be quantified by different imaging techniques, and this makes its assessment an appealing tool in both the clinical and research settings.

Despite the availability of different methods to assess epicardial fat, there is currently no clear guidelines for its use in clinical practice.

Future studies are needed to evaluate the prognostic value of quantitative imaging techniques of epicardial fat assessment when included in cardiovascular risk stratification approaches in various populations, such as in the population of HIV-infected patients.
References


27. Longenecker CT, Hileman CO, Funderburg NT, McComsey GA. Rosuvastatin preserves renal function and lowers cystatin C in HIV–infected subjects on antiretroviral therapy: the SATURN–HIV trial. Clinical infectious
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