Atrial Fibrillation
Risk Marker vs. Risk Factor
Marker vs. Mechanism
AF Stasis, clot formation, embolism

Heart House,
26th March, 2015

John Camm
Virchow’s Triad

1) Abnormal changes in flow are evident by stasis in the left atrium, and seen as spontaneous echocontrast

2) Abnormal changes in vessel walls—essentially, anatomical and structural defects—include progressive atrial dilatation, endocardial denudation, and oedematous or fibroelastic infiltration of the extracellular matrix.

3) Abnormal changes in blood constituents are well described, and include haemostatic and platelet activation, as well as inflammation and growth factor changes.

LAA and Thrombus

- Thrombus present in 12.6% of patients (47% in valvular HD - mostly rheumatic MS).
- 90% of the thrombi were found in the LAA in non-rheumatic AF

<table>
<thead>
<tr>
<th>Setting</th>
<th>N</th>
<th>LAA</th>
<th>LA body</th>
<th>Reference</th>
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<td>TEE</td>
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<td>66</td>
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<td>1</td>
<td>Klein; Int J Card '93</td>
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<td>3</td>
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<tr>
<td>SPAF III TEE</td>
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<td>Klein; Circ '94</td>
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<tr>
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<td>19</td>
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<td>Leung; JACC '94</td>
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<td>6</td>
<td>0</td>
<td>Hart; Stroke '94</td>
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<td><strong>Total</strong></td>
<td><strong>2018</strong></td>
<td><strong>201</strong></td>
<td><strong>21</strong></td>
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www.escardio.org/EHRA
LAA Morphology and Risk of Stroke

- N = 932 for AF ablation, (59±10 yrs, 79% men)
- PAF: 59%, persistent AF: 36%
- CHADS$_2$ 1: 40%, CHADS$_2$ ≥ 2: 14%
- CT: n = 499, MRI: n = 433
- Stroke/TIA; n = 78 (8%)

Non-chicken wing vs chicken wing:
- All: OR = 2.95 (1.75 - 4.99)
- CHADS2 0-1: OR = 10.1 (1.25-79.5)

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Left Atrial Appendage Morphology

LAA Casts

(A) Chicken wing. (B) Windsock. (C) Cauliflower. (D) Cactus. A, B and C, D are pairs of the same casts but viewed from different perspectives showing the overlap that exists regarding LAA morphology.

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# PROTECT-AF: Final Results

463 patients received the Watchman and 244 warfarin management
Average CHADS$_2$ scores 2.2 and 2.3, respectively
Mean follow-up: 45 months

Rate Ratios (95% CI) for Primary Efficacy and Safety End Points and Secondary End Points in PROTECT-AF, by Intention to Treat

<table>
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<tr>
<th>End points (2621 pt/years)</th>
<th>RR (95% CI)</th>
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<tr>
<td>Primary efficacy end point: Stroke, systemic embolism, or cardiovascular or unexplained death</td>
<td>0.60 (0.41–1.05)</td>
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<tr>
<td>All-cause mortality</td>
<td>0.66 (0.45–0.98)</td>
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<tr>
<td>Cardiovascular mortality</td>
<td>0.40 (0.21–0.72)</td>
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<tr>
<td>Hemorrhagic stroke</td>
<td>0.15 (0.03–0.49)</td>
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<tr>
<td>Primary safety end point: serious pericardial effusion, major bleeding, procedure-related stroke, hemorrhagic stroke, and device embolization</td>
<td>1.17 (0.78–1.95)</td>
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</tbody>
</table>

Reddy VY, et al. 2013
The Left Atrial Appendage

Left Atrial Appendage Flow Velocity

- SR: 4 waves - forward flow (0.46 ± 0.18 cm/s), probably owing to LAA contraction and emptying; retrograde wave that represents LAA filling (0.46 ± 0.17 cm/s). Then, additional forward and retrograde waves (0.23 ± 0.10 cm/s and 0.22 ± 0.11 cm/s resulting from ventricular relaxation and LAA elasticity.

- Heavily dependent on loading conditions and left ventricular function.

- LAA outflow velocity - parameter most significantly correlated with SEC.

- Velocities <40 cm/s are associated with higher risk of stroke and the presence of SEC with decreasing velocities of <20 cm/s associated with the identification of thrombus within the LAA.
Atrial Stunning

LAA flow velocities tend to diminish and SEC can develop immediately after pharmacological or electrical cardioversion, probably due to atrial stunning.

Could indicate a myopathic process, because the duration of AF is related to the degree of impaired left atrial or LAA function (does not occur after DCCV for VT/VF).

Full recovery of atrial stunning is achieved within 24 h in patients with brief AF (<2 weeks), within 1 week in patients with AF of moderate duration (2–6 weeks), and within 1 month in patients with prolonged AF (>6 weeks).

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Speckle Tracking, Strain Rates

Atrial Thrombus

82 assessed patients
LAA thrombi/sludge in 16 (19.5%)%

+ve correlation between peak positive strain rate and maximum emptying velocity (r = 0.589; P < 0.001) and maximum filling velocity of the LAA (r = 0.651; P < 0.001)

Peak negative strain rate associated with maximum emptying velocity (r = −0.513; P < 0.001) and maximum filling velocity of the LAA (r = −0.552; P < 0.001)

AF duration, PNSR and time-to-peak positive strain independent predictors of LAA thrombi or sludge on multivariate analysis logistic regression

Providência R et al. Cardiovascular Ultrasound 2013, 11:44
Spontaneous Echo Contrast (SEC)

- SEC is present in approximately 50% of patients with AF
- ~2% of patients in normal sinus rhythm
- Approximately 40% of patients with nonvalvular AF will develop SEC 2 years after the onset of the arrhythmia
- SEC will persist indefinitely unless AF is terminated
- Mitral regurgitation increases the flow velocity in the left atrium and, therefore, protects patients with AF from developing SEC and thrombi
- SEC is present in 90% of patients with LAA thrombus, and is the cardiac factor most strongly associated with LAA thrombus formation, stroke and other embolic events, and reduced survival
- Two parameters, left atrial dilatation and low LAA emptying and filling velocities, have been shown to be predisposing factors for SEC and thrombus formation

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Variables Predicting LAA Thrombus

Transesophageal echocardiography (TEE)

564 patients, of whom LAA thrombus was observed in 36 (6.4%) pts

Multivariate analysis:
CHADS\textsubscript{2} (Congestive heart failure, Hypertension, Age\textgreater{}75, Diabetes mellitus and prior Stroke or transient ischemic attack) score ($P$=0.002)
Left ventricular ejection fraction ($P$=0.01)
degree of spontaneous echo contrast ($P$=0.02)
Left atrial volume ($P$=0.02),
Number of LAA lobes ($P$<0.001) (Usually more than 3)

LAA volume significantly decreased in patients maintaining sinus rhythm after catheter ablation ($P$=0.0009).

Complex LAA morphology characterized by an increased number of LAA lobes was associated with the presence of LAA thrombus independently of clinical risk.

Association between VWF and SEC

Thrombotic Propensity in AF

Left atrial appendage size and function and whole blood stasis

Association between measures of whole blood stasis (spontaneous echo contrast [SEC]) and left atrial appendage thrombus (LAAT) and either left atrial appendage emptying velocity (LAAEV) (A) or left atrial volume index (LAVI)

AF patients with LAAT had higher VWF: Ag (20061 versus 15552, \(P=0.0006\)) and VWF: Act (17957 versus 14151 \(P=0.0026\)) compared with those without LAAT.

414 consecutive pts with non-valvular AF (age 63±13 years; 25% women) and in 100 pts (age 64±14 years; 39% women) with NSR
Improved Diagnosis of LAA Pectinate

Possible Clot

Obvious Pectinate
Diameter and Area Changes of the LAA Orifice During the Cardiac Cycle

Sinus Rhythm

Difference in area between systole and diastole in the patients in SR

Minimal change in the area in the patient in AF where there is considerably reduced contractility.

LAA orifice is markedly enlarged

AF is associated with structural remodeling of the LAA

which includes dilation of the chamber and reduction in pectinate muscles (not shown)

Areal Rhythm

Atrial Fibrillation

Comparison of the Different Imaging Modalities for Assessment of the LAA

<table>
<thead>
<tr>
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<th>TEE</th>
<th>MDCT</th>
<th>CMR</th>
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<tbody>
<tr>
<td>Sensitivity/specificity for LAA thrombi detection</td>
<td>92%-100%/98%-99%</td>
<td>96%/92%</td>
<td>67%/44%</td>
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<tr>
<td>Spatial resolution</td>
<td>0.2-0.5 mm</td>
<td>0.4 mm</td>
<td>1-2 mm</td>
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<tr>
<td>Temporal resolution</td>
<td>20-33 ms</td>
<td>70-105 ms</td>
<td>30-50 ms</td>
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<tr>
<td>3D volume rendering</td>
<td>Yes (with 3D)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Contrast required</td>
<td>No*</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Widely available, provides real-time assessment Semi-invasive</td>
<td>Noninvasive, dynamic assessment of LA function Cannot be performed real-time during procedures</td>
<td>Noninvasive, cannot be performed real-time during procedures Limited availability Cannot be performed in patients with pacemakers</td>
</tr>
</tbody>
</table>

Detection of LAA Thrombus in AF by Cardiac CT: A Meta-analysis

Schematic Approach for TEE Evaluation of the LAA Before Cardioversion

- TEE Performed for Evaluation Prior to Cardioversion
  - LAA Thrombus Present
    - No: Findings Suspicious for the Presence of Thrombi
      - Yes: Consider Administration of Echo Contrast for Further Evaluation
      - No: Doppler Evaluation of LAA Velocities: > 40 cm/s
        - No: Safe to Perform Cardioversion
          - Yes: Do Not Proceed with Cardioversion
    - Yes: 3D TEE should be used, if available, to increase sensitivity and specificity of findings

Areas of Current Research Interest

- Relationship between atrial fibrosis, atrial cardiomyopathy, and indices of LA stasis
- Predictive value of measures of LA stasis (strain/speckle mapping, left atrial size and contractility, spontaneous echo contrast) for spontaneous ischemic stroke, or stroke complications from interventional procedures within the LA – ablation, mitra clip, ASD occlusion etc.
- Combination of stasis, endothelial abnormalities and hypercoagulability issues for stroke prevention, in comparison with clinical risk stratifiers/biomarkers
- Value of left atrial appendage excision, occlusion for stroke prevention
- Predictive value of LAA /stasis risk based on LAA morphology
- Improved techniques for assessing stasis
LAA and Stasis: Key Points

- An estimated 47% of thrombi in valvular atrial fibrillation (AF) and 91% of thrombi in nonvalvular AF are localized in the left atrial appendage (LAA).

- **LAA flow stasis** (or spontaneous echocardiographic contrast; SEC) is a pattern of blood flow (echogenicity) attributed to ultrasonic backscatter from blood cell aggregates that form under low shear conditions.

- **SEC** is formed through protein-mediated (particularly fibrinogen) red cell aggregation promoting red cell rouleaux formation, and is the cardiac factor most-strongly associated with LAA thrombus formation.

- **Transoesophageal echocardiography is the gold standard** for the evaluation of LAA stasis and thrombosis, and promising results have been reported for intracardiac echocardiography and transthoracic echocardiography with contrast.

- **Cardiac CT** is an accurate, noninvasive imaging modality for the detection of LAA thrombi, particularly when delayed imaging acquisition protocols are used; CMR – not useful.