Could inflammatory biomarkers be of greater interest than troponins for patients admitted for myocardial inflammatory syndromes? A real life retrospective study.

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CHRU MONTPELLIER
Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

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☑️ I do not have any potential conflict of interest
BACKGROUND

Myocarditis = inflammatory disease of the myocardium diagnosed by fulfilling histological, immunological and immuno histochemical criteria (1)

Continuum of inflammatory damages from the pericardium to the myocardium (2)

Polymorphic disease / Remains a diagnostic challenge

Several clinical presentation and overlapping forms (3)

(2) Imazio M, Brucato A, Barbieri A, et al. Good Prognosis for Pericarditis With and Without Myocardial Involvement : Results From a Multicenter, Prospective Cohort Study. Circulation 2013
(3) Dennert R, Crijns HV, Heymans S. Acute viral myocarditis. Eur Heart J 2008
PROBLEMATIC

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio, Sabine Pankweitz, Eloisa Arbustini, Cristina Basso, Juan Gimeno-Blanes, Stephan B. Felix, Michael Fu, Tiina Helio, Stephane Heymans, Roland Jahns, Karin Klingel, Ales Linhart, Bernhard Maisch, William McKenna, Jens Mogensen, Yigal M. Pinto, Arsen Ristic, Heinz-Peter Schulteiss, Hubert Seggewiss, Luigi Tavazzi, Gaetano Thieme, Ali Yilmaz, Philippe Charron, and Perry M. Elliott

European Heart Journal (2013) 34, 2636–2648
doi:10.1093/eurheartj/het210

12 leads ECG / ST-T wave change (neither specific nor sensitive)
TTE (not specific)

Biomarkers
- Troponins levels (more sensitive than CK but not specific)
- CRP levels
- Erythrocyte sedimentation rate

Coronary angiography (rule out ACS)

EMB (gold standard) in life threatening situations

Cardiac MRI (Lake Louise criteria) 84% of sensibility, LGE high specificity -> non invasive tool


Positive diagnosis of myo/pericarditis
PROBLEMATIC

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)

Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS)

Pericarditis

- chest pain + increasing of biomarkers for cardiac damage (as hs-troponins) + without newly impairment of LVEF = myopericarditis should be suspected

Hs-troponin

- higher sensitivity in patients with suspected chest pain and possible ischemia than usual troponins
- while in other cardiovascular diseases needs a careful clinical observation and further diagnostic tests

**PROBLEMATIC**

Risk of increasing hospitalizations in ICCUs

Because hs-Troponin became central criterion in medical care of myopericarditis syndromes

Not consensual and increase costs of health

Adler Y. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In cases of pericarditis with suspected associated myocarditis, coronary angiography (according to clinical presentation and risk factor assessment) is recommended in order to rule out acute coronary syndromes</td>
<td>I</td>
<td>C</td>
<td></td>
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<tr>
<td>Cardiac magnetic resonance is recommended for the confirmation of myocardial involvement</td>
<td>I</td>
<td>C</td>
<td></td>
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<tr>
<td>Hospitalization is recommended for diagnosis and monitoring in patients with myocardial involvement</td>
<td>I</td>
<td>C</td>
<td></td>
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<tr>
<td>Rest and avoidance of physical activity beyond normal sedentary activities is recommended in non-athletes and athletes with myopericarditis for a period of 6 months</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Empirical anti-inflammatory therapies (lowest efficacious doses) should be considered to control chest pain</td>
<td>IIa</td>
<td>C</td>
<td></td>
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</tbody>
</table>
Determine which criteria are used by physicians in the care of patients presented with myopericardial inflammatory syndromes.
**Design**: Retrospective observational and monocentric database (CHU Montpellier) from January 2015 to December 2016, based on PMSI (French medicalized system) and ICD-10 codification.

**Population**

- **Inclusion**
  - Patients with ICD-10 codification: «acute myocarditis» (I40 and next), «myocarditis during unspecified diseases» (I41 and next).

- **Exclusion**
  - Paediatric population less than 10 years old.
  - Patients who did not undergo cardiac MRI.

**Collection database**

- Baseline characteristics were obtained retrospectively using patient’s medical electronic file.
- Positive hs-T-Troponin was defined according to standard of care (first sample > 50pg/ml, variation > 30% in second sample if the first was between 14 and 50pg/ml).
- Lake Louise criteria were used to define myopericarditis on cardiac MRI (oedema on T2 sequence, sub epicardial LGE).
RESULTS: population

91 patients screened

Post myopericarditis sd: 1 patient

Initial suspicion: 60 patients

After rule out other diagnosis: 30 patients

young age / previous infectious disease / chest pain / ECG / elevation of biomarkers
16 negative angiography coronary

Confirmed by cardiac MRI

54 cardiac MRI -> 41 positive

26 cardiac MRI -> 24 positive

25 negative coronary angiography angiography
3 negative CT scan for PE
1 coronary spasm

10 patients did not underwent MRI
- long delay to perform
- shock

81 cardiac MRI

66 positive for myopericarditis diagnosis

15 negative for diagnosis
- 8 normal
- 3 ischemia
- 1 tako-tsubo syndrome
- 3 inconclusive
## RESULTS: population

<table>
<thead>
<tr>
<th></th>
<th>Positive MRI (66 patients)</th>
<th>Negative MRI (15 patients)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±DS – years old</td>
<td>35±15</td>
<td>47±21</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex male - No. (%)</td>
<td>54 (82)</td>
<td>8 (53)</td>
<td>0.04</td>
</tr>
<tr>
<td>Personal history of myocarditis or pericarditis – no. (%)</td>
<td>8 (12)</td>
<td>0</td>
<td>0.34</td>
</tr>
<tr>
<td>Familial or personal history of extra cardiac auto immune disease - no. (%)</td>
<td>7 (11)</td>
<td>1 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Previous infectious disease - no. (%)</td>
<td>35 (53)</td>
<td>6 (40)</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis chest pain - no. (%)</td>
<td>27 (41)</td>
<td>7 (47)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyspnea - no. (%)</td>
<td>1 (1.5)</td>
<td>2 (13)</td>
<td>0.08</td>
</tr>
<tr>
<td>Palpitation - no. (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12-lead ECG at the admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST/T wave change - no. (%)</td>
<td>46 (70)</td>
<td>11 (73)</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular tachycardia - no. (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular ectopics - no. (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Complete atrioventricular block - no. (%)</td>
<td>1 (1.5)</td>
<td>1 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Bundle branch block - no. (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Echocardiography at the admission</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal LVEF - no. (%)</td>
<td>55 (80)</td>
<td>11 (73)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mild alteration - no. (%)</td>
<td>5 (7)</td>
<td>1 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate alteration - no. (%)</td>
<td>6 (9)</td>
<td>2 (14)</td>
<td>0.63</td>
</tr>
<tr>
<td>Severe alteration - no. (%)</td>
<td>0</td>
<td>1 (7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>7 (11)</td>
<td>4 (26)</td>
<td>0.11</td>
</tr>
<tr>
<td>Regional hypokinesia (lateral wall)</td>
<td>10 (15)</td>
<td>1 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Global hypokinesia</td>
<td>4 (6)</td>
<td>2 (13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Biomarkers at the admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±DS hs Troponin (ng/l)</td>
<td>722±782</td>
<td>351±488</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean±DS CK (UI/l)</td>
<td>460±611</td>
<td>219±241</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean±DS CRP (mg/l)</td>
<td>60±115</td>
<td>26±34</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean±DS leukocytes (G/l)</td>
<td>10±5</td>
<td>11±4</td>
<td>0.13</td>
</tr>
</tbody>
</table>
RESULTS: Biomarkers analysis

**HS-TROPONIN LEVELS**

Significant correlation between hs-Troponin at the admission and extent of myocarditis on cardiac MRI ($r=0.37$, $p=0.004$)

No significant correlation between hs-Troponin at the admission and ventricular tachycardia ($p=0.4$)
RESULTS: Biomarkers analysis

CRP LEVELS

CRP levels were correlated with LVEF after adjustment on hs-troponin levels T (p=0.0002)

Correlation between LVEF and CRP levels at the admission

CRP levels were not correlated with myocarditis extent on MRI (p=0.84 and p=0.69 respectively for CRP level at admission or CRP peak level)
RESULTS: ICCUs

+ Hospitalisation in ICCUs: **60 patients (91%)**
+ Length of hospitalisation: median of 2 days (IQR 2-3.75)

+ **Rare complications (27%)**
  - 12 ventricular arrhythmias
    - >7 ventricular ectopics
    - >4 short access of ventricular tachycardia
    - >1 ventricular fibrillation (during coronary angiography)
  - 2 supra ventricular tachycardia
  - 1 complete atrioventricular block
  - 2 vasopressive support
  - 1 circulatory support and died
RESULTS: Follow-up

- Median follow-up was 2 months (IQR 30-90)
- 4 patients presented symptoms (2 patients with chest pain, 1 patient with dyspnea, and 1 patient with both)
- 6 patients experienced a relapse and required another hospitalization at 6 months (IQR 6-10.5).
- 15 patients underwent a control by cardiac MRI
  - -> median 6 months (IQR 3-6.5)
  - -> decrease in LGE for 8 patients
DISCUSSION

- Diagnosis of myo/pericarditis is associated with young age, male sex, high hs-Troponin and CK levels at the admission -> **biomarkers thresholds** ??
- No correlation between hs-Troponins/LVEF at the admission
- No correlation between hs-Troponins/ventricular tachycardia
- Correlation between hs-Troponins/LGE on cardiac MRI -> **myocardial necrosis**
- CRP/LVEF -> trend toward correlation -> **power of the study**
- No correlation between CRP/LGE on cardiac MRI -> **due to pathophysiology of myocarditis and immune response** Mewton N, et al. J Cardiovasc Med 2015
- ST wave change/CRP-hs Troponins -> **electrical unsteady due to inflammatory injuries**
- > 90% of patients: hospitalization in ICCUs
- BUT: only 5% of health threatening complications / 1 death
DISCUSSION

Roubille F. Lettre du cardiologue 2012
DISCUSSION: Clinical Implications

- Hospitalisation in ICCUs is guided more by biomarkers levels than clinical features in myopericarditis syndromes
- BUT -> high troponin levels are not associated with complications (especially with alteration of LVEF, ventricular tachycardia)
- Misleading by reclassifying patients with simple pericarditis $\Rightarrow$ Hs-troponins threshold ????
- CRP levels could be use to classify patients at the admission before a systematic hospitalization in ICCUs

Imazio M. Good Prognosis for Pericarditis With and Without Myocardial Involvement: Results From a Multicenter, Prospective Cohort Study. Circulation 2013.
Imazio M, Trinchero R. Clinical management of acute pericardial disease: a review of results and outcomes. Ital Heart J 2004
DISCUSSION: Study limitations

- Retrospective and monocentric study
- Low number of patients
- => decreasing the power

- Our population presents low rate of complications: pericarditis or myopericarditis ++ -> selection bias

- We used only CRP levels as inflammatory biomarker in our study: innate immune response

- Cardiac MRI and Lake Louise criteria were our “gold standard”: non invasive tool
- Cardiac MRI was performed only in 81 patients (91 patients initially) -> delay to access at MRI / clinical features inconsistent with the procedure (45 minutes to perform)
- Exclusion of 8 patients with inconclusive diagnosis in cardiac MRI: underestimation of results
- Heterogeneous diagnosis in the subgroup considered as negative for myopericarditis -> bias
CONCLUSION

- This retrospective study assessed our clinical practice

- In clinical practice in myopericardial spectrum’ s diseases care is focused on troponins often forgetting clinical history

- This study highlights that in these syndromes inflammatory biomarkers could provide additional information than cardiac damages biomarkers as troponins (their role is unclear out of acute myocardial syndromes) : multimarkers approach?

- These observations should be assess by larger study
Thank you for your attention