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Cardiac troponin I in SARS-CoV-2-patients: The additional prognostic value of serial monitoring

Martina Zaninottoa,⁎, Monica Maria Miona, Andrea Padoanb, Luciano Babuin, Mario Plebanic,b

a Department of Laboratory Medicine, University Hospital of Padova, Padova, Italy
b Department of Medicine-DIMED, Medical School, University of Padova, Padova, Italy
c Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

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ABSTRACT

Background: Major cardiac complications have been described in SARS-CoV-2 patients. The study of cardiac troponin I kinetic release is the recommended approach to differentiate acute from chronic injury, in order to clinically manage different cardiac diseases.

Aim: To investigate whether serial measurements of high sensitivity troponin I (hs-cTnI) might provide additional information in SARS-CoV-2 patients’ clinical management.

Methods: 113 consecutive patients suffering from microbiology proven SARS-CoV2-infection have been studied. Hs-cTnI has been measured in lithium-heparin plasma samples using STAT High Sensitive Troponin I (Architect i2000, Abbott Diagnostics), being 99th percentiles 16 and 34 ng/L for females and males respectively.

Results: In 69 out of 113 patients hs-cTnI has been measured, showing in 31 (45%) values higher than 99th percentiles in at least one occasion. In 50 patients (72%) a kinetic evaluation (at least 2 measurements during 24 h) has been carried out. Patients were subdivided into five groups: 1 (n = 44) and 2 (n = 19) no measurement of hs-cTnI or no monitoring respectively; 3 (n = 15) no significant variations during monitoring; 4 (n = 8) and 5 (n = 27) significant variations with values persistently below or sometimes higher than 99th percentiles, respectively. Group 5 patients had a longer hospital stay (median 37 days, p = 0.0001), a more aggressive disease (6 out of 27, 22%, died), more often need admission to ICU (n = 25, 92.6%, p < 0.0001), and show one or more peak values, sometime preceded by severe hypoxia.

Conclusions: In SARS-CoV-2 patients, hs-cTnI serial monitoring may provide additional data to stratify risk, establish prognosis and gaining epidemiological insight on cardiac involvement in this pandemic disease.

1. Introduction

The epidemiology of COVID-19 infection has been evolved rapidly and actually several pathophysiological mechanisms have been identified and the understanding of clinical and diagnostic presentations has been refined [1]. Several papers have reported increased concentrations of cardiac biomarkers, in particular cardiac troponins and natriuretic peptides, in patients with COVID-19 disease [2–4]. Moreover, the elevation of cardiac troponins was found to be associated with severity of disease and poor prognosis, as in many other Non-Acute Coronary Syndromes (Non-ACS) diseases [5,6]. Indeed, the measurement of cardiac troponins (cardiac troponin I - cTnI - and cardiac troponin T - cTnT), nowadays based on the new high-sensitivity troponin assays (hs-Tn), is the first line laboratory test for the diagnosis of Acute Coronary Syndromes (ACS) and represents the gold standard for the detection of myocardial injury [7]. A recommended and distinctive approach to evaluate the circulating cardiac biomarker concentrations after a myocardial damage seems to be the time course of its kinetic release, which may help to differentiate acute from chronic myocardial injury according to its level of elevation and the pattern of variation of its concentrations over time. This issue represents a fundamental aspect to support clinicians in the differential diagnosis and in the management of different cardiac diseases [8,9].

Aim of our study has been to investigate in COVID-19 patients the kinetics of release of cardiac troponin I and time course of its concentrations, measured with a high-sensitivity method (hs-TnI), in order to verify if serial measurements may provide additional and clinically useful information in identifying the underlying mechanisms of release and patients’ risk stratification and prognosis.
2. Materials and methods

From 5th to 10th of March 2020, we screened 113 patients admitted to the University Hospital in Padua (Italy), suffering from COVID-19 microbiology proven infection. The biochemical parameters performed during the hospitalization period (January – May 2020) were measured using Cobas 8000 system (Roche Diagnostics, GmbH, Mannheim, Germany) with the exception of Procalcitonin (PCT) (Liaison Brahms PCT II gen, Diasorin SpA, Saluggia, Italy), C-reactive protein (CRP) (Dimension Vista, Siemens Healthcare Diagnostics Inc, Tarrytown USA), and D-Dimer (Sclavo reagents, Sysmex CS-5100), while hematological data were obtained using Sysmex XE 2100 (Sysmex, Kobe, Japan). Arterial blood gas analysis (ABG, RapidPoint 405, Siemens HealthCare Diagnostics) was performed in all patients, every 4 h during 24 h, but also as needed according to the clinical conditions.

Ctnl measurement (STAT High Sensitive Troponin I, Architect 2000, Abbott Diagnostics, hs-cTnI) was performed in lithium heparin plasma sample (Becton Dickinson) according to manufacturer’s recommendations, being confirmed in our study the analytical performance previously published [10]. The 99th percentiles adopted for female and male were 16 and 34 ng/L, respectively. A variation between two consecutive measurements has been considered significant if greater than ± 20% as suggested by guidelines [7,11]. bedside echocardiography and electrocardiogram have been carried out to confirm the diagnosis when necessary. In our hospital, since of the beginning of the pandemic, mobile computed tomography (CT) scanner in a truck was rented and became operative for all patients with a confirmed diagnosis of COVID-19. Indeed, CT can be used as an important tool for the diagnosis of COVID-19 pneumonia and a wide variety of CT findings in COVID-19 have been reported in the different studies [12]. However, all studies described that the most common pattern was the presence of ground glass opacities with bilateral patchy shadowing [13].

2.1. Statistical analysis

Statistical analyses were performed using Stata v13.1 (StataCorp, Lakeway Drive, TX, USA) and Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). For descriptive statistics median and interquartile range (IQR) were used for summarizing results, as data were highly skewed. Kruskal-Wallis equality-of-populations rank test was employed to define differences across groups of subjects, with or without Bonferroni’s criteria for adjusting p-values for multiple testing. Chi-square test and Fisher’s exact test were used for comparing proportions across groups.

3. Results

Among 113 screened patients suffering from COVID-19 microbiology proven infection, in 69 at least one high-sensitivity troponin I measurement (hs-cTnI) has been carried out during the hospitalization being higher than 99th percentiles in at least one occasion in 31 patients (45%). CT scans performed at the time of patients’ admission revealed abnormal results in 86.2% of patients being ground-glass opacity and bilateral patchy shadowing found in 56.4% and 51.8% of cases, respectively.

The main patients’ demographic characteristics and the principal clinical outcomes (discharged/dead) have been summarized in Table 1A. According to the severity and the evolution of the disease, n = 49 patients (43.4%) admitted to Infective Ward (IW) were moved after few days in Intensive Care Unit (ICU), while n = 7 (6.2%) died. In our study population, the results of laboratory tests showed (Table 1B): lymphopenia (lymphocytes < 1.50 × 10^{9}/L) and thrombocytopenia (platelets < 150 × 10^{9}/L) in 76% and 20% of patients respectively, increased D-Dimer (> 500 μg/L) and CRP concentrations (> 10 mg/L) in 31% and 73% respectively, while PCT values higher than 0.5 μg/L were observed in 21% only. According to the criteria concerning troponin I measurements and release kinetic patterns, the patients studied were classified into 5 different groups (Table 2A): Group 1 (n = 44, 38.9%), hs-cTnI not measured during hospitalization; Group 2 (n = 19, 16.8%), hs-cTnI measured during hospitalization without further monitoring (≤2 measurements within 24 h); Group 3 (n = 15, 13.3%), hs-cTnI measured during the hospitalization monitoring biomarker kinetics that showed no statistically significant variation in concentration (delta ≤ 20%); Group 4 (n = 8, 7.1%), hs-cTnI measured during hospitalization with kinetics showing a statistically significant variation in concentration (delta > 20%); Group 5 (n = 27, 23.9%), hs-cTnI measured during hospitalization with kinetics showing a statistically significant variation in concentration (delta ≥ 20%) with all values at ≤ 99th percentile levels; Group 5 (n = 27, 23.9%), hs-cTnI measured during hospitalization with kinetics showing a statistically significant variation in concentration (delta ≥ 20%), and at least one value ≥ 99th gender-specific percentile levels.

By evaluating troponin I values and kinetics, statistically significant differences with respect to clinical characteristics and outcome were observed (Table 2A): patients in group 5 were older (median 71 years, p < 0.005 vs group 1 and 2), had a longer hospital stay (median 37 days, p = 0.0001), more often need admission to ICU (median n = 25, 92.6%, p < 0.0001) and had a more aggressive form of the disease: 6 out of 27 (22.2%) died. However, no significant difference was found between groups for cardiovascular risk factors and/or previous cardiovascular disease.

On considering the biochemical parameters used as potential prognostic indicators of cardiovascular events (Table 2B), statistically significant differences were found across groups for troponin I and D-dimer concentrations (p = 0.0001 and p = 0.0003, respectively). Although no statistically significant differences were found for CRP and PCT values, 22 of the 27 (81.5%) Group 5 patients presented CRP >
10 mg/L compared to 28 of the 44 (63.6%) Group 1 patients. Furthermore, in two of the six patients who died (33.3%, Group 5) PCT values were higher than 0.5 μg/L.

Some exemplificative patterns observed in troponin I kinetics are reported in Fig. 1. These patterns seem to suggest different and differently severe cardiac injury and in particular: -in one patient (MP, 82 year-old man) without previous cardiovascular disease and a favorable outcome (40 days’ hospitalization), the kinetic release showed values persistently below the 99th percentile (1A); - in a hypertensive patient (SR, 77 year-old man) who developed acute viral myocarditis (1B), the cardiac biomarker showed a peak of concentrations (5326 ng/L), followed by a progressive decrease, normal values (34 ng/L) being attained after 20 days. The patient hospitalized for a significantly longer time (60 days) was transferred from the IW to the Intensive Care Unit (ICU). In another patient (MZ, 83 year-old man) who developed acute viral myocarditis (1C), the troponin I kinetics showed a trend to develop several concentration peaks associated with severe hypoxia (pO2 48.5 mmHg), thrombocytopenia (platelets 129x10^9/L), increased D-dimer (> 1500 μg/L) as well as increased CRP (290 mg/L) concentrations. During the time of hospitalization, the troponin I values remained significantly increased being 335 ng/L at discharge and 21.7 ng/L only 1 month later. Finally, the association between hs-cTnI peaks and respiratory parameters, in particular pO2, is shown in Fig. 1D. The patient (RO, 66 year-old man) had previous hypertension and ischemic dilated cardiomyopathy: the progressive increase in troponin I concentrations that peaked several times during the hospitalization appeared to be preceded, on some occasions, by severe hypoxia (pO2 < 80 mmHg) suggesting a possible type 2 myocardial infarction.

### Table 2
Demographic and Clinical Characteristics (2A), and Laboratory Findings (2B) of the n = 5 groups of Study patients (IQR, Interquartile Range; y, years).

| Patients’ Group | Patients number(%) | Sex | Age Median, IQR (years) | Pneumonia n (%) | ICU stay n (%) | Hospital stay Median, IQR (days) | Death n (%) | Previous cardiovascular risk factors* n (%) | Previous Cardiovascular diseases** n (%) |
|----------------|---------------------|-----|-------------------------|-----------------|---------------|-------------------------------|-------------|----------------------------------------|---------------------------------------|
| 1              | 44                  |     | 32 (73)                 | 12 (27)         | 64, 53-75     | 13 (29.5)                     | 9 (20.5)    | 11, 7-17                               | 1 (2.3)                              |
| (38.9)         |                     |     |                         |                 |               |                               |             |                                        |                                       |
| 2              | 19                  |     | 9 (47)                  | 10 (53)         | 62, 47-66     | 14 (73.7)                     | 2 (10.5)    | 13, 9-18                               | 0 (0)                                 |
| (16.8)         |                     |     |                         |                 |               |                               |             |                                        |                                       |
| 3              | 15                  |     | 11 (73)                 | 4 (27)          | 62, 61-69     | 13 (86.7)                     | 5 (33.3)    | 15, 14-23                              | 0 (0)                                 |
| (13.3)         |                     |     |                         |                 |               |                               |             |                                        |                                       |
| 4              | 8                   |     | 6 (75)                  | 2 (25)          | 65, 58-75     | 8 (100)                       | 8 (100)     | 32, 24-36                              | 0 (0)                                 |
| (7.1)          |                     |     |                         |                 |               |                               |             |                                        |                                       |
| 5              | 27                  |     | 22 (82)                 | 5 (18)          | 71, 68-78     | 26 (96.3)                     | 25 (92.6)   | 37, 35-48                              | 6 (22.2)                              |
| (23.9)         |                     |     |                         |                 |               |                               |             |                                        |                                       |

| Laboratory Findings - B. Median, IQR - (reference range) |
|----------------------------------------------------------|
| Patients/Group n (%) | Cardiac Troponin I ng/L (females: 16; males: 34) | Platelet count 10^9/L (150-450) | C-reactive protein mg/L (0-6) | Procalcitonin μg/L (0.0-0.5) | D-dimer μg/L (0-59 y: 0-250; 60-69 y: 0-300; 70-79 y: 0-350; > 79 y: 0-400) |
|---------------------|-----------------------------------------------|--------------------------------|-------------------------------|-----------------------------|---------------------------------|
| 1                   | 44                                            | 233, 181-335                  | 30, 11-75                     | 0.07, 0.04-0.31             | 204, 150-344                    |
| (38.9)              |                                               |                                |                               |                             |                                 |
| 2                   | 19                                            | 209, 153-305                  | 18, 3-42                      | 0.07, 0.04-0.24             | 199, 150-347                    |
| (16.8)              |                                               |                                |                               |                             |                                 |
| 3                   | 15                                            | 270, 175-333                  | 25, 11-66                     | 0.04, 0.04-0.14             | 202, 150-394                    |
| (13.3)              |                                               |                                |                               |                             |                                 |
| 4                   | 8                                             | 243, 192-270                  | 88, 19-142                    | 0.19, 0.05-0.40             | 374, 221-583                    |
| (7.1)               |                                               |                                |                               |                             |                                 |
| 5                   | 27                                            | 228, 172-329                  | 47, 22-88                     | 0.13, 0.06-0.61             | 593, 294-1305                   |
| (23.9)              |                                               |                                |                               |                             |                                 |

### Group 1 = hs-cTnI never measured during the hospitalization.

### Group 2 = hs-cTnI measured during the hospitalization without checking the kinetic (at least 2 measurements within 24 h).

### Group 3 = hs-cTnI measured during the hospitalization checking the kinetic (at least 2 measurements within 24 h) that showed no statistically significant variation of concentration (delta ≤ 20%).

### Group 4 = hs-cTnI measured during the hospitalization checking the kinetic (at least 2 measurements within 24 h) that showed statistically significant variation of concentration (delta ≥ 20%) but all values were ≤ 99th percentile levels.

### Group 5 = hs-cTnI measured during the hospitalization checking the kinetic (at least 2 measurements within 24 h) that showed statistically significant variation of concentration (delta ≥ 20%) and at least one value ≥ 99th percentile levels.

IQR = Interquartile range.

*Diabetes, hypertension, obesity, chronic obstructive lung disease; ** hypertensive cardiomyopathy, heart failure, atrial fibrillation, carotid artery stenosis.

§ Fisher’s exact test; χ² chi square test.

4. Discussion

Several papers in the recent literature have highlighted the complex interaction between the cardiovascular system and COVID-19, showing myocardial injury in 20 to 40% of hospitalized patients [14,15]: heart failure, acute coronary syndrome (ACS), arrhythmia and myocarditis, the most frequent complications, are all associated with elevated cardiac troponins, evidenced in particular by high-sensitivity immunoassays [16,6]. Indeed, cardiac troponin is the most sensitive and specific available biomarker, show increased concentrations above the 99th percentile with cardiac necrosis of just 40 mg of the myocardium.
as demonstrated in some studies [17]. For this reason, the differential diagnosis between cardiac diseases in the presence of increased troponin concentrations, calls for the evaluation of release kinetics of the biomarker [8,9,18]. In our study, aiming to describe troponin I behavior measured with high-sensitivity assay in a population of consecutive patients with SARS-CoV2-disease, we found serial measurement was of additional value in establishing the prognosis and stratifying risk in COVID patients, not only in those with previous cardiac diseases. In fact, while no difference in the clinical characteristics of the patients studied concerning previous cardiac diseases or risk factors was

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**Fig. 1A.** hs-TnI kinetic (from 5th of March to 10th of April) showing all values below the cut-off (99th percentile concentration) with clinically significant changes (delta value ≥ 20%) (82-year-old male in Group 4).

**Fig. 1B.** hs-TnI kinetic (from 17th of March to 20th of April) showing values above the cut-off (99th percentile concentration) with clinically significant changes (delta value ≥ 20%) (77-year-old male in Group 5) (acute viral myocarditis in patient with COVID-19 infection).
Fig. 1C. hs-TnI kinetic (from 9th to 27th of April) showing values above the cut-off (99th percentile concentration) with three main peak levels (83-year-old male in Group 5) (NSTEMI, pharmacologically cardiovert atrial fibrillation, first degree ventricular atrium block).

Fig. 1D. Relationship between hs-TnI and pO2 kinetics (from 28th of February to 4th of May) (66-year-old male in Group 5). Clinical decision level for cardiac damage: 16 ng/L and 34 ng/L for females and males, respectively; arterial blood partial oxygen pressure (pO2) normal values: 80–100 mmHg. Arterial blood partial oxygen pressure (pO2) = 80 mmHg (dotted line in the pO2 kinetic); clinical decision level of cardiac troponin I for cardiac damage = 34 ng/L (dotted line in cTnI kinetic). From top to down arrows (↓) = cardiac troponin I peak values; from down to top arrows = arterial blood partial oxygen pressure (pO2) lower “critical” values (< 80 mmHg).
observed, a different clinical outcome in terms of severity of cardiac injury, time of hospitalization, particularly in ICU, and prognosis, are related not only to troponin I concentrations observed on admission, as reported in other studies [3,19], but above all to the kinetic pattern observed throughout monitoring. While in patients with a clinically progressive disease recovery, troponin I show values constantly below the 99th percentile (Fig. 1A), in patients with a rapid and sudden increase reaching high peaks of concentrations (Figs. 1B and 1C), the onset of severe cardiac injury might be diagnosed early, thus allowing more specific and prompt therapy to be undertaken. Finally, serial monitoring according to the specific protocol and timing of blood drawing, as suggested in guidelines [7,11,18], may enable relevant pathophysiological information to be obtained on the origin of myocardial injury: as demonstrated by the results reported in Fig. 1D, several peaks of values observed in some patients seem to be strictly preceded by severe hypoxia, suggesting the onset of type 2 acute myocardial infarction in several different moments during hospitalization [19]. These results seem to provide clinically relevant and specific informations regarding the type and the severity of myocardial injury associated to COVID-19 disease [20,21], thus assuring additional clinical data for stratifying risk, establishing the prognosis, managing patients and gaining important epidemiological insight on cardiac involvement in SARS-CoV-2 patients [22,23]. The relative low numbers of patients monitored, however, represents a limitation of our study, but the clinical relevance of the obtained results may pave the way for further studies with more specific design in a larger patients cohort. Moreover, as additional limitation, we did not perform a comparison between CT findings and troponin I values, even if in many case the obtained results may pave the way for further studies with more specific design in a larger patients cohort. Moreover, as additional limitation, we did not perform a comparison between CT findings and troponin I values, even if in many case the mechanism of myocardial injury could be a severe hypoxia secondary to a lung damage showed by CT.

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