Cardiac Imaging Phenotype in Patients with Coronavirus Disease 2019: Rationale, design and protocol of the COCARDE study

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Abstract

Background: – The effects of SARS-Cov-2 (COVID-19) on the myocardium and their role in the clinical course of infected patients are still unknown. The severity of SARS-Cov-2 is driven by hyperinflammation and the effects of SARS-Cov-2 on the myocardium may be significant. The present study proposes to use bedside observations and biomarkers to characterize the association COVID-19 with myocardial injury.

Objectives: – The aim of the study is to describe the myocardial function and its evolution over the time in patients infected with SARS-COV-2; and to investigate the link between inflammation and cardiac injury.
Design – This prospective, monocentric observational study will enroll 150 patients with suspected or confirmed SARS-COV-2 infection at Toulouse University Hospital, Toulouse, France. Patients admitted in intensive care unit, regular cardiologic ward as well as geriatric ward of our tertiary university hospital will be included during the pandemic period. Blood sampling, electrocardiography, echocardiography, as well as morphometric and demographic data will be prospectively collected.
Implications – A better understanding of the effects of COVID-19 on myocardia function and the links with inflammation would improve patient follow-up and care.
Trial registration – Clinicaltrials.gov NCT04358952

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Abstract

Background – The effects of SARS-Cov-2 (COVID-19) on the myocardium and their role in the clinical course of infected patients are still unknown. The severity of SARS-Cov-2 is driven by hyperinflammation and the effects of SARS-Cov-2 on the myocardium may be significant. The present study proposes to use bedside observations and biomarkers to characterize the association COVID-19 with myocardial injury.

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Implications – A better understanding of the effects of COVID-19 on myocardia function and the links with inflammation would improve patient follow-up and care.

List of abbreviations

CMR: Cardiac Magnetic Resonance

COVID-19: Coronavirus Disease -19

CT: Computed Tomography

GLS: Global Longitudinal Strain

RT-PCR: Real-Time reverse transcriptase–Polymerase Chain Reaction

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2)

TAPSE: Tricuspid Annular Plane Systolic Excursion

TTE: Transthoracic Echocardiography

INTRODUCTION

Background

Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) infection, pathogen responsible for Coronavirus Disease 19 (COVID-19), which can lead to acute respiratory distress syndrome, is not limited to the pulmonary sphere and has systemic effects that contribute to its significant mortality. The effects of SARS-COV-2 on the myocardium and their role in the clinical course of infected patients are still unknown. Cardiovascular risk factors such as diabetes and hypertension, as well as coronary or cerebral cardiovascular history, have been associated with severe forms of infection [1–3]. In addition, most of the cohort data currently available report biological myocardial injury with troponin increase in about 12% of patients [4–6] with a prevalence ranging from 4 to 31% according to the burden of the disease and the need for resuscitative management [4,7,8]. Myocardial injury is associated with excess mortality, which is particularly prevalent in the elderly [7,8]. Individuals at greatest risk of severe disease and mortality are older patients, particularly those with underlying cardiovascular risk factors and chronic conditions.

The pathophysiology of the myocardial involvement of SARS-COV-2 remains poorly understood. Some observations suggest an association with the cytokine storm that accompanies the infection [5]. The more or less massive release of pro-inflammatory cytokines has been linked to the pathophysiology of organ failure that accompanies viral infection [9], further explaining the prognostic role of several biological parameters such as increased C-reactive protein, procalcitonin, D-dimers, creatine phosphokinase, lactate dehydrogenase, lymphopenia and leukopenia [2,4,10,11]. The cytokine storm is thought to cause an imbalance between myocardial oxygen needs and supply, leading to a type 2 myocardial infarction [12]. However, given the importance of cardiovascular risk factors in severe forms of the disease, a type 1 myocardial infarction [12] via an atheromatous

plaque rupture mechanism cannot be excluded [13,14]. Finally, the possibility of a myocardial tropism of the SARS-COV-2 though the myocardial angiotensin-converting enzyme 2 receptors [15] could explain a direct viral infection of the myocardium, which may lead to fulminant myocarditis [16,17]. More generally, the inflammatory mechanisms involved could also affect skeletal muscle tissue and body composition resulting in cardiac cachexia [18].

However, despite substantial biological data on cardiac injury during SARS-COV-2 infection, to date, there are no data on the functional impact of the infection on the myocardium.

Rationale

Based on the observation that cardiac injury, as evidenced by an increase in troponin, was associated with a poor prognosis, and that the most severe forms affected elderly subjects, the COCARDE study was designed in two arms: intensive care unit (COCARDE-ICU) and geriatrics (COCARDE-Geria) with the aim to describe the cardiac imaging phenotype of patients infected with SARS-COV-2.

Objectives

The objective of this study is to describe the myocardial function and its evolution during infection in high-risk patients infected with SARS-COV-2 and to establish the role of inflammation in the cardiac involvement.

Methods

Study design

The COCARDE study is an investigator-initiated, prospective, monocentric observational study with planned enrolment of 150 patients at Toulouse University Hospital, Toulouse, France. By April 23, 2020, a total of 71 patients have been included. Estimated final enrolment day is May 1, 2020, with reporting of first results at the end of the second quarter of 2020.

Patient flowchart is presented in Figure 1.

Notifications and registration

The study is notified to national ethics committees as appropriate (protocol number ID-RCB: 2020-A00852-37, positive endorsement of the protection of persons committee West IV dated April 8, 2020) and to the French Data Protection Agency. The study is registered with Clinicaltrials.gov NCT04358952. The investigation conforms with the principles outlined in the Declaration of Helsinki. All patients or their dependents are informed that the data collected can be used for research purposes and the absence of opposition is collected for each patient in accordance with French legislation.

Objectives

Primary and secondary objectives of the COCARDE study are listed in Table.

Primary objective

The primary objective is to prospectively describe the myocardial function at admission in a population of high-risk patients infected with SARS-COV-2 compared to a matched population of uninfected patients.

Primary objective definition

Myocardial function assessed by global longitudinal strain and myocardial work indices (global

work index and global work efficiency) by speckle-tracking echocardiography.

Secondary objectives

Secondary objectives will gather information on the evolution of myocardial function parameters over time in high-risk patients infected with SARS-COV-2 and the impact of inflammatory and morphometric parameters.

1. Describe the evolution of myocardial function over time (admission, day-3, day-7 and day-14) in high-risk patients (patients over 70-year-old with biological cardiac injury as expressed by increased troponin and patients requiring intensive care unit management – Figure 2).
2. Describe the relationship between myocardial function and biological parameters of inflammation in high-risk patients (patients requiring intensive care unit management).
3. Describe the relationship between myocardial function and vastus lateralis muscle architecture in patients over 70-year-old.
4. Describe the myocardial lesion pattern by cardiac magnetic resonance imaging in patients with biological cardiac injury as expressed by increased troponin.
5. Describe the impact of myocardial function on prognosis in hospitalized patients.

Secondary objective definition

1. Myocardial function assessed by global longitudinal strain and myocardial work indices (global work index and global work efficiency) by speckle-tracking echocardiography.
2. Biological parameters of inflammation: pro-inflammatory cytokines, anti-inflammatory cytokines, alarmins and resolvins.
3. Morphometric parameters assessed by muscle architecture to determine muscle thickness, penetration angle and muscle fiber length of the vastus lateralis.
4. Myocardial lesion pattern assessed by T2-weighted, T2 mapping and pre-contrast T1

mapping imaging (edema), early gadolinium enhancement (hyperaemia), late gadolinium enhancement and post-contrast T1 mapping (necrosis/edema) by cardiac magnetic resonance imaging.

5. Prognosis assessed by hospital length of stay and in-hospital mortality.

Patient population

Following the classification of the SARS-COV-2 infection as a pandemic by the World Health Organization on March 11, 2020, and following an epidemiological alert issued by the French health authorities on March 14, 2020, the organization of patient reception at our university hospital has been reviewed to allow for the screening and isolation of infected patients. All patients with suspected SARS-COV-2 infection undergo collection specimens from the upper respiratory tract for SARS-CoV-2 testing by real-time reverse transcriptase–polymerase chain reaction (RT-PCR), chest computed tomography (CT), cardiac biomarkers, including values of high-sensitivity troponin T (hs-TnT) and NT-proBNP, electrocardiography and transthoracic echocardiography (TTE) at admission, as part of the standard of care.

Diagnosis of SARS-COV-2 infection is retained in the presence of an evocative chest CT and a positive RT-PCR for SARS-COV-2 or an evocative chest CT in the presence of a negative RT-PCR for SARS-COV-2 after ruling out other common respiratory viral and bacterial infections [19]. Biological cardiac injury is defined as blood levels of hs-TnT above the 99th-percentile upper reference limit.

Patients are then categorized into 3 groups according to the presence of SARS-COV-2 infection and/or biological cardiac injury, and the study population is then divided into two arms: patients requiring or not intensive care unit (COCARDE-ICU) and patients over 70 year-old not referred to an intensive care unit (COCARDE-Geria).

The serum of patients from the COCARDE-ICU population is collected after centrifugation for a study of inflammatory parameters.

Patients from the COCARDE-Geria population are assessed for the muscle architecture of the vastus lateralis.

Patients with biological cardiac injury are referred for cardiac magnetic resonance imaging when suitable.

Inclusion criteria

Patient 18-year-old or older referred or suspected for SARS-COV-2 infection.

Non-inclusion criteria

Patient under 18-year-old.

Patients refusing to participate to the research.

Patients with history of heart disease and atrial fibrillation.

Patients under guardianship, curatorship or safeguard of justice.

Data collection

The demographic characteristics (age and sex), clinical data (weight, heught, symptoms, delay between first symptom and admission, comorbidities, treatments), arterial blood pressure and laboratory findings for patients during hospitalization are collected from electronic medical records and entered into the database by 2 investigators. Electrocardiography, transthoracic echocardiography (TTE), cardiac magnetic resonance imaging and muscle architecture assessment are performed and analyzed by independent investigators blinded to the clinical characteristics of the patients.

Biomarkers

Inflammatory pathway parameters are collected for plasma extracted from venous blood sampling into sodium citrate tubes. Blood samples are centrifuged at 3000g for 5 min at room temperature. Then superior 2/3 supernatant is recovered and again centrifuged for 5 min.

The following dosages are then performed in the same laboratory:

- Pro-inflammatoiry cytokines: TNFα, IL6, IL1β, IL1α, IFNγ, IFNα2, MCP1 (CCL2), IL12, IL17, IL23, IL33, IL8 (CXCL8),
- Anti-inflammatory cytokine: IL10,
- Alarmins: HMGB-1, S100 protein, DNA,
- Resolvins: 18-HETE, 15-HETE, 12-HETE, 17-HDOHE, 5-HETE, 14-HDOHE, EPA, ARA, DHA, PDX, PGE2, TXB2.

Electrocardiography

Electrocardiography (ECG) is analyzed for heart rate, rhythm, intraventricular conduction delay, QRS duration and QT duration.

Transthoracic Echocardiography and image analysis

Transthoracic echocardiography is performed with either a Vivid E95 or Vivid S70 ultrasound system (GE Healthcare) using a 3.5 MHz transducer, allowing to archive acquisitions for a deferred analysis. Doppler, M-mode and two-dimensional gray scale echocardiography including the three standard apical views (four-, three- and two-chamber) using high frame rates (>60 frames/s), the pulsed-Doppler transmitral inflow and left ventricular outflow and the pulsed-Doppler tissue imaging lateral mitral and tricuspid annular velocities are performed for each patient with simultaneous arterial blood pressure recording.

Image analysis are performed offline using the EchoPAC V.202 software (GE Medical Systems). Two-dimensional and Doppler echocardiography measurements and quantification are performed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines [20,21]. The following measurements are collected: diastolic parameters, including peak early (E) and late (A) diastolic mitral inflow velocity, E/A ratio, deceleration time, lateral mitral annular diastolic velocity (Ea), peak systolic tricuspid annular velocity and tricuspid annular plane systolic excursion (TAPSE). All Doppler measurements are made

over three cardiac cycles and averaged. Left ventricular end-diastolic and -systolic volumes, and ejection fraction are measured using the modified biplane Simpson's method from apical two- and four-chamber views. Global longitudinal strain (GLS) it is calculated from the average of the segmental strain on a 17-segment model using two-dimensional speckle tracking from greyscale images and the automated function imaging technique from the apical four-chamber, two-chamber and three-chamber views [22]. Myocardial work is calculated from left ventricular GLS and an estimated left ventricular pressure curve as proposed by Russell *et al* [23]. Wasted work is defined by the work performed by the myocardium during segmental elongation, and constructive work by the work performed during segmental shortening represented. During isovolumetric relaxation, this definition is reversed such that myocardial work during shortening is considered wasted work and work during lengthening is considered constructive work. Work efficiency is then calculated as constructive work divided by the sum of constructive and wasted works.

Muscle architecture processing and analysis

Skeletal muscle ultrasound assessment of the vastus lateralis is performed using a Vivid E95 ultrasound system (GE Healthcare) and a 15 MHz linear probe by acquisition at the lower third of the femur for the exploration as described by Aubertin-Leheudre *et al* [24]. Patient sit with hip and knee angles at 90° and with limb muscles relaxed. The probe is positioned perpendicular to the dermal surface of the vastus lateralis muscle and oriented along the median longitudinal plane of the muscle. Three sagittal ultrasounds of the vastus lateralis are then digitized and images analyzed offline using the EchoPAC V.202 software (GE Medical Systems) to determine muscle thickness (distance from the superior and deepest aponeurosis at the greatest distance), penetration angle (angle of insertion of the bundle of muscle fibers into the deep aponeurosis) and muscle fiber length (length of the fascicle between the superior and deep aponeurosis).

Cardiac magnetic resonance protocol and imaging analysis

CMR is performed in breath-hold mode with the use of a 1.5-T MRI system Ingenia Ambition X (Philips Medical Systems) using a 32-element phased-array cardiac coil with cardiac gating in accordance with the recommendations of the Society for Cardiovascular Magnetic Resonance endorsed by the European Association for Cardiovascular Imaging [25]. Following scout imaging, balanced steady-state free precession breath-hold images are acquired: slice thickness 6 mm (long-axis and 4-chamber views), or 8 mm (contiguous short-axis views (no gap between slices, from the atrioventricular ring to the apex). Subsequently, standard sequences for T2-weighted, T2 mapping and pre-contrast T1 mapping images are obtained in the short axis, through the basal, mid cavity, and apical slices, and then early gadolinium enhancement, late gadolinium enhancement images are obtained in the long-axis, 4-chamber and short-axis orientations 10 minutes after injection of 0.2 mmol/kg of gadolinium dimenglumine (Magnevist) using a phase-sensitive inversion recovery spoiled gradient echo sequence. Post-contrast T1 mapping are obtained in the short axis, through the basal, mid cavity, and apical slices.

Image analysis is performed using the clinically available imaging software workstation ViewForum (Philips Medical Systems). Endocardial border is outlined on the short-axis cine images on the right and left ventricles, in systole and diastole, from the base to the apex to calculate volumes and ejection fractions. T2 and pre- and post-contrast T1 mapping measurements are performed on motion-corrected maps, to cover the entire myocardium in short axis and six separate segments where both mean and maximum values were noted. The extent and pattern of late gadolinium enhancement is planimetered on the short-axis contrast images and confirmed on an orthogonal view (either long-axis or 4-chamber) with the use of an image intensity level ≥2 standard deviations above the mean of remote myocardium to define late gadolinium enhancement. The 17-segments model is used to localize late gadolinium enhancement within the left ventricle.

Sample size

This is a descriptive pilot study. As there is no data on the topic, to date, the number of subjects to be included will be 50 per group:

- Fifty patients without SARS-COV-2 infection (Cov-) – 25 in the COCARDE-ICU sub-study and 25 in the COCARDE-Geria sub-study.
- Fifty patients with SARS-COV-2 infection without biological cardiac injury (Cov+/TnT) – 25 in the COCARDE-ICU sub-study and 25 in the COCARDE-Geria sub-study.
- Fifty patients with SARS-COV-2 infection with biological cardiac injury (Cov+/TnT+) – 25 in the COCARDE-ICU sub-study and 25 in the COCARDE-Geria sub-study.

Statistical analysis

Continuous variables will be tested for normal distribution using the Kolmogorov–Smirnov test and expressed as mean ± standard deviation. Laboratory findings are not normally distributed, and results will be, therefore, presented as medians with interquartile ranges (IQR). Nominal values will be expressed as numbers and percentages. The study population was categorized into three groups: Cov-, Cov+/TnT- and Cov+/TnT+. Group comparisons will be made using nonparametric Kruskal–Wallis tests or ANOVA for continuous variables and $\chi 2$ test for categorical variables, using Bonferroni corrections for multiple comparisons. Logistic regression models and classification regression trees (CART) will be used to identify predictors of myocardial dysfunction at admission. Differences will be considered statistically significant for P-values of < 0.05. All analyses will be performed using standard statistical software SPSS version 20 (SPSS Inc., Chicago, Illinois).

Discussion

The COCARDE study is the first study to date to propose a cardiac imaging phenotyping of SARS-COV-2 infected patients. Data on myocardial injury in SARS-COV-2 infected patients are scarce and limited to biological parameters of myocardial injury. Although sensitive, these parameters do not

prejudge the mechanism and functional impact on the myocardium. Troponin is a marker of myocardial injury, including, but not limited to, myocardial infarction or myocarditis, and the clinical relevance of this distinction has never been clear, and is even less clear in the context of SARS-COV-2 infection, which causes a plethora of ischemic and non-ischemic causes of myocardial lesions [26]. But to date, most of the data regarding SARS-CoV-2 associated cardiovascular complications are anecdotal in the absence of systematic studies [27].

Expected results

The COCARDE study will be able to describe myocardial function assessed by GLS and myocardial work indices in a population of SARS-COV-2 infected patients. Furthermore, the study will be able to describe the evolution over the time of myocardial function among high-risk infected patients (i.e. patients hospitalized in intensive care unit and older patients with biological cardiac injury).

This study will help understand the impact of the kinetics of inflammatory parameters on myocardial function during infection. The magnetic resonance imaging data will allow to differentiate between direct myocardial involvement by the inflammatory process and indirect vascular involvement, whether it is a type 1 or type 2 myocardial infarction.

Study limitations

The COCARDE study has the limitations associated with single-site and limited sample studies. Therefore, our patients may not represent patients admitted to other facilities for SARS-COV-2 management. However, the study is carried out on a tertiary care teaching hospital where are referred the majority of patient of the suburban area. Moreover, the selection of high-risk patients, i.e. patients hospitalized in intensive care unit and older patients, provides a sample of choice to better understand myocardial injury in the SARS-COV-2 infected patient population.

Conclusion

Given the severity of illness and the primary focus on urgently managing infection and respiratory failure, it is understandable that not all patients have complete cardiac data, such as electrocardiography, and that information from more sophisticated cardiac testing, such as echocardiography, coronary angiography, and magnetic resonance imaging, are not available [13]. To date, there are no data on the relationship between myocardial function and biological parameters of inflammatory activation pathways in SARS-COV-2 infected patients. The present study proposes to use bedside observations and biomarkers to characterize the association SARS-COV-2 with myocardial injury.

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Table

Table - Primary and secondary end points

Primary objective
Describe the myocardial function at admission in a population of high-risk patients infected with SARS-COV-2
Secondary objectives
Describe the evolution of myocardial function over time (admission, day-3, day-7 and day-14) in high-risk patients infected with SARS-COV-2
Describe the relationship between myocardial function and biological parameters of inflammation in high-risk patients infected with SARS-COV-2
Describe the relationship between myocardial function and vastus lateralis muscle architecture in patients over 70-year-old infected with SARS-COV-2
Describe the myocardial lesion pattern by cardiac magnetic resonance imaging in patients infected with SARS-COV-2 with biological cardiac injury
Describe the impact of myocardial function on prognosis in hospitalized patients infected with SARS-COV-2

Figures

Figure 1. Patient flowchart

CMR: cardiac magnetic resonance; Cov: SARS-COV-2; CT: computed tomography; ECG: electrocardiography; RT-PCR: real-time reverse transcriptase–polymerase chain reaction; TNT: high-sensitive Troponin T; TTE: transthoracic echocardiography;

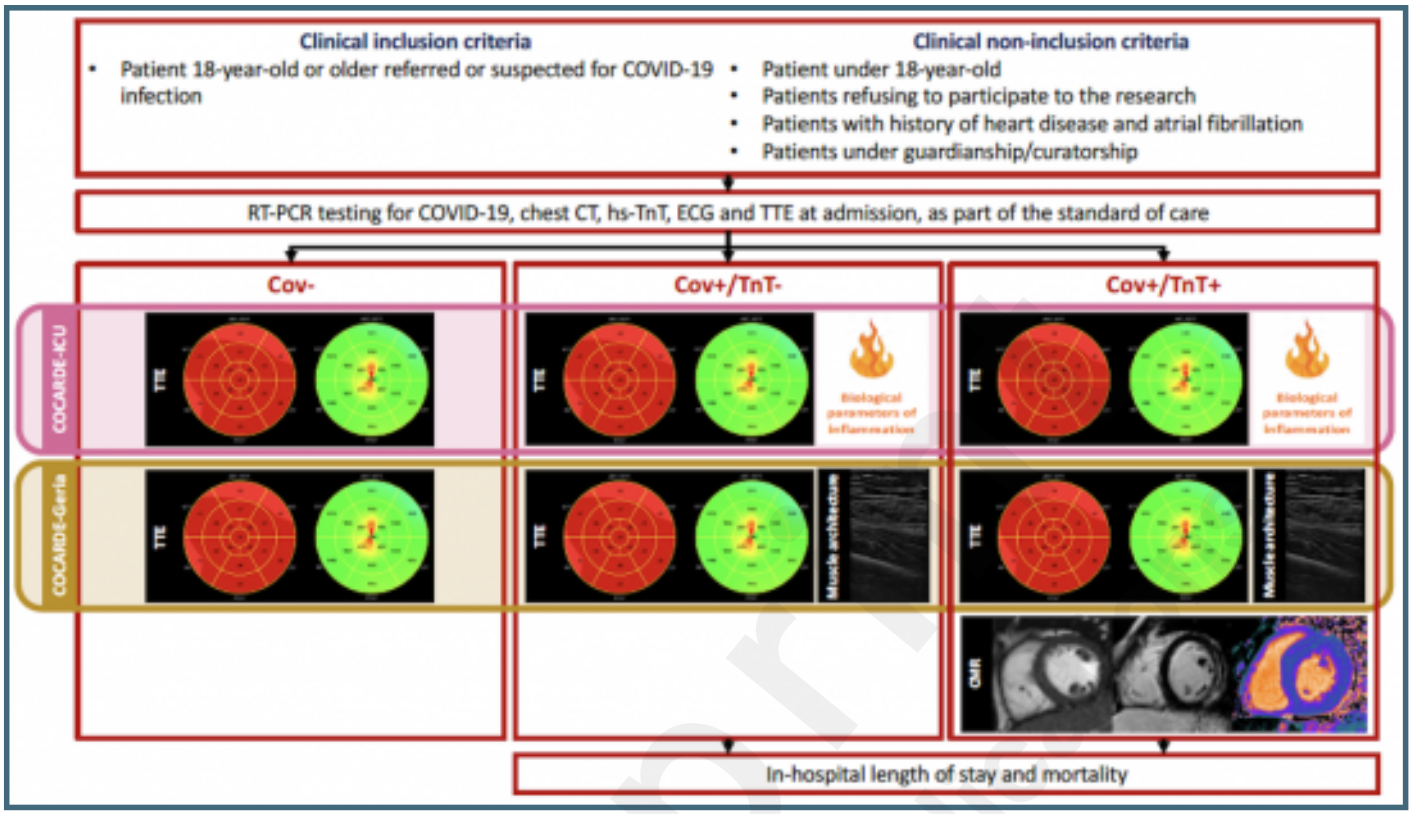
Figure 2. Timeline for myocardial function monitoring

IUC: intensive care unit; hs- TNT: high-sensitive Troponin T

Supplementary Files

Figures

Patient flowchart.



Timeline for myocardial function monitoring.