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ORIGINAL RESEARCH ARTICLE

Cardiac performance in patients hospitalized with COVID-19: a 6 month follow-up study

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Abstract

Aims Myocardial injury is frequently observed in patients hospitalized with coronavirus disease 2019 (COVID-19) pneumonia. Different cardiac abnormalities have been reported during the acute COVID-19 phase, ranging from infra-clinic elevations of myocardial necrosis biomarkers to acute cardiac dysfunction and myocarditis. There is limited information on late cardiac sequelae in patients who have recovered from acute COVID-19 illness. We aimed to document the presence and quantify the extent of myocardial functional alterations in patients hospitalized 6 months earlier for COVID-19 infection.
Methods and results We conducted a prospective echocardiographic evaluation of 48 patients (mean age 58 ± 13 years, 69% male) hospitalized 6 ± 1 month earlier for a laboratory-confirmed and symptomatic COVID-19. Thirty-two (66.6%) had pre-existing cardiovascular risks factors (systemic hypertension, diabetes, or dyslipidaemia), and three patients (6.2%) had a known prior myocardial infarction. Sixteen patients (33.3%) experienced myocardial injury during the index COVID-19 hospitalization as identified by a rise in cardiac troponin levels. Six months later, 60.4% of patients still reported clinical symptoms including exercise dyspnoea for 56%. Echocardiographic measurements under resting conditions were not different between patients with versus without myocardial injury during the acute COVID-19 phase. In contrast, low-level exercise (25W for 3 min) induced a significant increase in the average E/e' ratio (10.1 ± 4.3 vs. 7.3 ± 11.5, $P = 0.01$) and the systolic pulmonary artery pressure (33.4 ± 7.8 vs. 25.6 ± 5.3 mmHg, $P = 0.02$) in patients with myocardial injury during the acute COVID-19 phase. Sensitivity analyses showed that these alterations of left ventricular diastolic markers were observed regardless of whether of cardiovascular risk factors or established cardiac diseases indicating SARS-CoV-2 infection as a primary cause.
Conclusions Six months after the acute COVID-19 phase, significant cardiac diastolic abnormalities are observed in patients who experienced myocardial injury but not in patients without cardiac involvement.

Keywords Diastolic function; COVID-19; Myocarditis; Echocardiography; Heart failure

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Introduction

Myocardial injury has been reported in patients hospitalized with COVID-19 and is particularly marked in critically ill patients.[1–3] The proportion of myocardial injury varies from 5% to 68% with a recent meta-analysis reporting a prevalence of 20%.[4] Different cardiac abnormalities ranging from infra-clinic elevations of myocardial necrosis biomarkers to acute cardiac dysfunction and myocarditis have been linked to COVID-19 infections.[1,5] In-hospital trans-thoracic cardiac echography (TTE) imaging during the acute phase of COVID-19 revealed regional wall motion abnormalities, systolic left or right ventricle dysfunction, diastolic dysfunction, and pericardial effusion.[1] We note that an earlier study from 2003 examining SARS-CoV-1 showed the development of subclinical diastolic abnormalities 30 days following the infection.[6] These observations raise concerns for potential cardiac sequalae following COVID-19 infection. We therefore performed a prospective echocardiographic imaging follow-up of patients 6 months after hospitalization

for COVID-19 infection in order to document the presence and quantify the extent of myocardial functional alterations. We report here the results of the prespecified cardiac evaluation ancillary study from the COVID-19 effects on arterial stiffness and vascular aging (CARTESIAN, NCT04558450) study.

Methods

The study was conducted in adult patients who were hospitalized in a tertiary hospital (Hôpital Européen Georges Pompidou, APHP, Paris, France) for a COVID-19 infection and discharged alive 6 ± 1 month earlier. Inclusion criteria were a laboratory-confirmed COVID-19 with a SARS-Cov-2 positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) result, requiring a hospital stay (>48 h) for a symptomatic COVID-19 pneumonia requiring or not oxygen therapy. Pneumonia was confirmed from (i) a peripheral oxygen saturation level (SpO2) ≤ 94%, as measured by a pulse oximeter device and/or (ii) an abnormal chest computed tomography (CT)-scan with radiological patterns consistent with COVID-19. Patients were further eligible to participate the cardiac evaluation study if there was ≥1 measurement of cardiac troponin I during the index hospitalization. Exclusion criteria were pregnancy and inability to give their consent or participation to an interventional study. Participation to the cardiac evaluation study was proposed to eligible patients who were seen in the hospital for a 6 month follow-up clinical visit. The study was approved by the ethics committee (CPP: 3835-RM), complies with the Declaration of Helsinki, and all patients gave written informed consent to participate (CARTESIAN, NCT04558450).

Data collection

Demographic, clinical presentation, and co-morbidity data during the index COVID-19 hospitalization were extracted from the electronic medical records collected in a standardized data collection form in the Clinical Data Warehouse (CDW) of our hospital. The dedicated medical records were stored on an i2b2 platform in a CDW together with all other hospital health records. Myocardial injury was defined as an increase of serum high-sensitivity cardiac troponin I above 19.8 μg/L (defined as the upper reference limit in our laboratory) during the hospital stay.

Clinical data and residual symptoms 6 months after the index COVID-19 hospitalization were collected. Functional capacity was quantified using the New York Heart Association scale.

Echocardiographic examination

Rest and low-level exercise transthoracic echocardiography examinations were performed for all patients on a Vivid S70 model (General Electric Healthcare) 6 ± 1 month after the index COVID-19 hospitalization and according to guidelines.[7,8] All acquisitions were performed blinded for the presence or absence of myocardial injury during the acute COVID-19 phase. Echocardiographic data included left ventricular (LV) ejection fraction (LVEF by simpson biplane), LV volumes, LV mass, regional or global wall motion abnormalities; markers of the LV diastolic function according to the parameters described in the international recommendations[7] (mitral inflow with E/A ratio, tissue Doppler with lateral e', septal e', mean E/e'); left and right atrium volumes and surfaces; markers of right ventricle (RV) function (TAPSE, S' wave, visual analysis, systolic pulmonary artery pressure (PAPs) estimated from the tricuspid regurgitation (TR) peak velocity) was also evaluated according international recommendations. Additional parameters of interest were the presence of valvular and pericardial abnormalities.

After collecting data at rest, patients were placed on the supine position in order to perform a low-level exercise (workload of 25 W for 3 min, 60 r.p.m.) on a specific medical ergometer for exercise echocardiography (Schiller, Baar, CH), as previously reported.[9] Imaging acquisition was performed immediately after the peak exercise and included the mitral inflow, tissue Doppler, and TR peak velocities.

All measurements were made over three cardiac cycles and the average was used for statistical analysis. Left ventricular mass, LV end systolic and end diastolic volume, and LA volume were adjusted on body surface area. All measures were independently reviewed by two cardiologists (A. F. and V. T.).

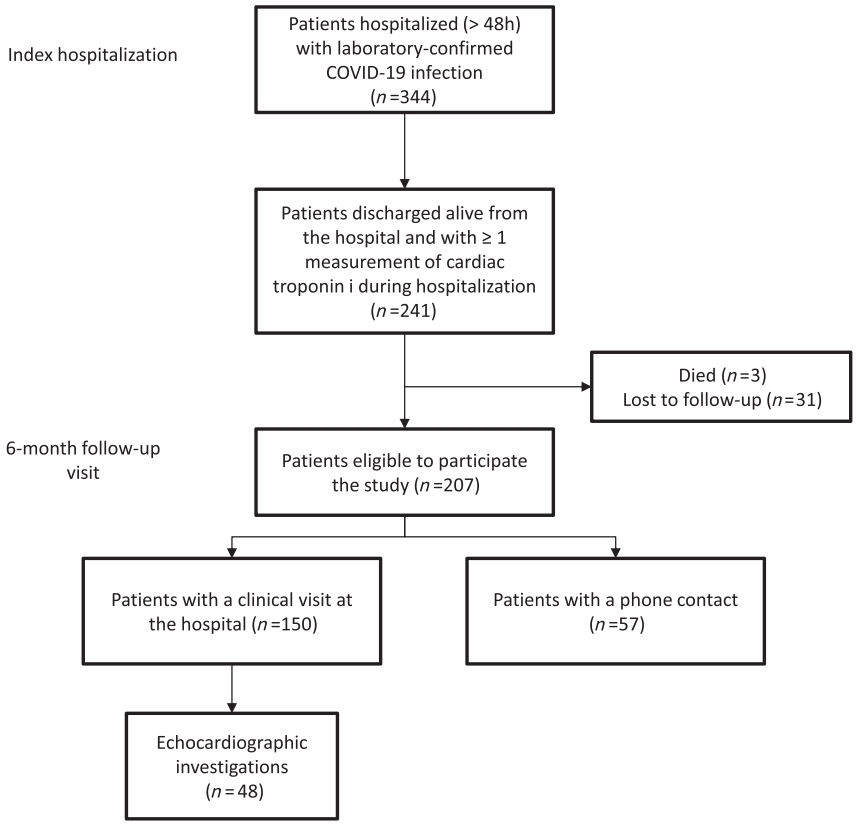
Statistics

Patients were categorized according to the presence or absence of myocardial injury during the COVID-19 index hospitalization. Statistics were performed using NCSS 2012 software (G Hintze, Kaysville, UT, USA). Continuous variables are reported as means (SDs) or medians (interquartile ranges [IQR]), when appropriate. Discrete variables are described as counts and percentages. Groups were compared by Wilcoxon rank test for continuous variables and Fisher's exact test or χ^2 for discrete variables as appropriate. For all analyses, *P* values <0.05 were considered significant.

Results

Forty-eight (48) consecutive patients were included in our study from 22 September to 17 November 2020 (*Figure 1*).

Figure 1 Flowchart of the study.



All patients were previously hospitalized in Hôpital Européen Georges Pompidou (Paris, France) for a symptomatic COVID-19 infection from 15 March 2020 to 15 April 2020 of which 27% of them were admitted to intensive care unit (ICU). The patients group consisted of 69% men (33/48) with a mean (±SD) age of 58 ± 13 years old and with pre-existing cardiovascular risks factors (arterial hypertension, diabetes, or dyslipidaemia) for 32/48 (67%). Three patients (6%) had a known prior myocardial infarction, and 16 (33%) had no past medical history of cardiovascular risk factors or cardiac disorders prior to COVID-19 infection. Patients' characteristics of the 48 participants are shown in *Table 1* and were not significantly different from the other patients seen for the 6 month clinical follow-up visit (Supporting Information, *Table S1*).

During the acute phase of COVID-19 infection, 33% of the patients experienced a myocardial injury as defined by elevation of cardiac troponin I levels. These patients did not differ from troponin-negative patients as to cardiovascular risk factors and cardiac disorders prior to COVID-19. The troponin-positive patients were more often managed in the ICU and showed a higher rate of cardiovascular outcomes during their hospital stay (*Table 1*) with four patients (25%) presenting paroxysmal atrial fibrillation, two patients (12%) with acute heart failure requiring intravenous diuretics, and two patients (12%) presented an identified pulmonary thromboembolic event (*Table 1*). All but one cardiovascular complication occurred in troponin-positive patients.

Six months after the index COVID-19 hospitalization, 60% of the patients continued to experience clinical symptoms, and 56% of them reported exercise dyspnoea (classified in grade II according the New York Heart Association classification), however with no difference between troponin-positive and troponin-negative patients.

Echocardiographic measures

At 6 month investigations, all patients were in sinus rhythm during the echocardiographic evaluation (*Table 2*). Overall, the echocardiographic parameters measured in resting conditions were within the normal ranges. Systolic function was normal except for two patients who had LV wall motion abnormalities and LVEF $<$50% that was due to a prior myocardial infarction known before COVID-19. We did not observe any valvular disease, pericardial effusion or right ventricle dysfunction. We also did not find any significant difference on parameters recorded at rest according to the occurrence

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Table 1 Demographic, risk factors, and clinical presentation during the acute phase, and clinical symptoms 6 months later in patients with versus without cardiac injury and COVID-19

	Overall (n = 48)	Myocardial injury (n = 16)	No myocardial injury (n = 32)	P value
Age, mean (SD), years	58 (13)	61 (11)	57 (14)	0.24
Male, n (%)	33 (69)	13 (81)	20 (62)	0.32
BMI, mean (SD) kg/m^2	26 (4)	25 (4)	27 (4)	0.21
BMI > 30 kg/m^2, n (%)	8 (17)	2 (12)	6 (19)	0.70
Admitted in ICU, n (%)	13 (27)	10 (62)	3 (9)	**<0.001**
Past medical history				
Hypertension, n (%)	17 (35)	5 (31)	12 (37)	0.76
Diabetes, n (%)	10 (21)	4 (25)	6 (19)	0.71
Hypercholesterolemia, n (%)	14 (29)	5 (31)	9 (28)	0.83
Prior myocardial infarction, n (%)	3 (6)	1 (6)	2 (6)	0.99
Prior valvular disease, n (%)	1 (2)	0 (0)	1 (3)	0.99
Prior atrial fibrillation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Without known cardiovascular risk factors or previous disease, n (%)	16 (33)	6 (37)	10 (31)	0.66
Cardiovascular manifestations during index COVID-19 hospitalization				
Total, n (%)	7 (15)	6 (37)	1 (3)	**0.004**
Heart failure, n (%)	2 (4)	2 (12)	0 (0)	0.11
Atrial fibrillation, n (%)	4 (8)	4 (25)	0 (0)	**0.009**
VTE disease, n (%)	3 (6)	2 (12)	1 (3)	0.25
High-sensitivity troponin I at admission, median (IQR), μg/L	7.6 (4.7–12.1)	13.5 (6.8–32.7)	6.9 (3.8–8.7)	**0.001**
Troponin I peak, median (IQR), μg/L	13.1 (5.9–27.5)	34.6 (26.8–57.5)	7.8 (4.4–13.1)	**<0.001**
Symptoms at 6 months				
Asymptomatic, n (%)	19 (40)	5 (31)	14 (44)	0.40
Chest pain, n (%)	3 (6)	0 (0)	3 (9)	0.54
Dyspnoea, n (%)	27 (56)	10 (62)	17 (53)	0.54
Asthenia, n (%)	10 (21)	4 (25)	6 (19)	0.72
Cough, n (%)	3 (6)	0 (0)	3 (9)	0.54

VTE, venous thrombo-embolic disease.

of a myocardial injury during the acute COVID-19 hospitalization (*Table 2*) or between patients hospitalized in Intensive Care Unit vs. non-ICU (data not shown).

At rest, markers of diastolic function on mitral inflow and tissue Doppler as well as pulmonary artery systolic pressure were within the normal range and were comparable between patients with or without myocardial injury during the COVID-19 acute phase. However, low-level exercise (feasible in 43 patients out of 48) revealed significant alterations of left ventricular diastolic markers in patients who previously presented a myocardial injury. The average E/e' ratio was significantly higher in those patients and we also observed a significant increase in PAPs with significant pulmonary hypertension in four (27%) patients, while none of these patients reported clinical symptoms during the exam (*Table 2*). In a sensitivity analysis excluding the three patients with a previous myocardial infarction, we similarly found a significant increase of the average E/e' ratio and the PAPs in patients with myocardial injury (average E/e' ratio 9.3 ± 3.2 vs. 7.2 ± 1.5, P-value = 0.02; PAPs: 33.4 ± 7.8 vs. 25.5 ± 5.4 mmHg, P-value = 0.01). Last, we performed another subanalysis in patients without any cardiovascular risk factors or cardiac disease prior to COVID-19 (n = 16). Among these 16 patients, six experienced myocardial injury during the COVID-19 acute phase. We found a non-significant increase of the average E/e' ratio but a significant increase of the PAPs in the six patients with myocardial injury compared to the 10 patients without myocardial injury (average E/e' ratio: 7.3 ± 0.6 vs. 6.6 ± 1.5, P-value = 0.34; PAPs: 37.0 ± 8.7 vs. 24.6 ± 5.1 mmHg, P-value = 0.04). In this subgroup of patients without cardiovascular conditions before COVID-19, one 45-year-old patient presented with a grade II diastolic dysfunction 6 months after the acute phase.

Discussion

Our findings reveal a significant cardiac diastolic impairment without systolic involvement in patients 6 months after being hospitalized for COVID-19 and who had experienced myocardial injury (as identified by a significant elevation in cardiac troponin) during the acute phase of COVID-19 infection. These abnormalities were detected after low-level exercise and included a significant alteration in tissue Doppler markers of left ventricular diastolic function as well as a significant rise of systolic pulmonary arterial pressure. In contrast, the echocardiographic measures at rest or after low-level exercise were normal in the other patients corresponding to those who did not display elevated levels of troponin during the acute phase of COVID-19 infection.

Table 2 Echocardiographic characteristics at 6 months post-COVID-19 in patients with versus without cardiac injury during the acute phase

Echo parameters	Overall population (n = 48)	Myocardial injury (n = 16)	No myocardial injury (n = 32)	P value
LVEF (%), mean (SD)	61 (7)	59 (9)	62 (6)	0.26
LVEF <50%, *n* (%)	2 (4)	1 (6)	1 (3)	1.0
LV end-diastolic volume, mean (SD), mL	66 (18)	67 (19)	65 (17)	0.54
LVEDV/BSA, mean (SD), mL/m^2	34 (8)	35 (8)	34 (8)	0.60
LV end-systolic volume, mean (SD), mL	25 (10)	27 (13)	24 (8)	0.70
LVESV/BSA, mean (SD), mL/m^2	13 (5)	14 (7)	12 (3)	0.74
LV wall motion abnormalities, *n* (%)	2 (4)	1 (6)	1 (3)	1.0
LV mass/BSA, mean (SD), g/m^2	81 (20)	84 (28)	80 (14)	0.77
LA volume index, mean (SD), mL/m^2	23 (6)	25 (7)	22 (6)	0.06
LAVI >34 mL/m^2, *n* (%)	3 (6)	2 (12)	1 (3)	0.25
RV function				
RV s' wave, mean (SD)	11.6 (1)	11.7 (1.4)	11.6 (1.5)	0.82
Tricuspid annular plane systolic excursion (TAPSE), mean (SD), mm	24.5 (4.6)	25.0 (5.1)	24.3 (4.4)	0.88
Diastolic parameters at rest				
Peak E-wave, mean (SD), cm/s	69 (18)	74 (20)	66 (16)	0.27
E/A ratio, mean (SD)	0.99 (0.40)	1.00 (0.40)	0.98 (0.40)	0.77
Septal e', mean (SD), cm/s	7.9 (1.8)	7.6 (1.8)	8.1 (1.9)	0.55
Lateral e', mean (SD), cm/s	10.3 (3.3)	9.4 (3.6)	10.8 (3.0)	0.10
Average septal-lateral E/e' ratio, mean (SD)	7.9 (3.1)	9.3 (4.7)	7.3 (1.5)	0.22
Average E/e' >14, *n* (%)	1 (2)	1 (6)	0 (0)	0.33
Tricuspid regurgitation velocity, mean (SD), m/s	2.2 (0.4)	2.2 (0.6)	2.2 (0.2)	0.61
Pulmonary artery systolic pressure, mean (SD), mmHg	23.8 (4.6)	23.9 (7.5)	23.8 (3.6)	0.80
Diastolic parameters after low-level exercise	(n = 43)	(n = 15)	(n = 28)	
Peak E-wave, mean (SD), cm/s	82 (20)	87 (25)	79 (17)	0.42
E/A ratio, mean (SD)	1.01 (0.20)	0.98 (0.20)	1.00 (0.20)	0.45
Septal e', mean (SD), cm/s	8.8 (2.2)	7.9 (1.7)	9.2 (2.3)	0.07
Lateral e', mean (SD), cm/s	11.7 (3.0)	10.6 (2.7)	12.2 (2.9)	0.08
Average septal-lateral E/e' ratio, mean (SD)	8.1 (3.1)	10.1 (4.3)	7.3 (1.5)	**0.01**
Average E/e' >14, *n* (%)	4 (8)	4 (27)	0 (0)	**0.009**
Tricuspid regurgitation velocity, mean (SD), m/s	2.4 (0.3)	2.7 (0.3)	2.3 (0.3)	**0.02**
Pulmonary artery systolic pressure, mean (SD), mmHg	27.5 (6.8)	33.4 (7.8)	25.6 (5.3)	**0.02**

BSA, body surface area; LA, left atria; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume.

To our knowledge, this study is the first prospective follow-up of a patient cohort with previous hospitalization for COVID-19 infection which were identified from a single tertiary reference hospital and underwent voluntarily a complete evaluation of cardiac structure and function by echocardiography. Our results reveal a residual cardiac damage following COVID-19 infection that typically involves left ventricular diastolic impairment. An increase in the mitral E/e' ratio (notably when >14) has been reported previously as a good predictor of elevated left ventricular diastolic pressure[7,10] that can induce a significant rise in the mean capillary pressure and systolic pulmonary artery pressure, as observed in our patients. Different guidelines recommend to acquire echocardiographic data during mild exercise in order to unmask LV diastolic dysfunction, as performed and evidenced in our study.[11] Because of the SARS-CoV-2 tropism for the pulmonary capillaries, an additional contribution of a pulmonary origin cannot be ruled out.

Myocardial inflammation was reported in 60% of patients with a recent (<3 months) COVID-19 infection, independent of pre-existing conditions.[5] Myocardial inflammation triggers a progressive fibrotic remodelling of the heart which will lead to cardiac tissue stiffening and alteration of cardiac relaxation.[12] Under this scenario, left ventricular compliance will be progressively altered which will be captured by abnormal markers (i.e., mitral E/e' ratio) in response to exercise, as found in our study.[13,14] An average E/e' ratio >14 is considered abnormal and was observed in an unexpectedly high proportion of patients (27%) with respect to their age, gender and their pre-existing cardiac conditions.[15] In line with previous reports, the patients investigated in this study were mostly 60 years old men and 67% had cardiovascular risk factors (mainly hypertension) whereas only three patients (6%) had a known prior myocardial infarction. Hypertension is known to alter cardiac diastolic function progressively in the context of a cardiac hypertrophic remodelling but this pattern was not observed in our patients who displayed a normal LV mass. The sub-analyses performed further showed that alterations of left ventricular diastolic markers were observed independently of the presence of cardiovascular risk factors or of previous cardiac diseases, thus suggesting that the observed diastolic abnormalities are a consequence of COVID-19 infection.

Our results provide important insights into the post-COVID-19 cardiovascular consequences. Different studies have reported myocardial injury during the acute COVID-19

phase[1,2,5] and our data shown here reveals that patients are likely to display left ventricular diastolic dysfunction 6 months later. Follow-up studies will be needed to understand if this pattern of cardiac diastolic dysfunction reflects a chronic pathological remodelling which ultimately leads to heart failure, or if whether a progressive recovery after the initial damage to the heart likely occurs. We note that recent studies suggest a direct cardiomyocyte tropism for SARS-CoV-2[16] with consequent myocarditis and the development of myocardial fibrosis.[5] SARS-CoV-2 can also infect endothelial cell and induce endothelial dysfunction.[17,18] Both mechanisms are compatible with the progressive development of left ventricular diastolic dysfunction as observed in our study. Concordantly, a study reported the development of subclinical diastolic abnormalities after MERS (SARS-CoV-1) infection, however with a shorter follow-up (30 days).[6]

Our study has limitations. As a pilot study, the sample size is limited and cannot recapitulate the whole spectrum of post-COVID-19 cardiovascular complications. We notably only investigated patients with symptomatic COVID-19 who required hospitalization. The patients' characteristics as well as the rate of myocardial injury are however coherent with previous reports in larger cohorts of patients hospitalized with COVID-19.[3] Patients with milder forms of the disease, or asymptomatic with COVID-19, were not explored in our study. In addition, we detected significant abnormalities in echocardiographic markers of LV diastolic function but this remains subclinical and we cannot provide evidence of a causal relationship with the persistent dyspnoea in 56% of our patients. A longer follow-up and repetitive cardio-pulmonary evaluations will thus be required.

Conclusions

Six months after the acute COVID-19 phase, significant cardiac diastolic impairment without systolic involvement is observed in patients who experienced myocardial injury but not in patients without cardiac involvement. These data argue for a systematic cardiac evaluation of post-COVID-19 patients, especially in those patients who experienced cardiac troponin elevation during the acute phase.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Main characteristics of the overall eligible patients and the participants to the echocardiographic follow-up study.

Appendix

Laurent Abel (Inserm UMR 1163, Paris, France), Claire Andrejak (CHU Amiens, France), François Angoulvant (Hôpital Necker, Paris, France), Delphine Bachelet, Krishna Bhavsar, Lila Bouadma, Anissa Chair, Camille Couffignal, Charlene da Silveira, Marie-Pierre Debray, Diane Descamps, Xavier Duval, Philippine Eloy, Marina Esposito-Farese, Nadia Ettalhaoui, Nathalie Gault, Jade Ghosn, Isabelle Gorenne, Isabelle Hoffmann, Ouifiya Kafif, Sabrina Kali, Antoine Khalil, Cédric Laouénan, Samira Laribi, Minh Le, Quentin Le Hingrat, François-Xavier Lescure, Jean Christophe Lucet, France Mentré, Jimmy Mullaert, Nathan Peiffer-Smadja, Gilles Peytavin, Carine Roy, Marion Schneider, Nassima Si Mohammed, Lysa Tagherset, Coralie Tardivon, Marie-Capucine Tellier, Jean-François Timsit, Théo Trioux, Sarah Tubiana, Benoit Visseaux, Yazdan Yazdanpanah (Hôpital Bichat, Paris, France), Romain Basmaci, Olivier Picone (Hô0pital Louis Mourier, Colombes, France), Sylvie Behilill, Sylvie van der Werf, Vincent Enouf, Hugo Mouquet (Pasteur Institute, Paris, France), Marine Beluze (F-CRIN Partners Platform, Paris, France), Dehbia Benkerrou, Céline Dorival, François Téoulé, Amina Meziane (Inserm UMR 1136, Paris, France), François Bompart (Drugs for Neglected Diseases Initiative, Geneva, Switzerland), Maude Bouscambert (Inserm UMR 1111, Lyon, France), Minerva Cervantes-Gonzalez, Eric D'Ortenzio, Oriane Puéchal, Caroline Semaille (REACTing, Paris, France), Catherine Chirouze (CHRU Jean Minjoz, Besançon, France), Alexandra Coelho (Inserm UMR 1018, Paris, France), Sandrine Couffin-

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