

Cardiac MRI of Children with Multisystem Inflammatory Syndrome (MIS-C) Associated with COVID-19: Case Series

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Abstract

This case series examines cardiac MRI findings in four children and adolescents admitted to intensive care in April 2020 for multisystem inflammatory syndrome and Kawasaki disease-like features related to COVID-19. Acute myocarditis occurred less than 1 week after onset of fever and gastrointestinal symptoms. Physical examination showed rash and cheilitis/conjunctivitis. All patients recovered after intravenous immunoglobulin therapy. SARS-CoV-2 RT-PCR was negative on nasopharyngeal, stool, and respiratory samples and was positive on serology. Cardiac MRI showed diffuse myocardial edema on T2-STIR sequences and native-T1 mapping, with no evidence of late gadolinium enhancement suggestive of replacement fibrosis or focal necrosis. These findings favor post-infectious myocarditis in children and adolescents with COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to affect fewer children than adults, with less severe presentation, and rapid recovery in most children (1). However, recent publications have reported multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease-like features related to COVID-19 in children (2-4). This case series examines the cardiac MRI findings in four children and adolescents with MIS-C and Kawasaki-disease like features associated with COVID-19 who were referred to our intensive care unit (ICU).

MATERIALS AND METHODS

Study sample and clinical characteristics

This study was approved by our institutional review board (CRM-2005-087) with a waiver of informed consent because of the retrospective nature of the study. In April 2020, we identified 8 children and adolescents with Kawasaki-like disease. Four had myocarditis and were consecutively admitted to our ICU with signs of cardiogenic and/or septic shock syndrome. All four underwent transthoracic echocardiography and cardiac MRI. The clinical course, laboratory data and cardiac imaging findings were retrospectively reviewed. The four patients who were not included in this study were not admitted to our ICU and did not undergo cardiac MRI. They were less than 6 years old and had a favourable outcome: 3 patients (5 months, 6 months and 3 years old) had 4 to 5 major diagnostic criteria for Kawasaki disease, without myocarditis, and one patient (5 years old) had rash and myocarditis and was transferred to another hospital.

COVID-19 assessment and treatment

Pathogen identification involved RT-PCR in nasopharyngeal swabs (technique Seegene® tested once in patients 1 and 2, tested twice in patient 3, technique Anatolia geneworks® in patient 4) and in stool samples (technique Anatolia geneworks® in patients 2 and 3) and serology for SARS-

CoV-2. Serology and PCR studies were performed for Epstein-Barr virus, parvovirus, cytomegalovirus, and influenza virus. Chest CT was performed. Treatments were recorded.

Cardiac MRI

Cardiac MRI was performed with a 1.5-Tesla scanner (Optima MR450w; General Electric, Waukesha, WI). No general anesthesia or sedation was required. Cardiac MRI included cine and T2-short tau inversion recovery (STIR) images (e.g., repetition time [TR] = 1154 ms, echo time [TE] = 102 ms), T2 mapping (e.g., TR= 612 ms, TE = 73 ms), and T1 mapping (e.g., TR= 3.3 ms, TE = 1.4 ms) before administration of contrast agents. Late gadolinium-enhanced (LGE) 2D segmented inversion recovery sequences were acquired at 8 min after intravenous administration of contrast agent (0.1 mmol/kg body weight gadoterate meglumine, Dotarem®, Guerbet, France) in patients 2, 3 and 4. Patient 1 could not initially undergo cardiac MRI, which was performed 14 days after hospital discharge without intravenous administration of contrast agent in accordance with the wishes of the parents.

Image analysis

Image analysis was performed with consensus by 2 radiologists (EB, AR) with 10 and 20 years, respectively, of experience in cardiac MRI. Endocardial and epicardial contours of the left ventricle (LV) and endocardial contour of the right ventricle (RV) were manually traced on end-diastole and end-systole phases by using Medis Suite 3.1.16.2 (Medis Medical Imaging Systems, Leiden, The Netherlands). Native-T1 maps were calculated on basal and mid-LV short-axis slices. Apical slices were not analyzed because of motion artifacts. Regions of interest were drawn on T1 and T2 images on the septal, inferior and lateral walls of the LV. Myocardial hyperemia was defined as T1 relaxation time > 1058 ms according to (5). Myocardial edema was defined as signal intensity ratio of myocardium to skeletal muscle ≥ 2.0 on T2 weighted imaging(6) or T2 relaxation time >50 ms. These thresholds were compatible with the local experience of cardiac MRI in

children on the same magnet with the same pulse sequences.

RESULTS

Patient characteristics

Patient characteristics of the four children and adolescents are in **Table 1**. The mean age was 9 years [SD \pm 3 years, range 6-12 years]; three were girls. Patients had no history of cardiovascular disease. The patients were admitted to the ICU for tachycardia and inflammatory shock syndrome with acute myocarditis. The patients presented < 1 week after symptoms onset. They reported abdominal pain (4 of 4), vomiting (2 of 4), diarrhea (2 of 4), and fever lasting for 2 to 7 days. They did not report cough, dyspnea or chest pain at any time. Physical examination showed cheilitis or conjunctivitis (3 of 4) and rash (4 of 4). All patients had relative lymphopenia and increased levels of brain natriuretic peptide, troponin I, and C-reactive protein. Three patients were presumably infected by relatives, with an unknown time between the last date of possible exposure and onset of Kawasaki-like symptoms. The timeline of illness onset, hospitalization, echocardiography/cardiac MRI, and symptom resolution among the four children is in **Figure 1**.

Echocardiography results

Electrocardiography revealed ST segment depression in patient 2 and decreased T-wave amplitude in inferior leads in patient 3. Initial transthoracic echocardiography showed severely decreased LV ejection fraction (LVEF) in one patient (LVEF < 30%) and low-normal LVEF in three patients (LVEF > 50%), although the four patients had transient systolic dysfunction (**Table E1 Supplemental data**). The initial LVEF was low-normal in patients 2, 3 and 4 due to marked vasoplegia with decreased afterload.

The myocardium appeared echogenic on 2D echocardiography in patient 2 and normal in the other patients. Three patients showed global or septal hypokinesia. Patients 1 and 3 showed functional mitral regurgitation related to LV dilatation. LV diastolic function was not impaired. Three

patients had moderate pericarditis. Coronary artery diameters were normal, without coronary artery dilatation or aneurysm at initial and follow-up echocardiography.

RT-PCR results

The patients tested positive for COVID-19 (IgG 4/4 and IgM 1/4), and all tested negative for SARS-Cov-2 on RT-PCR in nasopharyngeal swabs and respiratory and stool samples. Serology for other viral agents was negative in all patients except patient 2, for whom the blood PCR and serology for Epstein-Barr showed an acquired immunity (viral reactivation).

Chest CT results

Chest CT revealed typical COVID-19 opacities in patient 3 as described in (7): peripheral, posterior, multilobar and bilateral distribution of a combination of ground-glass opacities and consolidations, especially in the lower lobes. Chest CT was normal in the other patients.

Cardiac MRI results

The cardiac MRI findings are in **Table 2**. Three patients (patients 2, 3 and 4) underwent cardiac MRI during the acute phase, whereas in patient 1, cardiac MRI was performed during the recovery phase. In patients 2, 3 and 4, mean global values for T1-mapping were increased >1100 ms. T2-mapping was not contributive in patients 2 and 3 because of motion artifacts. T2-STIR sequences showed diffuse myocardial signal hyperintensity of the LV, suggesting interstitial edema, in patients 2, 3 and 4 (**Figure 2**). This finding was confirmed by signal intensity ratio of myocardium to infrapinnatus muscle ≥ 2.0 in these three patients and by T2 relaxation >50 ms in patient 4. For patient 1, who underwent cardiac MRI at 14 days after hospital discharge, native-T1 values were normal (1050 ms), and T2-STIR sequences did not reveal edema, confirmed by normal T2 mapping values. None of the patients showed late gadolinium enhancement.

Treatment and outcome

On follow-up echocardiography, all patients recovered normal ventricular function and kinetics in 48 hours to 5 days. No pericardial effusion was found (**supplemental data, Table E1**). Therapies included inotropic support (3/4), volume expanders (3/4), mechanical ventilation (1/4), intravenous immunoglobulin (4/4), and steroids (3/4) (**Table 1**). None required extracorporeal membrane oxygenation.

All four patients showed rapidly progressive clinical and hemodynamic improvement and were discharged from the hospital at 13 to 23 days after symptom onset. Patient 3 stayed for 8 days in the pediatric department after the ICU because of pancreatitis presumably related to COVID-19.

DISCUSSION

We report cardiac MRI findings for four children and adolescents admitted to our ICU for MIS-C and Kawasaki disease-like features associated with COVID-19. The children had prolonged fever and cheilitis, cervical lymphadenopathy, rash, pericarditis, myocarditis, elevated C-reactive protein level or mitral regurgitation suggestive of Kawasaki disease. They were negative for SARS-CoV-2 on RT-PCR of nasopharyngeal swabs and stool samples. They all had elevated SARS-CoV-2 antibody levels (IgG without IgM except in patient 4 who had elevated IgG and IgM levels). All children had signs of cardiac involvement without coronary artery abnormalities. Longitudinal findings of transthoracic echocardiography showed transient systolic dysfunction that lasted for 48 hours to 5 days. Cardiac MRI findings revealed elevated T1 mapping values and T2-STIR ratio suggesting myocardial hyperemia and edema without evidence of fibrosis replacement at LGE at the acute disease phase. At admission to our ICU, patients 1, 3 and 4 had signs of cardiovascular collapse or hypotension but responded well to volume expanders and vasoactive agents. None had signs of intravenous immunoglobulin resistance or prolonged myocardial dysfunction.

Current evidence suggests COVID-19 infection in children and adolescents is associated with

toxic shock syndrome and Kawasaki disease-like symptoms together with cardiac inflammation (4, 8). This new entity, called MIS-C for multisystem inflammatory syndrome in children, shares similarities with Kawasaki disease with different clinical signs and outcome. Kawasaki disease is an autoimmune systemic disease characterized by systemic inflammation in all medium-sized arteries during the acute febrile phase (9) that affects predominantly children < 5 years of age. In our series, patients were older, from 8 to 12 years old (9). In Kawasaki disease, a prominent feature is the appearance of coronary artery dilatation or aneurysm(9), which was not evidenced in our series.

In our institution, children with myocarditis admitted to the ICU undergo cardiac MRI as a clinical routine protocol to document the diagnosis and to assess the severity of myocarditis (10). We found MRI signs of diffuse myocardial edema and hyperemia without evidence of focal myocardial necrosis/fibrosis, contrary to recent published data for adults with myocarditis related to COVID-19 (11, 12). Our findings are consistent with histopathological analysis of hearts with Kawasaki disease, which demonstrated little evidence of myocardial cell degeneration or necrosis but mainly cell infiltration of macrophages and neutrophils in myocardial interstitium (13). Our findings might be explained by the difference between viral myocarditis and post-infectious myocarditis related to MIS-C in COVID-19. Viral myocarditis results from injury by virus infiltration and immune response to this injury. As in Kawasaki disease, the MIS-C myocarditis corresponds to an inflammatory infiltration of the interstitial myocardium. A potential mechanism for myocardial manifestations of Kawasaki disease is the occurrence of a cytokine storm syndrome. Rowley et al. suggested that the immunologic cascade of Kawasaki disease is due to infection with an RNA virus that enters through the upper respiratory tract (14). SARS-CoV-2 could be a candidate for such an inflammatory response in MIS-C.

Regarding the outcome, myocarditis resolved rapidly in our series as demonstrated by normal echocardiographic follow-up and cardiac MRI findings in patient 1, as in Kawasaki disease, in which myocardial inflammation peaks 10 days after disease onset and disappears gradually after

20 days (15). We did not find complications such as circulatory failure in the acute phase, development of artery aneurysm as in Kawasaki disease or resistance to intravenous immunoglobulin (16).

Our case series had limitations. First, we did not examine the coronary artery with MR angiography sequences. Instead, we used echocardiography in accordance with international recommendations of evaluation of the coronary artery. In the initial phase of Kawasaki disease, coronary artery abnormalities are usually screened by transthoracic echocardiography (17) with quantitative assessment of luminal dimensions several times during the acute and the recovery phases (9). Second, our patients might not reflect the entire spectrum of patients with myocarditis related to COVID-19 because of referral bias related to ICU admission. Finally, there are known issues with native-T1 such as variation in sequences, different sensitivities to T2 effects, lack of standardization and normal values, and partial dependence on heart rate.

In conclusion, this case series illustrates cardiac MRI findings in children and adolescents admitted to the ICU with myocarditis and MIS-C related to COVID-19. In our series, the most common findings were age > 5 years, increased levels of brain natriuretic peptide and troponin I, echocardiography changes with transient systolic dysfunction associated with cardiac MRI signs of diffuse myocardial edema and hyperemia without evidence of focal myocardial necrosis or replacement fibrosis. All patients recovered rapidly, with no evidence of coronary artery dilatation or aneurysm. The pathophysiology of MIS-C is still unexplained, but our cardiac MRI findings support the hypothesis of an immune response to an antigen rather than a direct complication secondary to SARS-CoV-2 infection.

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Table 1. Clinical and biological findings and treatment of patients with myocarditis related to COVID-19 infection

	Patient 1	Patient 2	Patient 3	Patient 4	
Clinical findings	Age (years)	8	12	11	6
	Body mass index (kg/m ²)	14.5	27.9	22.9	16.5
	Initial symptoms	fever for 4 days, abdominal pain	fever for 5 days, abdominal pain, vomiting and diarrhea	fever for 2 days, vomiting, abdominal pain, fatigue	fever for 7 days, abdominal pain, vomiting, diarrhea
	Physical examination at the ER	conjunctivitis, cheilitis and rash	conjunctivitis and pharyngeal enema, trunk and thighs rash	palm rash	cheilitis, cervical adenopathy, trunk and palm rash
	Body temperature (°C)	40.2	40	40.5	40
	Blood pressure	81/49 (60)	104/53 (68)	103/60 (74)	86/47 (61)
	Heart rate (bpm)	138	132	134	159
	Oxygen saturation % (ambient air)	92	99	91	94
	ECG	normal	ST segment depression	decreased T-wave amplitude	normal
	Biological findings	Troponin I (ng/L)	125	4607	545
BNP (ng/L)		2305	918	3214	3140
CRP (mg/L)		131	340	456	310
Sodium (mmol/L)		128	129	134	130
Potassium (mmol/L)		4.6	3	5.1/3.2	5.7/3
Lymphocytes (/mm ³)		780	510	400	710
Blood cultures		negative	negative	negative	negative
Nasopharyngeal SARS-CoV-2 RT-PCR		negative	negative	negative	negative
Blood SARS-CoV-2 serology		positive (IgG+, IgM-)	positive (IgG+, IgM-)	positive (IgG+, IgM-)	positive (IgG+, IgM+)
Stool SARS-CoV-2 RT-PCR		not performed	negative	negative	negative
Respiratory sample SARS-CoV-2 RT-PCR	not performed	not performed	negative	not performed	
Treatment	Intravenous Ig	yes	yes	yes	yes
	Vaso-active agents	yes	no	yes	yes
	Volume expanders	yes	no	yes	yes
	Prednisolone	yes	yes	no	yes
	Aspirin	yes	yes	no	yes
	High-flow oxygen therapy	yes	no	yes	yes
	Invasive ventilation	no	no	yes	no
	Out-of-hospital treatment	steroid, aspirin	steroid	no	steroid, aspirin

ER: emergency room, ECG: electrocardiography, BNP: brain natriuretic peptide, CRP: C-reactive protein, RT-PCR: reverse transcription polymerase chain reaction, Ig: immunoglobulin

Table 2. Cardiac MRI findings in patients with myocarditis related to COVID-19 infection

	Reference values	Patient 1	Patient 2	Patient 3	Patient 4
LV diameter (mm)		39	53	54	43
LV thickness (mm)		7.5	6.8	8.8	5.0
Dyskinesis/hypokinesis		no	no	no	no
LVEF (%)		68	51	56	52
LVEDV index (ml/m ²)		51	93	74	83
LVESV index (ml/m ²)		16	45	32	40
Mass index (g/m ²)		44	58	54	50
RVEF (%)		63	53	57	55
RVEDV index (ml/m ²)		60	87	70	57
RVESV index (ml/m ²)		22	41	30	26
RatioT2 myocardium/muscle	<2	1.1	2.2	2.4	2.4
Myocardial T2 (ms)	[46-50]	47	NA	NA	62
Myocardial native T1 (ms)	[950-1058]	1050	1112	1124	1169
LGE present		NA	no	no	no
Pericardial effusion		no	yes	yes	yes

LV: left ventricle, RV: right ventricle, EF: ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, LGE: late gadolinium enhancement

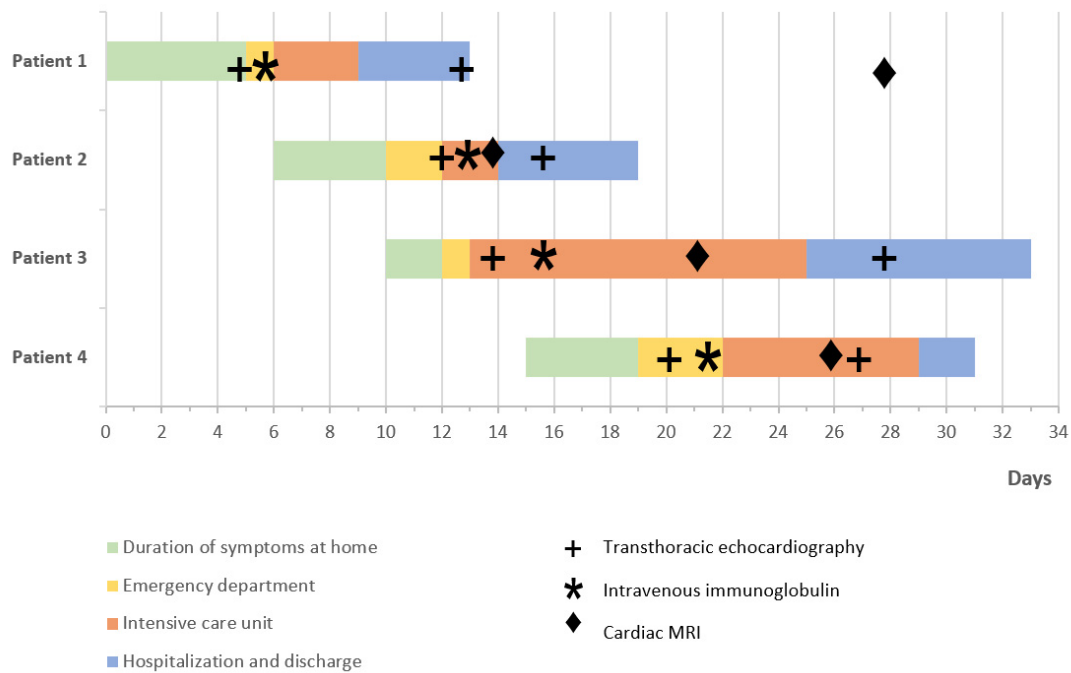


Figure 1. Timeline of illness onset, hospitalization, time of echocardiography and cardiac MRI and symptom resolution for the four children with COVID-19–related Kawasaki-like symptoms.

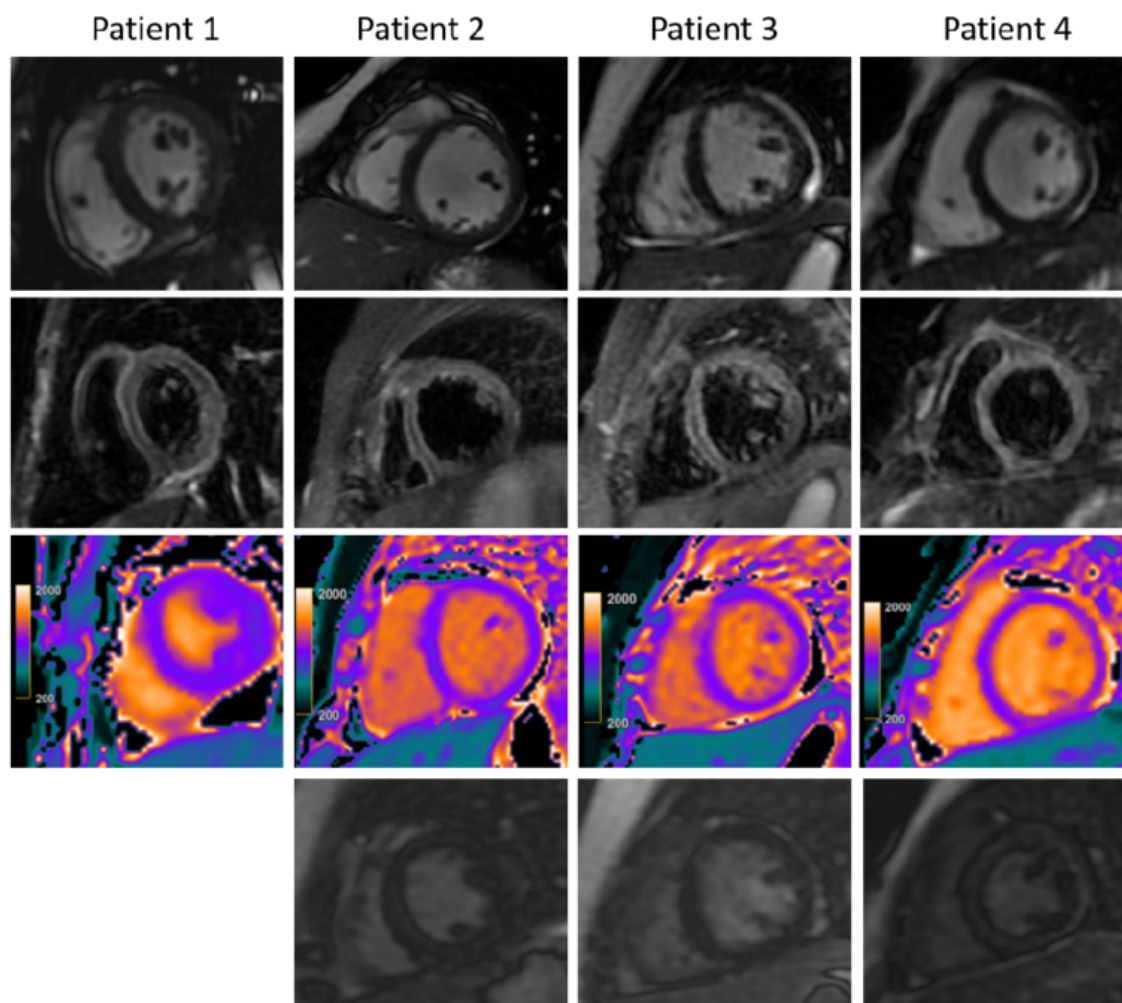


Figure 2. Cardiac MRI for four children with clinical diagnosis of acute myocarditis in the setting of COVID-19–related Kawasaki-like symptoms. The top panel demonstrates minimal pericardial effusion on cine images. The second panel demonstrates increased T2-STIR signal intensity with average ratios between myocardium and muscle > 2 in patient 2 (12-year-old male), patient 3 (11-year-old female) and patient 4 (6-year-old female). The third panel demonstrates abnormal native-T1 mapping, which was > 1100 ms in patients 2, 3 and 4 and normal in patient 1 (8-year-old female). The bottom panel demonstrates absence of late gadolinium enhancement (LGE) in patients 2 and 3. Myocardial null times were recognized as too short in patient 4 but could not be repeated due to lack of further patient cooperation; however review of Look Locker images and additional sequences revealed no LGE.

Supplemental data

Table E1. Transthoracic echocardiography findings at admission and at clinical follow-up in patients with myocarditis related to COVID-19 infection

	Patient 1	Patient 2	Patient 3	Patient 4
Transthoracic echocardiography at admission				
Appearance of myocardium	normal	diffuse echo-bright appearance	normal	normal
Dyskinesis/hypokinesis	hypokinesis	septal dyskinesis	hypokinesis	no
LVEF (%)	24	61	54	59
FS (%)	10	33	30	31
VTI (cm)	10.9	/	15	16.5
HR (bpm)	147	/	162	124
Valvular disease	mitral regurgitation	no	mitral regurgitation	no
Pericardial effusion	no	no	yes	yes
Coronary artery dilatation/aneurysm	no	no	no	no
Transthoracic echocardiography follow-up				
Appearance of myocardium	normal	normal	normal	normal
Dyskinesis/hypokinesis	no	no	no	no
LVEF (%)	70	74	68	67
FS (%)	39	43	37	36
VTI (cm)	/	29.8	25	23.1
HR (bpm)	/	51	75	98
Valvular disease	no	no	no	no
Pericardial effusion	no	yes	no	no
Coronary artery dilatation/aneurysm	no	no	no	no

LVEF: left ventricular ejection fraction, FS: fractional shortening, VTI: velocity time integral, HR: heart rate