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Original Paper

MULTISYSTEM INFLAMMATORY SYNDROME IMPACT ON THE CARDIOVASCULAR SYSTEM: SINGLE-CENTRE STUDY OF LATVIA

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MIS-C (Multisystem inflammatory syndrome in children) is a hyperinflammatory syndrome caused by the Sars-CoV-2 virus, still an ongoing issue worldwide. MIS-C is associated with an impairment of various organ systems, including the cardiovascular system, and up to 100% of all MIS-C patients have a broad spectrum and severity of symptoms. Identifying MIS-C early and starting therapy is crucial to minimise possible complications and clinical worsening. A prospective cohort study in a single centre was conducted at the Children's Clinical University Hospital in Latvia from January to December 2021. Patients between the ages of one and seventeen years who met the MIS-C criteria were included in the study. We evaluated the patient's demographic data, blood pressure, echocardiographic data, ESG data, and cardiac biomarkers such as proBNP and troponin I. Thirty-one patients were included who met the MIS-C criteria. The median age was 8.0 years, and 52% were boys. Of all patients, 77% initially presented with hypotension, and 42% required inotropic support. Treatment in the paediatric intensive care unit (PICU) was required in 58% of patients. Reduced left ventricular ejection fraction was observed in 35% of patients. Mildly decreased ventricular ejection fraction (< 55%) was observed in 19% of cases, and moderate dysfunction (ejection fraction < 45%) in 16% of patients. Twelve per cent of patients received milrinone to improve left heart function. Left heart function significantly improved in all patients during the hospitalisation. In 6% of all patients, coronary artery dilations were observed. All patients had dilation resolution at the time of discharge. The median length of hospitalisation was twelve days, and the median length of PICU stay was three days. Multisystem inflammatory syndrome in children is a significant and potentially life-threatening illness with cardiovascular involvement in 100% of cases. Patients who present primarily with higher ProBNP levels are more likely to have decreased left ventricle ejection fraction, which should be kept in mind when evaluating patients with MIS-C. Overall, patients with MIS-C have a good prognosis, and most cardiovascular changes have been resolved by discharge, but further follow-up and studies are needed to judge the long-term outcome.

Keywords: *MIS-C, hypotension, reduced left-sided ejection fraction, coronary artery dilation.*

INTRODUCTION

Initially, SARS-CoV-2 infection was considered a severe respiratory disease, mainly in older adults and people with co-morbidities. However, soon after the start of the pandemic, hyperinflammatory shock in children after COVID-19 infection was described in the United Kingdom. Soon, new reports of similar observations appeared worldwide (Riphagen *et al*., 2020).

In May 2020, the World Health Organization and the United States Centre for Disease Control and Prevention

named this new paediatric illness Multisystem Inflammatory Syndrome in Children (MIS-C) and developed specific diagnostic criteria. According to US data, MIS-C incidence is estimated to be about 4 per 10,000 children infected with SARS-CoV-2. In contrast, after the first wave of COVID-19 in the UK, the incidence of MIS-C was estimated to be 4.5 per 10,000 children infected with SARS-CoV-2 (Dionne *et al*., 2022). Until January 2022, 6431 cases of MIS-C have been reported in the United States, as well as 55 related deaths (CDC, 2020). The incidence of MIS-C remains unclear. US research data shows the incidence is about 2 per 100,000 children under 21 (Payne *et al*., 2021).

MIS-C is a late immune response to SARS-CoV-2 infection, most often observed in children 4–6 weeks after acute SARS-CoV-2 infection, resulting in damage of various organ systems, including the heart, lungs, brain, kidneys, gastrointestinal tract, skin, and eyes (Gottlieb *et al*., 2021). Cardiovascular involvement is described in 80–100% of MIS-C patients (Sperotto *et al*., 2020; Malviya and Mishra, 2021). Cardiovascular damage can have various causes, such as direct virus-induced cardiomyocyte damage, immune cell dysregulation resulting in cardiomyocyte damage, endothelial damage, or microvascular and ischemic damage (Alsaied *et al*., 2021). Cardiovascular changes in MIS-C in different studies are summarised in Table 1.

In direct cardiomyocyte damage, the Sars-CoV-2 S receptor binds to the ACI2 protein, enters the cell, and causes cardiomyocyte dysregulation, leading to apoptosis (Yang *et al*., 2020; Abdi *et al*., 2022). SARS-CoV-2-infected cells promote the dysregulation of T helpers by stimulating the release of cytokines such as Il-1, Il-4, Il-6, Il-12, Il-24, TNF, IFN-γ, TNFα, which promotes increased inflammatory response (Amirfakhryan and Safari, 2020). In the case of MIS-C, hypoxemia is often observed, which significantly reduces energy production and metabolism in cells, increasing anaerobic fermentation and causing intracellular acidosis. As a result of this chain, oxygen free radicals are produced, leading to damage to the phospholipid layer of the cell membrane. Similarly, a hypoxia-induced increase in calcium promotes myocyte apoptosis (Amirfakhryan and Safari, 2020; Liu *et al*., 2022; Son and Friedman, 2023).

In the case of MIS-C, there can be different causes for shock. In the case of MIS-C, the shock has a similar mechanism as in toxic shock. SARS-COV-2 complexes act as a superantigen, resulting in the stimulation of T helpers, which secrete vasoactive cytokines such as IL-2, TNF alpha, and INF gamma, which in large quantities act as vasodilators (Vasconcelos *et al*., 2010). Hypotension and shock can be caused by significantly reduced cardiac function, which is often observed in patients with MIS-C, as well as hypovolemia due to vomiting, diarrhea, inability to take in fluids, and fluid sequestration of the third space (Buerke *et al*., 2011; Patel *et al*., 2021; Taghavi *et al*., 2022).

According to the literature, ECG changes in patients with MIS-C are observed in up to 60% of cases (Sperotto *et al*., 2020). The most frequent changes are changes in the ST segment, prolongation of the QTc interval, atrial tachyarrhythmias, and less often observed ventricular arrhythmias (Minocha *et al*., 2020; Regan *et al*., 2021). Likewise, patients with MIS-C often have AV conduction disorders such as first-degree AV blocks and second- and third-degree AV blocks less often. In most patients, ECG changes are transient and resolvable until hospital discharge (Regan *et al*., 2021; Valverde *et al*., 2021).

In previous studies by echocardiography, a decrease in left-sided ejection fraction (LVEF) has been observed in up to 75% of cases (Sperotto *et al*., 2020). A mild decrease in LVEF (up to 41%) is mainly observed, rarely moderately or significantly decreased LVEF, which usually correlates with the severity of the patient contrition, i.e. shock and the need for inotropic medication support (Mannarino *et al*., 2022). In MIS-C patients, mitral regurgitation is observed in various degrees — in up to 43% of cases, tricuspid regurgitation in up to 6% of cases, and aortic regurgitation have also been described, although there are no data on its frequency (Valverde *et al*., 2021). According to literature data, the frequency of coronary artery changes is highly variable. Coronary artery dilation can be observed in up to 48% of MIS-C patients (Alsaied *et al*., 2021; Gottlieb *et al*., 2021). Mainly, coronary artery dilation has been mild. According to current data, in all patients who had coronary artery dilation, the changes resolved until discharge (Davies *et al*., 2021; Feldstein *et al*., 2021).

Table 1. Cardiovascular changes of MIS-C patents in different publications

Findings	Impact	Frequency
Symptoms	Shock/ Hypotension (cardiogenic or vasodilatation)	50–80% (Alsaied *et al*., 2021)
Analysis	Elevated Troponin I	50–93% (Alsaied *et al*., 2021)
	Elevated NT-proBNP	78–100% (Alsaied *et al*., 2021)
	Elevated D-Dimers	67–100% (Alsaied *et al*., 2021)
ECG	Atrial or ventricular extrasystoles	21% (Regan *et al*., 2021)
	ST-T segment changes	24% (Minocha *et al*., 2020)
	Prolongated QTc interval	9–22% (Minocha *et al*., 2020; Regan *et al*., 2021)
	AV block	3–6% (Minocha *et al*., 2020; Valverde *et al*., 2021)
EHOKG	Reduced LVEF	51–75% (Alsaied *et al*., 2021; Mannarino *et al*., 2022; Sperotto *et al*., 2020)
	Coronary artery dilation	14–50% (Alsaied *et al*., 2021; Gottlieb *et al*., 2021)
	Tricuspid valve insufficiency	6% (Valverde *et al*., 2021)
	Mitral valve insufficiency	42–43% (Mannarino *et al*., 2022; Gottlieb *et al*., 2021)
X-RAY/ US	Pericardial effusion	32% (Matsubara *et al*., 2020)
	Pleural effusion	39–82% (Matsubara *et al*., 2020; Gottlieb *et al*., 2021)

MATERIALS AND METHODS

We performed a retrospective study at Children's Clinical University Hospital, Rīga, Latvia, from 1 January 2021 to 31 December 2021. We included all children and adolescents who met the MIS-C diagnostic criteria developed by the Centers for Disease Control and Prevention (CDC) and the World Health Organisation (WHO).

For patients who met the MIS-C criteria demographic data, we collected data such as clinical parameters (weight, height, body mass index), vital signs, clinical manifestations, information on the clinical course (length of hospital stay, necessity for treatment in the intensive care unit, medications received, outcome) and laboratory data (troponin I, NT proBNP, D-dimers).

All patients with MIS-C underwent echocardiographic and electrocardiographic examination. The left ventricular ejection fraction (LVEF) was qualitatively and quantitatively evaluated with an echocardiograph (Philips EPIQ CVx) and calculated according to Simpson's two-dimensional method. LVEF was classified as usual (LVEF 55%), mildly reduced (LVEF > 45–54%), moderately reduced (LVEF 35–44%), or severely reduced (LVEF < 35%).

Statistical data analysis was performed using IBM SPSS v.26.0. Statistical significance was assessed at $p < 0.05$. Differences in clinical and diagnostic findings between the study groups were analysed using Chi-Square or Fisher's test in the case of categorical variables, and T-test, ANOVA or Mann–Whitney U test, Kruskal–Wallis test in case of continuous variables, if they corresponded to normal distribution. The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test.

RESULTS

In our study, we included 31 patients, of whom 16 were boys (52%) and 15 were girls (48%). All patients were Caucasian. The mean age of the patients was 9 years (med. 8 years). The average duration of hospitalisation is 14 days (med. 8). Of 31 patients, 18 (58%) required treatment in the intensive care unit (ICU), with an average duration of treatment in the ICU of three days. Of all patients with MIS-C, 24 (77%) had hypotension at admission, and 10 (32%) required inotropic drug support for blood pressure correction.

ECG changes were observed in 28 (90%) patients. In twelve (39%) patients, ST elevation was registered, in 13 (42%) non-specific ST-T changes, three (10%) patients had AV dissociation, and one case (3%) was registered as clustered supraventricular extrasystoles. Three (10%) patients had first-degree AV block, and 5 (16%) patients had right bundle branch block. All patients with ST-segment elevations and first-degree AV block had resolved cardiogram changes by the time they were discharged. A prolonged QTc interval was observed in nine (29%) patients, normalised at hospital discharge.

Eleven (34%) patients had visualised reduced LVEF. Six (19%) patients had mildly reduced LVEF, and 5 (16%) had moderately reduced LVEF. Four (13%) patients received milrinone to improve cardiac function. All patients had a significant improvement in LVEF, and at the time of discharge, it had normalised in all patients with previously reduced LVEF (Fig. 1).

Mitral valve insufficiency was observed in 22 (71%) patients, moderate mitral valve insufficiency in 3 (10%) patients, and mild mitral valve insufficiency was observed in 19 (61%) patients. Tricuspid valve insufficiency was observed in 23 (74%) patients, 11 (35%) patients had moderate tricuspid valve insufficiency, and 12 (39) had mild tricuspid valve insufficiency. Mild aortic valve insufficiency was observed in one (3%) patient, which had resolved at discharge.

Among 31 patients with MIS-C, we observed coronary artery dilatation in two (6%) patients. Grade I dilatation of the right coronary artery (+3.2 z-values) and grade I dilatation of the left anterior descending artery (+2.7 z-values) in one case, and the other patient had grade I dilatation of the left anterior descending artery (+2.1 z-values). Both patient's coronary artery dilatation resolved at discharge (Fig. 2).

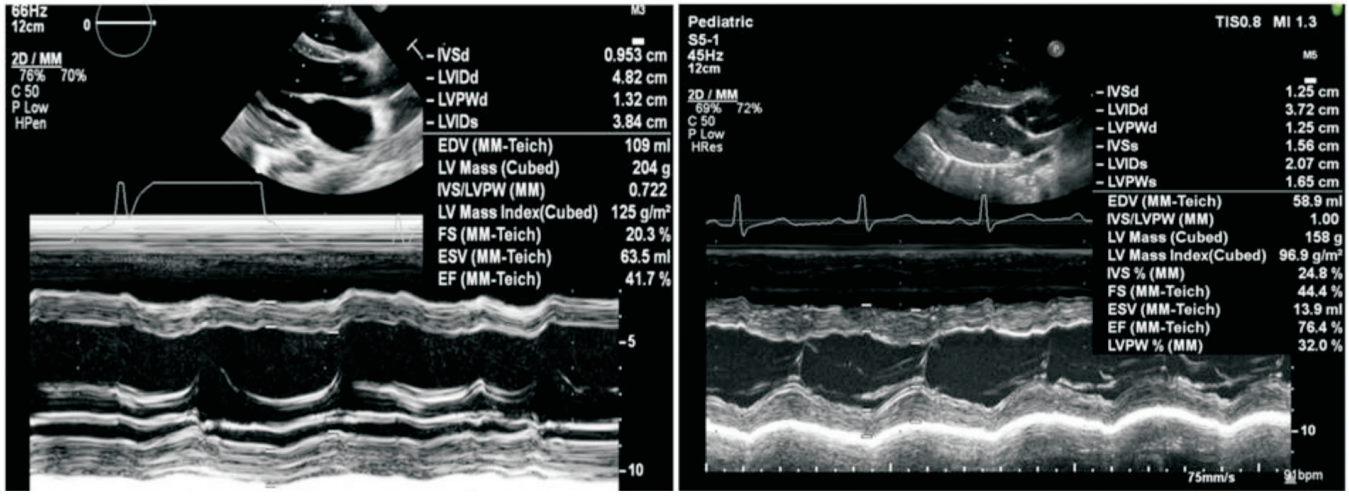

Fig. 1. Comparison of left-sided ejection fraction before and after the treatment.

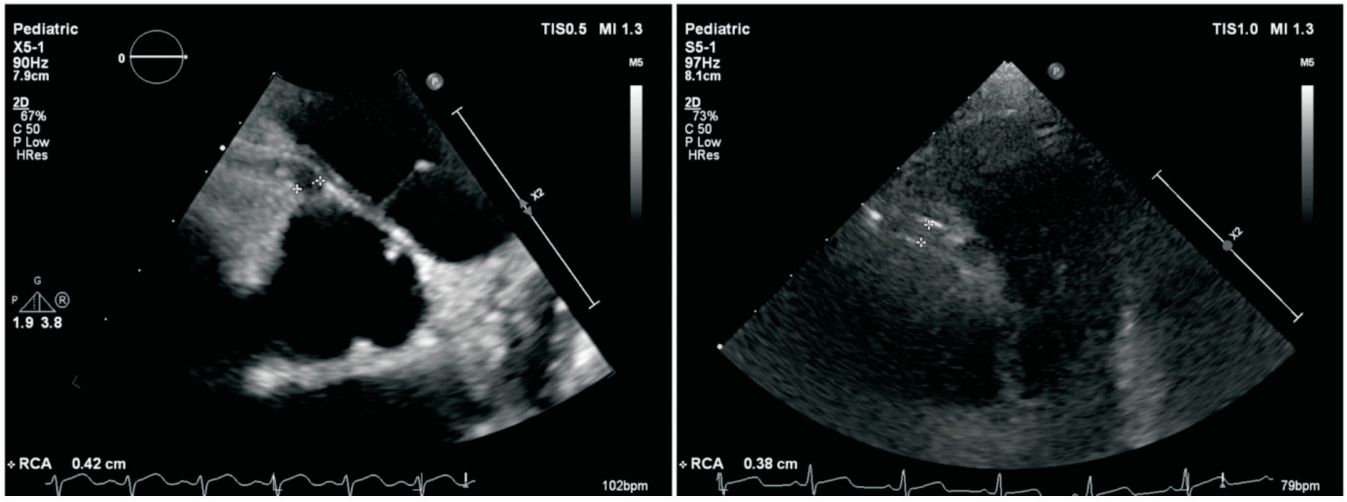

Fig. 2. Coronary artery dilatation before treatment and standard-size coronary artery after treatment.

We observed effusion in the pericardium in 20 (65%) patients and the pleural space in 24 (77%) patients. Elevated NT proBNP was observed in all (100%) patients with MIS-C, while elevated Troponin I levels were observed in 23 (74%) patients. D-dimers were elevated in all (100%) patients with MIS-C. Our study found that the mean proBNP level in blood plasma was statistically significantly different in patients with or without reduced left ventricular ejection fraction, ANOVA, $F(2,28) = 14.17$, $p < 0.036$. In patients with moderately reduced LVEF, proBNP levels were 19235 (95% CI 7079 to 31392) pg/ml higher compared to proBNP levels in patients with mildly reduced LVEF, and 21836 (95% CI 11798 to 31874) pg/ml higher compared to with proBNP level in patients with normal LVEF ($p < 0.001$) (Table 2).

Table 2. Cardiovascular changes of MIS-C patients

Findings	Impact	Frequency (percentage)
Vital signs	Blood pressure	Hypotension 24 (77%)
EHOKG	Reduced LVEF	Mild: 6 (19%) Moderate: 5 (16%) Total 11 (35%)
	Mitral valve insufficiency	Mild: 19 (61%) Moderate: 3 (10%) Total: 22 (71%)
	Tricuspid valve insufficiency	Mild: 12 (39%) Moderate: 11 (35%) Total: 23 (74%)
	Coronary artery dilation	2 (6%)
X-RAY/ US	Pleural effusion	24 (77%)
	Pericardial effusion	20 (65%)
ECG	ST-T segment changes	12 (39%)
	Neon-specific ST-T segment changes	13 (42%)
	Prolongated QTc	9 (29%)
	AV block	I degree AV block (10%)
	Hiss right bundle branch block	5 (16%)
	Arrhythmia	3 (10%) AV dissociation 1 (3%) group SVT
Analysis	Elevated proBNP	31 (100%)
	Elevated Troponin I	23 (74%)
	Elevated D- Dimers	31(100%)

DISCUSSION

MIS-C is a significant late complication of COVID-19 with variable impact on different organ systems. ProBNP is a vital biomarker evaluated in various cardiovascular diseases, indirectly indicating the impairment of the cardiovascular system (Cao *et al*., 2019). Our study observed elevated proBNP in 100% of cases, suggesting that cardiovascular involvement of varying severity was observed in all patients. We observed elevated troponin levels in 74% of cases, similar to Gottlieb *et al.* (2021) review study. However, our study did not observe an association between elevated cardiac markers and the necessity for treatment in the intensive care unit, as described by Valverde *et al.* (2021). In our study, echocardiography was performed by one person, which is why the obtained data are more objectively comparable in dynamic examinations. The negative aspect of examining multiple patients by one person has a greater risk of making the same mistakes.

Compared to similar studies, our study observed tricuspid valve insufficiency more often, mainly resulting from fluid overload. Respectively, patients with hypotension were primarily hospitalised in the emergency and observation department, where hypotension was primarily corrected with a fluid bolus (10–20 ml/kg). Considering the pathogenetic mechanism of MIS-C hypotension, fluid bolus administration may not resolve the hypotension but contribute to TVR (Valverde *et al*., 2021). This hypothesis is supported by the fact that TVR was reduced due to the administration of diuretics.

According to previous studies, the leading cause of hypotension in MIS-C is vasodilatation caused by the hyperinflammatory response. In a study by A. Alali at the Texas Children's Hospital in the USA, all patients with hypo-

tension underwent continuous cardiac output measurement (CCI) using Pulse Wave Cardiac Output (PiCCO) monitoring, which allowed to conclude that the hypotension was mainly due to vasodilation; PiCCO monitoring also allows to evaluate inotropic medication necessity and cancelation time objectively (Alsaied *et al*., 2021). Unfortunately, PiCCO monitoring was not possible at our centre, and inotropic medication was added and terminated by evaluation of vital signs. By implementing this method in our medical institution, hypotension could be controlled more effectively, reducing the incidence of AV valve insufficiency. Reduced LVEF has been observed relatively frequently, a severe life-threatening condition significantly affecting clinical status (Alsaied *et al*., 2021; Mannarino *et al*., 2022).

In our study, all patients with reduced LVEF function had normalised by the time they were discharged from the hospital, as studies previously reported (Kavurt *et al*., 2021; Sperotto *et al*., 2020). We observed a strong relationship between proBNP levels and reduced LVEF. Respectively, patients with higher ProBNP levels are more likely to have reduced LVEF. As patient cardiac biomarkers are commonly analysed first upon admission to the emergency, and the cardiologist's consultation is performed 12–24 hours after admission, ProBNP may be a prognostic marker for reduced LVEF or more severe cardiovascular involvement. More extensive cohort studies should be performed to evaluate the prognostic significance of proBNP.

The frequency of coronary artery involvement varies between studies (8–50%), and the pathogenetic mechanism is currently unclear. In our study, coronary artery dilatation was observed in two cases (6%), and coronary artery dimensions were normalised by discharge from the hospital. Considering that IVIG and methylprednisolone therapy were started early in all patients and that the clinical course and treatment of MIS-C are like Kawasaki disease, early therapy initiation may be an essential factor in why coronary artery involvement was observed less often in our study.

As in similar studies, we observed various changes in ECG (Minocha *et al*., 2020; Regan *et al*., 2021; Valverde *et al*., 2021). Considering the clinical presentation and ST-segment elevations (39%), non-specific ST-segment changes (42%), prolonged QTc interval (29%), and I degree AV block (10%) along with elevated proBNP (100%) and Troponin I (74%) suggest subclinical myocarditis. The patients' ECG changes had also resolved at discharge. Magnetic resonance is usually not performed primarily to confirm myocarditis in patients with MIS-C. All patients with MIS-C undergo regular further outpatient follow-up, including cardiac MR 6-12 months after hospitalisation with MIS-C.

CONCLUSION

Multisystem inflammatory syndrome in children is still a significant and potentially life-threatening disease with cardiovascular involvement in 100% of cases. Patients who present with higher ProBNP levels are more likely to be diagnosed with reduced LVEF, which should be kept in mind when evaluating patients with MIS-C. Overall, patients with MIS-C have a good prognosis, and the discharge from the hospital has resolved most cardiovascular changes, but further follow-up and studies are needed to evaluate the long-term outcome.

ETHICS

This study was reviewed and approved by Rīga Stradiņš University Ethics Committee and by the Institutional Review Board of the Children's Clinical University Hospital (No. 22-2/450/2021).

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MULTISISTĒMU IEKAISUMA SINDROMA IETEKME UZ SIRDS UN ASINSVADU SISTĒMU: LATVIJAS VIENA CENTRA PĒTĪJUMS

MIS-C (*Multisystem inflammatory syndrome in children*) ir hiperinflamators sindroms, ko izraisa Sars-CoV-2 vīruss. MIS-C joprojām ir aktuāla problēma visā pasaulē. Ir zināms, ka MIS-C ietekmē dažādas orgānu sistēmas, tai skaitā kardiovaskulāro sistēmu, līdz pat 100% gadījumu ar dažādu simptomu spektru un smagumu. Ir ļoti svarīgi laikus identificēt MIS-C un sākt terapiju, lai samazinātu iespējamās komplikācijas un klīnisko pasliktināšanos. Šis bija viena centra prospektīvs kohortas pētījums, kas tika veikts Bērnu klīniskajā universitātes slimnīcā no 2021. gada janvāra līdz decembrim. Pētījumā tika iekļauti pacienti vecumā no viena līdz septiņpadsmit gadu vecumam, kuri atbilda MIS-C kritērijiem. Mēs izanalizējām pacientu demogrāfiskos datus, asinsspiedienu, ehokardiogrāfiju, elektrokardiogrāfiju, kā arī sirds biomarķierus: proBNP un troponīnu I. Pētījumā tika iekļauti 31 pacients, kuri atbilda MIS-C kritērijiem. Vidējais pacientu vecums bija 8,0 gadi un 52% bija zēni. No visiem pacientiem 77%, iestājoties uzņemšanas nodaļā, tika konstatēta hipotensija. No visiem pacientiem 42% bija nepieciešams inotropu medikamentu atbalsts. Ārstēšana intensīvās terapijas nodaļā bija nepieciešama 58% no visiem pacientiem. Samazināta kreisā kambara izsviedes frakcija tika novērota 35%, viegli samazināta kambara izsviedes frakcija (LV EF < 55%) tika novērota 19% gadījumu, bet mēreni samazināta izsviedes frakcija (LV EF < 45%) tika novērota 16% pacientu. Divpadsmit procenti pacientu saņēma milrinonu, lai uzlabotu sirds kreisās puses funkciju. Hospitalizācijas laikā visiem pacientiem būtiski uzlabojās sirds kreisās puses funkcija. No visiem pētījumā iekļautajiem pacientiem sešiem procentiem tika novērota koronāro artēriju dilatācija. Visiem pacientiem, izrakstoties no stacionāra, koronāro artēriju dilatācija bija izzudusi.