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Should we fear infarct-like myocarditis?

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Prognóza

SOUHRN

Úvod: „Infarct-like" myokarditida je běžnou prezentací akutní myokarditidy. V literatuře je často uváděna dobrá prognóza a obvykle u ní bývá doporučována restrikce fyzické aktivity po dobu až šesti měsíců. Cílem studie bylo ukázat charakteristiky a vymezitelnost této prezentace myokarditidy, potvrdit její dobrou prognózu nezávisle na fyzické aktivitě prováděné po jednom měsíci od propuštění z hospitalizace.
Metodologie: V letech 2012 až 2016 bylo ve Fakultní nemocnici v Plzni hospitalizováno 93 pacientů s akutní myokarditidou, 73 (78 %) z nich mělo „infarct-like" myokarditidu a byly zhodnoceny základní diagnostické parametry. Z nich 32 pacientů s „infarct-like" myokarditidou bylo zařazeno do observační prospektivní studie, v rámci které byla prováděna pravidelná echokardiografická vyšetření, magnetickou rezonancí (MR) včetně vývoje objemu pozdního sycení gadoliniovou kontrastní látkou (LGE), bicyklovou ergometrií (BE) a náběr hypersenzitivních troponinů. Všichni pacienti podstoupili po jednom měsíci od propuštění z hospitalizace bicyklovou ergometrii bez limitace zátěže a byla jim povolena od jednoho měsíce postupná fyzická zátěž včetně výkonu zaměstnání. Žádný pacient nebyl profesionální sportovec.
Výsledky: Vstupně byla zjištěna lehká systolická dysfunkce levé komory u 43,8 % pacientů, která se normalizovala před první ambulantní návštěvou. Ostatní pacienti měli normální systolickou funkci. Všichni pacienti měli signifikantně zvýšenou hodnotu troponinu. Hodnoty hypersenzitivních troponinů zůstaly při kontrolách po jednom a šesti měsících od onemocnění pod 99. percentilem zdravé populace. Všichni sledovaní pacienti měli pozitivní LGE v subepikardiální lokalizaci. Po jednom měsíci poklesl medián objemu LGE na 53 %, po šesti měsících na 40 % původní hodnoty. Dosažená zátěž při BE byla po půl roce od myokarditidy statisticky významně vyšší (9,7 ± 2,2 MET) než při měsíční kontrole (8,9 ± 2,1 MET, p = 0,0023), při poslední provedené kontrole (9,3 ± 2,1 MET) se dále již nelišila (p = 0,2331). Průměrná doba sledování pacientů byla dva roky.
Závěr: „Infarct-like" myokarditida byla během sledovaného období nejčastější prezentací akutní myokarditidy. Žádný pacient neměl časnou recidivu myokarditidy (do jednoho roku) a u žádného se nevyvinula systolická dysfunkce LK. „Infarct-like" myokarditida má specifický průběh, odlišný od jiných forem myokarditid. Má dobrou prognózu nezávisle na fyzické aktivitě prováděné měsíc po propuštění z hospitalizace.

ABSTRACT

Introduction: Infarct-like myocarditis is the most common presentation of acute myocarditis. A good prognosis is mentioned in the literature and several months of restricted physical activity is usually recommended.
Objectives: The aim of our study was to show the characteristic features and specificity of this particular presentation of myocarditis and to evaluate its prognosis, relative to physical activity, after hospital discharge.

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Methodology: From 2012–2016, 73 patients with infarct-like myocarditis were hospitalized at the University Hospital of Pilsen and were evaluated by basic diagnostic parameters. Thirty-two patients from this group were involved in our prospective observational study where echocardiography (ECHO), magnetic resonance imaging (MRI) (including late gadolinium enhancement [LGE]), bicycle ergometry (BE) as well as troponin screening tests were regularly performed. One month after hospital discharge, all patients underwent bicycle ergometry without any load limitation. After the one-month follow-up, patients were allowed to increase physical exertion gradually to included job performance. None of the patients were professional athletes. During this observation time, 20 patients with different presentations of acute myocarditis were also admitted to hospital. These different presentations are discussed.

Results: None of the patients with infarct-like myocarditis had an early recurrence of the disease (i.e., within one year) or left ventricular (LV) systolic dysfunction (based on ECHO results). After one month, the LGE volume median had decreased by up to 53% and after six months it had decreased by up to 40% of the original value. After one and six months, hypersensitive troponin values were under the 99th percentile of the healthy population. The achieved exertion during BE, at the six-month follow-up (9.7 ± 2.2 METs) was statistically significantly better than after the one-month follow-up (8.9 ± 2.1 METs, p = 0.0023). On the last BE follow-ups (9.3 ± 2.1 METs), no significant change was seen (p = 0.2331). The average follow-up time was 2 years.

Conclusion: Infarct-like myocarditis has a specific feature that differs from other types of myocarditis. Infarct-like myocarditis has a good prognosis, which is independent of physical exertion starting one month after hospital discharge.

Keywords:
Bicycle ergometry
Infarct like myocarditis
Late gadolinium enhancement
Magnetic resonance imaging
Prognosis

Introduction

Infarct-like myocarditis with chest pain, ischemic ECG changes, troponin elevation, normal coronary arteries, and normal or early normalized LV systolic function is one of the most common presentations of acute myocarditis.

Chest pain symptoms are caused by a specific parvovirus, PVB19, which directly infects endothelial cells with microvascular ischemic changes and angina symptoms [1]. Schmidt-Lucke et al. [2] found that infecting angiogenic bone marrow cells lead to poorer endothelial regeneration and its dysfunction. Pathophysiology of viral myocarditis is described mostly with animal (murine) model of enterovirus myocarditis. This model has three phases with possible evolution to dilated (inflammatory) cardiomyopathy [3–5]. Although, this model is often presented and generalized, the course of PVB19 infection is apparently different. Moreover, EMB finding of PVB19 in patient with dilated cardiomyopathy is frequent and unclear and by latest studies it may be only "innocent bystander" [6–8]. As significant finding PVB19 is considered higher load – 500 genome equivalents (ge) per microgram [9] or microRNA [10,11]. A study by Mahrholdt et al. [12] found infarct-like myocarditis symptoms in PVB19-infected patients. Patients were young men and most had typical subepicardial LGE localized to the lateral wall of the heart. All patients had a good prognosis. However, patients with human herpesvirus (HHV6), or especially a HHV6/PVB19 combination, had symptoms of new heart failure with LGE localization mainly in the septal area and the disease often progressed to a chronic stage with a poor prognosis.

Apart from the above-mentioned studies, there have been many published works dealing with the prognosis of myocarditis patients based on their initial clinical presentation (i.e., ECG, ECHO or MRI results). Several studies [13–15] have shown that infarct-like myocarditis, with normal or early normalized systolic function, often has a good prognosis.

According to the European Society of Cardiology (ESC) recommendations, published in their Position Statement [5], prohibition of physical activity is recommended. However, the recommendation is based on the work of Basso et al. [16] and Pelliccia et al. [17], who were making recommendations for athletes. Athletes were allowed to continue sports activity 6 months after disease appearance, depending on follow-up examination results. Experts routinely recommend this schedule for non-athletes as well, regardless of myocarditis presentation.

Maintaining physical activity restrictions during the acute phase (up to normalization of LV systolic function and troponin values) is essential and is usually no problem for patients. Physical activity restrictions beyond this time are known to be associated with worse compliance. The reasoning behind physical activity restriction lasting several months is the risk of disease progression into dilated cardiomyopathy or disease recurrence. However, this rationale is suspiciously based on three-phase (murine) model of enterovirus myocarditis.

Methods

In this study, clinically suspected myocarditis was diagnosed in compliance with the position statement criteria of the ESC [5]. Due to the increase in sample representativeness, diagnostic parameters were evaluated in all 73 patients admitted for infarct-like myocarditis during the observation time. In 66 patients, LGE distribution was assessed. Within the observation study, ECHO, MRI, BE, as well as hypersensitive troponin screening tests were regularly performed in 32 of the above-mentioned patients.

MRI and troponin screening tests were performed during hospitalization, after 1 month, and after 6 months. ECHO was performed when patients were hospitalized, then after 1 month, after 6 months, after 1 year, and then once per year. BE was performed (in case of normal systolic function seen in previous ECHO, which was fulfilled by all patients) after 1 month, after 6 months, after 1 year, and then once per year. Endomyocardial biopsy (EMB) was not performed in patients with infarct-like myocarditis. On the contrary, it was performed to determine eosinophilic myocarditis, in malignant arrhythmias, and in patients with inflammatory cardiomyopathy.

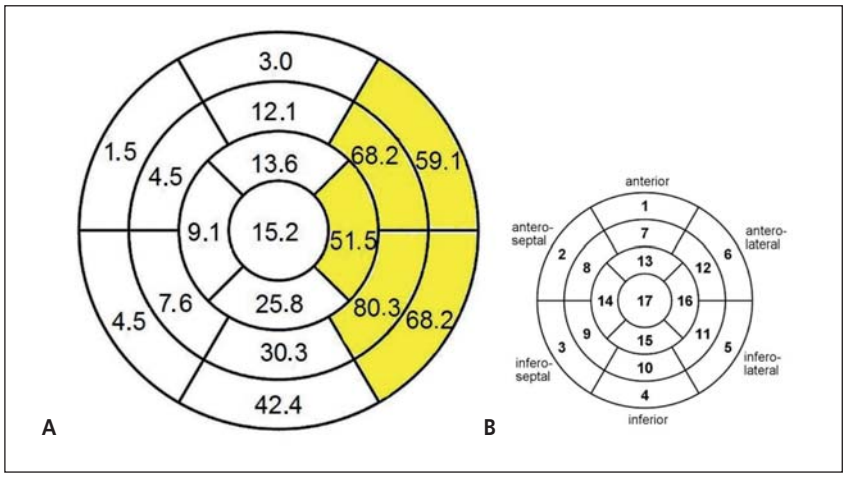

Fig. 1 – (A) LGE with subepicardial localization of particular LV segments in the 17-segment classification system, expressed as a percentage, the yellow-marked area of percentage affection > 50%; (B) numbers of particular LV segments (n = 66).

- Systolic function of both ventricles, in particular, was evaluated electrocardiographically. Ejection fraction (EF) was evaluated to within 5 units, decreased systolic function was evaluated as ≤ 50%.
- Bicycle ergometry: initial load was 50 W, afterwards it was increased by 25–50 W up to the maximum tolerated load. Maximum heart rate (HR), metabolic units (MET), as well as the presence of arrhythmias were monitored.
- MRI was performed in its entirety and included assessments of kinetics, edema, perfusion, and late gadolinium enhancement (LGE) of the left ventricular myocardium [18] (Fig. 1). In 66 patients with infarct-like myocarditis, LGE localization was analyzed using the 17-segment classification system. In 32 patients, changes in the LGE weight ratio were evaluated in 3 subsequent MRI exams. LGE quantification was performed using cross-screenings (SA), where the ratio of LGE extent to the whole thickness of myocardium was determined. Total myocardial mass, and as a result the LGE mass value (mg), was obtained by calculating the arithmetic mean of all layers, which was done during MRI analysis. Software at https://www.circlecvi.com/features/tissue-characterization.php was used for analysis. To draw comparisons with other patients, the LGE value was divided by myocardial weight (data obtained during ECHO using the cube formula).
- Basic screening including troponins was routinely performed in all patients during their hospital stays (in the course of the study, in 2015, troponin I was substituted for hypersensitive troponin T [Elecsys, Roche] at the University Hospital in Pilsen).
- Blood samples were taken during hospitalization as well as during the first two check-ups. Samples were frozen and subsequently analyzed using the hsTnI test (Architect, Abbott) and the hsTnT test (Elecsys, Roche).

Statistics

Numerical data were processed using MS Excel, IBM SPSS 24, and MedCalc 17.7.2. Data normality was evaluated using a histogram, the Shapiro–Wilk test, and the Kolmogorov–Smirnov test. Normally distributed data (heart rate and MET values in BE) were compared by using the paired 2-sample t-test, by determining the means. The Wilcoxon test for paired samples was used on non-normally distributed data.

Results

From 2012 to 2016, 93 patients presented with acute (clinically suspected) myocarditis at the University Hospital of Pilsen (a regional hospital serving 600,000 inhabitants). Of those, 78% (n = 73) suffered from infarct-like myocarditis. The remaining 22% presented with different type of acute myocarditis (see Table 1 for an overview).

Table 1 – Particular types of acute myocarditis in patients admitted to the University Hospital in Pilsen from 2012–2016 (n = 93).

	Number	Men	Women	Men (%)	Women (%)
Infarct-like	73	66	7	90.4	9.6
Malignant arrhythmia	5	0	5	0	100
3rd degree AV block	2	2	0	100	0
Fulminant myocarditis	3	0	3	0	100
In systemic diseases	10	5	5	50	50
In total	93	73	20	78.5	21.5

The development of infarct-like myocarditis differed from other acute myocarditis presentations during the observation time:

- **Malignant arrhythmias** affected mainly young women (aged between 17 and 45 years), in which cardiopulmonary resuscitation (CPR) was required. Initially, mild to moderate left ventricular systolic dysfunction was found. Afterwards, it normalized in most cases. Initial catecholamine support was either low or it was not required. In the long term, patients had a good prognosis (without recurrence of malignant arrhythmias).
- **Fulminant myocarditis** mainly affected young women (aged between 28 and 42 years). It was accompanied by severe left ventricular systolic dysfunction and refractory cardiogenic shock requiring considerable inotropic support. ECMO was used in two cases. The prognosis was poor for all patients. The diagnosis was histologically determined.
- **Atrioventricular conduction disorders** affected young men (2 cases, both aged 36 years). One of them improved after antibiotic treatment for Lyme carditis, while a cardiac stimulator had to be implanted in the other patient. There was no development of left ventricular systolic dysfunction and both prognoses were good.
- **Myocarditis related to systemic diseases** (aged between 26 and 64 years) was accompanied by specific symptoms of a systemic disease or status (sarcoidosis, SLE, ulcerative colitis, pathological pregnancy, hypereosinophilic syndrome, or sepsis). The prognosis was related to the underlying disease.

In the above-mentioned list of myocarditis presentations, there were no patients with symptoms of heart failure, which is more likely to be chronic. Patients suspected of having inflammatory cardiomyopathy, were partially diagnosed by performing EMB. This group also had more men than women. Left ventricular systolic function was most often moderately or severely decreased. None of the patients had infarct-like myocarditis in medical history. The long-term prognosis in these patients was generally poor.

Basic characteristics of patients with infarct-like myocarditis

During the 5-year study, there were 73 patients, mostly younger (average 33 ± 11) men (90%). Three patients, aged 18, were admitted to the Department of Pediatrics. Chest pain was the initial symptom in all patients. Most (68%) patients presented with nonspecific systematic inflammatory symptoms (fever, cough, muscle and joint pain, headache, and fatigue), while 14% also had digestive disorders (diarrhea and/or vomiting).

Most (68%) patients had ischemic ECG changes (ST-segment elevation), all had elevated troponin (hsTnT >14 ng/l, TnI >0.4 mg/l), and 77% had elevated CRP levels. Other quantitative physical and laboratory characteristics are presented in Table 2. Echocardiography showed left ventricular kinetic disorders in 41% of patients, initially mild LV systolic dysfunction (40% < EF LV ≤ 50%) was found in 36% patients. The others had normal systolic function. Ischemic cardiac disease was initially excluded in 71% of patients (by performing SCG in 40% and coronary CT angiography in 31%).

In most patients with clinically suspected myocarditis, the MRI showed characteristic subepicardial localization of LGE (69 patients in total). LGE was negative in 2 patients and myocardial MR was not performed in 2 patients.

Distribution of LGE in patients with infarct-like myocarditis

LGE affecting particular segments in the 17-segment classification system, expressed as a percentage, was evaluated in 66 patients (Fig. 2). The inferolateral, anterolateral, and inferior walls were most affected (segments 11, 12, 5, 6, and 16), the septal area was least affected (segments 1, 2, 3, and 8). The average number of affected segments per patient, using the 17-segment scheme, was 5 ± 2.5.

Results of the consecutive observation study

Thirty-two patients with infarct-like myocarditis (30 men/2 women) were enrolled in the observation study. These patients were admitted to the Cardiocenter in Pilsen, consented to be involved in the study, and underwent at least two subsequent outpatient check-ups, which included MRI examinations. Disease recurrence was seen in two patients, after more than 1 year (the first one at 1.5 years and the other at 3.2 years). However, these patients were statistically analyzed only once, since subsequent MRI evaluations would be suspect (i.e., uncertain differentiation between old and new lesions).

Troponin values

Within the study, values of troponin hsTnI (Architect, Abbott) and hsTnT (Elecsys, Roche) were determined at hospitalization, after 1 month, and after 6 months. Medians are mentioned in Table 3, the interquartile range, by using boxplots, can be found in Fig. 3. Complete screening was only performed in 23 patients. After 1-month, elevated hsTnI (over 27 ng/l [99th percentile of healthy population]), was found in 3 patients, while 3 other patients had elevated hsTnT (over 14 ng/l [99th percentile of healthy population]). No patients had both types of elevated troponin at the same time. Decreasing troponin values within the first weeks of hospitalization was not surprising. However, statistically significant decreases were seen between the first check-up (after 1 month) and the second (after 6 months) with values under the 99th percentile.

Echocardiography

All patients underwent a transthoracic examination at hospitalization. Initially, left ventricular kinetic disorders were found in 51% of patients, while mild systolic dysfunction was found in 43.8%. Systolic function in all patients was normalized before the first outpatient follow-up (i.e., was normal in the first check-up after one month and remained normal henceforth).

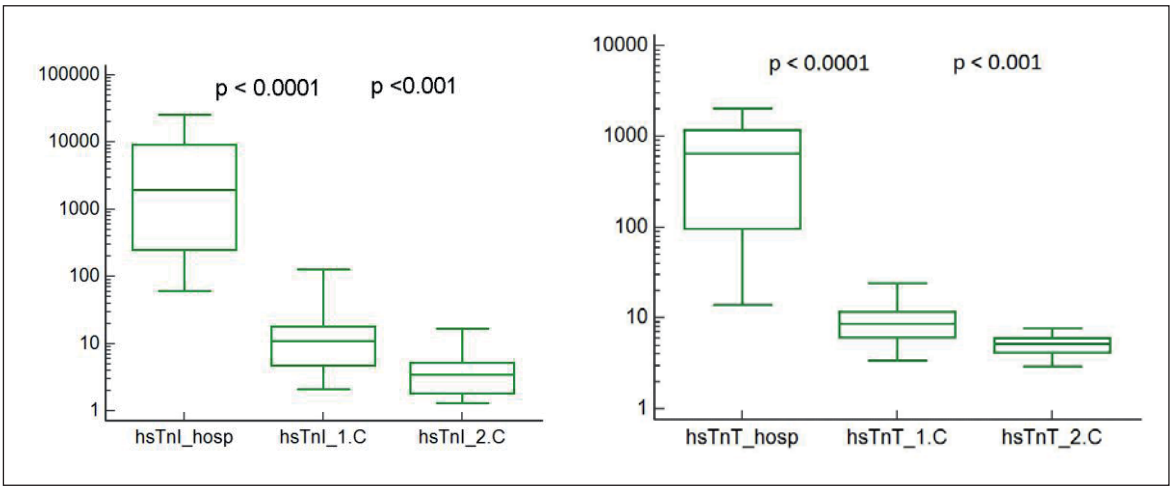

Fig. 2 – Boxplot of troponin I (hsTnI) and troponin T (hsTnT) development at time of hospitalization and two subsequent follow-ups (hosp – values at hospitalization; 1.C – follow-up after 1 month; 2.C – follow-up after 6 months).

Magnetic resonance imaging

Three cardiac MRI scans were performed. LGE volume was quantified using relative LGE mass parameters. The average values at specific follow-ups are presented in Table 3. After 1 month, LGE mass volume decreased by up to 52.8% and after 6 months it had decreased by up to 40% of the original value. The difference between follow-ups was statistically significant ($p < 0.001$).

Bicycle ergometry

Patients were examined after 1 month and after 6 months (afterwards once a year). In 70% of patients, the same load value was achieved during the first two follow-ups and an improvement could be seen in 1/3 patients at the second follow-up. In total, load tolerance statistically improved (also in MET values). Maximum heart rate values were also statistically significantly different (Table 3).

Table 2 – Characteristics of patients with infarct-like myocarditis (n = 73).

Characteristics	Minimum	Maximum	Median	Average
Age (years)	15	67	32	33 ± 11
BMI (kg/m^2)	16	44	27	27 ± 5
CRP (mmol/l)	1	242	32	51 ± 55
Myoglobin (mmol/l)	20	995	137	191 ± 180
Troponin I (µg/l)	1	29	9	11 ± 8
Troponin hsT (ng/l)	18	4593	922	1072 ± 1033

Table 3 – Median values (medians or average values) of specific parameters.

Parameters	Initial	After 1 month	After 6 months	Comparison after 1 month and 6 months (p)
Troponin				
hsTnT (ng/l) median (IQR)	547 (28–1158)	7 (6–10)	5 (4– 6)	< 0.001
hsTnI (ng/l) median (IQR)	1 522 (189–8 212)	7 (4-13)	4 (2–6)	< 0.001
ECHO				
Patients with LVEF ≤ 50%	43.8 %	0.0%	0.0%	
Magnetic resonance imaging				
Rel. LGE mass median (IQR)	4.0 (2.4–6.2)	2.1 (1.4–3.7)	1.6 (1.1 –2.9)	< 0.001
Percentage	100.0%	52.8%	40.4%	
Bicycle ergometry				
Maximum heart rate achieved		166 ± 14	169 ±13	0.1843
Load achieved (W)		195 ± 39	210 ± 40	< 0.005
METs		8.9 ± 2.1	9.7 ± 2.2	< 0.005

ECHO – echocardiography; IQR – interquartile range (n = 32); LGE – late gadolinium enhancement; LVEF – left ventricle ejection fraction.

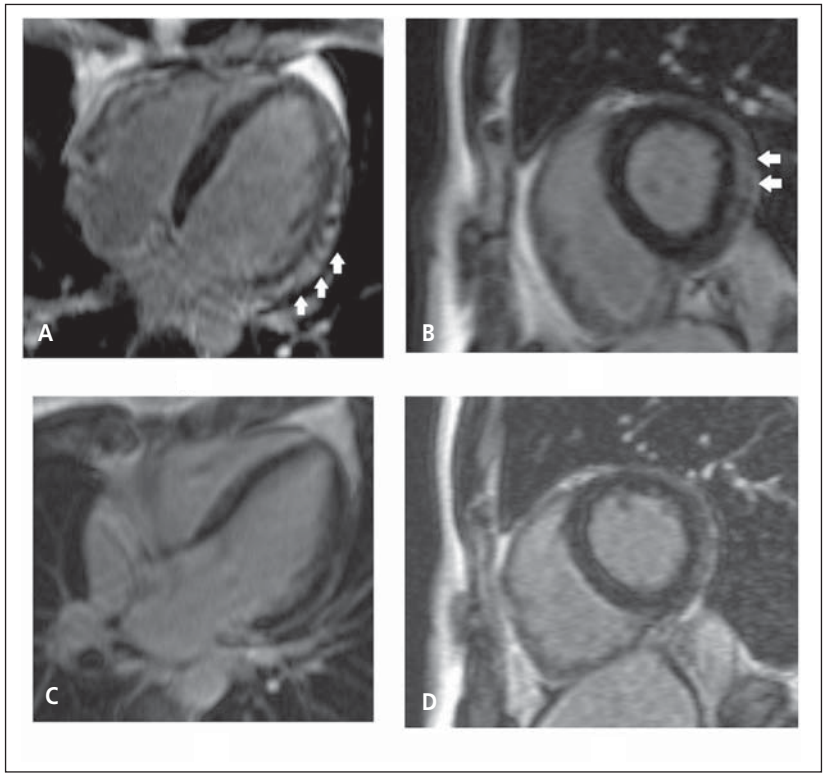

Fig. 3 – MRI – subepicardial localization LGE in one patient at hospitalization: (A) long axis, (B) short axis and decrease LGE load at the 1 month follow-up, (C) long axis, (D) short axis.

Final observations

The average length of patient monitoring was 2 years in October 2017. None of the patients, based on ECHO, had left ventricular systolic dysfunction at the 1-year check--ups. Results from the BE performance (achieved heart rate and maximum load) were not statistically significant compared to the second check-up (Table 4).

Discussion

We attempt here to make a contribution regarding the management of patients with infarct-like myocarditis. It should be noted that our study was on a relatively small number of patients and the follow-up period was intermediate in length. In spite of this, results show that pseudo-infarct presentation of myocarditis is associated with a benign long-term prognosis even if physical activity is not restricted for a prolonged period. Physical activity does not appear to increase the risk of an early recurrence.

During echocardiography examinations, we were satisfied with the formulation of normal or decreased overall systolic function, due to inaccuracy caused by the nature of method as well as the examining physicians' subjective estimations. Results from publications using deformation analysis, i.e., Speckle Tracking Echocardiography [19–22], are an incentive to evaluate myocardial affection after myocarditis more precisely.

It is recommended that myocarditis be demonstrated by performing an MRI using at least two of the three Lake Louise Criteria [5]. Edema and LGE, with typical subepicardial and intramyocardial localization, were found in patients involved in the study. This parameter is the only demonstrated method of noninvasive imaging of myocardial structural changes, which has high sensitivity and makes quantification of a myocardial affection possible. The sensitivity and distribution of an affection can also be improved by using T1 mapping [23].

According to the literature, the sensitivity for showing infarct-like myocarditis, using LGE, ranges from 70% to 90% and is higher than for other types of myocarditis

Table 4 – Development of bicycle ergometry parameters in 32 patients.

Bicycle ergometry: long-term development	After 6 months	Last follow-up	Comparison after 6 months/last follow-up (*p*)
Maximum heart rate achieved	169 ± 13	170 ± 14	0.6221
Load achieved (W)	210 ± 40	217 ± 41	0.2331
METs	9.7 ± 2.2	9.3 ± 2.1	0.2006

[24,25]. LGE volume correlates with the size of extracellular space, enlarging if patients have edema, inflammatory infiltration, or fibrosis. Considerable (50%) LGE volume reduction on the first two check-ups after 1 month showed that besides fibrosis, other – reversible – changes also play a role in enlargement of the extracellular space. LGE findings in all patients, after 6 months, showed the presence of irreversible cell necrosis and subsequent fibrosis. However, this fibrosis was too discrete to be seen using ECHO (without deformation analysis). Specific LGE distribution, related to infarct-like myocarditis in the left ventricular lateral wall, is commonly described in the literature; on the other hand, the interventricular septum is affected in patients with chronic myocarditis [12,13].

Bicycle ergometry after infarct-like myocarditis was considered an examination suitable for the evaluation of physical load tolerance and load arrhythmia occurrence. The achieved maximum load was, among other things, determined by the long-term sports activity of each patient (no one was a professional athlete) and the degree of motivation to achieve the greatest load. The benefit was especially seen in comparing patient follow-ups as well as the ability to sustain the same load. A small difference, which was, however, statistically significant, was seen between follow-ups at 1 month and 6 months after discharge, and were associated with the rest phase of treatment (i.e., worsening physical conditioning) that patients followed during the first month after admission. The differences between follow-ups more than half a year after myocarditis were not statistically significant and reflected the current physical activity of the patients. No patients had arrhythmias.

No patients with infarction-like myocarditis underwent EMB, therefore the diagnosis remained clinically suspected myocarditis. The ECS position statement [5] recommends an EMB in all patients with clinically suspected myocarditis. Issues related to EMBs in patients with infarct-like myocarditis are dealt with by one of authors of the recommendations in a recent work [26]. The author quotes publications which mention good prognoses and spontaneous recoveries from infarct-like myocarditis. As far as works [14,27,28] stated few percentages of a poor prognosis, admits that the reason is inaccurate determination of patients with infarct-like myocarditis.

However, the author recommends EMBs in patients with infarct-like myocarditis, in compliance with the position statement. In her opinion, it is caused by the absence of a sufficient amount of prospective data that show a benign prognosis, which would definitely be confirmed by EMB, including etiologic agents. Another argument might be that a condition with a similar initial clinical presentation, i.e., more rare and serious types of myocarditis such as eosinophilic, giant-cell myocarditis, and autoimmune diseases, would be detected quickly by EMB, and would facilitated an immediate start of immunosuppressive therapy.

Hypereosinophilic syndrome, including eosinophilia, which is a diagnostic criterion as well as a pathological condition, indicates suspected eosinophilic myocarditis. In cases of systemic autoimmune diseases, other systemic symptoms should serve as warning signs. The prevalence of giant-cell myocarditis is very low (1 : 200,000) and manifests as heart failure or arrhythmia in most patients. Only in a small number of patients, does it manifest as infarct-like myocarditis with a normal EF LV. Early normalization of initially mild systolic dysfunction is a significant feature of benign infarct-like myocarditis [29,30].

Although a routine EMB would be informative, it cannot be expected to become a routine diagnostic method for this presentation of myocarditis, at least according to European professionals and experts (despite the recommendations of the ECS position statement). However, MRI cannot replace endomyocardial biopsy in patients with suspected inflammatory cardiomyopathy where the potential treatment (i.e., immunosuppressive, antiviral) depends on EMB confirmation of the etiologic agent. Moreover, MRI has considerably lower sensitivity and specificity in this case.

Conclusion

Infarct-like myocarditis was the most common presentation of acute myocarditis during the observation time (78% of patients). The subacute or chronic presentation of heart failure wasn't included. Infarct-like myocarditis has specific and characteristic development relative to other types of myocarditis, and has a good prognosis. Physical activity after the acute phase of disease (including BE) did not result in chronic myocarditis or recurrence of the disease within 1 year.

Conflict of interest
I have no conflict of interest.

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Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
All patients involved in the study signed an informed consent.

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