Heart failure with severely reduced ejection fraction after liver transplantation : a case report and review of the literature

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Dr. Dorien Pint[a]*, dr. Andreas B. Gevaert[b,c], prof. dr. Thomas Vanwolleghem[a,d,e], prof. dr. Thiery Chapelle[f] and dr. Karolien Dams[g,h]

[a] *Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium;* [b] *Research Group Cardiovascular Diseases, GENCOR department, University of Antwerp, Antwerp, Belgium;* [c] *Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium;* [d] *Viral Hepatitis Research Group, Laboratory of Experimental Medicine and Pediatrics (LEMP), Antwerp University, Antwerp, Belgium;* [e] *European Reference Network RARE-LIVER;* [f] *Department of Hepatobiliary, Transplantation and Endocrine Surgery, Antwerp University Hospital, Antwerp, Belgium*; [g] *Department of Critical Care Medicine, Antwerp University Hospital, Antwerp, Belgium;* [h] *Laboratory of Experimental Medicine and Paediatrics (LEMP), Faculty of Medicine and Health Sciences, Antwerp University, Antwerp, Belgium*

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Abstract

Background

Liver transplantation (LT) is a strenuous event for the cardiovascular system. Cardiovascular events (CVE), including heart failure (HF), arrhythmias and myocardial ischemia, are important causes of peri- and post-liver transplantation morbidity and mortality.

Case presentation

We describe the case of a 45-year-old male patient who developed heart failure with severely reduced ejection fraction (HFrEF) after receiving liver transplantation (LT) for end-stage post-alcoholic liver cirrhosis. Preoperative transthoracic echocardiography (TTE) demonstrated borderline left ventricular ejection fraction (LVEF) of 50% and diastolic dysfunction grade 2. On coronary angiography, the patient had no coronary stenoses. Persistent vasopressor need, increasing creatinine levels and progressive pleural effusion characterized the early postoperative period. TTE on postoperative day six revealed a new finding of a markedly reduced LVEF of 15%, accompanied by a discrete increase in hs-TnI and CK-MB without electrocardiographic (ECG) ST-T abnormalities. LVEF did not recover completely (EF 45%) during follow-up. The patient had sudden death 4.5 months post liver transplantation.

Conclusion

Our case demonstrates that the risk of post-LT systolic dysfunction is not excluded by preoperative resting examinations within normal range, and highlights the need for preoperative cardiac stress assessment (e.g. dobutamine echocardiography or stress cardiac magnetic resonance imaging) before LT. In addition, patients on a liver-transplant waiting list with cardiac dysfunction should be followed by a multidisciplinary team including a dedicated cardiology team experienced in managing liver-related cardiac pathology.

Keywords

Left ventricular systolic dysfunction, Left ventricular heart failure, Systolic heart failure, Heart failure with reduced ejection fraction, Diastolic dysfunction, Stress-induced cardiomyopathy, Liver cirrhosis, Liver transplantation, Cirrhotic cardiomyopathy.

Background

The only curative therapy for end-stage liver disease is liver transplantation (LT). LT is a strenuous event for the cardiovascular system. Cardiovascular events (CVE) are an important cause of peri- and post-LT morbidity and mortality [1]. The incidence of CVE after LT varies between different studies ranging from 6% to more than 70% [2–4]. Different factors contribute to this wide observed range of post-LT cardiovascular events. Firstly, a broad definition of CVE is applied in different studies. CVE is defined differently in studies as heart failure with reduced

ejection fraction (HFrEF), myocardial ischemia, arrhythmias, or a combination. Secondly, recipient age and disease severity have increased significantly in the last decade due to a lack of suitable donors. Lastly, there is a shift in the aetiology of cirrhosis requiring LT. The incidence of LT for non-alcoholic steatohepatitis (NASH) is increasing. Patients with NASH tend to have more co-morbidities and risk factors for coronary artery disease, like metabolic syndrome. Increasing recipient age and NASH will cause cardiovascular events after LT to rise further in the following years [5]. Cardiovascular complications together with graft rejection, and infections are the most important causes of mortality in LT patients [6].

Cardiac workup aims to detect coronary artery disease, left ventricular systolic dysfunction (LVSD) and diastolic dysfunction before LT. Cardiac dysfunction in patients with cirrhosis can be caused by cirrhotic cardiomyopathy, which is characterized by (i) abnormal systolic contractile response to stress (diminished inotropic and chronotropic response to stress), (ii) impaired diastolic relaxation, (iii) hyperdynamic circulatory state and (iv) electrophysiological repolarization changes (prolonged QTc) [7]. At rest, cirrhotic cardiomyopathy is often asymptomatic. Cirrhosis causes peripheral vasodilatation and shunting in splanchnic and sometimes pulmonary vasculature. Both cause the systemic vascular resistance (afterload) to decrease, which in turn causes a compensatory increase in preload. Decreased afterload and increased preload both increase cardiac output, preventing the development of symptoms. Cirrhotic cardiomyopathy may evolve into symptomatic heart failure under stress, such as after LT [8, 9]. Cirrhotic cardiomyopathy shows an

important overlap with stress-induced cardiomyopathy. We will use the term 'post-LT LVSD' throughout this manuscript for a new onset of left ventricular systolic dysfunction after liver transplantation.

LT procedure causes a sudden increase in afterload because of a rise in systemic vascular resistance (SVR). Fluid administration during and after the LT procedure causes a rise in cardiac preload. Both increased preload and afterload cause strain on the pre-existing LVSD. Pre-existing cardiac dysfunction is associated with worse clinical outcomes after LT, especially when diastolic dysfunction and prolonged QTc are present pre-LT [4].

In most transplant centres, standard cardiac workup contains at least transthoracic echocardiography (TTE) and electrocardiogram (ECG). In addition, most LT centres also perform a right heart catheterization, dobutamine stress echocardiography (DSE), or both to guide peri- and postoperative hemodynamic management. Unfortunately, there is still a significant difference in how transplant centres evaluate peri- and postoperative cardiac risk [10].

The presented case highlights the importance of including stress testing during cardiac workup. Additionally, a review of the literature was performed.

Case presentation

A 45-year-old male patient received LT for end-stage post-alcoholic liver cirrhosis. One week prior to LT, blood sample analysis showed hyperbilirubinemia, thrombocytopenia, normochromic anaemia and a cirrhotic coagulopathy (see Table 1). [Table 1 near here]. Calculated Model for End-stage Liver Disease (MELD) score, Na-MELD and Child-Pugh score one week prior to transplantation were 20, 17 and C10, respectively. Relevant past medical history included a semi-urgent transjugular intrahepatic portosystemic shunt (TIPS) placement for refractory oesophageal variceal bleeding. End-stage liver disease was complicated by hepatic encephalopathy (started after TIPS procedure) and mild ascites. In the standard preoperative workup seven months prior to LT, TTE was performed. TTE showed a normotrophic but slightly dilated left ventricle with a borderline reduced left ventricular ejection fraction (LVEF 50%) due to global hypocontractility. In addition, moderate diastolic dysfunction (grade 2), high-normal estimated pulmonary artery pressure (32mmHg), and mild bi-atrial dilatation were observed. See Table 2 for the evolution of the echocardiographic parameters. [Table 2 near here]. Based on the borderline reduced LVEF, left and right heart catheterisation were performed and showed no significant coronary stenoses and a hyperdynamic circulation with a cardiac output of 12.5 L/min (227 % of the theoretical value) typical for post-TIPS decompensated cirrhosis. Preoperative ECGs demonstrated normal sinus rhythm with a QTc interval ranging from 428 to 470 msec. Alcohol

abstinence was monitored using ethyl glucuronide measurement in hair, confirming alcohol abstinence 10 months prior to transplantation.

During LT procedure there was a need for vasopressor support with norepinephrine (NE) and fluid administration, giving 6 litre fluid in total, 3 packed cells and 0.718 litre blood through cell saver blood. After wound closure, vasopressor need increased. Upon arrival at the intensive care unit, NE dose was 0.32 µg/kg/min, Terlipressin was started on postoperative day one at a dose of 3mg/24h. Figure 1 shows the kinetics of vasopressor requirement in the postoperative period. [figure 1 near here]. Per local liver transplant immunosuppression protocol, daily mycophenolate mofetil 2x1000mg, methylprednisolone 20 mg, basiliximab 20 mg on day 0 and 4, and tacrolimus on day five were given. Because of persistent high vasopressor need, increasing creatinine levels despite positive fluid balance and progressive pleural effusion, a TTE was performed on postoperative day six. TTE revealed a markedly reduced LVEF of 15% (see Supplementary file 1). The cardiac enzyme assay revealed a discrete increase in hs-TnI (ng/L) and CK-MB (µg/L) on day one and two after transplantation (see Figure 2). [figure 2 near here]. The ECG showed no ST-T abnormalities. A pulse contour cardiac output (PiCCO) was placed, and a continuous infusion with dobutamine as inotropic therapy started at a dose of 2.5 µg/kg/min. Moreover, several episodes of atrial fibrillation complicated the postoperative period, which resolved after intravenous amiodarone.

Control TTE on postoperative day eleven showed improvement of the EF to 29%. At this moment, the patient was still on dobutamine (2.49 μg/kg/min). Further improvement was noted at week four in the liver-transplant ward with an improvement of the EF to 42% but generalised mild to moderate hypokinesia persisted. A cardiac MRI four months after LT showed an undifferentiated cardiomyopathy with slightly dilated left and right ventricle, moderately reduced left (34%) and mildly reduced right (44%) ventricular ejection fraction, and no late gadolinium enhancement meaning there was no myocardial scarring or fibrosis (see Supplementary File 2). A genetic panel performed to search for underlying susceptibility to cardiomyopathy returned negative. A 24-hour Holter recording revealed frequent atrial extrasystoles (15%), no other arrhythmias, and no QTc prolongation.

After the patient was transferred from the intensive care unit to the conventional ward, treatment for heart failure including a beta-blocker, ACE-I and spironolactone was initiated. Unfortunately, there were difficulties optimising heart failure therapy because of recurrent acute kidney injury and hyperkalaemia. In addition, because of persistent symptomatic hypotension, ACE-I and spironolactone needed to be discontinued.

Four and a half months after the LT, the patient died unexpectedly at home. Cardiac arrhythmias are more prevalent in patients with post-LT LVSD, especially those with prolonged QTc [1]. Our patient had a prolonged preoperative QTc and postoperative complication of atrial

fibrillation, both risk factors for developing ventricular arrhythmias and cardiac arrest [1, 3]. Cardiac arrhythmia seems plausible; however, Holter monitoring a few weeks prior showed no anomalies except frequent atrial extrasystoles. No approval for an autopsy was obtained from relatives. The cause of death, therefore, remains uncertain.

Differential diagnosis

The aetiology of HFrEF after LT is poorly defined in the literature. Most of the described cases of post-LT LVSD are attributed to (i) stress-induced cardiomyopathy, (ii) inadequate cardiac reserve due to cirrhotic cardiomyopathy, or (iii) overlap between the two [2, 3, 11]. Less frequent causes of heart failure in the perioperative period after LT include transfusion-associated circulatory overload, heart failure due to thrombotic complications, heart failure due to porto-pulmonary hypertension [12] and heart failure associated with tacrolimus [13].

The Mayo Clinic diagnostic criteria for stress cardiomyopathy include a combination of (i) transient left ventricular systolic dysfunction; (ii) absence of obstructive coronary disease; (iii) new electrocardiographic abnormalities or modest elevation in cardiac troponin, and (iv) the absence of pheochromocytoma or myocarditis [14]. Stress-induced cardiomyopathy is hypothesized to be caused by increased release of adrenergic hormones due to physical stress associated with LT. In cirrhotic cardiomyopathy an inadequate response to the increase in afterload (increasing

SVR) and preload (liberal fluid administration) results in increased left ventricular filling pressure and symptoms of heart failure [3]. Eyvazian et al. [2] differentiated between stress-induced cardiomyopathy and overt heart failure in cirrhotic cardiomyopathy by dividing patients into two groups. The first group recovered after 30 days, meaning LVEF > 50% and the second group did not recover after 30 days, meaning LVEF < 50%. A complete recovery of the LVEF after 30 days was deemed suggestive of stress cardiomyopathy.

In our case, the post-LT left ventricular systolic dysfunction was most likely due to an overlap between overt HF due to cirrhotic cardiomyopathy and stress-induced cardiomyopathy. A modest elevation in cardiac troponin and absence of coronary disease on coronary angiogram seven months prior suggest stress-induced cardiomyopathy. Unlike the definition for stress cardiomyopathy, LVEF did not completely resolve after 30 days. Incomplete recovery and pre-transplant TTE with borderline LVEF (50%) and diastolic dysfunction grade 2, suggest a contributing factor of cirrhotic cardiomyopathy. There may however be a considerable overlap between the clinical presentations of stress cardiomyopathy and cirrhotic cardiomyopathy. There is usually no demonstrable structural cardiomyocyte damage in both syndromes, also demonstrated by the absence of late gadolinium enhancement on cardiac MRI in our patient. This is why we prefer the general term ‘post-LT LVSD’ for a new onset of left ventricular systolic dysfunction after liver transplantation.

Discussion

Our case demonstrates that a pre-LT cardiac workup is paramount to ascertain if patients can tolerate this high-risk operation. Diastolic dysfunction predicts poor outcome in patients with cirrhosis, with a one-year survival rate of 95%, 79% and 39% in patients with grade 1, 2 and 3 diastolic dysfunction, respectively [1, 15]. After LT, diastolic dysfunction is an independent risk factor for mortality, graft failure and allograft rejection. This risk correlates with the grade of diastolic dysfunction. Nonetheless, grade 1 diastolic dysfunction is not associated with an increased mortality risk [15, 16]. Systolic dysfunction is mainly a predictor of late mortality and less of early outcome after LT [17]. Moon et al. [17] showed that a combination of left ventricular diastolic and systolic dysfunction predicts early and late outcome better than evaluated separately.

Most standard cardiac workups include TTE and ECG. DSE is often performed when diastolic, systolic dysfunction, or both are present on TTE. A major limitation of DSE is that most patients eligible for LT have difficulties reaching the target heart rate on exercise and pharmacological stress testing [18]. The latest guidelines of the American Heart Association (AHA) advise against using DSE to detect coronary heart disease (CHD). The sensitivity of DSE to detect CHD in liver transplant candidates is low (13-37%) and has a negative predictive value of 75-80%. When CHD is suspected, coronary computed tomography angiography (CCTA) or coronary angiogram should be performed. There may, however, still be a place for DSE to detect a blunted

cardiac response to dobutamine stimulation for evaluating LVSD in cirrhotic patients [19]. However, the same limitation applies here; most patients eligible for LT are not able to reach the target heart rate. Stress imaging with cardiac MRI is an emerging imaging modality with significantly better sensitivity to detect abnormal inotropic responses to stress [11, 18]. Gadolinium-enhanced cardiac MRI can identify myocardial fibrosis and oedema [20].

There is limited data on the management of LVSD in cirrhotic patients in the pre-, peri- and post-transplant period. Sonny et al. [4] stated that preoperative beta-blockers could improve post-LT LVSD. Premkumar et al. [21] showed promising results with combination therapy of carvedilol and ivabradine. A better understanding of the pathophysiology of cirrhotic cardiomyopathy could aid in the management of cirrhotic cardiomyopathy [7]. Mild to moderate systolic or diastolic dysfunction is not an absolute contraindication for LT, especially as LVSD, cirrhotic cardiomyopathy, is expected to improve post-LT [3, 22].

Conclusion and recommendation

Standard cardiac workup before LT should include TTE and ECG. If systolic dysfunction is present, coronary angiogram must be performed to exclude coronary artery disease. Stress cardiac imaging, either dobutamine echocardiography or stress cardiac MRI, can be of additional use to detect a blunted cardiac response to stress if moderate or severe diastolic dysfunction (grade

2 or 3), systolic dysfunction, or both are present on TTE. Mild to moderate heart failure is not an absolute contraindication for LT, but these patients should be monitored more closely. Systematically planning a TTE after 3-5 days post-LT should be considered in patients with pre-LT moderate or severe diastolic dysfunction or any grade of systolic dysfunction. Earlier identification of post-LT HF could help to start adequate therapy sooner and improve outcome [4]. Monitoring the fluid balance even more carefully in these patients could prevent undesired hypervolemia. The optimal pre- and postoperative treatment in patients with cirrhosis and LVSD is something that should be investigated further.

There is still a significant difference in how transplant centres evaluate peri- and post-transplant cardiac risk. Clear guidelines on standardized cardiologic workup and cardiac criteria for exclusion for LT or optimal perioperative treatment are lacking [10]. We propose that patients on a liver-transplant waiting list with LVSD or moderate to severe diastolic dysfunction should be followed by a multidisciplinary team, including a dedicated cardiology team experienced in managing liver-related cardiac pathology. A more standardized method could help allocate the limited available livers and improve clinical outcomes.

Disclosure Statement

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Abbreviations (in order of appearance)

LT = liver transplantation

CVE = cardiovascular events

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NASH = non-alcoholic steatohepatitis

SVR = systemic vascular resistance

TTE = transthoracic echocardiography

ECG = electrocardiogram

DSE = dobutamine stress echocardiography

MELD = Model for End- stage Liver Disease score

TIPS = transjugular intrahepatic portosystemic shunt

NE = norepinephrine

PiCCO = pulse contour cardiac output

CHD = coronary heart disease

CCTA = computed tomography angiography

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Tables and figures

Hemoglobin (g/dL)	8,0
Trombocytes (mm^3)	100
INR	1.53
Creatinine (mg/dL)	1.30
Natrium (mEq/L)	141
Bilirubin (mg/dL)	4.70
Albumin (g/L)	20
MELD	14
MELD-Na	14
Child-Pugh	C10

Table. 1 *Blood sample 1 week prior to transplantation*

		Echocardiography				
	cutt-off normal values	pre-LT	D6	D11	D26	D106
LVEF (%)	> 55	50	15	29	42	45
E/A	< 1	2.26	/	0.69	0.69	0.67
E/E'	< 14	15.50	/	11.64	6.17	7.05
PAP (mmHg)	< 30	32	40	normal	normal	normal

Table. 2 *Evolution of the echocardiographic parameters*

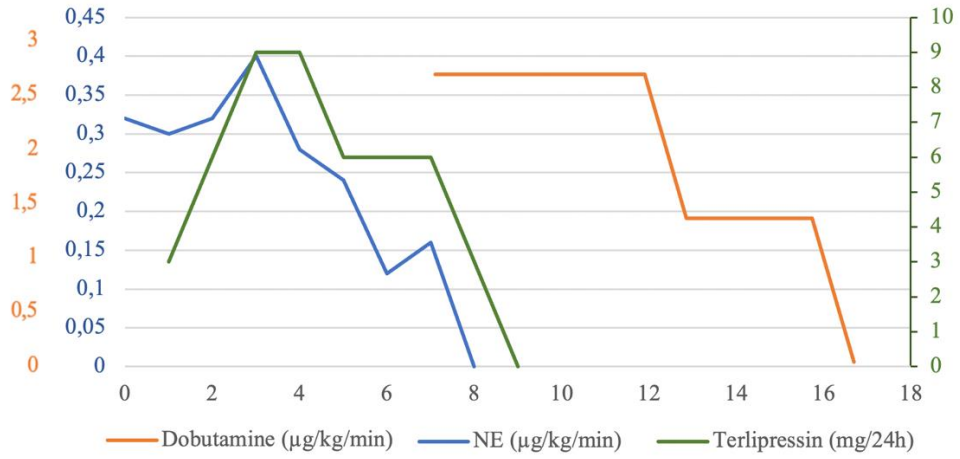


Fig 1. Vasopressor medication in the postoperative period
x-axis representing the postoperative days
y-axis dose dobutamine (µg/kg/min), NE (µg/kg/min) and terlipressin (mg/24u)

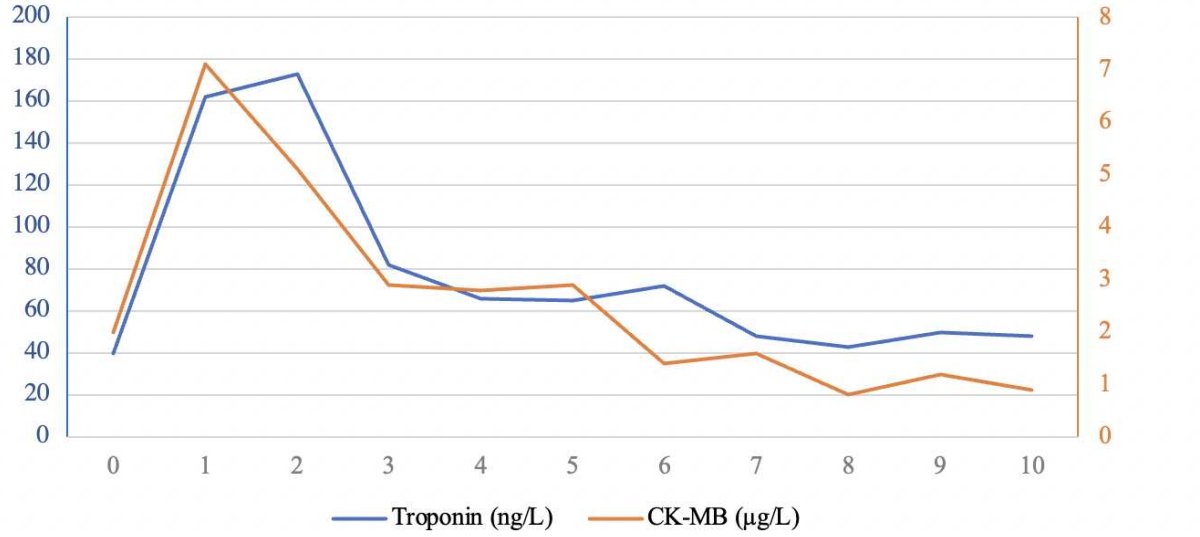
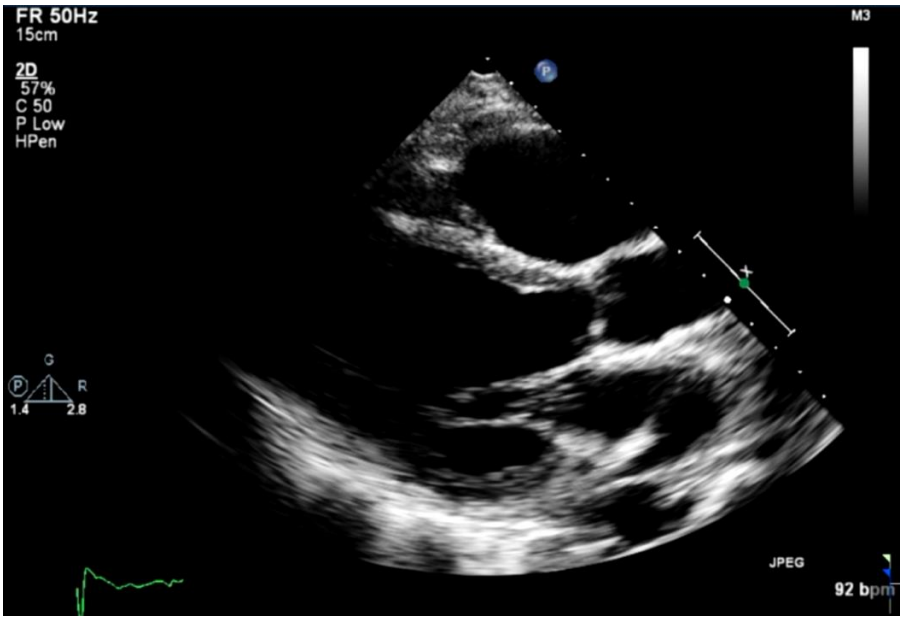
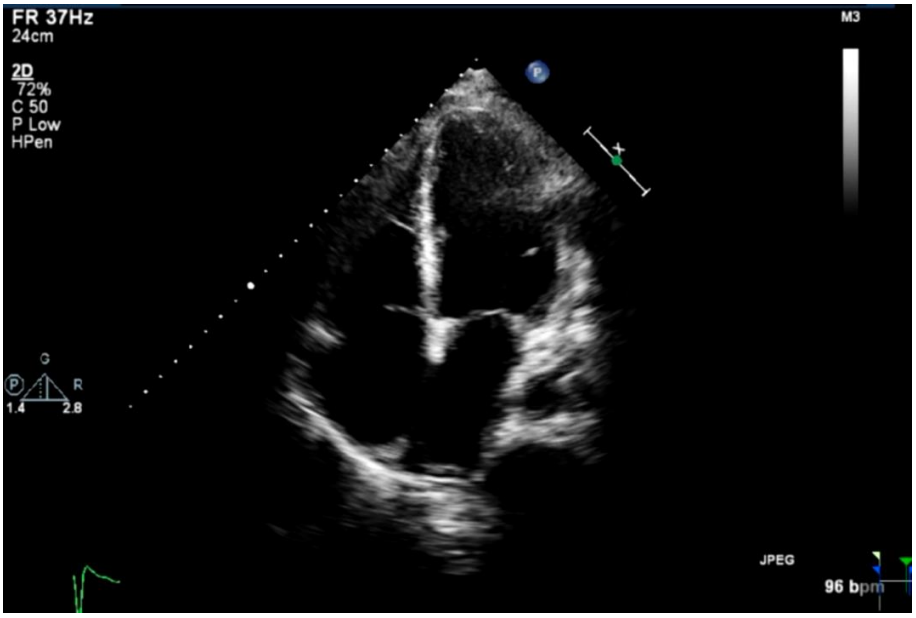


Fig 2. Evolution of cardiac enzymes in the postoperative period
x-axis representing the postoperative days
y-axis dose cardiac enzymes level: troponin (ng/L), CK-MB (µg/L)

Supplementary file 1





Supplementary file 2