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Levosimendan for acute right heart failure in COVID-19: another arrow in our quiver?

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Abstract. – OBJECTIVE: SARS-CoV-2 infection is associated with a higher risk of acute right heart failure (RHF) due to primary right ventricle (RV) dilation and systemic inflammatory response, which in turn lead to microvascular and cardiomyocytes dysfunction, local hypoxia and multi-organ failure. In this clinical setting, levosimendan could be a viable therapy thanks to its right-heart tropism and its additional pleiotropic properties.

CASE REPORT: We present the case of a 72 years-old man with positive nasopharyngeal swab for SARS-CoV-2 infection, mild pulmonary involvement and clinical signs of new-onset RHF. We started a 12-hour levosimendan cycle to improve RV performance and reduce cardiac filling pressures.

RESULTS: We obtained a net clinical benefit in terms of acute RHF-related signs and symptoms, progressive renal and liver function improvement and concomitant reduction of high-sensitivity C-Reactive Protein and Interleukin-6 (IL-6) levels.

CONCLUSIONS: Acute RHF during SARS-CoV-2 infection could be related to a convergent widespread systemic inflammatory response. Thanks to its anti-inflammatory and anti-remodeling properties, levosimendan might represent a viable therapy in this clinical setting, contributing to the dampening of the inflammatory response.

Key Words:
Acute right heart failure, SARS-CoV-2, Levosimendan, Cytokine storm, Personalized medicine.

Case Report

A 72-year-old male patient was admitted to our Emergency Department for fatigue, worsening dyspnea (NYHA class III) and abdominal distension. He had a medical history of chronic obstructive pulmonary disease and coronary artery disease with multiple previous percutaneous coronary interventions, and subsequent implantation of a single-chamber pacemaker (PM) for brady-atrial fibrillation. On last follow-up, the transtoracic echocardiogram (TTE) showed normal biventricular function, and the PM check showed less than 30% of right ventricular (RV) pacing.

On admission, a nasopharyngeal swab confirmed SARS-CoV-2 infection. A chest computed tomography (CT) scan was performed, showing bilateral Covid-related pneumonia, enlarged right heart chambers without evidence of acute pulmonary embolism. An abdominal CT scan also was performed, showing ascites, hepatomegaly and signs of cardiogenic cirrhosis, in absence of other causes of hepatic congestion.

An arterial blood gas analysis was performed, without oxygen support, showing near-normal blood gas levels (pH 7.37, pCO_2 36 mmHg, pO_2 93.6 mmHg, SpO_2 97.7%, lactate 1.5 mmol/L, HCO3 21.6 mmol/L). The electrocardiogram revealed atrial fibrillation, right bundle branch block and signs of previous inferior myocardial infarction.

A cycle of parenteral diuretic therapy together with low molecular weight heparin started and the patient was transferred to our Cardiology Department for further investigation.

During the first days of hospitalization, the patient did not experience any clinical sign or symptom of severe lung involvement. A maximum 40%-fraction of inspired oxygen (FiO_2) was provided, with good blood oxygenation and normal arterial oxygen saturation. Laboratory findings are reported in Table I.

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Table I. Laboratory findings.

Variable	Admission	III day	VII day	X day	XI day	XII day	XV day	On discharge	Normal range
Creatinine	1.02	0.92	0.93	1.19	1.25	1.01	1.07	0.8	0.67-1.17 mg/dL
Glutamic oxalo acetic transaminase	44	18	17	20	17	26	18	17	7-45 UI/L
Glutamic-pyruvic transaminase	22	25	14	13	18	18	20	26	7-45 UI/L
Alkaline phosphatase	49	400	301	288	302	397	304	397	40-129 UI/L
yGlutamyl Transferase	67	317	379	356	520	573	408	573	8-61 UI/L
Total bilirubin	2	2	1.9	1.9	1.8	2	1.8	2	0.3-1.2 mg/dL
Hemoglobin	14.2	10.5	10.7	11.8	10.8	11.4	11.5	11.4	13.0-17.0 g/dL
White blood cell count	3.60	4.38	4.55	8.61	6.7	8.73	10.8	11.98	4.00-10.00 $\times 10^9$/L
Neutrophil granulocytes $\times 10^9$/L	2.80	2.63	2.97	7.8	5.49	7.34	8.1	9.57	2.00-7.00 $\times 10^9$/L
Lymphocytes $\times 10^9$/L	0.57	1.06	1.13	8.1	0.64	0.97	0.01	1.7	1.00-3.00 $\times 10^9$/L
Neutrophil granulocytes %	77.8	60.1	65.3	86.2	5.49	84.1	78.8	79.9	40.0-80.0%
Lymphocytes %	15.9	24.3	24.7	8.1	0.64	11.1	13.6	14.2	20.0-40.0%
Platelets	110	214	210	241	202	261	338	294	150-450 $\times 10^9$/L
International normalized ratio (INR)	2.08	1.4	1.2	1.1	1.17	1.46	1.06	1.02	0.80-1.20
Activated partial thromboplastin time	63.5	39.1	53.2	45	50	45.3	41	39.1	20.0-38.0 s
Fibrinogen	453	385	400	385	342	400	392	392	200-400 mg/dL
D-dimer	577	341	648	605	190	379	624	649	< 500 ng/mL
NT-pro BNP	211	3,459	3,574	3,000	2,800	3,208	2,901	2,759	< 150 pg/mL
C-reactive protein	126.7	135	104	99	75	58	42	7.5	< 5.0 mg/L
Procalcitonin	0.19	00.2	0.01	0.01	0.01	0.01	0.01	00.7	< 0.5 mg/L
IL-6	5.1	45	58	62	50	5.1	3.4	3.6	<4.4 ng/L

TTE showed an isolated acute RHF with a severely dilated and dysfunction RV (due to a both radial and longitudinal reduced performance), a torrential functional tricuspid regurgitation (TR) (due to a 20 mm coaptation gap of the leaflets), together with systo-diastolic D-shape deformation (flattening) of the septum, indicative of RV pressure and volume overload, a marked dilated inferior vena cava with no respiratory changes and hepatic systolic flow reversal. A mildly reduced left ventricle ejection fraction was observed (52%, due to ventricular interdependence), in absence of other relevant valvular diseases. Common causes of secondary pulmonary hypertension (PH) were excluded.

Oxygen supply and diuretic infusional therapy were optimized. Due to SARS-CoV-2 disease and the lung involvement, a right-heart catheterization was not performed.

Despite the parenteral diuretic therapy, in the subsequent days the patient experienced worsening of symptoms with increased respiratory distress and pulmonary edema due to a further worsening of RHF. For this reason, we decided to start a 12 hour-Levosimendan cycle in addition to diuretic therapy in order to improve RV function and consequently reduce cardiac filling pressures and PH.

The subsequent echocardiographic re-evaluation confirmed the previous findings, particularly the RV dilatation and the massive TR, but showed a significant partial recovery of both longitudinal and radial RV function (with a moderate global dysfunction).

Moreover, systemic levels of interleukin-6 (IL-6) significantly reduced (Figure 1). Blood gas exchanges and RHF-related symptoms progressively improved together with a reduction of ascites. Consequently, we switched to an oral diuretic therapy, the oxygen therapy was discontinued, and the patient was finally discharged.

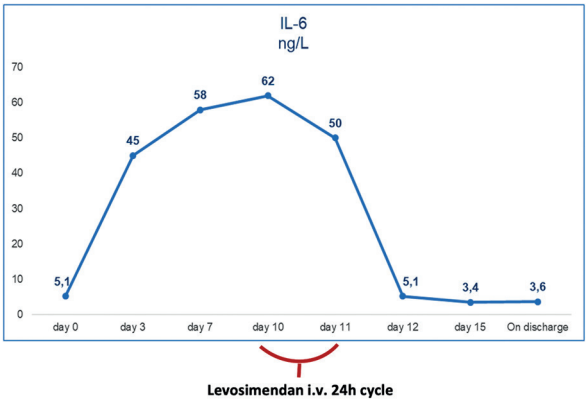

Figure 1. IL-6 trend during hospitalization and after Levosimendan.

Discussion

This paper presents a case of new onset isolated RHF related to SARS-CoV2-infection with mild pulmonary involvement, successfully treated with levosimendan by virtue of its pleiotropic anti-inflammatory, anti-oxidative and anti-apoptotic properties[1].

Recent evidence[3,4] extend the classic paradigm of acute heart failure (HF) from an exclusive problem of low cardiac output to a complex syndrome comprising, among the others, an exaggerated inflammatory response. The progressive failing myocardium represents itself a major source of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, which perpetuate the myocardial damage and provoke the transition from asymptomatic to symptomatic heart failure by depressing myocardial contractility and promoting cardiomyocyte apoptosis and adverse remodeling. HF patients show an immune imbalance due to increased levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, and reduced production of counter-regulatory mediators, such as IL-10. Moreover, evidence in literature suggest that IL-6 levels are an independent predictor of RV dilation, correlating with the severity of myocardial injury, and, together with TNF-α, it modulates adrenergic system and cardiac sympathetic response[5,6].

The increased mortality in HF, beyond the general frailty, and the increased risk for venous thromboembolism and endothelial injury associated with blood stasis and reduced cardiac output, is related to an impaired immune response and a reduced hemodynamic ability to cope with more severe infections[6]. In this scenario, SARS-CoV-2 infection could exacerbate a pre-existing HF or trigger a new-onset HF as part of the clinical course of the infectious disease. Patients with previous history of HF are more prone to develop acute HF with significantly higher mortality. Also, arrhythmias occurring during hospitalization, both related to pre-existing heart disease and emerging as side-effect of COVID-19 medications, might precipitate acute HF[7].

Abnormal elevation of biomarkers of cardiac injury is a common finding during SARS-CoV-2 infection, due to a variety of direct and/or indirect mechanisms of myocardial injury, involving direct intracellular viral entry, enhanced systemic metabolic demand, pro-thrombotic and sympathetic pathways activation, severe hypoxia secondary to acute respiratory damage and oxidative stress. Of note, SARS-CoV-2 infection often develops in parallel to an uncontrolled inflammatory response called "cytokine-released syndrome", driven by IL-6 and other pro-inflammatory cytokines, and possibly leading to myocardial damage[8].

Acute RHF is defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced flow output with consequent chamber dilation, tricuspid regurgitation, hepatomegaly, ascites, peripheral oedema, and further RV dilation, which in turn affects LV filling, due to ventricular-interdependence, and leads, in the more advanced stages, to multi-organ failure. Most cases of RV failure follow existing or new-onset cardiac or pulmonary diseases or a combination of both.

SARS-CoV-2 infection may be associated with a higher risk of acute RHF due to the fragile cardiopulmonary imbalance secondary to the hypoxic vasoconstriction during pneumonia and/or acute or chronic thromboembolism. Nevertheless, recent evidence[2] suggest that a primary isolated RV radial dysfunction and dilation can be observed in COVID-19 affected patients, and this finding is strongly associated with an increased in-hospital mortality. Elevated pulmonary vascular resistance from acute respiratory distress syndrome and/or pulmonary embolism, negative inotropic effects of cytokines, micro- and macro-vascular dysfunction, direct angiotensin-converting enzyme 2 (ACE2)-mediated cardiac injury from SARS-CoV-2 infection are potential mechanisms invoked for RV dysfunction, in addiction to loss of ACE2-mediated anti-inflammatory and cardiac protective properties[2].

Benefits of levosimendan on RV systo-diastolic function are well known in literature, but its effects in several clinical context, including HF during SARS-CoV-2 infection, are still unexplored[9]. Levosimendan exhibits additional anti-inflammatory effects on cardiac myocytes and endothelial cells by attenuating IL-1β-induced expression of IL-6 and IL-8 in human adult cardiac myocytes, as well as adhesion proteins in endothelial cells[10]. It also attenuates adverse cardiac remodeling by turning-off IL-1β-induced reactive oxygen species production and nuclear factor-kappa B activation with anti-apoptotic effects, and by modulating the expression of several genes, including those involved the renin-angiotensin-aldosterone system. Moreover, it seems to act on extracellular matrix metabolism, by reducing the levels of myocardial IL-6, monocyte chemo-attractant proteins, connective tissue growth factors and matrix metalloproteinases[11,12].

Conclusions

Although further data are needed, this case, consistently with current evidence in literature, suggests a potential role for levosimendan as the preferred inotropic drug for the treatment of acute RHF during SARS-CoV-2 infection, thanks to its pleiotropic properties consisting in the dampening of the systemic inflammatory response and the modulation of adverse cardiac remodeling.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed consent has been obtained from the patient in accordance with istitutional policy Fondazione Policlinico Gemelli n.153 (25/december/ 2020).

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