Ultrasound assessment of diaphragmatic dysfunction and its improvement with levosimendan in patients with chronic obstructive pulmonary disease

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Key words: COPD; diaphragmatic dysfunction; diaphragmatic ultrasound; levosimendan.

Contributions: CADR, carried on and developed the trial, by performing ultrasound assessments and elaborating the following data; GC, was in charge of the patient at that time, established her therapy and followed the effects over time; MG, got the idea to test this particular drug, levosimendan, on this patient and to describe its role on diaphragm motility; GC, MG, both assisted CADR, every hour for bedside measurements.

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Abstract

Diaphragmatic Dysfunction (DD) is a clinical condition in which the diaphragm becomes weak or paralyzed, because of muscle strength reduction. It can be due to muscular issues or loss of proper innervation, but, also, to pulmonary hyperinflation or air trapping, such as in Chronic Obstructive Pulmonary Disease (COPD). DD impacts on COPD induced dyspnea, determining its progressive worsening, but levosimendan, an inodilator better known as Ca^{2+} *sensitizer*, may limit this phenomenon and diaphragmatic ultrasound assessment can be useful in monitoring its effect. Here, we show the case of a 77-year-old woman admitted to the Emergency department for acute exacerbation of chronic dyspnea in COPD, related to right ventricular failure and DD, which did not respond to medical therapy and non-invasive mechanical ventilation but did experience a favorable outcome after intravenous administration of levosimendan.

Introduction

An increased work of breathing in Chronic Obstructive Pulmonary Disease (COPD) leads to muscle fiber shift towards type I fibers and length shortening, which is an adaptive mechanism to maintain diaphragm strength and endurance. However, as soon as air trapping becomes unbearable, it can cause muscle fatigue and atrophy through the activation of the protease pathway by reactive oxygen species.[1] These aspects contribute to the development of COPD induced Diaphragmatic Dysfunction (DD), which is generally bilateral and related to lung hyperinflation. This has a negative clinical impact on survival and long-term outcomes, length of mechanical ventilation and difficulty in weaning.[2] Diaphragmatic ultrasound is a very useful tool to assess its entity: in the clinical case we present, we applied this technique to evaluate if continuous intravenous (i.v.) levosimendan infusion could stimulate diaphragm motility.

Case Report

A 77-year-old woman was carried to our emergency department for dyspnea, ongoing since the beginning of the week. She was a former smoker with a past history of COPD lacking follow-up visits, hypertension, diabetes mellitus type 2, chronic iron deficiency anemia, Chronic Kidney Disease (CKD) stage III, obesity (body weight: 85 kg). Her home therapy was based on oral antihypertensive, hypoglycemic and lipid-lowering drugs, P2Y-19 in primary prophylaxis, oral iron supplementation. She appeared confused, but awake and conscious. Her Oxygen saturation (SpO2) at the entrance was 75% on room air, so an Arterial Blood Gas (ABG)

test was soon collected before the application of nasal cannulae [fraction of inspired oxygen (FiO2) 35%] and then she was visited. ABG on room air showed respiratory and metabolic acidosis, for both hypercapnia and bicarbonate loss (pH 7.21, PaO_2 56 mmHg, $PaCO_2$ 52 mmHg, HCO_3^- 20.8 mmol/L, lactatemia 1.9 mmol/L, Na^+ 128 mEq/L, K^+ 5.6 mEq/L, Cl^- 98 mEq/L, P(A-a) O_2 29 mmHg, P/F 267 mmHg). Clinical examination showed valid heart sounds, normosphygmic peripheral pulses, pitting edema of the abdomen and legs; vesicular murmur was diffusely low. Point Of Care Ultrasounds (POCUS) revealed a bilateral B-profile with irregular pleural line, multiple consolidations and pleural effusion, more represented on the right chest (at least 1000 mL); the Inferior Vena Cava (IVC) was dilated and poorly collapsible with an inferior vena cava maximum diameter of 2.36 cm and an inferior vena cava minimum diameter of 2.10 cm, IVC index 11.01%. There was also right ventricle dilation with inefficient contractility, as confirmed by low tricuspid annular plane systolic excursion (TAPSE, <17 mm) and high pulmonary artery systolic pressures (PASP >40 mmHg), but only mildly reduced left ventricle ejection fraction (45%). Neither troponin raising curve nor D-dimer elevation were registered on blood analysis, but acute kidney injury on CKD, likely due to fluid accumulation in the venous compartment (urea 135 mg/dL and creatinine 2.44 mg/dL), and hyperkalemia (K^+ 6.3 mEq/L). The estimated glomerular filtration rate (e-GFR) was 20.4 mL/min/L.73 m^2 on Modification of Diet in Renal Disease (MDRD) formula.

In a clinical picture of acute exacerbation of COPD contributing to right ventricle dysfunction, O_2-therapy was soon upgraded to Non-Invasive Ventilation (NIV) [Pressure Support Ventilation (PSV) modality: PS 15 cmH_2O, PEEP 5 cmH_2O, F_iO_2 50%]. Inhaled bronchodilators and i.v. steroids were also administered; hyperkalemia was corrected with i.v. calcium gluconate 2 g, followed by 10 UI of the rapid insulin analogue lispro in 5% dextrose 500 mL and diuretic therapy with furosemide 40 mg. She was then hospitalized in our emergency medicine ward. There, since the first hours, in order to counteract the right ventricular failure and stimulate the renal function, diuretic therapy was potentiated by administering 2 vials of 20 mg furosemide, both after albumin 20% 50 mL at 2 pm and 3% hypertonic solution 150 mL boluses repeated twice, at 8 am and 8 pm. A urinary catheter was placed to control urinary output. She continued her home therapy, except for the oral hypoglycemic drug, which was substituted with a subcutaneous rapid insulin analogue.

However, the patient, in less than 24 hours, became little by little drowsy. At a new deeper bed-side ultrasound evaluation, something came up: her diaphragm was almost still, bilaterally. Diaphragmatic dysfunction was contributing to her clinical deterioration. Since it is possible to evaluate Diaphragmatic excursion (DE) through diaphragmatic ultrasound, as reported in current literature, we decided to study if levosimendan, known *Ca^{2+} sensitizer*, could ameliorate our patient's work of breathing by influencing diaphragm motion. In consideration of the possible reversibility of her acute worsening of chronic severe renal dysfunction, as displayed by the improvement in patient's renal function on the blood tests of that morning (urea 121 mg/dL, creatinine 2.0 mg/dl, e-GFR up to 26 mL/min/L.73 m^2 according to the MDRD formula) and the always active diuresis, we decided to administer the drug, although the e-GFR was still lower than 30 mL/min/L.73 m^2, knowing that levosimendan has been shown to increase renal blood perfusion in patients with congestive heart failure.[3,4]

Levosimendan was infused at 0,1 mcg/kg/min, 1 ampoule of 2.5 mg/mL (5 ml) in 50 ml of i.v. normal saline continuous infusion at 2.2 mL/H over 24 hours.

At the beginning of the infusion, our patient's was in a semi recumbent position, with a tendency to lie on her left hemisoma; Glasgow Coma Scale (GCS) 8/15, PA 120/90 mmHg, SR 80 bpm, SpO2 92%, in NIV [Assisted/Pressure Controlled Ventilation (A/PCV) modality: PInsp 20 cmH_2O, PEEP cmH_2O 7, FiO2 30%, RR 18/min, 100ms of ramp, I:E 1:2.5].

Every hour until the sixth hour after the start of levosimendan infusion, we performed a bilateral diaphragmatic ultrasound to describe DE. We decided to visualize the diaphragm using a low frequency convex probe (2.5-5.0 MHz) placed between the midclavicular and mean-axillary lines below the right subcostal margin,[5] for right hemidiaphragm views; the probe was instead placed between the anterior and posterior axillary lines on the lowest costs of left chest side for left hemidiaphragmatic motion recording.[5] The purpose was to visualize, in motion mode (M-mode), the maximal DE during our patient's quiet breathing (normal values range 10-25 mm during quiet breathing),[5] on both chest sides and calculate subsequently the right-to-left ratio of hemidiaphragmatic excursion (normal values range 0.5-1.6).[6] Every DE value was an average of three measurements per side of the inspiratory excursion (D1), to take into account not only normal breaths but also the ineffective efforts and double triggers of our patient, who was always fighting against the ventilator (Figures 1, 2, 3, 4).

We assisted to a progressive increase in DE since the start of levosimendan infusion, especially on the right hemidiaphragm: if DE was of 0,3 cm on the right chest before starting the infusion, six hours later its value was of 1.12 cm, although without a linear improvement. In fact, at Time 3 and 4, three and four hours since the start of infusion respectively, our DE values were lower than the previous ones. We did not register an important change in DE values on the left side, maybe because of the patient's position, which hampered good records. Anyway, the right-to-left ratio of maximal excursion changed from 0.392 before the start of infusion to 1.27 six hours after (Table 1).

Every six hours we also checked if any improvement in ABG was present. ABG test obtained before starting the infusion (Time 0, Table 2) was compared with the one corresponding to 6, 12 and 24 hours after the start of infusion (Time 6, 12 and 24, Table 2). Just six hours after, $PaCO_2$ had decreased, although without solving the acidemia because of persistent HCO_3^- loss (in CKD). Therefore, there has been a little but good increase of PaO_2 from 72 to 81 mmHg, despite the absence of P(A-a) O_2 reduction (72 vs 75 mmHg), perhaps because of the patient's hyperinflation. However, we saw P(A-a) O_2 reduction and pH level increase 24 hours later, at the end of infusion, when our patient was now awake, conscient and able to talk, GCS 15/15, thus we stopped levosimendan infusion. From that moment, we could start her weaning from NIV, alternating nasal cannulae O_2 3 L/min to PSV modality every three to four hours per day, with good tolerance by the patient.

Discussion

Different works have described the use of ultrasounds to evaluate diaphragm motility. We decided to visualize the diaphragm using a low frequency convex probe (2.5-5.0 MHz) between the hemi-clavear and mean-axillary lines on the right Subcostal Area (SCA), the anterior and posterior axillary lines on the lowest costs of the left chest side.[5] The diaphragm is showed in brightness mode as a deeply located curved structure that separates the thorax from the abdomen, where, in M-mode, it is possible to measure its inspiratory excursion in centimeters, the duration of its displacement in

seconds and the subsequent velocity.[5,6] During quiet breathing, DE has been described as good when it is between 10 mm and 25 mm on both sides.[5] Also, right inspiratory excursion can be compared to the left one, and a right-to-left ratio of maximal excursion outside a range of 0.5 to 1.6 has to be considered abnormal.[6] Another method to study the diaphragm on ultrasounds involves the use of a high-frequency linear probe (7.5-10.0 MHz) over the Zone Of Apposition (ZOA), where the diaphragm is identifiable as a three-layer structure which shortens and thickens during the phases of breathing. With this method, in M-mode, a different series of data can be collected to characterize diaphragm contractility: diaphragmatic Thickening (Tdi), the minimal muscle contraction, which rules out muscle atrophy if it is of at least 0.11-0.12 cm;[5,7] the Thickening Ratio (TR) between diaphragmatic Thickness in inspiration (Tdi insp) and expiration (Tdi exp): Tdi insp/Tdi esp, normal value >1.2 cm;[7,8,9] and the Thickening Fraction (TF), which is the difference between thickness in inspiration and expiration, divided by

Table 1. The average values of maximal diaphragmatic excursion in inspiration on both chest sides. Time 0: before starting the infusion; Time 1: 1 (one) hour after infusion start; Time 2: 2 (two) hours after infusion start; Time 3: 3 (three) hours after infusion start. Time 4: 4 (four) hours after infusion start. Time 5: 5 (five) hours after infusion start. Time 6: 6 (six) hours after infusion start.

	DE (cm) average		Right-to-left ratio average
	Right	Left	
Time 0	0.300	0.765	0.392
Time 1	0.740	0.797	0.928
Time 2	1.070	1.067	1.00
Time 3	0.927	1.020	0.909
Time 4	0.885	0.795	1.11
Time 5	1.047	1.027	1.02
Time 6	1.12	0.88	1.27

DE, Diaphragmatic excursion.

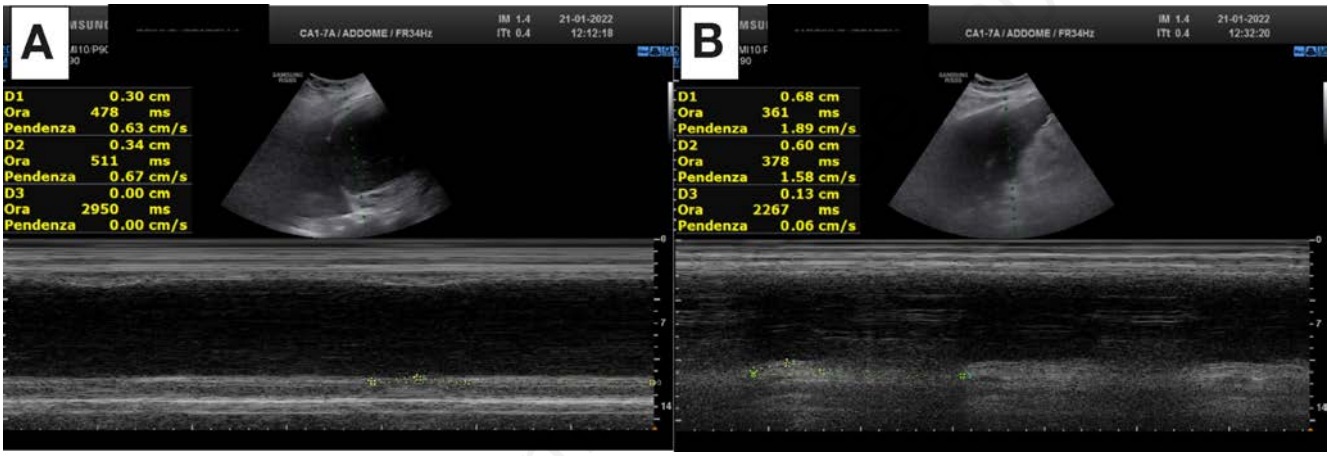

Figure 1. A) Time 0 (before starting the continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the right chest side; B) Time 0 (before starting the continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the left chest side.

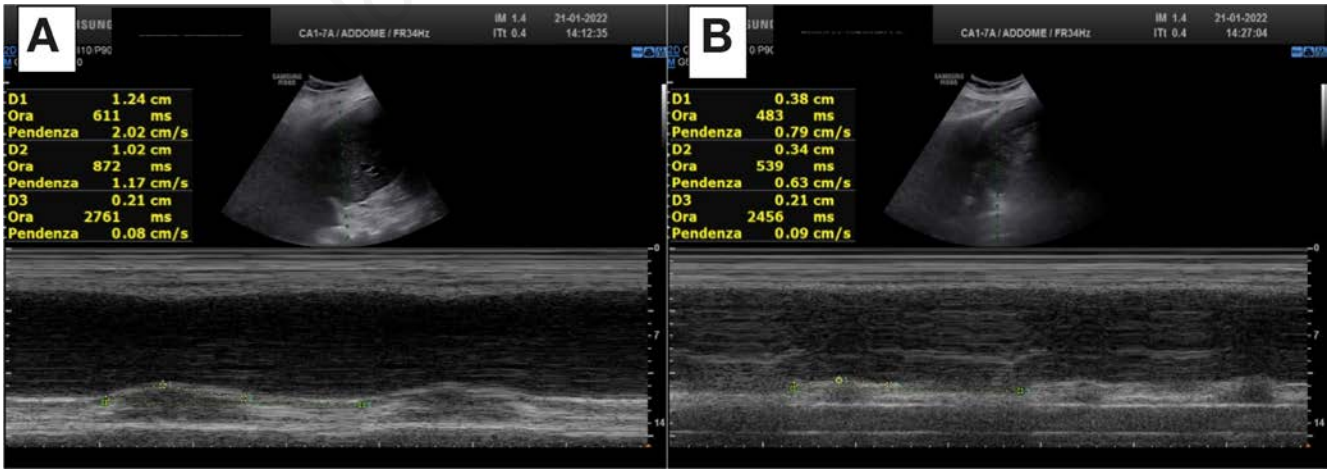

Figure 2. A) Time 1 (one hour after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the right chest side; B) Time 1 (one hour after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the left chest side.

thickness in expiration: [(Tdi insp – Tdi esp)/Tdi esp]*100, normal value >20%.[7]

The data we recorded showed a progressive improvement in diaphragm excursion on the right hemidiaphragm since the start of infusion, which was already more than 10 mm two hours after. There was also an increase of the right-to-left inspiratory excursion ratio, which entered the normal values range (0.5-1.6). No satisfactory results were registered on the patient's left hemidiaphragm, because the patient's position impeded a good ultrasound assessment, but the left DE values corresponding to the first hours might have been better than the contralateral ones because of less pleural effusion influencing diaphragmatic motility on left chest side.

Levosimendan is an inotrope, working to improve systolic function through the stabilization of calcium-troponin C interaction, with no influence on Ca^{2+} levels in cardiomyocytes nor VO_2 worsening,[4,10] with an absolute indication in acute decompensated heart failure when there has been no answer to cathecolamines.[11] It also mediates the opening of ATP-dependent K^+ channels in vascular smooth muscles, to improve coronary, pulmonary and peripheral perfusion, decrease cardiac filling pressure,[10] and determine lactate-to-piruvate ratio reduction.[4] Two isoforms of troponin C exist in muscle tissue: the cardiac/slow skeletal isoform, present in cardiac and slow-type skeletal muscle, and the fast skeletal isoform,

Table 2. Comparison between arterial blood gas test results at Time 0 (before infusion starting) and every six hours until the end of the continuous i.v. levosimendan infusion.

ABG test	Time 0	Time 6	Time 12	Time 24
pH	7.24	7.25	7.26	7.31
$PaCO_2$	56	46	49	53
PaO_2	72	81	81	86
SpO_2	97.2	98.6	98.9	98.2
HCO_{3-}	24	20.2	22.0	26.7

ABG, arterial blood gas.

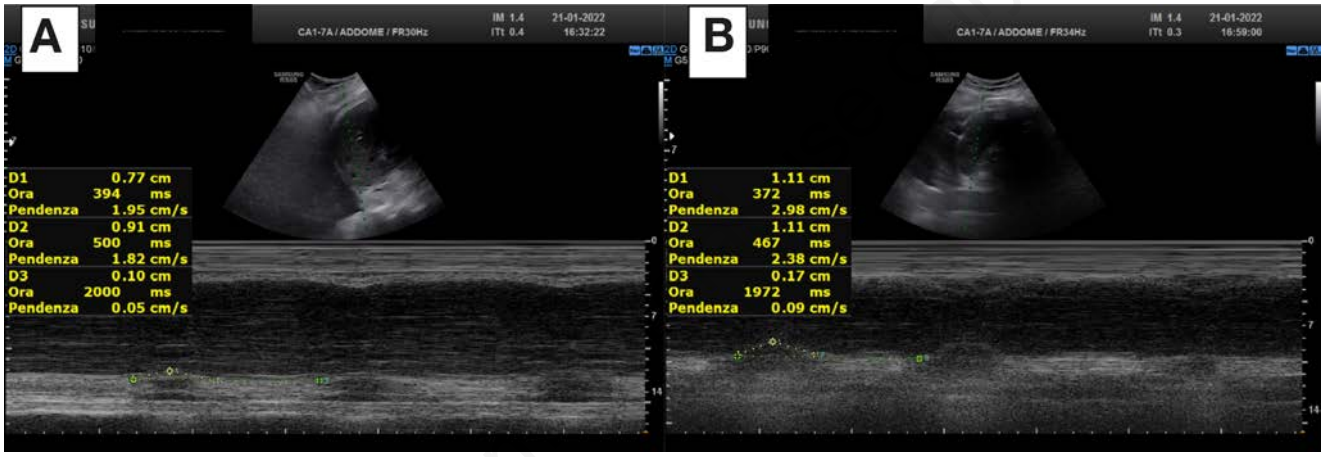

Figure 3. A) Time 3 (three hours after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the right chest side; B) Time 3 (three hours after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the left chest side.

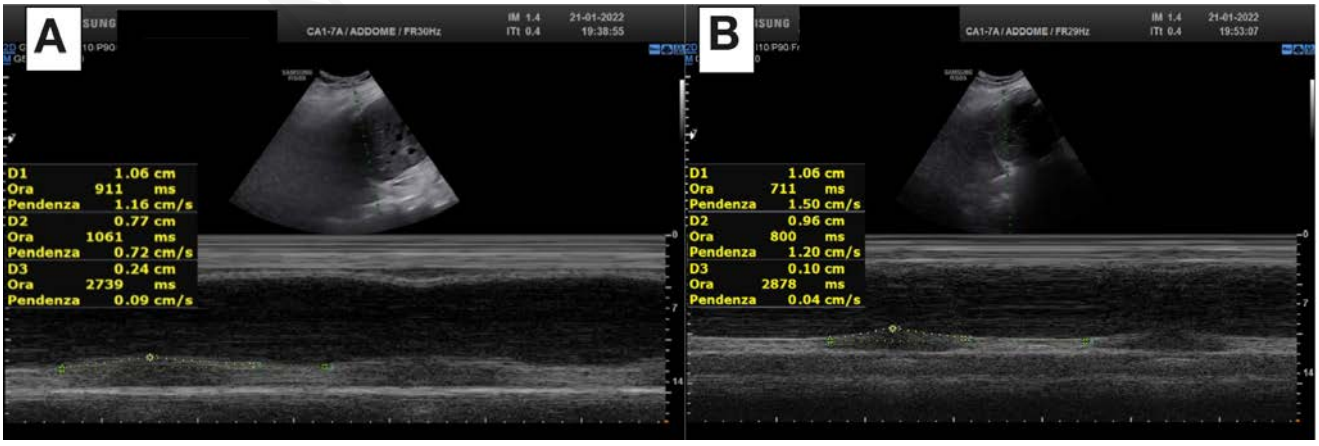

Figure 4. A) Time 6 (six hours after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the right chest side; B) Time 6 (six hours after the start of continuous-24 hours i.v. levosimendan infusion). D1 represents one out of three measurements per hour of diaphragm excursion in inspiration (cm), on the left chest side.

present in fast-type skeletal muscles. Levosimendan may interact with the slow troponin C in both the myocardium and the diaphragm, and the switch from diaphragm fast-type toward slow-type fibers, along with their quantity increase, promotes this interaction. Thus, an improvement in diaphragm efficiency could be established by generating the same amount of force with less calcium.[12]

In our trial levosimendan seemed to work; however, we cannot exclude that its benefits may be a consequence of the drug effect on the right ventricle contractility as well. In fact, the TAPSE value of our patient had improved during all our observation from 1.9 cm at time 0 up to 2.8 cm 24 hours later, although there had not been any variation in PASP value. Also, diuretic therapy was potentiated by administering a loop diuretic dose after 3% hypertonic saline in small boluses (150 mL) twice a day, according to the literature,[13,14] where it is suggested as an effective strategy against refractory volume overload. It could have stimulated our patient's renal function during all levosimendan infusion and worked synergistically to maintain her renal output.

We attributed the immediate muscle excursion improvement to levosimendan quick pharmacology: the drug has a short half-life (about 1-1.5 hours), which enables fast onset of action, and steady-state concentrations are reached within 4-8 hours, while, instead, its metabolites OR-1855 and OR-1896 accumulate slower over time and prolong the drug effect.[15,16] Their maximum concentration is seen on average 2 days after stopping a 24-hour infusion, their effect in reducing the filling pressures and enhancing myocardial contraction could last 7 days.[15] The drug pharmacokinetics in heart and liver failure patients is similar to the one in healthy subjects; instead, the metabolites half-life is longer in patients with severe renal failure, even 80-90 hours, especially if undergoing hemodialysis.[15,17]

Eventually, we stopped levosimendan infusion after 24 hours, according to the guidelines, because we had already got an optimal result on our patient's work of breathing and consciousness. Could it have meant something different to our patient if levosimendan infusion was prolonged and the effect still monitored until 48 or 72 hours later? What impact did the patient's GCS's improvement in cognitive function from 8 to 15 have on the diaphragm's motility?

To really understand the role of levosimendan in stimulating the diaphragm, it should be tested on more patients, maybe affected by COPD only, with no subsequent CHF and without CKD, and its action should be compared between those who need and those who do not necessitate NIV. We do not know, in fact, if positive pressures have somehow influenced our patient's muscle contractility, since our first diaphragm scans have been performed after the beginning of NIV.We must say that levosimendan has already been tested *in vivo*, where it greatly worked to improve human diaphragm neuromechanical efficiency by 21% during loaded breathing.[18] In another trial, when administered to patients in continuous positive airway pressure, it seemed to increase tidal volumes, along with $PaCO_2$ reduction, but with no effect on diaphragm contractile efficiency.[19] In our case report, despite the factors that could have influenced the results, not only we confirmed the efficacy of levosimendan as a *Ca^{2+} sensitizer* on diaphragm muscle, but we also focused on the role of diaphragmatic ultrasound as a very useful instrument to control its effect at the patient's bed side.

Conclusions

Diaphragmatic ultrasound is an essential instrument in the bedside assessment of COPD induced DD. Levosimendan continuous i.v. infusion seems to reduce its entity by improving DE on ultrasound scannings since the very few hours of administration, with a subsequent $PaCO_2$ and P(A-a) O_2 reduction on ABG tests.

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