Microcirculatory effects of norepinephrine in patients with septic shock: a microdialysis study

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Research

Keywords: Septic shock, Norepinephrine, Microcirculation, Microdialysis

Posted Date: March 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17259/v1

Abstract

Background: The management of septic shock requires the administration of an alpha-adrenergic drug such as norepinephrine, after optimization of the patient's preload, to maintain adequate mean arterial pressure. Nevertheless, with optimal macrocirculatory parameters, alterations of tissue perfusion can occur. This study aimed to investigate the effect of norepinephrine dosage on microcirculation parameters, studied by microdialysis, in patients with septic shock.

Methods: We conducted a retrospective study. We included all patients aged over 16 years in septic shock. We studied three groups (levosimendan, dobutamine, and control group). We administrated norepinephrine before inclusion, at stable flow for more than an hour. We performed hemodynamic monitoring of macrocirculation by echocardiography. We analyzed microcirculation parameters (lactate, pyruvate, and lactate/pyruvate ratio) every six hours during the first three days, by muscle microdialysis (CMA 600, CMA microdialysis AB, Stockholm, Sweden). We studied correlations between microcirculation parameters and norepinephrine doses.

Results: We included thirty patients in the study (ten patients in each group). Demographic characteristics and mortality were comparable across the three groups. In total, we analyzed 390 samples of interstitial muscle fluid. We did not find any correlation between norepinephrine doses and the lactate concentration in the muscle, as well as the ratio of lactate/ pyruvate concentration in the muscle ($p > 0.05$) for all groups. We found a weak inverse correlation between norepinephrine doses and muscle pyruvate levels ($p < 0.05$) for the dobutamine group and the control group and but not for the levosimendan group.

Conclusions: Noradrenaline dose has little effect on microcirculation when administered for hemodynamic optimization, as recommended by the Surviving Sepsis Campaign.

Background

Severe sepsis is frequent in intensive care units and remains a significant public health problem due to considerable morbidity and mortality [1,2]. This high mortality is related to multiple-system organ failure due to septic shock [3]. Mechanisms involved are perfusion anomalies, cellular injury, and alteration of metabolic chains [4,5]. Although early hemodynamic optimization reduces mortality after a septic shock [6], the risk of multiple-organ failure remains high. Some new therapeutic protocols reduced this mortality by the improvement of the microcirculatory and the mitochondrial dysfunction [4]. The optimization of macrocirculatory parameters is not sufficient to maintain perfusion and tissue oxygenation [7,8].

Recently, a considerable literature has grown up around the theme of microcirculation. Microcirculatory perfusion alterations may occur despite hemodynamic optimization [9]. A growing field of experimentation on microcirculatory and metabolic changes during septic shock has developed in recent years [10,11]. Microdialysis allowed a quantitative evaluation of tissue metabolic changes by the concentration measurement of the biomarkers present in the interstitial tissue of many organs (brain, subcutaneous tissue, muscle, lung, myocardium) [11–13].

The restoration of the arterial oxygen transport function depends on the regulation of cardiac output and mean arterial pressure (MAP) that reflects organ perfusion. The adjunction of a vasopressor treatment should be started immediately in case of non-restoration of the MAP after fluid resuscitation [14]. Few studies have focused on the effect of noradrenaline on microcirculation.

This study aimed to investigate the effect of norepinephrine dosage on microcirculation in patients with septic shock.

Methods

We conducted a retrospective study in the anesthesiology and critical care department of The Military Hospital of Tunis. We analyzed the patients' database of Meddeb et al. study [15]. This study was conducted from August 2011 to May 2014.

After approval of the hospital ethics committee, the patient was included according to the emergency procedure or after receiving his family agreement. In all cases, we asked for the final consent of the patient or his family subsequently before the definitive inclusion.

We included in the study, all patients over the age of 16 years in septic shock defined by the Bone criteria of the consensus conference of the American College of Chest Physicians / Society of Critical Care Medicine (ACCP/ SCCM) of 1991 [16].

We carried out fluid challenges until reaching a total volume of 20 to 40 ml/kg of crystalloids or colloids. The therapeutic objectives were a MAP greater than 65 mm Hg, a diuresis greater than 0.5 ml/kg/h, and a lactatemia less than 2 mmol/l. In case of failure, we used norepinephrine to optimize the hemodynamic state. To be included, patients must be sedated, intubated and under mechanical ventilation support.

After inclusion, the patients were randomized using a randomization table in three groups:

- Dobutamine group: each patient received continuous perfusion of dobutamine using an electric syringe pump at a rate of 5 µg/kg per minute for at least three days.
- Levosimendan group: each patient received continuous perfusion of levosimendan using an electric syringe pump at a rate of 0.2 µg/kg per minute for 24 hours then continuous perfusion with an electric syringe pump of normal saline solution for 48 hours.
- Control group: 10 patients who were not on inotropes.

We did not include moribund patients (age <18 years, pregnant women, uncontrolled hemorrhage, history of cardiopathy, and/or severe heart failure). The exclusion criterion was a decision to limit care for the first 48 hours. The principle of the study was to analyze the effect of vasopressors on microcirculation in patients with septic shock resuscitated and stabilized according to the recommendations of Surviving Sepsis Campaign (SSC) 2002 [17].

Sedation was conducted with continuous perfusions of midazolam and remifentanil. The goal was a Ramsay score of 4 to 5. Firstly, all the patients were under a probabilistic intravenous antibiotic therapy that was adapted secondly, to the infectious site and the eventual germs found. We performed veno-venous hemofiltration or conventional dialysis in patients with acute oligo-anuric renal failure. Attending physician did not have any information on the results of the microdialysis until study end. We collected the data on a notebook that bears the patient's name, the patient's history, the starting point of sepsis, the responsible germs, and the Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score (SAPS II), the duration of septic shock, the duration of mechanical ventilation, the discharge status from the intensive care unit (whether alive or dead).

Every six hours, we measured hemoglobin and blood glucose levels every six hours and collected arterial samples to analyze blood gases and lactates. We performed hemodynamic and classic parameters monitoring by a Swan-Ganz catheter. We collected macrocirculation data, the dose of norepinephrine required, and the corresponding microcirculation data (lactate and pyruvate concentration in the interstitial tissue) every six hours during the first five days, by muscle microdialysis. We used for the analysis a microdialysis machine (CMA600, CMA Microdialysis AB, Stockholm, Sweden). The lactate/pyruvate ratio was calculated automatically by the machine.

The primary endpoint was the correlation between the administered dose of norepinephrine and the microcirculatory metabolic parameters (lactate, pyruvate, and muscle lactate pyruvate ratio) measured by microdialysis.

We expressed qualitative variables in number and percentage. We applied Pearson-Fischer Chi-square tests to these variables. We used the Kolmogorov-Smirnov test to evaluate the normality of the distribution of continuous variables. We presented continuous variables as mean and standard deviations of either the mean or the median (interquartile range), depending on the normality of the distribution. We used the ANOVA test for analysis of variance when appropriate. We assessed correlations between quantitative variables with Pearson's r test or Spearman test based on the normality of variables.

The correlation was assessed according to the significance threshold (*p)* and the Pearson's r coefficient or Spearman's rho in:

- Strong correlation: [- 1, - 0.75] [0.75, 1]
- Average correlation:] –0.75, - 0.5] [0.5, 0.75 [
- Weak correlation:]–0.5, 0 [] 0, 0.5 [
- Zero correlation: r or rho = 0

These tests were two-tailed with a significance threshold (*p)* set at 0.05.

Results

We included 30 patients. We analyzed 3 groups with 10 patients for each group (Figure 1). The mortality was 43 % (13 patients). We did not find a statistically significant difference between these three groups regarding sex, weight, height, the Simplified Acute Physiology Score (SAPS II), high blood pressure, diabetes, dyslipidemia, and sepsis site. Table 1 presents the patients' demographic characteristics.

We analyzed 390 samples of muscle lactate and pyruvate by microdialysis. The number of micro vials with insufficient samples for the analysis of muscle lactate and pyruvate by microdialysis was respectively 19 and 31. Finally, we respectively analyzed 371 and 359 muscle lactate and pyruvate samples by microdialysis. We calculated 356 ratios of muscle lactate/pyruvate (Table 2).

We did not find a correlation between the norepinephrine dose and the muscle lactate level ($p > 0.05$) for all groups: control, dobutamine, levosimendan and when analyzing all patients included in the study (Figure 2). We observed a weak inverse correlation for the control group and the dobutamine group between the norepinephrine dose and muscle pyruvate (Figure 3).

We did not find a correlation between norepinephrine dose and lactate pyruvate muscle ratio ($p > 0.05$) for all groups: control, dobutamine, levosimendan, and during the analysis of all patients included in the study. (Figure 4).

Discussion

We did not find a statistically significant difference between the norepinephrine dose and the lactate concentration in the muscle, as well as the ratio of lactate/pyruvate concentration in the muscle. A weak inverse correlation between the norepinephrine dose and the muscle pyruvate concentration was observed for the levosimendan group, the dobutamine group, and all patients included in the study.

The use of vasopressors is widespread in the intensive care unit. However, the benefit/risk balance for vasopressors should guide their administration. They may cause excessive vasoconstriction and alter microcirculation and tissue perfusion. We found that norepinephrine dose rate, used for macrocirculation optimization according to the Surviving Sepsis Campaign recommendations, has little effect on microcirculation. Our findings are consistent with those of Jihanial et al [18]. However, an excessive administration of norepinephrine to increase mean arterial blood pressure above 75 mmHg may alter the microcirculation [19,20]. Another study has shown that hemodynamic optimization with norepinephrine improves regional tissue perfusion [21].

The hyperlactatemia in patients in the intensive care unit and particularly in septic shock, was interpreted as a marker of anaerobic metabolism secondary to inadequate oxygen supply that induces cellular distress [22]. Many arguments are contradictory to this explanation [18]. The advent in the clinical practice of muscle microdialysis has allowed progress in understanding the mechanisms of lactate formation in shock. In our study, we found no statistically significant difference between the norepinephrine dose and lactate concentration in the muscle ($p> 0.05$) for all groups: levosimendan, dobutamine, control and during the analysis of all patients included in the study.

The glycolysis accentuation results from the glycogenolysis stimulation of and the glycogen-synthetase inhibition by the sepsis inflammation mediators [24,25]. The aerobic glycolysis result in an increase in pyruvate levels which is transformed into lactates by a mass effect as described by Gore et al. [24]. These reactions occur in the presence of oxygen thus, independently of microcirculatory blood flow.

Michaeli et al [12] evaluated, by muscle microdialysis, the clearance profile of muscle lactate and systemic lactate in healthy volunteers who have received attenuated endotoxin (LPS). The authors concluded that the metabolic response to endotoxemia increases plasma lactate levels ($p = 0.016$), the energy expenditure measured by calorimetry ($p = 0.011$) and the lactate production (not mainly occurred at the muscle level). This last observation is contradictory with the results of Levy. B [26]. The main explanation is the metabolic conditions induced by a septic shock are different from those caused by the attenuated toxin injection in Michaielli's study.[12]. The key conclusion from these studies is that lactates production during sepsis is a metabolic adaptation regardless of the tissue hypoxia.

For the pyruvate, we found a weak inverse correlation between the norepinephrine dose and muscle pyruvate for the levosimendan group, the dobutamine group and all patients included in the study. This result was found by several studies [27–29]. Gore and his colleagues [24] have shown that the pyruvate production and its oxidation are accentuated during sepsis. This increase is not only due to the hypoxia phenomenon but also to an increase in glycolysis and sepsis-specific mitochondrial dysfunction, which they termed "inhibition of mitochondrial respiration"[24,30].

Loanna Dimopoulou et al. [31] found in a study published in 2011 that the lactate/pyruvate ratio was not correlated with the prognostic scores or the mortality. Levy et al.[28] found a correlation between the lactate/pyruvate ratio, the sepsis severity, and the mortality. However, the low sensitivity of this ratio indicates tissue metabolic disorders. They showed that the muscle has an essential role in the production of lactates during sepsis, which results in muscle lactates higher than lactatemia. An increase in pyruvate production is also observed during sepsis which indicates that these metabolic disorders result from an exaggeration of aerobic glycolysis rather than cellular hypoxia. For Levy et al. [32], this hyperproduction of lactates is a phenomenon of cellular self-protection as it may provide an energetic substrate for several organs and a high lactate/pyruvate ratio is a marker of an intra-cytoplasmic accumulation of reducing equivalents useful for ATP synthesis.

Conclusions

The microcirculatory alterations are frequent in patients with septic shock. The norepinephrine dose has little effect on microcirculation when administered for hemodynamic optimization according to the recommendations of *the Surviving Sepsis Campaign.*

Declarations

List of abbreviations

MAP: mean arterial pressure

ACCP: American College of Chest Physicians

SCCM: Society of Critical Care Medicine

SSC: Surviving Sepsis Campaign

SOFA: Sequential Organ Failure Assessment

SAPS: Simplified Acute Physiology Score

Acknowledgements

None

Authors' contributions

AF was responsible for data acquisition and contributed to manuscript writing. CR had full access to all study data, performed the statistical analysis, and wrote the final version of the manuscript. WK contributed to manuscript writing. IL and MF supervised the study design and conduct. ZH and WS contributed to data interpretation. All authors revised the manuscript for scientific content and approved the final manuscript.

Funding

The present study was self-funded.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Hospital ethics committee.

Consent for publication

All the authors consent for publication of the present study. Informed consent was obtained from the patient or their family for data publication.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, Tables 1 & 2 are only available for download from the Supplementary Files section.

Figures

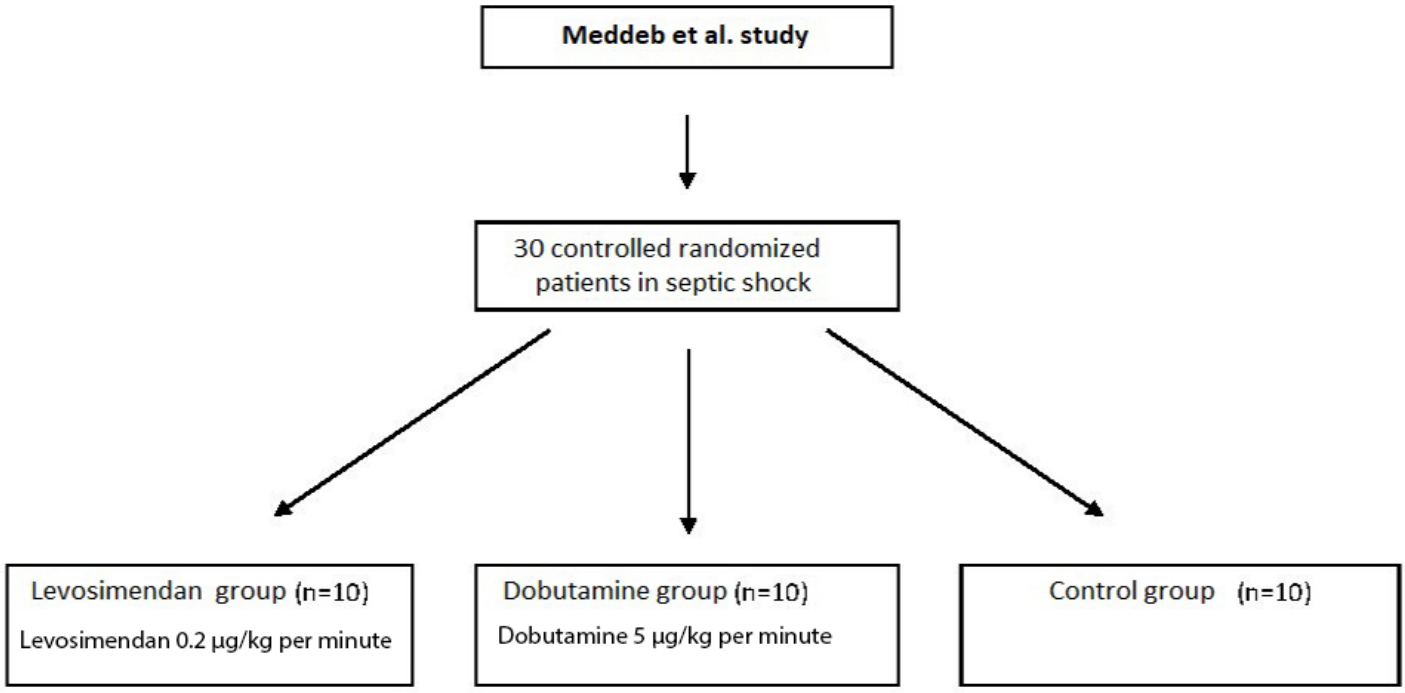

Figure 1

Flow diagram.

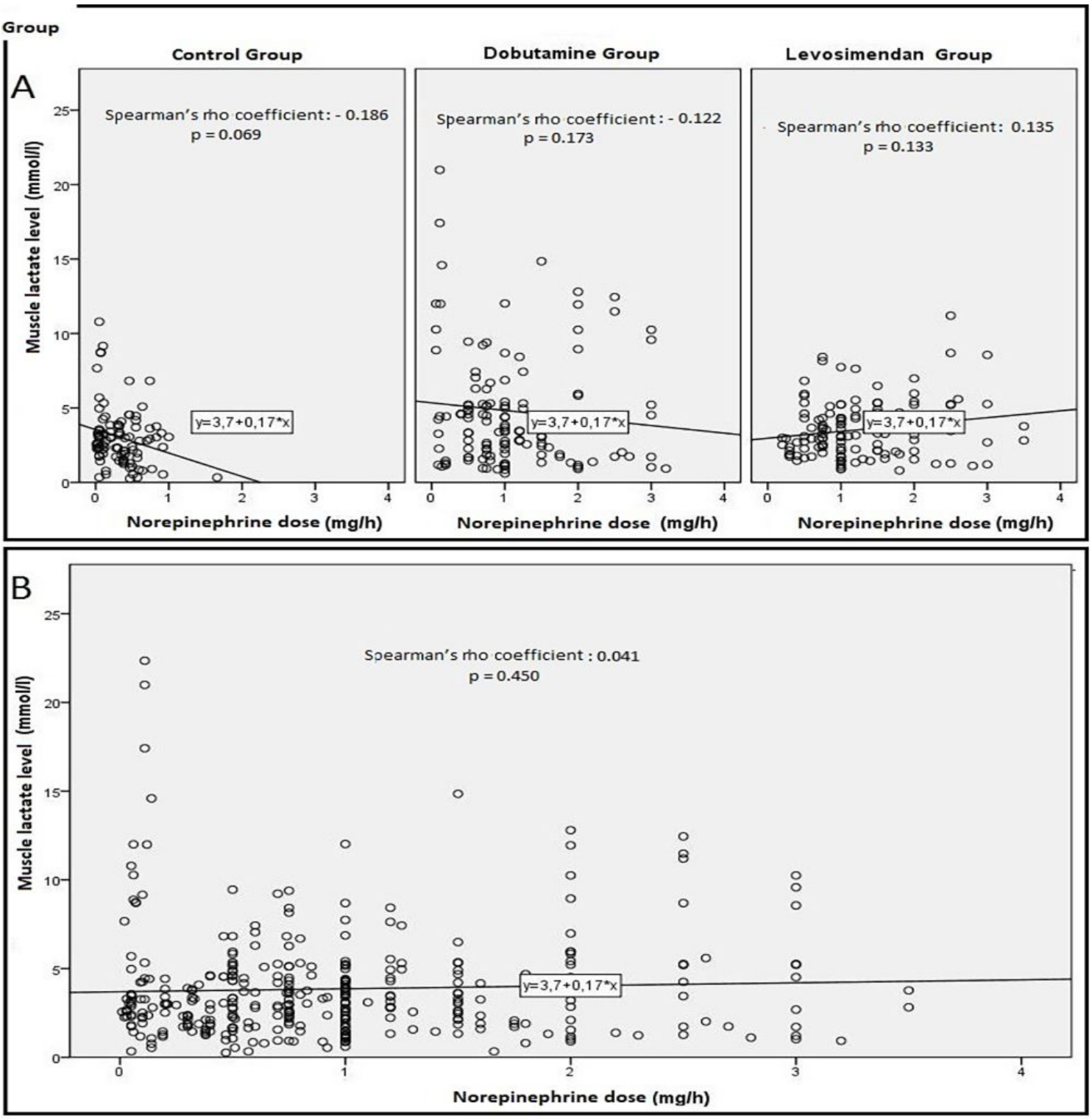

Figure 2

Evolution of muscle lactate levels as a function of noradrenaline dose. (A) for the different groups. (B) for all patients included in the study.

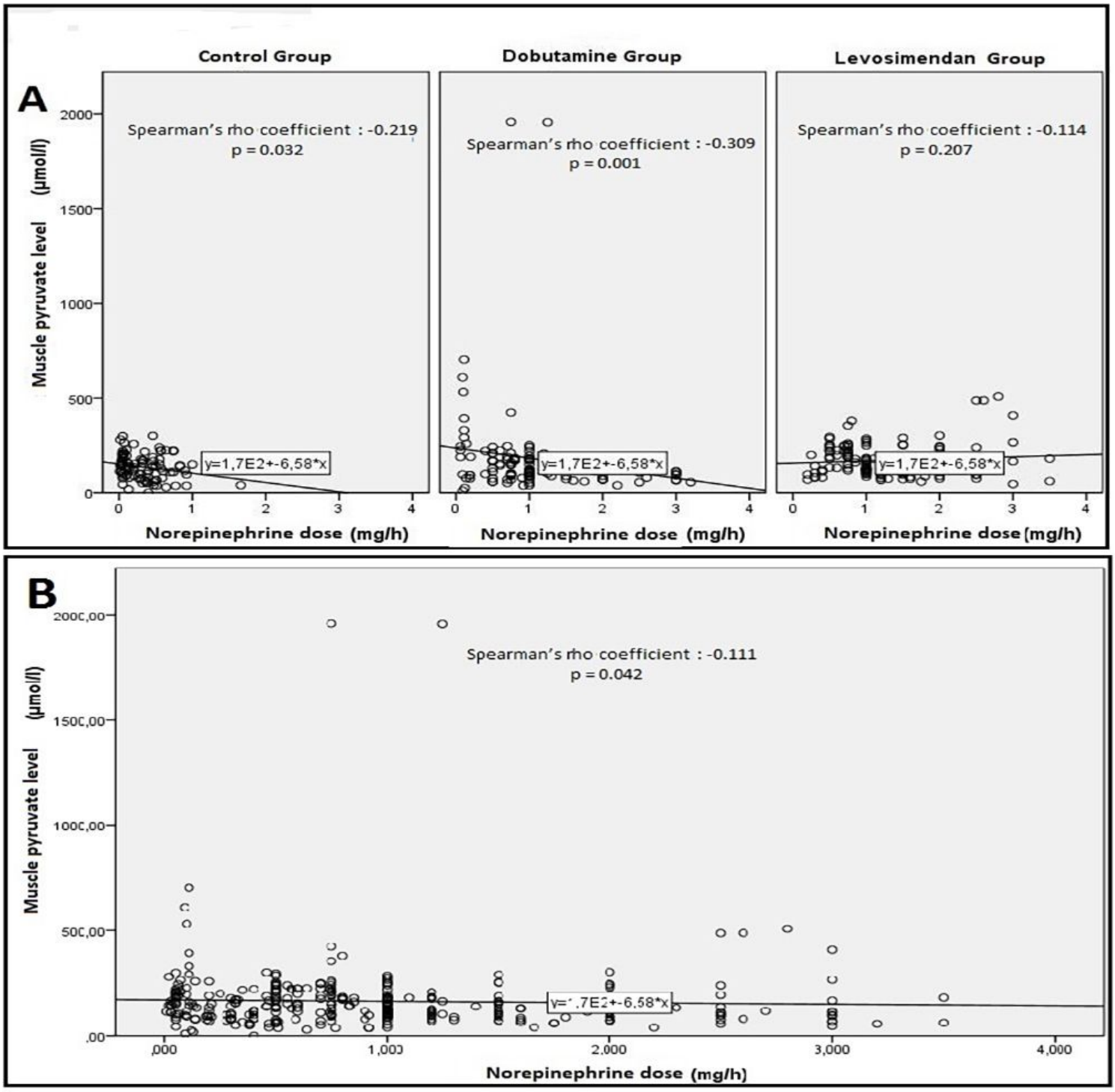

Figure 3

Evolution of muscle pyruvate levels as a function of noradrenaline dose. (A) for the different groups. (B) for all patients included in the study.

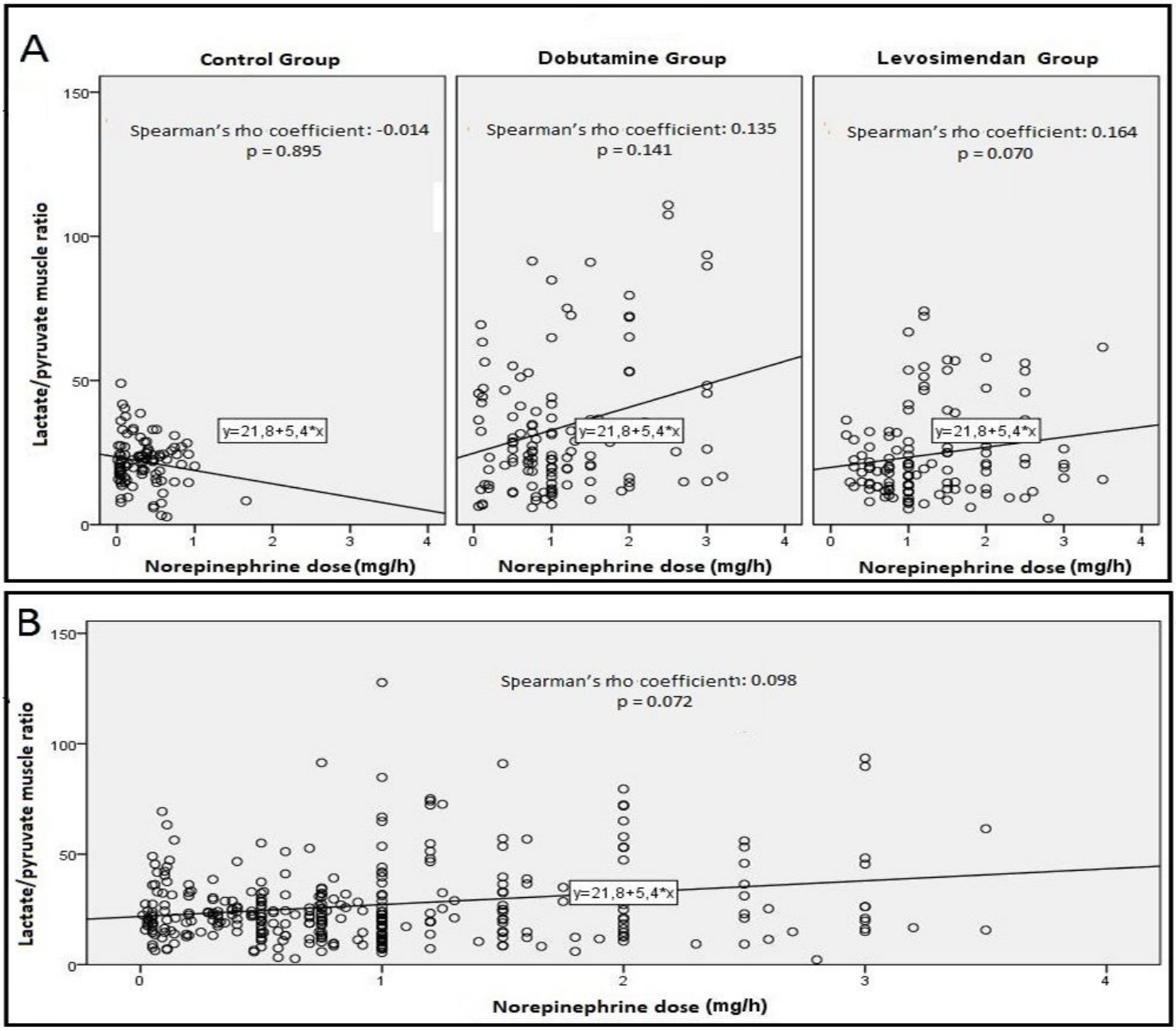

Figure 4

Evolution of muscle pyruvate lactate ratios as a function of norepinephrine dose. (A) for the different groups. (B) for all patients included in the study.

Supplementary Files

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- Tables12.docx