Critical Care

CORRESPONDENCE

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Lower oxygen saturation with higher rates of norepinephrine in bone fractures of polytrauma patients: a pilot study

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Hypoxia is a risk factor for non-union and appears to be one of the causes of the higher incidence of non-union in patients with multiple injuries [1]. Norepinephrine (NE) decreased bone perfusion in animal studies [2]. While the intramedullary bone-marrow pressure usually correlates with the systemic blood pressure, the contrary was observed under NE treatment: the systemic blood pressure increased, and simultaneously, the intramedullary bone-marrow pressure dropped [2]. This effect was independent of the systemic blood pressure and is probably caused by α-receptor-transmitted vasoconstriction of the nutrient vessels. Patients in a more severe state receive NE to increase their systemic blood pressure. The target systolic blood pressure, according to current guidelines, is 80–90 mmHg [3]. NE is currently the most frequently used and recommended catecholamine for polytraumatized patients in intensive care units [3, 4]. In human patients, the effect of *i.v.*-NE administration on the blood perfusion in fractures and the correlation with the systemic arterial blood pressure have not yet been investigated. We hypothesized lower oxygen saturation (SO_2) in the fracture gap with higher doses of NE, independent of MAP.

In a pilot trial, we used the laser-Doppler device 'Oxygen to see' (O2C, LEA Medizintechnik, Winchesterstr. 2, D-35394 Gießen, Germany) to measure SO_2, haemoglobin (Hb), and blood flow (BF) in 3, 10, and 14/16 mm depth in four tibial and clavicle fractures of three patients with multiple injuries who received NE. The O2C operates with a laser (wavelength 820 nm) and a detector in the white-light spectrum range (wavelength 500–800 nm) [5]. Probes were covered in single-use 'Ultracover for TEE Endocavity Probe Cover' (ECOLAB, Microtek Medical B.V., Hekkehorst 24, 7207 NL-Zutphen, The Netherlands), 25 × 11 × 1000 mm, made of polyurethane. The non-invasive probe was fixed on the skin with black kinesiology tape to avoid measurement error by the ambient light and to standardize the contact pressure. In each of the fractures, multiple measurements were conducted throughout the time course of treatment with varying NE

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rates. During each measurement, three recordings of 10 s each were taken in slightly different spots over each fracture gap and averaged. MAP was measured by an arterial probe as part of regular patient monitoring and recorded for each measurement. Of note, the present study was purely observational and did not interfere with the NE administration rate. NE was administered through injection pumps solely operated by the intensive care unit staff independent of the study. Multiple linear regression statistics were conducted with forced entry for each of the perfusion parameters and each depth separate as the dependent variable. The relationships of each of these parameters with the NE rate and the MAP as independent variables were explored.

Three male patients with three tibial fractures and a clavicle fracture were included (age 57.3 ± 33.1 years, weight 77.7 ± 6.8 kg, height 177.7 ± 4.0 cm, BMI 24.7 ± 3.1 kg/cm^2). A total of 125 measurements were taken, all within the first week after fracture. Significantly higher NE rates were associated with lower SO_2 in 10 mm ($p = 0.018$) and 14/16 mm depth ($p = 0.006$) of fractures (Fig. 1A–C). Significant correlations between the MAP and SO_2 were found in 3 ($p = 0.007$) and 10 mm depth ($p = 0.030$) (Fig. 1D–F). Higher NE administration rates and lower MAP were associated with lower SO_2. Hb and BF in the fracture gap were neither affected by the NE rate nor the MAP. In 10 mm depth, up to 16.2% (adjusted R^2) of the variability of SO_2 could be explained by NE and MAP. In 3 mm, up to 14.7% of the variability could be explained by MAP alone, and in 14/16 mm, up to 13.5% by NE alone. Thus, only NE and not MAP had an effect on SO_2 in 14/16 mm depth inside the fractures.

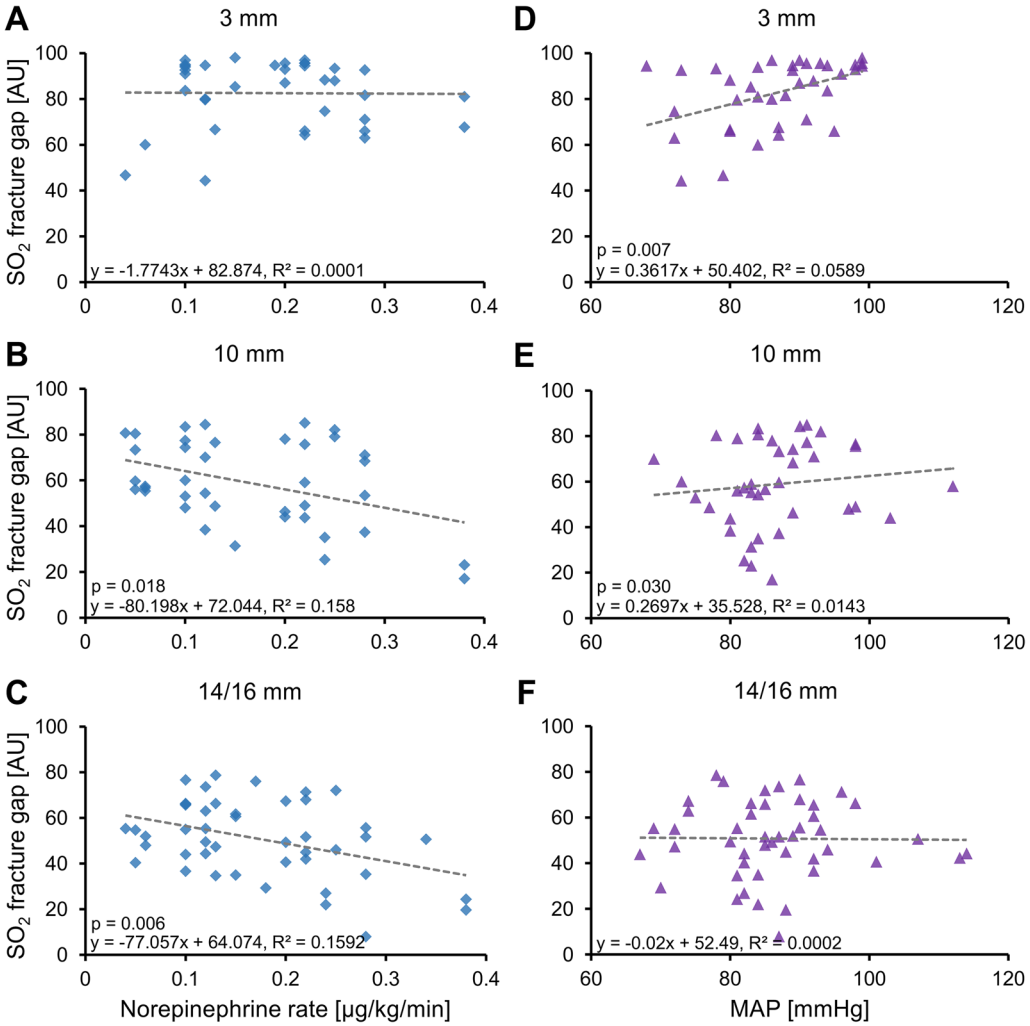

Fig. 1 Relationships of the NE rate (**A**–**C**) and the MAP (**D**–**F**) with the measured SO_2 values. *P* values from the multiple linear regression analysis are shown only, if significant

The present pilot study is the first to measure fracture perfusion in patients with NE. The presented findings need to be confirmed in larger cohorts. The reported data indicate an association of NE administration rates with decreases in bone fracture oxygenation that may be caused by the NE, but could also be related to other mechanisms associated with the more severe state of the patients that require NE treatment. As lower SO_2 in fractures may lead to delayed bone healing and non-union, it might be of interest to study the effects of alternative drugs for blood pressure elevation on bone perfusion that do not show a vasoconstrictive effect on bone. Among the catecholamines, dobutamine mainly has an effect on β_1 receptors, but shows almost no α-receptor-mediated vasoconstriction. If it can be confirmed that NE decreases bone blood supply, NE might be used to decrease blood loss from fractures. Laser-Doppler-based devices and other instruments should be validated for perfusion measurements and SO_2-monitoring in bone fractures of patients.

Abbreviations

BF	Blood flow
Hb	Haemoglobin
i.v.	Intravenous
MAP	Mean arterial pressure
mmHg	Millimetre of mercury
NE	Norepinephrine
O2C	Oxygen to see (device)
SO_2	Oxygen saturation

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Author contributions
LK conducted the measurements. MO, TPO, TF, AM and TV provided the patients and patient access. LK, MDM, MWL, TPA, and MK helped with data interpretation. TPO acquired the funding. BG contributed the study idea and conceptualization, obtained IRB approval, analysed the data, made the figure, and drafted the manuscript. All authors have interpreted and discussed the results, revised the manuscript, and agreed to its publication in its present form.

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Availability of data and materials
The data set obtained in the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the IRB of Saarland Medical Board (Ärztekammer des Saarlandes, Germany, application number 127/22). Written informed consent was conducted according to the Declaration of Helsinki prior to the start of measurements.

Consent for publication
All authors have consented to the publication of the present manuscript.

Competing interests
TP is president and board member of the AO Foundation, Switzerland, and extended board member of the German Society of Orthopaedic Trauma Surgery (DGU), the German Society of Orthopaedic Surgery and Traumatology (DGOU), and the German Society of Surgery (DGCH). TP is also the speaker of the medical advisory board of the German Ministry of Defence. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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