Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock

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Abstract

Introduction

Recent clinical studies have shown a relationship between abnormalities in peripheral perfusion and unfavorable outcome in patients with circulatory shock. Nitroglycerin is effective in restoring alterations in microcirculatory blood flow. The aim of this study was to investigate whether nitroglycerin could correct the parameters of abnormal peripheral circulation in resuscitated circulatory shock patients.

Methods

This interventional study recruited patients with circulatory shock who persisted with abnormal peripheral perfusion, despite normalization of global hemodynamic parameters. Nitroglycerin started at 2 mg/h and doubled stepwise (4 mg/h, 8 mg/h and 16 mg/h) each 15 minutes until an improvement in peripheral perfusion was observed. Peripheral circulation parameters included capillary refill time (CRT), skin-temperature gradient (Tskin-diff), perfusion index (PI) and tissue O2 saturation (StO_2) during a reactive hyperemia test (RincStO2). Measurements were performed before, at the maximum dose and after cessation of nitroglycerin infusion. Data were analyzed using linear model for repeated measurements and are show as mean (SE).

Results

Of the 15 patients included, 4 patients (27%) responded with a nitroglycerin initial dose of 2 mg/h. In all patients, nitroglycerin infusion resulted in significant changes in CRT, Tskin-diff and PI towards normal at the maximum dose of nitroglycerin: from 9.4 (0.6) to 4.8 (0.3) sec (P <0.05), from 3.3 (0.7) to 0.7 (0.6) °C (P <0.05), and from [log] -0.5 (0.2) to 0.7 (0.1)% (P <0.05), respectively. Similar changes in StO_2 and $RincStO_2$ were also observed: from 75 (3.4) to 84 (2.7)% (P <0.05) and 1.9 (0.08) to 2.8 (0.05)%/s (P <0.05), respectively. The magnitude of changes in StO_2 was more pronounced for StO_2 < 75%: 11% versus 4%, respectively (P < 0.05).

Conclusions

Dose-dependent infusion of nitroglycerin reverted abnormal peripheral perfusion and poor tissue oxygenation in patients following circulatory shock resuscitation. Individual requirements of nitroglycerin dose to improve peripheral circulation vary between patients. Simple and fast physical examination of peripheral circulation at bedside can be used to titrate nitroglycerin infusion.

Introduction

In the early 60's, the use of vasodilators in shock started with the interest in flow more than in pressure [1]. This was followed by clinical observations and some experimental studies showing the beneficial effects of vasodilators in severe (irreversible) shock [2,3]. It took many years before this topic was subject of additional experimental studies including new techniques to monitor the effects of vasodilators [4-9]. These findings inspired some clinical investigators to propose the administration of nitroglycerin as a therapeutic approach to recruit the (sublingual) microcirculation in septic shock and cardiogenic shock [10-12]. Although these studies showed that nitroglycerin is effective in restoring an abnormal sublingual microcirculation, the implementation of such therapeutic approach in clinical practice is still hampered by technical aspects and complex offline analysis of the images.

A real-time evaluation of peripheral microcirculatory disorders would provide bedside assessment for timely application of nitroglycerin targeting improvement in microcirculatory perfusion. In addition, recent observations have demonstrated significant association between the persistence of abnormalities in peripheral circulation, measured in skin, muscle or sublingual mucosa, with more severe organ dysfunction and worse prognosis when compared to traditional global variables of resuscitation [13-21]. While these abnormalities in peripheral perfusion predict unfavorable outcome in critically ill patients, it still needs to be proven that these abnormalities can not only be treated but also result in improved morbidity and/or mortality. It is reasonable, therefore, that these fundamental questions should be ideally answered before the introduction of a new monitoring parameter in clinical practice [22].

Monitoring of peripheral perfusion can be performed using simple clinical assessment, in particular, the physical examination by touching the skin or measuring capillary refill time, body temperature gradient, and optical devices, such as pulse oximeter signal and tissue oxygen saturation (StO_2) [23]. We question whether these easy, reliable and robust clinical parameters of peripheral perfusion can be an effective monitoring approach at the bedside to

titrate the beneficial effects of nitroglycerin. Therefore, we designed the present study to address two general hypotheses. First, can nitroglycerin revert abnormal peripheral circulation that persists after initial resuscitation in patients with circulatory shock? And second, is there a dose-dependent effect that would require individualization of the nitroglycerin dose?

Materials and methods

Setting and participants

This was an intervention study within the intensive care unit of a university hospital. The local accredited Medical Research Ethical Committee from Erasmus MC Hospital approved the study. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision maker, as appropriate. All consecutive patients admitted in the intensive care for circulatory shock resuscitation were eligible for inclusion. Circulatory shock was defined as hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or a systolic blood pressure decrease >40 mmHg below normal range) despite adequate fluid resuscitation or the requirement for continuous norepinephrine infusion, and the presence of metabolic acidosis (arterial pH < 7.35 or Base Excess < -3 mmol/L) in association with increased lactate levels (>2 mmol/L). Patients were eligible for inclusion if after 6 hours of ICU admission and continuous resuscitation and stabilization, abnormal peripheral perfusion was still present despite normalization of global hemodynamic parameters. Accordingly, all patients included shared common abnormalities in peripheral perfusion as baseline characteristics. Exclusion criteria were arm injury or ischemia from trauma (disturbing measurement of peripheral circulation), liver failure and any neurological insult that could lead to increased intracranial pressure (stroke, subarachnoid haemorrhage, brain trauma injury).

Measurements

All patients were monitored with a radial artery catheter for continuous arterial pressure monitoring. Global hemodynamic variables included heart rate, central venous pressure, and mean arterial pressure. All measurements were obtained using standard equipments. Cardiac output was obtained if the patient was monitored with continuous pulse contour cardiac analysis (PiCCO®, Pulsion Medical Systems AG, Munich, Germany).

Peripheral circulation parameters included physical examination of peripheral perfusion with capillary refill time, forearm-to-fingertip skin-temperature gradient (Tskin-diff) and peripheral perfusion index from pulse oximeter signal. Capillary refill time was measured by applying firm pressure to the distal phalanx of the index finger for 15 seconds. A chronometer recorded the time for the return of the normal colour and 5 seconds was defined as the upper limit of normality [24]. Tskin-diff was obtained with two skin probes (Hewlett Packard 21078A) attached to the index finger and on the radial side of the forearm, midway between the elbow and the wrist. Tskin-diff can better reflect changes in cutaneous blood flow than skin temperature itself. When being evaluated under constant environmental conditions, Tskin-diff increases during vasoconstriction, and a threshold of 2 ºC has been shown to reflect vasoconstriction in critically ill patients [25,26]. Peripheral perfusion index provides a noninvasive method for evaluating perfusion and has been shown to reflect changes in peripheral circulation [27]. In this study, the peripheral perfusion index value was

obtained using a pulse oximeter (Masimo® SET Radical-7, Masimo Corp., Irvine CA, USA), which displays a range from 0.02% (very weak pulse strength) to 20.0% (very strong pulse strength). In addition, we used near-infrared spectroscopy for StO_2-derived tissue oxygenation measurements to investigate the dynamic changes between tissue oxygenation and condition of peripheral perfusion. StO_2-derived tissue oxygenation was continuously monitored using an InSpectra Tissue Spectrometer Model 650 with a 15-mm probe over the thenar eminence. A vascular occlusion test was performed by arrest of forearm blood flow using a conventional sphygmomanometer pneumatic cuff. The cuff was placed around the upper arm and was inflated to a pressure approximately 30 mmHg greater than patient systolic pressure for 3 minutes. On the completion of the ischemic period, the occluding cuff was rapidly deflated to 0 mmHg. The derived StO_2 parameters were divided into three components: resting StO_2 values, rate of StO_2 desaturation ($RdecStO_2$, expressed as%/min) and rate of StO_2 recovery ($RincStO_2$, expressed as%/s).

Patients were considered to have abnormal peripheral circulation if the examined extremities (both hands) had an increase in capillary refill time >5 seconds or indicated the presence of peripheral vasoconstriction (Tskin-diff >2 ºC and peripheral perfusion index <1.4%). The intensive care unit has single-person closed rooms and the ambient temperature in each patient's room was individually and actively set at 22 °C.

Study design

To avoid significant hypotension during nitroglycerin infusion, each patient was evaluated for adequate intravascular volume as evidenced by repeated volume challenges (250 ml of crystalloid over 10 minutes) up to a point where central venous pressure raised by more than 2 mmHg or stroke volume did not increase more than 10%. After documentation of central venous pressure or stroke volume changes, a set of measurements was obtained during a control period. After baseline measurements, nitroglycerin was given as a bolus equal to the volume of the used infusion line followed by a continuous intravenous infusion initiated at 2 mg/h (33.3 mcg/min). When peripheral circulation did not normalize within 15 min after start of the nitroglycerin infusion, repeated measurements of hemodynamic and peripheral perfusion parameters were recorded and the dose was doubled. This was repeated until peripheral perfusion was normalized or a dose of 16 mg/h was reached (Figure 1). The stepwise increase in nitroglycerin infusion rate resulted in the following dosages used: 4 mg/h (66.6 mcg/min); 8 mg/h (133.3 mcg/min) and 16 mg/h (266.6 mcg/min). We defined improvement in peripheral perfusion as a change of more than 50% in baseline parameters of capillary refill time or the presence of peripheral vasodilation (Tskin-diff <2 ºC or peripheral perfusion index >1.4%). At the end of the step wise increase in nitroglycerin when peripheral circulation was corrected and a final set of measurements had been made, the infusion of nitroglycerin was stopped. A second set of baseline measurements was recorded 30 minutes after cessation of the infusion (Figure 1).

Figure 1 Flowchart of the study protocol. Time points of the study were defined as T_{BL1} (Baseline 1 before nitroglycerin infusion), T_{MX} (time-point when peripheral perfusion was normalized at the maximum dose of nitroglycerin) and T_{BL2} (Baseline 2 recorded 30 min after cessation of nitroglycerin infusion).

The nitroglycerin infusion was stopped if the patient developed significant hypotension (mean arterial pressure <50 mmHg). During the study, infusion rates of noradrenaline or other vasoactive drugs were not changed and no additional fluids were administered.

Statistical analysis

Unless otherwise specified, descriptive analyses are reported as median [25^{th}-75^{th}]. Time points of the study were defined as T_{BL1} (baseline before nitroglycerin infusion), T_{MX} (at the maximum dose of nitroglycerin) and T_{BL2} (30 min after cessation of nitroglycerin infusion). We used a Kolmogorov-Smirnov test and

stratified distribution plots to verify the normality of distribution of continuous variables. Not normally distributed data underwent log-transformation to achieve close to normal distribution and then qualified for longitudinal testing. We used linear model for repeated measurements (time points as independent factor) to investigate changes in the average of hemodynamic and peripheral perfusion parameters (dependent variables). The analyses of linear model are reported as mean response (standard error). Differences between groups' means were tested by Mann-Whitney U test. A multiple regression analysis was applied to estimate the effect of nitroglycerin dose (independent variable) on parameters of peripheral perfusion (dependent variables) so that we could predict changes in capillary refill time, Tskin-diff, peripheral perfusion index and StO_2 for a given nitroglycerin dose. SPSS (version 15.0, SPSS, Chicago, IL) was used for statistical analysis. A *P*-value <0.05 was considered statistically significant.

Results

Of the15 patients included in the study, 12 had septic shock and 3 had non-septic shock. Patients' demographic data are summarized in Table 1. At moment of inclusion (after 6 hours of ICU admission), all patients had central venous oxygen saturation ≥70% and 4 patients had hyperlactatemia (lactate > 2.0 mmol/L). The total amount of volume for fluid challenge necessary for each patient was 416 ± 204 ml. As the protocol was based on dose-response, some patients had longer durations of nitroglycerin infusion than others. In only four patients (27%), nitroglycerin infusion response was observed with the initial dose of 2 mg/h. In 2 patients, the highest dose of nitroglycerin (16 mg/h) was necessary to improve peripheral perfusion; five patients required 4 mg/h and four patients required 8 mg/h. Table 2 shows the haemodynamic effects of nitroglycerin infusion during execution of the study protocol stratified by the time points. In all patients, mean arterial pressure was significantly lower at the maximum dose time point (T_{MX}). Cardiac index and stroke volume were measured in six patients, and although both parameters showed a slight decrease, no significant differences were observed during nitroglycerin infusion.

Table 1 Baseline characteristics of the patients

Patient demographic data	
Number of patients	15
Age (years)	63 [48-71]
Male/Female	9/6
SOFA	10 [5-11]
APACHE II	22 [16-27]
Admission category:	6 abdominal sepsis
	5 pneumonia
	2 postoperative
	1 hemorrhagic shock
	1 meningitis
Noradrenaline use, N (%)	14 (93%)
Noradrenaline dose (µg/kg/min)	0.13 [0.03-0.40]
Mechanical ventilation, N (%)	15 (100%)
Lactate (mmol/L)	1.8 [1.1-2.1]
Survivor/Non-survivor	10/5

Values are expressed as median [25^{th}-75^{th}].

Table 2 Global hemodynamic variables recorded in the three different time points during execution of the study protocol (n = 15)

	T_{BL1}	T_{MX}	T_{BL2}
HR (bpm)	95 (4.3)	97 (4.4)	98 (4.4)
SBP (mmHg)	113 (4.6)	94 (4.0)*	111 (3.8)*
DBP (mmHg)	52 (4.9)	49 (4.8)*	57 (4.9)*
MAP (mmHg)	75 (3.0)	61 (2.9)*	71 (2.3)*
CVP (mmHg)	12 (4.0)	9 (5.0)*	10 (6.0)
CI, n = 6 (L/min/m2)	4.1 (0.4)	3,8 (0.5)	3,9 (0.4)
SV, n = 6 (ml)	78 (15)	66 (14)	77 (12)

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure; CVP = central venous pressure; CI = cardiac index; SV = stroke volume.

* $P < 0.05$ vs. previous time point (linear model for repeated measurements).

Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}) and 30 min after cessation of nitroglycerin (T_{BL2}). Cardiac index and stroke volume were measured in 6 patients. Data are mean (SE).

Baseline parameters of peripheral perfusion and the effects of nitroglycerin on these parameters are shown in Table 3. Two patients did not tolerate the 3 min vascular occlusion test and therefore neither $RincStO_2$ nor $RdecStO_2$ are reported for these patients. Improvement in peripheral perfusion was reached in all patients. All 15 patients responded with more than 50% of capillary refill time and PI > 1.4% at the maximum dose of nitroglycerin, and 9 patients responded additionally with Tskin-diff < -2. Twelve patients required low dose of nitroglycerin (<8 mg/h) to normalize the peripheral perfusion parameters. We did not find difference in CRT, PI and Tskin-diff baseline between patients requiring low dose and patients requiring high doses. Therefore, all patients included shared common abnormalities in peripheral perfusion before nitroglycerin infusion. Figure 2 shows

the time course of peripheral perfusion parameters for each patient during nitroglycerin infusion at T_{BL1}, T_{MX} and T_{BL2}. Nitroglycerin infusion resulted in significant changes in capillary refill time, Tskin-diff and peripheral perfusion index towards normal compared to baseline values: 51% [50-44], 85% [30-112] and 178% [105-295], respectively. Similarly, we observed a significant increase in StO_2 and $RincStO_2$ values, but not in $RdecStO_2$ at T_{MX}. All parameters returned to baseline values after cessation of nitroglycerin infusion.

Table 3 Peripheral perfusion parameters recorded in the three different time points during execution of the study protocol (n = 15)

	T_{BL1}	T_{MX}	T_{BL2}
CRT (sec)	9.4 (0.6)	4.8 (0.3)*	7.1 (0.8)*
Tskin-diff (°C)	3.3 (0.7)	0.7 (0.6)*	1.8 (0.6)*
PI.log (%.)	-0.5 (0.2)	0.7 (0.1)*	0.2 (0.1)*
StO_2 (%)	75 (3.4)	84 (2.7)*	79 (2.8)
THI (a.u.)	11.1 (1.3)	13.2 (1.4)*	11.6 (1.2)*
$RincStO_2$, n = 13 (%/sec)	1.9 (0.08)	2.8 (0.05)*	2.4 (0.09)*
$RdecStO_2$, n = 13 (%/min)	8.6 (0.5)	9.2 (0.6)	9.14 (0.7)

CRT = capillary refill time Tskin-diff = forearm-to-fingertip skin-temperature gradient; PI = Perfusion Index; THI = tissue hemoglobine index; $RincStO_2$ = rate of StO_2 increase after arterial occlusion; $RdecStO_2$ = rate of StO_2 deoxygenation during arterial occlusion.
*$P < 0.05$: previous time point (linear model for repeated measurements).
Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}) and 30 min after cessation of nitroglycerin (T_{BL2}). $RincStO_2$ and $RdecStO_2$ were collected from 13 patients. Data are mean (SE).

Figure 2 Temporal behaviour of peripheral circulation parameters (CRT, Tskin-diff, PI) and StO_2-derived variables (StO_2, $RincStO_2$, $RdecStO_2$) during study protocol. Time points are defined as before nitroglycerin infusion (T_{BL1}), at the maximum dose of nitroglycerin (T_{MX}) and 30 min after cessation of nitroglycerin (T_{BL2}). Abbreviation: CRT = capillary refill time (sec); PIlog = log of perfusion index (%.); Tskin-diff = forearm-to-fingertip skin-temperature gradient (°C); StO2 = peripheral tissue oxygenation (%); $RincStO_2$ = rate of StO_2 recovery after arterial occlusion (%/sec); $RdecStO_2$ = rate of StO_2 desaturation during arterial occlusion (%/min). Lines represent individual values for each patient. Bars are mean ± 95%CI

Table 4 shows estimate from multiple regression analysis with respective confidence intervals predicting changes in capillary refill time, Tskin-diff, peripheral perfusion index and StO_2 for a given nitroglycerin dose. The effect of changes in nitroglycerin dose had significant effect on capillary refill time, Tskin-diff and peripheral perfusion index, but not on StO_2. When taking into account StO_2 baseline values before nitroglycerin infusion, the effect of changes in nitroglycerin dose become clearly significant. The magnitude of changes in StO_2 was more prominent at lower StO_2 values (Figure 2). Compared to baseline, patients with $StO_2 < 75\%$ at T_{BL1} had bigger response than patients with $StO_2 > 75\%$: 10% [9.0-11.1] vs. 7% [4.7-10.5], $P < 0.05$.

Table 4 Estimation of the effect of nitroglycerin dose on all parameters of peripheral perfusion

	Estimate	95% CI	*P*-value
Constant	8.9	[4.60, 13.10]	0.001
CRT (sec)	-0.91	[-1.10, -0.50]	0.001
Tskin-diff (°C)	0.35	[0.09, 0.61]	0.008
PI (%)	1.2	[0.55, 1.85]	0.001
StO_2 (%)	-0.02	[-0.07, 0.03]	0.42
StO_2 (%), corrected for baseline StO_2	0.30	[0.14, 0.47]	0.001

CRT = capillary refill time Tskin-diff = forearm-to-fingertip skintemperature gradient; PI = Perfusion Index; StO2 = peripheral tissue oxygenation.

Discussion

We have demonstrated that intravenous infusion of nitroglycerin improves peripheral perfusion and oxygenation in shock patients with persisting abnormal peripheral circulation following initial resuscitation to global hemodynamic endpoints. Although nitroglycerin is generally used for its cardio-circulatory effects, its precise application in septic or non-septic circulatory shock continues to be debated and investigated. The use of vasodilators in shock was introduced into the clinic in the early 1960s as an additional therapeutic option for circulatory shock with or without cardiac dysfunction to counteract peripheral vasoconstriction [1,2,28]. However, the concept of using vasodilator therapy to target microcirculatory flow in critically ill patients originated in the 1990's with clinical trials of different types of vasodilators (prostacyclin, N-acetylcysteine) targeting splanchnic perfusion as assessed by gastric tonometry [29-32]. These studies demonstrated an improvement in gastric perfusion with vasodilator administration suggesting successful microcirculatory recruitment. More recently, with the advent of video microscopy techniques allowing direct visualization of the (sublingual) microcirculation, some studies have evaluated short-term infusions of nitroglycerin in septic or non-septic shock and demonstrated significant improvements in capillary perfusion [10-12]. In a randomized controlled trial in 70 patients with septic shock, Boerma et al. failed to show significant differences in the evolution of the sublingual microcirculation between the control and nitroglycerin group [11]. Although this study precluded the effectiveness of nitroglycerin in the sublingual microvascular flow, the fixed dose of nitroglycerin used (2 mg/h) was able to significantly increase skin blood flow as measured by central-to-toe temperature gradient in the treatment group. In addition to that finding, the authors also reported lower SOFA score in patients who were treated with nitroglycerin compared with the placebo group. In our study, a dose of 2 mg/h was not sufficient to improve peripheral perfusion in almost 80% of the patients, indicating that the nitroglycerin dose aiming to normalize abnormal peripheral perfusion should be individualized. In addition, since its dose-dependent effect can be easily predicted (Table 4) and the parameters of abnormal peripheral circulation can be easily obtained at the bedside, the use of nitroglycerin to correct an abnormal peripheral circulation can be easily implemented in clinical practice.

The persistent abnormalities in peripheral circulation have been shown to predict a poor outcome in critically ill patients in terms of mortality and multiple organ dysfunction [13-15,18,20,33]. To what extend peripheral perfusion parameters result in abnormal vital organ dysfunction causing these reported increases in morbidity and mortality is currently

speculative. Nevertheless, the true clinical usefulness of peripheral perfusion monitoring can only be supported if it can be used to guide therapy to change outcome. Studies have shown that resuscitation procedures aiming at supporting global perfusion fail to normalize peripheral perfusion [34]. Therefore, more specific direct interventions to correct abnormalities in peripheral perfusion, such as vasodilator, would be a first step to meet this resuscitation goal. The rational of vasodilator therapy is based on the concept that blood flow in the peripheral circulation is regulated by changes in perfusion pressure, which is determined by intravascular pressure gradient and vessel radius of arterial peripheral circulation. Although the vessel radius has an important effect on flow (fourth power of the radius), the flow only occurs if there is a difference of pressure [35]. Microcirculatory perfusion pressure is, therefore, the net result of precapillary inflow pressure minus venular outflow pressure. From this physiologic perspective, a series of clinical studies have assessed the effect of vasodilators as potential adjunctive therapy to recruit microvascular perfusion in circulatory shock [10-12,29-32,36].

Nitroglycerin has some attributes that favour its use to recruit the microcirculation in critically ill patients. First, nitroglycerin has a quick onset of action (2 to 5 minutes) with half-life elimination of 1 to 3 minutes. Second, nitroglycerin has specific hemodynamic effects in the venous capacitance vessels resulting in pressure gradient increase in the microvasculature and thus in microvascular blood flow. In this study, improvements in the clinical parameters of peripheral circulation were obtained in all patients. Capillary refill time improved in parallel with changes in Tskin-diff and peripheral perfusion index suggesting that the improvement in cutaneous circulation was likely the result of increase in cutaneous blood flow. As the major role of cutaneous circulation is thermoregulation, blood flow to the skin typically exceeds metabolic requirements. Therefore, the high blood flow relative to its oxygen demand makes the skin an appropriate organ to detect variations in peripheral blood flow.

Another interesting finding in our study was that nitroglycerin infusion led to a significant improvement in peripheral tissue oxygenation. In addition, the magnitude of changes in StO_2 was more pronounced in patients who had lower StO_2 values (<75%). This finding may be explained by the shift of blood volume from arterial to venous compartment due to predominant venous dilation with a subsequent increase in the oxyhemoglobin levels within the volume of the vascular bed in the catchment area of the NIRS probe. Significant gain in StO_2 is, therefore, observed in conditions in which the functional microcirculatory reserve is poor, such as those seen in abnormal peripheral circulation. In these conditions, a low initial StO_2 value yields a greater percent change. Alternatively, we found parallel changes in StO_2 reoxygenation rate, but not in the StO_2 deoxygenation rate. Unlike the StO_2 deoxygenation rate during arterial occlusion in which venous outflow and arterial inflow are blocked, StO_2 recovery after the vascular occlusion reflects the sudden increase of arterial inflow during the hyperemic response. Infusing a vasodilator will result in a larger flow-mediated dilation following reactive hyperemia, and therefore in a higher rate of reoxygenation. This pattern of changes in tissue oxygenation parameters is consistent with previous reports, including some of our own group, showing that StO_2-derived parameters are influenced by peripheral vasoregulation [37-40]. Considering that oxygen demand remained unchanged as reflected by constant StO_2 deoxygenation rate in our patients, any increase in flow would result in an increase in microcirculatory hemoglobin saturation levels. Thereby, the noticeable changes in StO_2 and StO_2 recovery rate in our patients provide evidence that nitroglycerin markedly improves tissue oxygenation.

Although this study makes novel observations, a limitation to our study is the small number of patients. Despite this sample size, our patients shared same baseline common abnormality in peripheral perfusion, and our study was designed to allow every patient to serve as his or her own control thereby minimizing bias. Hence, the evident significant improvement and worsening in the clinical parameters of peripheral circulation in all patients during and after nitroglycerin infusion strengthens our findings. Another important point to mention is that the effect of nitroglycerin on skin and muscle perfusion as measured in our patients cannot be extrapolated on other organs, such as gastric perfusion, liver or kidneys. However, the accumulating evidence from the literature supports the efficacy of vasodilator therapy in improving microcirculatory perfusion in these different vascular beds. We speculate, therefore, that nitroglycerin infusion in our patients had same beneficial effect as seen in the peripheral tissues. Finally, our study supports the hypothesis that nitroglycerin dose should be individualized and shows that noninvasive and rapidly available measures of peripheral circulation at the bedside are available to predict its response and monitor the effect to reach an effective dose (Table 4). However, a next important step before the introduction of monitoring peripheral circulation and its treatment with individualized dose of nitroglycerin should be a randomized clinical trial showing clinical benefit for the critically ill patients with persistent abnormal peripheral perfusion.

Conclusion

We demonstrated with this study that stepwise dose of intravenous infusion of nitroglycerin reverses clinical abnormalities of peripheral circulation in patients with circulatory shock. In addition, we showed that the easy and reliable clinical parameters of peripheral perfusion can be an effective monitoring approach at the bedside to titrate the beneficial effects of nitroglycerin on peripheral circulation in individual patient with circulatory shock following initial resuscitation.

Key messages

- Stepwise dose of intravenous infusion of nitroglycerin reverses clinical abnormalities of peripheral circulation in patients with circulatory shock.
- Nitroglycerin infusion response in some patients was observed with the dose higher than the conventional dose of 2 mg/h.
- The easy and reliable clinical parameters of peripheral perfusion can be an effective monitoring approach at the bedside to titrate the beneficial effects of nitroglycerin on microcirculation in individual patient with circulatory shock following initial resuscitation.

Competing interests

The authors declare no competing interests.

Authors' contributions

AL was involved with the conception and design of the work; acquisition, analysis, and interpretation of data; drafting and revising the work critically for important intellectual content; and with the final approval of the version to be published. JB was involved with the

conception and design of the work; analysis, and interpretation of data; revising the work for important intellectual content for the final approval of the version to be published. MvG carried out the experiments and the data acquision. EK helped to carry out the experiments. TJ helped to carried out the experiments. JvB participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final version to be published.

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References

1. Weil MH, Sudrann RB, Shubin H: **Treatment of endotoxic shock–the dilemma of vasopressor and vasodilator therapy.** *Calif Med* 1962, **96:**86–88.

2. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG: **The nature of irreversible shock: experimental and clinical observations.** *Ann Surg* 1964, **160:**682–710.

3. Singh SP: **Use of vasodilator drug in shock.** *Br Med J* 1966, **2:**765.

4. Bakker J, Zhang H, van Asbeck BS, Vincent JL: **N-Acetylcysteine improves tissue oxygenation in a dog model of endotoxin shock.** *Med Intensiva* 1993, **17:**S30.

5. Zhang H, Spapen H, Nguyen DN, Rogiers P, Bakker J, Vincent JL: **Effects of N-acetyl-L-cysteine on regional blood flow during endotoxic shock.** *Eur Surg Res* 1995, **27:**292–300.

6. Pastor CM, Losser MR, Payen D: **Nitric oxide donor prevents hepatic and systemic perfusion decrease induced by endotoxin in anesthetized rabbits.** *Hepatology* 1995, **22:**1547–1553.

7. Zhang H, Rogiers P, Smail N, Cabral A, Preiser JC, Peny MO, Vincent JL: **Effects of nitric oxide on blood flow distribution and O2 extraction capabilities during endotoxic shock.** *J Appl Physiol* 1997, **83:**1164–1173.

8. Siegemund M, van Bommel J, Sinaasappel M, Schwarte LA, Studer W, Girard T, Vollebregt K, Ince C: **The NO donor SIN-1 improves intestinal-arterial P(CO(2)) gap in experimental endotoxemia: an animal study.** *Acta Anaesthesiol Scand* 2007, **51:**693–700.

9. He X, Su F, Velissaris D, Salgado DR, de Souza BD, Lorent S, Taccone FS, Vincent JL, De Backer D: **Administration of tetrahydrobiopterin improves the microcirculation and outcome in an ovine model of septic shock.** *Crit Care Med* 2012, **40:**2833–2840.

10. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF: **Nitroglycerin in septic shock after intravascular volume resuscitation.** *Lancet* 2002, **360:**1395–1396.

11. Boerma EC, Koopmans M, Konijn A, Kaiferova K, Bakker AJ, van Roon EN, Buter H, Bruins N, Egbers PH, Gerritsen RT, Koetsier PM, Kingma WP, Kuiper MA, Ince C: **Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial.** *Crit Care Med* 2010, **38:**93–100.

12. den Uil CA, Caliskan K, Lagrand WK, van der EM, Jewbali LS, van Kuijk JP, Spronk PE, Simoons ML: **Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure.** *Intensive Care Med* 2009, **35:**1893–1899.

13. Hasdai D, Holmes DR Jr, Califf RM, Thompson TD, Hochman JS, Pfisterer M, Topol EJ: **Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries.** *Am Heart J* 1999, **138:**21–31.

14. Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, Harnden A, Mant D, Levin M: **Clinical recognition of meningococcal disease in children and adolescents.** *Lancet* 2006, **367:**397–403.

15. Evans JA, May J, Ansong D, Antwi S, Asafo-Adjei E, Nguah SB, Osei-Kwakye K, Akoto AO, Ofori AO, Sambian D, Sylverken J, Busch W, Timmann C, Agbenyega T, Horstmann RD: **Capillary refill time as an independent prognostic indicator in severe and complicated malaria.** *J Pediatr* 2006, **149:**676–681.

16. Poeze M, Solberg BC, Greve JW, Ramsay G: **Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: What is a better predictor of outcome in critically ill septic patients?** *Crit Care Med* 2005, **33:**2494–2500.

17. Trzeciak S, McCoy JV, Phillip DR, Arnold RC, Rizzuto M, Abate NL, Shapiro NI, Parrillo JE, Hollenberg SM: **Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis.** *Intensive Care Med* 2008, **34:**2210–2217.

18. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J: **The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients.** *Crit Care Med* 2009, **37:**934–938.

19. Lima A, van Bommel J, Jansen TC, Ince C, Bakker J: **Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients.** *Crit Care* 2009, **13:**S13.

20. van Genderen ME, Lima A, Akkerhuis M, Bakker J, van Bommel J: **Persistent peripheral and microcirculatory perfusion alterations after out-of-hospital cardiac arrest are associated with poor survival*.** *Crit Care Med* 2012, **40:**2287–2294.

21. Shapiro NI, Arnold R, Sherwin R, O'Connor J, Najarro G, Singh S, Lundy D, Nelson T, Trzeciak SW, Jones AE: **The association of near-infrared spectroscopy-derived tissue oxygenation measurements with sepsis syndromes, organ dysfunction and mortality in emergency department patients with sepsis.** *Crit Care* 2011, **15:**R223.

22. Jansen TC, van Bommel J, Bakker J: **Blood lactate monitoring in critically ill patients: a systematic health technology assessment.** *Crit Care Med* 2009, **37:**2827–2839.

23. Lima A, Bakker J: **Noninvasive monitoring of peripheral perfusion.** *Intensive Care Med* 2005, **31:**1316–1326.

24. Schriger DL, Baraff L: **Defining normal capillary refill: variation with age, sex, and temperature.** *Ann Emerg Med* 1988, **17:**932–935.

25. Sessler DI: **Skin-temperature gradients are a validated measure of fingertip perfusion.** *Eur J Appl Physiol* 2003, **89:**401–402.

26. House JR, Tipton MJ: **Using skin temperature gradients or skin heat flux measurements to determine thresholds of vasoconstriction and vasodilatation.** *Eur J Appl Physiol* 2002, **88:**141–145.

27. Lima AP, Beelen P, Bakker J: **Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion.** *Crit Care Med* 2002, **30:**1210–1213.

28. Webb WR: **Vasodilators in shock–when?** *South Med J* 1966, **59:**257–261.

29. Eichelbronner O, Reinelt H, Wiedeck H, Mezody M, Rossaint R, Georgieff M, Radermacher P: **Aerosolized prostacyclin and inhaled nitric oxide in septic shock–different effects on splanchnic oxygenation?** *Intensive Care Med* 1996, **22:**880–887.

30. Radermacher P, Buhl R, Santak B, Klein M, Kniemeyer HW, Becker H, Tarnow J: **The effects of prostacyclin on gastric intramucosal pH in patients with septic shock.** *Intensive Care Med* 1995, **21:**414–421.

31. Spies CD, Reinhart K, Witt I, Meier-Hellmann A, Hannemann L, Bredle DL, Schaffartzik W: **Influence of N-acetylcysteine on indirect indicators of tissue oxygenation in septic shock patients: results from a prospective, randomized, double-blind study.** *Crit Care Med* 1994, **22:**1738–1746.

32. Rank N, Michel C, Haertel C, Lenhart A, Welte M, Meier-Hellmann A, Spies C: **N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a prospective, randomized, double-blind study.** *Crit Care Med* 2000, **28:**3799–3807.

33. Kaplan LJ, McPartland K, Santora TA, Trooskin SZ: **Start with a subjective assessment of skin temperature to identify hypoperfusion in intensive care unit patients.** *J Trauma* 2001, **50:**620–627.

34. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R: **Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.** *Crit Care Med* 2013, **41:**580–637.

35. Guyton AC, Hall JE: **Overview of the circulation; Medical physics of pressure, flow, and resistance**. In *extbook of Medical Physiology*. Edited by Guyton AC, Hall JE. Philadelphia: W.B. Saunders Company; 1996:161–170.

36. De Backer D, Dubois MJ, Creteur J, Vincent J-L: **Effects of dobutamine on microcirculatory alterations in patients with septic shock.** *Intensive Care Med* 2001, **27:**S237.

37. Lima A, van Genderen ME, Klijn E, Bakker J, van Bommel J: **Peripheral vasoconstriction influences thenar oxygen saturation as measured by near-infrared spectroscopy.** *Intensive Care Med* 2012, **38:**606–611.

38. Buono MJ, Miller PW, Hom C, Pozos RS, Kolkhorst FW: **Skin blood flow affects in vivo near-infrared spectroscopy measurements in human skeletal muscle.** *Jpn J Physiol* 2005, **55:**241–244.

39. Yanagisawa O, Homma T, Okuwaki T, Shimao D, Takahashi H: **Effects of cooling on human skin and skeletal muscle.** *Eur J Appl Physiol* 2007, **100:**737–745.

40. Lima A, van Bommel J, Sikorska K, van Genderen M, Klijn E, Lesaffre E, Ince C, Bakker J: **The relation of near-infrared spectroscopy with changes in peripheral circulation in critically ill patients.** *Crit Care Med* 2011, **39:**1649–1654.

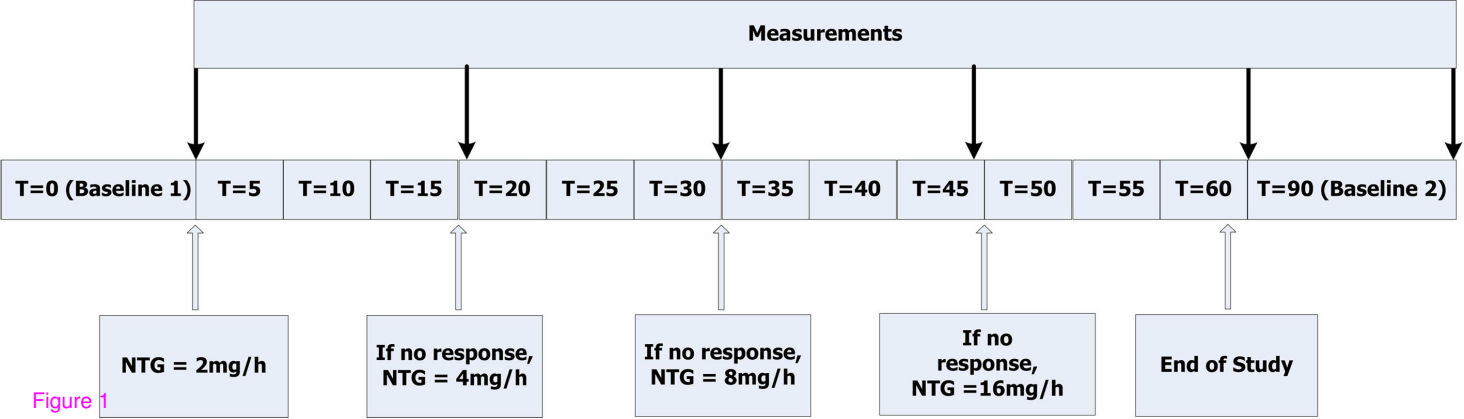
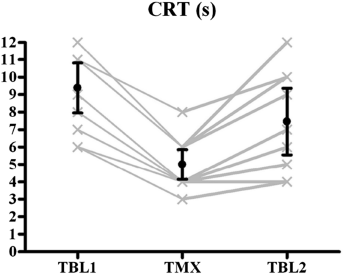
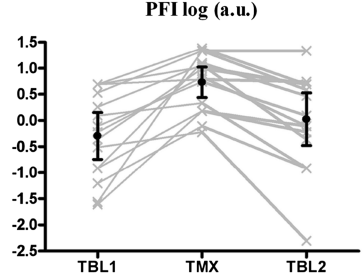
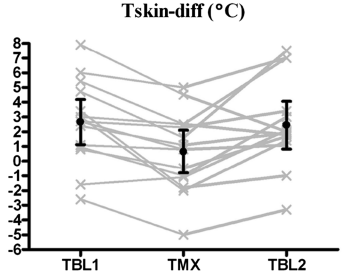
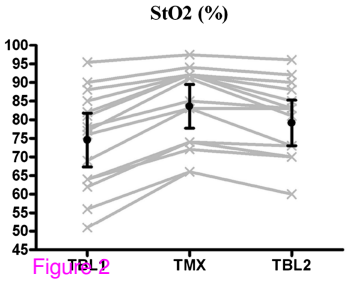

Measurements
T=0 (Baseline 1)
T=5
T=10
T=15
T=20
T=25
T=30
T=35
T=40
T=45
T=50
T=55
T=60
T=90 (Baseline 2)
NTG = 2mg/h
If no response, NTG = 4mg/h
If no response, NTG = 8mg/h
If no response, NTG =16mg/h
End of Study

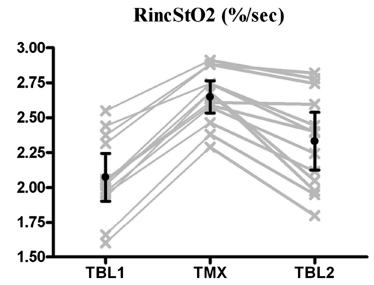
Figure 1


CRT (s)
12
11
10
9
8
7
6
5
4
3
2
1
0
TBL1
TMX
TBL2


PFI log (a.u.)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
TBL1
TMX
TBL2


Tskin-diff (°C)
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
TBL1
TMX
TBL2


StO2 (%)
100
95
90
85
80
75
70
65
60
55
50
45
TBL1
TMX
TBL2


RincStO2 (%/sec)
3.00
2.75
2.50
2.25
2.00
1.75
1.50
TBL1
TMX
TBL2

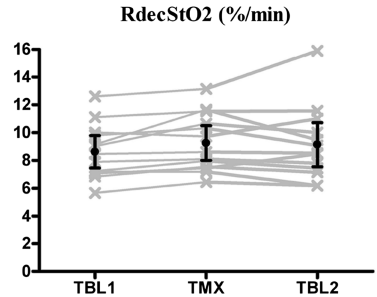

RdecStO2 (%/min)
16
14
12
10
8
6
4
2
0
TBL1
TMX
TBL2

Figure 2