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Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure

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Abstract *Introduction:* Microcirculatory abnormalities are frequently observed in patients with severe heart failure and correlate to worse outcomes. We tested the hypothesis that nitroglycerin dose-dependently improves perfusion in severe heart failure and that this could be monitored by measuring central-peripheral temperature gradient and with Sidestream Dark Field imaging of the sublingual mucosa. *Methods:* A dose-response study was performed in 17 patients with cardiogenic shock ($n = 9$) or end-stage chronic heart failure ($n = 8$) admitted to Erasmus University Medical Center. We did hemodynamic measurements at baseline and during increasing infusion rates of nitroglycerin (up to a maximum dose of 133 μg min^{-1}). As parameters of tissue perfusion, we measured central-peripheral temperature gradient (delta-T) and sublingual perfused capillary density (PCD). *Results:* Nitroglycerin dose-dependently decreased mean arterial pressure ($p < 0.001$) and cardiac filling pressures (both central venous pressure (CVP) and pulmonary capillary wedge pressure: $p < 0.001$). It increased cardiac index ($p = 0.01$). Nitroglycerin decreased delta-T ($p < 0.001$) and increased sublingual PCD ($p < 0.001$). Significant changes in delta-T and PCD occurred earlier, i.e., at a lower doses of NTG, than changes in global hemodynamics. Macrohemodynamic and microcirculatory responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure. Changes in microcirculatory parameters occurred independently of changes in cardiac index. *Conclusions:* Nitroglycerin dose-dependently increases tissue perfusion in patients with severe heart failure, as observed by a decrease in central-peripheral temperature gradient and an increase in sublingual perfused capillary density.

Keywords Cardiogenic shock · Cardiovascular monitoring · Heart failure · Imaging · Microcirculation · Multiple organ failure · Nitroglycerin · Oxygen consumption and delivery · Perfusion · Perfusion imaging · Pharmacology · Shock: clinical studies

Introduction

In recent years, investigators have increasingly acknowledged severe heart failure and cardiogenic shock not only as a cardiac problem but also as a disease of derangements in the entire circulatory system [1, 2]. Moreover, it has been found that global hemodynamic parameters do not reflect differential patterns of regional organ blood

flow or compromised tissue perfusion of the splanchnic bed associated with shock states [3–10]. Therefore, optimization of tissue microcirculation should be an objective of the treatment of critically ill patients [11]. However, it is still largely unknown whether pharmacologic interventions improve tissue capillary perfusion. Goal-directed manipulation of hemodynamics is the key to understanding the interventions required to reduce the morbidity and mortality associated with multi-organ and hepatorenal failure in patients with end-stage heart disease or cardiogenic shock.

Nitric oxide (NO) bioavailability is reduced in patients with heart failure, contributing to contractile dysfunction, ventricular hypertrophy and remodelling, as well as microvascular endothelial dysfunction [12–14]. In addition, hypervolemia, as reflected by an elevated central venous pressure, may cause organ dysfunction [15]. To overcome this clinical problem, nitrates, which are powerful NO donors and venodilators, are often given to patients with heart failure [16, 17]. We recently demonstrated that, in patients with decompensated heart failure, nitroglycerin (NTG), administered at a fixed low dose, lowered cardiac filling pressures and increased sublingual perfused capillary density (PCD) [18], which is an important measure for tissue perfusion [19]. However, in 30% of the patients measured in this study, the microcirculation did not respond. To investigate whether significant changes in PCD occur at the same dose as global hemodynamic changes, and to investigate the maximum response of the microcirculation to NTG, we performed the current dose-response study. We tested the hypothesis that NTG, presumably by enhancement of NO bioavailability and venodilation, dose-dependently improves tissue perfusion, as assessed by measurements of central-peripheral temperature gradient (delta-T) and sublingual PCD in patients with cardiogenic shock or end-stage chronic heart failure.

Materials and methods

Study design

This dose-response study was conducted at the Intensive Cardiac Care Unit and at the Heart Failure/Heart Transplant ward of the Thoraxcenter, Erasmus University Medical Center, the Netherlands. We included patients who were admitted with cardiogenic shock or end-stage chronic heart failure. Cardiogenic shock was defined as a cardiac index <2.2 L min^{-1} m^{-2} and clinical signs of hypoperfusion (cold extremities, oliguria or altered mental state), not responsive to fluid resuscitation. The patients with end-stage heart failure were included after they underwent right heart catheterization for screening for cardiac transplantation. Exclusion criteria were: (1) oral bleeding, (2) mean arterial pressure below 55 mmHg, (3) acute right ventricular myocardial infarction and (4) severe aortic valve stenosis. In cardiogenic shock patients, nitroglycerin was given for study purposes. In chronic heart failure patients, nitroglycerin was routinely given to assess reversibility of pulmonary hypertension (i.e., mean pulmonary artery pressure >25 mmHg). The institutional ethical committee approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Haemodynamic monitoring

Cardiogenic shock patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK). In the other patients, arterial blood pressure was measured non-invasively. All patients were monitored with a pulmonary artery catheter (Criticath SP5107H, Becton Dickinson, Sandy, UT, USA or CCOmbo, Edwards Lifesciences, Saint-Prex, Switzerland). Macro-hemodynamic data collection included central body temperature (measured at the tip of the pulmonary artery catheter), heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), cardiac index (CI), systemic vascular resistance (SVR), and mixed-venous oxygen saturation (SvO_2). SVR was calculated as (MAP − CVP) × 80/Cardiac output.

Microcirculatory assessment and analysis

Central-peripheral temperature gradient (delta-T) was defined and calculated as the difference between central blood and skin temperature. Skin temperature was measured with a probe affixed to the dorsum of the foot under constant room temperature (temperature probe 170075; Ellab Inc., Centennial, CO, USA).

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described and validated previously [20]. In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. This is the reason why oral bleeding was an exclusion criterion for the study. Per time point, three steady video sequences of at least 20 s duration were obtained, stored and analyzed. Quantification of the images was

performed using software (Automated Vascular Analysis 3.0, MicrovisionMedical, Amsterdam, the Netherlands) by an investigator blinded to the timing of the images. Perfused capillary density (PCD) was calculated by measuring total length of perfused capillaries divided by image area. Capillaries were regarded as perfused if they had either of the following flow classifications obtained by visual inspection: sluggish, continuous or hyperdynamic [21]. Since SDF imaging enables visualization of flowing intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary recruitment. This approach has been validated previously [22, 23]. Capillaries were defined as microvessels with a diameter less than 20 μm.

Study protocol

To minimize the effect of regression to the mean due to spontaneous variation in microcirculatory perfusion, two series of baseline measurements were performed with a time interval of 15 min. PCD values from both baseline measurements were averaged to obtain one baseline value (T0). After the second baseline measurement, NTG was given as a bolus equal to the volume of the used intravenous line. Immediately thereafter, a continuous intravenous infusion of NTG was started at a dose of 8 μg min^{-1} for 15 min. Then, all measurements were repeated (T1). Eight micrograms per minute (i.e, 0.5 mg h^{-1}) is the lowest nitroglycerin infusion rate given in our hospital. Subsequently, the nitroglycerin infusion rate was doubled stepwise (i.e., 17 μg min^{-1} (T2); 33 μg min^{-1} (T3); 67 μg min^{-1} (T4); 133 μg min^{-1} (T5)). Each infusion rate was maintained for 30 min, which was the time period necessary to reach the intended effect (15 min) plus the time period necessary to collect all data (15 min). The nitroglycerin infusion was stopped when patients developed significant hypotension (i.e., MAP <50 mmHg). In each patient, all measurements were repeated when NTG had been stopped for 20 min (T6). During execution of the study, dosages of other intravenous medications were stable.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages. Continuous variables are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR), when appropriate. The one-sample Kolmogorov-Smirnov goodness of fit test was used to test normal distribution of the data. Reproducibility of the PCD measurements was defined as the standard deviation of the differences between both baseline measurements. Changes over time were tested with one-way repeated measures analysis of variance (ANOVA), followed by Bonferroni's multiple comparison tests. Comparisons between repeated measurements within subgroups were tested with two-way repeated measures ANOVA. We defined improvement of cardiac index as an increase ≥ two times the standard deviation of the differences between both baseline measurements, relative to T0. A p value <0.05 was regarded statistically significant.

Results

Study population and execution of the protocol

Seventeen patients were included in this study. Nine patients (53%) had cardiogenic shock and eight patients (47%) had end-stage chronic heart failure and were screened for heart transplantation (Table 1). Mean age was 55 ± 12 years, 65% were male and median NT-proBNP level was 418 [204–733] pmol L^{-1} (reference values 0–17 pmol L^{-1}). Mean central body temperature was 36.0 ± 1.7°C. All patients received NTG up to 67 μg min^{-1} (T4). In seven patients, the highest dose of nitroglycerin (i.e., T5) could not be given because of arterial hypotension (MAP below 50 mmHg; $n = 6$) or pulmonary shunting and hypoxia (PaO_2 60 torr; $n = 1$). Accordingly, the dose of 133 μg min^{-1} was given to ten patients.

Effects of nitroglycerin on parameters of global hemodynamics

There were no significant differences in global hemodynamic parameters between the two baseline measurements, indicating that patients were in a stable condition before NTG was started. NTG infusion decreased MAP ($p < 0.001$) and cardiac filling pressures (CVP: $p < 0.001$; PCWP: $p < 0.001$; Table 2 and Electronic Supplementary Material). It increased cardiac index ($p = 0.01$). Between time points T4 and T5, there were no further changes in macrocirculatory parameters. Systemic parameters returned to baseline values after cessation of NTG infusion. Haemodynamic responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure.

Effects of nitroglycerin on parameters of microcirculation

There were no statistically significant differences in microcirculatory parameters between the two baseline measurements. Mean difference ± standard deviation (reproducibility) in PCD between both baseline

Table 1 Baseline characteristics of the study population ($n = 17$)

Characteristic	
Age, years (mean ± SD)	55 ± 12
Gender, male	11 (65%)
Cardiovascular risk factors	
Hypertension	5 (29%)
Current smoking	3 (18%)
Dyslipidaemia	2 (12%)
Diabetes mellitus	3 (18%)
Diagnosis at admission	
Cardiogenic shock	9 (53%)
End-stage chronic heart failure	8 (47%)
Underlying disease	
Acute myocardial infarction (complicated by shock)	8 (47%)
Mitral valve disease (complicated by shock)	1 (6%)
Dilated cardiomyopathy	7 (41%)
Ischemic cardiomyopathy	1 (6%)
NT-proBNP level, pmol L^{-1} (median [IQR])	418 [204–733]
Mechanical ventilation	7 (41%)
IABP counterpulsation	4 (24%)
Pharmacologic therapy	
Any inotropic agent	9 (53%)
Dobutamine	5 (29%)
Norepinephrine	3 (18%)
Enoximone	1 (6%)

Values are expressed as *n* (%) unless otherwise noted
SD standard deviation, *IQR* interquartile range, *NT-pro-BNP* N-terminal brain natriuretic propeptide, *IABP* intra-aortic balloon pump

measurements was 0.3 ± 1.1 mm mm^{-2}. Nitroglycerin decreased delta-T ($p < 0.001$) and improved sublingual PCD ($p < 0.001$, Table 2; Fig. 1). Significant changes in delta-T and PCD occurred earlier, i.e., at a lower dose of NTG (T2), than changes in global hemodynamics. Between time points T4 and T5, there were no further changes in microcirculatory parameters. Mean PCD values returned to baseline after the NTG infusion had been stopped for 20 min, but mean delta-T values did not. Microcirculatory responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure. Finally, temporal behavior of microcirculatory parameters was not different between patients who improved in cardiac index vs those who did not improve (Fig. 2).

Discussion and conclusions

Using conventional and novel microcirculation assessment technologies, this is the first study demonstrating that the nitric oxide (NO) donor and venodilator nitroglycerin dose-dependently improves tissue perfusion, as demonstrated by a gradual decrease in temperature gradient and a progressive increase in perfused capillary density in patients with severe heart failure.

Global hemodynamics

Elkayam et al. have demonstrated the hemodynamic effects of nitroglycerin given to eight patients hospitalized for acute decompensated heart failure. These investigators up-titrated NTG to achieve a 30% or greater reduction in pulmonary capillary wedge pressure or until a maximum dose of 560 μg min^{-1} [24, 25]. They reported a substantial reduction in right and left ventricular filling pressures, systemic vascular resistance, and

Table 2 Parameters of macro- and microcirculation during execution of the study protocol ($n = 17$)

	T0 (Averaged baseline)	T1 (8 μg min^{-1})	T2 (17 μg min^{-1})	T3 (33 μg min^{-1})	T4 (67 μg min^{-1})	T5[a] (133 μg min^{-1})	T6 (NTG stop)	*p* value for trend
HR (bpm)	73 ± 16	72 ± 15	72 ± 15	71 ± 15	72 ± 16	74 ± 16	70 ± 13	0.08
MAP (mmHg)	78 ± 14	75 ± 14	75 ± 14	74 ± 13	70 ± 13	67 ± 15	75 ± 12	<0.001
CVP (mmHg)	11 ± 6	10 ± 6	9 ± 6	9 ± 6	6 ± 5	4 ± 3	10 ± 7	<0.001
PCWP (mmHg)	21 ± 8	18 ± 8	18 ± 8	16 ± 7	14 ± 7	13 ± 6	17 ± 7	<0.001
Mean PAP (mmHg)	31 ± 7	28 ± 6	29 ± 6	28 ± 6	24 ± 5	23 ± 5	28 ± 6	<0.001
CI (L min^{-1} m^{-2})	2.2 ± 0.5	2.5 ± 0.5	2.6 ± 0.6	2.7 ± 0.6	2.5 ± 0.4	2.4 ± 0.5	2.5 ± 0.5	0.01
SVR (dyne s cm^{-5})	1327 ± 348	1182 ± 440	1120 ± 356	1069 ± 355	1081 ± 334	1175 ± 376	1173 ± 394	0.005
SvO2 (%)	68 ± 9	68 ± 8	67 ± 8	67 ± 7	66 ± 7	64 ± 7	66 ± 8	0.07
Lactate (mmol L^{-1})	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.8	1.2 ± 0.7	0.9 ± 0.4	1.3 ± 0.8	0.99
Delta-T (°C)	6.1 ± 2.7	5.4 ± 2.2	5.2 ± 2.1	5.0 ± 2.1	4.8 ± 2.1	4.5 ± 2.1	5.0 ± 2.2	<0.001
PCD (mm mm^{-2})	7.8 ± 1.4	8.8 ± 2.5	10.0 ± 2.1	11.1 ± 2.1	11.4 ± 1.8	11.2 ± 1.7	8.9 ± 1.8	<0.001

Values represent median [interquartile range]
T0, averaged baseline values; T1, NTG 8 μg min^{-1}; T2, NTG 17 μg min^{-1}; T3, NTG 33 μg min^{-1}; T4, NTG 67 μg min^{-1}; T5, NTG 133 μg min^{-1}; T6, NTG stop
HR heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure, *PAP* pulmonary artery pressure, *CI* cardiac index, *SVR* systemic vascular resistance, SvO_2 mixed-venous oxygen saturation, *Delta-T* central-peripheral temperature gradient, *PCD* perfused capillary density
[a] Measurements were performed in ten patients

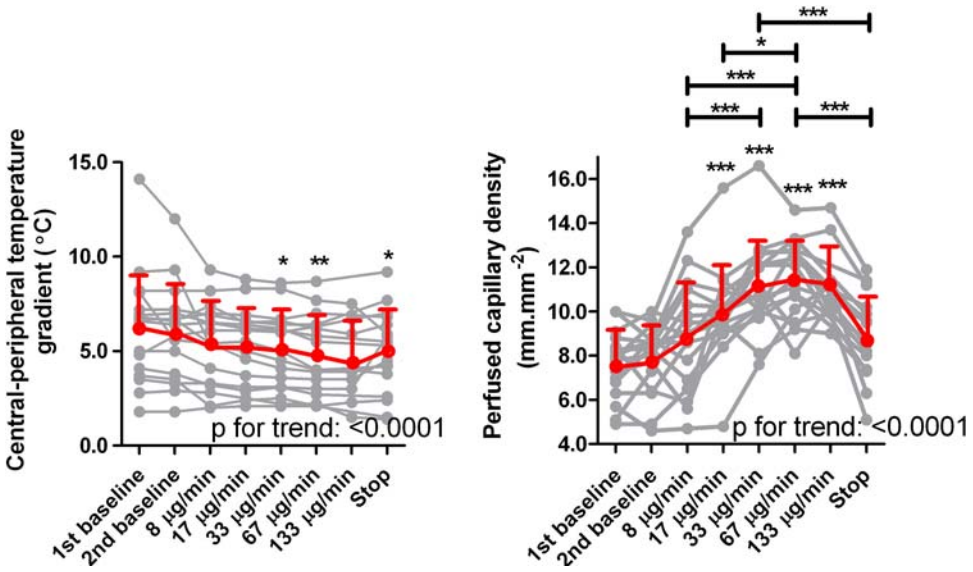

Fig. 1 Individual values of microcirculatory parameters at each dose of nitroglycerin. *p* Values were obtained with one-way repeated measures ANOVA, followed by Bonferroni's multiple comparison tests comparing all pairs of time points. *Asterisks* just above the upper individual line represent statistical significance versus second baseline measurement, whereas the other *asterisks* represent significance between time points (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). *Red lines* represent mean + SD

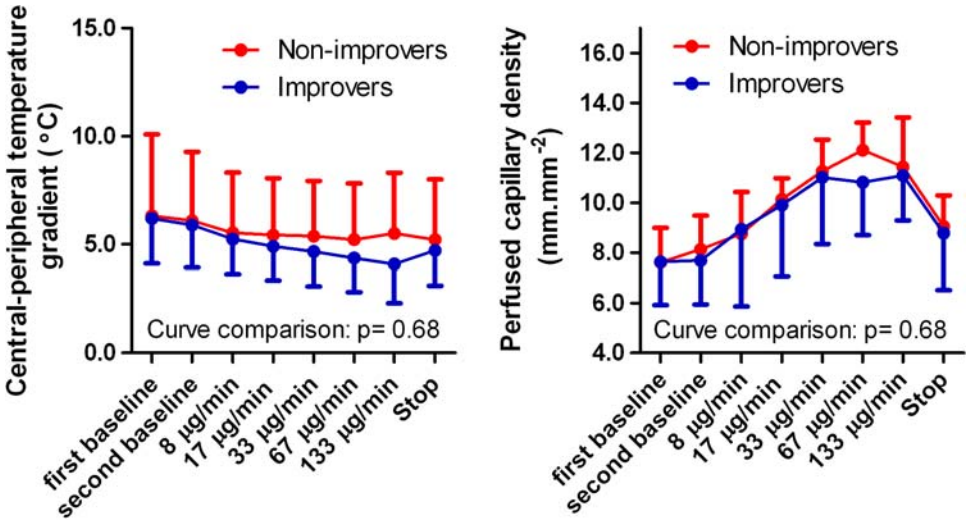

Fig. 2 Temporal behavior of microcirculatory parameters in patients with and without improvement in cardiac index. *Lines* represent mean ± SD for improvers and non-improvers in cardiac index. Improvement of cardiac index was defined as an increase ≥ two times the standard deviation of the differences between both baseline measurements (i.e, 0.6 L min^{-1} m^{-2}), relative to T0. Curve comparison was performed using two-way repeated measures ANOVA

systemic blood pressure, as well as an increase in cardiac index. Our study confirms those findings.

Microcirculation

We observed a significant improvement in tissue perfusion, measured by two independent parameters, i.e., delta-T and sublingual PCD. Measuring peripheral temperature is a conventional approach to assess peripheral perfusion [26] that can be used to monitor changes in tissue perfusion, as also demonstrated by our study. However, the accuracy of this technique depends highly on stability of the ambient temperature [27]. The novel, validated, bed-side Sidestream Dark Field imaging technique allows clinicians to directly observe blood flow in capillaries covered by a thin epithelial layer, as is the case in the sublingual area [20]. De Backer et al. [6] were the first to describe sublingual microvascular alterations in patients with severe heart failure, and they found that these alterations correlated with in-hospital mortality. Our study is the first to demonstrate a progressive improvement of microcirculatory parameters following increasing rates of nitroglycerin. Due to the microcirculation's autoregulatory nature, changes in the microcirculation may occur independently from changes in macrocirculation [28–30]. Interestingly, as clearly demonstrated by our study, changes in microcirculation (i.e., both delta-T and PCD) occurred earlier, at a lower dose of NTG, than did changes in global hemodynamics. In addition, these

changes occurred independently of changes in cardiac index. These findings underline the great value of monitoring microcirculation in critically ill patients.

Methodological considerations

Microcirculation experts recently published an important consensus statement [21]. The core of this statement was that measurement of flow alone, such as microvascular flow index (MFI), is regarded as insufficient reporting. However, as opposed to several previous studies which presented only MFI [10, 31–33], we used a software-derived parameter in which flow and density are combined, i.e., perfused capillary density. This parameter has recently been demonstrated to be accurate and precise [22, 23]. The relatively low standard deviation (1.1 mm mm^{-2}) of the differences between both baseline measurements confirms the precision of PCD measurements.

Limitations

Several limitations of our study should be acknowledged. The small and heterogeneous sample size limits drawing strong conclusions. Nevertheless, the consistent and reproducible microvascular response to NTG in almost all patients strengthens our findings. Moreover, whether the beneficial effects of nitroglycerin also apply to other microvascular beds, and whether recruitment of the microcirculation will reduce cellular dysfunction, organ failure and mortality in patients with severe heart failure, needs to be investigated.

Clinical perspective

Measuring tissue perfusion with SDF imaging might be a novel tool to tailor inotropic and vasodilator therapy to patients with severe heart failure. Our study is a preliminary confirmation of this concept, demonstrating the feasibility of serial monitoring of the microcirculation, while a gradual and consistent improvement of tissue perfusion was observed by titration of an intravenous vasodilator.

In conclusion, this study provides evidence for a dose-dependent improvement of microvascular perfusion by administration of nitroglycerin. Whether monitoring of tissue microcirculation optimizes current treatment strategies in patients with severe heart failure, and whether such a strategy will favorably affect outcome, warrants further investigation.

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