

Aus der Universitätsklinik für Intensivmedizin, Inselspital Bern
Direktor: Prof. Dr. med. Stephan Jakob
Arbeit unter der Leitung von Prof. Dr. med. Stephan Jakob

Evaluation of the clinical assessment of peripheral perfusion by capillary refill time and peripheral perfusion index

Inaugural-Dissertation zur Erlangung der Doktorwürde der Humanmedizin
der Medizinischen Fakultät der Universität Bern

vorgelegt von
Manuel Luca Vestner

aus Schönholzerswilen TG

Originaldokument gespeichert auf dem Webserver der Universitätsbibliothek Bern



Dieses Werk ist unter einem
Creative Commons Namensnennung-Keine kommerzielle Nutzung-Keine Bearbeitung 2.5
Schweiz Lizenzvertrag lizenziert. Um die Lizenz anzusehen, gehen Sie bitte zu
<http://creativecommons.org/licenses/by-nc-nd/2.5/ch/> oder schicken Sie einen Brief an
Creative Commons, 171 Second Street, Suite 300, San Francisco, California 94105, USA.

Urheberrechtlicher Hinweis

Dieses Dokument steht unter einer Lizenz der Creative Commons
Namensnennung-Keine kommerzielle Nutzung-Keine Bearbeitung 2.5 Schweiz.
<http://creativecommons.org/licenses/by-nc-nd/2.5/ch/>

Sie dürfen:



dieses Werk vervielfältigen, verbreiten und öffentlich zugänglich machen

Zu den folgenden Bedingungen:



Namensnennung. Sie müssen den Namen des Autors/Rechteinhabers in der von ihm festgelegten Weise nennen (wodurch aber nicht der Eindruck entstehen darf, Sie oder die Nutzung des Werkes durch Sie würden entlohnt).



Keine kommerzielle Nutzung. Dieses Werk darf nicht für kommerzielle Zwecke verwendet werden.



Keine Bearbeitung. Dieses Werk darf nicht bearbeitet oder in anderer Weise verändert werden.

Im Falle einer Verbreitung müssen Sie anderen die Lizenzbedingungen, unter welche dieses Werk fällt, mitteilen.

Jede der vorgenannten Bedingungen kann aufgehoben werden, sofern Sie die Einwilligung des Rechteinhabers dazu erhalten.

Diese Lizenz lässt die Urheberpersönlichkeitsrechte nach Schweizer Recht unberührt.

Eine ausführliche Fassung des Lizenzvertrags befindet sich unter
<http://creativecommons.org/licenses/by-nc-nd/2.5/ch/legalcode.de>

Von der Medizinischen Fakultät der Universität Bern auf Antrag der
Dissertationskommission als Dissertation genehmigt.

Promotionsdatum:

Der Dekan der Medizinischen Fakultät:

Table of content

1	Abstract.....	5
2	Introduction	6
3	Patients and Methods.....	6
3.1	Rationale and aim of the Study.....	6
3.2	Objective.....	7
3.3	Study Design	7
3.4	Study Population	7
3.4.1	Healthy volunteers.....	7
3.4.2	Cardiac surgery patients	8
3.4.3	Septic shock patients	8
3.5	Study Protocols	9
3.5.1	Study procedure in healthy volunteers.....	9
3.5.2	Cardiac surgery patients	9
3.5.3	Septic shock patients	9
3.5.4	Definition of measurements.....	9
3.5.5	Calculations and Statistical Analysis	10
4	Results.....	11
4.1	Basic Data of Study population.....	11
4.1.1	Healthy volunteers.....	11
4.1.2	Cardiac surgery patients	11
4.1.3	Septic shock patients	11
4.1.4	Descriptive statistics	11
4.2	Primary endpoints.....	11
4.2.1	Healthy volunteers.....	11
4.2.2	Cardiac surgery patients	13
4.2.3	Septic shock patients	18
4.3	Secondary endpoints.....	22
4.3.1	Between and within- investigator related variability	22
4.3.2	Correlation with central perfusion measured by sonography	22
5	Discussion.....	24
6	Acknowledgments	26
7	Appendices.....	27
8	References.....	29

1 Abstract

Background: Impaired peripheral perfusion is among the first manifestations of shock and the last to restore in the critically ill patient. In acute circulatory failure the activation of the sympathetic nervous system leads to a redistribution of blood from non-vital organs to the core in order to conserve oxygen delivery and tissue function of vital organs. Therefore, the clinical assessment of peripheral perfusion is an early and easily applicable parameter for detecting and evaluating tissue hypoperfusion and can help guiding therapy in acute circulatory failure. The peripheral perfusion index (PPI) is a simple, non-invasive tool to assess peripheral perfusion by calculating a quotient of pulsatile versus non-pulsatile blood flow of distal extremities using simple commercial pulse-oximetry, with lower values indicating poorer perfusion.

Objectives: With this study we aim to establish the peripheral perfusion index as a non-invasive, objective and continuous measurement comparable to other clinical assessments of peripheral perfusion such as capillary refill time (CRT), mottling score and temperature gradient from core and knee to toe. Furthermore, we aim to establish the relationship between PPI and urine production, arterial lactate concentration and perfusion of solid organs measured by ultrasound.

Methods: In this prospective cohort study at a tertiary teaching hospital we analyzed repeated measurements of peripheral perfusion, urine and lactate in 59 critically ill patients admitted to the ICU after cardiac surgery or in septic shock during the first 72 hours after admission, as well as sonographic assessment of organ perfusion in septic patients. Additionally, we established normal values of PPI in 30 healthy volunteers at ambient temperature and at vasoconstriction state by cooling of the upper extremities.

Results: In healthy volunteers, patients after cardiac surgery and in septic shock patients, PPI was 4.07 (3.36-4.79), 0.88 (0.66-1.88) and 1.29 (0.86-1.80), respectively and CRT 1.28s (0.96-2.02), 5.32s (4.41-6.23) and 4.07s (3.15-7.28), respectively for initial values in patients and during cooling state in healthy volunteers (median, IQR, all $p < 0.001$ between volunteers and patients and $p = 0.42$ for PPI and $p = 0.63$ for CRT between patient groups). Cooling in volunteers reduced PPI but did not change CRT ($p < 0.001$, $p = 0.190$). Correlation coefficients between PPI and CRT were -0.44, -0.32 and -0.19, respectively in the three groups (all $p < 0.003$), with better correlation initially $r = -0.59/-0.37/-0.34$ and $-0.54/-0.29/-0.26$ for correlation of PPI and CRT in cardiac and septic shock patients (initial measurement/first 10h/first 24h, all $p < 0.003$). However, concordance for changes was low (51% and 46% of CRT and PPI measurements changed in the same direction towards improvement or impairment in cardiac and septic patients). PPI correlated best with temperature gradient ($r = -0.47$, $r = -0.13$, both $p < 0.001$). Correlation coefficients between PPI and lactate were -0.31 and -0.13 (both $p < 0.013$), and in septic shock patients ($n = 17$) between PPI and resistive index of right kidney $r = 0.51$, and left kidney $r = 0.45$ (both $p < 0.037$).

Conclusions: While in healthy volunteers with artificially induced vasoconstriction PPI correlated well with clinical assessment of peripheral perfusion, the agreement between PPI and CRT, mottling score, temperature gradient, urine, lactate and abdominal organ perfusion measured by ultrasound was low in cardiac surgery and in septic shock patients. Correlation between PPI and CRT was better during the initial period of most impaired peripheral perfusion. The results encourage further investigation of PPI as automated assessment of peripheral perfusion in critically ill patients with acutely impaired hemodynamic function.

2 Introduction

Adequate tissue perfusion is crucial for maintaining oxygen supply and organ function in the critically ill patient. To avoid organ damage, an early recognition of inadequate tissue perfusion and immediate installation as well as accurate guiding of therapy is necessary. For monitoring tissue perfusion and oxygenation of the patient in the intensive care unit, global measurements such as blood pressure, oxygen-derived variables such as mixed or central venous oxygen saturation, and blood lactate levels are used. But direct, rapid and sequential evaluation of function of most organs is limited or the evaluation interferes with therapeutic measures, as for example cerebral function in the sedated patient. In circulatory failure, the body shifts blood from less important tissues as the skin and gastrointestinal tract to vital organs as brain, heart and kidneys, which results in apparent pale, cold and mottled skin. This clinical manifestation of cold, clammy skin is due to peripheral vasoconstriction in response to sympathetic nervous system activation or can follow capillary leak and fluid sequestration in sepsis. Since the peripheral tissues are sensitive to alterations in global perfusion, tissue hypoperfusion can be anticipated by assessing the peripheral perfusion.¹

A strong correlation of capillary refill time and 14d- mortality after initial resuscitation of septic shock has been noted.² Evidence shows that patients with septic shock remaining with poor peripheral perfusion have a poor outcome despite stabilization of macrocirculatory parameters.^{3,4}

For clinical assessment of peripheral tissue perfusion, capillary refill time, central-peripheral temperature gradient and mottling score of the skin are widely used because of simplicity of their measurements.^{5,6} But wide variability depending on age and temperature, and normal values in a substantial proportion of shock patients² call for further reliable signs. The peripheral perfusion index (PPI), measured by a simple commercial pulse-oximetry, could provide further information on tissue perfusion. In the same manner as the absorption of light is measured to calculate the oxygen saturation, the quotient of pulsatile versus non-pulsatile blood flow can be measured for calculating the peripheral perfusion index, with lower values indicating poorer perfusion. A PPI under 1.4 reflects poor peripheral perfusion in critically ill patients and a PPI ≤ 0.2 is predictive of mortality in septic shock patients after resuscitation, comparable to increased arterial blood lactate concentration.^{7,8} Recent recommendations favor tissue-perfusion over macrocirculatory-guided therapy in septic shock.^{9,10,11} Whereas in one of the first studies investigating peripheral-perfusion-targeted resuscitation, Hernandez et al. could not show improved 28d-mortality, but less organ dysfunction at 72 hours compared to lactate based resuscitation.¹²

The aim of this study was to evaluate PPI for monitoring peripheral perfusion in critically ill patients in comparison with established perfusion parameters, and, in a subset of septic patients, to evaluate its correlation with abdominal organ perfusion.

3 Patients and Methods

3.1 Rationale and aim of the Study

In the group of healthy volunteer, normal values in ambient temperature and after heating and cooling of upper extremity with resulting peripheral vasoconstriction were determined. The cardiac surgery patients in their post-surgical stabilization, characterized usually by poor tissue perfusion without metabolic failure and without abundant demand for vasopressors, served as another control population. The values from healthy volunteers and cardiac surgery patients were compared to those of patients in septic shock, in which additionally to the

peripheral perfusion parameters the perfusion of solid organs was evaluated by ultrasonography.

This allowed on one hand to establish normal values and on the other hand to study the potential effects of the underlying pathophysiology. We intended to answer the question in which clinical situations the PPI is or is not a reliable estimate of peripheral perfusion. Finally, the simultaneous assessment of peripheral and solid organ perfusion indicates how well the organ perfusion is reflected by the peripheral tissue perfusion.

3.2 Objective

The objective of this study is to validate the PPI as a continuous, objective parameter for peripheral perfusion by comparing it to conventional clinical signs of peripheral tissue perfusion (CRT, mottling score, temperature gradient) and to regional abdominal perfusion measured by ultrasound in septic patients.

3.3 Study Design

This single-center, prospective cohort study at a tertiary teaching hospital consisted of repeated, parallel measurements of the peripheral perfusion in two different patient populations (cardiac surgery and septic shock) during the first 72 hours of ICU stay and in a group of healthy volunteers.

3.4 Study Population

Study participants were between 18 and 80 years of age, without known peripheral artery disease, acute myocardial infarction or acute pulmonary embolism. ICU patients with use of extracorporeal membrane oxygenation (ECMO) were excluded because of impossibility to measure PPI without pulsatile blood flow. Informed consent was obtained before study inclusion in healthy volunteers and by general consent at admission in elective cardiac surgery patients. Septic patients were included after agreement of an independent doctor and informed consent was obtained directly from the patient after recovery or data used with agreement of an independent doctor only in accordance to legal instructions of the ethic committee in case of death. Research protocol was approved by the local ethic committee on 4th of August 2016.

3.4.1 Healthy volunteers

30 healthy volunteers were included in July and August 2016 as a control group. The first four volunteers served as test persons for study set-up and testing of cooling measurements and data recording.

Inclusion criteria:

- Signed informed consent

Exclusion criteria:

- Age <18 or >80 years
- Any acute illness with considerable cardiovascular interference
- Peripheral artery disease

3.4.2 Cardiac surgery patients

30 patients after cardiac surgery with cardiopulmonary bypass were included in August 2016, unless on vasopressor (norepinephrine or epinephrine) $>300\mu\text{g}/\text{h}$ at study inclusion (within 2 hours after ICU admission). For logistic reasons, a maximum of two patients per day were included. The first two patients served as test persons for study set-up and testing data recording.

Inclusion criteria:

- Signed general consent
- ICU admission after coronary artery bypass grafting or valve surgery with cardiopulmonary bypass

Exclusion criteria:

- Age <18 or >80 years
- Present or suspected myocardial ischemia
- Acute pulmonary embolism
- Peripheral artery disease
- Use of ECMO
- Dose of vasopressors ($>300\mu\text{g}/\text{h}$) at study inclusion period (within 2 hours after ICU admission)

3.4.3 Septic shock patients

From August 2016 to April 2017 29 patients with septic shock were included consecutively at ICU admission. Seven Patients in septic shock with lactate $\geq 3\text{mmol}/\text{l}$ were additionally included in the TARTARE-2S study⁹ with either conventional macrocirculatory or specific peripheral perfusion guided septic shock management.

Inclusion criteria:

- Inclusion after consent of independent doctor (with informed consent after recovery)
- ICU admission with septic shock defined as:
 - documented infection (suspected or confirmed) AND
 - systemic mean blood pressure $<65\text{mmHg}$ requiring any dose of vasopressor despite adequate fluid resuscitation (min. $20\text{ml}/\text{kg}$ crystalloids) to reach a systemic mean blood pressure of $\geq 65\text{mmHg}$ AND
 - lactate $\geq 2\text{mmol}/\text{l}$

Exclusion criteria:

- Age <18 or >80 years
- Present or suspected myocardial ischemia
- Acute pulmonary embolism
- Peripheral artery disease
- Use of ECMO

3.5 Study Protocols

3.5.1 Study procedure in healthy volunteers

In healthy volunteers the clinical parameters of tissue perfusion (capillary refill time, PPI) and vital signs were measured in ambient temperature (room temperature set at 23°C) and during warming and cooling of an extremity with gel-cold/hot-packs (Nexcare Cold/Hot Pad). The gel-packs were stored in the heating cabinet (set on 50°C) or the refrigerator (set on 4°C) overnight to ensure constant temperature. The dominant upper extremity was wrapped with the gel-packs from the axilla to the wrist. Measurements were taken when a steady state temperature (two identical skin temperature measurements during a minimum of 10 minutes) was achieved. Because of lack of significant prolongation of CRT after the first 15 healthy volunteers with measurements during ambient temperature and cooling with cold packs only, the second half of healthy volunteers underwent additionally warming of the upper extremity before cooling to maximize the difference of temperature and thus change in peripheral perfusion. This change in protocol was amended and accepted by the local Ethics Committee.

3.5.2 Cardiac surgery patients

In patients after cardiac surgery the clinical parameters of tissue perfusion (CRT, PPI, mottling score, temperature gradient) as well as other parameters of impaired perfusion (vital signs and urine production) were evaluated hourly until extubation or for a maximum of 72 hours. Arterial blood samples with determination of lactate were obtained at admission and as clinically indicated and ordered by the treating doctors.

3.5.3 Septic shock patients

In septic shock patients, parameters of peripheral perfusion and shock parameters were elaborated hourly till normalization of lactate or for maximally 72 hours. Blood samples with determination of lactate were obtained at admission and as clinically indicated judged by treating physicians or 2-hourly until normalization of lactate for patients also included in the TARTARE study.⁹ Besides monitoring of the peripheral perfusion parameters, the perfusion of solid organs was evaluated by ultrasonography once within 24h of ICU admission and 24h after first measurement. For logistic reasons, evaluation was only possible during weekdays. Ultrasonography was done by a certified radiologist following a standardized imaging protocol.¹³ The patients were examined in supine position, the artery of interest was identified by color doppler imaging and measurements of resistive index RI (peak systolic velocity-end-diastolic velocity)/peak systolic velocity and pulsatility index PI (peak systolic velocity-end-diastolic velocity)/mean velocity were measured by spectral Doppler, as well as the peak systolic velocity (cm/s), the end-diastolic velocity (cm/s) and acceleration (cm/s²). Three-fold measurements of the renal, hepatic, superior mesenteric artery, celiac trunk and portal vein were elaborated and a mean value calculated for each vessel (details see in sonographic protocol in annex).

3.5.4 Definition of measurements

Capillary refill time was measured by firm pressure on the distal phalanx of the index finger of the dominant hand for 10 seconds recording the time of return to normal color by a conventional clock. Measurements were made by two trained ICU-nurses. In healthy

volunteers the clock was covered and the time was recorded by a third person to guarantee that investigators weren't aware of previously measured values of the partner or themselves. The peripheral perfusion index was measured photometrically by the finger clip from pulse-oximetry at the middle finger of the dominant hand and displayed in the patient data management system as 2min-median-value, ranging from 0.02 – 20 according to producers' information. SpO2 sensor forms part of Carescape Monitor B850, SW 2.4.189.288, GE Healthcare Finland Oy, Kuortaneenkatu 2, FI-00510 Helsinki and values are measured by the Nellcor method.

Temperature gradient. Temperature sensors (Flexmax sensors produced by Covidien™) were attached on knee and toe (Dig. 1) and compared with central temperature and between each other.

Mottling score at knee (scale 0-5) was obtained using the mottling score described by Ait-Oufella 2011.¹⁴

Measurement of temperature and mottling score were elaborated at the same side as the measurements on the upper extremity of PPI and CRT, unless a superficial vein had been used for CABP surgery or the femoral artery punctured at this leg.

Data collection of PPI, temperature and lactate were automatically recorded by the PDMS (patient data management system, Centricity Critical Care®, GE Healthcare, Barrington, IL, USA) while CRT, mottling score and urine production were entered manually into PDMS.

3.5.5 Calculations and Statistical Analysis

As defined beforehand in the research protocol, mean values of three reported 2min-median-PPI-values were calculated at the respective time points of clinical assessments. For correlation, arterial lactate concentrations were matched if elaborated within 30min of clinical assessment of perfusion. In patients, mean hourly urine production was calculated throughout the observation period. For calculating correlation, measurements were tested for linearity, and if there was exponential correlation, data underwent logarithmic transformation.

Statistical analyses were performed and graphs designed using RStudio Version 1.1.423. Data were tested for normal distribution with Shapiro-Wilk-Test and displayed by mean with 95% confidence interval or median with 75% interquartile range. P-values were calculated using T-Test for normal distributed and Mann-Whitney Test for non-normally distributed values with a p-value <0.05 considered statistically significant.

Besides displaying the evolution of measurements over time and correlation, concordance was visualized with a four-quadrant-concordance plot, and concordance calculated as fraction of changes in the same direction towards improving or impairing of peripheral perfusion. For repeated pairwise comparisons between PPI and the different measurements of clinical assessment of peripheral perfusion, correlation coefficients for repeated observations were used as described by Bland-Altman.¹⁵ For two-time measurements (in healthy volunteers and sonographic assessments of solid organs in septic patients) Spearman correlation for independent measurements was used. Agreement of CRT between and within investigator coefficient was tested using variation (CV%), Cohen Kappa and Bland-Altman plots for limits of agreement.

4 Results

4.1 Basic Data of Study population

4.1.1 Healthy volunteers

16 females and 14 males with a mean age of 55 years (29-62) were studied (Tab.1).

4.1.2 Cardiac surgery patients

36 patients after cardiac surgery were assessed. The first patient was excluded as test patient, another for refusal of informed consent, further three because of technical problems with data recordings, and one patient because of an initially ignored exclusion criterion. The included 30 cardiac surgery patients (7 females and 23 males) had a mean age of 62 years (50-71, Tab. 1).

4.1.3 Septic shock patients

Of 31 patients included, one patient was later excluded because of discovering an exclusion criterion and one patient refused the informed consent and couldn't be replaced following legal instructions of the ethics committee. Mean age was 66 years (58-72 years) with 10 females and 19 males (Tab. 1).

4.1.4 Descriptive statistics

descriptive statistics					
	healthy volunteers	cardiac surgery patients	septic shock patients	p-value (volunteers- cardiac)	p-value (cardiac-septic)
number of participants	30	30	29		
age (years)	55 (29 - 62)	62 (50 - 71)	66 (58 - 72)	p<0.001	p=0.447
sex (female)	16 (53%)	7 (23%)	10 (34%)	p=0.018	p=0.354
number of measurements	77	323	1711		
outcome (alive)	30 (100%)	28 (93%)	21 (72%)		p=0.035
inclusion time (h min)	0h 32min (19-42min)	8h 42min (7h 49min - 16h 22min)	50h 42min (40h 35min - 60h 50min)	p<0.001	p<0.001

Tab.1 Descriptive statistics. Values show calculated mean with 95% confidence interval in parenthesis or median with inner and outer quartile. P-values are computed between healthy volunteers and cardiac surgery patients (4th column) and between cardiac and septic patients (5th column)

4.2 Primary endpoints

4.2.1 Healthy volunteers

Cooling produced a mean reduction in skin temperature of a non-enclosed finger of 2.19°C (1.51 - 2.88°C). This resulted in a slight, non-significant prolongation of mean CRT from 1.11s (0.88 – 1.43) to 1.28s (0.96 – 2.02, p=0.190), reaching pathological values of CRT >2sec only in 10 healthy volunteers (33%). In contrast PPI significantly decreased from 7.72 (6.75 – 8.70) to 4.07 (3.36 – 4.7, p<0.001), with only one pathological value <1.40 (3%) (Tab. 2, Fig. 3-4).

measurements healthy volunteers				
	ambient	warming	cooling	p-value
CRT (sec)	1.11 (0.88 - 1.43)	1.35 (1.05 - 1.61)	1.28 (0.96 - 2.02)	p=0.190
PPI	7.72 (6.75 - 8.70)	6.98 (6.38 - 7.58)	4.07 (3.36 - 4.79)	p<0.001
difference of temperature finger (ambient-cooling) (°C)			2.19 (1.51- 2.88)	p<0.001
difference of temperature finger (ambient-warming) (°C)			-0.43 (-1.41 - 0.56)	p=0.340
difference of temperature finger (warming-cooling) (°C)			2.59 (1.74 - 3.43)	p<0.001

Tab.2 Measurements healthy volunteers in ambient, warming and cooling state. Values show calculated mean with 95% confidence interval in parenthesis or median with inner and outer quartile.

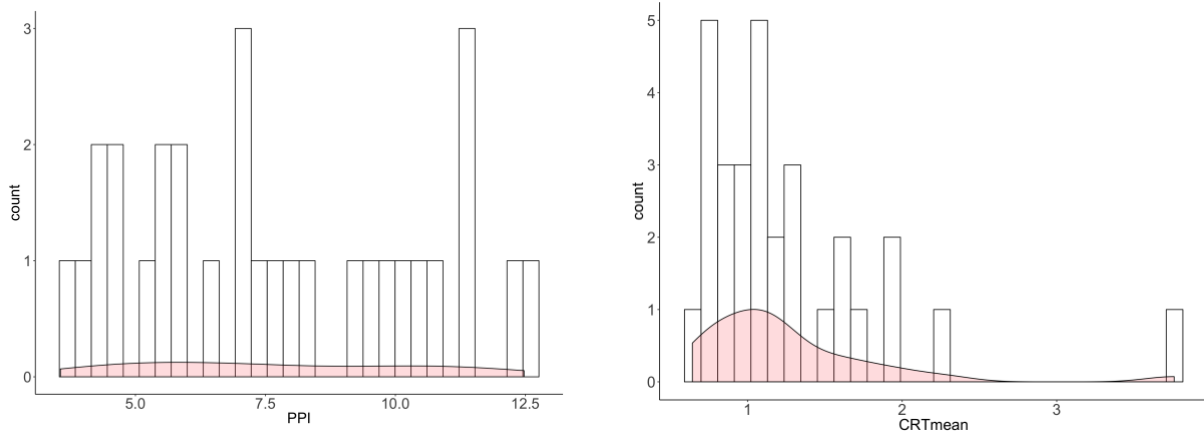


Fig. 1&2 Histogram of normal values of PPI and CRT of healthy volunteers in ambient state

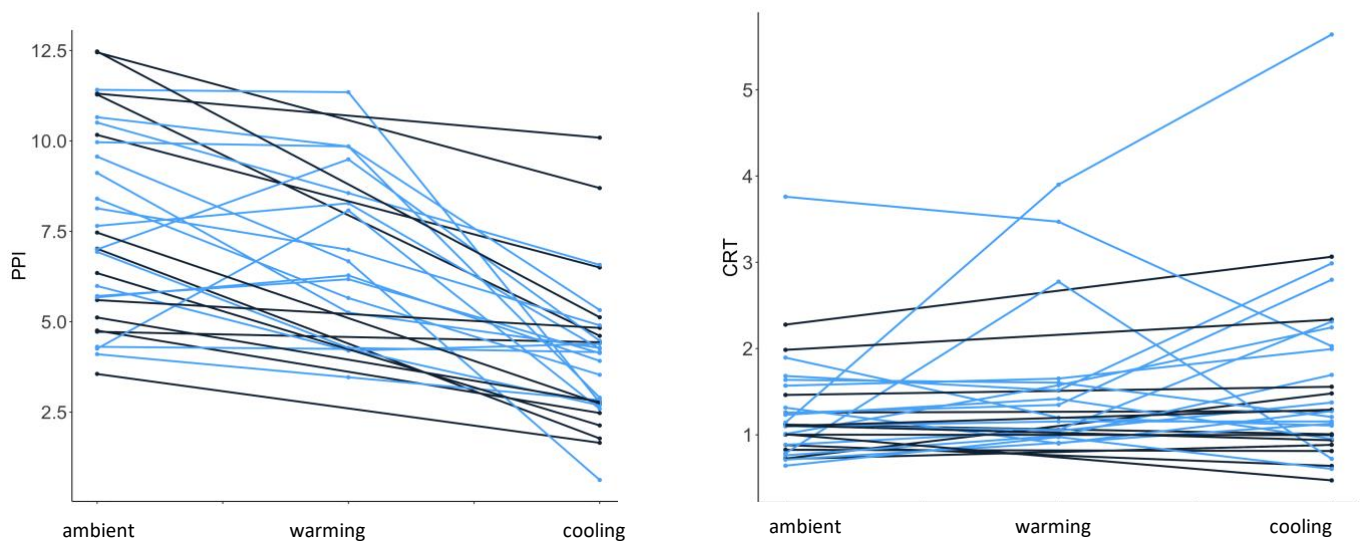


Fig. 3&4 CRT and PPI per participant during temperature states in healthy volunteers. Volunteers with additionally warming in-between are marked blue.

The four-quadrant concordance plot shows weak overall concordance (60%), where a given prolongation of CRT (positive difference) leads to a reduction of PPI (negative difference). In contrast significant correlation of PPI and CRT of $r=-0.44$ in healthy volunteers can be highlighted (Tab. 3, Fig. 5&6).

correlation of PPI and other measurements in healthy volunteers			
	correlation coefficient	n	p-value
CRT	-0.44 (-0.65 -0.17)	77	p=0.002

Tab.3 Correlation coefficient of CRT and PPI in healthy volunteers with 95% CI in parenthesis.

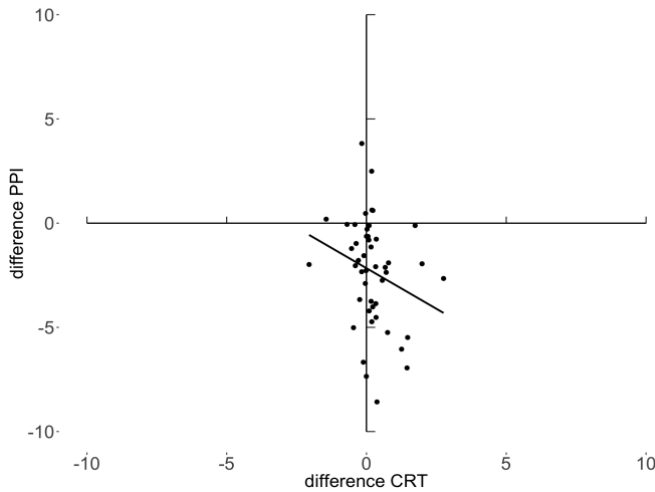


Fig.5 Four-quadrant concordance plot of PPI and CRT in healthy volunteers

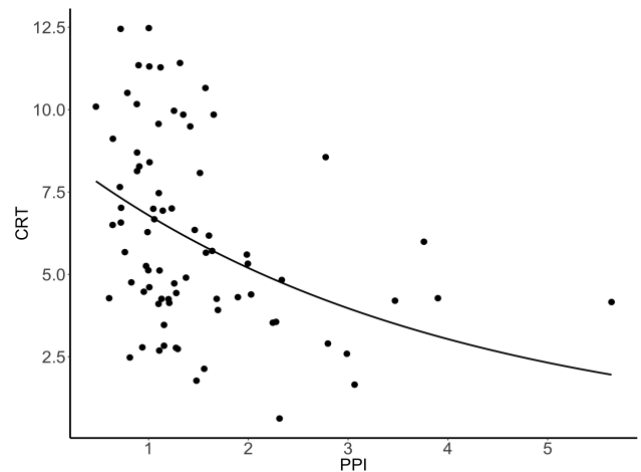


Fig.6 Correlation of PPI and CRT in healthy volunteers (displayed without logarithmic transformation)

4.2.2 Cardiac surgery patients

CRT, mottling score, urine, temperature gradient and serum lactate levels decreased while PPI increased over the course of the postoperative period (Fig.7 and individual courses of CRT and PPI displayed in Fig. 8).

Comparing with the artificially produced vasoconstriction in healthy volunteers during cooling state, more pathological values with initial CRT of 5.32 (4.41 – 6.23) and initial PPI of 0.88 (0.66 – 1.88) can be noted (both $p < 0.001$, Tab.4). Initial lactate levels were non or mildly pathologic with a non-pathologic lactate $< 2\text{mmol/l}$ in 63%, between 2-4mmol/l in 30%, and $> 4\text{mmol/l}$ in 7%. In 6 patients (20%) increasing lactate values greater than initial lactate was measured with a peak lactate after 6h24min (5h12min – 8h 01min) and mean normalization time reaching lactate $< 2\text{mmol/l}$ after 17h06min (16h31min – 19h38min) (patients with increasing lactate but always below 2mmol were excluded from analysis).

Overview of measurements of peripheral perfusion and comparison between groups					
	healthy volunteers	cardiac surgery patients	septic shock patients	p-value (volunteers- cardiac)	p-value (cardiac-septic)
initial/cooling CRT (sec) <i>min-max</i>	1.60 (1.21 - 1.99) 0.47- 5.64	5.32 (4.41 - 6.23) 1.16 - 10.51	4.07 (3.15 - 7.28) 1.00 - 23.69	p<0.001	p=0.628
CRT overall mean (sec) <i>min-max</i>	1.20 (0.98 -1.64) 0.47 - 5.64	3.96 (2.33 - 5.96) 0.54 - 19.18	4.80 (2.99- 8.03) 0.50 - 41.35	p<0.001	p<0.001
initial/cooling PPI <i>min-max</i>	4.07 (3.33 - 4.82) 0.63 -10.10	0.88 (0.66 - 1.88) 0.10 - 17.35	1.29 (0.86 - 1.80) 0.03 - 7.35	p<0.001	p=0.417
PPI overall mean <i>min-max</i>	5.60 (4.20 - 8.28) 0.62- 12.48	1.80 (0.76 - 4.20) 0.07 - 17.35	1.59 (0.75 - 3.15) 0.03 - 17.06	p<0.001	p=0.011
Mottling Score		0=78.5% 1=18.2% 2=2.3% 3=0.9% 4=0%	0=73.0% 1=15.4% 2=10.1% 3=1.1% 4=0.4%		p=0.032
Urine production (ml/h)		89 (57 - 133)	18 (0 - 47)		p<0.001
Difference of temperature core-knee (°C)		4.65 (3.33 - 10.08)	6.30 (3.10 - 9.58)		p=0.875
Difference of temperature knee-toe (°C)		-3.5 (-5.9 - -0.7)	-1.7 (-4.5 - 0.6)		p<0.001
Initial lactate (mmol/l) <i>min-max</i>		1.70 (1.33 - 2.10) 0.70 - 8.10	4.0 (2.9 - 6.6) 1.90 - 13.90		p<0.001
Lactate overall mean (mmol/l) <i>min-max</i>		1.70 (1.30 - 2.38) 0.60 - 9.60	3.70 (2.60- 6.30) 1.10 - 19.00		p<0.001

Tab. 4 Overview of measurements of peripheral perfusion and comparison between participants. Values show calculated mean with 95% confidence interval in parenthesis or median with inner and outer quartile. P-values are computed between healthy volunteers and cardiac surgery patients (4th column) and between cardiac and septic patients (5th column)

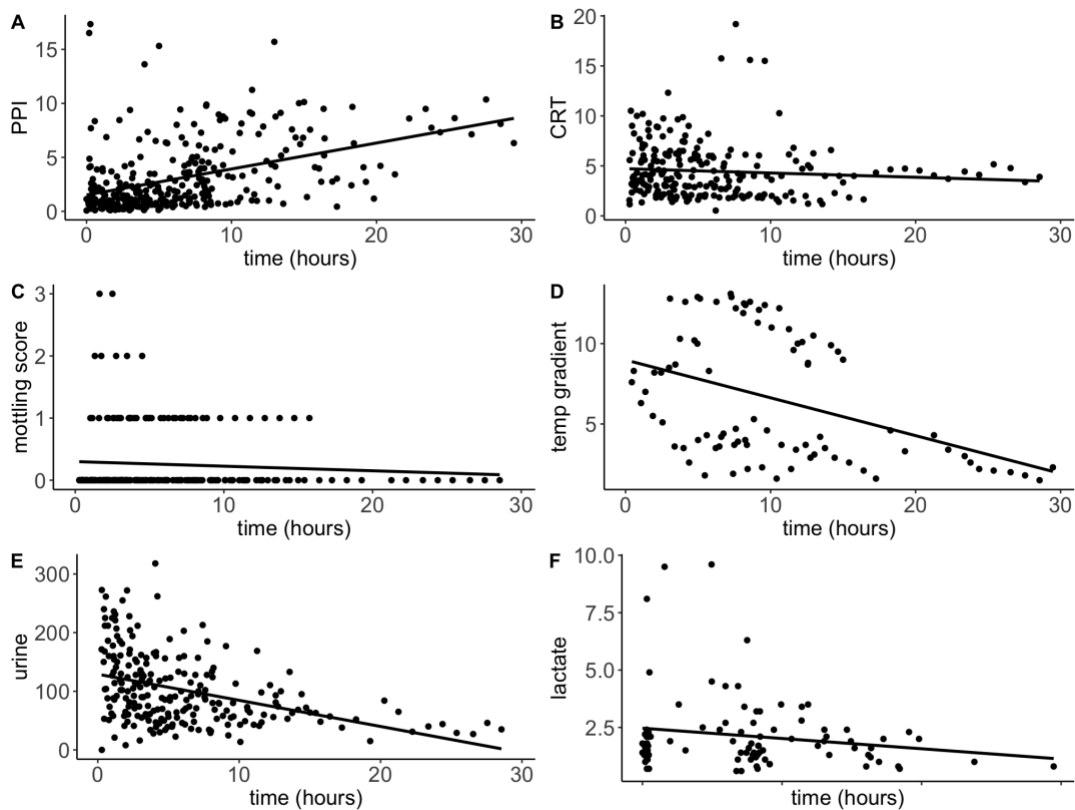


Fig. 7 Measurements over time in cardiac surgery patients with linear regression line. Correlation of measurements with time PPI r=0.47, CRT r=-0.35, MS r=-0.21, urine r=-0.28, lactate r=-0.45 (all p<0.004)

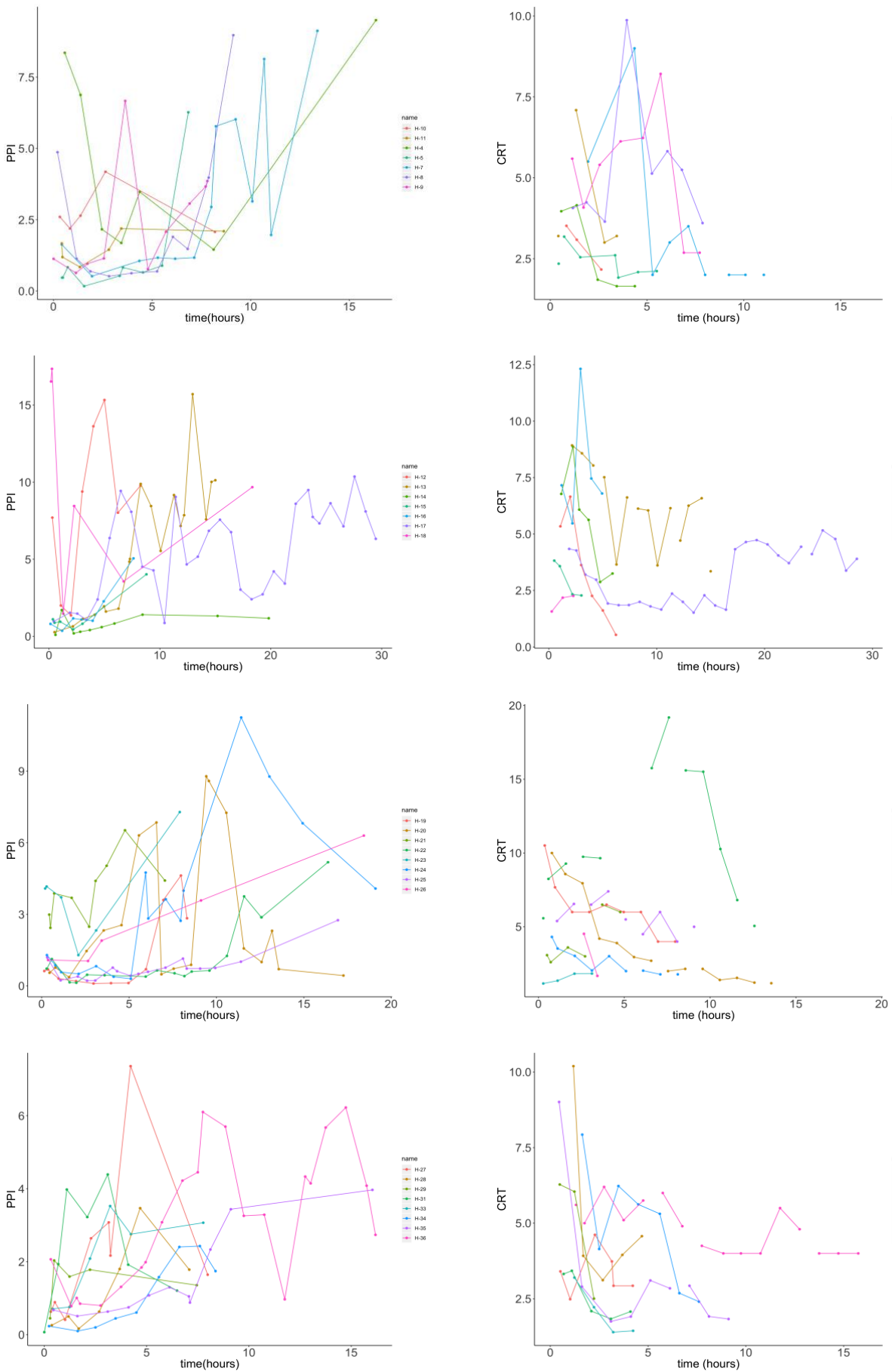


Fig. 8 Individual course of PPI (left column) and CRT (right column) over time in cardiac surgery patients colored by participant. For better visualization splitted in four graphs.

In cardiac surgery patients, concordance of measurements is weak with concordance of PPI and CRT of 51%, mottling score 5%, temperature gradient 51%, urine 62% and lactate 53% (Fig. 9). Correlation is displayed in Tab. 5 and Fig. 9. Correlation is stronger in the initial period the disease course with a correlation coefficient of PPI and CRT of $r=-0.59^*/-0.37^*/-0.34^*$; mottling score $r= -0.37^*/-0.31^*/-0.35^*$; temperature gradient $r= 0.98/-0.60^*/-0.44^*$; urine $r=0.28/-0.13/-0.13$; lactate $r= -0.45/-0.11/-0.30^*$ (for initial measurement/first 10h/first 24h after admission. *statistically significant with all $p<0.049$)

correlation of PPI and other measurements of peripheral perfusion in cardiac surgery patients			
	correlation coefficient	n	p-value
CRT	-0.32 (-0.44 - -0.19)	230	$p<0.001$
mottling score	-0.35 (-0.47 - -0.22)	219	$p<0.001$
urine production	-0.14 (-0.27 - 0.01)	230	$p=0.053$
temperature gradient (core-knee)	-0.47 (-0.63 - -0.28)	86	$p<0.001$
temperature gradient (knee-toe)	0.29 (-0.09 - 0.60)	259	$p=0.114$
lactate	-0.31 (-0.52 - -0.07)	94	$p=0.013$

Tab 5. Correlation of PPI and other measurements of peripheral perfusion in cardiac surgery patients with 95% CI in parenthesis.

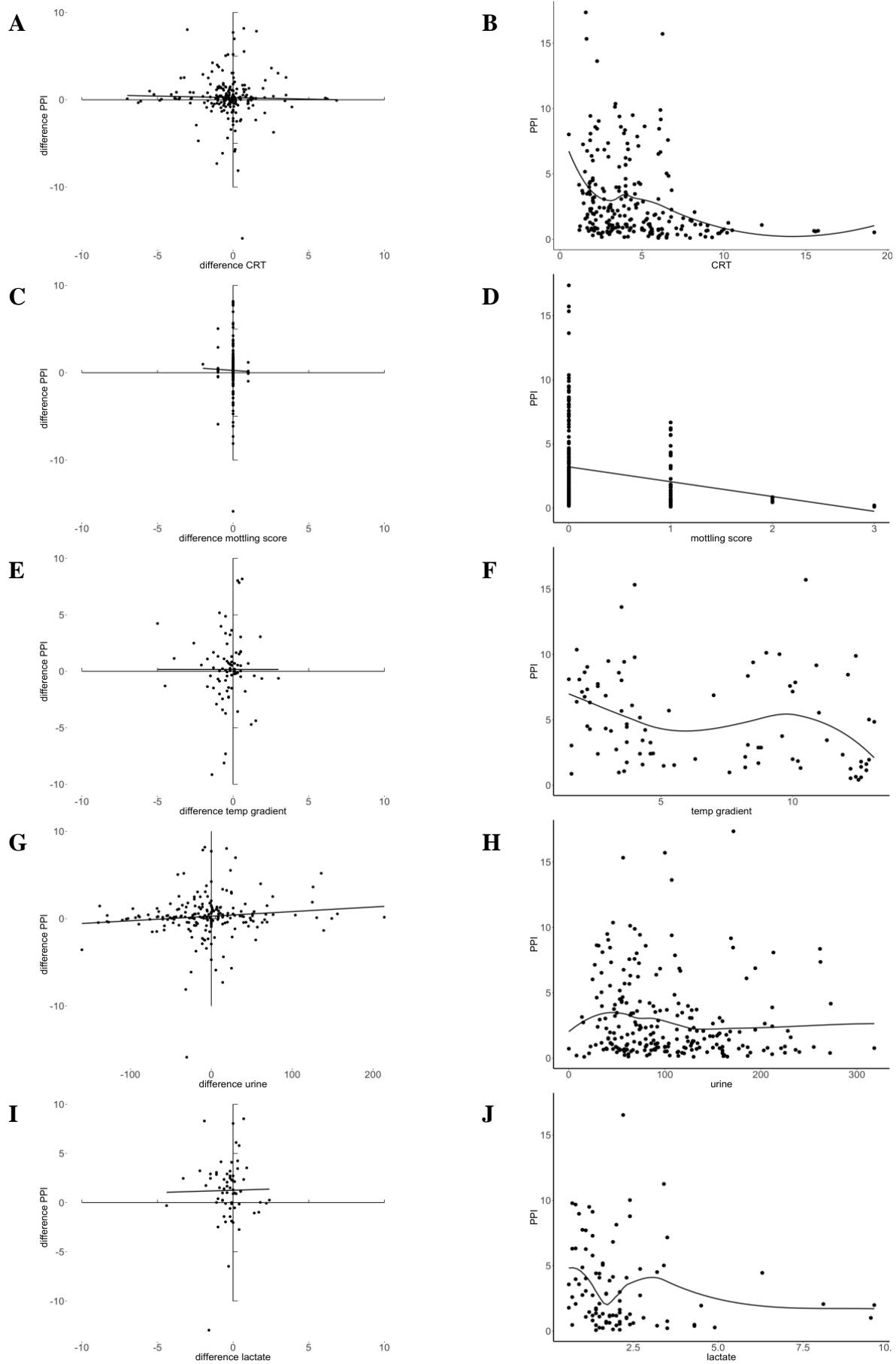


Fig. 9 Concordance in four-quadrant concordance plot and correlation of PPI and other measurements of peripheral perfusion with a loess regression line in cardiac surgery patients.

4.2.3 Septic shock patients

Patient characteristics are presented in Table 1. On average recording lasted 51 hours. CRT, mottling score, urine, temperature gradient and serum lactate levels decreased while PPI increased over the course of the disease (Fig.10). Initial PPI 1.29 (0.86 – 1.80) and initial CRT 4.07 (3.15 - 7.28) are more impaired compared to artificially produced vasoconstriction of healthy volunteers ($p < 0.001$ both), but not different from initial values of cardiac surgery patients (initial PPI $p = 0.42$ and initial CRT $p = 0.63$) but initial lactate 4.0 (2.9-6.6) as well as mean lactate were higher than in cardiac surgery (both $p < 0.001$, Tab.4).

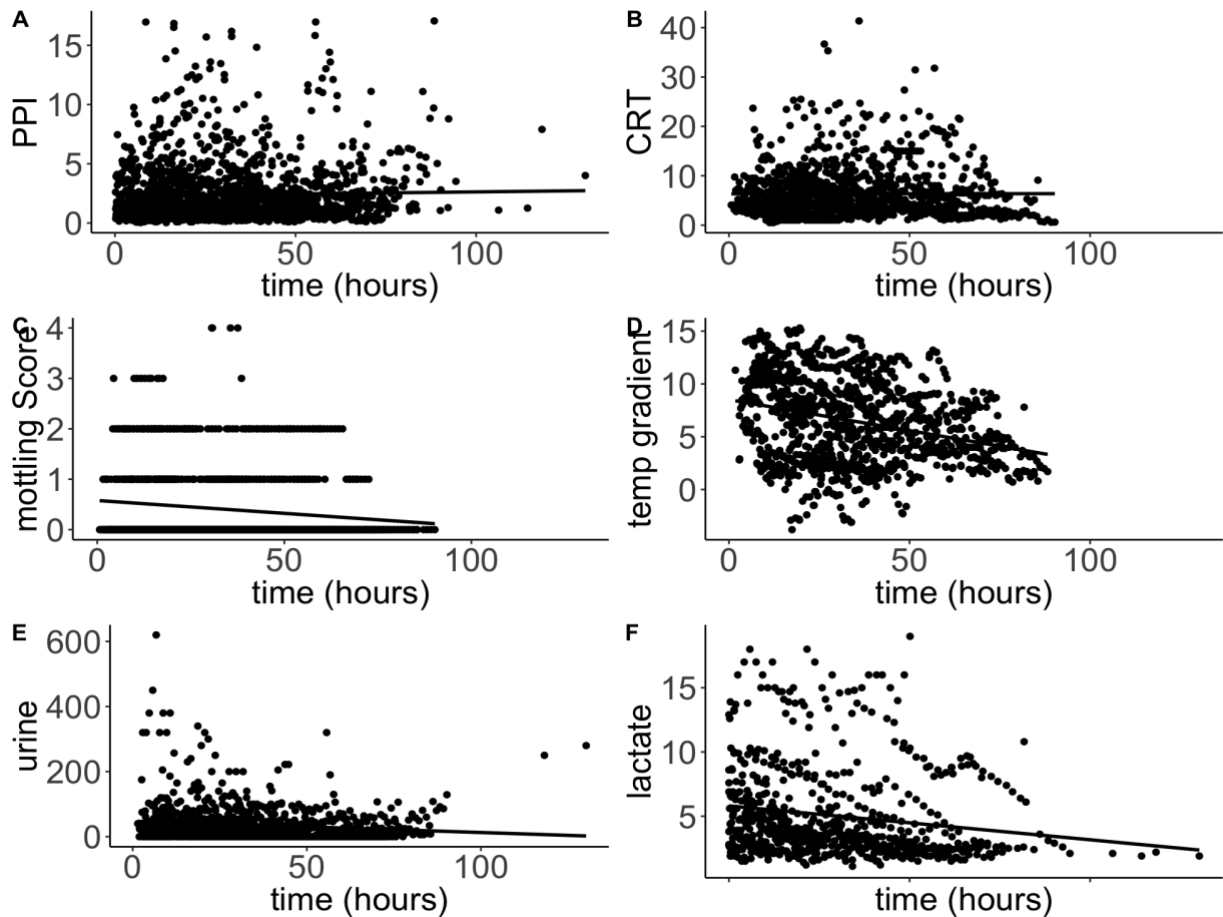


Fig.10 Measurements over time in septic shock patients with linear regression line. Correlation of measurements with time PPI $r=0.18^*$, CRT $r=-0.03$, MS $r=-0.35^*$, urine $r=-0.11$, lactate $r=-0.31$ (* statistically significant with $p < 0.002$).

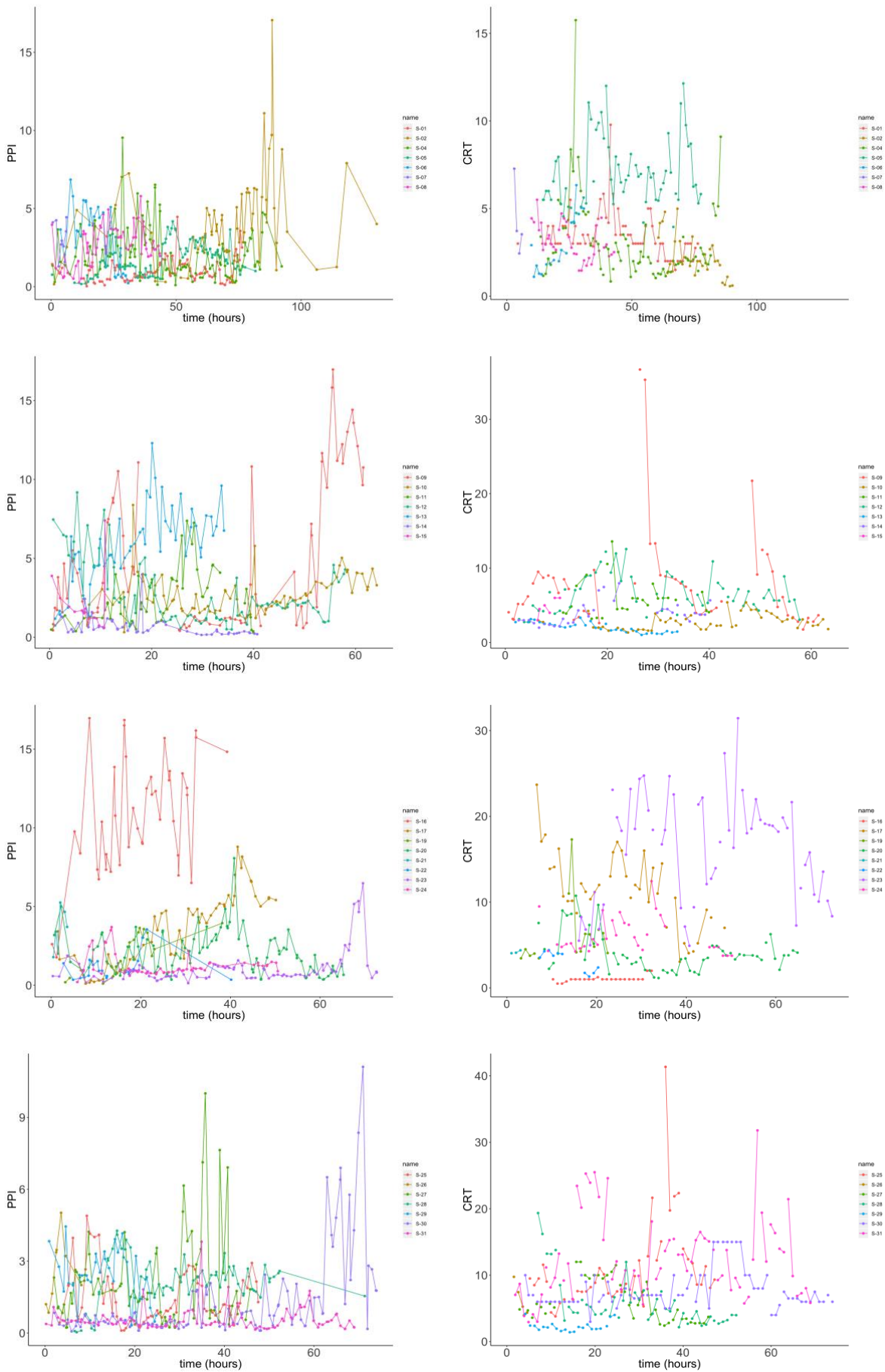


Fig. 11 Individual course of PPI (left column) and CRT (right column) over time in septic patients colored by participant. For better visualization, splitted in four graphs.

In septic shock patients, concordances of measurements are weak with concordance of PPI and CRT of 46%, mottling score 3%, temperature gradient 45%, urine 37% and lactate 52% (Fig. 12). Correlation is displayed in Tab. 6 and Fig. 12.

Correlation is stronger in the initial period of course of the disease with a correlation coefficient of PPI and CRT of $r=-0.54^*/-0.29^*/-0.26^*$; mottling score $r= -0.29/-0.11/-0.09$; temperature gradient core-to-knee $r= -0.55/-0.30^*/-0.02$; urine $r=0.28/0.03/-0.02$; lactate $r= -0.13/-0.19^*/-0.18$ (for initial measurement/first 15h/first 24h after admission. *statistically significant with all $p<0.014$)

correlation of PPI and other measurements of peripheral perfusion in septic shock patients			
	correlation coefficient	n	p-value
CRT	- 0.19 (-0.24- -0.13)	1064	$p<0.001$
mottling Score	- 0.13 (-0.19 - -0.07)	1020	$p<0.001$
urine production	- 0.03 (-0.09 - 0.03)	980	$p=0.34$
temperature gradient (core-knee)	- 0.13 (-0.18 - -0.07)	1242	$p<0.001$
temperature gradient (knee-toe)	0.06 (-0.04 - 0.17)	1254	$p=0.22$
lactate	- 0.13 (-0.20 - -0.05)	681	$p=0.002$

Tab 6. Correlation of PPI and other measurements of peripheral perfusion in septic shock patients with 95% CI in parenthesis.

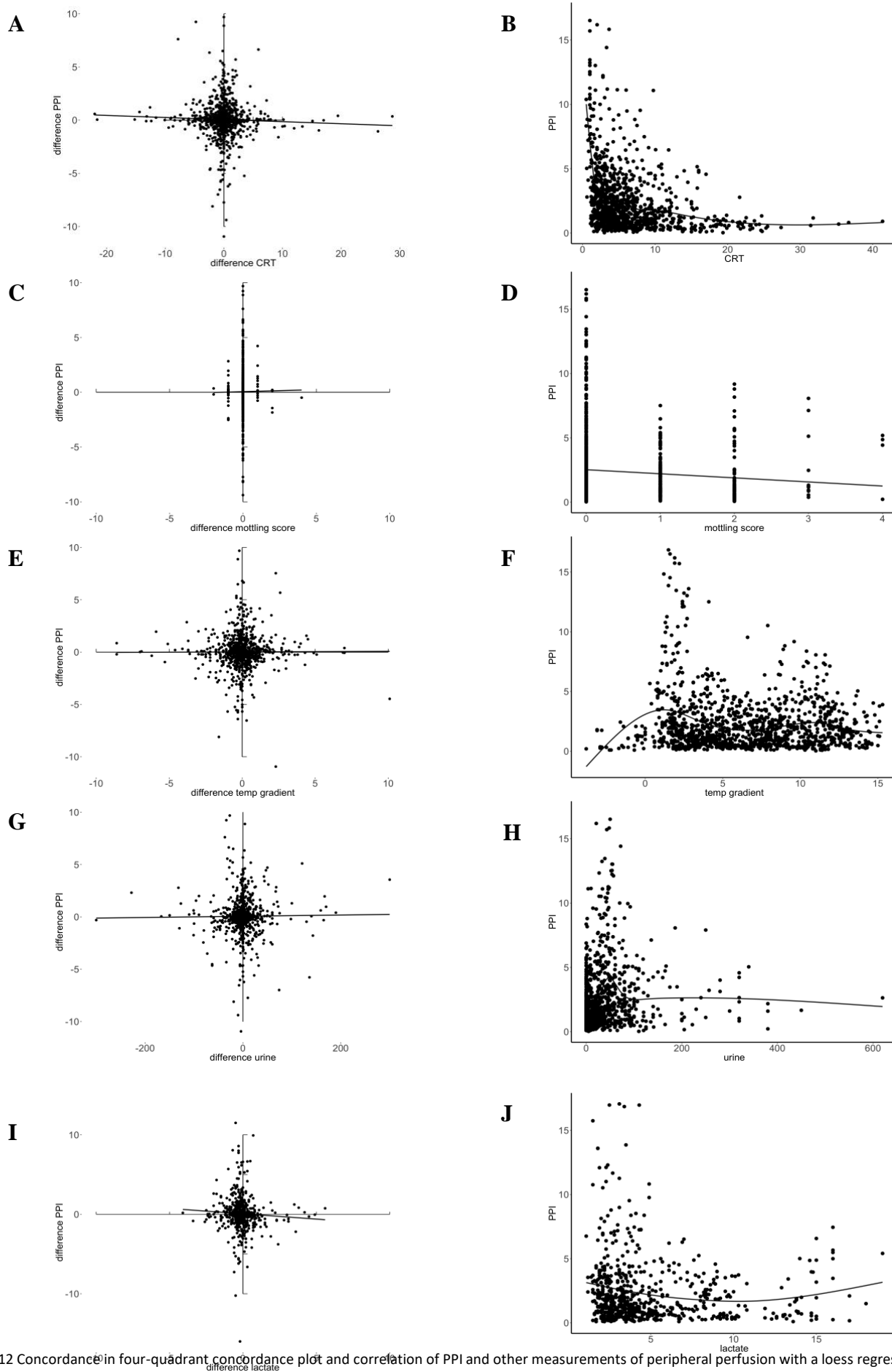


Fig. 12 Concordance in four-quadrant concordance plot and correlation of PPI and other measurements of peripheral perfusion with a loess regression line in septic shock patients.

4.3 Secondary endpoints

4.3.1 Between and within- investigator related variability

Variability of sequential measurement of capillary refill time in healthy volunteers within the same investigator were 12.3% (7.7 – 19.3) with an intra-rater reliability by Cohen Kappa of 0.03 (n=150, p<0.001).

Variability between experienced ICU-nurses was 12.4% (3.9 – 24.5) with an inter-rater reliability by Cohen Kappa of 0.10 between investigators (n=1296, p<0.001).

Bland-Altman plot for bias (mean of differences=-0.01) and limits of agreement (lower limits=-5.48, upper limit 5.45) shows wider differences of CRT measurements in severe prolonged CRT over 9 seconds. (Fig. 13)

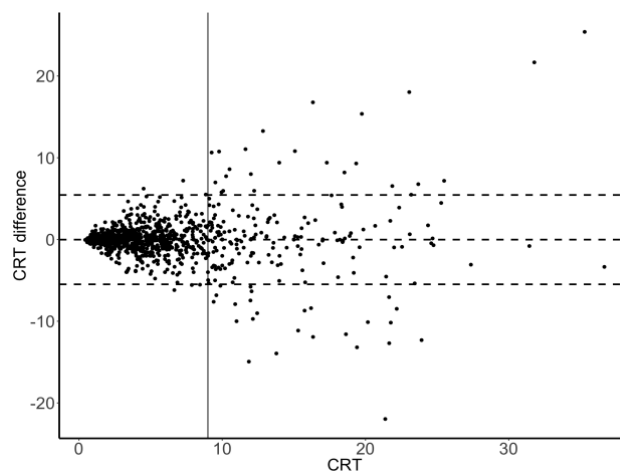


Fig.13 Bland-Altman plot with bias and limits of agreement of CRT measurements. Critical difference = 5.46 and visually acceptable limit=9 (displayed in graph).

4.3.2 Correlation with central perfusion measured by sonography

In septic shock patients, correlation of peripheral and abdominal organ perfusion was analyzed with sonography (n=17, two-timed sonography n=9). For limited number of repetitive measurements in the same patients analysis was made using Pearson correlation. Unless fair correlation only resistive index of right and left kidney turned out statistically significant (p<0.036) (Tab 7, Fig. 14).

correlation of central perfusion measured by sonography			
	correlation coefficient	n	p-value
pulsatility index right kidney	0.41 (-0.1 - 0.75)	16	p=0.119
resistive index right kidney	0.51 (0.10 - 0.77)	21	p=0.018
pulsatility index left kidney	0.32 (-0.19 - 0.69)	17	p=0.210
resistive index left kidney	0.45 (0.03 - 0.73)	22	p= 0.036
pulsatility index spleen	0.27 (-0.33 - 0.71)	13	p= 0.381
resistive index spleen	0.40 (-0.19 - 0.78)	20	p=0.175
pulsatility index liver	0.23 (-0.47 - 0.75)	10	p= 0.521
resistive index liver	0.40(-0.19 - 0.78)	13	p=0.175

Tab 7. Correlation of PPI and sonographic measurements of central perfusion in septic shock patients with 95% CI in parenthesis.

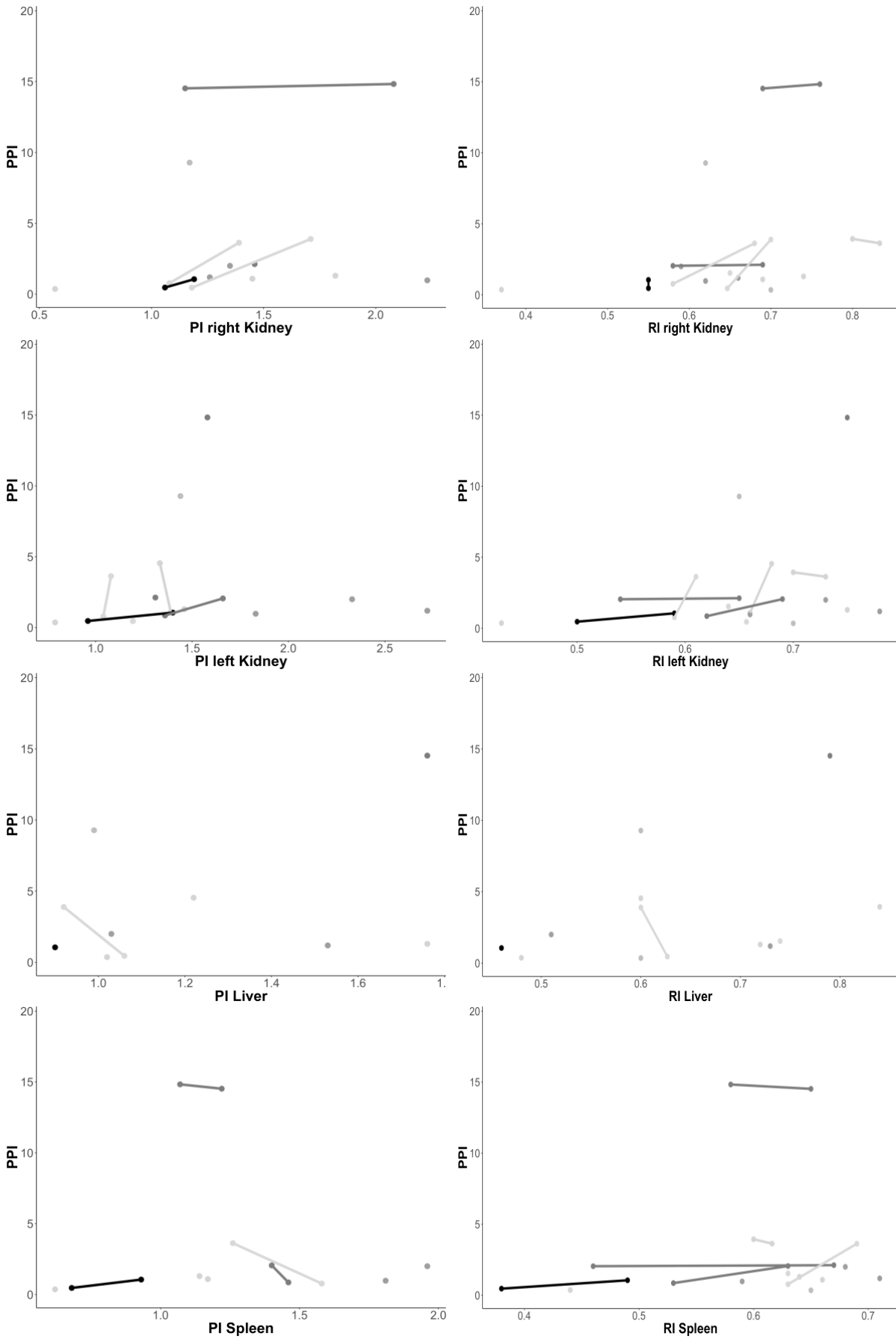


Fig.14 Correlation coefficient of PPI and resistive index (RI) and pulsatility index (PI) colored by participant and linked if two-timed sonography.

5 Discussion

The aim of this prospective cohort study was to validate PPI as a continuous, objective parameter for peripheral perfusion comparable to already used clinical signs of tissue perfusion. Furthermore, we aimed to demonstrate that peripheral perfusion reflects abdominal organ perfusion as measured by sonography.

Our main findings are the following: 1) PPI tracked decreases in peripheral perfusion induced by relatively small temperature changes in healthy volunteers better than CRT; 2) PPI correlated weakly with CRT, temperature gradients, mottling score and arterial lactate concentration, but concordance for changes was low 3) PPI failed to correlate with most of the ultrasound-derived assessments of abdominal organ perfusion.

In our study design for healthy volunteers, CRT was the gold standard to measure peripheral perfusion. In a study investigating 1000 participants, Anderson et al defined a CRT normal upper limit of 3.5s (median 1.9s, range 0.8-6.1s).⁵ These authors found that predictors of CRT such as age, sex, ambient and patient temperature together explained only 8% of CRT variability. On the other side, in healthy adults, PPI follows a skewed distribution with high inter-individual variability with values ranging from 0.3 to 10.0 (inter-quartile range 0.7-3.0).⁷ It is well possible that predictors of PPI, a signal reflecting arterial pulsation, are different from those for CRT, a measurement of more peripheral perfusion, including venous filling and flow. Accordingly, the extent and mechanism of reducing peripheral perfusion may also influence how the measured parameter (CRT vs. PPI) will react: Schriger et al. showed that CRT lacks the ability to detect mild blood loss from blood donors and van Genderen et al. demonstrated that increasing hypovolemia impairs PPI only to a certain limit without the ability to differentiate between mild and progressive hypovolemia.^{16,17}

Furthermore, in contrast to previous studies,^{18,19} with our cooling method in healthy volunteers, we were only able to reduce the peripheral temperature by a few degrees of Celsius and the related changes in CRT may well have been below the detection limit of a stop watch including the reaction time of the observer. Finally, the intra- and inter-observer variabilities in our study were substantial – a reason why we consider PPI as potentially advantageous. In fact, in our setting with volunteers, PPI seemed to be more sensitive in detecting impaired peripheral perfusion than CRT.

While we found that all our parameters assessing perfusion changed towards normalization over time in cardiac surgery and septic shock patients, correlation between PPI and the other parameters was weak. Hernandez et al highlighted the differences between normalization rates of perfusion parameters in septic shock patients:¹⁶ CRT normalized within the first 2 hours after starting ICU-based resuscitation, earlier than temperature gradients or lactate.²⁰ With markedly different normalization rate, perfusion related variables exhibited a biphasic response with an initial rapid improvement, followed by much slower trend thereafter in another group of septic shock survivors.²¹ In this manner weak correlation of continuous measurements over full course of disease could be explained by different sensitivities in detecting changes and therefore different normalization rates of peripheral perfusion.

Correlation between CRT and PPI in our study was comparable to results from other studies: Espinoza et al. evaluated in healthy volunteers CRT agreement within two observers, measured by chronometer or by video²² and correlated CRT with PPI. The correlation was significant if CRT was assessed by video-analysis ($r=-0.36$ and $r=-0.26$ for different observers), but not if measured by chronometer ($r=-0.24$ and $r=-0.20$).

Lima et al. showed in 37 measurements in septic shock patients near perfect concordance when comparing PPI and temperature gradient differences at initial state of impaired and at the state after normalization of conventional measurements (CRT and temperature gradient).⁷ Also in our study in patients, correlation between PPI and CRT was best in the initial phase, when parameters were most abnormal and improved during the initial, intense treatment. In this manner, correlation of initial measurements of PPI and CRT, including most impaired values in patients and normal values in healthy volunteers, reached a good correlation coefficient of $r=0.80$. As shown in the individual trends of our patients, there were very different patterns of CRT and PPI over time, underlining that change of PPI is strongly dependent of individual baseline with lesser vasoconstriction potential for persons with smaller baseline PPI.²³ Overall improving circulation is the result of several factors, including rewarming, spontaneous vasodilatation, improving cardiac function, and effects of administered fluids and vasoactive drugs. Low correlation, especially in septic shock patients, can be explained by marked hemodilution that provokes dissociation from systemic and regional hemodynamics,²⁴ as well as concomitant tissue perfusion heterogeneity,^{4,25,26} which is likely to alter CRT more than arterial pulsatility.

Lima et al.³ described that a temperature gradient from core to toe over 7°C and a temperature gradient from forearm to fingertip $>0^{\circ}\text{C}$ are indicators of vasoconstriction and Van Genderen showed correlation with outcome in abdominal surgery patients.²⁷ As well as Lima et al.⁷, we could not find a correlation of PPI with the temperature difference from core-to-toe. Because of much more error-prone temperature measurements on the toe, we additionally investigated core-to-knee temperature, which resulted in mean differences of 4.65 (3.33 – 10.08) in cardiac and 6.30 (3.10 – 9.58) in septic shock patients, indicating peripheral vasoconstriction, with a significant correlation of $r=-0.47$ in cardiac surgery and $r=-0.13$ in septic shock patients.

In our study, PPI did not correlate with urine production, whereas Ait-Oufella found a weak correlation between PPI and urine production ($r=0.12$).²⁸ Since urine production depends on multiple factors such as prior kidney function, length of extra-corporeal circulation, fluid and vasopressor management and diuretic therapy, (transient) uncoupling from microcirculation seems likely.

He et al. described similarly low correlation coefficient for PPI and lactate ($r= -0.31$ by single measurement of lactate in 46 septic patients;⁸ $r=-0.26$ for multiple lactate measurements²⁹) as we did ($r=-0.31$ in cardiac surgery and $r=-0.13$ in septic shock patients). Another study investigating CRT and outcome in septic shock patients showed a correlation of $r=0.53$ between CRT and lactate,² whereas we noted substantially lower correlation with $r=0.19$ in cardiac surgery and $r=0.07$ in septic shock patients. As Ait-Oufella measured CRT and lactate only once in 59 patients 6 hours after admission, we found similar result with a correlation coefficient of $r=0.53$ for CRT and lactate during the first 6 hours after admission in septic shock patients. Various studies show that peripheral perfusion is highly dissociated from systemic hemodynamics, with earlier restoration in survivors and persistent impairment despite stabilization of global hemodynamics in non-survivors.^{4,21,30} Additionally, microscopic investigations show heterogenous perfusion within organs, as well as highly variable territorial disparities in septic shock patients, possibly explaining the lack of strong correlation.³¹

Concerns over the variability and the cut-off limit of CRT measurements are raised regularly in recent literature.^{22,32} In contrast to investigations with interrater variability as primary endpoint, our data obtained in clinical circumstances by experienced ICU-nurses but without

further specific instructions, show wide interrater variability with a coefficient of variation of 12.3% between the same investigator and 12.4% between different investigators and a Cohen Kappa of 0.03 within and 0.10 between investigators. In healthy children fair inter-observer variability with ICC of 0.70 and a Cohen Kappa of 0.54 was found,³³ whereas in a systematic review highly variable interobserver reliability ranging from $\kappa < 0.15$ to 0.65 and an intra-observer reliability of ICC=0.96 are reported.³² In healthy adults Klupp et al were able to demonstrate reasonable intra-rater reliability (ICC=0.72) but poorer inter-rater reliability (ICC range= 0.12-0.81).³⁴ Regarding adult septic patients, Ait-Oufella demonstrated an inter-rater concordance of 80% and Van Genderen a Cohen Kappa of 0.74-0.91 in abdominal surgery patients.^{2,27} Our inferior results may therefore partly be explained by CRT measurements conducted in clinical practice. Bland Altman plots demonstrated a limit of agreement of -5.48 – 5.45 seconds for CRT measurements with considerably higher interrater variability for CRT measurements >9 s, but well above the actually claimed cut-off of 2.5-5 seconds.³⁵

Using ultrasound we could demonstrate significant correlation of peripheral perfusion only with resistive index of the kidney. Brunauer et al. demonstrated in septic shock patients comparable results evaluating pulsatility index with CRT, mottling score and temperature perception with significant results for CRT and pulsatility index of intestines ($r=0.33$), and pulsatility index of kidney and mottling score ($r=0.40$) but not temperature.³⁶ Despite few correlations being significant, all correlation coefficients are low and do in our opinion not allow to draw conclusions from peripheral on abdominal organ perfusion. This may partly be related to effects of vasoconstrictors which help to improve organ perfusion pressure but simultaneously may decrease peripheral perfusion.

Limitations of this study are the single-center design, exclusive measurement of PPI on the fingertip and lack of recording of vasopressor dose and administered fluids.

In summary, we demonstrate low agreement of PPI with clinical assessment of peripheral perfusion obtained by CRT, mottling score and temperature gradients. Correlation was better in the initial period with substantial improvement of most impaired peripheral perfusion and was also higher in cardiac surgery than in septic shock patients. PPI but not CRT tracked impairment in peripheral perfusion induced by small temperature changes in volunteers. PPI correlated weakly with lactate and abdominal organ perfusion measured by ultrasound-derived pulsatility and resistive indices.

PPI may have a place as part of the assessment of peripheral perfusion in the evaluation and early recognition of patients with impairing hemodynamic function.

6 Acknowledgments

I like to warmly thank my tutors Prof. Dr. Stephan Jakob and Sabine Berger for their support, patience, motivations and eye-openers in the evolution of my work. I learned a lot during the whole process of compilation of study protocol, application to the ethic committee and realization, analysis and interpretation of the study investigations.

7 Appendices

7.1 Schedule of assessment

Healthy volunteers	Before cooling	During warming	During cooling
Demographic Data	x		
Vitals (BP, P, SpO2)	x	x	x
Capillary refill time	x	x	x
Peripheral Perfusion index	x	x	x
Skin temperature	x	x	x

Cardiac surgery patients	ICU Admission	Hourly up to Extubation or max. 72h
Demographic Data ¹	x	
Vitals (BP, P, SpO2) ¹	x	x
Capillary refill time ¹	x	x
Peripheral Perfusion index ¹	x	x
Skin mottling score ¹	x	x
Temp. difference ¹	x	x
Urine production ¹	x	x
Blood samples (Lactat)	x	²

¹ Included in the patient data management system (PDMS), measured at each full hour following ICU admission

² only at times when clinically indicated

Septic shock patients	ICU Admission	Hourly up Normalization of Lactat ³ or max. 72h
Demographic Data ¹	x	
Vitals (BP, P, SpO2) ¹	x	x
Capillary refill time ¹	x	x
Peripheral Perfusion index ¹	x	x
Skin mottling score ¹	x	x
Temp. difference ¹	x	x
Urine production ¹	x	x
Blood samples (Lactat)	x	2-hourly
Sonographic assessment of organ perfusion ²	x	

¹ Included in the patient data management system (PDMS), measured at each full hour following ICU admission

² Within 24h after ICU admission and second measurement 24h after first ultrasound

³ Normalization of lactate is defined as two consecutive measurements of lactate <2mmol/l

7.2 Sonography protocol

time points

1st sonography: in the first 24 hours after study inclusion (only during weekdays)
 control sonography: in the first 24 hours (only during weekdays) respectively the 1st weekday after cessation of vasopressors

measurements

- sonography performed by junior radiologists from the University Department for Diagnostic, Interventional and Pediatric Radiology instructed by senior radiologists in the standardized imaging protocol;

Sacerdoti et al, Journal of Hepatology, 1997:

"Interobserver variability in the measurement of hepatic, splenic and renal arterial resistance indexes can be decreased to non-significant levels by a common training program"

- sonography machine: Acuson S 2000, Siemens
 transducer: Acuson 4C1 - curved vector transducer (bandwidth: 1 – 4,5 MHz), Siemens

- patients in supine position
- identification of the artery of interest by color doppler imaging
spectral Doppler measurements in the artery of interest
recording during several heart beats
- recording of the following measurements:
 - resistive index $RI = (\text{peak systolic velocity} - \text{end-diastolic velocity}) / \text{peak systolic velocity}$
 - pulsatility index $PI = (\text{peak systolic velocity} - \text{end-diastolic velocity}) / \text{mean velocity}$
(Petersen, Nephrol Dial Transplant, 1997)
 - peak systolic velocity (cm/s)
 - end-diastolic velocity (cm/s)
 - acceleration (cm/s²)
- 3-fold measurements of each vessel to limit variability (Paulson et al., Radiology, 1996), RIs/PIs then averaged to obtain mean RI values (Deruddre, Intensive Care Med, 2007)
- reporting of the average

arteries of interest

kidney:

- oblique longitudinal approach
- one interlobar artery („RI at the level of interlobar/arcuate artery most consistent“, Knapp et al., J Ultrasound Med, 1995) along the border of the medullary pyramids (Degirmenci, Jpn J Radiol, 2013) in pars intermedia on both sides
- average of the averaged values of the right and left kidney

liver:

- right intercostal approach
- one intraparenchymal artery in segment VII/VIII

spleen:

- left intercostal approach
- one sub-branch of the splenic artery

8 References

1. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. *Intensive Care Med.* 2005;31(10):1316-1326.
2. Ait-Oufella H, Bige N, Boelle PY, et al. Capillary refill time exploration during septic shock. *Intensive Care Med.* 2014;40(7):958-964.
3. 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(3):934-938.
4. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med.* 2004;32(9):1825-1831.
5. **Anderson B, Kelly AM, Kerr D, Clooney M, Jolley D. Impact of patient and environmental factors on capillary refill time in adults. *Am J Emerg Med.* 2008;26(1):62-65.**
6. Coudroy R, Jamet A, Frat JP, et al. Incidence and impact of skin mottling over the knee and its duration on outcome in critically ill patients. *Intensive Care Med.* 2015;41(3):452-459.
7. **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(6):1210-1213.**
8. He HW, Liu DW, Long Y, Wang XT. The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation. *Crit Care.* 2013;17(3):R116.
9. Pettila V, Merz T, Wilkman E, et al. Targeted tissue perfusion versus macrocirculation-guided standard care in patients with septic shock (TARTARE-2S): study protocol and statistical analysis plan for a randomized controlled trial. *Trials.* 2016;17:384.
10. Palizas F, Dubin A, Regueira T, et al. Gastric tonometry versus cardiac index as resuscitation goals in septic shock: a multicenter, randomized, controlled trial. *Crit Care.* 2009;13(2):R44.
11. Gruartmoner G, Mesquida J, Ince C. Fluid therapy and the hypovolemic microcirculation. *Curr Opin Crit Care.* 2015;21(4):276-284.
12. Hernandez G, Ospina-Tascon GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA.* 2019;321(7):654-664.
13. Sacerdoti D, Gaiani S, Buonamico P, et al. Interobserver and interequipment variability of hepatic, splenic, and renal arterial Doppler resistance indices in normal subjects and patients with cirrhosis. *J Hepatol.* 1997;27(6):986-992.
14. Ait-Oufella H, Lemoine S, Boelle PY, et al. Mottling score predicts survival in septic shock. *Intensive Care Med.* 2011;37(5):801-807.
15. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1--Correlation within subjects. *BMJ.* 1995;310(6977):446.
16. **van Genderen ME, Bartels SA, Lima A, et al. Peripheral perfusion index as an early predictor for central hypovolemia in awake healthy volunteers. *Anesth Analg.* 2013;116(2):351-356.**
17. Schriger DL, Baraff LJ. Capillary refill--is it a useful predictor of hypovolemic states? *Ann Emerg Med.* 1991;20(6):601-605.
18. Lima A, Bakker J. Clinical assessment of peripheral circulation. *Curr Opin Crit Care.* 2015;21(3):226-231.
19. **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(4):606-611.**
20. Hernandez G, Pedreros C, Veas E, et al. Evolution of peripheral vs metabolic perfusion parameters during septic shock resuscitation. A clinical-physiologic study. *J Crit Care.* 2012;27(3):283-288.

21. Hernandez G, Luengo C, Bruhn A, et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. *Ann Intensive Care*. 2014;4:30.
22. **Espinoza ED, Welsh S, Dubin A. Lack of agreement between different observers and methods in the measurement of capillary refill time in healthy volunteers: an observational study. *Rev Bras Ter Intensiva*. 2014;26(3):269-276.**
23. **Hoiseth LO, Hisdal J, Hoff IE, Hagen OA, Landsverk SA, Kirkeboen KA. Tissue oxygen saturation and finger perfusion index in central hypovolemia: influence of pain. *Crit Care Med*. 2015;43(4):747-756.**
24. Dubin A, Henriquez E, Hernandez G. Monitoring peripheral perfusion and microcirculation. *Curr Opin Crit Care*. 2018;24(3):173-180.
25. Ait-Oufella H, Maury E, Lehoux S, Guidet B, Offenstadt G. The endothelium: physiological functions and role in microcirculatory failure during severe sepsis. *Intensive Care Med*. 2010;36(8):1286-1298.
26. **Edul VS, Enrico C, Laviolle B, Vazquez AR, Ince C, Dubin A. Quantitative assessment of the microcirculation in healthy volunteers and in patients with septic shock. *Crit Care Med*. 2012;40(5):1443-1448.**
27. **van Genderen ME, Paauwe J, de Jonge J, et al. Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. *Crit Care*. 2014;18(3):R114.**
28. Ait-Oufella H, Joffre J, Boelle PY, et al. Knee area tissue oxygen saturation is predictive of 14-day mortality in septic shock. *Intensive Care Med*. 2012;38(6):976-983.
29. He H, Long Y, Liu D, Wang X, Zhou X. Clinical classification of tissue perfusion based on the central venous oxygen saturation and the peripheral perfusion index. *Crit Care*. 2015;19:330.
30. 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(8):2287-2294.
31. Ait-Oufella H, Bourcier S, Lehoux S, Guidet B. Microcirculatory disorders during septic shock. *Curr Opin Crit Care*. 2015;21(4):271-275.
32. Fleming S, Gill P, Jones C, et al. Validity and reliability of measurement of capillary refill time in children: a systematic review. *Arch Dis Child*. 2015;100(3):239-249.
33. **Gorelick MH, Shaw KN, Baker MD. Effect of ambient temperature on capillary refill in healthy children. *Pediatrics*. 1993;92(5):699-702.**
34. Klupp N, Keenan A-M. An evaluation of the reliability and validity of capillary refill time test. *The Foot*. 2007;17:15-20.
35. Hasanin A, Mukhtar A, Nassar H. Perfusion indices revisited. *J Intensive Care*. 2017;5:24.
36. Brunauer A, Kokofer A, Bataar O, et al. Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: A pilot study. *J Crit Care*. 2016;35:105-109.