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Influence of systemic hemodynamics on microcirculation during sepsis

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ABSTRACT

Purpose: During sepsis, improvement of hemodynamic may not be related to improvement of microcirculation. The aim of this study was to investigate influence of systemic circulation on microcirculation in septic ICU patients.

Methods: This is a prospective cohort study of septic ICU patients. Microcirculation was investigated with Near infrared spectrometry (NIRS) measuring tissue oxygen saturation (StO_2). StO_2 desaturation ($desStO_2$) and resaturation ($resStO_2$) slopes were determined. Analyses were made at baseline and after fluid challenges.

Results: Seventy-two patients were included. One hundred and sixty measures were performed at baseline. StO_2 was 77.8% [72.4–85.0] and $resStO_2$ was 87.3%/min [57.8–141.7]. Univariate analysis showed an association between $resStO_2$ and diastolic arterial pressure (DAP) ($p = .001$), and norepinephrine dose ($p = .033$). In multivariate linear regression, there was an association between $resStO_2$ and DAP ($\beta = 1.85$ (0.64 to 3.08), $p = .004$). Fluid challenges ($n = 60$) increased CO, and $resStO_2$ (all $p < .001$). In multivariate analysis, variation of stroke volume was associated with variation of $resStO_2$ ($p = .004$) after fluid challenge. There was no association between CVP and $resStO_2$.

Conclusions: DAP was the only independent determinant of resStO2 in septic patients. Fluid challenges may improve microcirculation. CVP did not influence $resStO_2$.

1. Introduction

Sepsis is a common and severe condition in ICU patients. This syndrome is often associated with vasoplegia and alterations of microcirculation. Guidelines recommend treating aggressively any hemodynamic alterations that render the patient hypotensive or with elevated lactate levels. The hemodynamic resuscitation has been extensively studied and relies on volume and vasopressors. During sepsis, capillary reactivity is impaired with a lack of arterioles reactivity [1-5]. The alterations in microvascular responsiveness related to sepsis [6-9] are characterized by a decrease in perfused microvascular density, and an increase in microvascular flow heterogeneity which limits the number of capillaries that can be "recruited" after a hypoxic stimulus. Dissociation between macrocirculation and microcirculation during sepsis is a highly debated topic [10]. Most of the studies focused on the association between sublingual videomicroscopy and arterial pressures or cardiac output. It seems now that correlation between those 2 entities is dependent of the resuscitation phase of the patients. During early sepsis, patients may be vasoplegic and hypovolemic, here improvement of macrohemodynamics is associated with improvement of microcirculation. Later, when microvascular and endothelial inflammation is predominant studies suggest a lack of hemodynamic coherence between macro- and microcirculatory parameters. This means that correction of systemic hemodynamic at this point is not necessarily associated with microcirculation improvement [11-18].

Microcirculatory alterations are associated with unfavorable outcome. Correction of these alterations could be associated with better chances of survival. Anyway, to date, no strategy aiming at improving microcirculation was shown to be beneficial.

In addition, there is a gap of knowledge regarding the precise influence of macrocirculation, which is daily evaluated by ICU physicians, on microcirculation, which is only assessed in research [6].

This study aimed to evaluate the influence of macrocirculation on microcirculations parameters measured by NIRS and the influence of fluid challenges in septic ICU patients.

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2. Materials and methods

2.1.1. Study design and population

This is a prospective observational cohort study aiming to evaluate the influence of macrocirculation on microcirculatory parameters in ICU patients diagnosed with sepsis. The study was approved by an institutional ethic committee (Comité d'éthique de la Société Française d'Anesthésie-Réanimation, IRB 00010254-2016-088) that waived written patient consent.

All patients referred to Lariboisière Hospital 20 beds surgical ICU (Paris, France), between 2009 and 2014, were screened.

Patients with the following criteria were included: age > 18 years old, diagnosed with sepsis during hospitalization, presence of an arterial line, a central venous catheter located in the superior vena cava, a monitoring of the cardiac output and a monitoring of the microcirculation with a Near infrared spectroscopy device (NIRS) located on the hand thenar eminence.

2.1.2. Patient management

Patients were treated according to the Lariboisière Hospital Surgical ICU protocols in compliance with international guidelines. The diagnosis of sepsis was at physician discretion in accordance with the Surviving sepsis campaign guidelines [19]. Schematically, hemodynamics management aimed for the following targets: mean arterial blood pressure > 65 mm Hg, Central venous oxygen saturation > 70% and plasmatic lactate value < 2 mmol/l. A cross-mark corresponding to the phlebostatic level (4th or 5th intercostal space on the axillary line) was drawn on patients' skin in to order to ensure consistency of measures. Central venous and arterial line pressure transducers were zeroed before each measure. Vasopressors or fluid infusion was administrated when required to reach predefined targets. Cardiac output was monitored with Esophageal Doppler or echocardiography. When mechanical ventilation was initiated, tidal volume was limited to 6–7 ml/kg to maintain inspiratory plateau pressure of <30 cmH20 and a transpulmonary driving pressure < 15 cmH_2O. Enteral nutrition was initiated after 48 h of care. Glycemic control was at the discretion of the physician. Antibiotics were administrated the earliest possible after sepsis diagnosis and were chosen according to local protocols.

2.1.3. Measurements and data collection

Following data were collected: demographic data (age, sex, body mass index (BMI), origin of sepsis, severity scores (SAPS II, SOFA), surgical or medical treatment); time of sepsis diagnosis, time of ICU admission, length of hospitalization, clinical data and biological data of patients; treatments administrated during sepsis (mechanical ventilation, renal replacement therapy, antibiotics, vasopressors), 28-day mortality.

Systemic macrocirculation was assessed with the following parameters: heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressure, central venous pressure (CVP), cardiac output (CO), stroke volume (SV) and central venous oxygen saturation ($SvcO_2$). Microcirculation parameters were monitored by NIRS (In-Spectra Model 650, Hutchinson Technology, Hutchinson, Minnesota, USA) on the thenar eminence as previously described [20]. Tissue oxygen saturation (StO_2) on the thenar eminence opposite to the arterial line side was recorded, and a vascular occlusion test was performed, using a cuff inflated to 50 mm Hg above systolic blood pressure for 3 min, for evaluation of the StO_2 desaturation ($desStO_2$) and resaturation ($resStO_2$) slopes, as well as the minimal value reached during ischemia ($minStO_2$). Slopes were calculated using InSpectra Analysis V3-03. The slope values were considered adequate when the linear adjustment showed a correlation (R2) value over 0.95. When a fluid challenge was decided by the physician in charge, data were recorded before and after a fluid infusion (NaCl 0.9% or Lactated Ringer 250 ml or 500 ml in 10 min). Fluid challenge could be repeated several times in a same patient. Only the data obtained during the first day of NIRS monitoring were used in this study. $ResStO_2$ was selected as the main microcirculation parameter to be studied in accordance with previously published studies [3,7,20-22].

2.2. Statistical analysis

The results are expressed as median [interquartile range]. Continuous variables were compared by a Mann-Whitney test. Continuous variables before and after FC were compared by a Wilcoxon Rank Sum test and categorial variables by Fisher's test.

Linear regressions were used to test the influence of microcirculation parameters on $resStO_2$. Confidence intervals for the slopes of the regression lines were constructed by generating 200 bootstrap resamples of the prediction and removing the extreme values. To take into account the fact that a patient may have been included multiple times, linear mixed-models were used with $resStO_2$ as dependent variable, the tested variable as fixed effect and the patient as random effect. A sensitivity analysis based only on the first measurement was also performed. Variables with a *p*-value lower than 0.20 in univariate analysis were tested in multivariate analysis. To avoid multicollinearity, we did not include variables mathematically related to each other's in the same model, by focusing on stroke volume and heart rate over cardiac output, and SAP and DAP over MAP. Variance inflation factor (VIF) was used to detect multicollinearity in the regression analysis. A value lower than 5 has been chosen to exclude collinearity between predictors.

Regarding association of $resStO_2$ with outcome, in case of multiple measurements for a subject, only first assessment was used.

All statistical analyses were performed using R statistical software version 3.4.3 (R Core Team, 2017, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org). The R package 'lme4' version 1.1–15 was used for mixed-models with its 'bootMer' function for bootstrapping (Bates D, Maechler M, Bloker B and Walker S, 2015, Linear Mixed-Effects Models using 'Eigen' and S4, https://cran.r-project.org/web/packages/lme4/index.html). A *p* value lower than 0.05 was considered significant.

3. Results

3.1. Patients

Between 2009 and 2014, seventy-two patients were included in the study. Median age was 72 [61–83] years; 30/72 (42%) were males. Patients' characteristics are summarized in Table 1. Sepsis origin was

Table 1
Patients characteristics ($n = 72$).

Variables	Median [Q1, Q3]
Age, years	72 [61, 83]
Male, n (%)	30 (42)
BMI, kg/m^2	24 [21, 27]
SAPS II	59 [50, 70]
SOFA without neuro	9 [7, 12]
Mechanical ventilation, n (%)	72 (100)
Origin of sepsis, n (%)	
Abdominal	43 (60)
Pulmonary	14 (19)
Other	15 (21)
Comorbidities, n (%)	
Hypertension	47 (65)
Congestive Heart failure	10 (14)
Ischemic heart disease	15 (21)
Stroke	6 (8)
Chronic renal failure	9 (12)
Diabetes mellitus	21 (26)
28-day mortality, n (%)	27 (37.5)

Data are numbers (percentage) or median [25–75% interquartile]. BMI: Body Mass Index, SOFA Sequential Organ Failure Assesment, SAPS: Simplified Acute Physiologic Score.

Table 2
Hemodynamic and NIRS variables at baseline ($n = 160$ measures).

Variables	Values
Norepinephrine, n (%)	87 (54)
Norepinephrine dose, mcg/kg/min	0.48 [0.29, 0.75]
Epinephrine, n (%)	13 (8)
Epinephrine dose, mcg/kg/min	0.17 [0.14, 0.26]
Dobutamine, n (%)	3 (2)
Dobutamine dose, mcg/kg/min	5 [5, 7]
Cardiac Output, l/min	5.0 [3.7, 6.4]
Stroke volume, ml	50 [38, 67]
Mean arterial pressure, mmHg	74 [67, 82]
Systolic arterial pressure, mmHg	114 [102, 129]
Diastolic arterial pressure, mmHg	54 [49, 61]
Heart rate, bpm	101 [85, 116]
Central venous pressure, mmHg	10 [7, 13]
Lactate, mmol/l	2.30 [1.78, 3.30]
Hemoglobin, g/dl	10.8 [9.7, 12.4]
$SvcO_2$, %	76 [68, 80]
StO_2, %	77.8 [72.4, 85]
$desStO_2$, %/minute	−9.7 [−12.4, −6.4]
$resStO_2$, %/minute	87.3 [57.8, 141.7]
$minStO_2$ after Occlusion (%)	48.5 [38.0, 59.6]

Data are numbers (percentage) or median [25–75% interquartile]. $SvcO_2$ central venous oxygen saturation, StO_2 transcutaneous oxygen saturation, $desStO_2$: desaturation slope of tissue oxygen saturation, $resStO_2$: resaturation slope of tissue oxygen saturation. N = 72 patients.

mainly abdominal (43/72 (60%)) or pulmonary (14/72 (19%)). The median SAPS II score was 59 [50; 70]. Mortality at day-28 was 37.5%.

3.2. Macrocirculation and microcirculatory parameters at baseline

One hundred and sixty measures were performed at baseline in the seventy-two patients. The systemic hemodynamic and microcirculation parameters measurements were performed within 24 h of admission for most patients (median day of measurement = 1 [0–3]).

Regarding systemic hemodynamics, median cardiac output was 5.0 l/min [3.7–6.4], MAP 74 mm Hg [67–82], CVP 10 mm Hg [7–13]. NIRS variables were: median StO_2 77.8% [72.4–85.0] and $resStO_2$ 87.35%/min [57.85–141.75]. Lactate levels were 2.3 mmol/l [1.8–3.3]. Characteristics of the baseline values are described in Table 2.

Univariate analysis showed an association between $resStO_2$ and diastolic arterial pressure ($p = .001$), and Norepinephrine dose ($p = .033$) (Table 3). In multivariate linear regression, there was an association between the $resStO_2$ and diastolic arterial pressure ($p = .004$). In contrast, there is no association in uni- or multivariate analysis between CVP and $resStO_2$, see Supplementary Fig. 1 panel c. We did not identified multicollinearity between the tested variables.

When using only one measurement per patient in sensitivity analysis, no macrocirculation parameter was associated with microcirculation (Supplementary Table 1).

3.3. Changes in macrocirculation and microcirculatory parameters after a fluid challenge

Sixty fluid challenges were analyzed; median volume was 500 ml [500–500]. Regarding the macrocirculation, fluid challenge significantly increased CO (4.5 to 5.3 l/min; $p < .001$), SV (46 to 50 ml; $p < .001$), MAP (72 to 78 mm Hg; $p < .001$), CVP (8 to 11 mm Hg; $p < .001$) and $SvcO_2$ (74.4 to 77.2%; $p = .007$) and decreased HR (103 to 100 bpm; $p < .001$). There was no significant difference in StO_2 or $desStO_2$ before and after fluid challenge, however $resStO_2$ was significantly increased (87.0 to 106.5%/min; $p < .001$) (Supplementary Table 2).

In univariate analysis, the variation of systolic ($p < .001$) and diastolic ($p = .012$) arterial pressure, and the variation of SV ($p < .001$) were associated with the variation of $resStO_2$. In multivariate analysis, only SV was associated with the variation of $resStO_2$ ($p = .004$) (Table 4). There was no association between the variation of $resStO_2$ and the variations of CVP in uni-or multivariate analysis (see Supplementary figure). We did not identify multicollinearity between the tested variables.

When using only one measurement per patient in sensitivity analysis, SV variation was the only independent predictor of microcirculation improvement (Supplementary Table 3).

3.3.1. Macrocirculatory and microcirculatory parameters and outcome

$ResStO_2$ was significantly higher in survivors compared to non-survivors ($p = .001$), see Fig. 1a. There was no difference in variation of $resStO_2$ after fluid challenge between survivors and non-survivors ($p = .531$), Fig. 1b.

4. Discussion

In the present study, we showed that diastolic arterial pressure at baseline was the only independent macrocirculatory determinant of $resStO_2$ measured by NIRS in septic patients. Fluid challenges significantly improved macrocirculation and microcirculatory parameters.

We aimed to investigate the relationship between macrocirculation and microcirculation in septic patients at steady state and after a fluid challenge. Among the documented methods to assess microcirculation in ICU patients [23-25], we chose the most routinely feasible method in clinical context: the near infrared spectroscopy measuring tissue hemoglobin oxygen saturation (StO_2) on the hand thenar eminence. This method has several advantages: it is non-invasive and it can be used without extensive training, and it has an adequate time response for the goal of the research. Occlusion test is a functional test evaluating microvascular reactivity to hypoxia. NIRS has been validated in the ED and ICU settings in several clinical studies [13,26-31]. During sepsis, adequate restoration of the macrocirculation can still be associated with microcirculation alterations [12,32]. Values of $resStO_2$ after a vascular occlusion test are strongly associated with outcome [8,23]. Therefore, we focused our analyses on $resStO_2$ rather than StO_2.

Table 3
Macrocirculatory and microcirculatory determinants of resaturation slope of tissue oxygen saturation ($resStO_2$) at baseline (n = 160 measures).

	Univariate linear regression analysis			Multivariate linear regression analysis			
Parameters	β	95% CI	p	β	95% CI	p	VIF
Systolic Arterial Pressure	0.05	−0.56 to 0.64	0.873				
Diastolic Arterial Pressure	2.08	0.87 to 3.30	0.001	1.85	0.64 to 3.08	0.004	1.1
Mean Arterial Pressure	1.38	0.40 to 2.36	0.007				
Central Venous Pressure	0.89	−2.22 to 3.89	0.563				
Cardiac Output	1.70	−7.01 to 10.17	0.686				
Stroke Volume	0.27	−0.47 to 1.00	0.459				
Heart Rate	−0.35	−1.04 to 0.33	0.312				
Tissue Oxygen Saturation	−0.29	−1.99 to 1.38	0.734				
Norepinephrine dose	−28.42	−54.56 to −2.38	0.033	−20.23	−46.21 to 5.46	0.126	1.1
Epinephrine dose	−35.56	−121.84 to 50.76	0.422				

CI: Confidence interval, VIF: Variance inflation factor. N = 72 patients.

Table 4
Fluid challenge: macrocirculatory and microcirculatory determinants of resaturation slope of tissue oxygen saturation ($resStO_2$) (n = 60 paired measures).

	Univariate linear regression analysis			Multivariate linear regression analysis			
Parameters	β	95% CI	p	β	95% CI	p	VIF
Systolic Arterial Pressure	1.02	0.47 to 1.50	<0.001	0.10	−0.66 to 0.90	0.789	3.1
Diastolic Arterial Pressure	1.49	0.31 to 2.65	0.012	0.87	−0.58 to 2.32	0.260	2.2
Mean Arterial Pressure	1.03	0.15 to 1.88	0.018				
Central Venous Pressure	2.15	−1.01 to 5.29	0.187	1.76	−0.90 to 4.46	0.219	1.2
Cardiac Output	17.04	9.49 to 23.17	<0.001				
Stroke Volume	1.62	0.74 to 8.91	<0.001	1.48	0.56 to 2.41	0.004	1.7
Heart Rate	−0.78	−1.87 to 0.33	0.172	−0.65	−1.65 to 0.41	0.178	1.1
Tissue Oxygen Saturation	−1.20	−3.51 to 1.12	0.315				
Baseline Norepinephrine dose	3.90	−6.07 to 13.85	0.447				
Baseline Epinephrine dose	−7.28	−31.59 to 17.13	0.561				
Baseline Resaturation Slope	0.08	−0.06 to 0.08	0.817				

CI: Confidence interval, VIF: Variance inflation factor. $N = 42$ patients.

We showed in our study that diastolic arterial pressure markedly influenced microcirculatory parameters at baseline. Higher diastolic arterial pressure has already been shown to be associated with better outcome in various shock state [33]. Its influence on microcirculation was underestimated to date and could have possible been put aside because of a focus on the MAP.

Improvement of macrocirculation with a fluid challenge led to variations of $resStO_2$. Even if CO values are within normal ranges, we believe the observed variations are clinically significant. $ResStO_2$ rose from 87 to 106.5%/min as compared to the normal values that range between 200 and 342%/min [34]. The clinical impact of these increase of resStO2 needs to be further investigated. Despite an improvement of diastolic arterial pressure, SV appears to be the only independent parameter related to those variations.

The interactions between macro- and microcirculation are debated in the literature. Thooft et al. found a positive association between MAP and microcirculation parameters ($resStO_2$ and MFI (microvascular flow index) measured with sidestream dark field) during septic shock [26]. Georger et al. focused on hypotensive septic patients and showed that norepinephrine improved $resStO_2$ [35]. Though, Jhanji et al. could not find any improvement of MFI in septic shock patients having their MAP increased with norepinephrine [36]. The impact of increase of cardiac index is not well established. De backer et al. and Morelli et al. showed respectively that inotropes such as dobutamine or levosimendan improved microcirculation but there was no association between cardiac index and microcirculation [37,38]. It is to note that in those studies the number of patients was limited.

Fluid challenge aims to improve macrocirculation but its impact on microcirculation is uncertain. Ospina-Tascon et al. [17] showed that FCs may improve both macro- and microcirculation in the early phase of sepsis but not in the late phase. Pottecher et al. [18] showed that FC in hypovolemic patients could improve macrocirculation via an increase of CO and not via a rise of arterial pressures which is in line with our results. The discrepancies between CO increase and microcirculation improvement was recently shown by Edul et al. [39]. In post-operative patients with abdominal sepsis, during the early phase of sepsis, improvement of CO was poorly correlated to improvement of sublingual red blood cell velocities in microvessels. Altogether, these data show that improvement of macrocirculation may be associated with improvement of microcirculation parameters mainly through an increase of CO. Our study helps to identify patients with microcirculation alterations that could possibly benefit from FC.

The impact of CVP on microcirculation remains elusive. CVP measurement is subjected to high variability and requires trained teams with consistent method. Thus, the quality of this measure is difficult to assess in most of studies. One strength of this work is that our protocol limits this variability and ensures the reliability of the values. We did not found any association between CVP and any of the microcirculation parameters at baseline or during a fluid challenge test. This result is different from Vellinga study [40]. To explain this difference, we can observe that in our study, patients had higher SAPS II and SOFA scores, and baseline CVP was lower (10 [7–12] vs 12.3 ± 4.3 mm Hg). There were no association between CVP variation and microcirculatory parameters variation after a fluid challenge, so that precision of the measure could

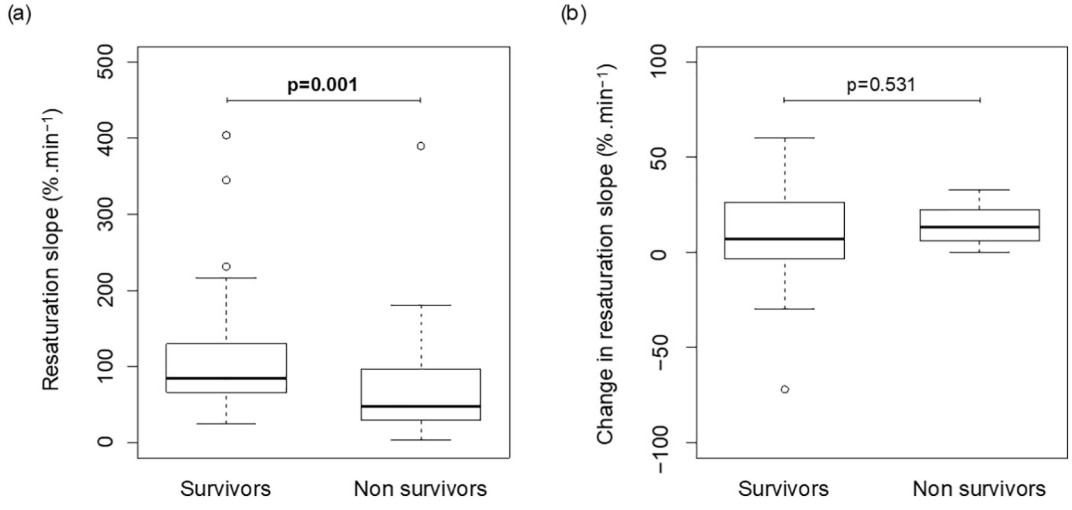

Fig. 1. Relationship between resaturation slope of tissue oxygen saturation ($resStO_2$) and outcome. Boxplots of the values of the first resaturation slopes dichotomized by outcome at day 28. (a) is first baseline value of the patient and (b) is the change in slope after the first fluid challenge.

not be suspected. However, increase of CVP is detrimental for the perfusion of encapsulated organs [41].

Our study had some limitations. It was a single center study and the number of patients is still limited. The inclusion rate was low and could have induced selection bias. We included already resuscitated patients who achieved macrocirculatory targets, but remain dependent of hemodynamic support and still experience multiple organ failure. This subset of patient has a high mortality rate despite a median MAP of 74 mm Hg and a median CO of 5 l/min. Thus, the results cannot be extrapolated to microcirculation alterations observed in early septic patient with hypotension and low cardiac output. The number of patient is limited, sensitivity analysis failed to identify macrohemodynamic parameters associated with microcirculation due to a lack of power, preventing the generalization of our conclusions. Last, measures of microcirculation were made on thenar eminence, a distal territory which could not reflect the microcirculation status in profound organs.

In conclusion, we showed that macrocirculation influenced microcirculatory parameters. Diastolic arterial pressure was the only independent determinant of resaturation slope measured by NIRS in septic ICU patients. Improvement of macrocirculation with fluid challenges impacts moderately microcirculatory parameters. CVP did not influence $resStO_2$. The effects of strategies aiming to improve microcirculation through correction of low diastolic pressures should be evaluated.

Contributions

Study design: BH, CD, MC, DP.
Data collection: BH, CD, MC.
Data analysis: MC, BH, RB, CD, AM, BC.
Drafting of the manuscript: MC, BH, RB, AM, BC.
Critical review and editorial assistance: MC, BH, CD, AM, BC.
All authors read and approved the final manuscript.

Conflicts of interest

All authors have disclosed any potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.002.

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