A holistic approach for perfusion assessment in septic shock: Basic foundations and clinical applications
Hernández Poblete, Glenn

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Relationship of systemic, hepatosplanchnic, and microcirculatory perfusion parameters with six-hour lactate clearance in hyperdynamic septic shock patients: an acute clinical-physiological, pilot study

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Abstract

Background

Recent clinical studies have confirmed the strong prognostic value of persistent hyperlactatemia and delayed lactate clearance in septic shock. Several potential hypoxic and non-hypoxic mechanisms have been associated to persistent hyperlactatemia, but the relative contribution of these factors has not been specifically addressed in comprehensive clinical physiological studies. Our aim was to determine potential hemodynamic and perfusion-related parameters associated to 6 h lactate clearance in a cohort of hyperdynamic hyperlactatemic septic shock patients.

Methods

We conducted an acute clinical physiological pilot study including 15 hyperdynamic septic shock patients undergoing aggressive early resuscitation. Several hemodynamic and perfusion-related parameters were measured immediately after preload optimization and 6 hours thereafter, with 6 h lactate clearance as the main outcome criterion. Evaluated parameters included cardiac index, mixed venous oxygen saturation, capillary refill time and central-to-peripheral temperature difference, thenar tissue oxygen saturation (StO2) and its recovery slope after a vascular occlusion test, sublingual microcirculatory assessment, gastric tonometry (pCO2 gap) and plasma disappearance rate of indocyanine green (ICG-PDR). Statistical analysis included Wilcoxon and Mann-Whitney tests.

Results

Five patients presented a 6 h lactate clearance < 10%. When compared to 10 patients with a 6 h lactate clearance ≥10%, they presented a worse hepatosplanchnic perfusion as represented by significantly more severe derangements of ICG-PDR (9.7 (8-19) vs. 19.6 (9-32) %/min, p<0.05) and pCO2 gap (33 (9.1-62) vs. 7.7 (3-58) mmHg, p<0.05) at 6 hours. No other systemic, hemodynamic, metabolic, peripheral or microcirculatory parameters differentiated these subgroups. We also found a significant correlation between ICG-PDR and pCO2 gap (p=0.02).

Conclusions

Impaired 6 h lactate clearance could be associated to hepatosplanchnic hypoperfusion in some hyperdynamic septic shock patients. Improvement in systemic, metabolic and peripheral perfusion parameters does not rule out the persistence of hepatosplanchnic hypoperfusion in this setting. Severe microcirculatory abnormalities can be detected in hyperdynamic septic shock patients, but their role on lactate clearance is unclear. ICG-PDR may be a useful tool to evaluate hepatosplanchnic perfusion in septic shock patients with persistent hyperlactatemia.
Introduction

Several recent clinical studies have confirmed the strong prognostic value of hyperlactatemia in septic shock [1-3]. Both a single abnormal level and an impaired lactate clearance are related to morbidity and mortality [1-4]. Nguyen et al. demonstrated the relevance of lactate clearance in a study involving one hundred and eleven septic patients [4]. Patients exhibiting a lactate clearance > 10% after 6 h of early resuscitation exhibited a significant lower mortality than patients with less than 10% [4]. Furthermore, at least two randomized controlled trials have explored lactate clearance as a potential resuscitation goal for septic shock patients with encouraging results [5,6].

The physiologic basis of lactate generation during shock has been matter of debate and research [7-11]. Hypovolemia-related hypoperfusion is probably the predominant pathogenic mechanism during the early pre-resuscitative phase. Some patients resolve sepsis-related circulatory dysfunction and clear lactate after initial fluid resuscitation, while others evolve into a persistent circulatory dysfunction with hyperlactatemia [12]. Although several potential hypoxic and non-hypoxic mechanisms have been associated to persistent hyperlactatemia [7-14], recent literature has highlighted the role of microcirculatory abnormalities [14] or hyperadrenergia [10,11,13] as the most likely determinants. This has occurred in parallel to a decline in the availability of gastric tonometry precluding clinicians to assess hepatosplanchnic perfusion in this setting. More importantly, the relative contribution of several potential factors to persistent hyperlactatemia after initial septic shock resuscitation has not been specifically addressed in comprehensive clinical physiological studies.

To address this subject, we designed an acute clinical physiological study to determine potential hemodynamic and perfusion-related parameters associated to 6 h lactate clearance in a cohort of hyperdynamic septic shock patients with persistent hyperlactatemia. This pilot study evaluated several macrohemodynamic, metabolic, peripheral, hepatosplanchnic and microcirculatory parameters immediately after preload optimization and 6 h thereafter.

Material and methods

This prospective study was conducted in a 16-bed mixed medical-surgical ICU at a university hospital in Santiago, Chile from September 2010 to December 2011. The local Institutional Review Board approved this study and informed consent was obtained from each patient or surrogates.

This study is part of an ongoing randomized double blind crossover controlled trial exploring the acute effects of dobutamine on tissue hypoperfusion in hyperdynamic septic shock patients.

Patient selection

All consecutive adult patients (>18 years) admitted to the ICU within 24 hours of onset of septic shock were considered eligible for this protocol. Specific inclusion criteria were:
1) septic shock according to the 2001 Consensus Definition (septic-related volume-refractory hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) > 65 mmHg) [15]; 2) persistent hyperlactatemia (arterial lactate > 2.0 mmol/l after initial fluid loading); 3) cardiac index (CI) ≥ 2.5 L/min/m²; 4) sinus rhythm; and 5) mechanical ventilation and pulmonary artery catheter in place.

Patients were excluded according to the following criteria: 1) pregnancy; 2) anticipated surgery or dialytic procedure during the study period; 3) Child B or C liver cirrhosis; 4) do-not-resuscitate status or life expectancy less than 24 hours; and 5) preexisting conditions precluding peripheral perfusion assessment, such as hypothermia, Raynaud’s disease or severe peripheral vascular disease.

General management of hyperdynamic septic shock patients
Recruited patients were resuscitated with a local norepinephrine (NE)-based, perfusion-oriented management protocol [16,17]. All patients were subjected to early aggressive source control. The main endpoint of ICU resuscitation was lactate normalization. Initial fluid resuscitation was directed at correcting basic hemodynamic parameters. NE was started and titrated to a MAP > 65 mmHg in patients with persistent hypotension after fluid loading. Early intubation and mechanical ventilation were indicated for oxygen consumption reduction in patients with progressive hyperlactatemia or increasing NE requirements. Mechanical ventilation and sedation were managed in accordance to current protective strategies [18]. CI and related parameters were evaluated with a pulmonary artery catheter. Intravascular volume status was optimized following pulse pressure variation criteria [19]. Red blood cell transfusions were prescribed as necessary to maintain hemoglobin levels ≥8 gr/dL. High-volume hemofiltration was used as a rescue therapy in refractory patients [17].

Study protocol
Total study period was of 6 hours. Two sets of hemodynamic and perfusion assessments were considered for the purpose of this specific study. A baseline set was performed immediately after preload optimization in the ICU as defined by a pulse pressure variation <10%. The second set was performed 6 h thereafter.

Specific measured parameters at each time-point were:
1. Macro-hemodynamic parameters: MAP, heart rate, NE dose, pulse pressure variation (%), and pulmonary artery catheter-derived values.
2. Metabolic-related perfusion parameters: Mixed venous O₂ saturation (SvO₂), arterial lactate (Radiometer ABL 735, Copenhagen Denmark), and mixed venous to arterial pCO₂ gradient (p(cv-a)CO₂). Six-hour lactate clearance was defined as the percent change in lactate level after 6 h from the baseline measurement. It was calculated by using the following formula: baseline ICU lactate (hour 0) minus lactate at hour 6, divided by baseline ICU lactate, then multiplied by 100.
3. Peripheral perfusion parameters: a) Central to toe temperature gradient (Tc-toe), where central temperature was obtained from the pulmonary artery catheter, and toe
temperature from the ventral face of the great toe of the right foot. A difference up to 7°C was considered as normal. All skin temperatures were obtained with skin probes (HP 21078A, Hong Kong Kabeil Technology, Guangdong, China); and b) Capillary refill time (CRT), measured by applying firm pressure to the distal phalanx of the index finger for 10 seconds. A chronometer recorded the time for return of the normal color at the ventral surface, and 4.0 seconds was defined as the upper normal limit.

4. Near-infrared spectroscopy (NIRS)-derived parameters [20]: Tissue oxygen saturation (StO₂) was measured by a tissue spectrometer (InSpectra Model 325, Hutchinson Technology, Mn, USA). The NIRS probe was placed on the skin of the thenar eminence and a sphygmomanometer cuff was wrapped around the arm over the brachial artery. After a 3 min period to stabilize the NIRS signal, a vascular occlusion test (VOT) was performed. Arterial inflow was stopped by inflating the cuff to 50 mmHg above the systolic arterial pressure. After 3 min of ischemia cuff pressure was released, and StO₂ recorded continuously for another 3 min period (reperfusion period). Baseline StO₂ before VOT was recorded. During the reperfusion phase, the recovery slope of the StO₂ signal was registered (expressed in percent per second).

5. Microcirculatory-derived parameters [21]: Sublingual microcirculation was assessed with sidestream dark field videomicroscopy imaging obtained with a 5x lens (Microscan* for NTSC, Microvision Medical, Amsterdam, NL). At each assessment, at least five 10-20 sec video images were recorded. Image acquisition and analysis were performed following recent recommendations of a consensus conference [21]. A trained investigator performed image analysis in all cases. Parameters considered for this study were proportion of perfused vessels, perfused vessel density (PVD), and microcirculatory flow index (MFI).

6. Hepatosplanchnic-related perfusion parameters: a) Gastric tonometry calculating the gastric-to-arterial pCO₂ gradient (pCO₂ gap) with a upper normal limit of 8 mmHg (Tonocap, Datex-Ohmeda Division, Helsinki, Finland) [22]; and b) Plasma disappearance rate of indocyanine green (ICG-PDR) as a dynamic test for the assessment of liver function and global hepatosplanchnic blood flow [23]. The ICG-PDR was assessed with a non-invasive liver function monitoring system (LiMon, Pulsion Medical Systems, Munich, Germany). Each patient received an ICG finger clip that was connected to the liver function monitor. A dose of 0.25 mg/kg of ICG was injected through a central venous catheter. A range of ICG-PDR of 20-30%/min was considered as normal.

**Statistical analysis**

To address our objectives, we compared hemodynamic and perfusion-related parameters at baseline and at 6 h in relation to lactate evolution. Specifically, we evaluated changes of hemodynamic and perfusion parameters in patients with a 6 h lactate clearance ≥ 10% as compared to those with less than 10%.
Non-parametric statistics were performed including Wilcoxon test for paired measurements and Mann-Whitney test for independent measurements. Spearman correlation was used to explore the relationship between ICG-PDR and pCO$_2$ gap.

Results are expressed as median and range. A p value of <0.05 was considered as statistically significant. All reported p values are two-sided.

**Results**

Fifteen hyperdynamic septic shock patients were included. Baseline characteristics of each individual patient are shown in table 1. Nine of 15 patients had an abdominal sepsis (six with peritonitis secondary to gastrointestinal perforation, two with infected pancreatitis and one with non-occlusive colonic ischemia).

Six-hour lactate clearance was ≥ 10% in ten patients and lower in five (16% (12.9-66) vs 3.6% (-14.3 - 9), respectively; p<0.05). During the protocol both groups received the same amounts of fluids (6 h lactate clearance ≥ 10%: 780 ± 520 ml vs. 6 h lactate clearance < 10%: 690 ± 380 ml; p=0.8).

Compared to patients with a 6 h lactate clearance ≥ 10%, patients with a lower lactate clearance presented a worse hepatosplanchnic perfusion as represented by significantly more severe derangements of ICG-PDR and pCO$_2$ gap at 6 hours (Figure 1 and table 2). In the case of gastric pCO$_2$ gap, this difference was also significant at baseline (table 2). No other parameter differentiated these subgroups as shown in table 2. When all data were pooled together, a significant correlation between delta lactate (baseline lactate – final lactate) and delta ICG-PDR (p=0.05, R$^2=0.3$) was found.

Liver-related parameters were also not different between patients with 6 h lactate clearance ≥ vs < 10% (bilirubin 0.9 (0.2-1.7) vs. 1.8 (0.6-4.1) mg/dl, p=0.3; prothrombin time 46 (11-86) vs. 46 (34-59)%, p=0.9; SGOT 174 (10-92) vs. 48 (18-105) U/l, p=0.4). Nine patients exhibited intra-abdominal hypertension, but no patient had an abdominal compartment syndrome. Intra-abdominal pressure was not significantly correlated with lactate (p=0.3), pCO$_2$ gap (p=0.3), neither with the ICG-PDR (p=0.32).

We found a mild but significant correlation between pooled ICG-PDR and pCO$_2$ gap values (Figure 2).

**Discussion**

Our main finding was the association of delayed 6 h lactate clearance to hepatosplanchnic hypoperfusion but not to systemic hemodynamics or other perfusion parameters in hyperdynamic septic shock patients undergoing aggressive resuscitation.

The relevance of the concept of lactate clearance has been recently highlighted [4-6,24]. Therefore, it appears as critical to gain insight into potential pathogenic mechanisms associated to failure to clear lactate, especially in hyperdynamic septic shock patients in whom a low flow state is by definition a less probable mechanism. However, this task may
Table 9.1 Baseline characteristics of 15 hyperdynamic septic shock patients according to a 6 hour-lactate clearance higher or lower than 10%.

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Pt, patient; Survival, hospital survival; APACHE II, Acute Physiology and Chronic Health Evaluation II; IAP, intra-abdominal pressure (mmHg); SOFA, Sequential Organ Failure Assessment; MAP, Mean Arterial Pressure (mmHg), ∆PP, Pulse pressure variation (%), NE, Norepinephrine requirements (mcg/kg/min); Lactate, (mmol/l); MFI, Microcirculatory flow index; CO₂ gap, gastric/arterial pCO₂ gradient (mmHg); PDR, indocyanine green plasma disappearance rate (%min).
be particularly complex in the setting of septic shock where an easy assumption to make is to attribute persistent hyperlactatemia to inadequate resuscitation. Indeed, although hypoperfusion is the most common cause of hyperlactatemia, increasing evidence for non-hypoxic related mechanisms such as sustained hyperadrenergia with accelerated aerobic glycolysis, has recently expanded our understanding of the physiological meaning of lactate in sepsis [7-13]. Nevertheless, a limited number of factors such as persistent global hypoperfusion, microcirculatory dysfunction, impaired hepatosplanchnic perfusion or liver dysfunction are more likely involved in a resuscitation scenario. A multimodal perfusion monitoring approach relying on relatively simple or non-invasive clinical tools can identify persistent global hypoperfusion. In our series of hyperdynamic septic shock patients, evolution of metabolic and peripheral perfusion parameters tends to rule-out global hypoperfusion as a cause of impaired lactate clearance. In fact, these patients presented a median CI > 4 L/min/m², SvO₂ > 70%, p(v-a)CO₂ <5 mmHg, CRT <4 sec, and a thenar StO₂ >80%, which is consistent with an hyperdynamic state.

Videomicroscopic bedside techniques have allowed to directly visualize microvascular flow, especially at the sublingual mucosa [25]. Microcirculatory flow or density abnormalities have been described and linked to bad outcome during septic shock [26,27]. Microcirculatory dysfunction with microvascular shunting could contribute to the genesis of hyperlactatemia in selected patients [12]. We recently demonstrated a significant correlation between hyperlactatemia and microcirculatory derangements in a large series.
Table 9.2 Multimodal perfusion parameters comparing patients with a lactate clearance higher or lower than 10%.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Lactate Clearance ≥ 10% (n=10)</th>
<th>Lactate Clearance &lt; 10% (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>End</td>
</tr>
<tr>
<td><strong>Hemodynamic parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure variation (%)</td>
<td>7 (0-10)</td>
<td>7 (0-12)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>97 (80-119)</td>
<td>107 (65-132)</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>3.4 (2.5-4.7)</td>
<td>4.1 (3-6.1)</td>
</tr>
<tr>
<td>NE dose (mcg/kg/min)</td>
<td>0.23 (0.1-0.44)</td>
<td>0.2 (0.08-0.7)</td>
</tr>
<tr>
<td><strong>Metabolic parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>77 (65-91)</td>
<td>77 (71-94)</td>
</tr>
<tr>
<td>P(cv-a)pCO₂ (mmHg)</td>
<td>4.3 (0.7-7)</td>
<td>3.5 (0.2-6)</td>
</tr>
<tr>
<td><strong>Peripheral perfusion parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT (s)</td>
<td>3.5 (1-7)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Central-peripheral temp. difference (°C)</td>
<td>8.6 (5.2-12.2)</td>
<td>6.5 (4-11.2)</td>
</tr>
<tr>
<td><strong>NIRS-derived parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>StO₂ (%)</td>
<td>84 (55-94)</td>
<td>85 (77-95)</td>
</tr>
<tr>
<td>StO₂ recovery slope (%/s)</td>
<td>1.71 (0.4-4)</td>
<td>2.35 (0.8-3.4)</td>
</tr>
<tr>
<td><strong>Microcirculatory parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFI (score)</td>
<td>2.1 (1.3-2.8)</td>
<td>1.95 (1.8-2.9)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>78.9 (62-93)</td>
<td>74.9 (67-99)</td>
</tr>
<tr>
<td>PVD (n/mm)</td>
<td>8.7 (7.5-10.7)</td>
<td>9.1 (6-11.3)</td>
</tr>
<tr>
<td><strong>Splanchnic perfusion parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-PDR (%/min)</td>
<td>19.9 (6.1-28)</td>
<td>19.6 (9-32)</td>
</tr>
<tr>
<td>pCO₂ gap (mm/Hg)</td>
<td>5.3 (2-10.7)</td>
<td>7.7 (3-58)</td>
</tr>
</tbody>
</table>

Data presented as median (range). p-value#: Wilcoxon test for paired measurements. p-value*: p <0.05 by Mann-whitney test for independent measurements comparing end values between both subgroups. NE: norepinephrine; SvO₂: mixed venous oxygen saturation; P(cv-a)pCO₂: central venous to arterial pCO₂ gradient; CRT: capillary refill time; NIRS: near-infrared spectroscopy; StO₂: tissue oxygen saturation; MFI: microcirculatory flow index; PPV: proportion of perfused vessels; PVD: perfused vascular density; ICG-PDR: indocyanine green plasma disappearance rate; pCO₂ gap: gastric to arterial pCO₂ gradient.
of septic shock patients [14]. Interestingly, the majority of our patients exhibited significant microcirculatory abnormalities, irrespective of the status of lactate clearance. The median 6 h values of proportion of perfused vessels, MFI and PVD among microcirculatory parameters are well beyond the thresholds associated to morbidity or mortality in previous studies [1,2]. This is consistent with a profoundly abnormal StO2 recovery slope after VOT in our patients with a low lactate clearance, suggesting a persistent microvascular dysfunction.

Splanchnic contribution to hyperlactatemia may be secondary to an increased hypoxic or non-hypoxic gut lactate production, a decreased hepatic lactate clearance secondary to hypoperfusion or dysfunction, or a combination of both [28-31]. In our study, patients with a lactate clearance <10%, increased pCO2 gap and decreased ICG-PDR to extremely abnormal values (medians of 33 mmHg and 9.7%, respectively) after 6 hours of resuscitation, suggesting the presence of sustained hepatosplanchnic hypoperfusion despite a global hyperdynamic flow status. Moreover, since no difference in liver enzymes between these subgroups was found, it is highly probable that alterations in hepatic flow rather than function were responsible for the low ICG-PDR. Our results confirm and expand previous findings by Friedman et al. demonstrating a significant association of persistent hyperlactatemia at 24 h with gastric mucosa hypoperfusion, but without correlation to systemic hemodynamics [32]. Our study, using a more comprehensive and multimodal monitoring approach, supports a relationship between persistent hyperlactatemia and hepatosplanchnic hypoperfusion, this latter confirmed by an independent technique such as ICG-PDR.

Several factors could theoretically have contributed to the development of both gut hypoperfusion and hyperlactatemia in our patients. An ischemic bowel may be a source of anaerobic lactate production that depending on hepatic clearance could result in

![Figure 9.2](image.png)

**Figure 9.2** Correlation between pooled indocyanine green plasma disappearance rate (ICG-PDR) and gastric-to-arterial pCO2 gradient (pCO2 gap) values.
systemic hyperlactatemia, but only one of these patients was operated for a non-occlusive colonic ischemia with secondary peritonitis. Some clinical reports have emphasized that intraabdominal hypertension could induce hyperlactatemia through gut mucosal hypoperfusion and also decrease hepatic lactate clearance [33,34]. However no difference in intra-abdominal hypertension between subgroups was observed in our series. Hypovolemia or high doses of vasoconstrictors could hasten hepatosplanchnic hypoperfusion, but this was not the case for our patients since final pulse pressure variation was of 2 (0-5)% with NE doses of only 0.08 (0.05-0.6) mcg/kg/min.

The presence of occult hepatosplanchnic hypoperfusion in the setting of a global hyperdynamic state and with parallel improvements or no change in peripheral perfusion, metabolic and microcirculatory parameters, may appear as contradictory. However, regional hepatosplanchnic vasoconstriction is a physiologic and early neurohumoral response to shock that can cause prolonged hypoperfusion and gut ischemia. Persistence of this state as represented by an abnormal gastric tonometry at 24 h has a strong prognostic significance, irrespective of the status of systemic hemodynamics [35]. Unfortunately, a decline in the availability of gastric tonometry has precluded intensivists to use this valuable physiological monitor. Rather novel techniques such as transcutaneous assessment of indocyanine green plasma disappearance rate have become available, offering an opportunity for the early diagnosis of hepatic dysfunction or hypoperfusion [23]. Previous studies demonstrated a strong association between ICG-PDR and outcome in critically ill patients [36,37]. The ICG-PDR is influenced both by liver function and perfusion, but when evaluated in short periods of time, it mainly reflects hepatosplanchnic perfusion since the function of liver cells does not change rapidly [38]. Thus, this method could eventually be used as a surrogate for gastric tonometry, and indeed we found a significant correlation between both techniques (Figure 2).

Our study has several limitations. Since it was designed as an acute clinical physiological pilot study it included a limited number of patients, thus making it difficult to generalize conclusions. Only 2 sets of measurements were considered, thus precluding the possibility of capturing earlier or late changes of some of these parameters. The majority of patients were of an abdominal source, factor that eventually could influence the results of the hepatosplanchnic perfusion assessment. We did not address potential non-hypoxic causes for persistent hyperlactatemia. Despite these limitations, we think that our data may be useful to reconsider the approach to persistent hyperlactatemia in hyperdynamic septic shock patients.

**Conclusions**

Impaired 6 h lactate clearance could be associated to hepatosplanchnic hypoperfusion in some hyperdynamic septic shock patients subjected to aggressive early resuscitation. An improvement in systemic, metabolic and peripheral perfusion parameters does not rule out the persistence of hepatosplanchnic hypoperfusion. Relatively new techniques such as non-

Relationship of systemic, hepatosplanchnic, and microcirculatory perfusion parameters...
invasive assessment of ICG plasma disappearance rate could aid in interpreting a persistent hyperlactatemia. Severe microcirculatory abnormalities can be detected in hypedynamic septic shock patients, but their role on lactate clearance is unclear. Future clinical studies should determine the best strategy to address persistent hyperlactatemia in hyperdynamic septic shock patients. Evaluation of hepatosplanchnic perfusion with current or developing technologies should probably be considered as a useful complementary tool in this setting.

References


