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Perfusion Instability During Hyperthermic Intraperitoneal Chemotherapy: The Utility of a Problem-solving Flowchart

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Abstract. *Background/Aim: During hyperthermic intraperitoneal chemotherapy (HIPEC), perfusion instability (PI) is defined as the inability to maintain a proper perfusion flow without impairment of the target temperature. The management and resolution of this adverse event is underreported and poorly investigated. The study aimed to evaluate the incidence of PI during closed cytoreductive surgery (CRS)-HIPEC and how a problem-solving approach might limit the effects of this adverse event. Patients and Methods: A retrospective analysis of patients who underwent CRS-HIPEC at our Institution was performed. PI was defined when the patient's outflow pressure of the circuit was not able to maintain target flow and temperature (1,100 ml/min and 41˚C). A step-by-step problem-solving flowchart, which included checking the drain position, proper muscle relaxation, changing the bed position, adjusting the perfusion volume and switching the drain flow switch, was used. Results: A total of 208 HIPEC procedures were reviewed between May 2018 and January 2023. PI occurred in 21 cases (10.1%). Patients with PI had a significantly longer perfusion time (p<0.001). Although the mean outflow pressure and flow rate were significantly lower in patients with PI (p<0.001), the target temperature was maintained until the end of HIPEC. Conclusion: A scheduled problem-solving approach by HIPEC perfusionist team was able to resolve most cases of PI. Further research on perfusion technical details and volume calculation is needed to prevent and limit the effects of this complication.*

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Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) represents a valuable option for improving oncological outcomes in patients with peritoneal metastases. Current evidence shows that CRS-HIPEC provides durable tumor control and, in some cases, a cure in selected patients with peritoneal metastases, such as those with pseudomyxoma peritonei, malignant mesothelioma, colorectal cancer and ovarian cancer (1). Although CRS-HIPEC has been included in most of the national oncological guidelines, one of the main concerns of HIPEC administration is a certain lack of standardized and shared protocols (2). Moreover, HIPEC suffers from extreme variability in the technology adopted, with multiple machines available and a significant number of centers using in-house systems to perform HIPEC. The management of the HIPEC machine in most referral centers is managed by a team of well-trained surgical nurses (3). During HIPEC, nurses are actively involved in monitoring all parameters (flow rate, temperature, pressure levels in the circuit) (4). One of the most underestimated problems of HIPEC is perfusion instability (PI), which can affect a significant number of procedures. PI results in suboptimal drug delivery, impedes the achievement of the target temperature, prolongs the procedure, and has a potentially detrimental effect on patient care (5, 6). Although PI is frequently reported by centers performing HIPEC, as far as we are aware, no data exist in the current literature on its true incidence and management. The aim of this study was to evaluate the incidence of PI during closed CRS-HIPEC and how a problem-solving approach can limit the effects of this adverse event.

Patients and Methods

Study design and data collection. All institutional HIPEC procedures from May 2018 to January 2023 were retrospectively reviewed. The study was approved by the Ethics Committee of the Veneto Institute of Oncology (QualyHIPEC CE IOV 2018/85). Patient demographic and perioperative data were retrieved from our institutional health record software and prospectively collected in an electronic database.

Peritoneal perfusion was achieved at the end of CRS by an open circuit consisting of two inflow and two outflow catheters connected to a dedicated machine (Performer HT RAND; RanD Medolla, Modena, Italy), supplied with a heater and a heat exchanger. Four standard perfusion catheters were placed in the abdominal cavity: two in the subdiaphragmatic space (right and left) and two in the pelvis. In particular, the specific positioning of the inflow and outflow catheters depended on the clinical context, with the inflows placed in the regions with the highest tumor burden. The circuit also included a temperature-monitoring system consisting of five thermal probes placed in the peritoneal cavity and at various locations in the circuit. The dilution volume was calculated based on body surface area and sex (2,000 ml/m^2 for females, 2,500 ml/m^2 for males) with an adjunct of 1,000 ml as a reservoir. Once the target temperature (41˚C with ± 0.5˚C tolerance) and perfusion flow rate (1,000-1,300 ml/minute) were reached, drugs were bolus-injected (25 mg/m^2/l cisplatin plus 3.3 mg/m^2/l mitomycin-C in patients with gastrointestinal histology, and 45 mg/l cisplatin plus doxorubicin at 15 mg/l in ovarian carcinomatosis, mesothelioma, and peritoneal sarcomatosis). HIPEC was maintained for 60 min with the abdomen closed. Anesthesia was induced with propofol (2-3 mg/kg) and intravenous fentanyl (3-5 mg/kg) and maintained with sevoflurane in combination with intravenous fentanyl or epidural ropivacaine. All procedures were performed by trained and certified surgical nurses according to an institutionally standardized operating protocol.

PI was defined when the patient's outflow pressure of the circuit was not able to maintain target flow and temperature (1,100 ml/min and 41˚C). A step-by-step problem-solving flowchart was adopted to prevent or treat PI, including a) checking the drain position before skin closure, b) checking for proper muscle relaxation, c) changing the bed position, d) adjusting the perfusion volume, and e) switching the drain flow. Intraoperative perfusion data were retrieved from the treatment data records of the perfusion machine software and nursing charts. Failure was defined when conversion to open technique or HIPEC interruption was required.

The efficacy of the flowchart was defined as the rate of PI resolution.

Statistical analysis. Continuous variables are reported as the mean and standard deviation or median and interquartile range (Q1-Q3), whereas categorical variables are reported as frequency counts and percentages. Patients were divided into two groups according to the stability of perfusion. Comparison between the two groups was performed using chi-squared or Fisher's exact test for categorical variables and *t*-test for continuous variables. Values of $p<0.05$ were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows v.27.0 (IBM Corporation, Armonk, NY, USA).

Results

During the study period, 208 HIPEC procedures were performed at our Institution to treat peritoneal metastases of various origins. Demographic and perioperative data are summarized in Table I. PI was observed in 21 cases (10.1%). No significant differences in clinical and operative characteristics were observed between patients with and without stable perfusion (Table I). As expected, we observed a lower mean patient outflow pressure (4.71 *vs.* –2.37 mm/Hg, $p<0.001$) and flow rate (1,170 *vs.* 951 ml/min, $p<0.001$) in patients with unstable perfusion (Figure 1). In 11 patients, the mean flow rate was less than 1,000 ml/min, four of whom had a flow rate of less than 800 ml/min during HIPEC. Despite this, the mean temperature was not statistically different between the two groups. Temporary complete cessation of perfusion was required in 16 patients. The total perfusion time was longer in patients with PI (75 *vs.* 82 min, $p=0.001$) due to the time required to complete all steps of the problem-solving flowchart and achieve stability before drug injection. Indeed, a longer time to drug injection was observed in patients with unstable perfusion (14 *vs.* 21 min, $p<0.001$), whereas the drug circulation time was similar for the two groups (60 *vs.* 61 min, $p=0.384$). The perfusion volume was adjusted in six patients (28.6%), with a median of 400 ml of perfusate added. Two cases of failure were noted: one required conversion to an open procedure, and the other resulted in the interruption of HIPEC before the end of the planned perfusion time.

Discussion

HIPEC is a complex technique that requires close collaboration between surgeons, nurse perfusionists, and anesthesiologists (7). The main goal during HIPEC is to maintain target temperature and optimal intraperitoneal drug delivery (8). Experimental data have shown that maintaining a proper flow rate is necessary to guarantee the target temperature (6, 9). Moreover, HIPEC is performed at an unconventional site for drug management, and the issue of safety is critical for both patients and surgical staff (10).

PI is an underestimated adverse event in closed HIPEC, and no data on its incidence seem to be available in the literature. PI is an important issue, and preventive measures should be taken by any surgical team performing HIPEC for several reasons. Firstly, PI is potentially associated with suboptimal drug and heat administration, with a detrimental effect on the oncological efficacy of HIPEC. Moreover, the inability to maintain a proper flow rate may also be

Table I. *Comparison between patients with stable and unstable perfusion*.

		Stable perfusion (N=187)	Unstable perfusion (N=21)	*p*-Value
Age, years, Median (IQR)		63 (52-70)	60 (48-69)	0.111
Sex, n (%)	Female	133 (71.5)	16 (76.2)	0.800
	Male	53 (28.5)	5 (23.8)	
BMI, kg/m^2, Median (IQR)		24.8 (21.5-27.5)	25.6 (21.9-28.3)	0.665
Body surface, m^2, Median (IQR)		1.73 (1.60-1.90)	1.75 (1.58-1.97)	0.907
ASA class, n (%)	ASA 1	8 (4.3)	2 (9.5)	0.467
	ASA 2	119 (63.6)	14 (66.7)	
	ASA 3	60 (32.1)	5 (23.8)	
Histology, n (%)	Ovarian	68 (36.4)	8 (38.1)	0.304
	Colorectal	42 (22.5)	3 (14.3)	
	Pseudomyxoma	46 (24.6)	6 (28.6)	
	Mesothelioma	11 (5.9)	1 (4.8)	
	Sarcomatosis	7 (3.7)	3 (14.3)	
	Other	13 (7.0)	0 (0.0)	
SC before surgery, n (%)	Yes	103 (55.1)	12 (57.1)	0.857
PSS, n (%)	0-1	81 (43.5)	13 (61.9)	0.164
	2-3	105 (56.5)	8 (38.1)	
CC score, n (%)	CC0	169 (90.4)	20 (95.2)	0.700
	CC1	18 (9.6)	1 (4.8)	
Surgery duration, min, Median (IQR)		540 (465-635)	540 (425-595)	0.289
Ascites, n (%)	No	144 (77.4)	16 (76.2)	0.899
	Yes	42 (22.6)	5 (23.8)	
PCI, Median (IQR)		14 (6-23)	10 (5-19.5)	0.170
Peritonectomies, Median (IQR)		2 (1-3)	1 (1-2)	0.220
Visceral resection, Median (IQR)	4 (3-5)	3 (2-5)	0.188	
Blood loss, ml, Median (IQR)		200 (465-635)	540 (425-595)	0.789

ASA: American Society of Anesthesiologists; BMI: body mass index; CC: completeness of cytoreduction; PCI: peritoneal cancer index; PSS: prior surgical score; SC: systemic chemotherapy.

associated with an intraoperative risk to the patient, as the increase in negative suction pressure often associated with PI may cause suction damage to the bowel loops, especially of the more mobile small intestine. In addition, interrupting HIPEC due to flow problems and ultimately converting to an open procedure increases the risk of operating room contamination as the conversion is managed with the abdomen filled with chemoperfusate. Finally, PI is always associated with a prolonged perfusion time. It is well known that CRS-HIPEC is a lengthy procedure and optimizing time reduces costs and improves patient outcomes.

In this study, PI occurred in a significant number of procedures (10%), and a problem-solving approach was proposed to overcome this complication. In our HIPEC protocol, a flowchart has been included with an accurate evaluation of the correct cannula position before wound closure and a step-by-step problem-solving approach in the case of PI. There are several causes of PI. One of the most common is an inadequate perfusion volume. Volume calculation for HIPEC is based on body surface area, which may not be the best tool for predicting intra-abdominal volume in patients. In our study, the perfusion volume was adjusted in six out of 21 patients with PI. Data on the effect of volume dilution on patient outcomes are limited (11). Further research is needed in this field to investigate different volume calculation methods that may limit the occurrence of PI. Preoperative computed tomography scan volumetry with adaptation to the planned organ resection may be an avenue of interest. In an interesting study, the peritoneal cavity volumes were calculated on preoperative computed tomography computed tomography scan and correlated with size, body mass index and weight. It was found that weight was the best parameter related to intra-abdominal volume (12).

Another method of improving perfusion flow is to change patient positioning to favor the mechanical accumulation of fluid around the outflow catheters. PI can also be caused by cannula obstruction due to tissue debris. In this case, flow reversal between in and outflow catheters may be successful.

In only two cases were all of these steps unsuccessful. Our experience confirms that closed HIPEC can be performed in most patients without any PI problems. In the event of PI, most procedures can be successfully completed using this problem-solving approach. Although the flow rate remained suboptimal compared to the target flow rate, the mean temperature in procedures patients with PI did not differ from that in

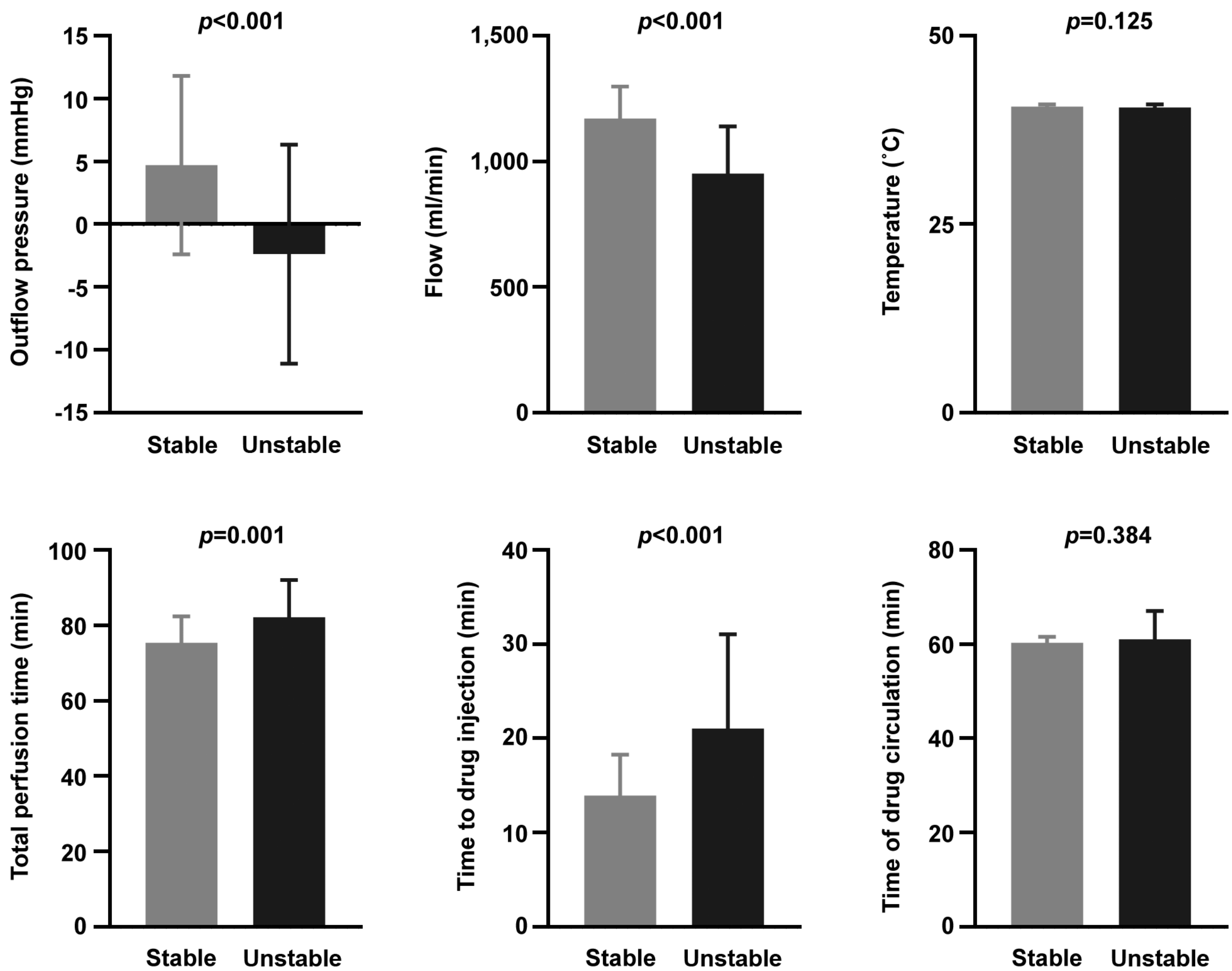

Figure 1. *Comparison of intraoperative perfusion data between patients with stable and unstable perfusion. Data are reported as the mean±standard deviation. Statistical significance was set at* $p<0.05$.

procedures in those with stable perfusion. Furthermore, PI led to a longer HIPEC time, and any preventive measure to avoid this adverse effect should be considered.

This study has several limitations. Due to the retrospective nature of the data review, it is impossible to accurately assess the effect of each step of the flowchart on PI resolution, as different causes of PI may have coexisted. However, the same surgical team performed all procedures and all HIPEC perfusionists were trained according to the same protocol.

Conclusion

During closed HIPEC, PI occurred in 10% of cases. PI can be resolved in most cases by adopting specific measures through a standardized problem-solving approach. Further research is needed to investigate other models to optimize perfusion volume and new catheter/circuit systems to prevent PI.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: CS, FF, BB, CC, RC, PP and AS. Data Curation: CS, CC, FF, BB, GM, PP, TT and AS. Formal analysis: CS, CC, FF, BB and AS. Investigation and methodology: all the authors. Software: CS, CC and AS. Supervision: RC, AS and PP. Validation, visualization, writing original draft, writing – review and editing: all Authors.

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