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Hemodynamic Monitoring During Heated Intraoperative Intraperitoneal Chemotherapy Using the FloTrac/Vigileo System

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Cytoreductive surgery with HIPEC has provided a chance for long-term survival in selected patients. However, perioperative management remains a challenge for the anesthesiology team. The aim of this study was to evaluate the changes in hemodynamic parameters during hyperthermic intraperitoneal chemotherapy (HIPEC) using the FloTrac/Vigileo system. Forty-one consecutive patients undergoing cytoreductive surgery and HIPEC were enrolled. Heart rate (HR), esophageal temperature, and cardiac output (CO) steadily increased until the end of HIPEC. In the first half of HIPEC, systolic blood pressure (SBP) and central venous pressure (CVP) increased whereas systemic vascular resistance (SVR) decreased; SVR stabilized in the second half. Diastolic blood pressure (DBP), mean arterial pressure (MAP), and stroke volume (SV) showed no significant variation. Male gender was related to increased CVP, CO, and SV, and decreased SVR; age >55 years was related to increased SBP, and peritoneal cancer index (PCI) was correlated with HR, DBP, and SV. PCI >14 was associated with increased HR and decreased DBP and MAP. American Society of Anesthesiologists score >1 was related to decreased CO and SV. Patients undergoing HIPEC develop a hyperdynamic circulatory state because of the increased temperature, characterized by a steady decrease in SVR and continuous increase in HR and CO. FloTrac/Vigileo system may provide an easy-to-handle, noninvasive monitoring tool.

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Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is evolving as an attractive option for the treatment of patients with primary or secondary peritoneal surface malignancy.[1–3] It is a complex procedure that includes abdominal and pelvic peritonectomies with combined organ resections in order to eradicate all macroscopic disease, and then perfusion of the abdominal cavity with heated chemotherapeutic agents, in an effort to eradicate all microscopic residual disease.[4] The indications of the method continue to expand because favorable 5-year survival rates were observed in low-grade malignancies, such as peritoneal adenomucinosis.[5] Cytoreductive surgery and HIPEC for high-grade malignancy is still debatable, with most surgeons agreeing that the volume of disease and the completeness of cytoreduction are crucial for the overall prognosis.[6]

Although the morbidity rate of cytoreductive surgery is acceptable and similar to that associated with other major oncologic procedures,[5] perioperative management of patients during HIPEC remains a challenge for surgeons, anesthesiologists, and intensive care unit physicians. A major issue is the observed hemodynamic instabilities even in low–ASA score patients.[7] Therefore, understanding the pathophysiologic changes that may be triggered by HIPEC is important in order to adjust standard resuscitation protocols.

The purpose of this study was to monitor and evaluate changes in the hemodynamic parameters during HIPEC by using the FloTrac/Vigileo device.

Patients and Methods

Patients

This is a prospective study of 41 consecutive patients with peritoneal carcinomatosis, treated with cytoreductive surgery and HIPEC in the Department of Surgery of Didimoticho General Hospital between May 2011 and April 2012. The study was approved by the ethics committee of the hospital, and all patients gave written informed consent. Inclusion criteria were age >16 years, American Society of Anesthesiologists (ASA) score I to III, and Karnofsky performance status scale >50%.[8] Exclusion criteria were ASA score >III, physical activity <50%, severe cardiovascular or respiratory disease, white blood cell count <4000/mm^3, platelet count <150,000/mm^3, urea level >50 mg/dL, serum creatinine level >1.5 mg/dL, hepatic failure, pregnancy, drug addiction, multiple partial intestinal obstruction, presence of distant and nonresectable metastases, and extensive involvement of the peritoneal surface of the small bowel.

Induction of anesthesia and intraoperative monitoring

Anesthesia was induced with intravenous infusion of propofol 2.5 mg/kg, rocuronium 1 mg/kg, and fentanyl 150 μg/kg. Maintenance of anaesthesia was achieved with sevoflurane and additional intravenous rocuronium according to the patient's needs. After the induction of anesthesia and hemodynamic stabilization, the patients received via the epidural catheter 5 mg/mL solution of ropivacaine bolus in doses of 2 mL per neurotome (from the point of entry of the epidural catheter up to the level of T6). After the settlement of the epidural analgesia, the patients received epidurally a continuous infusion of 2 mg/mL solution of ropivacaine with a flow of 8 mL/h until the end of the operation.

Intraoperative monitoring included heart rate (HR), invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), stroke volume (SV), and systemic vascular resistance (SVR). The hemodynamic monitoring was performed with the Vigileo/Flotrac system (Edwards Lifesciences, Irvine, California).

All parameters were recorded at the beginning of HIPEC (time point 1); in the middle of the procedure, at 45 minutes (time point 2); and at the end of HIPEC, at 90 minutes (time point 3).

Perioperative fluid resuscitation

All patients were admitted at least 24 hours prior to the scheduled operation. Preoperative fasting was prescribed as usual and bowel cleansing was routine. Patients were given intravenous fluids for a minimum of 12 hours prior to surgery and according to their needs. During surgery patients were liberally given crystalloids, with close monitoring of the urine output. Transfusions were kept to a minimum and, depending on intraoperative losses, aimed to keep hemoglobin levels above 9

mg/dL. Fresh frozen plasma was given in an effort to stabilize prothrombin time/international normalized ratio below 1.2. During HIPEC, patients were given additional crystalloids in order to establish a minimal level of urine output of 1500 mL/h.

Operative technique and HIPEC

All patients underwent surgery with the intention of performing complete cytoreduction. Common peritonectomy procedures included pelvic peritonectomy, greater omentectomy with or without splenectomy, lesser omentectomy with resection of the omental bursa, cholecystectomy, right and left subdiaphragmatic peritonectomy, and parietal peritonectomy. Resections of other organs, small and/or large bowel, and the stomach were performed if necessary in order to achieve complete cytoreduction. The completeness of cytoreduction was indicated as CC0 to CC3 as previously described,[9] whereas the extent and distribution of peritoneal dissemination were assessed by using the peritoneal cancer index (PCI).[10]

After the completion of cytoreduction and before the necessary intestinal reconstructions, HIPEC was performed using the Coliseum technique[10] for 90 minutes. The abdominal cavity was filled with normal saline (3–5 L). After reaching the desired temperature of 42°C the chemotherapeutic agents were circulated in the abdominal cavity. The choice of chemotherapy regimens depended on the origin of the malignancy according to locally approved protocols: for colorectal cancer, mitomycin C (20 mg/m^2); and for ovarian cancer, a combination of cisplatinum (50 mg/m^2) with doxorubicin (15 mg/m^2). Heated chemotherapy was performed using the SunChip system (Gamidatech, Eaubonne, France). The heat exchanger kept the fluid at >43°C so that the intraperitoneal fluid was maintained at approximately 42°C.

Statistical analysis

All statistical analyses were performed using the statistical package SPSS statistics 18.0 (SPSS Inc, Chicago, Illinois). Quantitative data were expressed as mean (SD), median, or range. Univariate analysis was performed with the χ^2 test and the Fisher exact test where applicable for categoric variables and the Mann-Whitney *U* test for numeric variables. Differences between time points were analyzed by Wilcoxon test, whereas Spearman correlation test was applied for data correlations. Significance was tested at the 5% level of statistical significance ($P < 0.05$).

Results

The study enrolled 11 men and 30 women with a mean age of 56.8 years (range, 16–77 years). The mean PCI was 13.7 (range, 2–39). Patients' demographic data are depicted in Table 1.

Operative time from induction of anesthesia to the beginning of HIPEC ranged from 120 to 360 minutes (mean, 231.6 minutes). All patients received crystalloids, colloids, and fresh frozen plasma (mean, 4.8; range, 2–12) during the operation, whereas 27 patients were transfused with red blood cells (mean, 2.8; range, 1–6). No serious intraoperative complications during HIPEC were recorded.

Changes in cardiopulmonary parameters

The mean (SD) HR in the beginning of HIPEC was 75.1 (13.7) beats per minute. It increased significantly to a mean of 80.3 (21.1) beats per minute 45 minutes later ($P < 0.001$) and continued to elevate, reaching at the end of the HIPEC procedure a mean of 86.0 (12.7) beats per minute ($P < 0.001$).

SBP increased from 134.4 (15.3) mmHg to 141.3 (15.6) mmHg ($P = 0.017$), and then it presented a nonsignificant decline to 140.2 (20.3) mmHg. Both DBP and MAP showed no significant variation throughout the 90 minutes of HIPEC, although both tended to decrease during the procedure.

The mean CVP was 11.6 (4.5) mmHg at the first measurement and increased significantly to 13.7 (3.7) mmHg at the second measurement. Then it was stabilized at 13.2 (3.8) mmHg. SV was 82 (27.4) mL per beat at the beginning of HIPEC and remained without any significant change throughout the course.

Esophageal temperature increased from a mean (SD) of 34.4°C (1.3°C) to 36.8°C (0.9°C) in the middle of the procedure ($P < 0.001$), and it reached a maximum at the end of HIPEC with values up to 37.8°C (0.8°C; $P < 0.001$).

The SVR was 1203.2 (328.6) dyn·s·cm^{-5} at the beginning, showed a significant decrease to values of 1092.1 (321.0) dyn·s·cm^{-5} at the second measurement ($P < 0.001$), and showed stabilization at values of 1016.7 (311.4) dyn·s·cm^{-5} at the third measurement. The mean (SD) CO at the beginning

Table 1 Demographic characteristics of 41 patients undergoing cytoreductive surgery and HIPEC

Characteristic	Frequency (%)
Age, y (range)[a]	56.8 (16–77)
Gender	
Male	11 (26.8)
Female	30 (73.2)
Diagnosis	
Ovarian cancer	19 (46.3)
Peritoneal mesothelioma	4 (9.8)
Colon cancer	6 (14.6)
Gastric cancer	2 (4.9)
Pancreatic cancer	1 (2.4)
Primary peritoneal cancer	6 (14.6)
Peritoneal pseudomyxoma	2 (4.9)
Peritoneal sarcomatosis	1 (2.4)
PCI (range)[a]	13.7 (2–39)
Cytoreduction score	
CC0	28 (68.3)
CC1	11 (26.8)
CC2	0
CC3	2 (4.9)
ASA score	
ASA 1	10 (24.4)
ASA 2	12 (29.3)
ASA 3	19 (46.3)

[a]Mean values.

of heated intraoperative intraperitoneal chemotherapy was 6.1 (2.1) L/min, and it had increased to 6.6 (2.2) L/min at 45 minutes, which reaches statistical significance ($P = 0.01$). At the end of HIPEC, CO was elevated again, at 7.1 (2.4) L/min ($P = 0.02$). Table 2 compares the cardiopulmonary parameters studied between the different time points.

Associations between cardiopulmonary parameters and demographic characteristics

Correlations between the measured cardiopulmonary parameters at every time point and patients' demographics were also investigated. Male gender was related to increased CVP (14.2 mmHg in men versus 10.6 mmHg in women; $P = 0.05$), increased CO (7.5 L/min versus 5.9 L/min; $P = 0.02$), increased SV (100.2 mL per beat versus 75.4 mL per beat; $P = 0.03$), and decreased SVR (995 dyn·s·cm^{-5} versus 1279 dyn·s·cm^{-5}; $P = 0.009$) at time point 1. Age >55 years was marginally related only to increased SBP at time point 1 ($P = 0.05$). PCI was correlated with HR ($r = 0.32$, $P = 0.04$), DBP ($r = -0.39$, $P = 0.01$), and SV ($r = -0.32$, $P = 0.04$) at time point 1; with HR ($r = 0.32$, $P = 0.04$) and SV ($r = -0.36$, $P = 0.02$) at time point 2; and with SV ($r = -0.31$, $P = 0.04$) at time point 3. When a cutoff point of 14 was set, PCI >14 was associated with increased HR (78.8 beats per minute in PCI >14 patients versus 70.7 beats per minute in PCI <14 patients; $P = 0.04$), decreased DBP (69.8 mmHg versus 78.8 mmHg; $P = 0.006$), and decreased MAP (93.6 mmHg versus 100.5 mmHg; $P = 0.03$) at time point 1, and marginally increased HR (83.1 beats per minute versus 76.1 beats per minute; $P = 0.05$) at time point 2. PCI was not related to any of the monitoring parameters, whereas ASA score >1 was related to decreased CO at time points 1, 2, and 3 (time point 1: 5.8 L/min in ASA 2 and 3 patients versus 6.9 L/min in ASA 1 patients; $P = 0.04$; time point 2: 6.1 L/min versus 8.1 L/min; $P = 0.008$; and time point 3: 6.1 L/min versus 8.6 L/min; $P = 0.02$), and decreased SV at all time points as well (time point 1: 78.6 mL per beat in ASA 2 and 3 patients versus 92.6 mL per beat in ASA 1 patients; $P = 0.03$; time point 2: 76.2 mL per beat versus 100 mL per beat; $P = 0.006$; and time point 3: 75.8 mL per beat versus 100.2 mL per beat; $P = 0.01$).

Discussion

Diffuse primary or secondary peritoneal malignancy is no longer considered a terminal disease. Recent data suggest that the combination of cytoreduction surgery with HIPEC provides a chance for long-term survival for selected patients, with an acceptable morbidity and mortality rate. Thus, it could be regarded as an option in the multidisciplinary care of patients with peritoneal surface malignancy in designated centers.[11,12]

Hemodynamic instability has been observed and reported during HIPEC.[13,14] This may be attributed to the rapid and important fluctuations of core temperature. During cytoreduction, the patient is becoming gradually hypothermic because of the long exposure of the abdominal viscera. However, during HIPEC, body temperature rises considerably because of the circulation of the heated solution, and it reaches levels of 38°C or more, leading to a significantly increased metabolic rate.[15,16] This was also observed in our series, with temperatures that reached mean values of 37.8°C at the end of HIPEC. Different cooling measures are necessary at this time to avoid central hyperthermia—measures such as intravenous administration

Table 2 Changes in cardiopulmonary parameters between the three different time points of HIPEC[a]

Cardiopulmonary parameters	Time point 1	Time point 2	Time point 3	P_1[b]	P_2[c]	P_3[d]
Temp, °C	34.4 (1.3)	36.8 (0.9)	37.8 (0.8)	<0.001	<0.001	<0.001
HR, beats per min	75.1 (13.7)	80.3 (12.1)	86.0 (12.7)	0.001	<0.001	<0.001
SBP, mmHg	134.4 (15.3)	141.3 (15.6)	140.2 (20.3)	0.017	0.6	0.11
DBP, mmHg	74.0 (10.0)	71.1 (10.8)	71.4 (10.6)	0.11	0.70	0.17
MAP, mmHg	96.9 (11.1)	96.6 (12.3)	95.2 (12.7)	0.74	0.52	0.63
CVP, mmHg	11.6 (4.5)	13.7 (3.7)	13.2 (3.8)	<0.001	0.15	0.02
CO, L/min	6.1 (2.1)	6.6 (2.2)	7.1 (2.4)	0.01	0.01	0.02
SV, mL per beat	82 (27.4)	82.3 (27.6)	82.2 (27.5)	0.50	0.83	0.81
SVR, dyn·s·cm^{-5}	1203.2 (328.6)	1092.1 (321.0)	1016.7 (311.4)	<0.001	0.02	<0.001

[a]Values are expressed as mean (SD).

[b]Time point 1 versus time point 2.

[c]Time point 2 versus time point 3.

[d]Time point 3 versus time point 1.

of cold crystalloids, placement of ice packs around patient's head and neck, and turning off the air heating blankets.[17]

The dilatation of the peripheral vasculature, which aims increase heat loss from the core to the environment, is one of the initial responses to heat stress, and it can be demonstrated by the recorded significant decrease of SVR in our patients. As a result of decreasing peripheral vascular resistance, heart rate increases in order to maintain CO.[13,18] Increased CO and HR were measured by Vigileo during HIPEC (from 6.1 L/min to 7.1 L/min, and from 75.1 beats per minute to 86.0 beats per minute, respectively), which is in line with previous reports.[15,19]

Both SBP and DBP, as well as MAP, showed no significant variation throughout the 90 minutes of HIPEC, with the exception of a moderate increase of SBP in the second measurement, probably due to the temperature increase, which agrees with previous reports.[15,16] SV remained unaltered during HIPEC. Cafiero *et al*[18] observed a moderate decrease in their series of patients, which can be explained by the choice of a closed abdomen technique. It has been demonstrated that by using an open abdomen procedure (coliseum technique), hemodynamic alterations caused by reduced venous return due to increasing intra-abdominal pressure, such as SV decrease, can be avoided.[19] Moreover, during HIPEC, adequate adjustment of fluid and blood loss should be a basic goal for the anesthesiologist to maintain normovolemia and sufficient SV during HIPEC.[20]

We chose for monitoring hemodynamic parameters the FloTrac/Vigileo device, which is considered to be a helpful tool in obtaining information on the patient's fluid and hemodynamic "real-time" status by calculating SV and CO from a single sensor attached to an arterial line at any site, with an acceptable risk to benefit ratio. Furthermore, it can be used in addition to the standardized monitoring devices (central venous catheter, arterial line, and urinary catheter).[18] FloTrac/Vigileo presents significant benefits compared with other methods of hemodynamic monitoring. It is less invasive compared with Swan-Ganz catheter, transesophageal echocardiography, and pulse-contour device, and presents a lower complication rate. Moreover, less invasive methods when used alone may not accurately predict response to fluid therapy. CVP, for instance, is considered a poor indicator of patients' volume state and cardiac preload because of the increased intra-abdominal pressure and changes in the operating table's inclination during HIPEC,[19] whereas urine output can be influenced by other factors apart from afterload, like neurohormonal changes.[21] On the other hand, esophageal Doppler is a popular and useful noninvasive device, but it presents high user variability.[22] Pulse Contour Cardiac Output (PiCCO) system, which requires the placement of a femoral arterial line, and Non Invasive Cardiac Output monitoring (NICO) system, which measures cardiac output from rebreathing CO_2, are two other noninvasive devices, but they are difficult to use, and they cannot use monitors already in place.[23]

Hence, monitoring dynamic parameters of cardiac preload and fluid responsiveness, such as CO, SV, and SVR, is mandatory for the anesthesiology team in order to maintain normovolemia and prevent acute renal failure. A device that could

accurately measure the above parameters from a standard arterial line without requiring external calibration like other devices, such as PiCCO, would appear to be a major step forward. This can be provided by the FloTrac/Vigileo system, combined with a monitoring system volume responsive algorithm (decision tree) that can assist the anesthesiologist in making clinically relevant decisions to obtain fluid optimization versus the need for other interventions, such as inotropic/vasopressor support or diuretic therapy, based on the obtained values.[15,24]

Conclusion

Patients in our study developed a hyperdynamic circulatory state due to increased body temperature, characterized by a steady decrease in SVR and a continuous increase in HR and CO, reaching their minimum or maximum values, respectively, at the end of the HIPEC procedure. During HIPEC, the anesthesiologist is in front of many challenges, including systemic hyperthermia, increased metabolic rate, alterations in hemodynamic status, fluid or blood loss, and maintenance of normovolemia. The FloTrac/Vigileo system provided an easy-to-handle, noninvasive tool with high reliability in monitoring hemodynamic changes during the HIPEC procedure.

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