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Cytoreductive Surgery and Continuous Hyperthermic Peritoneal Perfusion in Patients with Mesothelioma and Peritoneal Carcinomatosis: Hemodynamic, Metabolic, and Anesthetic Considerations

Ning Miao, MD¹, James F. Pingpank, MD², H. Richard Alexander, MD², Richard Royal, MD², Seth M. Steinberg, PhD³, Martha M. Quezado, MD⁴, Tatiana Beresnev, MD², and Zenaide M. N. Quezado, MD¹

¹Department of Anesthesia and Surgical Services, National Institutes of Health Clinical Center, National Institutes of Health, 10 Center Drive, MSC-1512, Building 10, Room 2C624, Bethesda, MD 20892-1512, USA

²Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

³Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

⁴Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

Cytoreductive surgery and continuous hyperthermic peritoneal perfusion (CHPP) involve the conduct of a complex surgical procedure and delivery of high-dose hyperthermic chemotherapy to the peritoneum. This therapeutic modality has been shown to benefit patients with peritoneal carcinomatosis resulting from gastrointestinal and ovarian tumors and mesothelioma. However, it is unknown whether the primary disease (mesothelioma versus peritoneal carcinomatosis) affects hemodynamic and metabolic perturbations during the course of CHPP with cisplatin. We examined the perioperative course of patients undergoing CHPP with cisplatin and evaluated the effect of primary diagnosis (mesothelioma versus peritoneal carcinomatosis) on hemodynamic and metabolic parameters in response to peritoneal perfusion. Sixty-nine mesothelioma and 100 peritoneal carcinomatosis patients underwent 169 consecutive cytoreduction and CHPP procedures with general anesthesia. During CHPP, patients from both groups developed significant increases in central venous pressure, and heart rate, decreases in mean arterial pressure (all $P < 0.0001$), metabolic acidosis with significant decreases in pH and bicarbonate ($P < 0.0001$), deterioration of gas exchange with significant increases in PaCO₂ and oxygen alveolar–arterial gradient ($P < 0.0001$), and significant increases in activated partial thromboplastin time (aPTT) and prothrombin time (PT) and decreases in hematocrit and platelet counts (all $P < 0.0001$). However, patients with mesothelioma had lesser increases in temperature ($P < 0.01$) and heart rate ($P < 0.0001$) and lesser decreases in hematocrit ($P = 0.0013$) during CHPP and greater decreases in sodium bicarbonate ($P = 0.0082$) after completion of CHPP compared with patients with peritoneal carcinomatosis. We conclude that the transient hemodynamic and metabolic perturbations associated with cytoreductive surgery and CHPP with cisplatin can vary according to the primary diagnosis (mesothelioma versus peritoneal carcinomatosis) warranting this therapy.

Mesothelioma and peritoneal carcinomatosis resulting from gastrointestinal and gynecological malignancies are associated with decreased quality of life, significant morbidity, and poor survival with currently available systemic chemotherapies.^{1,2} Often in patients with mesothelioma and peritoneal carcinomatosis the peritoneal surface is the only site of disease progression, and distant metastases are absent. For these reasons, regional treatment of mesothelioma and peritoneal carcinomatosis resulting from various primary malignancies may offer significant advantages over systemic therapy.¹ In order to treat patients with peritoneal carcinomatosis and mesothelioma, surgical oncologists have developed procedures involving cytoreductive surgery and continuous hyperthermic peritoneal perfusion (CHPP) with high-dose chemotherapy.³ This procedure for the delivery of locoregional high-dose chemotherapy can improve control of local disease and minimize systemic toxicity. In fact, such strategy has proven beneficial for patients with peritoneal carcinomatosis resulting from colon cancer, and held promise for treatment of patients with mesothelioma and other gastrointestinal malignancies.^{4–13} As a result, in some centers, cytoreductive surgery and CHPP has become standard treatment for patients with mesothelioma and peritoneal carcinomatosis associated with gastrointestinal and ovarian malignancies.^{5,14–17} Recently, these promising results have led to the publication of a consensus statement strongly suggesting that cytoreductive surgery and CHPP become standard treatment for patients with colon cancer and peritoneal carcinomatosis without distant metastasis.¹⁸

Cytoreductive surgery entails a complex surgical procedure which may be associated with significant fluid shifts, blood loss, and significant postoperative morbidity.^{19,20} While the techniques and chemotherapeutic agents used for CHPP vary among institutions, all involve the regional delivery of hyperthermic chemotherapy that may lead to hemodynamic and metabolic perturbations which can add to the morbidity associated with CHPP.^{21,22} Therefore, in order to safely anesthetize patients undergoing cytoreductive surgery and CHPP, anesthesiologists and surgeons alike should have an understanding of the profound hemodynamic and metabolic perturbations associated with the therapy.

Herein we describe the hemodynamic and metabolic changes associated with cytoreductive surgery and CHPP using high-dose cisplatin in a large cohort of patients with mesothelioma or peritoneal carcinomatosis associated with gastrointestinal malignancies. We also examine the effect of primary disease on these metabolic and hemodynamic perturbations during the procedure.

PATIENTS AND METHODS

Patients

We examined the perioperative course of patients with mesothelioma and peritoneal carcinomatosis from gastrointestinal adenocarcinomas who underwent consecutive cytoreductive surgery and CHPP. The study was approved by the Institutional Review Board of the National Cancer Institute, National Institutes of Health and conducted between 1999 and 2007. Patients were enrolled in phase II and III trials of cytoreduction and CHPP with cisplatin (250 mg/m²). Preoperative evaluation included detailed history, physical examination, routine hematologic and chemistry profile, chest radiograph, electrocardiogram, computerized tomography, and magnetic resonance imaging when indicated to complete a standard disease staging evaluation. Echocardiography and/or cardiac stress test were obtained when clinically indicated.

Surgical Procedure: Cytoreduction and CHPP

All patients underwent exploratory laparotomy, cytoreduction, and CHPP as previously described.²³ Briefly, after cytoreduction aimed at rendering each patient grossly free of

disease, two large-bore catheters are inserted through the abdominal wall. One catheter is placed over the right lobe of the liver for influx and the other in the pelvis for efflux of the perfusate. The catheters are connected to a roller pump and the circuit includes a heat exchanger and a reservoir. In order to monitor temperature, two probes are placed in the peritoneum along each of the paracolic gutters. After the catheters and temperature probes are placed, the fascia is closed and the abdominal cavity perfused with approximately 4 L warmed to 41°C at 1.5 L/min. Cisplatin (250 mg/m² diluted in 1 L 0.9% sodium chloride) is added to the perfusate and peritoneal perfusion continued for 90 min. To improve cisplatin distribution to the peritoneal surface, the abdomen is manually agitated throughout perfusion time. Once CHPP is completed, the abdomen is reopened, catheters and probes are removed, and the chemotherapy solution irrigated out of the abdomen. Subsequently, needed bowel anastomoses are done, hemostasis verified, and abdominal wall is closed.

Sodium thiosulfate [loading dose of 7.5 g/m² (20 min prior to cisplatin) followed by a 12-h continuous infusion (2.13 g/m²/h)] is administered to all patients in order to minimize cisplatin-induced auditory and renal toxicity.

Anesthetics and Measurements

All anesthetics are conducted by anesthesiologists familiar with the procedure and institutional practices using standard (electrocardiography, noninvasive blood pressure, pulse oximetry and capnography) and continuous central venous and invasive arterial pressure monitoring. All patients have general anesthesia and, in the absence of contraindications, insertion of an epidural catheter prior to induction. General anesthesia is induced with propofol and fentanyl and, after muscle relaxation with cisatracurium, rocuronium, or succinylcholine the trachea is intubated. Continuous epidural infusion of local anesthetic and opioids was started only when patients were extubated. When patients are maintained on mechanical ventilation after completion of CHPP, epidural infusion of local anesthetics is held and pain control is achieved with systemic opioids. For the purpose of this investigation hemodynamic and metabolic parameters were measured and analyzed at times shown in Fig. 1. Temperature was measured with an esophageal probe placed at the middle third of the esophagus, and fluid warmers and air blankets were used as needed during the procedure. In preparation for and during the 90-min CHPP, in order to ameliorate and/or prevent increases in core temperature, all warming devices are turned off and ice packs were placed on both axillae, both sides of the neck, and groin. Crystalloid and colloid were administered liberally to meet maintenance requirements, replace fluid loss, and to maintain adequate urine output throughout the procedure. At the discretion of the anesthesiologist, vasoactive drugs (norepinephrine, phenylephrine or dopamine) are administered to treat decreases in arterial blood pressure aiming to keep mean arterial pressure above 60 mmHg and within 20% of baseline values. In addition, during CHPP with cisplatin and for 12 h after surgery, patients are aggressively hydrated to maintain an hourly urine output greater than 200 ml. Furosemide and small doses of dopamine were administered to facilitate diuresis as needed.

Statistical Methods

Hemodynamic and metabolic parameters measurements obtained before, during, and after CHPP are shown in Fig. 1, and the differences of interest constructed using these measurements are listed in Table 1. Analyses were performed to identify if there were changes in these parameters throughout the perioperative period and the statistical significance of each of the constructed differences from zero was determined using a Wilcoxon signed rank test. In addition, we examined whether these changes were related to the primary diagnosis (mesothelioma versus peritoneal carcinomatosis from gastrointestinal malignancies, including low- and high-grade appendiceal adenocarcinoma, colon adenocarcinoma, and others), sex, age, estimated blood loss, total urinary output or total intravenous fluid. Differences between

changes according to sex or diagnosis category were determined using a Wilcoxon rank-sum test. Comparisons of a set of surgical and anesthesia parameters according to the five more specific primary diagnoses (appendiceal high grade, appendiceal low grade, colon, mesothelioma, and other) were performed using Kruskal–Wallis test. Correlations of the parameters described above with age, estimated blood loss, total urinary output or total intravenous fluid were determined using Spearman correlation coefficients. The coefficients, r , are interpreted as follows: $|r| > 0.70$ is a strong correlation; $0.5 < |r| < 0.70$ is a moderately strong correlation; $0.3 < |r| < 0.50$ is a weak to moderately strong correlation, and if $|r| < 0.30$, the correlation would be considered to be weak.

All P -values are two tailed and presented without adjustment for multiple comparisons. Given that a large number of statistical tests were performed and that the comparisons made inherently have varying degrees of independence and dependence (as the same time points are being used in various comparisons and the parameters themselves may be inherently correlated with one another to varying degrees) it would be very difficult to identify a completely valid adjustment for multiple comparisons. For these reasons, we determined that P values < 0.01 would be considered statistically significant, while those with $0.01 < P < 0.05$ would be considered trends. In addition, the identification of multiple statistical trends among related parameters would be indicative of a meaningful association even if individual findings are not statistically significant.

RESULTS

Patients and Anesthetic Techniques

One-hundred sixty-nine patients who underwent 169 consecutive CHPP procedures were included in this study. Results of the clinical effects of CHPP with cisplatin in patients included in this series have been previously reported.¹⁶ Table 2 shows the demographic profile of patients studied.

For the procedure, all patients had general anesthesia and 133 (79%) had an epidural catheter inserted to provide postoperative analgesia. Anesthesia was maintained with volatile anesthetics [with (45%) or without N₂O (55%)] fentanyl (96%) or sufentanyl (4%), and cisatracurium (98%) or rocuronium (2%). Anesthetic time was 585 ± 132 min [mean $\pm$ standard deviation (SD)] and surgical time was 479 ± 123 min (mean $\pm$ SD). When comparing results among the various groups per primary diagnosis there was no overall difference in surgical time for cytoreduction by group [mean $\pm$ SD for appendiceal high grade (484 ± 22 min), appendiceal low grade (468 ± 18 min), colon (457 ± 23 min), mesothelioma (494 ± 16 min), and other (445 ± 74 min); $P = 0.63$]. All CHPP times were 90 min for each group, and the post-CHPP times [after completion of CHPP to arrival to the intensive care unit (ICU)] also did not vary by diagnosis [mean $\pm$ SD for appendiceal high grade (76 ± 5 min), appendiceal low grade (82 ± 3 min), colon (88 ± 6 min), mesothelioma (89 ± 4 min), and other (60 ± 5 min), $P = 0.10$]. Table 3 shows fluid shifts and blood products administration during all CHPPs. Fifty (30%) patients received furosemide, and 146 (86%) required intravenous replacement of magnesium, calcium, and sodium bicarbonate. After CHPP, six patients required thoracostomy to drain pneumothoraces and/or hydrothoraces.

After completion of the procedure and emergence from anesthesia, in 104 patients (62%) the trachea was extubated in the operating room. Sixty-five (38%) patients remained intubated and on mechanical ventilation overnight [46 (27%) patients], for 48 h [14 (8%)], or 72–96 h [5 (3%) patients] either because of metabolic disturbances, increased oxygen requirements, facial edema, or prolonged emergence from anesthesia (3 patients). There were no perioperative deaths during this study nor anesthesia-related complications or morbidities.

Changes in Hemodynamics and Temperature During Cyto reduction and CHPP

The overall hemodynamic changes observed during all 169 CHPPs are shown in Fig. 2. From baseline (within 10 min after induction of anesthesia) to end of cyto reduction (5 min before start of CHPP), there were significant decreases in mean arterial pressure and temperature and increases in heart rate (Fig. 2, all $P < 0.0001$). During CHPP (30, 60, and 90 min), compared with measures obtained 5 min before, there were significant increases in mean temperature, central venous pressure, and heart rate, and decreases in mean arterial pressure (Fig. 2, all $P < 0.0001$). Thirty minutes after, compared with measurements obtained during CHPP (90 min), there were significant decreases in temperature, heart rate, and central venous pressure, and increases in mean arterial pressure (Fig. 2, all $P < 0.0001$). Overall, after completion of surgery and upon arrival to the ICU, there were still significant increases in temperature and heart rate (both $P < 0.0001$), and decreases in mean arterial pressure ($P = 0.0005$) compared with baseline measurements. During the procedures, vasoactive drugs were administered to treat decreases in arterial blood pressure (aiming to keep the mean arterial pressure above 60 mmHg) or to facilitate diuresis during CHPP at the discretion of anesthesiologists. Sixty-two patients (37%) received dopamine and 32 (19%) phenylephrine and/or ephedrine. Despite the described cooling measures, in 31 (18%) patients, during CHPP, core temperature reached levels greater than 39°C.

Correlations between hemodynamic changes and age, sex, blood loss, urine output, and fluid management were typically weak (data not shown).

Changes in Metabolic Parameters During Cyto reduction and CHPP

Overall acid–base, gas exchange, and hematologic changes observed during all 169 CHPPs are shown in Fig. 3. Compared with baseline measurements, during CHPP, metabolic acidosis ensued as shown by significant decreases in pH and bicarbonate (Fig. 3, $P < 0.0001$). In addition, during CHPP there was deterioration of gas exchange, as there were significant increases in PaCO₂ and in oxygen A-a gradient (Fig. 3, $P < 0.0001$) compared with baseline. With regards to hematologic parameters, during CHPP compared with baseline, there were significant increases in aPTT and PT and decreases in hematocrit and platelet counts (Fig. 3, $P < 0.0001$). Thirty minutes after, compared with measurements obtained during CHPP, there were significant decreases in PaCO₂ and oxygen A-a gradient ($P < 0.0001$, Fig. 3), a trend toward further decreases in serum bicarbonate ($P = 0.029$), but no significant changes in arterial pH ($P = 0.37$) suggesting persistence of metabolic acidosis. In addition, upon its completion, compared with measurements obtained during CHPP (Fig. 3), there were significant decreases in aPTT ($P = 0.01$) and PT ($P = 0.0046$), increases in hematocrit ($P < 0.0001$), and a trend towards decreases in platelet counts ($P = 0.031$). Overall, upon arrival to the ICU, compared with baseline levels, there was persistent metabolic acidosis, coagulopathy, anemia, and impairment in gas exchange as shown by significant decreases in pH, bicarbonate, hematocrit, and platelet counts, and significant increases in aPTT, PT, and oxygen A-a gradient (all $P < 0.0001$, Fig. 3). In the ICU, all acid–base abnormalities resolved within 24 h in 73% of patients; PT and APTT normalized within 5 days in 78%, and platelet counts within 5 days in 89%.

The correlations between metabolic changes identified and age, sex, blood loss, urine output, and fluid management were typically weak (data not shown) except for a moderately strong correlation between decreases in pH measured upon arrival to the ICU compared with baseline and total urine output during procedure ($|r| = 0.54$, $P = 0.0015$).

Effect of Primary Diagnosis on Hemodynamic and Metabolic Changes During Cyto reduction and CHPP

We performed analysis to evaluate the effect of the primary diagnosis and in turn disease biology on changes identified during cyto reduction and CHPP. Table 4 displays demographics

and anesthetic and surgical variables of patients with mesothelioma and peritoneal carcinomatosis from gastrointestinal malignancies. There were no significant differences in operative times for cytoreductive surgery, CHPP, and time after CHPP comparing the mesothelioma and peritoneal carcinomatosis groups (Table 3). While the total amount of fluid administered during the procedure was similar in both groups, patients in the mesothelioma group had a trend towards receiving less crystalloid before and after CHPP ($P = 0.02$) but more crystalloid during CHPP ($P = 0.02$) compared with patients with peritoneal carcinomatosis. In addition, while total urine output during the procedure was similar in both groups, patients with mesothelioma had lower urine output before and after CHPP compared with patients with peritoneal carcinomatosis (Table 4, $P = 0.006$).

Figure 4 shows differences in hemodynamic and metabolic changes between patients with mesothelioma and those with peritoneal carcinomatosis. In patients with mesothelioma compared with patients with peritoneal carcinomatosis, during CHPP, there were smaller increases in temperature (at 30 min, $P = 0.0046$ and at 60 and 90 min, $P < 0.0001$) and heart rate (at 90 min, $P < 0.0001$) and smaller decreases in hematocrit ($P = 0.0013$) compared with measurements obtained at baseline. Upon arrival to the ICU compared with baseline measurements, in patients with mesothelioma, there were smaller increases in temperature ($P < 0.0001$) and smaller increases in heart rate ($P = 0.01$) compared with patients with peritoneal carcinomatosis. In patients with mesothelioma compared with patients with peritoneal carcinomatosis, there were greater decreases in sodium bicarbonate ($P = 0.0082$) upon completion of CHPP, and upon arrival to the ICU, persistent greater decreases in sodium bicarbonate ($P = 0.003$) and PT (-4.5 ± 1.6 versus -1.1 ± 0.7 s mesothelioma versus peritoneal carcinomatosis, $P = 0.01$) compared with measurements obtained during CHPP.

DISCUSSION

We describe the perioperative course and anesthetic considerations in patients with mesothelioma and peritoneal carcinomatosis treated with cytoreductive surgery and CHPP with high-dose cisplatin. During the procedure, patients develop significant hemodynamic (hypotension, tachycardia, and hyperthermia) and metabolic (acidosis, coagulopathy, and deterioration of gas exchange) perturbations. However, when addressed timely, these changes are short lived, variables return to baseline, and do not appear to contribute to perioperative morbidity. Interestingly, we found that those patients with peritoneal carcinomatosis from gastrointestinal malignancies have greater increases in heart rate and temperature and greater decreases in hematocrit compared with mesothelioma patients, and that those patients with mesothelioma have greater decreases in serum bicarbonate than do patients with peritoneal carcinomatosis. Therefore our findings suggest that the primary diagnosis affects hemodynamic and metabolic responses to peritoneal perfusion.

Why might the primary disease (mesothelioma versus peritoneal carcinomatosis) impact on metabolic and hemodynamic changes during cytoreductive surgery and CHPP? One possibility is that there were differences in the extent of surgery and/or cytoreduction between the two groups. However, in our series, mesothelioma and peritoneal carcinomatosis patients had statistically similar cytoreductive surgery times, blood loss, and total fluid resuscitation requirements. Therefore, if one uses surgical time and fluid resuscitation requirements as an indicator of extent and complexity of surgical resection, it is unlikely that differences in surgical procedure explain the distinct responses to CHPP. Another hypothesis is that differences in pathologic features of mesothelioma versus peritoneal carcinomatosis and associated changes in the peritoneum might explain the different metabolic and hemodynamic responses to CHPP. Studies suggesting that pathologic features of mesothelioma, such as presence of deep invasion, can have impacts beyond limiting resection of the tumors and in fact can affect survival might support this possibility.¹⁶ Yet another hypothesis is that mesothelioma and peritoneal

carcinomatosis, by having different expression profile of permeability-inducing factors, can distinctly affect peritoneal permeability and yield different responses to peritoneal hyperthermia during CHPP.²⁴ In support of this hypothesis are animal studies showing that ascites tumor cells alter peritoneal vascular permeability and human studies showing that ascites from gastric and colon cancer patients have increased vascular endothelial growth factors and increases endothelial cell permeability in vitro.^{25,26} One could then postulate that tumor-produced permeability-inducing factors, by distinctly changing peritoneal vascular permeability, explain why patients with peritoneal carcinomatosis have greater increases in temperature and greater decreases in hematocrit than do patients with mesothelioma. Nevertheless, while the mechanisms of our findings were not explored in this investigation, our results suggest that differences in tumor biology might lead to different responses to peritoneal hyperthermia in patients with mesothelioma compared with peritoneal carcinomatosis. Therefore, knowledge of the primary diagnosis is important to properly anticipate and treat metabolic and hemodynamic changes in patients undergoing cytoreductive surgery and CHPP.

In this investigation, we examined a large cohort of patients undergoing cytoreductive surgery and CHPP with high-dose cisplatin using a closed-abdomen technique and observed changes in coagulation parameters and gas exchange that are qualitatively similar to but quantitatively different from those described by others using different chemotherapeutic agents.^{21,27,28} During CHPP, we observed greater increases in central venous pressures, heart rate, and temperature and transient decreases instead of no significant changes in mean arterial pressure compared with other series.^{21,27} These differences could possibly be explained by differences in patient population, differences in the chemotherapy agents used, and length of surgery. In addition, because the chemotherapy agent used in this investigation may be associated with renal toxicity, we used more aggressive fluid resuscitation than that reported in other series.²¹ Researchers who use an openabdomen technique observe yet milder hemodynamic changes compared with those observed in our patients.^{22,29} Nevertheless, it appears that, when treated timely, as is done as part of the anesthetic management during the procedure, the hemodynamic and metabolic changes observed during cytoreductive surgery and CHPP are transient and do not lead to significant morbidity.

It is our institutional bias to insert epidural catheters prior to cytoreductive surgery and CHPP but, contrary to the practice in other centers, to use epidural infusions of local anesthetics and/or opioids only for postoperative pain management and not intraoperatively.²¹ We adopted this practice because the hemodynamic and metabolic perturbations could conceivably be worsened or confounded by the injection of epidural local anesthetics. Others have reported that patients receiving epidural analgesia required less postoperative mechanical ventilation than did patients receiving intravenous analgesia (56 versus 86% respectively).²¹ In our series, only 38% of patients required mechanical ventilation postoperatively for reasons other than inadequate pain control. Therefore, while effective postoperative pain control is an important matter in cytoreductive surgery and CHPP, it can be achieved with or without epidural infusions of local anesthetics and seldom impacts on the need for postoperative mechanical ventilation.

Similar to other centers, we observed the development of acidosis during cytoreductive surgery and CHPP that appears to have both metabolic and respiratory components.²¹ Several factors including significant fluid shifts partially caused by peritoneal cavity hyperthermia, decreases in blood pressure, increases in intra abdominal pressure, and mild systemic hyperthermia contribute to these drops in pH and bicarbonate and increases in arterial carbon dioxide and consequent acidosis. However, contrary to others who report significant improvement in pH levels soon after CHPP, our patients had persistent mild metabolic acidosis after completion of CHPP.²¹ As in our patients metabolic acidosis outlasted the duration of hyperthermia and mild decreases in arterial pressure during CHPP it is possible that other factors contributed to

metabolic acidosis. One could postulate that the 12-h infusion of sodium thiosulfate, which has been shown to produce a high anion gap metabolic acidosis, may have contributed to the acidosis seen in our patients.³⁰ Therefore, our findings of mild acidosis that persists after completion of CHPP and may last longer than 24 h strongly suggest that close monitoring of acid–base status in patients undergoing cytoreductive surgery and CHPP with cisplatin is warranted.

With regard to other metabolic changes, we found that CHPP leads to significant deterioration of gas exchange which improves after its completion but remains impaired during the initial postoperative course. It is likely that, during CHPP, increases in intra-abdominal pressure associated with filling of the peritoneum with chemotherapy agents along with agitation of the abdomen contributes to increases in airway pressure and carbon dioxide retention and impairment of A-a gradient during CHPP. However, we observed that, even after completion of CHPP and removal of intra-abdominal fluid, gas exchange remained impaired. While we did not measure extravascular lung water index in this investigation, it has been shown to increase during the rewarming phase of whole-body hyperthermia.³¹ One can postulate that, albeit mild, persistent impairment in gas exchange after CHPP could be partially related to the effects of hyperthermia in extravascular lung water index.³¹ Nevertheless, despite continued mild impairment in gas exchange, we were able to remove the endotracheal tube in most patients after cytoreductive surgery and CHPP and mechanical ventilation was required in a minority of patients.

The morbidity and mortality associated with cytoreductive surgery and CHPP in patients enrolled in this study has been published elsewhere.¹⁶ It is noteworthy that most of the morbidity associated with this procedure is related to infectious processes and complications associated with the cytoreductive surgery itself.¹⁶ Others have shown that most of the morbidity and mortality associated with cytoreductive surgery and CHPP is related to infectious complications and correlates with the extent of cytoreduction and number of bowel anastomoses performed.^{8,20,32} While we did not examine the relationship between hemodynamics and metabolic changes with morbidities of the procedure, given that the metabolic and hemodynamic changes observed in our study were easily treated and short-lived, it appears unlikely that they significantly contribute to the overall morbidity associated with cytoreductive surgery and CHPP.

In summary, we showed that cytoreductive surgery and CHPP with cisplatin is associated with significant hemodynamic and metabolic perturbations that, if anticipated and diagnosed timely, are transient, easily treated, and unlikely to contribute to major morbidity or mortality. It is noteworthy that, for reasons incompletely understood, the primary diagnosis can significantly alter these hemodynamic and metabolic perturbations. Therefore, understanding the events of the procedure and the diseases that could potentially warrant cytoreductive surgery and CHPP with cisplatin is paramount for the administration of a safe anesthetic to patients with mesothelioma and peritoneal carcinomatosis.

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Hemodynamic Parameters

Mean Arterial Pressure	↓	↓	↓	↓	↓	↓	↓
Heart Rate	↓	↓	↓	↓	↓	↓	↓
Central Venous Pressure	↓	↓	↓	↓	↓	↓	↓
Temperature	↓	↓	↓	↓	↓	↓	↓

Metabolic Parameters

pH	↓		↓		↓		↓
PaO2	↓		↓		↓		↓
PaCO2	↓		↓		↓		↓
Bicarbonate	↓		↓		↓		↓
(A-a) gradient	↓		↓		↓		↓
PT, aPTT	↓		↓		↓		↓
Hematocrit, Platelets	↓		↓		↓		↓

FIG. 1. Parameters measured during the perioperative course of CHPP. Baseline measurements were obtained within 10 min after induction of general anesthesia and ICU measurements upon arrival to the ICU after completion of surgical procedure

FIG. 2.

Mean ($\pm$ SEM) hemodynamic and temperature variables at various stages of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CHPP). The symbols represent the comparisons among times. With cytoreduction (from induction of anesthesia to 5 min before CHPP, *), there were significant decreases in mean arterial pressure (*), and temperature (*), and increases in heart rate (*, all $P < 0.0001$). During CHPP (30, 60, and 90 min), compared with measures 5 min prior ($\dagger$), there were significant increases in mean temperature, central venous pressure, and heart rate, and decreases in mean arterial pressure ($\dagger$, all $P < 0.0001$). Thirty minutes after completion of CHPP, compared with measurements obtained at 90 min of CHPP ($\ddagger$), there were significant decreases in temperature, heart rate, and central venous pressure, and increases in mean arterial pressure ($\ddagger$, all $P < 0.0001$). Overall, after completion of surgery and upon arrival to the ICU compared with baseline measurements ($\S$), there were still significant increases in temperature and heart rate (both $P < 0.0001$), and decreases in mean arterial pressure ($P = 0.0005$).

FIG. 3.

Mean (±SEM) metabolic variables at various stages of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CHPP). The symbols represent the comparisons among times. In all patients, during CHPP compared with baseline (*), metabolic acidosis shown by significant decreases in pH and sodium bicarbonate (*, $P < 0.0001$), deterioration of gas exchange shown by significant increases in PaCO₂ and in oxygen A-a gradient (*, $P < 0.0001$) and hematologic abnormalities, shown by significant increases in aPTT and PT, and decreases in hematocrit and platelet counts (*, $P < 0.0001$) were observed. Upon its completion, compared with measurements obtained during CHPP (†), there were significant decreases in PaCO₂ and oxygen A-a gradient (†, $P < 0.0001$), a trend toward further decreases in serum bicarbonate ($P = 0.029$), but no significant changes in arterial pH ($P = 0.37$), and significant decreases in aPTT (†, $P = 0.01$) and PT ($P = 0.0046$), increases in hematocrit (†, $P < 0.0001$), and a trend towards decreases in platelet counts (†, $P = 0.031$). Overall, upon arrival to the ICU, compared with baseline levels (§), there was persistent metabolic acidosis, coagulopathy, anemia, and

deterioration of gas exchange as shown by significant decreases in pH, bicarbonate, hematocrit, and platelet counts and significant increases in aPTT, PT, and oxygen A-a gradient (§, all $P < 0.0001$)

FIG. 4.

Mean ($\pm$ SEM) hemodynamic and metabolic changes during cytoreductive surgery and CHPP in patients with mesothelioma compared with patients with peritoneal carcinomatosis. During CHPP, patients with peritoneal carcinomatosis from gastrointestinal malignancies had greater increases in temperature (at 30, 60, and 90 min during CHPP versus baseline, $P = 0.006$, $P < 0.0001$, and $P < 0.0001$, respectively, left three portions of upper-left panel) and heart rate (at 90 min during CHPP, $P < 0.001$, left portion of upper-right panel) and smaller decreases in hematocrit (lower-left panel, $P = 0.0013$) than did patients with mesothelioma. Upon arrival to the ICU compared with baseline measurements, patients with mesothelioma had smaller increases in temperature ($P < 0.0001$, right portion of upper-left panel) and smaller increases in heart rate ($P = 0.01$, right portion of upper-right panel) compared with patients with peritoneal carcinomatosis. Upon completion of CHPP (lower-right panel), patients with mesothelioma had greater decreases in sodium bicarbonate ($P = 0.0082$) and, upon arrival to the ICU, persistent greater decreases in sodium bicarbonate ($P = 0.003$) compared with patients with peritoneal carcinomatosis (lower-right panel).

TABLE 1

Differences constructed among measurements of hemodynamic and metabolic variables obtained at times before, during, and after CHPP^a

Hemodynamic measurements	Metabolic measurements
Baseline versus 5 min before CHPP	Baseline versus during CHPP
Baseline versus arrival in ICU	Baseline versus arrival in ICU
Five minutes before CHPP versus 30 min during CHPP	During CHPP versus after CHPP
Five minutes before CHPP versus 60 min during CHPP	During CHPP versus arrival in ICU
Five minutes before CHPP versus 90 min during CHPP	
Thirty minutes after CHPP versus 90 min during CHPP	
Arrival in ICU versus during CHPP (90 min)	

^aHemodynamic and metabolic variables were measured at times describe in Fig. 1. The statistical significance of each of these differences from zero was determined using a Wilcoxon signed-rank test

TABLE 2

Demographic characteristics of patients undergoing cytoreductive surgery and continuous hyperthermic peritoneal perfusion (CHPP) with cisplatin

Characteristic	Number of patients or value (%)
Sex	
Male	80 (47)
Female	89 (53)
Age (years)	
Mean $\pm$ SD	50 $\pm$ 13
Range	15–77
Weight (kg)	
Mean $\pm$ SD	78 $\pm$ 22
Range	49–173
Primary diagnosis	
Mesothelioma	69 (41)
Appendiceal Ca (low grade)	52 (31)
Appendiceal Ca (high grade)	23 (14)
Colon Ca	22 (13)
Gastric Ca	3 (1)

TABLE 3

Fluid management and blood product administration in 169 patients undergoing cytoreduction and continuous hyperthermic peritoneal perfusion (CHPP) with cisplatin^a

Blood product	Mean $\pm$ SEM	Range	Number of patients (%)
Total crystalloid (ml)	12,991 $\pm$ 349	4,000–27,000	169 (100)
Crystalloids during CHPP (ml)	8,217 $\pm$ 285	1,100–18,500	169 (100)
Red blood cells (units)*	3.8 $\pm$ 0.35	1–17	77 (46)
Fresh frozen plasma (units)	4.24 $\pm$ 0.43	1–10	29 (17)
Platelets (units)	8.3 $\pm$ 2.7	3–12	3 (2)
Albumin (25%, ml)	425 $\pm$ 36	100–2,300	115 (68)
Estimated blood loss (ml)	1,085 $\pm$ 97	100–8,000	169 (100)
Total urine output (ml)	2,572 $\pm$ 77	900–7,200	169 (100)
Urine output during CHPP (ml)	1441 $\pm$ 59	300–4,500	169 (100)

^aSEM represents standard error of the mean and number of patients reflects those patients receiving the product described

TABLE 4

Mesothelioma patients compared to patients with peritoneal carcinomatosis from gastrointestinal malignancies undergoing cytoreduction and continuous hyperthermic peritoneal perfusion (CHPP) with cisplatin^a

Variable	Mesothelioma	Peritoneal carcinomatosis from GI malignancies	P value
Number of patients	69	100	
Male	35	45	0.53
Female	34	55	
Age (years)	49.9 ± 1.7	50.3 ± 1.2	0.96
Anesthesia time (min)	591 ± 17	581 ± 13	0.51
Surgery time (min)			
Total	494 ± 16	468 ± 12	0.16
Cytoreduction	308 ± 14	287.2 ± 11	0.30
CHPP	90	90	1
Off CHPP to ICU	89 ± 4	81 ± 3	0.07
Blood loss (ml)	947 ± 119	1,180 ± 135	0.39
Crystalloids (ml)			
Total	13,466 ± 596	12,664 ± 423	0.36
During CHPP	9,103 ± 473	7,606 ± 343	0.02
Before and after CHPP	4,363 ± 379	5,058 ± 264	0.02
Urine output (ml)			
Total	2,511 ± 129	2,614 ± 96	0.28
During CHPP	1,184 ± 87	1,102 ± 74	0.43
Before and after CHPP	1,327 ± 105	1,520 ± 68	0.006
Albumin (units)	4.9 ± 0.7	3.7 ± 0.3	0.76
Red cells (units)	3.9 ± 0.6	3.7 ± 0.4	0.74
FFP (units)	4.6 ± 0.6	3.9 ± 0.6	0.29
Platelets (units)	None	8.3 ± 2.7	NA

^aVariables are shown as mean ± standard error of the mean (SEM), anesthesia time reflects that from induction of to emergence from general anesthesia, and surgery time that from incision to closure of the abdomen. *GI* gastrointestinal