

# Exploring flow rate selection in HIPEC procedures

## *Explorando parâmetros de fluxo em procedimentos de HIPEC*

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### ABSTRACT

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of peritoneal malignancies. However, current data on the literature are very heterogeneous in terms of its technical particularities, which require some efforts to standardization of practices. In these setting, we present some early data from a pioneering clinical trial in Brazil (ClinicalTrials.gov Identifier: NCT02249013) to explore the dynamic relationships between flow rates and temperature parameters in the first cases of our study, which may help in selecting better technical parameters during HIPEC procedures.

**Keywords:** Injections, Intraperitoneal. Hyperthermia, Induced. Drug Therapy. Peritoneal Neoplasms.

### INTRODUCTION

Cytoreductive surgery (CRS) plus hypertermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of peritoneal malignancies. The rationale of combining heat with intraperitoneal chemotherapy is the synergistic effect of heat with the cytotoxic drugs. Heat has a direct cytotoxic effect, potentiates the action of certain antimetabolic agents, as well as increasing their penetration into tumor tissue. Similarly, hyperthermia can also reduce the mechanisms of tumoral resistance to chemotherapy and induce an efficient anticancer immune response<sup>1</sup>. In summary, these arguments have highlighted HIPEC as a promising oncological approach.

Many HIPEC techniques have been described and the current data are heterogeneous in terms of technical procedures, which require some standardization of practices that might permit systematic comparisons. The technical particularities of HIPEC include instillation circuit, timing of parietal closure, length of perfusion, target temperatures, and choice and dosage of antimetabolic agents. Herein, flow rate is an important variable in achieving and maintaining goal temperatures during HIPEC, whereas a minimal temperature threshold is also critical to improve chemotherapy effects and

survival outcomes<sup>2,3</sup>. In this setting, we aimed to explore the dynamic relationship between flow rates and temperature parameters during HIPEC procedures to help selecting a target flow rate set up.

### TECHNICAL NOTE

This note involves a cross-sectional analysis of early data from our ongoing clinical trial (ClinicalTrials.gov Identifier: NCT02249013) regarding HIPEC procedures – the very first Brazilian clinical trial on this matter. This study is testing a short-term protocol of cisplatin-based HIPEC for treatment of peritoneal carcinomatosis of ovarian origin. Details of the study design are available at <https://clinicaltrials.gov/ct2/show/NCT02249013?term=HIPEC+AND+ovarian+cancer&rank=4>. Shortly, HIPEC was held immediately after cytorreduction according to the closed-abdomen technique. Our protocol involves the use of cisplatin (25mg/L of perfusate/m<sup>2</sup>, total limit of 240mg) for 30 minutes with an intra-abdominal target temperature of 41-43°C. Perfusate (2L/m<sup>2</sup>, ranging from 4L to 6L) circulated using an extracorporeal circulation device named *Performer HT* (RanD, Medolla, Italy – Figure 1), and the goal temperature was set up to 44°C. A flow rate of 300-500 ml/min was applied during the “patient filling phase” and increased to 700-1000 ml/min during

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**Table 1.** Summary of relationship between flow rates and temperature parameters in HIPEC procedures.

Parameters[1]	600ml/min	700ml/min	800ml/min	900ml/min	1000ml/min	p-value[2]
Inlet Temperature	43.6 (43.6-43.7)	43.3 (43.2-43.4)	42.8 (42.8-42.9)	42.8 (42.7-42.8)	41.8 (41.7-41.8)	< 0.001
Outlet Temperature	40.6 (40.5-40.7)	41.2 (41.1-41.3)	41.0 (40.9-41.0)	40.6 (40.5-40.6)	40.7 (40.6-40.7)	< 0.001
Mean Temperature[3]	42.1 (42.1-42.2)	42.2 (42.2-42.3)	41.9 (41.9-41.9)	41.7 (41.6-41.7)	41.2 (41.1-41.2)	< 0.001
Temperature Lost[4]	3.1 (2.9-3.2)	2.1 (2.0-2.3)	1.8 (1.8-2.0)	2.2 (2.2-2.3)	1.1 (1.0-1.2)	< 0.001

[1] Descriptive statistics summarized as median and IQR (interquartile range).

[2] According to Kruskal-Wallis test.

[3] Mean temperature: mean between inlet and outlet temperature probes.

[4] Temperature lost: difference between the inlet and outlet temperature probes.

the early “circulation phase”. Thereafter, flow rate was adjusted between 600 to 1000 ml/min at intervals of 100ml/min, maintaining stable parameters into the peritoneal cavity just before the “drug circulation phase”.

The device provided us with the main functional and patient parameters, and we recorded data from the “HIPEC phase” every minute. We permitted variations of ±10% in the flow rate values and rounded them accordingly. Flow rates were related to temperature parameters. We summarize descriptive statistics as median and interquartile range. We performed the statistical analysis and graph construction applying conventional methods in the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA).

Data from the first five cases enrolled into our trial were analyzed involving 148 time-points of information, since two records were excluded because a variation higher than 10% in the flow rate. The mean of inlet temperature and losses from solution to peritoneal cavity was lower at 1000ml/min. Conversely, a lower rate resulted in higher inlet temperatures and temperature losses. Differences between inlet and outlet temperature probes were about 3°C at a flow rate of 600ml/min, and 1°C at 1000ml/min. The temperature lost to peritoneal cavity remained virtually stable by about 2°C at flow rates of 700, 800 and 900 ml/min. Table 1 summarizes these temperature parameters in regards to flow rates. Data on difference between inlet and outlet temperature probes is also presented in Figure 2.

## DISCUSSION

HIPEC is now a preferred treatment of many peritoneal surface malignancies<sup>1</sup>. Unfortunately, no single technique has so far demonstrated its superiority, and several variations in techniques have produced heterogeneous and incomparable results. In this scenario, further efforts are needed to standardize the technical particularities of HIPEC, whereas temperature parameters and their dynamic relationship with other variables are important points to be scrutinized<sup>2-5</sup>.

HIPEC involves the continuous heating and circulation of chemotherapy throughout the abdominal cavity in an attempt to enhance cytotoxicity<sup>4</sup>. Accordingly, flow rate is an important variable in achieving and maintaining goal temperatures during HIPEC, and a temperature threshold above 40°C is also critical to significantly enhance chemotherapy effects and improve survival outcomes<sup>2-4</sup>. By exploring the dynamic relationship between temperature parameters and flow rates in the first cases of our clinical trial, we noted that a higher flow rate may minimize the exchanging of heat from the system to the perfusate solution (i.e.: the mean inlet temperature was lower at 1000ml/min) and from the solution to the peritoneal cavity (i.e.: the mean of temperature losses was also lower at 1000ml/min). Conversely, a lower rate resulted in higher inlet temperatures and temperature losses. These findings confirm that heat exchanges are mitigated by higher flow rates, and that the peritoneal cavity may absorb



**Figure 1.** Performer HT device in use during HIPEC procedure.

more heat at lower flow rates. Herein, we found that the difference between inlet and outlet temperature probes were about 3°C at a flow rate of 600ml/min, and 1°C at 1000ml/min. Interestingly, the temperature lost to peritoneal cavity remained virtually stable at about 2°C at a flow rate of 700, 800 and 900 ml/min.

Despite increased flow rates are important to achieve and maintain uniform temperature distribution throughout the abdominal cavity during HIPEC, the assumption of added benefit for increased flow rates requires further considerations<sup>2,4</sup>. For example, even though there is a greater rise in overall esophageal temperature during perfusion at higher rates of flow, the average esophageal temperatures were lower as the flow rate was increased according to Furman *et al.*<sup>2</sup>. In their study, the average esophageal temperature rise during perfusion was 1.0°C at 2500ml/min, a similar temperature gradient that we found at a flow rate of 1000ml/min. Thus, we could suppose stable differences between inlet and outlet temperature (i.e.: heat lost to the peritoneal cavity and/or viscera)

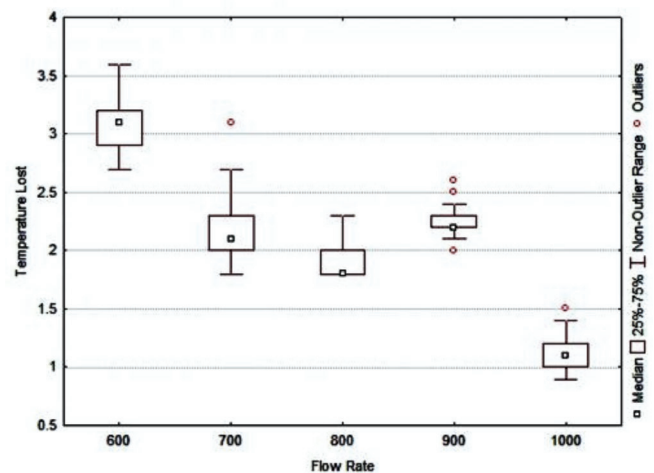
from 1000ml/min to 2500ml/min, as we found at a flow rate between 700ml/min and 900ml/min, and also, as these authors reported, at rates of 2000ml/min and 3000ml/min – about 0.8°C for both flow rates<sup>2</sup>.

Another point of interest in this context is the dynamic relationship between hyperthermia and intra-abdominal pressures. Hyperthermia enhances diffusion in the visceral peritoneum, whereas increased pressure may enhance both visceral and parietal tissue concentrations of chemotherapy agents, without leading to increased systemic levels. The combination of the two achieves the highest tissue concentrations of chemotherapy, whereas a maximal distention of the abdomen by the perfusate is probably required to improve the synergism between such factors<sup>4,5</sup>.

In conclusion, we present some dynamic relationships between flow rates and temperature parameters that may help in selecting better technical parameters during HIPEC procedures. These data resulted from our pioneering clinical trial in Brazil and also the very first to use the Performer HT device.

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**Figure 2.** Box Plot of temperature losses to peritoneal cavity (i.e.: differences between inlet and outlet temperature probes) according to flow rates.

## R E S U M O

Cirurgia citoredutora avançada e quimioterapia intraperitoneal hipertérmica (i.e.: *HIPEC*, sigla em inglês) têm se consagrado como promissora abordagem terapêutica multidisciplinar para neoplasias malignas peritoneais. Contudo, dados da literatura corrente são muito heterogêneos em torno de muitos de seus aspectos técnicos, o que demanda algum esforço na busca por padronizações do procedimento. Neste sentido, são apresentados dados de um ensaio clínico pioneiro no Brasil (*ClinicalTrials.gov Identifier*: NCT02249013), relacionando parâmetros dinâmicos de taxas de fluxo e temperaturas de perfusão nos primeiros casos do estudo, o que pode ajudar na seleção de melhores parâmetros técnicos para procedimentos de *HIPEC*.

**Descritores:** Injeções Intraperitoneais. Hipertermia Induzida. Quimioterapia. Neoplasias Peritoneais.

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