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Establishment of a human intrapleural hyperthermic perfusion model and analysis of pleural malignancy treatment depth

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ABSTRACT

Introduction: Although human intrapleural hyperthermic perfusion (HIHP) has achieved excellent palliative effects in metastatic pleural malignancies, the optimum treatment conditions, including inlet temperature and treatment times based on tumor size, have yet to be determined. However, such information is recognized to be critical for treatment planning in clinics. Therefore, the current research aimed to solve these issues.
Methods: Using the finite-element method (FEM), a simplified three-dimensional HIHP model was established and verified according to the temperature data of specific measuring points based on a clinical therapeutic case. Ultimately, the treatment depth of pleural malignancies was obtained by employing an equivalent thermal dose of 80 min as the damage threshold.
Results: The treatment depth of parietal pleural malignancies (PPM) is much larger than that of visceral pleura malignancies (VPM), and can therefore be overlooked. In addition, the average treatment depth of the PPM increased by 1 mm as treatment time increased by 30 min during the 60–120 min time frame and as the inlet temperature increased by 1 °C, while there was no further increase when treatment time exceeded 120 min.
Conclusions: HIHP can provide superior treatment for PPM and only provided faintly therapeutic effects on VPM, and may not be appropriate for the larger VPM. Although we only studied one example in this article, this is the beginning of an intensive study into the detailed thermal behavior of pleural tissues under HIHP, and further analysis on more realistic cases is currently underway.

1. Introduction

Due to the antitumor effects of hyperthermia [1], human intrapleural hyperthermic perfusion (HIHP) used as an adjuvant to chemotherapy has begun to play a greater role in the clinical therapy of metastatic pleural malignancies and pleural effusion. Although many researchers [1–7] have concluded that intrapleural perfusion with hyperthermic chemotherapy (IPHC) can effectively improve the efficacy of chemotherapy for malignant pleural dissemination and enhance antitumor effects, and that it demonstrates fewer side effects, high levels of toxicity of chemotherapeutic agents to normal cells have also been demonstrated in the course of IPHC [8].

To protect organ function, maintenance of healthy tissue at a safe temperature during treatment is a complex therapeutic challenge [9]. More importantly, HIHP has demonstrated positive benefits to healthy tissues due to its intrinsic temperature control. Taking advantage of less pain, and pro-immune effects, HIHP has gradually received attention and achieved remarkable results in the clinical treatment of intrapleural disseminated lesions. During HIHP, a thermal source and temperature control device are used to heat the perfusate above the critical damage temperature of the tumor (clinically recognized as 42.5°C–43 °C)[10]; this temperature is then maintained for a set period of time. Typically, two drainage tubes are placed in the pleural space and used to inject and drain the perfusate. The thermo-tolerance of normal cells is higher than tumor cells. Therefore, the tumor cells undergo generate degeneration, necrosis, and gradually disintegrate at 42 °C [11,12], whereas normal cells can survive at higher temperatures, resulting in the killing of cancerous cells without damage to normal cells. However, issues, such as the effective treatment depth under different treatment conditions, still exist with the use of HIHP in the treatment of pleural malignancies. These knowledge gaps make it difficult to determine the most advantageous treatment paradigm when relying solely on clinical experience.

In the present study, we aimed to solve these problems using the finite-element method (FEM). A simplified three-dimensional HIHP model was established and verified according to the temperature data of specific measuring points in a clinical therapy case, and ultimately the treatment depth of pleural malignancies at different perfusate inlet

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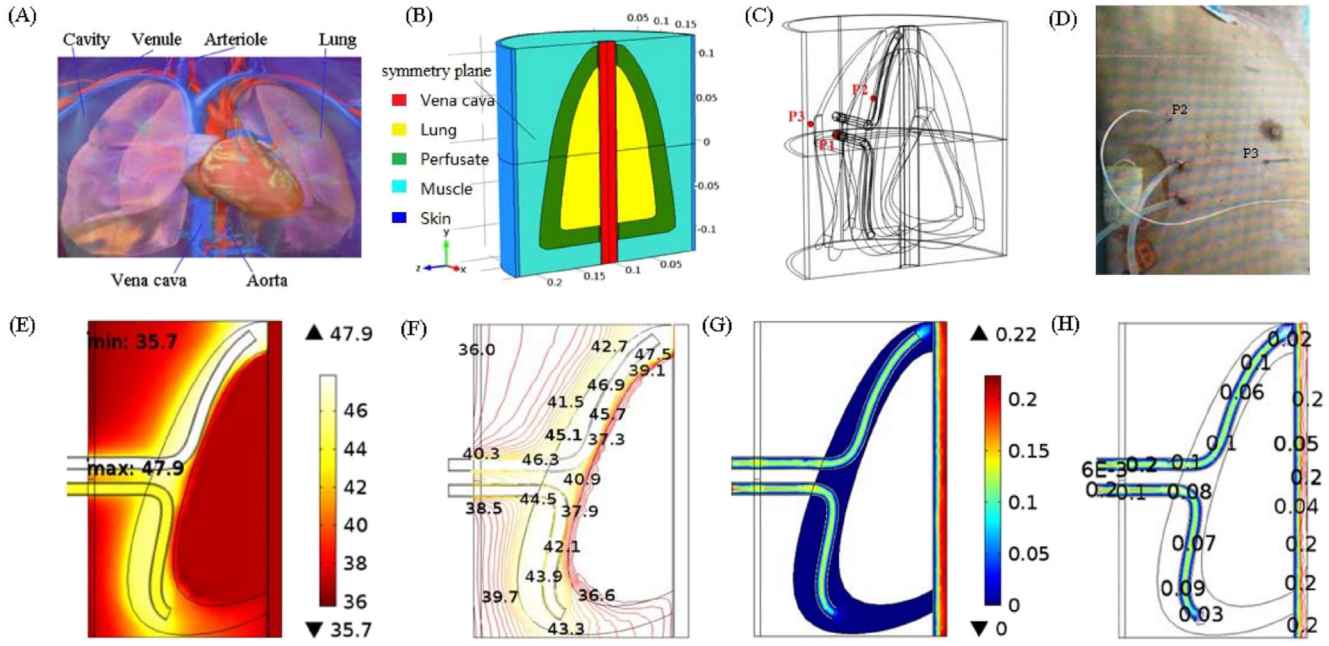

Fig. 1. Schematic diagrams of the intrapleural hyperthermic perfusion model and the distribution of steady-state temperature field and velocity field, with the inlet temperature of 48 °C. (A) is the internal pattern diagram of the human thoracic cavity; (B) is the schematic diagram of the simplified intrapleural hyperthermic perfusion model; (C & D) are the distribution of temperature monitoring points and measuring points, respectively; (E & F) are the steady-state temperature distribution and isotherm of midaxillary line section, respectively (the unit of temperature is°C); (G & H) are the velocity map and velocity contour of midaxillary line sections, respectively (the unit of velocity is m/s).

temperatures and treatment times was obtained by adopting the equivalent thermal dose of 80 min as the damage threshold.

2. Numerical method

2.1. Determination of the HIHP model

A diagram of the internal human thoracic cavity is shown in Fig. 1A. As can been seen in the diagram, the pleural cavity can be considered symmetrical (ignoring the placement of the heart), thus the pleural cavity on the right side of the vena cava central line was selected as the computational domain. Disregarding the heat dissipation of the aorta, arterioles, and venules in the cavity, the simplified three-dimensional thoracic perfusion model was established and is shown in Fig. 1B and C. The model is based on a male patient whose height, weight, and chest size are shown in Table 1. Referring to the characteristics of male chest contours the external contours of skin tissue were assumed as semi-elliptical, and the dimensions of the major axis and minor axis are chest width and thickness, respectively. Because the mean lung volume of males and the perfusion dynamic volume are 5000 ml and 1000–2000 ml, to simplify the complicated initial perfusion process, it was assumed that lung and perfusate remain at a constant volume of 1000 ml and 1500 ml, respectively. This is the volume when HIHP achieved stability. Depending on the clinical therapy, the insertion site of infusion and drain tubes was located in the 6th and 7th intercostal space of the midaxillary line, respectively. The diameter of the two drainage tubes was 8 mm.

Table 1
The height, weight and chest size of the patient.

	Height (cm)	Weight (kg)	Chest height (mm)	Chest width (mm)	Chest thickness (mm)	Skin thickness (mm)	Vena cava diameter (mm)
size	165	75	245	310	220	5	20

2.2. Physical parameters

Since the perfusate is typically normal saline, the physical parameters of the perfusate reasonably adopted that of water in COMSOL's material library, and the drainage tubes were the commonly used medical PVC conveying hose. Table 2 [13,14] shows the physical parameters of tissue, blood, and the PVC hose.

2.3. Governing equations and boundary conditions

Metabolic heat production and perfusion of biological tissues were both considered in the numerical simulation of HIHP. The Pennes bioheat transfer equation was applied to solve temperature distribution within tissues [15].

$$\rho C_P \frac{\partial T}{\partial t} = \nabla(k\nabla T) + \rho_b C_b w_b (T_b - T) + Q_{met} + Q_w \quad (1)$$

where ρ is the tissue density [kg/m^3], C_P is the tissue heat capacity [J/kg/°C], t is the time of therapy [s], T is the tissue temperature [°C], k is the tissue thermal conductivity [W/m/°C], w_b is the tissue blood perfusion rate [1/s], C_b is the heat capacity of blood [J/kg/°C], T_b is the blood temperature [°C], Q_{met} is the tissue metabolic heat production [W/m^3], and Q_w is the heat absorbed by the unit volume tissue or tumor

Table 2
Physical parameters.

Tissue	Specific heat C_p [J/kg/°C]	Thermal conductivity k [W/m/°C]	Density ρ [kg/m^3]	Blood perfusion rate w_b [m^3/s/m^3]	Basal metabolic heat rate Q_{met} [W/m^3]
Muscle	3720	0.49	1090	0.54e-3	684
Skin	3450	0.32	1100	1.05e-3	368
Lung	3520	0.28	560	1.30e-3	339
Blood	4000	0.49	1055	–	–
PVC tube	980	0.10	1760	–	–