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THE MODELING OF TEMPERATURE FIELDS IN VERTEBRA BONE AT STABILIZING VERTEBROPLASTY*

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Моделирование температурных полей в костной ткани позвонков при стабилизирующей вертебропластике

ABSTRACT

Purpose: To study the temperature fields caused by bone cement polymerization at the stabilizing vertebroplasty. To verify experimental data by thermohydraulic simulation. To modify program codes, applied in nuclear installations in order to adapt them to new object region.

Material and methods: Two groups of experiments involving the non-stationary temperature distribution measurements were done, namely, the cement polymerization: a) in the isolated cuvette; b) in a vertebra. For numerical modeling of experiments, the 3D non-stationary KANAL code applied in thermohydraulics of nuclear power plants is adapted.

Results: The satisfactory coherence of measured data and simulated ones is obtained for temperature distributions, the spatial and time-dependent as well. The most important is the closeness in experimental and simulating temperature maximum values at cement polymerization in a vertebra. The executed study grants the theoretical support of vertebroplasty in two aspects: a) by providing with the developed calculation techniques; b) by estimating the curative effect because of the bone tissue heating.

Ключевые слова: *spinal metastases, vertebroplasty, temperature fields, experimental and simulating modeling, numerical simulation, curative effect*

РЕФЕРАТ

Цель: Применительно к задачам стабилизирующей вертебропластики выполнить исследования температурных полей, обусловленных полимеризацией костного цемента. Верифицировать полученные результаты посредством термогидравлических расчетов. Модифицировать программные коды, используемые для расчета нестационарных температурных полей в ядерных установках, с целью их адаптации к новой предметной области.

Материал и методы: Выполнены две группы экспериментов по измерению нестационарного распределения температуры: a) при полимеризации цемента в изолированной кювете; b) при полимеризации цемента в позвонке. Для расчетного моделирования экспериментов адаптирован 3D нестационарный код КАНАЛ, применяемый в задачах теплогидравлики ядерных энергетических установок.

Результаты: Для обоих экспериментов достигнута удовлетворительная согласованность измеренных и рассчитанных температурных характеристик — как их пространственного, так и временного распределения. Особо существенной является близость экспериментальных и расчетных значений максимума температуры при полимеризации цемента в позвонке: типичные расхождения эксперимента и расчета не превышают 1–2 °С. Выполненное исследование обеспечивает теоретическую поддержку вертебропластики в двух аспектах: a) применением созданных расчетных технологий; b) оценкой степени терапевтического воздействия в результате нагрева костной ткани.

Key words: *метастазы в позвоночнике, вертебропластика, температурные поля, экспериментальное и расчетное моделирование, терапевтический эффект*

Introduction

Percutaneous vertebroplasty (PVP) as a way of vertebral structures stabilization was offered in 1987 by Galibert and Deramond [1, 2], and soon there were publications about its high efficiency for patients with metastatic defeat of vertebra bodies [3]. The first publications, in which the results of PVP were estimated, had very optimistic character. In them there was reported about disappearance or essential reduction of a pain syndrome for 80–97 % of patients with the lytic and mixed metastasizes in a backbone [3–6]. For 15 % of patients the pain disappeared completely, for 55 % — it was considerably decreased, and for 30 % — the reduction of the pain intensity had moderate type. As result, the PVP technique began to be used widely as a method of pain suppression, at first at

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metastatic spinal compression fractures for patients with malignant new growths, and then and at the expressed pain syndrome against metastatic defeat of vertebras when conservative therapy was inefficient [7–11].

Improvement of patients' life quality, in the main at the expense of the pain reduction and restoration of physical activity [12–18], was noted. In [19] it was claimed that for 75 % of patients the positive changes remained within 6 months. However, the subsequent estimates of PVP at metastatic defeats of a backbone in [20] showed that in 6 months only for about 40 % of the patients who have underwent vertebroplasty the need for anesthetics remained less, than before operation, and satisfactory quality of life remained. All these patients had isolated metastases of the minimum distribution in a vertebra of I, II, III types (K. Tomita [21] classification).

The extended tumors growth for them was not revealed due to the provided composite treatment. The patients with V, VI, and especially VII types of distribution had short-term efficiency of the PVP. In these cases, in 2 ÷ 6 months after vertebroplasty the expressed violations of the vertebra function were developed, quality of life was sharply decreased — it was caused, first of all, by fast increase of a pain syndrome. The metastatic zones tended to growth, settling down on the periphery of implanted bone cement, and they extended towards the vertebral channel, that also led to increase of a pain syndrome.

Summing up, it is possible to note that the positive effect of the stabilizing palliative vertebroplasty is shown only at rather early manifestations of metastatic growth in a vertebra. Thus, the metastatic zone should not overcome the terminate plate (i.e. vertebral arch), be accompanied with pathological fractures, be localized in 2–3 vertebras or be of multiple distribution mode. In all cases of the stabilizing vertebroplasty the lack of the continued tumor growth can be provided only in the combination therapy [22].

It is supposed in [23, 24] that the necrosis of tumor tissue because of its heating as a result polymerization after cement implantation in the destructed zone is the reason of metastases relapse reduction after vertebroplasty. However, the experiments *ex vivo* [25, 26] as well as *in vivo* [27, 28] don't allow to draw an unambiguous conclusion that temperature in places of the maximum warming up of the bone tissue surrounding a cement kernel, reaches the values capable to cause a tumor tissue necrosis.

Analysis of the results of investigations performed formerly concerning temperature resistance of tumor cells testifies to:

- at 72 ° C the necrosis of tumor cells arises immediately;
- at 60 ° C — after 5 s exposure;
- at 55 ° C — after 30 s exposure;
- at 50 ° C — after 5 min exposure;
- at 47 ° C — after 7 ÷ 13 min exposure;
- at 46 °C — after 20 ÷ 50 min exposure;
- at 45 °C — after 30 ÷ 60 min exposure;
- at 44 °C — after 45 ÷ 80 min exposure [29–31].

Apoptosis of cells occurs at lower temperatures, but at longer exposure [29, 30 and 32]. It is necessary up-to 4÷20 hours at 42 °C for complete destruction of various tumor cells [31]. Long-term action of insignificant temperature (less than 42 °C) is able to stimulate the proliferation of tumor cells [29–32].

Data published [29, 33 and 34] concerning the temperature characteristics of exothermic polymerization of quick-hardening bone cement on the base of polymethylmethacrylate, which is used at verteroplasty, vary in wide limits and do not give the chance to define, whether there is enough temperature increase in the bone tissue surrounding the area of malignant growth, for the antitumor effect.

The simulation technique designing and its validation on experimental data which allows to prognosticate the level, depth and duration of a vertebra spongy bone substance warming up at exothermal polymerization of methyl acrylate (to get polymethylmethacrylate) at vertebroplasty was the goal of the work.

A series of experiments on the thermohydraulics characteristics study of bone cement hardening both in experimental cuvettes of various volume (the first stage of experiment) and in spongy tissue of the isolated vertebra (the second stage) is executed.

For the simulation of temperature time-dependence of bone warming up at implantation of bone cement, the calculation technology based on adaptation of the software applied in thermo-hydraulic calculations for nuclear power and another type plants was used.

Comparison of the temperature characteristics obtained at simulation with experimental data is carried out and the conclusion is drawn on possibility of reliable calculation the temperature level and duration of a bone tissue warming.

Experiments

At the first stage (experiment No. 1), measurements of the maximum temperature at bone cement polymerization in experimental cuvettes were carried out. Experiments at the first stage purposed to

- development of measurement technique;
- key parameters identification which influence the energy release under specific conditions of polymerization, which simulate real conditions at vertebroplasty.

Experimental cuvettes represented a set of aluminum cylinders (four pieces), each with two thermocouples. One of thermocouples was fixed on border of cement and a lateral cuvette wall, another — practically in the geometrical center of a cuvette (fig. 1).

Cuvette internal diameter was varied from 1.2 to 2.2 cm, and height of a volume filled with cement in a tube– from 1.5 to 1.8 cm. Cement with a density 1.34 g/cm^3 and with heat conductivity coefficient 0.2 W/(m×K)

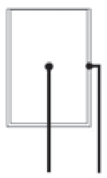


Fig. 1 Experimental tube with thermocouples (schematic)

was applied. Reference temperature of a mix before cement preparation was 21 °C.

To approach the real vertebroplasty conditions, cement at polymerization was isolated by means of a polyfoam (5 cm thick layer). In fig. 2 the polyfoam box photo, in which an experimental cuvette was placed, is submitted.

Temperature measurement at cement polymerization was carried out by means of the differential thermal analysis. The ZET 210 hardware module [35] with 16 inputs, connected to the computer, was basis of the measuring facility. As the sensing devices, standard normalizing amplifiers were used. The software of the ZET 210 module represents the complex integrated with the graphic interface; the one provides continuous signals registration.

Four series of experiments with four experiments in each were executed. During experiments, the bone cement Surgical Cement For Vertebroplasty "CementoFixx" (OptiMed) [36] was used. Cement was kneaded during 30 s and then it was injected into a cuvette by a syringe. This procedure takes 1 min — 1 min 20 s usually.

Results of measurements are presented in table 1 and in fig. 3. These data show that the temperature both on a cement kernel axis and on experimental cuvettes lateral surface nonlinearly depends on the volume of cement.

At the cuvette's small volume, there is a great role of a cuvette surface size in temperature formation both on a surface, and in the cuvette center. With the growth of cuvette volume, the role of a cuvette surface in the convective heat exchange decreases, and the cuvette volume effects more and more, therefore the ratio t_a/t_l grows and changes with volume increase not so quickly as at the small cuvette volume.

Table 1

The temperature of cement (°C) on the cuvette axis (t_a) and on its lateral surface (t_l)

Tube No.	Cuvette dimensions*			t_l					t_a, Average value
	h, cm	d, cm	V, cm	Experiment No.				Average value	
				1	2	3	4		
1	1.6	1.2	1.8	92	96	93	96	94 ± 2	101 ± 3
2	1.5	1.6	3.0	104	107	105	106	105 ± 2	109 ± 1
3	1.8	1.8	4.6	107	109	108	109	108 ± 1	120 ± 3
4	1.7	2.2	6.5	110	112	113	113	111 ± 1	123 ± 2
Ambient air temperature, °C				20	19	21	21	20 ± 1	

*h — height; d — diameter; V — volume

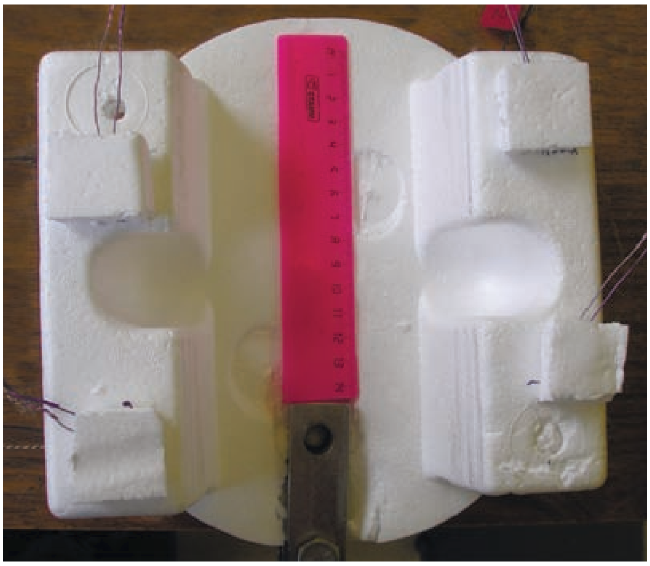


Fig. 2. Polyfoam isolating box for cuvette in the first experiment

At the second stage (experiment No. 2), time-dependence of temperature is obtained at polymerization of bone cement in vertebra cavity.

For measurements at the second stage the cylindrical cavity with $d{\times}h$ sizes = 1.8×1.8 cm, modeling a lytic metastasis, was formed in the center of the isolated vertebra. This cavity just before measurement was filled with bone cement by the same procedure as in the first experiment. Non-stationary temperature profile in the volume of a vertebral spongy bone was studied.

One of thermocouples in measurements was placed in the center of cement kernel (i.e. in the cylindrical cavity filled with cement) on its axis, other 15 thermocouples were settled down in a bone at various distances from a surface of cement contact with a bone. These thermocouples were located practically in the same plane on the middle of height of a vertebra (fig. 4).

The distance from a surface of a cement kernel is the most essential parameter that influences the sensor indications. The detector distance to a surface of the thermohydraulic characteristics rupture (i.e., to external

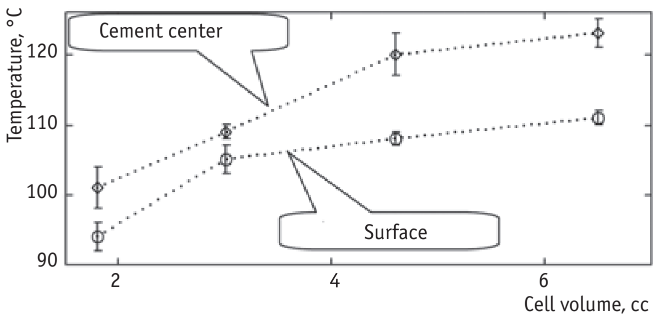


Fig. 3. The maximum temperature of bone cement on a surface and in the cuvette center as a function of its volume

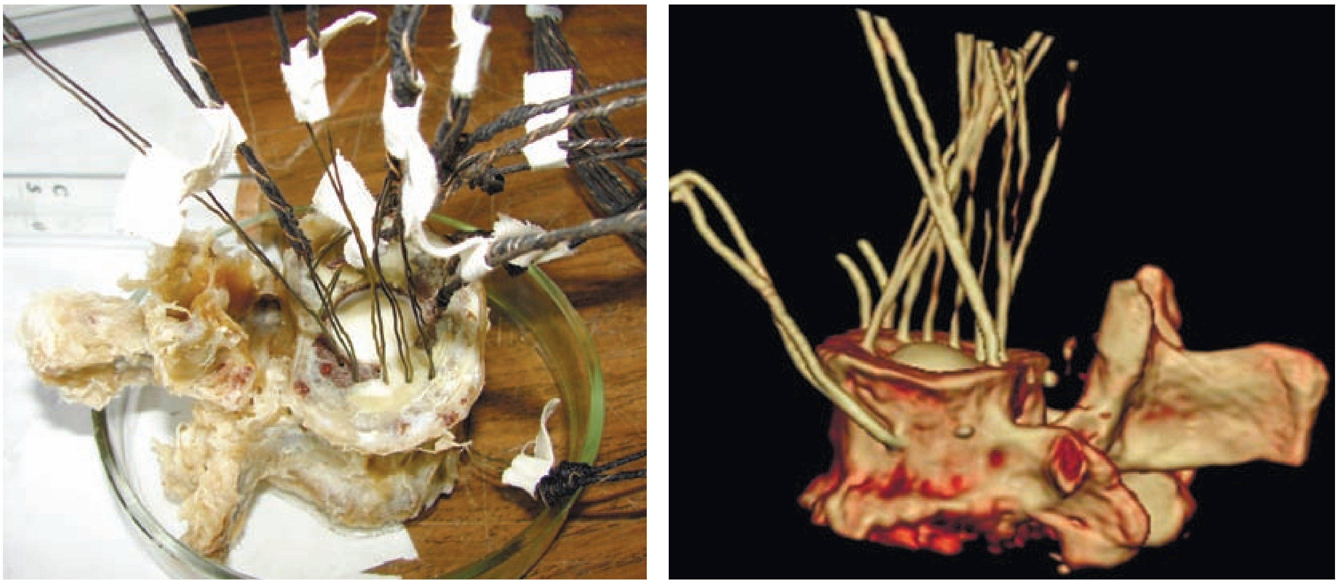


Fig. 4. The vertebra photo with thermocouples (at the left); the 3D-reconstruction based on tomography scans (on the right)

border of a vertebra or to any other heterogeneity) is much less essential.

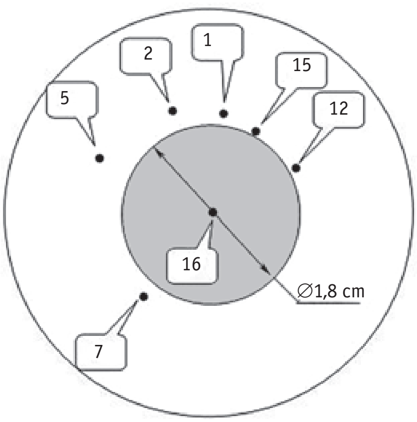
The vertebra prepared for experiment with the thermocouples installed in it was located in Petri dish filled with formalin isotonic 10 %-solution. Previously the bottom lamina of vertebral arch was removed for providing a uniform liquid elevation which prevents drying of bone tissue of a vertebra body. The specimen was incubated in the thermostat during not less than 3 h up to the uniform temperature in a spongy bone. The specified procedures are directed to (a) approach the experimental conditions to conditions at vertebroplasty, and (b) provide constancy of thermohydraulic conditions during experiment.

Process of polymerization was fixed by measurement instruments and checked visually on the display screen. At a temperature of air (38 °C) the temperature of bone tissue was established at lower level (32.6 ± 0.1 °C), that is explained by heat removal at liquid evaporation from a surface of a vertebra body.

The chosen detectors, the distance from which to a cement surface monotonously increases, are conditionally represented in fig. 5, and in fig. 6 the vertebra tomogram is submitted.

The time-dependant temperature in the center of a cement kernel, and also in bone tissue at different distance from a cement surface are given in fig. 7 for the chosen detectors. The characteristics of a spongy bone tissue warming up in experiment are provided in table 2: the maximum temperature in the detector location and an exposure time at a temperature above some value.

Properly both from measurements and from calculations, the effect of a hyperthermia is short-range (inside 2 ÷ 4 mm from a surface of a cement kernel); therefore the influence of the actual geometry of a vertebra as well as metastatic «cavity» and its localization on temperature at polymerization is rather insignificant — no more than 10–20 % in a value. It follows that results of measurements possess sufficient generality and



Thermo-couple No.	Distance from a surface of cement, mm
15	0,4
12	1,8
1	3,0
7	4,1
2	5,2
5	6,0
16	in the center

Fig. 5. The thermocouples location in a vertebra (conditionally; not in scale)

Table 2

The characteristics of the vertebra spongy bone's warming up

Distance from border of bone cement, mm	Maximum tempera-ture, °C	Time (min ('), s (")),during which temperature is higher than the specified level			
		50 °C	47.5 °C	45 °C	42.5 °C
Center	118 ± 3				
Bone border	80 ± 3	6′	6′	7′	8′30″
0.4	58 ± 3	3′	4′	6′	7′30″
1.8	52 ± 1.1	1′30″	3′	4′30″	6′30″
2.5	50 ± 0.8	30″	2′30″	3′20″	6′
3.0	46. ± 0.3	—	—	2′30″	5′
3.5	45 ± 0.3	—	—	< 30″	4′
4.1	41.5 ± 0.2	—	—	—	—

are applicable for the wide range of the geometrical characteristics, which are realizing at vertebroplasty.

Simulation

Computation of 2D non-stationary temperature field in the cuvettes was carried out by means of the KANAL code [37] intended for non-stationary thermohydraulic calculations for coolant systems of nuclear reactors. At calculation models design the code was adapted to provide heat generation and heat transfer in spongy bone tissue [38].

Two-dimensional non-stationary calculation of temperature in a vertebra with the cylindrical cement-filled cavity was executed. The data illustrating high consistency degree of temperature values shown in fig. 8, 9 were obtained:

- in experiment No. 1 for heat-insulated cuvette of 4.6 cm^3 (fig.8, experimental curve);
- in computational simulation of the experiment No. 1 (fig. 8, calculated curve);
- in experiment No. 2 simulating lytic metastasis cavity of 4.6 cm^3 surrounded with spongy bone tissue at a temperature of 32.6 ± 0.1°C (fig. 9, experimental curve);
- in computational simulation of the experiment No. 2 (fig. 9, calculated curve).

The basic data accepted for calculation of temperature distribution in bone tissue are given in table 3.

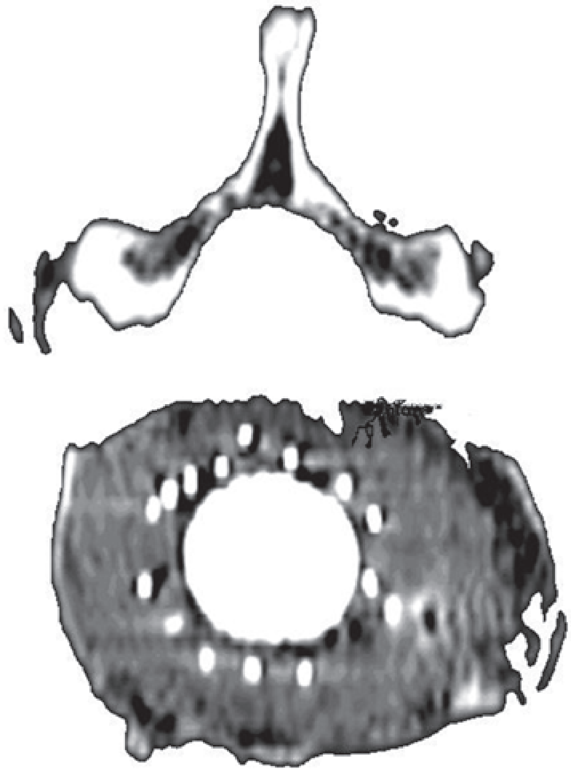


Fig. 6. The vertebra tomogram with the installed thermocouples

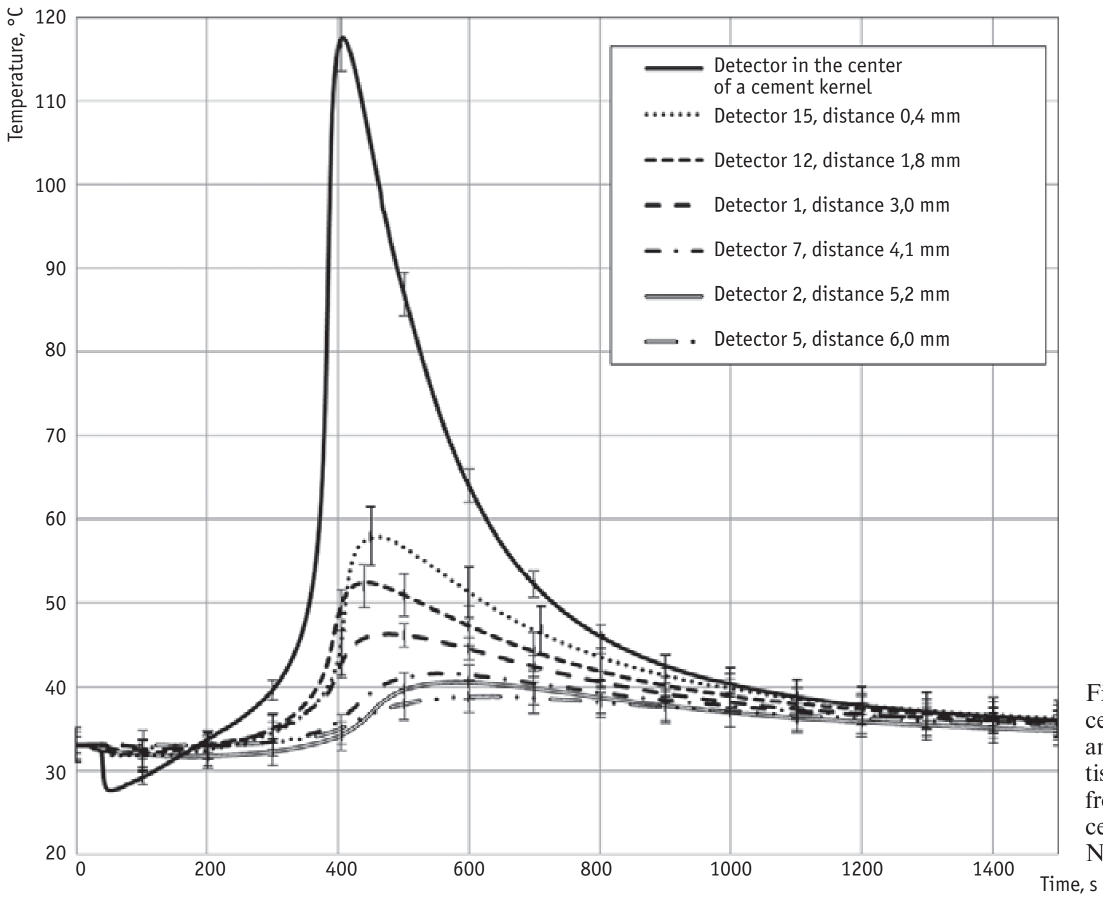


Fig. 7. Temperature in the center of cement “kernel” and in vertebra bone tissue at various distance from a surface of bone cement (the experiment No. 2)

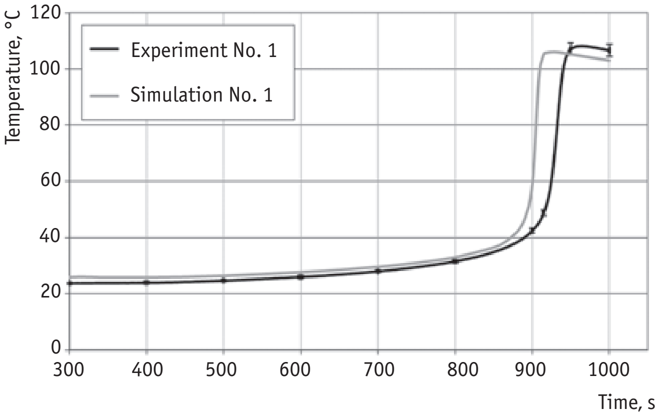


Fig. 8. Temperature time dependence on an internal surface of a cuvette wall (experiment and calculation No. 1)

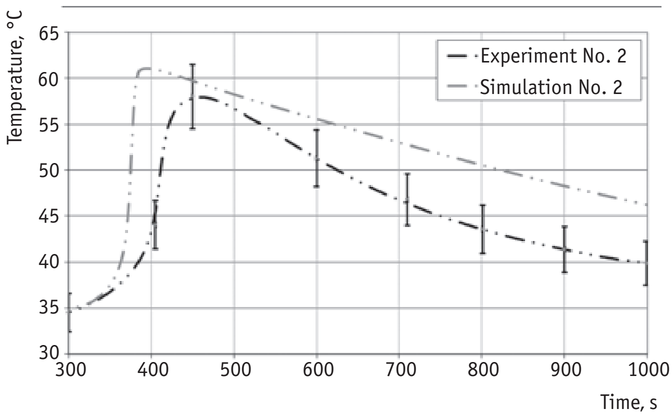


Fig. 9. Temperature time dependence on lateral surface of a cement kernel (experiment and calculation No. 2)

Table 3

Input data for 2D non-stationary calculation of temperature in a vertebra with a cylindrical cavity

Diameter and height of the cement-filled cavity, mm	18; 18
Diameter and height of the vertebra, mm	36; 24
Density of bone tissue of a vertebra, kg/m^3	1180
Specific heat of bone tissue, J/(kg×K)	2270
Heat conductivity of bone tissue, W/(m×K)	0.31
Starting temperature of water, cement, vertebra, °C	32.6; 27.5; 32.6

Discussion

The obtained results allowed to apply the developed technique to simulate a warming up of bone tissue on interface with cement and on various distances from it. Comparison of calculated results with the data obtained in a series of experiments with bone cement-filled cavity of the same volume (fig. 10) shows high degree coherence of simulated and experimental data. It allows to draw a conclusion on possibility of thermal impact prediction on surrounding cells and tissues at bone cement implantation in a metastatic cavity of known volume.

From Fig. 7 and Table 2 follows that the temperature necrosis of all tumor cells can arise at distance no more than 0.4 mm from border of bone cement where temperature remains above 50 ± 3 °C during 3 min reaching maximum value 58 °C. At distance from 0.4 to 1 mm there is a mass death of tumor cells, however their total elimination cannot be reached. At distance from 1 to 2.5 mm profound dystrophic changes of tumor cells and considerable delays of their growth are provided. At distance of 2.5 mm and more, the death of tumor cells caused by thermal influence is not predicted; the apoptosis activation is prognosticated. On the basis of numerous studies of a tumor cells temperature radiosensibility (see, for example, [39]), it is possible to expect that at a distance up to 7 mm from border of bone cement the radiosensitivity of tumor cells increases.

There is a diagram (fig. 11) of temperature effects on tumor cells in bone tissue of the vertebra surrounded with biological tissue. Borders of effects were defined based on data [29–31] that associate duration of influence and effect from this influence. As levels of temperature and the time exposure necessary for destruction of tumor cells, the following values were accepted:

- at 72 °C the necrosis arises instantly;
- at 60 °C the necrosis arises after 5 s exposure;
- at 55 °C the necrosis arises after 30 s exposure;
- at 50 °C the necrosis arises after 5 min exposure;
- at 47 °C the necrosis arises after 10 min exposure.

In fig. 11, all possible effects of thermal influence are presented at temperatures reached in experiment. These effects are shown depending on the volume V of bone cement and distance r from a surface of bone cement. Three effects can be observed: necrosis, apoptosis

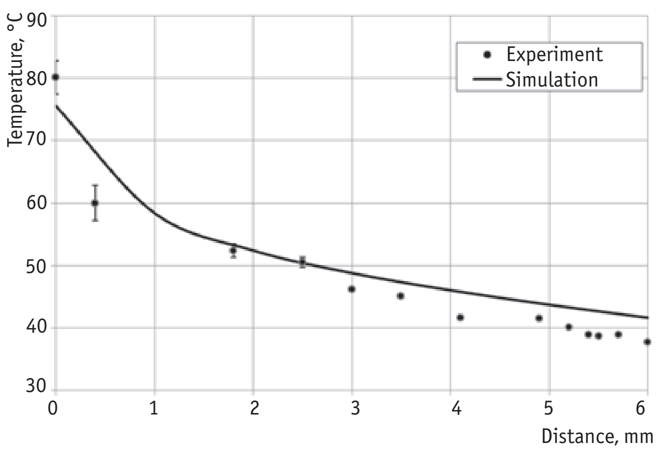


Fig. 10. Temperature maximum distribution in bone tissue of a vertebra body at different distance from a surface of bone cement

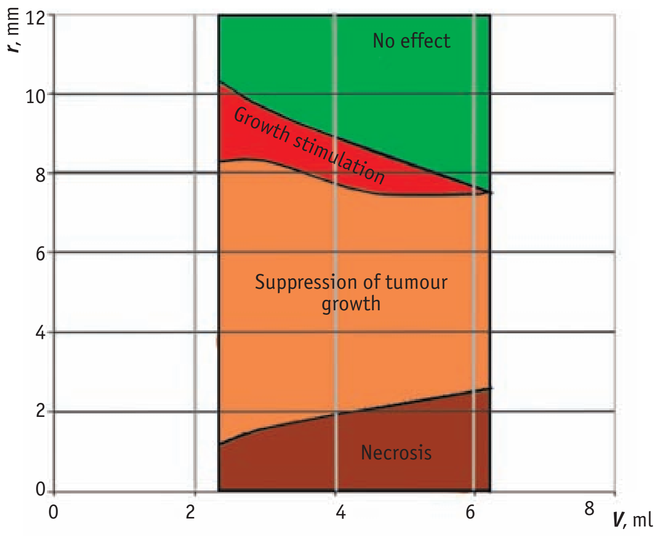


Fig. 11. Possible effects in vertebra bone tissue depending on the volume of bone cement and distance from a contact surface of cement and bone tissue

activation with suppression of growth of tumor cells and stimulation of their growth.

The temperature 40 °C at time exposure no more than 100 s is chosen as the temperature at which thermal influence does not render any effect. Tumor cells growth stimulation is possible in the range of temperature 40–41.5 °C and in any time exposure [29–32].

The necrosis of tumor cells, even at implantation more than 6 cm^3 of bone cement in a cavity of the lytic or mixed metastasis, doesn't reach border of infiltrative growth of a tumor. Areas of apoptosis stimulation, suppression of tumor growth and radiosensibilization of tumor cells are significantly more. Stimulation of tumor growth (at temperatures 40–41.5 °C) arises at implantation of small cement volume when the area of suppression of malignant growth does not extend to an arch plate of a vertebra body or when the soft-tissue component of metastatic growth takes place. At the sufficient volume of a cement implanted in a lytic cavity of a metastasis, the temperature radiosensibilization of tumor cells is reached practically in all volume of a vertebra body.

Conclusion

1. Experimental researches of non-stationary temperature fields have been conducted at polymerization of bone cement in a vertebra at stabilizing vertebroplasty.
2. The experimental model of a local hyperthermia in the area of tumor growth in spongy tissue of a vertebra body is developed.
3. The calculation technology and the software allowing to predict (with a sufficient accuracy for practical application) a warming up of bone tissue at different distances from border of bone cement is developed and approved.
4. It is shown that at implantation of high-temperature bone cement into a cavity of a lytic metastasis, the temperature more than 70 °C is reached on border between cement surface and bone tissue.
5. Results obtained can be used at dosimetric planning of the external-beam or intervention radionuclide therapy carried out after the PVP operation of vertebra bone metastases.

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