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Research Article

Bio-heat transfer in cancer treatment using cryo-freezing method

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ABSTRACT

The objective of this study is to investigate the effect of bio-heat transfer from large blood vessels on freezing region size of tumorous liver tissue using cryo-freezing method. Bio-heat transfer, one of the cancer treatment method, in tumorous tissue has been investigated experimentally using cryo-freezing method for vessels. Investigated parameters are the blood mass flow rate, the diameter of vessel, the number of vessel, and the location of tumorous tissue. Study is carried out for nine different blood mass flow rates varying from 10 g/min to 1200 g/min. Tissues without blood vessel, with single, double and branched vessels are used for the experimental study. Vessels with inner diameter of 2.4, 3.2 and 4.0 mm are used. Liver of beef is employed as a tissue. Refrigerant is the nitrogen protoxide gas. Results show that the number of vessel, the diameter of vessel, the location of tumorous tissue, and the blood mass flow rate affect the freezing region size. Freezing region size decreases with increasing in diameter of vessel, number of vessel and blood mass flow rate. The large blood vessel located near the tumorous tissue affects the freezing time to destroy the tumor. The desired freezing region obtained in tumorous tissue with vessel develops later than the tumorous tissue without vessel. Results indicate that a tumorous tissue about 23 mm may be destroyed in a short time using cryo-freezing method when nitrogen protoxide gas is used as refrigerant gas.

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INTRODUCTION

Tumor happens generally near the large vessels. It is desirable surgically to destroy the tumorous tissue which is developed near the vessel. Therefore, it does not recur and spread.

One of the method for cancer treatment is the cryotherapy. This treatment method is an efficient method employed for destruction of tumor by supplying freezing thanks to cryoprobes within the biological tissue. The time of short staying in hospital and minimal recovery time are within the advantages. Some important advantages of this treatment are being fast, easy and cheap. Thus, anesthesia is not required. Bleeding risk is extremely low after the procedure of cryo-freezing. It is not needed any variances in daily life. Negative effect is not seen for human reproduction-potential. Complications or serious injury risk is quite low. This treatment method is employed to destroy the liver and prostate tumors.

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Literature investigation indicates the cancer treatment method employing the cryo-freezing has been examined by some scientists. Deng and Liu [1–3] numerically investigated the cryotherapy treatment using finite difference method. It was observed that using the Monte Carlo solution method produces excellent effects for freezing and heating performance. Chua et al. [4] developed an analytical method to investigate the destruction of tumorous liver cell. They explained that the enhancement of the tumorous cell destruction is the potential in order to use freeze–thaw cycles. Deng et al. [5] conducted an experimental and numerical study to examine the large vessel thermal effects for cryosurgery. It was concluded that the blood temperature in the large blood vessels prevents the destruction of the tumor during cryotherapy. Chua and Chou [6] developed a model to examine the freeze-thaw-heat treatment within a biological tissue. It was found that greater tumorous cell destruction within the tissue is obtained for double freeze–thaw cycles. Silveira et al. [7] determined both arterier branch and main artery diameters of human liver tissue. Average main arterial diameters of human liver were given. Majchrzak and Tarasek [8] analyzed the thermal interactions between a biological tissue and single blood vessel enclosing it. The temperature distribution in the tissue was examined. Chua [9] implemented a numerical study to explore the nonstandard shaped liver tumor. A novel piecewise method was introduced to estimate quickly the volume of frozen tissue. The value of lower temperature is needed in order to freeze the tumorous tissue near large vessel [10]. Sun et al. [11] conducted the first experiments for in vivo animals. In order to freeze completely tumorous tissue where blood vessels are inserted nano-surgical method was employed. It was concluded that injecting nanoparticles into freezing target can significantly shorten the freezing time, decrease the heating effect of blood vessel, and enlarge the freezing range. Chua [12] performed a numerical and experimental study to explore transient temperature distribution of tumor in a blood network. Results show that injecting nanoparticles into tissue increases the freezing region volume. Wang et al. [13] developed a multiscaled three-dimensional cell-tissue model in order to evaluate the effects of cardiovascular network thinking the conclusions acquired from hyperthermia and cryosurgery treatments. It was found that increasing the distance between the tumor and the vascular network results in increasing the tumor damage degree. Kizilirmak and Turgut [14] experimentally investigated the bio-heat transfer in tumorous tissue using cryo-freezing method for single and without blood vessel. It was concluded that the freezing time is shorter in tissue without vessel.

Literature survey indicates that cryo-freezing method to destroy the tumorous tissue needs further investigation. Therefore, this study investigates the effect of blood mass flow rate flowing in vessel, the location of tumorous tissue, and the vascular structure (the number and diameter of blood vessels) on freezing region size has been investigated experimentally using cryo-freezing method. Studies are carried out for various blood mass flow rates changing from 10 g/min to 1200 g/min. The novelty of present study is the experimentally investigation of the effect of both tumorous tissue location and vessel diameter on freezing region size for branched vessel structures. The using of nitrogen protoxide (N_2O) gas as a refrigerant is also the other novelty of this study. This study aims to obtain new temperature and freezing region data required for optimum cryo-freezing process for single, double and branched vessels.

PROBLEM STATEMENT

The effect of bio-heat transfer on freezing region size of tumorous liver tissue is experimentally investigated using cryo-freezing method for cancer treatment. Nitrogen protoxide (N_2O) gas is used as refrigerant. The location of tumorous tissue, the diameter size of vessel, the mass flow rate of blood, and the number of vessel are the investigated parameters to obtain the freezing region size.

MATERIALS AND METHODS

Figure 1(a) indicates the experimental set-up employed in this study. Cryo-freezing procedure is carried out using a cryotherapy machine. This device involves a needle valve, a cryoprobe gun, a pressurized nitrogen protoxide tube, and a manometer. A pressurized N_2O gas controlled by a needle valve is stored in a cylinder. The tube pressure is measured using a pressure gauge. N_2O gas flows inside an internal tube which is located within cryoprobe gun when the valve is open.

Two calibrated 24-gage copper-constantan thermocouples are employed in order to measure cryoprobe tip temperature and surroundings temperature. In addition, ten thermocouple probes are employed in order to determine the temperature of tissue at different points as seen in Figure 1(b). As will be noticed from Figure 1(b), thermocouple probes are placed as L-shaped. The distance between two thermocouple probes is taken as 3 mm. The distance between the cryoprobe inner surface and the thermocouple probes located horizontally and vertically is 5 mm. Thermocouple probe tips are located at a distance 10 mm from the top surface of tissue. Thermocouple temperature values are read using a datalogger connected to a computer.

A thermal imager camera with accuracy of 0.1°C is employed to display the temperature distribution. Thermal camera is placed at 50 cm above the ground. The distance between the thermal camera and tissue is arranged to 80 cm.

The temperatures taken from thermocouple probes are the inner part temperatures of beef liver sample while the temperatures taken from thermal camera are the top surface temperatures of beef liver sample. Temperature maps

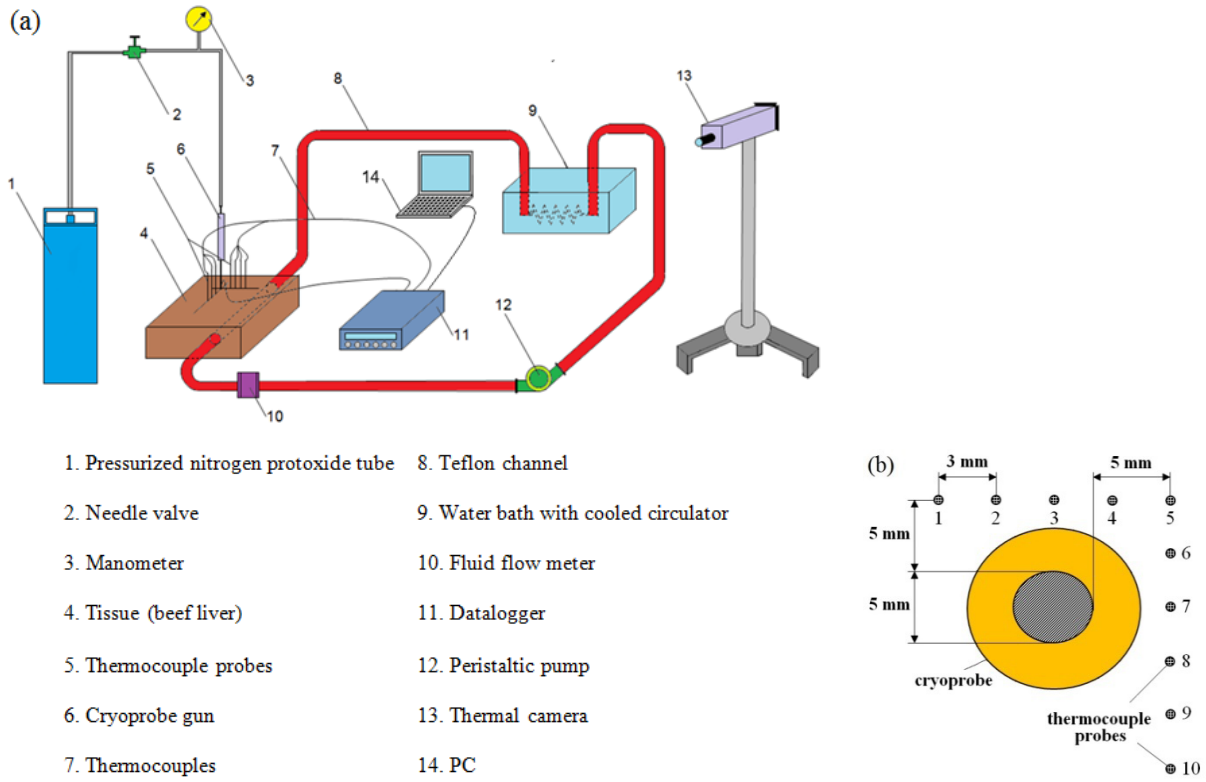


Figure 1. (a) The schematic presentation of the experimental set-up and (b) the locations of thermocouples.

are obtained using the temperature values taken from thermocouples and thermal camera using SigmaPlot 10.0 software.

To investigate the cryogenic freezing process, commercially usable beef livers are bought and employed in in-vitro experiments. The beef liver samples used in this study are seen in Figure. 2. The beef liver samples used are the without vessel, with single, double and branched vessels. Y-connectors are used to branch blood vessels. Diameter reducers are employed to enlarge and reduce the diameter in the branched blood vessel. Figure 2 also shows the thermocouple probes used to measure the temperature distribution of freezing region. Teflon channel is used to simulate the blood vessel due to its similarity to the blood vessel [5, 7, 8, 10, 13]. Three different teflon channels with inner diameters (inner diameter=2.4 mm, 3.2 mm and 4.0 mm) are employed in order to examine the blood flow thermal effect. Corresponding outer diameters are 3.0 mm, 4.0 mm and 5.0 mm, respectively. Nitrogen protoxide gas passing through a 5 mm-diameter-cryoprobe is used as refrigerant for cryo-freezing procedure.

Livers belonging to two-year-old dairy beef are used in the experiments. Thermophysical properties of biological beef liver tissue and blood are listed in Table 1.

Typical view of tumorous tissue and the insertion position of cryoprobe tip at –40°C are shown in Figure 3 on x-y-z coordinates and on A-A section for double vessel. Vessels are placed into liver tissue at a 20 mm distance from top surface of the tissue. The distance between two vessels for both double and branched vessels is 20 mm. Fluid flows in the arrow direction. Beef liver size is taken as 84 mm x 60 mm x 40 mm as seen in Figure 3. Cryoprobe with inner diameter D_{cp}=5 mm is located at a 5 mm distance from top surface of the arter vessel.

Pure water is used as fluid in vessel due to its similarity to the physical blood properties. A water bath is employed to supply water temperature at 37°C. A peristaltic pump with a precision of 1 rpm is used to simulate the pumping blood of heart. The mass flow rates of blood employed during the experiments are chosen to be suitable with the mass flow rates of blood within the normal adult human liver [5, 10, 12]. Mass flow rate of water is measured using a bucket and stopwatch. Present study is carried out for nine various blood mass flow rates Q=10, 30, 79, 128, 195, 600, 800, 1000 and 1200 g/min at eight cases given in Table 2.

In Table 2, ID1 is the inner diameter of arter in single, double and branched vessels. ID2 is the inner diameter of the vein in double vessel and the inner diameter of the arter in branched vessel.

Figure 4 shows the typical view of branched vessel dimensions and flow direction. As shown in Figure 4, fluid flows inside the 2.4 mm-vessel. Then fluid enters the

branched vessel, flows through it, and leaves the branched vessel. Finally, fluid flows inside a 2.4 mm-vessel after branched vessel. As can be seen in Figure 4, 60°-Y-connector is used for branched vessel. The diameter ID1 is taken as constant while ID2 is changed as seen in Table 2.

Error in temperature measurements, obtained from thermocouples and thermocouple probes, was estimated to be around ±0.3°C of which 0.1% resulted from the datalogger. Error in temperature measurements obtained from thermal camera was estimated to be about ±0.1°C. Errors in weighing and time were estimated to be ±1 g and 1 s, respectively. The maximum relative uncertainty of mass flow rate was determined to be 10.1% following the method explained by Holman [16]

A typical experimental study consists of placing the teflon channel into beef liver (see Figure 2), connecting teflon channel to peristaltic pump, operating peristaltic pump, measuring mass flow rate of fluid, operating water bath, obtaining water at 37°C, placing thermocouples into beef liver to determine the temperature distribution in beef liver, arranging the thermal camera position, and starting experiments. Experimental study is lasted for ten minutes to supply the stable temperature of beef liver sample. Cryoprobe tip is placed into beef liver sample. After that, cryo-freezing method is initiated and continued for

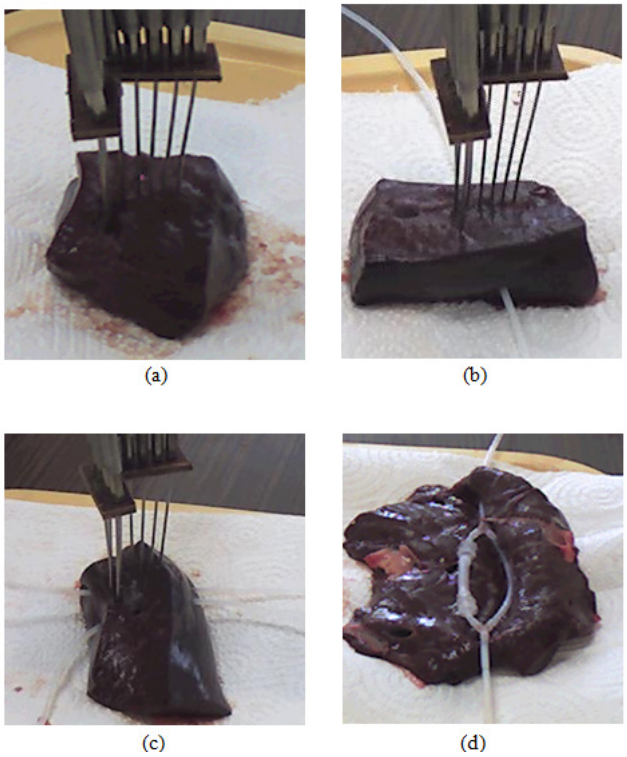


Figure 2. Samples of beef liver without (a), with single (b), with double (c) and with branched vessel (d).

Table 1. Properties of biological blood and beef liver tissue [1–3, 12, 15]

Definition	Value
Unfrozen liver tissue density	1000 kg/m^3
Frozen liver tissue density	1000 kg/m^3
Density of blood	1000 kg/m^3
Heat capacity of unfrozen liver tissue	3470 kJ/m^3·°C
Heat capacity of frozen liver tissue	2160 kJ/m^3·°C
Heat capacity of blood	3600 kJ/m^3·°C
Unfrozen liver tissue thermal conductivity	0.488 W/m·°C
Frozen liver tissue thermal conductivity	2 W/m·°C
Normal liver tissue metabolic heat rate	4.2 kW/m^3
Tumoruos liver tissue metabolic heat rate	42 kW/m^3
Latent heat	230 MJ/m^3
Normal liver tissue blood perfusion	0.0005 ml/s/ml
Tumoruos liver tissue blood perfusion	0.002 ml/s/ml
Transition temperature of upper phase	−1°C
Transition temperature of lower phase	−8°C
Artery blood temperature	37°C

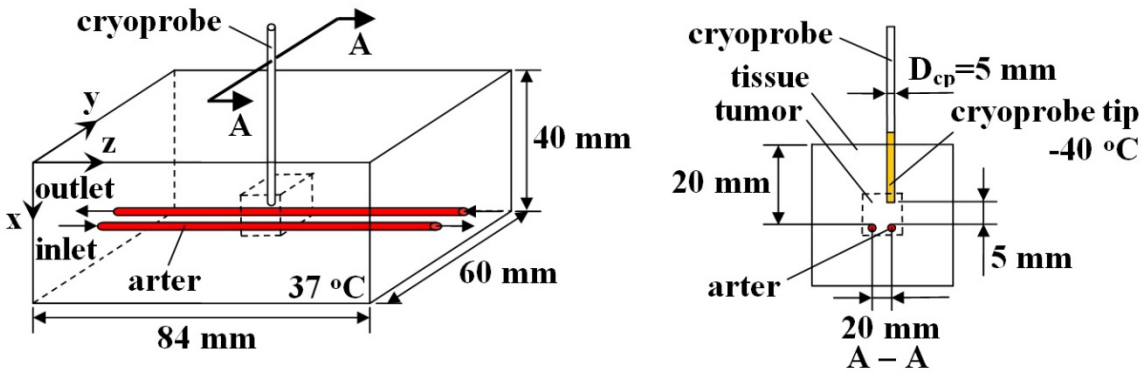


Figure 3. Typical schematic presentation of tumorous tissue with double blood vessel and insertion location of cryoprobe tip.

120 seconds. After beginning cryo-freezing procedure, temperatures are recorded every 10 seconds using thermocouple probes and thermal camera. After the experiment, the beef liver is changed for other experimental study.

RESULTS AND DISCUSSION

Experimental studies are carried out using cryo-freezing procedure for beef liver with and without blood vessels. Single, double and branched vessels are used in the experimental survey. The effects of the mass flow rate of fluid in vessel, the location of tumorous tissue and the type of the vessel are investigated.

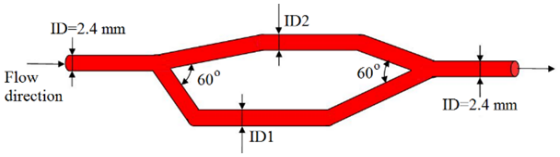
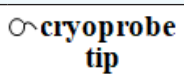
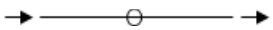
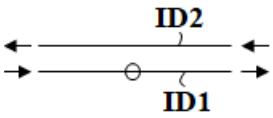
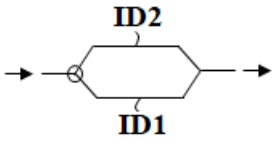
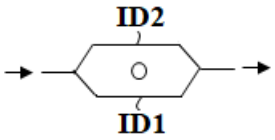
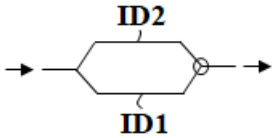
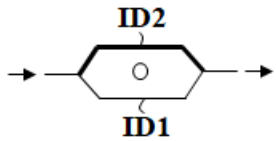
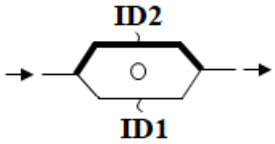


Figure 4. Typical view of branched vessel.

Repeatability tests for experimental study are conducted for Case 3 and Case 6 (please see Table 2) at mass flow rate of Q=600 g/min. Experimental results are shown in Figure 5. It can be said that repeatability of experimental results is good. Good repeatability of experimental study indicates the stability of experimental study.

Cryo-freezing procedure for liver tissue with and without vessels is conducted for the time period of 140 seconds at different fluid mass flow rates. Freezing region diameters at the temperature 273K are plotted in Figure 6 as a function of time for various cases. As will be recognized from Figure 6, freezing region diameter increases suddenly between 0–20 seconds. Then it continues to increase with time to 120 seconds. It reaches a constant value 23 mm after 120 seconds for all cases studied. That is, freezing region diameter does not change with time after 120 seconds. Therefore, hereafter experiments are conducted for 120 seconds.

Table 2. Cases studied during cryo-freezing procedure

Case no	Type of vessel	Freezing process region	ID1 (mm)	ID2 (mm)	Position of cryoprobe tip and vessels
Case1	No	Middle	–	–	
Case2	Single	Top of arter	2.4	–	
Case3	Double	Top of arter	2.4	2.4	
Case4	Branched	First connection point	2.4	2.4	
Case5		Middle of branched	2.4	2.4	
Case6		Second connection point	2.4	2.4	
Case7		Middle of branched	2.4	3.2	
Case8		Middle of branched	2.4	4.0	

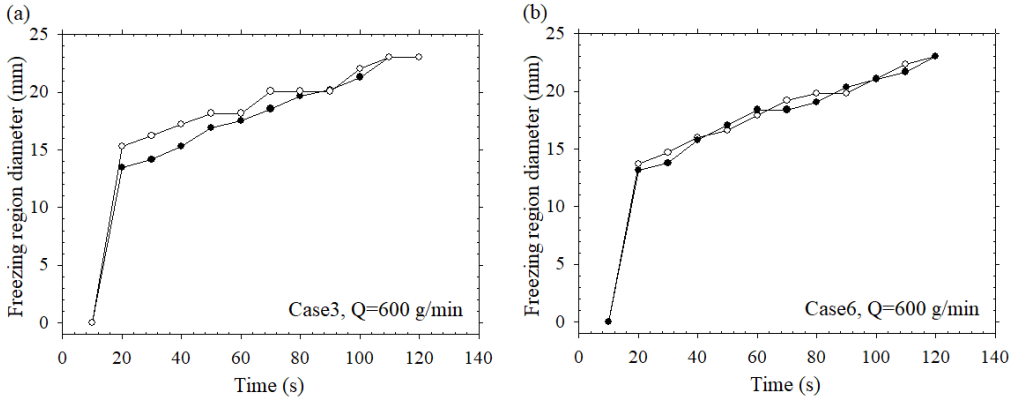


Figure 5. Freezing region diameter versus time for repeatability tests.

The images taken from thermal camera are shown in Figure 7 after 30, 60 and 120 seconds for a tumorous tissue without vessel. Results show that increasing time ends up with the increasing cryo-freezing region size. In other words, 17.13 mm, 21.53 mm, and 23 mm are the cryo-freezing region diameters after 30, 60 and 120 seconds, respectively.

A validation study is conducted in order to compare the present conclusions with the conclusions of Chua [12]. For this reason, the study of Chua [12] was repeated here for nitrogen protoxide gas. Cryo-freezing procedure is applied to the tumorous beef liver tissue with single vessel for the mass flow rate of 79 g/min. Figure 8 shows the cryo-freezing areas for a cancer tissue with single vessel after 30, 60 and 120 seconds.

Results demonstrate that 23 mm, 18.98 mm and 16.24 mm are the cryo-freezing area diameters for a tumorous tissue with single vessel after 120, 60 and 30 seconds, respectively. Results indicate that cryo-freezing region diameter increases with increasing time.

Figures 7 and 8 show that cryo-freezing region diameters are the same for the tissues with and without vessels after 120 seconds. Comparison of the results after 60 seconds shows that the diameter of cryo-freezing area of the tumorous tissue with blood vessel is lower than that of the tumorous tissue without blood vessel.

According to the conclusions of Chua [12], the diameters of cryo-freezing area for the tissue without vessel are 28 mm and 19 mm after 20 min and 10 min, respectively, when liquid nitrogen is employed. Moreover, the diameters of cryo-freezing area for the tissue with a single vessel is

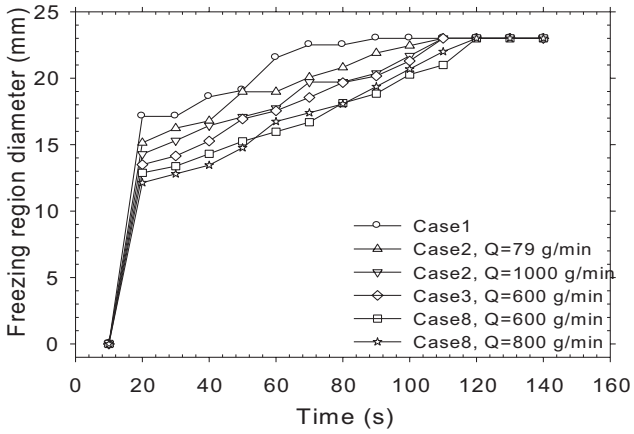


Figure 6. Cryo-freezing region diameter versus time.

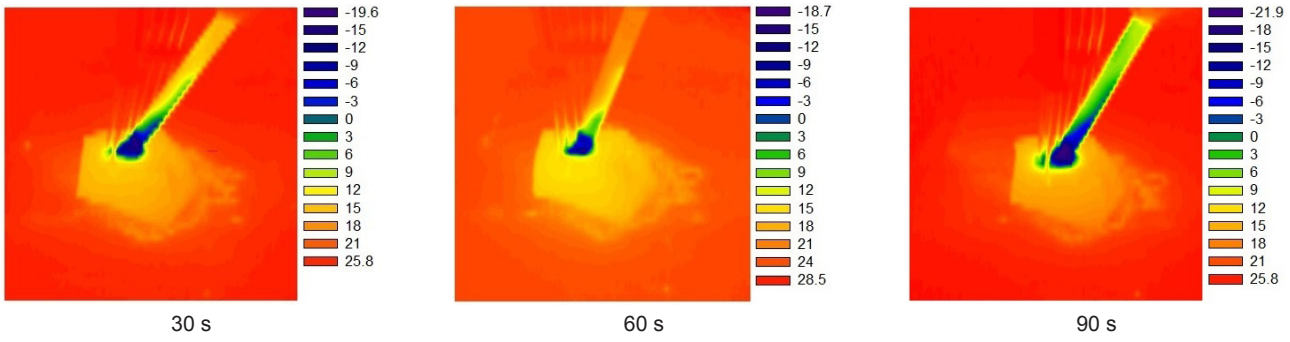


Figure 7. Regions of cryo-freezing after 30, 60 and 120 sec for a tumorous tissue without vessel.

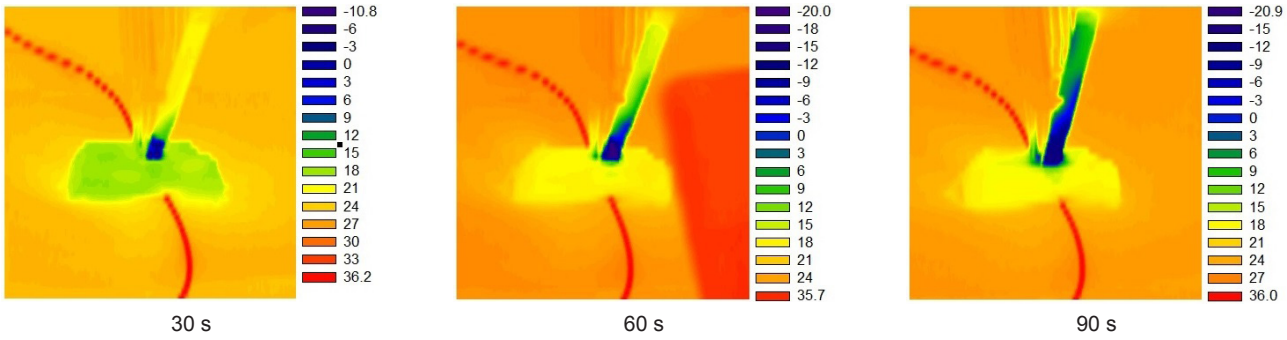


Figure 8. Regions of cryo-freezing after 30, 60 and 120 sec for a tumorous tissue with a single vessel.

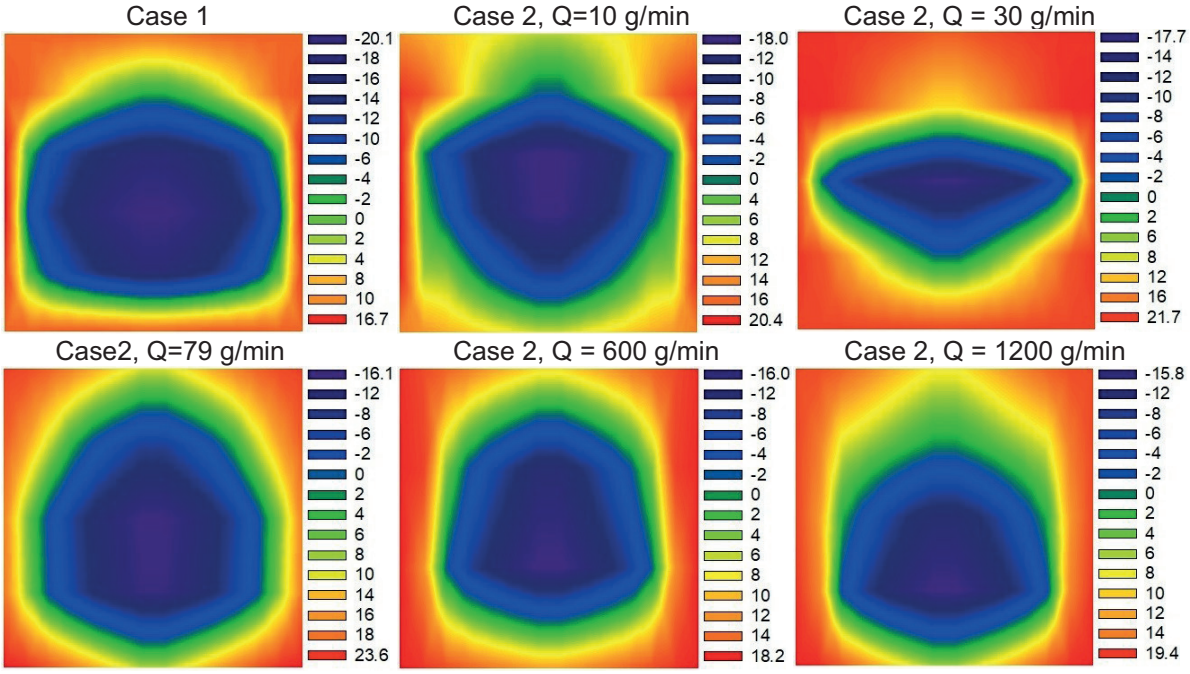


Figure 9. The impact of blood mass flow rate on temperature distribution in tissue after 60 sec.

26 mm and 18 mm after 20 min and 10 min, respectively, while liquid nitrogen is employed [12]. Present experimental results conducted for nitrogen protoxide demonstrate that nearly the same diameters of cryo-freezing area are determined at a short time period while nitrogen protoxide gas is employed. The temperature distributions, obtained in the present study, given in Figure 7 and Figure 8 are compared with the temperature distributions presented in Figure 9(a) and Figure 9(b) of Chua [12]. Results show that temperature distribution within the same freezing region size show similar distributions in two studies.

In order to see the blood mass flow rate effect on temperature distribution in a tissue, temperature distributions taken from thermocouples for Case1 and Case2 are shown in Figure 9 for various blood mass flow rates after 60 seconds. It is seen that mass flow rate in vessel affects the distribution of temperature in a tissue. Results show that the temperature of freezing region increases with increasing in mass flow rate due to the increasing in bio-heat transfer from fluid to tissue. Increasing temperature of freezing region results in decreasing cryo-freezing region size.

Figure 10 shows the typical temperature distribution, obtained from thermocouple probes, in tissue at a mass flow rate of 600 g/min for all cases after 60 seconds. It is seen that the number of vessel and the type of vessel affect the freezing region size.

To see the impact of blood mass flow rate on cryo-freezing region, temperature images taken from thermal camera are shown in Figure 11 for a tissue with single vessel after 60 seconds. Cryo-freezing region diameters at 273K are calculated using thermal camera images. Cryo-freezing region diameters D_{fr} are given in parenthesis in Figure 11

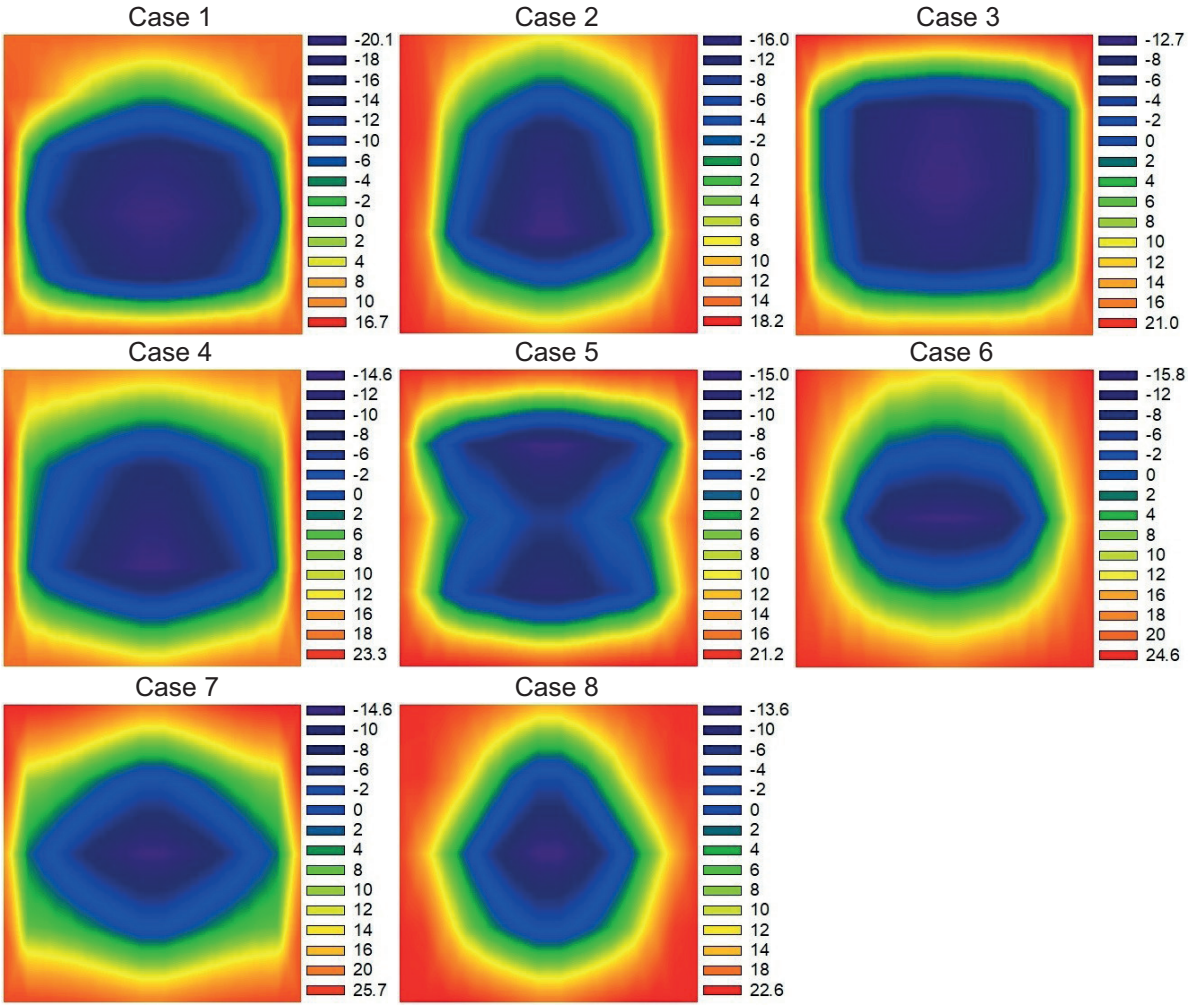


Figure 10. Temperature distributions after 60 sec for all cases at a mass flow rate of 600 g/min.

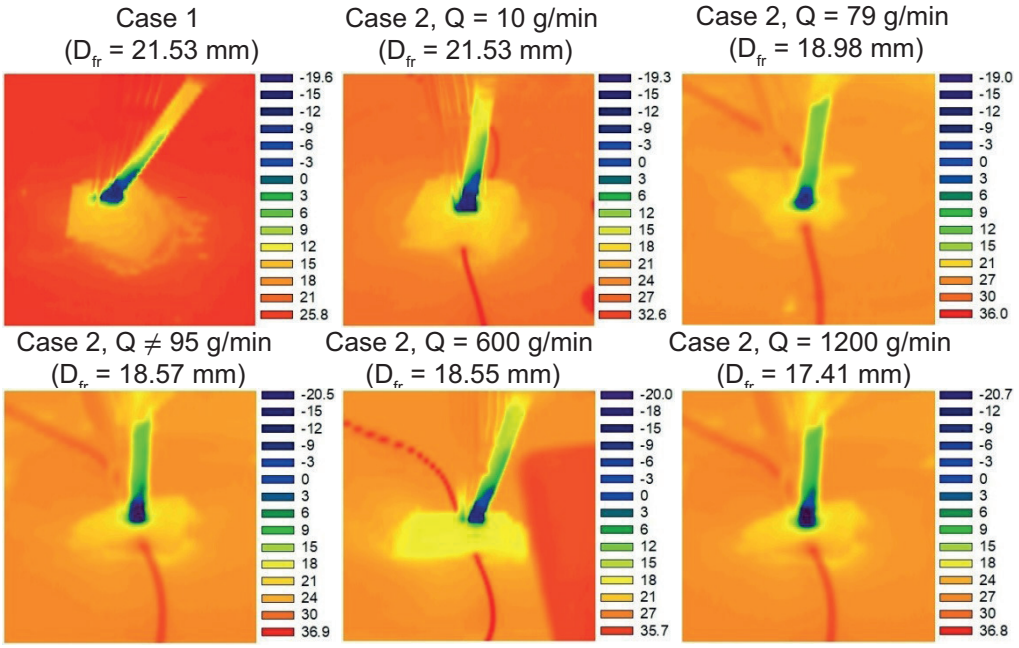


Figure 11. The effect of mass flow rate on cryo-freezing region.

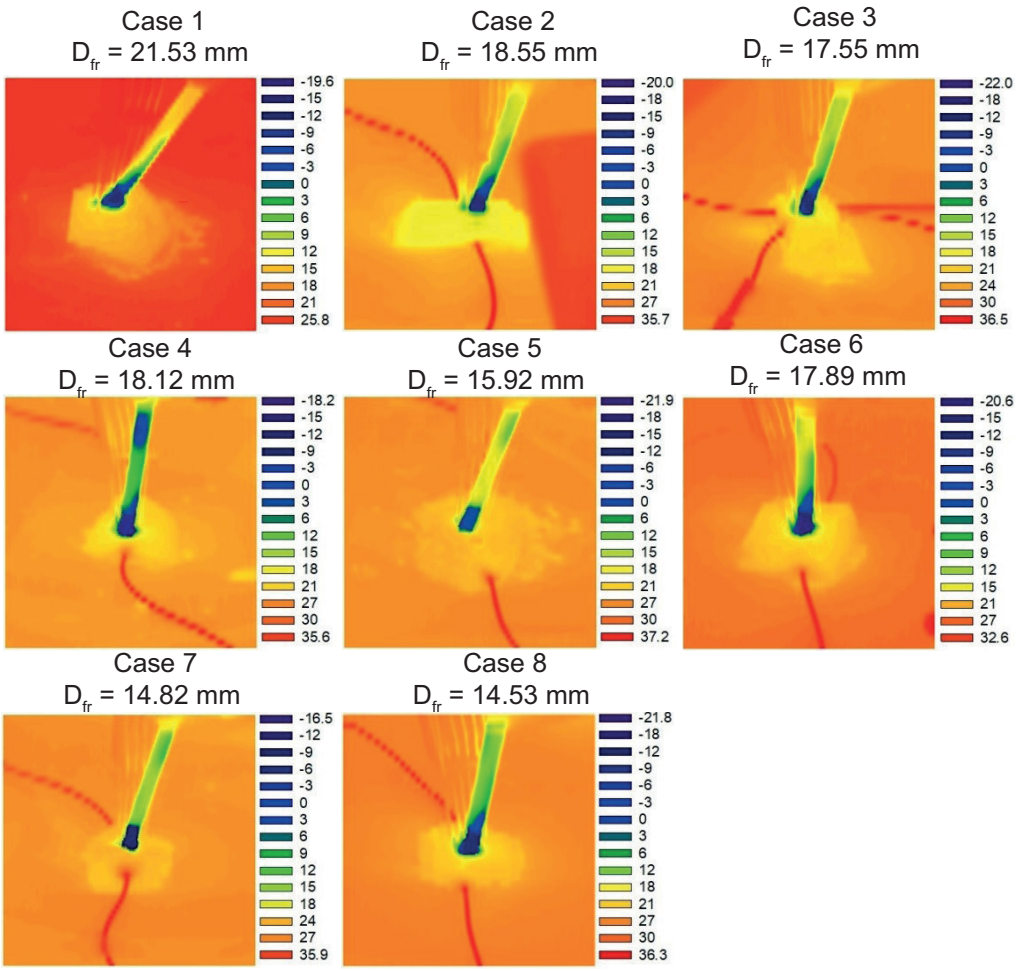


Figure 12. Temperature images taken from thermal camera after 60 sec for all cases at a mass flow rate of 600 g/min.

as well. It is seen that increasing mass flow rate results in decreasing the diameter of cryo-freezing area. It can be explained that heat transfer rate from fluid in vessel to cryo-freezing area enhances with enhancement fluid mass flow rate. Increasing heat transfer rate results in decreasing cryo-freezing region diameter. The biggest diameter of cryo-freezing area is determined for the Case1 while the smallest cryo-freezing region diameter is obtained at the highest mass flow rate 1200 g/min.

In order to see the impact of blood mass flow rate on cryo-freezing region size, temperature images taken from thermal camera for all cases are shown in Figure 12 at a mass flow rate of 600 g/min after 60 seconds. Freezing region diameters D_{fr} are also given in Figure 12 in parenthesis.

It is obtained that maximum diameter of freezing area D_{fr}=21.53 mm is obtained for the tissue without vessel, Case1, while the minimum freezing region diameter D_{fr}=14.53 mm is obtained for Case8. When the results of non-branched vessels, i.e. Case2 and Case3, are compared, it is viewed that the diameter of freezing area for single vessel (Case2) is greater than that of double vessel (Case3). Similarly, when the results of Case4-Case6 for which vessel diameters are the same are compared, it is seen that the location of tumor affects the freezing region diameter.

In order to see the effect of vessel diameter on freezing region size, the results of Case5, Case7 and Case8 are compared. For these cases, ID2 is 2.4, 3.2 and 4.0 mm, respectively, while ID1 is 2.4 mm for each case. It is viewed that the diameter of freezing area reduces with increasing ID2 due to increasing bio-heat transfer surface area. That is, maximum and minimum freezing region diameters are obtained for Case5 and Case8, respectively.

Cryo-freezing region diameter is plotted in Figure 13 versus time for various cases in order to view the effect of mass flow rate on the diameter of cryo-freezing area. Results show that the diameter of cryo-freezing area increases rapidly up to 20 seconds, then it continues to increase with increasing time up to 120 seconds. Results indicate that the diameter of cryo-freezing area for tissue without vessel reaches a constant value 23 mm at 90 seconds. It is seen that mass flow rate of blood affects the cryo-freezing region

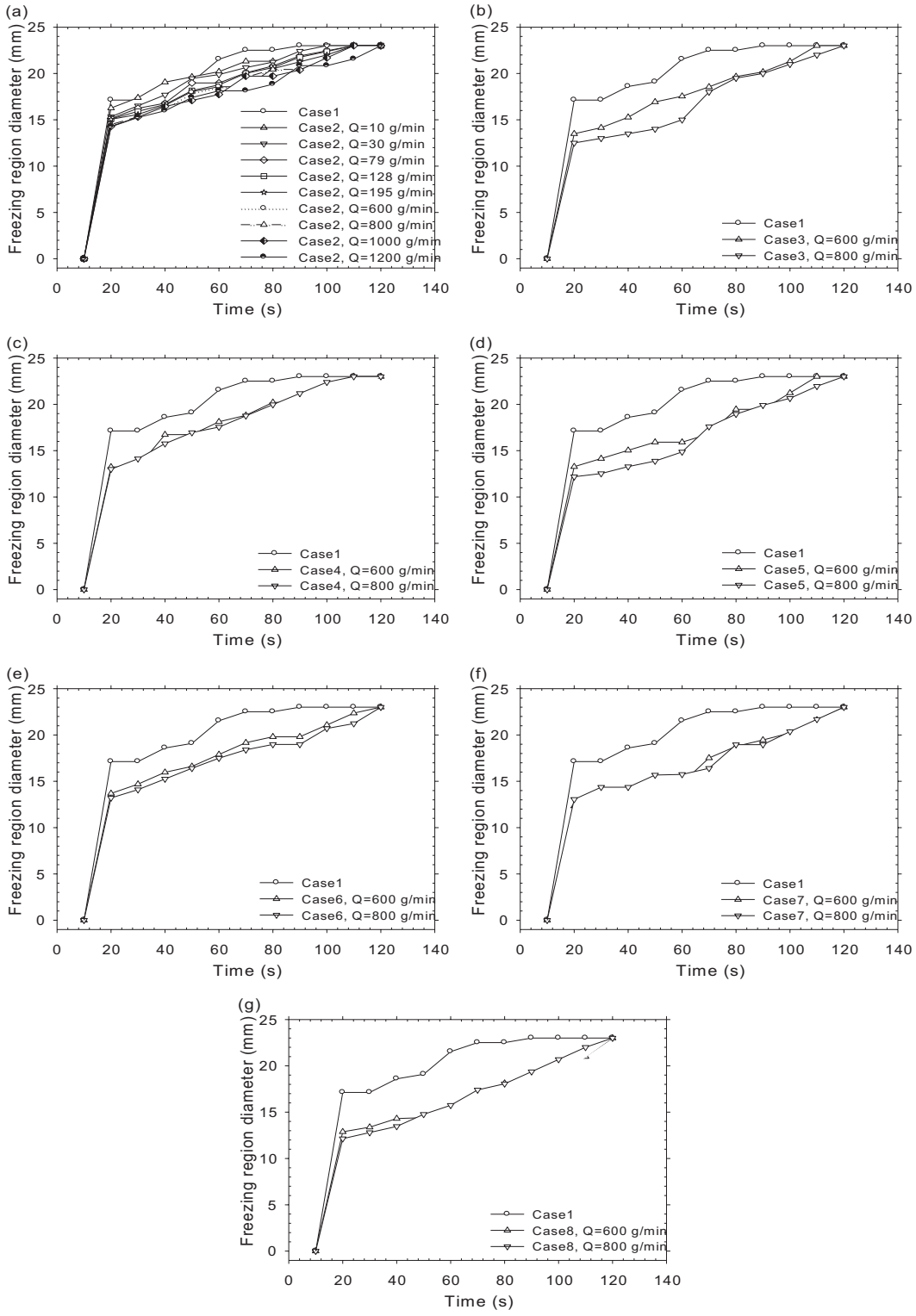


Figure 13. The diameters of cryo-freezing area at various mass flow rates for Case2 (a), Case3 (b), Case4 (c), Case5 (d), Case6 (e), Case7 (f) and Case8 (g).

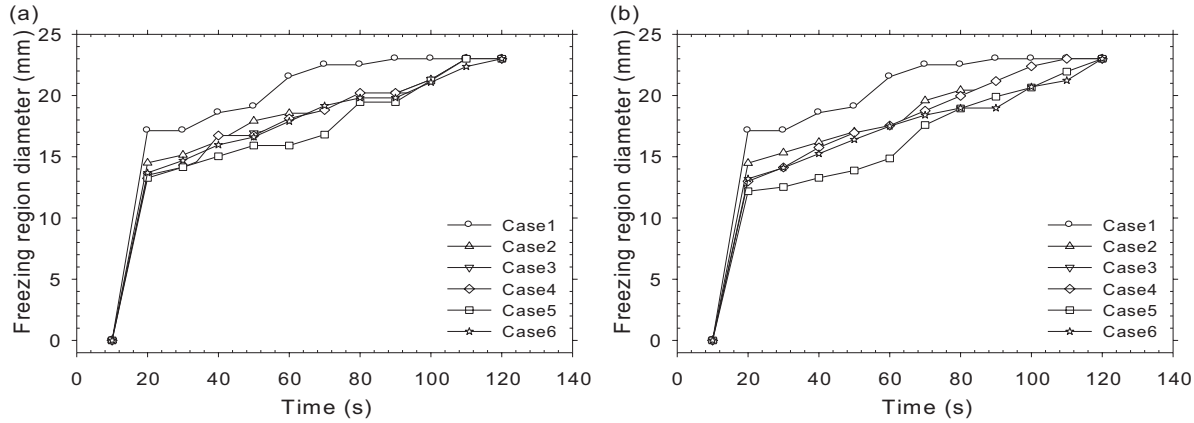


Figure 14. Freezing region diameter versus time; (a) Q=600 g/min and (b) Q=800 g/min.

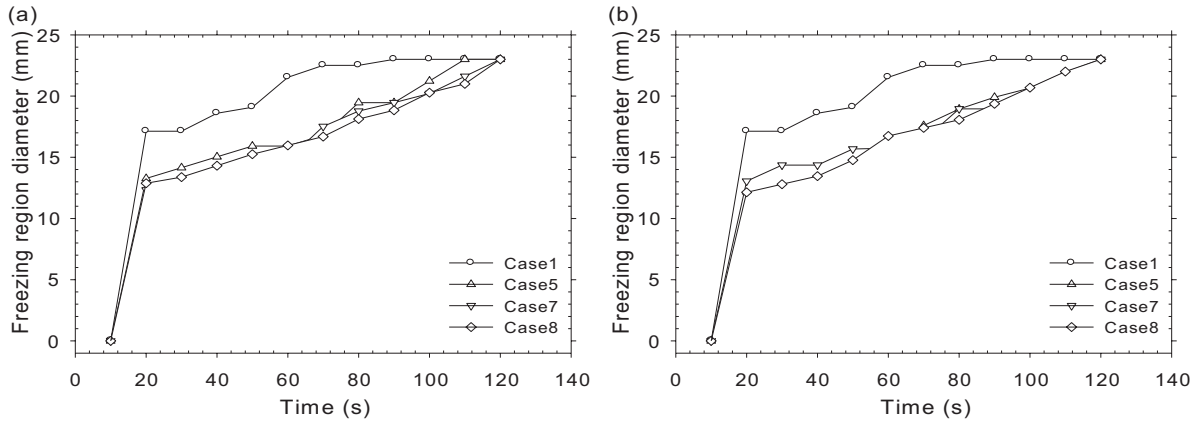


Figure 15. The effect of ID2 on freezing region diameter; (a) Q=600 g/min and (b) Q=800 g/min.

diameter before reaching constant value. This can be interpreted as that the diameter of cryo-freezing area reduces with enhancing fluid mass flow rate of fluid up to 120 seconds due to increasing bio-heat transfer from fluid to tissue. However, cryo-freezing region diameters for all cases are the same after 120 seconds. The diameter of cryo-freezing area for tissue without vessel reaches a constant value earlier than that of tissues with vessel.

Figure 14 shows the diameters of freezing area as a function of time at two various blood mass flow rates 600 g/min and 800 g/min for Case1 through Case6. It is seen that vessel in tissue affects the freezing region diameter when Case1 (no vessel) is compared with other cases. It is also seen that the type of the vessel affects the freezing region diameter for the freezing time between 0–120 seconds. However, results show that the type of the vessel does not affect the freezing region diameter after 120 seconds. That is, freezing region diameters for all cases are the same, and its value is 23 mm for two mass flow rates. It is seen that the number of vessel in a tumorous tissue affects the cryo-freezing region diameter. In other words, cryo-freezing region diameter decreases with increasing in the number of vessel due to increasing of bio-heat transfer. Cases 4–6 are compared to see the effect of freezing location in tissue on freezing region diameter. It is viewed that less diameter of freezing area is determined when freezing location is the middle of branched vessel (Case5). It is interpreted as bio-heat transfer surface area increases when artery is branched. Thus, increasing bio-heat transfer surface area results in increasing bio-heat transfer; increasing bio-heat transfer ends up with decreasing freezing region diameter. When Cases4 and 6 are compared, it is seen that freezing region diameters are almost the same if tumorous tissue is assumed at the front and back junction points of the branched vessel. Results show that surface area of heat transfer increases as the number and diameter of vessel increase. Enhancing surface area of heat transfer results in enhancing bio-heat transfer from the vessel to the tissue. Thus, increasing heat transfer causes to the less freezing region size diameter.

In order to see the impact of the artery diameter in branched vessel, freezing region diameter is shown in Figures 15(a) and 15(b) at the mass flow rates 600 g/min and 800 g/min, respectively. Diameter of one artery ID1 is kept constant at 2.4 mm while the second artery diameter is taken

as 2.4 mm, 3.2 mm and 4.0 mm. Figure 15 shows the results of tissue without vessel for the purpose of comparison. As can be seen that vessel affects the diameter of freezing area. Results show that freezing region diameter depends on bio-heat transfer surface area. That is, less bio-heat transfer surface area ends up with less freezing region diameter. Under the same conditions, results show that bio-heat transfer from the vessel to the tissue increases while the mass flow rate of blood increases. Therefore, increasing bio-heat transfer from vessel to tissue results in decreasing in freezing region size.

CONCLUSION

Mass flow rate of blood, tumorous tissue location and the type of the vessel on freezing region effects are investigated experimentally using cryo-freezing procedure. Nitrogen protoxide gas is used as refrigerant gas. The temperature regions are obtained from measured thermocouple probes and thermal camera images. Freezing region diameters are given as a function of time. It is seen that vessel in a tissue, blood mass flow rate, the diameter of vessel, the location of tumorous tissue affect the freezing region size. Results show that bio-heat transfer from fluid to tissue increases with increasing mass flow rate of fluid. Freezing region diameter decreases with increasing bio-heat transfer. Maximum freezing region size is obtained for the tissue without vessel. The location of tumorous tissue for branched vessel affects the freezing region diameter. It is concluded that tumorous tissue about 23 mm may be destroyed in a short time using cryo-freezing method when nitrogen protoxide gas is used as refrigerant gas.

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AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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