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GAZİ ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMA PROJELERİ
PROJE KESİN RAPORU

Kriyo-Dondurma Yöntemiyle Yapılan Kanser Tedavisi için Bio-Isı Transferinin Deneysel Olarak İncelenmesi

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(Proje kesin raporu ekler hariç 15 sayfayı geçmemelidir. Projeler A4 formatında, Times New Roman karakterinde, 12 punto büyüklüğünde ve tek satır aralıkla yazılmadır Proje raporu aşağıdaki başlıklar dikkate alınarak hazırlanmalıdır)

Özet (Proje başlığı, özeti ve anahtar kelimeler Türkçe ve İngilizce yazılmalıdır. (Proje özeti 250 kelimeyi geçmemelidir.)

Proje Adı: Kriyo-Dondurma Yöntemiyle Yapılan Kanser Tedavisi için Bio-Isı Transferinin Deneysel Olarak İncelenmesi
Proje Özeti: Bu çalışmada, içerisinde kan damarı olan ve olmayan tümör dokusunda oluşan bio-ısı transferi, kanser tedavisinde uygulanmak üzere kriyo-dondurma yöntemi kullanılarak deneysel olarak araştırılmıştır. İncelenen parametreler, damardaki kanın kütle akış hızı ve damar yapısıdır. Çalışma 10 gr/dak ila 1200 gr/dak arasında değişen dokuz farklı kan akış hızı değeri için gerçekleştirilmiştir. Deneysel çalışmalarda içerisinde kan damarı olmayan, tek, çift ve dallanmış damar bulunan dokular kullanılmıştır. İç çapı 2,4, 3,2 ve 4,0 mm olan damarlar kullanılmıştır. Biyolojik doku olarak dana karaciğeri kullanılmıştır. Soğutucu akışkan olarak 5 mm iç çaplı kriyoprobun içinden geçen azot protoksit (N_2O) gazı kullanılmıştır. Elde edilen sonuçlar, damarlı tümör dokusunda istenen donma bölgesinin damarsız tümör dokusundan daha sonra geliştiğini göstermektedir. Donma bölgesinin büyüklüğü, kan ve damar iç çapındaki kütle akış hızının artmasıyla azalmıştır. Bir dokudaki dallanmış damarın artması ile, donma bölgesi büyüklüğünün azaldığı görülüştür. Tümör dokusunun yakınında bulunan büyük kan damarı, donma süresini etkileyerek tümörü tahrip etmektedir. Sonuçlar, azot protoksit gazı kullanıldığında kriyo-dondurma yöntemi kullanılarak yaklaşık 23 mm'lik bir tümör dokusunun tahrip edilebileceğini göstermiştir. Azot protoksit gazı, sıvı azot ile karşılaştırıldığında soğutucu gaz olarak kullanıldığı zaman, 23 mm'lik bir tümör dokusunun kısa sürede tahrip edilebileceği göstermiştir. Bu çalışmanın sonuçlarının literatürde bulunan sonuçlar ile uyumlu olduğu görülmüştür.
Anahtar Kelimeler: Kriyo-dondurma, bio-ısı transferi, kanser tedavisi, kan akışı, kan damarları.

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Title: Experimental and Numerical Investigation of Bio-Heat Transfer for Cancer Treatment Using Cryo-Freezing Method

Abstract: In this study, bio-heat transfer in tumorous tissue with and without blood vessel has been investigated experimentally using cryo-freezing method for cancer treatment. Investigated parameters are the mass flow rate of blood in vessel and vascular structure. Study is carried out for nine different blood flow rate values 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. Beef liver is used as a biological tissue. Nitrogen protoxide (N_2O) gas passing through a cryoprobe with inner diameter of 5 mm is employed as refrigerant. Results show that the desired freezing region obtained in tumorous tissue with vessel develops later than the tumorous tissue without vessel. The size of freezing region decreases with increasing mass flow rate of blood and vessel inner diameter. It is seen that vessel in a tissue and branched of vessel result in decreasing freezing region size. The large blood vessel located near the tumorous tissue affects the freezing time to destroy the tumor. Results indicate that a tumorous tissue about 23 mm may be destroyed using cryo-freezing method when nitrogen protoxide gas is used. It is seen that a 23 mm tumorous tissue may be destroyed in a short time when nitrogen protoxide gas is used as refrigerant gas compared to liquid nitrogen. The results of present study agree with the literature results.

Keywords: Cryo-freezing, bio-heat transfer, cancer treatment, blood flow, blood vessels.

1- Projenin Amacı ve Kapsamı

(En fazla 1 sayfa olmalıdır.)

Tümör büyümesi sıklıkla büyük kan damarlarının üzerinde veya yakınında oluşmaktadır. Tümör oluşumunun cerrahi olarak yok edilmesi ve aynı doku bölgesinde tekrarlanmaması ve başka dokulara yayılmaması arzu edilir. Kriyocerrahi en az nüks etme ve hastanede kalış süresi kısa olan kanser tedavisi olması nedeniyle, kullanılması sıklıkla çekici bir seçenek olarak görülmektedir. Yapılacak olan bu çalışmada ise, kriyo-dondurma yöntemiyle yapılan kanser tedavisi esnasında tümörlü bir dokuya yakın bir bölgede bulunan termal etkinliği diğer damarlara göre ihmal edilemeyecek kadar büyük kan damarlarındaki bio-ısı transferinin dokular için sıcaklık ve dondurulan bölgedeki donma alanı büyüklüğüne olan etkisini tespit etmek için deneysel çalışma yapılması amaçlanmıştır. Bu çalışma sonucunda, klinisyenlere dondurulacak tümörlü bölgenin dondurulması için gerekli olan zaman hakkında bilgi verilmesi amaçlanmaktadır. Bu amaca ulaşmak içinde tümörün büyüklüğü (dondurulacak bölgesinin büyüklüğü), kan damarının dondurulacak bölgeye olan uzaklığı, kullanılacak azotprotoksit (N_2O) gazı debisi ve kullanılan prob ucu çapı hakkında bilgi verilmiştir.

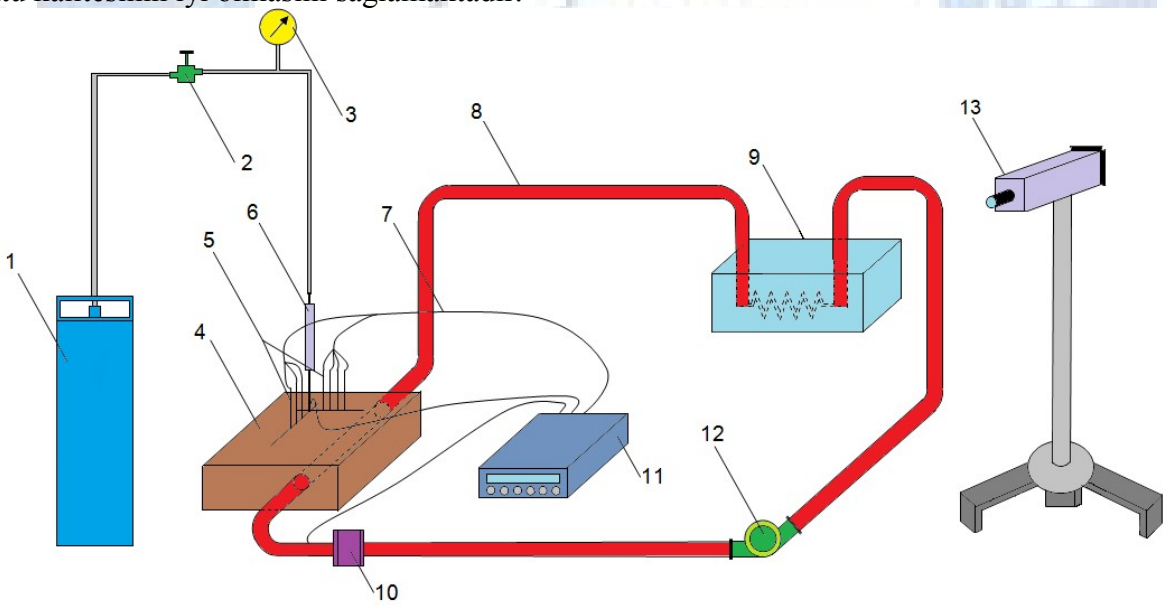
Bunun için, içerisinde azotprotoksit (N_2O) gazı bulunan basınçlı tüpü, akış, sıcaklık ve basınç kontrol cihazları, kriyoproblar ve peristaltik pompa kullanılmıştır. Bu çalışmanın sonunda elde edilen teorik anlayış ile kriyocerrahi prosedürlerinin tasarımı yapılarak, klinisyenlerin termal olarak önemli kan damarlarının yakınındaki tümörlerin kriyoterapi ile yok edilmesi etkinliğini arttırmak için daha iyi bir tedavi planının hazırlamasına yardımcı olunulması amaçlanmaktadır. Kriyo-dondurma işleminin başarı ile gerçekleştirilebilecek tıbbi operasyonlar sonucu hastaların iyileşme yüzdesinin arttırılabilmesi amaçlanmaktadır.

Projenin sonuçlanması ile bu konuda bilim insanlarının yetişmesi sağlanmış olacaktır. Bu konuda yapılan çalışma diğer araştırmacıları da cesaretlendirecektir. Böylesine önemli bir konuda çalışmaların artması ile pahalı tedavi yöntemi olan kemoterapiye alternatif bir yöntem ülkemizde de uygulanmaya başlanmış olacak ve ülke ekonomisine büyük katkıları sağlanmış olacaktır. Kanser tedavisinde kriyo-dondurma yöntemi henüz ülkemizde uygulanmaya başlamamıştır. Bu yöntemin uygulanmaya başlanılması ile daha mutlu ve sağlıklı bir toplum öngörülmektedir. Kriyo-dondurma yönteminin ülkemizde yaygınlaşması ile birlikte gerekli araç ve gereçlerin temin edilmesi hususunda sanayide bu alanda bir canlanma sağlanacaktır ve bu alanda yeni iş istihdamları ortaya çıkmış da olacaktır.

Yapılan deneysel çalışmada; içerisinde damar bulunan ve bulunmayan tümörlü bir dokuya uygulanan kriyo-dondurma işlemleri için gerçekleştirilmiştir. Biyolojik doku olarak dana karaciğeri kullanılmıştır. Kan damarını taklit etmek için teflon malzemeden yapılmış, iç çapı 2,4, 3,2 ve 4,0 mm olan teflon kanallar ile akışkan olarak kana çok benzeyen su kullanılmıştır. Bütün deneylerde kriyo-dondurma işlemi için soğutucu akışkan olarak içinden azot protoksit (N_2O) gazı geçen 5 mm çaplı kriyoprob kullanılmıştır. Kan akış debisinin 10 gr/dak-1200 gr/dak arasında değişen değerleri için deneyler tekrarlanmıştır. İçerisinde büyük kan damarı bulunan tümörlü doku ile içerisinde kan damarı bulunmayan tümörlü dokuda elde edilen donma alanı karşılaştırıldığında içerisinde kan damarı bulunan tümörlü dokuda elde edilen donma alanının daha geç sürede oluştuğu görülmüştür. İçerisinde kan damarı bulunan tümörlü dokuda elde edilen donma alanları da birbiriyle karşılaştırıldığında tümör yakınında bulunan kan damarlarındaki kan akış debisi, damar ve dallanmış damar sayısı ile damar çapı arttıkça tümörü yok etmek için elde edilmek istenen donma alanı büyüklüğü azalmıştır.

2- Projenin Materyal-Yöntemi

Kullanılan deneysel düzeneğin şematik bir diyagramı Şekil 1'de gösterilmektedir. Kriyodondurma işlemi için bir kriyo terapi cihazı (Üzümcü KRY-10S) kullanılmıştır. Basınçlı azotprotoksit tüpü, iğne valfi, manometre ve kriyoprob tabancasından oluşan söz konusu cihazda; basınçlı azotprotoksit gazı (N_2O), bir iğne valfi tarafından kontrol edilen bir silindirde depolanmıştır. Tüp basıncı ise bir manometre ile kontrol edilmektedir. Valf açıkken azotprotoksit, kriyoprob tabancası içinde bulunan bir iç tüpten geçerek kriyoprobun dış duvarı ile iç boru arasında bir ara tabakadan akmıştır. Kriyoprobun ucundan yaklaşık -90 ^{o}C'de geçtikten sonra etkisi sıfırlanarak sıcaklığı artan ve basıncı düşen azotprotoksit manometre çıkışında dış ortama atılmıştır. Kriyoprob ile kan ve ortam sıcaklığını ölçmek için iki, numune sıcaklıklarını ölçmek için on T-tipi termokapul prob kullanılmıştır. Termokapul sondaları tarafından okunan değerler, soldan sağa 1 ile 10 arasında etiketlenmiş numaralarıyla belirtilmiştir. Bitişik termokapullar arasındaki mesafe 3 mm iken, kriyoproba en yakın termokapul probu 5 mm uzaklıkta alınmıştır. Veriler, bir veri kaydedici (Agilent 34970A) tarafından dijitalleştirilmiştir. Deneyde, sıcaklık okumaları bu veri kaydedicinin bağlı olduğu bir masaüstü bilgisayarda yapılan ayarlar sayesinde 2 dakikada bir her 10 saniyede kaydedilmiştir. Ayrıca mevcut deneydeki geçici sıcaklık dağılımını görüntülemek için (Testo 882) termal görüntüleyici kamera (Gazi Üniversitesi Makine Mühendisliği envanterinde bulunan) kullanılmıştır. Bu termal görüntüleme ekipmanı, ortam sıcaklığını minimum 0,1 ^{o}C aralıklarla, alt ölçüm sınırı olarak -20 ^{o}C'ye kadar sıcaklık ölçümü yapmaktadır. Bu termal kamera, geniş mesafelerden doğru odaklanabilir. Deneyler sırasında termal kamera test edilecek nesnenin önüne yerleştirilmiştir ve kamera ile nesne arasındaki dikey mesafe yaklaşık 80 cm seçilmiştir. Fotoğraf makinesinin içine yerleştirilmiş otomatik odaklama lensi, görüntü kalitesinin iyi olmasını sağlamaktadır.

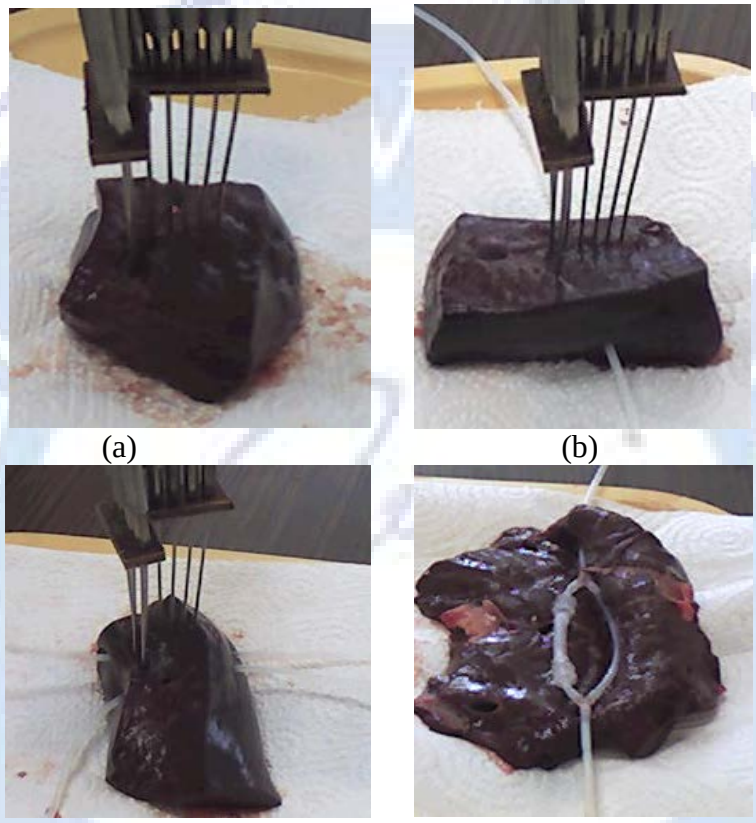


1. Basınçlı azotprotoksit tüpü
2. İğne valfi
3. Manometre
4. Doku (dana karaciğeri)
5. Termokapul problar
6. Kriyoprob tabancası
7. Termokapullar
8. Teflon kanal
9. Soğutmalı sirkülatörlü su banyosu
10. Sıvı akış metresi
11. Veri kaydedici
12. Peristaltik pompa
13. Termal Kamera

Şekil 1. Deney setinin şematik gösterimi

Piyasadan temin edilen dana karaciğerleri, kriyojenik dondurma işlemini ve damar dallarının yapısını araştırmak için in-vitro deneylerde numune olarak kullanılmıştır. Teflon kanallar, damarlardaki

kan akımının benzetimini yapmak için kullanılmıştır. Üzerinde deney yapılan ve içerisinden damar geçmeyen, tek damar, çift damar ve dallanmış damar geçen dana karaciğeri numuneleri ile bunların şematik görünümleri Şekil 2'de gösterilmiştir. Suyun ve teflon kanalın maddesel özelliklerinin kana ve kan damarına benzemesinden dolayı kan akışının termal etkisini araştırmak için teflon kanalda dolaşan su kullanılmıştır. Deneylerde insan karaciğerindeki kan damarlarını taklit etmek iç 3 farklı çapa sahip teflon kanallar ile bu kanalları dallandırıp çaplarını büyütüp küçültebilmek için çap düşürücüler ve eşit bacaklı Y konnektörler kullanılmıştır. Litaratürde bu şekilde çap düşürücü veya Y konektör kullanılan bir çalışmaya rastlanılmamıştır.

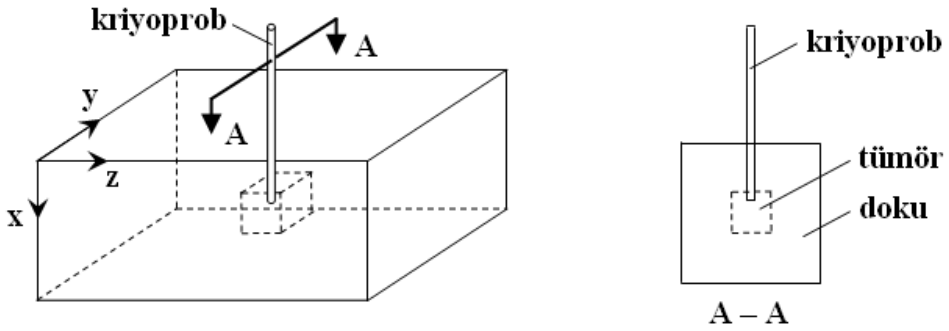


Şekil 2. Üzerinde deney yapılan (a) damarsız, b) tek damarlı, c) çift damarlı ve d) dallanmış damarlı) dana karaciğeri numuneleri

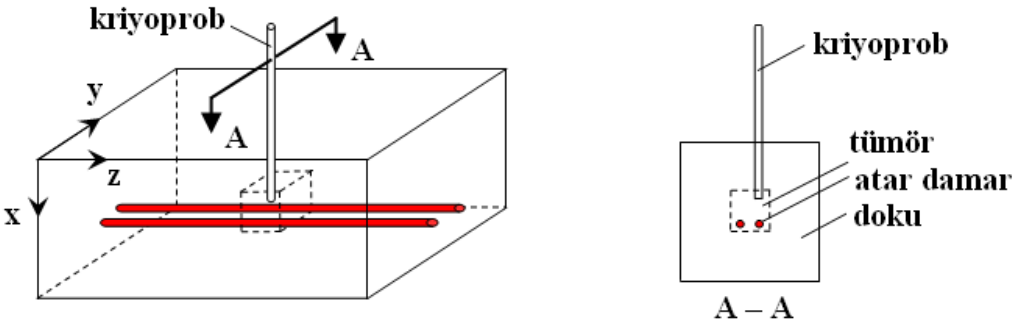
Sirkülatörlü su banyosu vasıtasıyla (Thermo Fisher Scientific SC100-S6T) sıcaklığı insan kanının normal sıcaklığı olan 37^{o}C de sabit tutulan su, kalbin kanı pompalama şeklini taklit etmek için bir peristaltik pompa (Watson-Marlow 323 S/D) vasıtasıyla teflon kanal içine pompalanmıştır. Sirkülatörlü su banyosunda laboratuvar ortamında üretilen saf su kullanılmıştır. Giriş ve çıkış ucu sirkülatörlü su banyosuna daldırılmış olan teflon kanal 3 roller'lı peristaltik pompa başlığına bağlanmıştır. Bu sayede deneyde sürekli olarak bir su sirkülasyonunun dolaşması sağlanmıştır. Peristaltik pompa ile 1 rpm hassasiyetle 3-400 rpm aralığında dijital ayarlı hız kontrolü sağlanmaktadır. Deneylerde kullanılacak kan akış hızı yani debisi normal bir yetişkin insanın karaciğerinde akan kanın hızına uygun olacak şekilde seçilmiştir. Deneyler toplam 9 farklı kan akış debisi için tekrarlanmıştır.

3- Projenin Bulguları

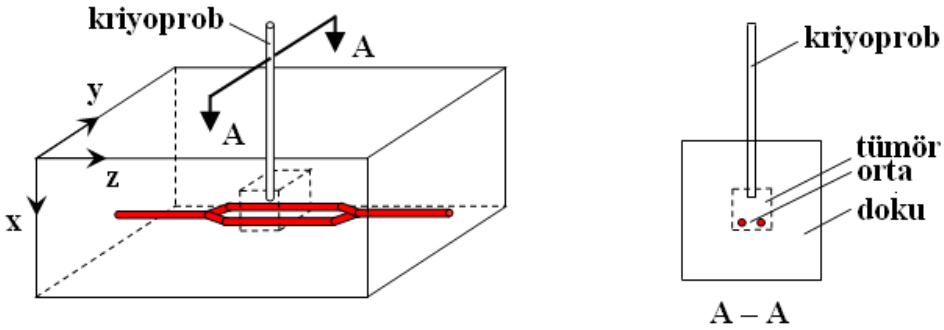
Mevcut deneysel çalışma ile literatürde elde edilen deneysel sonuçlara ulaşılabileceği gösterildikten sonra bu deneysel çalışmanın özgünlüğünü ortaya koymak için literatürden farklı olarak kriyo-dondurma yöntemiyle yapılan kanser tedavisi esnasında, tümörlü dokuya yakın bir bölgede bulunan büyük kan damarları içinden akan kanın farklı debilerinde farklı damar çapları sahip tek atar damar, çift damar ve dallanmış atar damarların bio-ısı transferinin tümörü yok etmek için gerekli donma alanı büyüklüğüne etkisi çeşitli deneyler yapılarak incelenmiştir. Yapılan deneylerin şematik görünümleri aşağıdaki şekillerde gösterilmiştir.



Şekil 3. İçerisinde damar bulunmayan dana karaciğeri dokusuna uygulanan kriyo-dondurma işleminin şematik görünümü



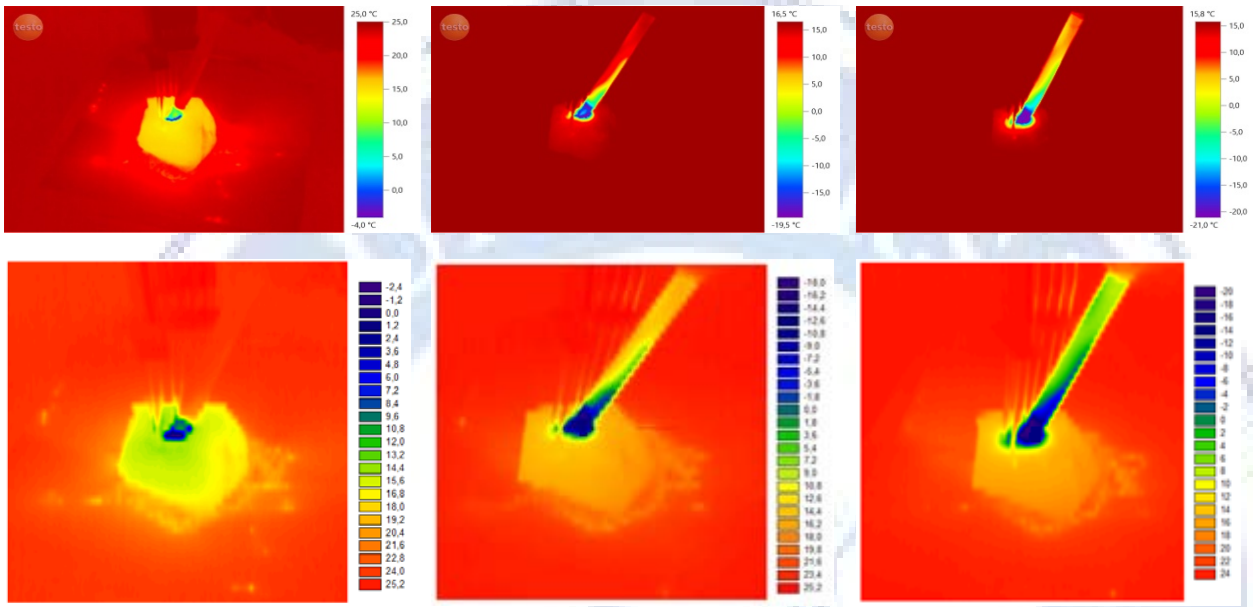
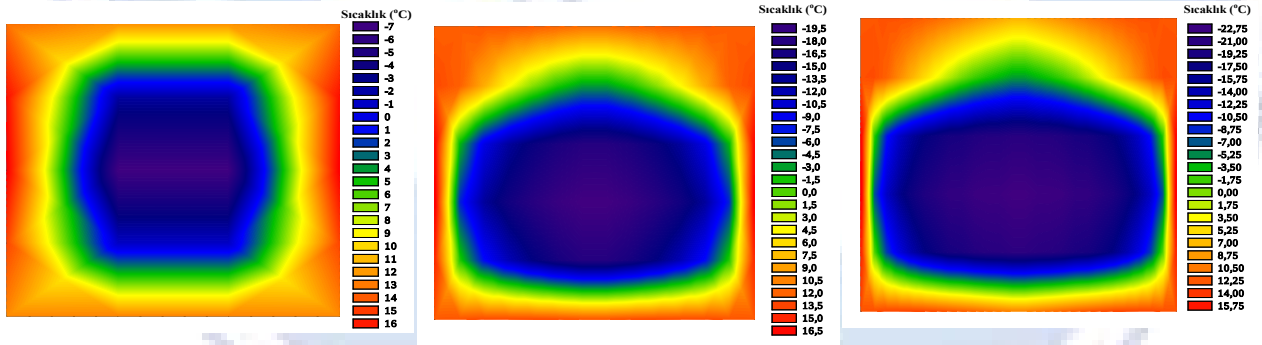
Şekil 4. İçerisinden paralel damar çifti geçen tümörlü bir dokuya uygulanan kriyo-dondurma işleminin şematik görünümü



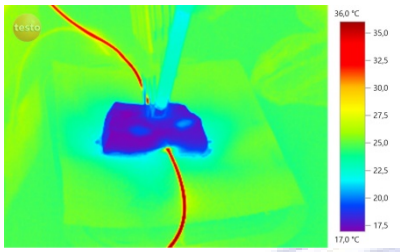
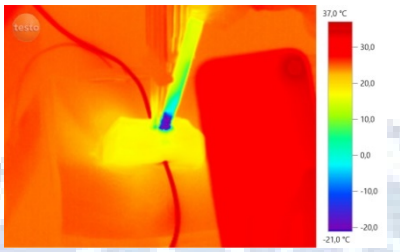
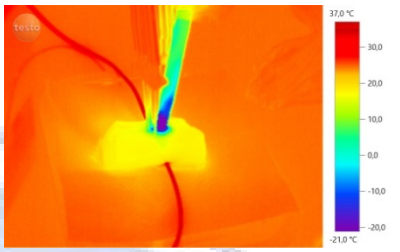
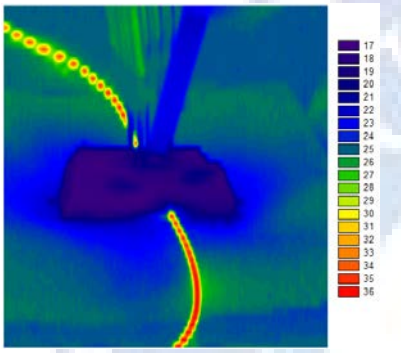
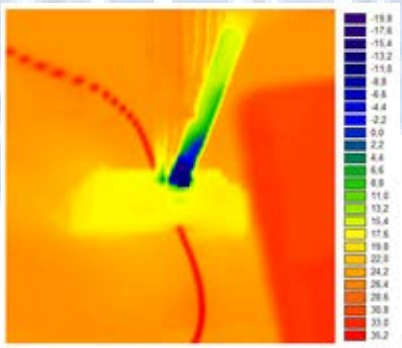
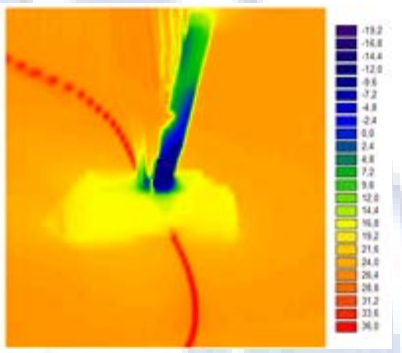
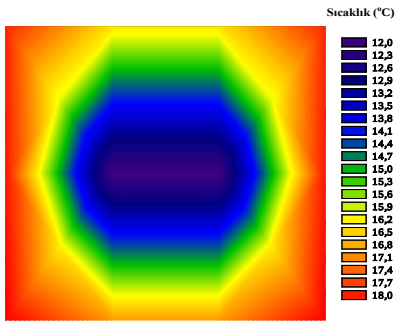
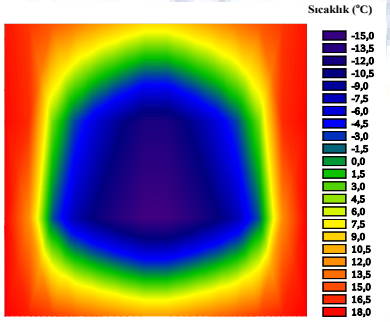
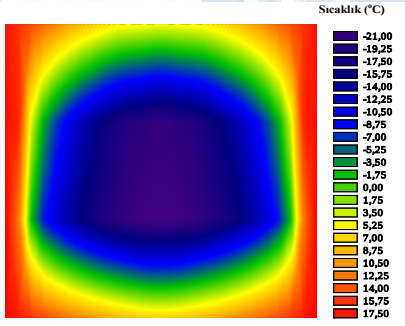
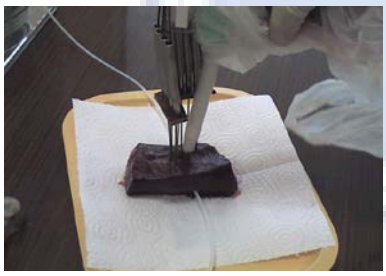
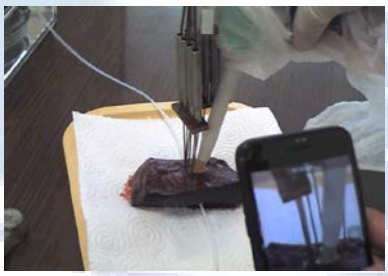
Şekil 5. İçerisinden iki dallı dallanmış damar geçen tümörlü bir dokuya uygulanan kriyo-dondurma işlemlerinin
(Dallanmış damarın a)1. çatal, b) orta ve c) 2. çatal bölgesi) şematik görünümü

İçerisinde damar bulunmayan, tek damar ve dallanmış damarlar bulunan dana karaciğeri üzerinde yapılan deneylere ait sonuçların birer örneği aşağıdaki tablolarda gösterilmiştir.

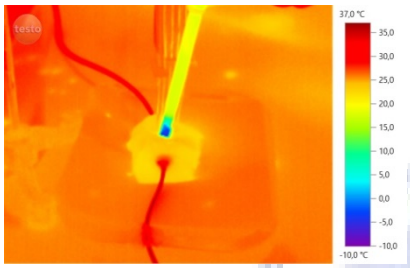
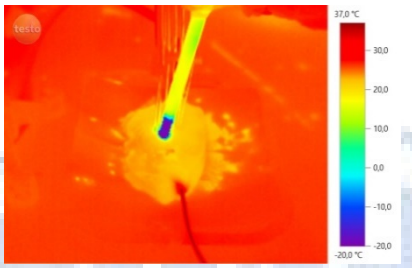
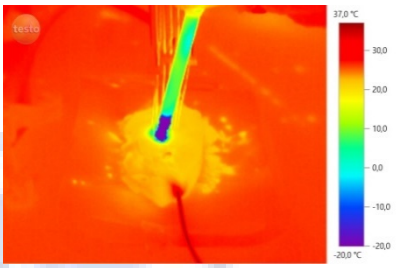
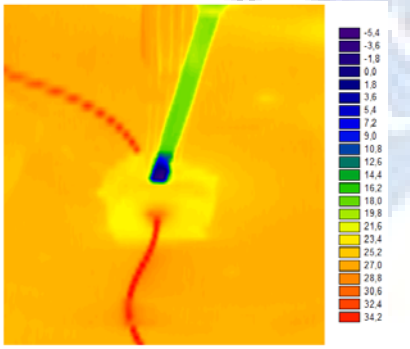
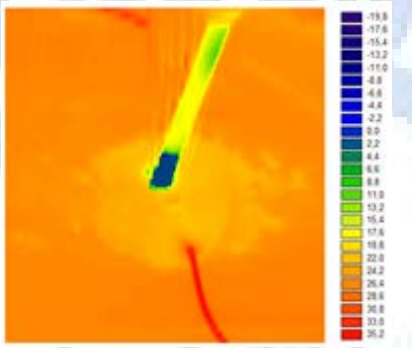
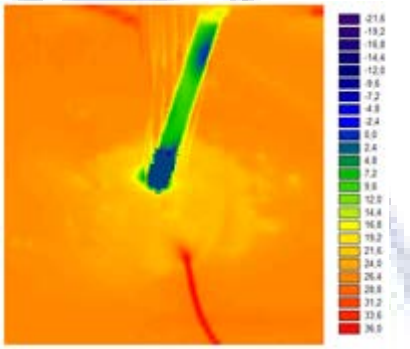
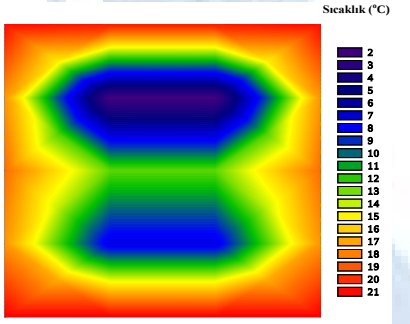
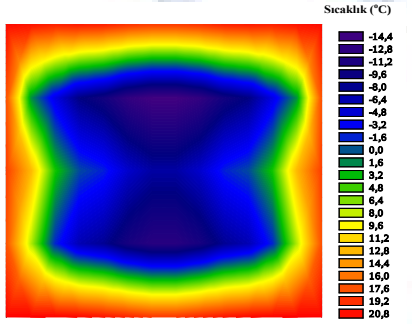
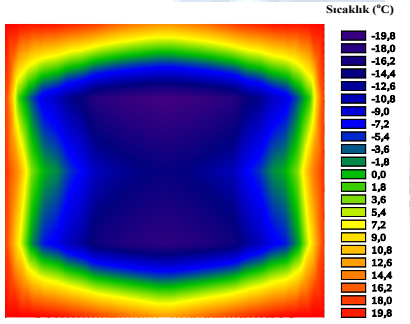
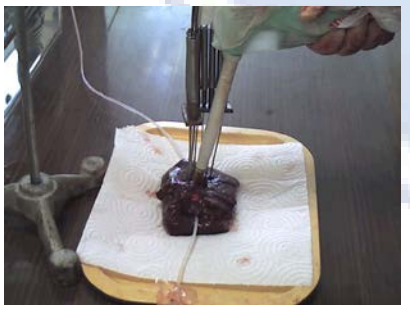
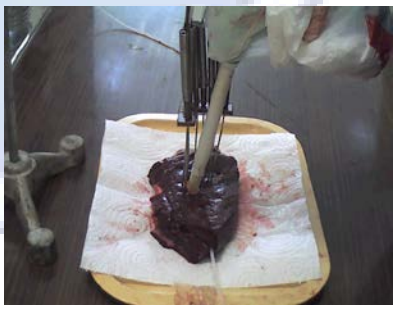
Tablo 1. İçerisinde Damar Bulunmayan Karaciğer Dokusuna Uygulanan Kriyo-Dondurma İşleminin 10., 60. ve 120. Saniyesi Sonunda Elde Edilen Sonuçlar

10. Saniye	**60. Saniye**	**120. Saniye**
		
D_{da} = 0,00 mm	D_{da} = 21,53 mm	D_{da} = 23,00 mm
		
		

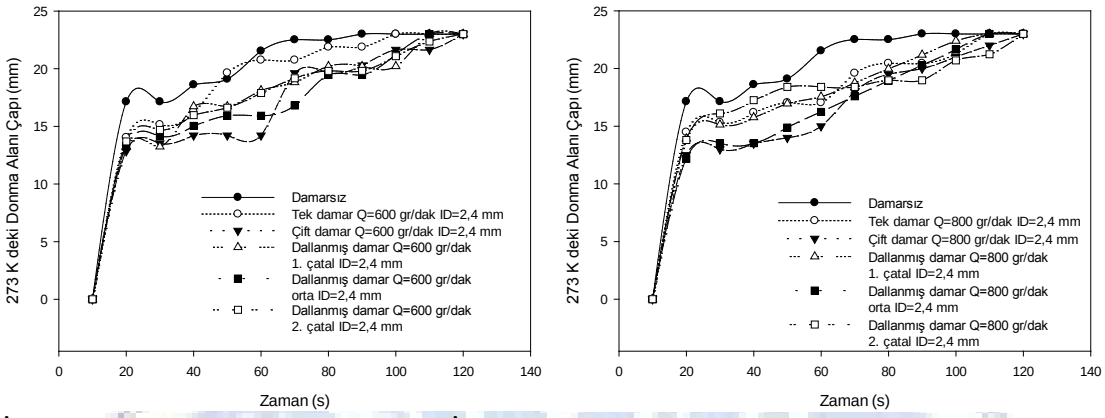
Tablo 2. İçinden 600 gr/dak Debi ile Kan Akan ve 2,4 mm'lik İç Çaplı Tek Damar Geçen Karaciğer Dokusuna Uygulanan Kriyo-Dondurma İşleminin 10., 60. ve 120. Saniyesi Sonunda Elde Edilen Sonuçlar

10. Saniye	**60. Saniye**	**120. Saniye**
		
		
D_{da} = 0,00 mm	D_{da} = 20,75 mm	D_{da} = 23,00 mm
		
		

Tablo 3. İçinden 600 gr/dak Debi ile Kan Akan ve 2,4 mm'lik İç Çapa Sahip İki Dallı Dallanmış Damar Geçen Karaciğer Dokusunda Dallanmış Damarın Orta Bölgesine Uygulanan Kriyo-Dondurma İşleminin 10., 60. ve 120. Saniyesi Sonunda Elde Edilen Sonuçlar

10. Saniye	**60. Saniye**	**120. Saniye**
		
		
D_{da} = 0,00 mm	D_{da} = 15,92 mm	D_{da} = 23,00 mm
		
		

a) **b)**



Şekil 6. İçerisinde Damar Bulunmayan ve İçinden (a) 600 gr/dak, b) 800 gr/dak) Farklı Debilerle Kan Akan ve Birinin 2,4 mm'lik İç Çapa Sahip Tek, Çift ve Dallanmış Damar Geçen Karaciğer Dokusunda 120 Saniye Boyunca Uygulanan Kriyo-Dondurma İşlemi Sonunda Elde Edilen Donma Alanı Çaplarının Değişimi

Şekil 6'da içerisinde damar bulunmayan ve içinden a) 600 gr/dak, b) 800 gr/dak debi ile kan akan, 2,4 mm'lik iç çapa sahip tek ve birbirine paralel damar çifti iki dallı dallanmış damar geçen ve dallanmış damarların 1. çatal, orta ve 2. çatal bölgeleri üzerinde bulunan dana karaciğer dokusunda elde edilen donma alanı çaplarının değişimi gösterilmektedir.

Burada damarların ısı transfer yüzeyi ele alındığında en çok ısı transfer yüzeyi birbirine paralel damar çiftinde ve dallanmış damarın çift damar etkisi göstermesi nedeniyle iki dallı dallanmış damarın orta bölgesinde bulunmaktadır. Ancak paralel damar çiftinde dolaşan kan dokudan çıkarken kriyo-dondurma işleminden kaynaklı olarak sıcaklığı düşer. Aynı damar, dokuya girdiği akış yönüne ters akışlı olarak, ilk durumda dokudan çıktığı bölgeden tekrar dokuya girmektedir. Yeniden dokuya giren düşük sıcaklıklı damarın dokuya olan bio ısı transferi azalmaktadır. İki dallı dallanmış damarda ise damar doku girişinde aynı akış yönünde ikiye dallanıp doku çıkışında tekrar birleşerek dokuyu terk etmektedir. Paralel damar çiftinden farklı olarak tekrar dokuya dönmemektedir. Bu nedenle iki dallı dallanmış damarın orta bölgesinden dokuya olan bio ısı transferi paralel damar çiftine göre daha fazladır. İki dallı dallanmış damarın 1. çatal ve 2. çatal bölgelerindeki ısı transfer yüzey alanı tek damara göre daha fazladır ancak paralel damar çiftine ve iki dallı dallanmış damarın orta bölgesine göre de daha azdır. Damarların ısı transfer yüzey alanı arttıkça damardan dokuya olan bio ısı transferi de artmaktadır.

Damar içinde akan kan miktarı ele alındığı paralel damar çiftinde ve iki dallı dallanmış damarın orta bölgesinde akan kan miktarı aynı olup tek damarda ve iki dallı dallanmış damarın 1. ve 2. çatal bölgelerinde akan kan miktarından fazladır. Tek damar içinden akan kan miktarının iki katıdır. Damar içinde akan kan miktarı arttıkça dokuya olan bio ısı transferi de artmaktadır.

Bundan dolayı damarların ısı transfer yüzey alanı ve damar içinde akan kan miktarı arttıkça damardan dokuya olan bio ısı transferi artmaktadır. Bio ısı transferi arttıkça da elde edilmek istenen donma alanı çapı azalmaktadır. Yapılan deneyler sonucunda sabit kan debisi şartı altında bio ısı transferi en fazla iki dallı dallanmış damarın orta bölgesinde elde edilmiş olup paralel damar çiftine, iki dallı dallanmış damarın 1. çatal ve 2. çatal bölgelerine ve tek damara gidildikçe azalmıştır. Buna paralel olarak aynı süreler içinde donma alanı çapı en az iki dallı dallanmış damarın orta bölgesinde elde edilmiş olup paralel damar çiftine, iki dallı dallanmış damarın 1. çatal ve 2. çatal bölgelerine ve tek damara gidildikçe artmıştır. Damarsız karaciğer dokusunda ise maksimum seviyeye ulaşmıştır.

4- Projenin Sonucu ve Öneriler

Bu çalışmanın günümüzde en önemli sağlık sorunlarından birisi olan kanser hastalığının tedavi edilmesinde ülkemiz tıp endüstrisine önemli katkılarının olacağı düşünülmektedir. Makine mühendisliğinin uzmanlık alanında, Dünyada kriyo-dondurma yöntemiyle yapılan kanser tedavisi konusunda çok az akademik çalışma yapılmış olup henüz ülkemizde bu konuda akademik bir çalışmaya rastlanılmamıştır. Bu araştırmada makine mühendisliği açısından optimum kriyo-dondurma işlemi için gerekli şartlar belirlenerek kriyo-dondurma işleminin cerrahlar için özelleştirilmiş bir uygulama planı içinde yapılmasının sağlanması için literatüre katkıda bulunulacaktır. Diğer tedavilere göre uygulanışı oldukça kolay ve klasik yöntemler kadar başarılı sonuçlar elde edilen yöntem sayesinde, yaşı veya mevcut hastalıkları (diabet, hipertansiyon, kalp-damar hastalıkları gibi) nedeniyle ameliyat edilemeyen hastalar da tedavi olma şansına sahip olacaklardır. Etkili ve ekonomik bir yöntem olan Kriyo-dondurma yönteminin ülkemizde geliştirilmesiyle pahalı olan diğer kanser tedavisi yöntemlerine kıyasla ülke ekonomisine önemli ölçüde katkıda bulunulacaktır.

Bu projenin sonuçlanması ile bu konuda bilim insanlarının yetişmesi sağlanmış olacaktır. Ayrıca, bu çalışma ülkemizde bu konuda çalışacak araştırmacılar için bir ön çalışma olmuş olacaktır. Bu konuda diğer araştırmacıları da cesaretlendirecektir. Böylesine önemli bir konuda çalışmaların artması ile pahalı tedavi yöntemi olan kemoterapiye alternatif bir yöntem ülkemizde de uygulanmaya başlanmış olacak ve ülke ekonomisine büyük katkıları sağlanmış olacaktır. Kanser tedavisinde kriyo-dondurma yöntemi henüz ülkemizde uygulanmaya başlamamıştır. Bu yöntemin uygulanmaya başlanılması ile daha mutlu ve sağlıklı bir toplum öngörülmektedir. Kriyo dondurma yönteminin ülkemizde yaygınlaşması ile birlikte gerekli araç ve gereçlerin temin edilmesi hususunda sanayide bu alanda bir canlanma sağlanacaktır ve bu alanda yeni iş istihdamları ortaya çıkmış da olacaktır.

5- Geleceğe İlişkin Öngörülen Katkılar

Söz konusu deneysel çalışmayı yapılabilmek için gerekli araç ve gereçler belirlenerek bunlarla ilgili detaylar tamamlanmış ve Mayıs 2017 ayı başında BAP projesine başvuru yapılmıştır.

Mayıs 2017 ayı başında başvurulan BAP projesi Gazi Üniversitesi BAP Birimince onaylanarak Eylül 2017 tarihinde yürürlüğe girmiştir.

Eylül 2017 tarihinden itibaren BAP projesi kapsamında yer alan makine ve teçhizatlar için Üniversite bünyesinde doğrudan temin ilanlarınna çıkılmıştır. Yaklaşık 1 haftalık ilan süresi sonucunda BAP birimine gelen teklifler değerlendirilmiş, BAP bütçesinin kısıtlı olması nedeniyle pazarlıklar yapılmış ve deneysel çalışmalar için tüm makine ve techizatlar için ilgili firmalara siparişler verilmiştir.

Sipariş verilen firmaların tamamı yerli firmalar olmasına rağmen bazı firmaların istenilen makine ve techizatları yurt dışından sipariş ettiği ve makinaların gemi ile geleceği ve gümrük işlemlerinin süre alabileceği konusunda bilgi alınmıştır.

Verilen bu siparişlerden yurt dışından gelen 1 adet soğutma sirkülatörü, 3 farklı tip teflon kanal kanal Nisan 2018 tarihinde temin edilebilmiştir. Deneysel çalışma için gerekli tüm makine ve teçhizat temin edildikten hemen sonra organik olduğundan ve uzun süre muhafaza edilemeyeceğinden en sona bırakılan dana karaciğeri ilanına çıkılmıştır. Deneyde kullanılacak dana karaciğeri Mayıs 2018 tarihinde temin edilmiştir.

Ayrıca BAP projesinin kısıtlı bir bütçeye sahip olmasından dolayı BAP projesi kapsamında bir termal kamera temin edilememiştir. Makine Mühendisliği Bölümümüz envanterine kayıtlı olan ve Prof. Dr. Nuri YÜCEL hocamız tarafından temin edilerek kullanılan termal kamera hocamızdan ödünç alınarak deneylerde kullanılmıştır.

Mayıs 2018 tarihinde deneyde kullanılacak bütün makine ve teçhizat temin edilmiş ancak Haziran 2018 tarihi sonuna kadar yapılmak istenen deneylerin alt yapısı ve birkaç deneme deneyi yapılabilmiştir. Aralık 2018 tarihinde Tez İzleme Komitenize bu tezin deneysel aşaması detaylı bir şekilde anlatılarak sunulmuştur.

Haziran-Ekim 2018 tarihleri arasında deney düzeneğindeki bazı sorunlar giderilmiş deney düzeneğinin alt yapısı tamamen sorunsuz bir şekilde kurularak tasarlanan bütün deneyler yapılmıştır. Yapılan deneysel çalışmada elde edilen sonuçlar ile ilgili Şubat 2019 tarihinde bir bildiri yayınlanmış ve aynı ay içerisinde bir makale hazırlanarak uluslararası hakemli SCI-Expanded indeksli bir dergiye gönderilmiştir. Hazırlanan makale yaklaşık 3 aydan bu yana hakem değerlendirmesinde bulunmaktadır.

6- Kaynaklar

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7- Ekler

a. Proje Bütçesi (Harcamalar tablo halinde verilmelidir.)

Proje Süresi: 24 (Ay)				
Başlama Tarihi	**Bitiş Tarihi**	**Ek Süre (Ay)**	**Ek Süre Dahil Bitiş Tarihi**	**Toplam Proje Süresi (Ay)**
16.06.2017	30.06.2019	---	30.06.2019	24

Proje Bütçesi: 24.624,22-TL		
Harcanan	**Kalan**	**Ek Bütçe**
24.624,00-TL	0	

b. Makine –Teçhizatın Konumu, Anabilimdalı/ Bölüm/ Fakülteye Devir Bilgisi ve devir yapıldığına dair taşınır işlem fişi)

Fakülte ayniyat bürosu tarafından demirbaşların Devir Bilgisine ait bir yazının verilemeyeceği ifade edilmiştir.

c. Bilimsel ve teknik ayrıntılar

d. Sunumlar (Kongre ana web sayfası, Düzenleme ve Bilim Kurulu üyeleri çıktısı, sunum tam metni, teşekkür yazısı)

Bu deneysel çalışmada deneyler Aralık 2018 tarihinde tamamlanmış ve elde edilen sonuçların içerdiği bir bildiri hazırlanmış ve 18-20 Ocak 2019 tarihleri arasında Gaziantep ilinde gerçekleştirilmiş Zeugma 2. Uluslararası Multidisipliner Çalışmalar Kongresi'ne katılım sağlanmıştır. Katılım sağlanan bilimsel kongrede 18.02.2019 tarihinde **"THE EFFECT OF LARGE BLOOD VESSEL ON BIO-HEAT TRANSFER IN CANCER TREATMENT BY CRYO-FREEZING METHOD" (**Zeugma 2. Uluslararası Multidisipliner Çalışmalar Kongresi ISBN 978-605-7875-00-6, Cilt 1, Sayfa 61-68**)** başlıklı bildirinin tam metni yayımlanmıştır.

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Hazırlanan bildirinin tam metni aşağıda sunulmaktadır.

ZEUGMA

II. ULUSLARARASI

MULTİDİSİPLİNER ÇALIŞMALAR KONGRESİ

18-20 Ocak 2019

Gaziantep



TAM METİN KİTABI

CİLT - 1

Editörler

Dr. Tural MEHMETOĞLU

Zhuldyz SAKHI

ISBN 978-605-7875-00-6

TAM METİN KİTABI

ZEUGMA II. ULUSLARARASI MULTİDİSİPLİNER ÇALIŞMALAR KONGRESİ

18-20 OCAK 2019
GAZİANTEP /TÜRKİYE

Editörler
Dr. Tural MEHMETOĞLU
Zhuldyz SAKHI

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TARİHİ VE YERİ

18-20 Ocak 2019, GAZİANTEP

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THE EFFECT OF LARGE BLOOD VESSEL ON BIO-HEAT TRANSFER IN CANCER TREATMENT BY CRYO-FREEZING METHOD

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ABSTRACT

In this study, the effect of mass flow rate of blood on bio-heat transfer in tumorous tissue with and without blood vessel during cancer treatment of cryo-freezing method was investigated experimentally by using temperature and flow measurements for tissue with different vascular structures. Experiments were repeated for cryo-freezing applied to a tumor tissue with and without arteries. Beef liver was used as a biological tissue. Teflon ducts with internal diameter of 2.4 mm were used to simulate the blood vessel. Water was employed as fluid which is very similar to blood. Nitrogen protoxide (N_2O) gas passing through a cryo-probe with a diameter of 5 mm was used as refrigerant. Experiments were repeated for four different blood flow rate values ranging from 10 gr/min to 128 gr/min. When the frozen tissues obtained in the tumor tissue with no blood vessel and with large blood vessel are compared, it is seen that the freezing area obtained in the tumor tissue with blood vessel develops later. Results show that the desired freezing region size to destroy tumor reduces when the blood flow rate in the blood vessels increases. It is seen that the large blood vessel located near the tumor play an important role on the time of acquisition of the desired freezing region size to destroy the tumor. The accuracy of the results obtained in this study was confirmed by comparing the thermal graphs of cryo-freezing processes applied to the tissue with large blood vessels which are present in the literature.

Keywords: Cryo-freezing, Bio-heat transfer, Cancer treatment, Blood flow, Large blood vessels.

1. INTRODUCTION

The growth of tumor occurs frequently on or near some large blood vessels. It is desirable that the tumor formation near the vessel should be destroyed surgically and not be repeated in the same tissue region and not be spread to other tissues.

Cryotherapy, one of the methods of cancer treatment, is an effective medical treatment method used to destroy the tumor by providing freezing in the biological tissue by means of cryoprobes. It is considered as a good treatment option because of least relapsing and short time staying in hospital. Being fast, easy to apply and cheap are the important advantages of this treatment. It can be conducted under policlinic conditions, and it does not require anesthesia.

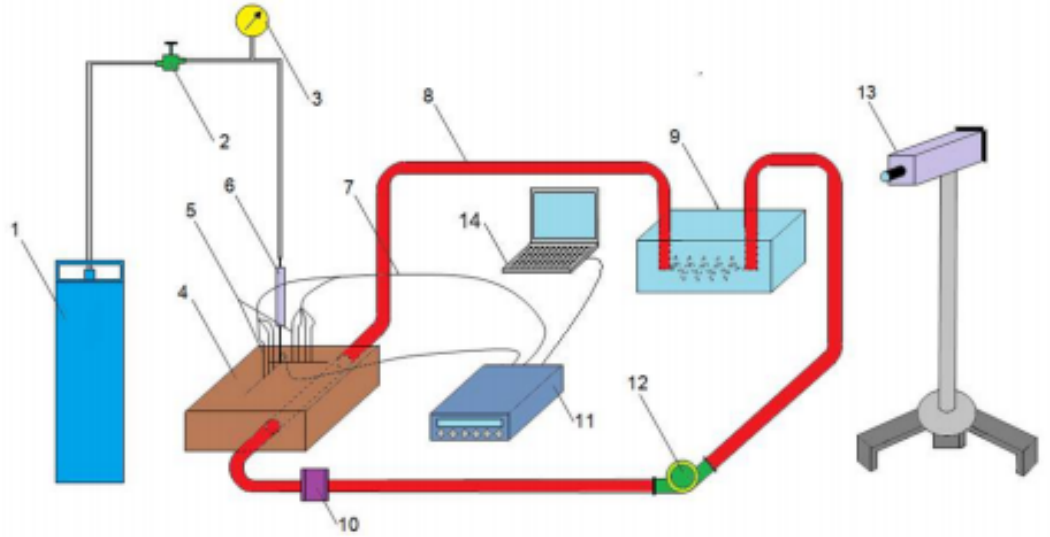
The risk of bleeding after the procedure is extremely low, and it does not require any changes in normal life. There is no negative effect on the potential of reproduction. The risk of serious injury or complications is extremely low. This treatment method has been used in the world to destroy the prostate and liver tumors.

Literature survey shows that cancer treatment using cryo-freezing method was investigated by many researchers. The cryotherapy treatment was examined numerically using finite difference method by some authors [1-3]. An analytical model was developed to examine a liver tumor cell destruction within the freeze-thaw process in cryotherapy by Chua and Chou [4]. Thermal effects of large vessels during cryosurgery were experimentally and numerically investigated by Deng et al. [5]. A model was developed to investigate the freeze-thaw-heat treatment in a biological system by Chua and Chou [6]. The diameters of the liver main arteries and arter branches were determined for human liver by Silveira et al. [7]. The thermal interactions were analyzed between a single blood vessel and biological tissue surrounding it by Majchrzak and Tarasek [8]. A numerical study was carried out to investigate the irregularly shaped liver tumor by Chua [9]. A lower temperature value is needed to freeze the tissue through the large blood vessel [10]. The first in vivo animal experiments was conducted by Zi-Qıao et al. [11] using a nano-cryosurgical method to freeze completely tumor tissues in which large blood vessels are embedded. A computational cryo-freezing model with a simplified mathematical definition of the vascular network structure was formed by Chua [12]. A multiscaled three-dimensional cell-tissue model was developed by Wang et al [13] for quantitative evaluation of vascular network effects considering the results obtained from cryosurgery and hyperthermia treatments used in cancer treatment.

Literature review shows that there is a lack information on cryo-freezing to destroy the tumor tissue. In this study, the effect of mass flow rate of blood passing through vessel on bio-heat transfer in tumorous tissue has been investigated experimentally. The experiments are carried out using cryo-freezing procedures applied to a tumorous tissue with and without vessels. Beef liver is used as a biological tissue. Teflon channels with inner diameter of 2.4 mm are used to simulate the blood vessel. Water is used as fluid which is similar to blood. A 5 mm diameter cryoprobe with nitrogen protoxide (N_2O) gas is employed as the refrigerant for cryo-freezing procedure. Experiments are repeated for four different blood flow rate values ranging from 10 gr/min to 128 gr/min.

2. MATERIALS AND METHODS

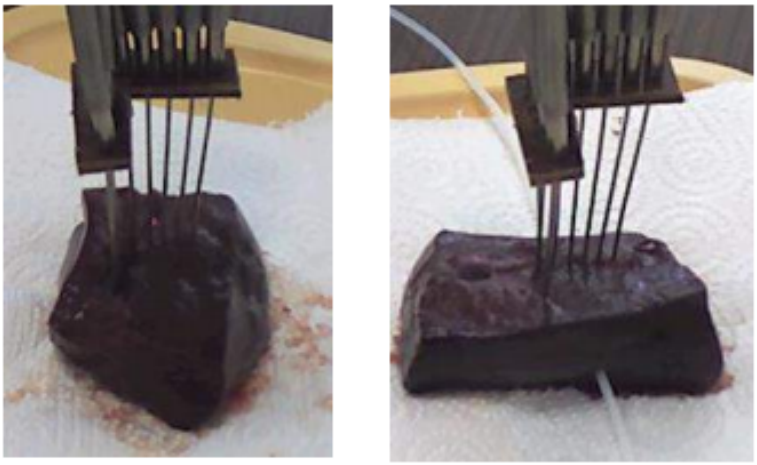
Study is carried out experimentally. A schematic view of the experimental set-up used is shown in Figure 1. A cryotherapy device is used for cryo-freezing procedure. Cryotherapy device consists of a pressurized nitrogen protoxide tube, a needle valve, a manometer and a cryoprobe gun; the pressurized nitrogen protoxide gas (N_2O) is stored in a cylinder controlled by a needle valve. The tube pressure is controlled by a pressure gauge. When the valve is open, the nitrogen protoxide is passed through an internal tube located inside the cryoprobe gun. Then gas flows from an intermediate layer between the outer wall of the cryoprobe and the inner tube. T-type thermocouple probes are used to measure the cryoprobe, tissue and ambient temperatures. Totally twelve thermocouples are used. A datalogger connected to a computer is used to read the thermocouple temperature values. Temperature readings are recorded every 10 seconds for 2 minutes. In addition, a thermal imager camera is used to display the temperature distribution.



1. Pressurized nitrogen protoxide tube
2. Needle valve
3. Manometer
4. Tissue (beef liver)
5. Thermocouple probes
6. Cryoprobe gun
7. Thermocouples
8. Teflon channel
9. Water bath with cooled circulator
10. Fluid flow meter
11. Datalogger
12. Peristaltic pump
13. Thermal camera
14. PC

Figure 1. Schematic view of the experimental set-up

The commercially available beef livers are used as a sample in in-vitro experiments to investigate the cryogenic freezing process. Teflon channels are employed to simulate the blood flow in the vessels [5, 7, 8, 10, 13]. The samples of the beef liver without and with arteries are shown in Figure 2a and 2b, respectively. Teflon channel is very similar to the blood vessel, therefore, teflon channel is employed as blood vessel. Likewise, since the physical properties of the water is very similar to the blood, water is used to investigate the thermal effect of the blood flow in the teflon channel. To simulate the blood vessels in the human liver, teflon channels with inner diameter ID=2.4 mm and outer diameter OD=3.0 mm are used in the experiments [7]. The diameter of the cryoprobe used in this study is 5 mm.



(a) (b)

Figure 2. Beef liver samples (a) without vessel and (b) with single vessel

Water bath is used to kept the temperature of water constant at 37°C similar to normal temperature of the human blood. A peristaltic pump is employed to simulate the pumping blood of heart. Pure water is used. The blood flow rates used in the experiments are selected to be appropriate with the blood flow rates in the liver of a normal adult human [5, 10, 12]. Experimental study is conducted for four different mass flow rates of 10, 30, 79, and 128 gr/min.

Before starting the cryo-freezing procedure, the water kept constant at temperature of 37°C is circulated in the beef liver for 10 minutes to ensure that the experimental starting temperature is stable. Then cryo-freezing procedure is started and lasted for 120 seconds. The size of the freezing region diameter is measured.

Tumors occur more frequently around the arteries. Thus, normal tissue region located on the arteries is assumed to be tumorous tissue to which cryo-freezing is applied. A tumorous tissue with a single blood vessel is shown in Figure 3. The position of the cryoprobe located in tumorous tissue is also shown in Figure 3.

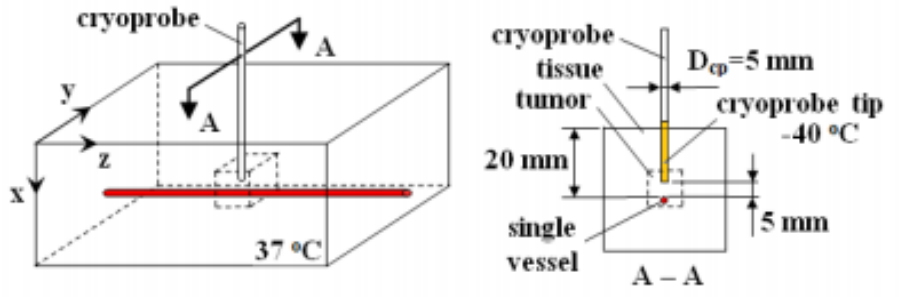
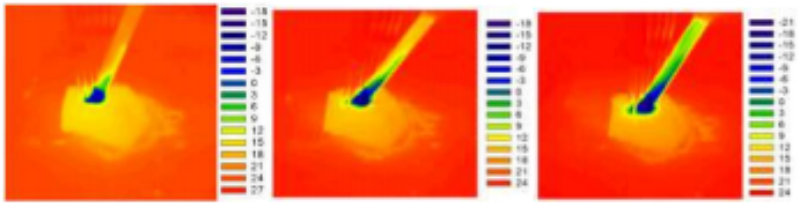


Figure 3. Schematic view of a tumorous tissue with single blood vessel and the position of cryoprobe.

3. RESULTS

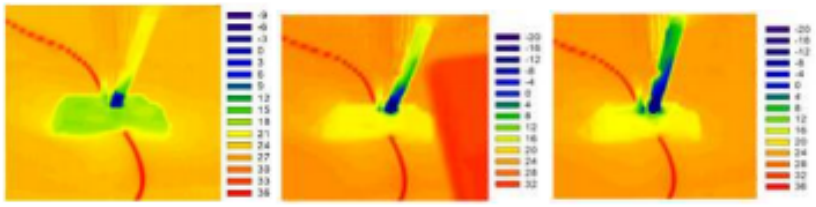
In this study, the effect of mass flow rate of blood on cryo-freezing is investigated experimentally. Study is conducted for a tissue with and without blood vessel. Figure 4 shows the typical freezing regions taken from thermal camera after 30, 60, and 120 seconds for a tumor tissue without vessel. It is seen that cryo-freezing region increases with increasing time. That is, cryo-freezing region diameter after 30, 60, and 120 seconds are 17.13 mm, 21.53 mm and 23 mm, respectively.



30 s 60 s 120 s

Figure 4. Cryo-freezing regions after 30, 60 and 120 seconds for a tumor tissue without vessel.

Similarly, typical cryo-freezing regions taken from thermal camera for a tumor tissue with a single vessel is shown in Figure 5 for the mass flow rate of 79 gr/min. Results show that cryo-freezing region diameter after 30, 60, and 120 seconds are 16.24 mm, 18.98 mm and 23 mm, respectively. It is seen that cryo-freezing region diameter increases with time. It is also seen that lower cryo-freezing region diameter is obtained for tumor tissue with single vessel as compared to tumor tissue without vessel. As can be seen from Figure 4 and Figure 5, cryo-freezing region diameters after 120 seconds are the same for the tissues with and without vessel. When the cryo-freezing region diameters of the tumor tissue with and without vessel are compared after 60 seconds, it is seen that the cryo-freezing region diameter of the tumor tissue wihout blood vessel is greater than that of the tumor tissue with blood vessel. In other words, blood flow in a vessel affect the cryo-freezing region diameter.



30 s 60 s 120 s

Figure 5. Cryo-freezing regions after 30, 60 and 120 seconds for a tumor tissue with a single vessel.

Literature results show that cryo-freezing region diameter for the tissue without vessel is 19 mm and 28 mm after 10 minutes and 20 minutes, respectively, when liquid nitrogen is used as refrigerant [12]. In addition, cryo-freezing region diameter for the tissue with a single vessel is 18 mm and 26 mm after 10 minutes and 20 minutes, respectively, when liquid nitrogen is used as refrigerant [12]. Present experimental results show that almost the same cryo-freezing region diameter is obtained at a short time when nitrogen protoxide is used as a refrigerant.

Cryo-freezing regions taken with thermocouple probes for a tumor tissue without vessel and with a single vessel is shown in Figure 6 for four different mass flow rates which are 10 gr/min, 30 gr/min, 79 gr/min and 128 gr/min. Results show that cryo-freezing region diameter after 60 seconds is 21.53 mm in tumor tissue without vessel. In addition, cryo-freezing region diameters after 60 seconds are 20.20 mm, 19.88 mm, 18.98 mm and 18.77 mm in tumor tissue with a single vessel for 10 gr/min, 30 gr/min, 79 gr/min and 128 gr/min, respectively. It is seen that cryo-freezing region diameter decreases with increasing mass flow rate. It is also seen that lower cryo-freezing region diameter is obtained for tumor tissue with blood vessel having 128 gr/min mass flow rate compared to tumor tissue without vessel.

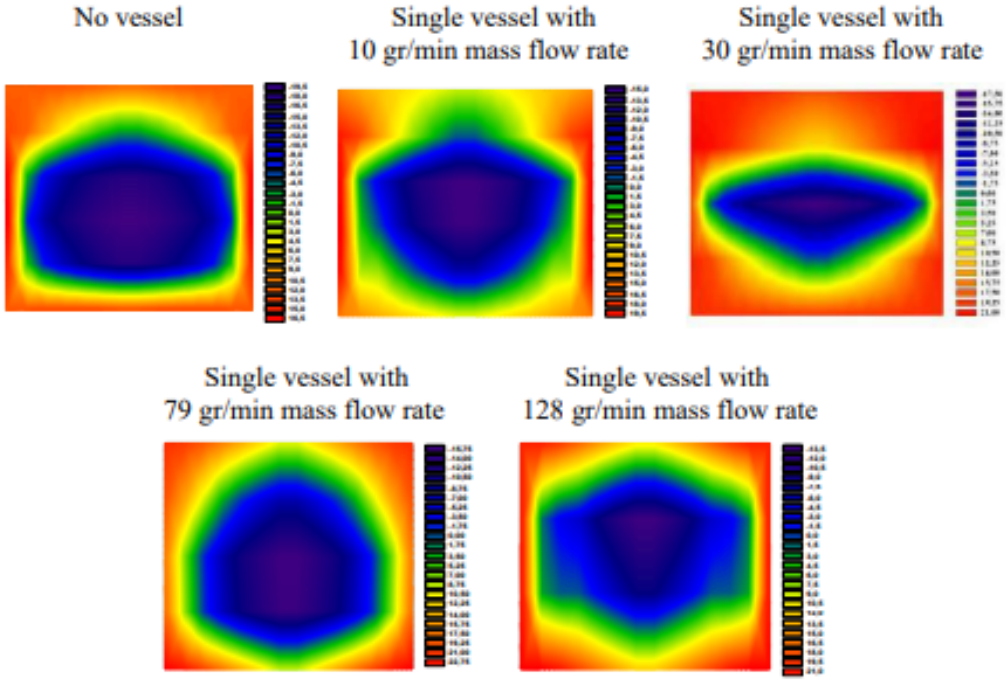


Figure 6. Cryo-freezing regions after 60 seconds for a tumor tissue without vessel and with a single vessel.

The variation of freezing region diameters, obtained as a result of cryo-freezing applied to liver tissues with a single blood vessel having inner diameter of 2.4 mm, through 120 seconds for four different mass flow rates is shown in Figure 7. The results of tumor tissue without vessel is also given in Figure 7. It is seen that freezing region diameter decreases with increasing mass flow rate of blood. It is also seen that bigger freezing diameter is obtained for tissue without vessel. Results show that cryo-freezing region diameter almost remains constant after 110 seconds. Thus, cryo-freezing procedure is applied for 120 seconds in the experiments. As can be seen in Figure 7, cryo-freezing region diameters for four different mass flow rates are the same.

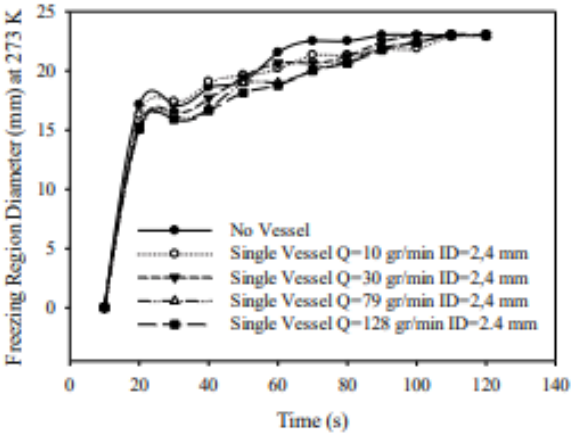


Figure 7. Variation of cryo-freezing region diameter as a function of time at different mass flow rates.

In the experiments, it is observed that the diameter of the freezing area increases with time; but when the mass flow rate of pure water increases in the teflon channel, this growth slows down. This can be interpreted as more bio heat transfer occurs from the vessel to the tissue when mass flow rate of water is increased.

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e. Yayınlar (Hakemli bilimsel dergiler, tam metni)

Yapılan bu deneysel çalışmada elde edilen sonuçların içerdiği "**EXPERIMENTAL INVESTIGATION OF BIO-HEAT TRANSFER IN CANCER TREATMENT USING CRYO-FREEZİNG METHOD"** başlıklı kapsamlı bir makale hazırlanmış olup Şubat 2019 tarihinde uluslararası hakemli **SCI** indekste taranan **International Journal of Sciences** isimli dergiye gönderilmiş olup gönderilen bu makale halen değerlendirme aşamasındadır.

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Hazırlanan makalenin tam metni aşağıda sunulmaktadır.

Form-5

Manuscript Details

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Article type	Research Paper

Abstract

Bio-heat transfer in tumorous tissue with and without blood vessel has been investigated experimentally using cryofreezing method for cancer treatment. Investigated parameters are the mass flow rate of blood in vessel and vascular structure. Study is carried out for nine different blood flow rate values 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. Beef liver is used as a biological tissue. Nitrogen protoxide (N2O) gas passing through a cryoprobe with inner diameter of 5 mm is employed as refrigerant. Results show that the desired freezing region obtained in tumorous tissue with vessel develops later than the tumorous tissue without vessel. The size of freezing region decreases with increasing mass flow rate of blood and inner diameter of vessel. It is seen that vessel in a tissue cause to decrease freezing region size. The large blood vessel located near the tumorous tissue affects the freezing time to destroy the tumor. Results indicate that a tumorous tissue about 23 mm may be destroyed using cryo-freezing method when nitrogen protoxide gas is used as refrigerant. It is seen that a 23 mm tumorous tissue may be destroyed in a short time when nitrogen protoxide gas is used as refrigerant compared to liquid nitr ogen. The results of present study agree with the literature results.

Keywords	cryo-freezing; bio-heat transfer; cancer treatment; tumorous tissue; experimental study

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Prof. Dr. U. Gross
Editor-in-Chief
Technische Universität
Bergakademie Freiberg
Freiberg, Germany

February 12, 2019

Form-5

Dear Prof. Dr. U. Gross,

Enclosed please find manuscript of our **original scientific paper** titled "**Experimental Investigation of Bio-Heat Transfer in Cancer Treatment Using Cryo-Freezing Method**" by **Erkan Kizilirmak and Oguz Turgut** to be considered for publication in the "**International Journal of Thermal Sciences**".

Our paper is unpublished work and not considered elsewhere for publication. The authors declare that they have **no conflict of interest**.

Literature survey indicates that there is a lack of information about cryo-freezing to destroy the tumorous tissue. In this study, the effect of mass flow rate of blood in vessel and vascular structure such as the number and diameter of blood vessel has been investigated experimentally. Cryo-freezing method is used to destroy tumorous tissue with and without blood vessels. Experiments are carried out for different blood mass flow rate values changing from 10 g/min to 1200 g/min. The **novelty** of present study is the experimentally investigation of tumorous tissue with **branched vessel structures** using cryo-freezing method. The using of **nitrogen protoxide** (N_2O) gas as a refrigerant is the other **novelty of this** study. Therefore, this study aims to obtain the new temperature and freezing region data required for optimum cryo-freezing process for single, double and branched vessels with different vessel diameters at different blood mass flow rates in large blood vessels and for different tumor locations formed near these vessels.

Looking forward to hearing from you soon.

Sincerely Yours,



Dr. Oguz Turgut

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Experimental Investigation of Bio-Heat Transfer in Cancer Treatment Using Cryo-Freezing Method

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Abstract:

Bio-heat transfer in tumorous tissue with and without blood vessel has been investigated experimentally using cryo-freezing method for cancer treatment. Investigated parameters are the mass flow rate of blood in vessel and vascular structure. Study is carried out for nine different blood flow rate values 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. Beef liver is used as a biological tissue. Nitrogen protoxide (N_2O) gas passing through a cryoprobe with inner diameter of 5 mm is employed as refrigerant. Results show that the desired freezing region obtained in tumorous tissue with vessel develops later than the tumorous tissue without vessel. The size of freezing region decreases with increasing mass flow rate of blood and vessel inner diameter. It is seen that vessel in a tissue and branched of vessel result in decreasing freezing region size. The large blood vessel located near the tumorous tissue affects the freezing time to destroy the tumor. Results indicate that a tumorous tissue about 23 mm may be destroyed using cryo-freezing method when nitrogen protoxide gas is used. It is seen that a 23 mm tumorous tissue may be destroyed in a short time when nitrogen protoxide gas is used as refrigerant gas compared to liquid nitrogen. The results of present study agree with the literature results.

Keywords: Cryo-freezing, bio-heat transfer, cancer treatment, tumorous tissue, experimental study

1. INTRODUCTION

The development of tumor happens generally on or near the large blood vessels. It is desirable that the tumor development near the vessel should be destroyed surgically and not be repeated in the same tissue region and not be spread to other tissues.

One of the methods of cancer treatment is cryotherapy. It is an effective medical treatment method employed to destroy the tumor by providing freezing in the biological tissue by means of cryoprobes. It is considered as a good treatment method due to least relapsing and short time staying in hospital. Some important advantages of this treatment are being fast, easy and cheap. Thus, it does not require anesthesia. The risk of bleeding after the cryo-freezing procedure is extremely low. It does not need any changes in normal life. There is no negative effect on the potential of reproduction. The risk of serious injury or complications is quite low. This treatment method is used to destroy the liver and prostate tumors.

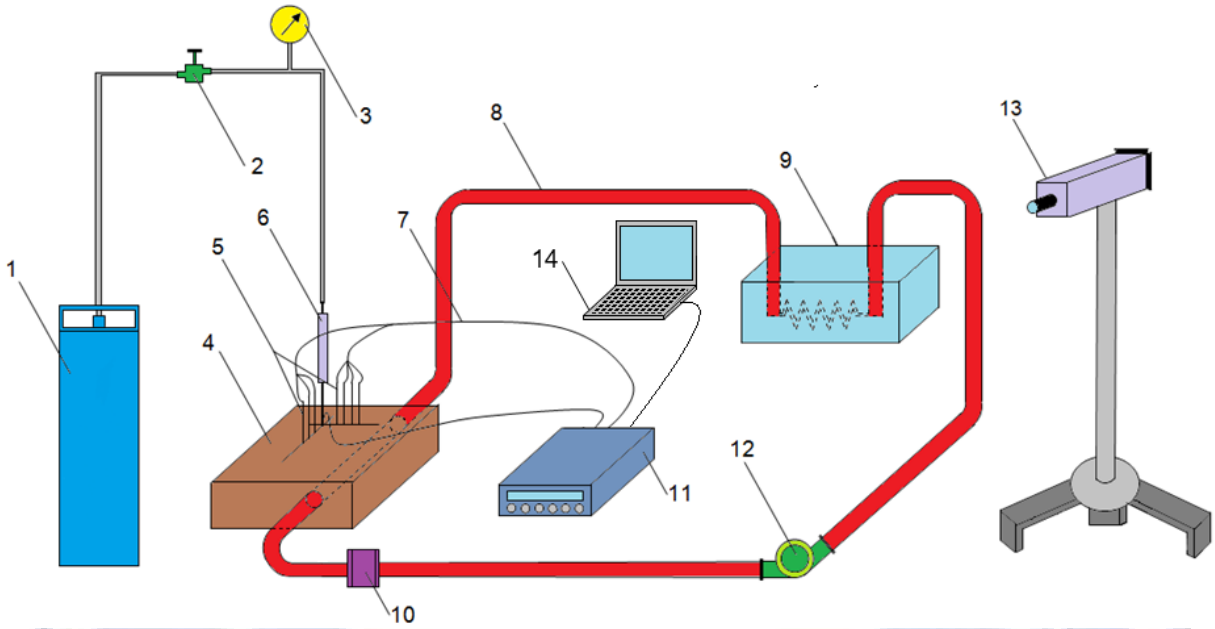
Literature investigation indicates that cancer treatment employing cryo-freezing method was investigated by some scientists. Deng and Liu [1-3] numerically investigated the cryotherapy treatment using finite difference method. An analytical model was developed to examine a liver tumor cell destruction within the freeze-thaw process in cryotherapy by Chua et al. [4]. Thermal effects of large vessels during cryosurgery were experimentally and numerically investigated by Deng et al. [5]. Chua and Chou [6] was developed a model to investigate the freeze-thaw-heat treatment in a biological system. Silveira et al. [7] determined the diameters of the liver main arteries and arter branches for human liver. Majchrzak and Tarasek [8] analyzed the thermal interactions between a single blood vessel and biological tissue surrounding it. A numerical study was implemented to explore the irregularly shaped liver tumor by Chua [9]. A lower temperature value is required to freeze the tissue along the large blood vessel [10]. The first in vivo animal experiments was carried out using a nano-cryosurgical method to freeze completely tumor tissues in which large blood vessels are embedded by Sun et al. [11]. Chua [12] formed a computational cryo-freezing model with a simplified mathematical definition of the vascular network structure. Wang et al [13] developed a multiscaled three-dimensional cell-tissue model for quantitative evaluation of vascular network effects considering the results obtained from cryosurgery and hyperthermia treatments used in cancer treatment.

Literature survey indicates that there is a lack of information about cryo-freezing to destroy the tumorous tissue. In this study, the effect of mass flow rate of blood in vessel and vascular structure such as the number and diameter of blood vessel has been investigated experimentally. Cryo-freezing method

is used to destroy tumorous tissue with and without blood vessels. Experiments are carried out for different blood mass flow rate values changing from 10 g/min to 1200 g/min. The novelty of present study is the experimentally investigation of tumorous tissue with branched vessel structures using cryo-freezing method. The using of nitrogen protoxide (N_2O) gas as a refrigerant is the other novelty of this study. Therefore, this study aims to obtain the new temperature and freezing region data required for optimum cryo-freezing process for single, double and branched vessels with different vessel diameters at different blood mass flow rates in large blood vessels and for different tumor locations formed near these vessels.

2. MATERIALS AND METHODS

The experimental set-up used in this study is shown in Figure 1. Cryo-freezing procedure is carried out using a cryotherapy device consisting of a pressurized nitrogen protoxide tube, a manometer, a needle valve, and a cryoprobe gun. Pressurized nitrogen protoxide gas (N_2O) controlled by a needle valve is stored in a cylinder. The tube pressure is measured using a pressure gauge. Nitrogen protoxide gas is passed through an internal tube located inside the cryoprobe gun when the valve is open. Two calibrated 24-gage copper-constantan thermocouples and ten thermocouple probes are used to measure the temperatures of cryoprobe tip, tissue and surroundings. The distance between two thermocouple probes are 3 mm, and the thermocouple probe tips are placed at a distance of 10 mm from the top surface of tissue. Thermocouple temperature values are read using a datalogger connected to a computer. A thermal imager camera is employed to display the temperature distribution. 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.



1. Pressurized nitrogen protoxide tube
2. Needle valve
3. Manometer
4. Tissue (beef liver)
5. Thermocouple probes
6. Cryoprobe gun
7. Thermocouples
8. Teflon channel
9. Water bath with cooled circulator
10. Fluid flow meter
11. Datalogger
12. Peristaltic pump
13. Thermal camera
14. PC

Figure 1. Schematic view of the experimental set-up

To investigate the cryogenic freezing process, commercially available beef livers are employed as a sample in in-vitro experiments. The beef liver samples without vessel, single vessel, double vessel, and branched vessel are seen in Figure 2. Y-connectors are used to branch blood vessels. Diameter reducers are employed to enlarge and reduce the diameter in the branched blood vessel experiments. Figure 2 also shows the thermocouple probes used to measure the temperature distribution of freezing region. As can be seen from Figure 2, thermocouple probes are placed as L-shaped. Teflon channels are used to simulate the blood vessel due to similarity to the blood vessel [5, 7, 8, 10, 13]. Three different teflon channels with inner diameters ID=2.4 mm, 3.2 mm and 4.0 mm are used to investigate the thermal effect of the blood flow in the teflon channel. 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.

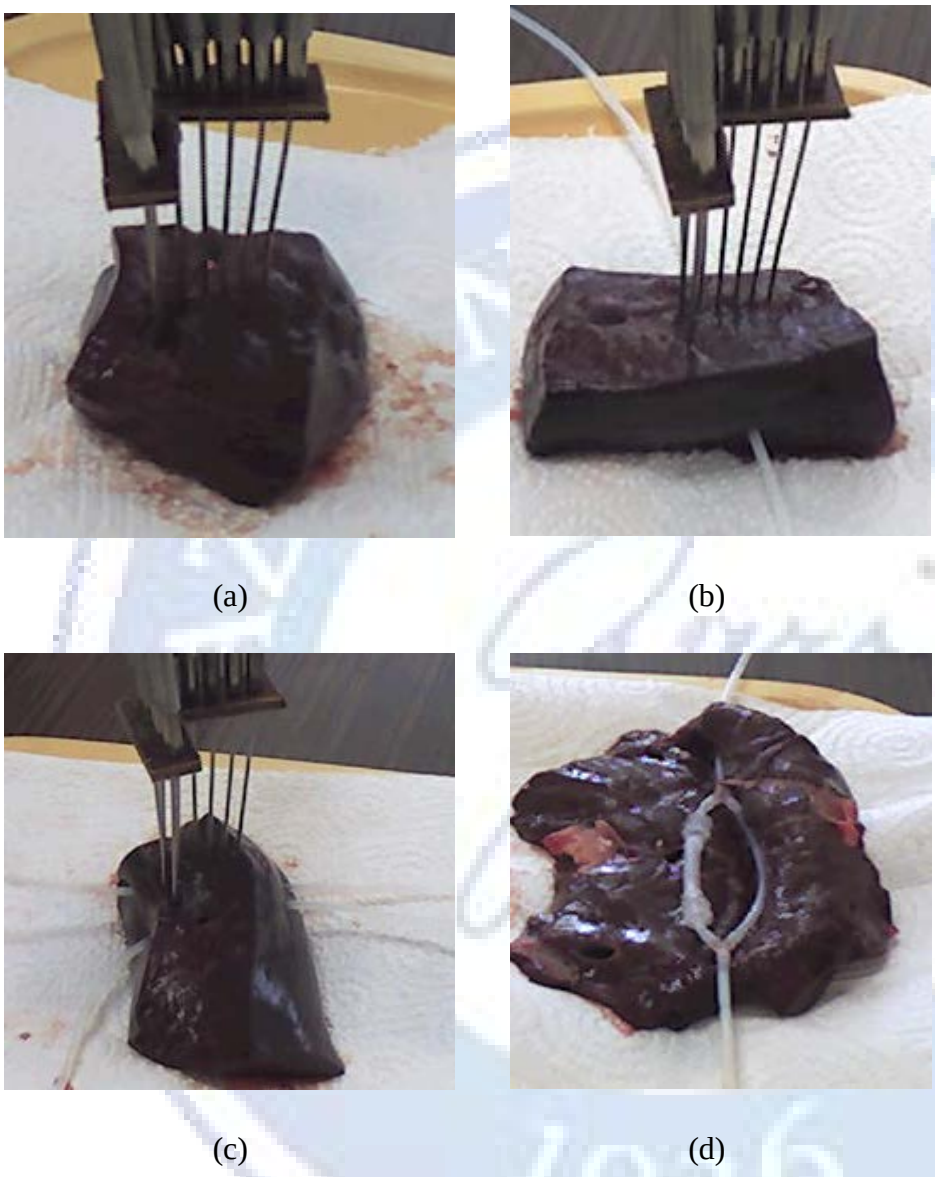


Figure 2. Beef liver samples without vessel (a), with single vessel (b), with double vessel (c) and with branched vessel (d).

Typical view of tumorous tissue and the insertion position of cryoprobe tip at -40^{o}C is given in Figure 3 on x-y-z coordinates and A-A section for double vessel. Vessel is placed into liver tissue at a 20 mm distance from top surface of the tissue. The distance between two vessels for double and branched vessels is 20 mm. Fluid flows in the arrow direction. Cryoprobe with inner diameter D_{cp}=5

mm is located at a 5 mm distance from top surface of the arter vessel. That is, cryo-freezing procedure is applied to the arter.

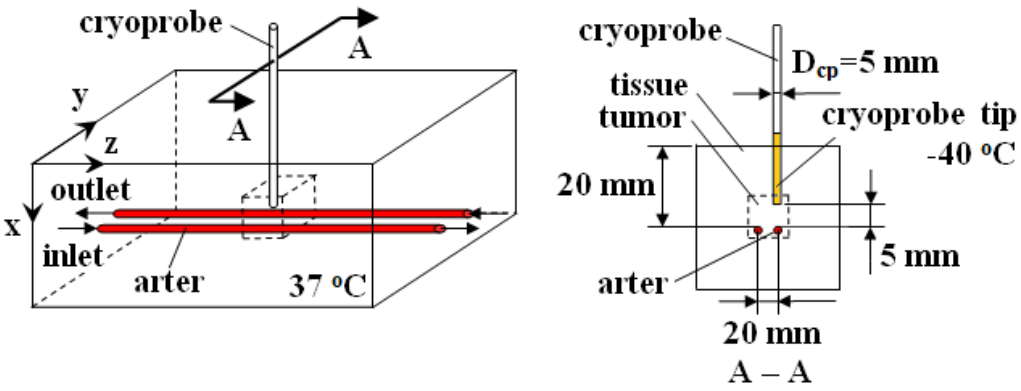


Figure 3. Typical schematic view of a tumorous tissue with double blood vessel and insertion position of cryoprobe tip.

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

Table 1. Cases studied during cryo-freezing procedure

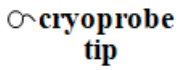
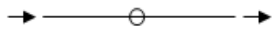
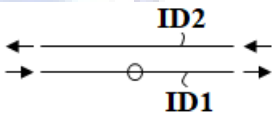
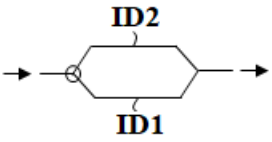
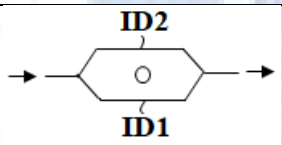
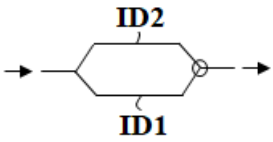
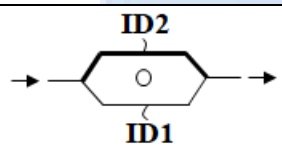
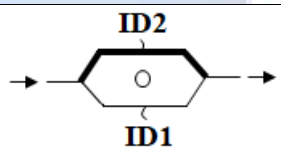
Case no	Type of vessel	Freezing process region	ID1 (mm)	ID2 (mm)	Position of cryoprobe tip and vessels
Case1	No	Middle	-	-	
Case2	Single	Top of arter	2.4	-	
Case3	Double	Top of arter	2.4	2.4	
Case4	Branched	First connection point	2.4	2.4	
Case5		Middle of branched	2.4	2.4	
Case6		Second connection point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

Figure 4 shows the typical view of branched vessel dimensions and flow direction. As shown in Figure 4, fluid flows inside a 2.4 mm-vessel before branched vessel, flows through branched vessel, and flows inside a 2.4 mm-vessel after branched vessel. As can be seen in Figure 4, 60^{o}-Y-connector is used for branched vessel.

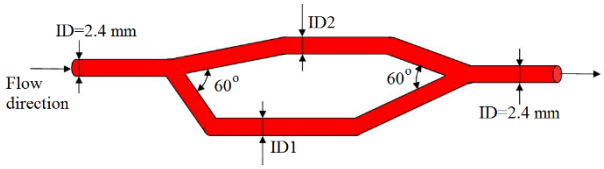


Figure 4. Typical view of branched vessel

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. Error in weighing and time was estimated to be ±1 g and 1 s, respectively. Following the procedure described by Holman [14] the maximum relative uncertainty of mass flow rate was estimated to be 10.1%.

A typical experimental study consists of placing the teflon channel into beef liver (see Fig. 2), connecting teflon channel to peristaltic pump, operatig peristaltic pump and measuring mass flow rate of fluid, operating water bath and 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 without cryo-freezing. Experimental study is lasted for ten minutes to supply the stable temperature of beef liver sample. Cryoprobe tip is placed into beef liver sample. Then, cryo-freezing procedure is started and continued for 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.

3. RESULTS AND CONCLUSIONS

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

Cryo-freezing procedure for liver tissue with and without vessel is conducted for the time period of 140 seconds at different mass flow rates of fluid. Freezing region diameters at the temperature 273 K are plotted in Figure 5 as a function of time for different cases studied. As can be seen from Figure 5, 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. That is, freezing region diameter does not change with time after 120 seconds. Therefore, experiments are conducted for 120 seconds.

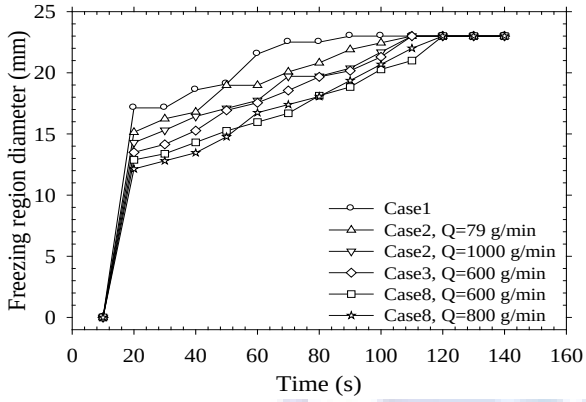


Figure 5. Cryo-freezing region diameter versus time

The images taken from thermal camera are shown in Figure 6 after 30, 60 and 120 seconds for a tumorous tissue without vessel. Results show that cryo-freezing region size increases with increasing time. In other words, cryo-freezing region diameters are 17.13 mm, 21.53 mm, and 23 mm after 30, 60 and 120 seconds, respectively.

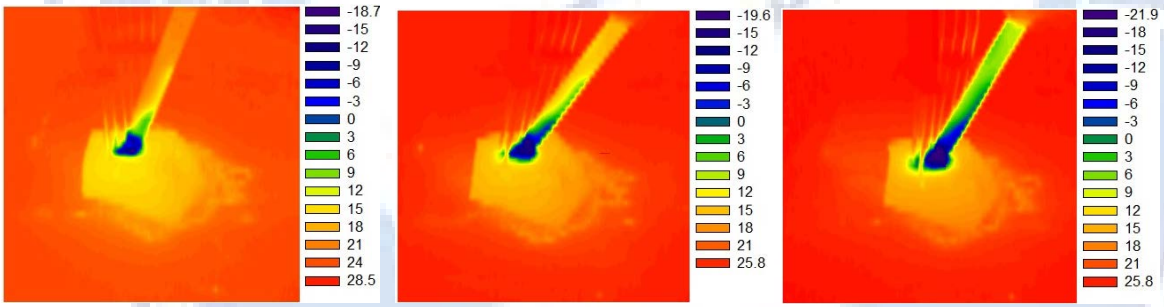


Figure 6. Cryo-freezing regions after 30, 60 and 120 seconds for a tumorous tissue without vessel.

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. Cryo-freezing regions for a tumorous tissue with single vessel are shown in Figure 7 after 30, 60 and 120 seconds. Results show that cryo-freezing region diameters for a tumorous tissue with single vessel are 16.24 mm, 18.98 mm and 23 mm after 30, 60 and 120 seconds, respectively. As can be seen from Figure 7, cryo-freezing region diameter increases with increasing time.

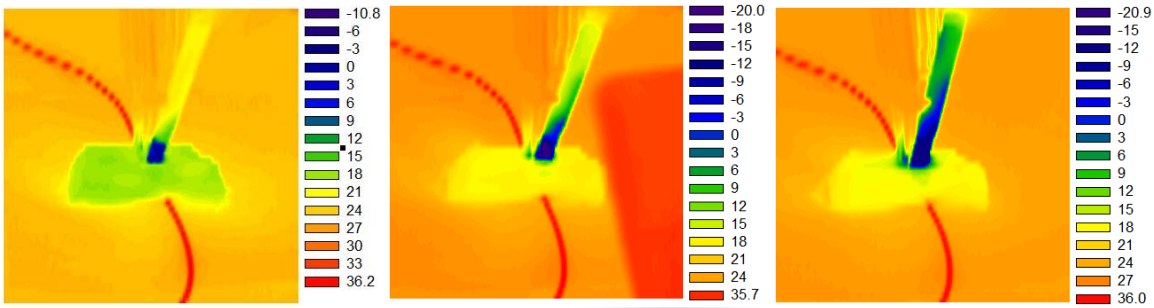


Figure 7. Cryo-freezing regions after 30, 60 and 120 seconds for a tumor tissue with a single vessel.

As can be seen from Figure 6 and Figure 7, cryo-freezing region diameters after 120 seconds are the same for the tissues with and without vessel. When the cryo-freezing region diameters of the tumor tissue with and without vessel are compared after 60 seconds, it is seen that the cryo-freezing region diameter of the tumorous tissue without blood vessel is greater than that of the tumorous tissue with blood vessel. In other words, blood flow in a vessel affects the cryo-freezing region diameter.

According to the results of Chua [12], cryo-freezing region diameters for the tissue without vessel is 19 mm and 28 mm after 10 minutes and 20 minutes, respectively, when liquid nitrogen is used as refrigerant. In addition, cryo-freezing region diameters for the tissue with a single vessel is 18 mm and 26 mm after 10 minutes and 20 minutes, respectively, when liquid nitrogen is used as refrigerant [12]. Present experimental results conducted for nitrogen protoxide show that almost the same cryo-freezing region diameters are obtained at a short time when nitrogen protoxide gas is used as a refrigerant.

In order to see the effect of mass flow rate on temperature distribution in tissue, temperature distributions taken from thermocouple probes for a tumorous tissue without vessel (Case1) and with a single vessel (Case2) are shown in Figure 8 for different mass flow rates after 60 seconds. It is seen that mass flow rate in vessel affects the temperature distribution. Results show that the temperature of freezing region increases with increasing mass flow rate due to the increasing bio-heat transfer from fluid to tissue. Increasing temperature of freezing region results in decreasing cryo-freezing region size.

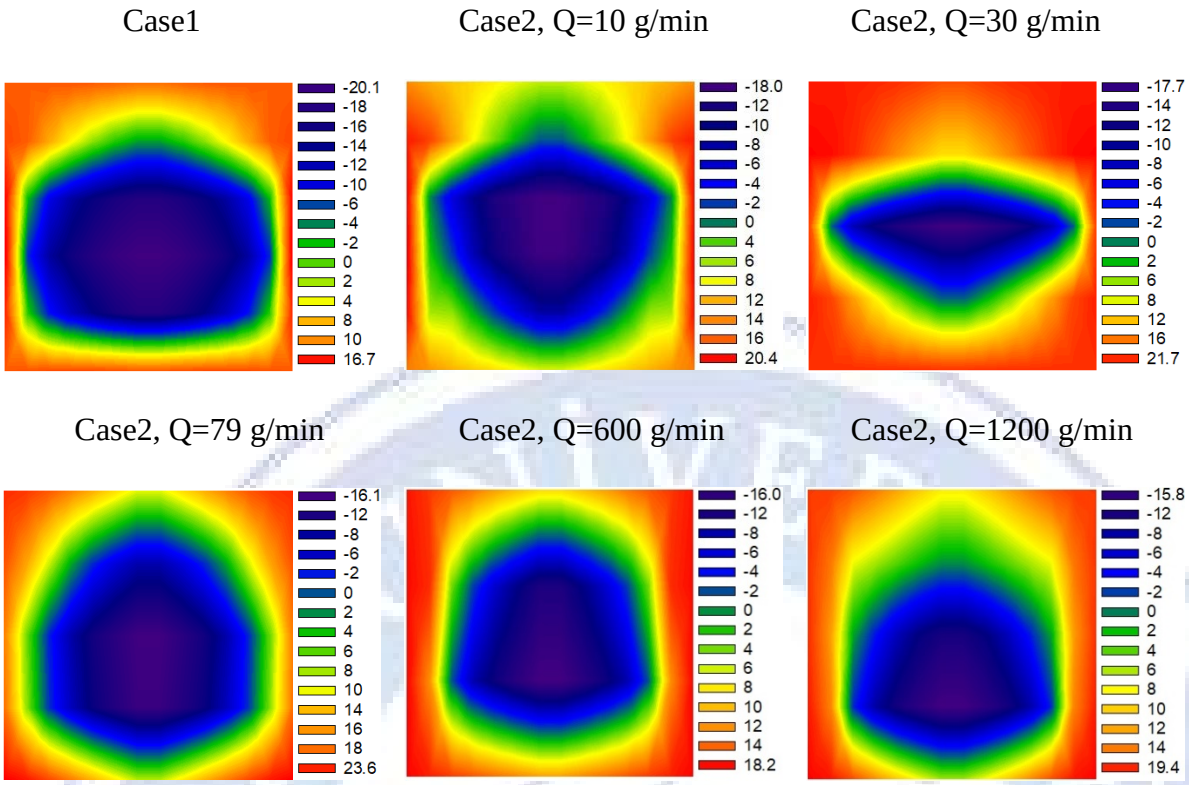


Figure 8. The effect of mass flow rate on temperature distribution in tissue after 60 seconds

Figure 9 shows the typical temperature distribution, obtained from thermocouple probes, in tissue at a mass flow rate of 600 g/min for all cases studied after 60 seconds. It is seen that the number of vessel and the type of vessel affect the freezing region size.

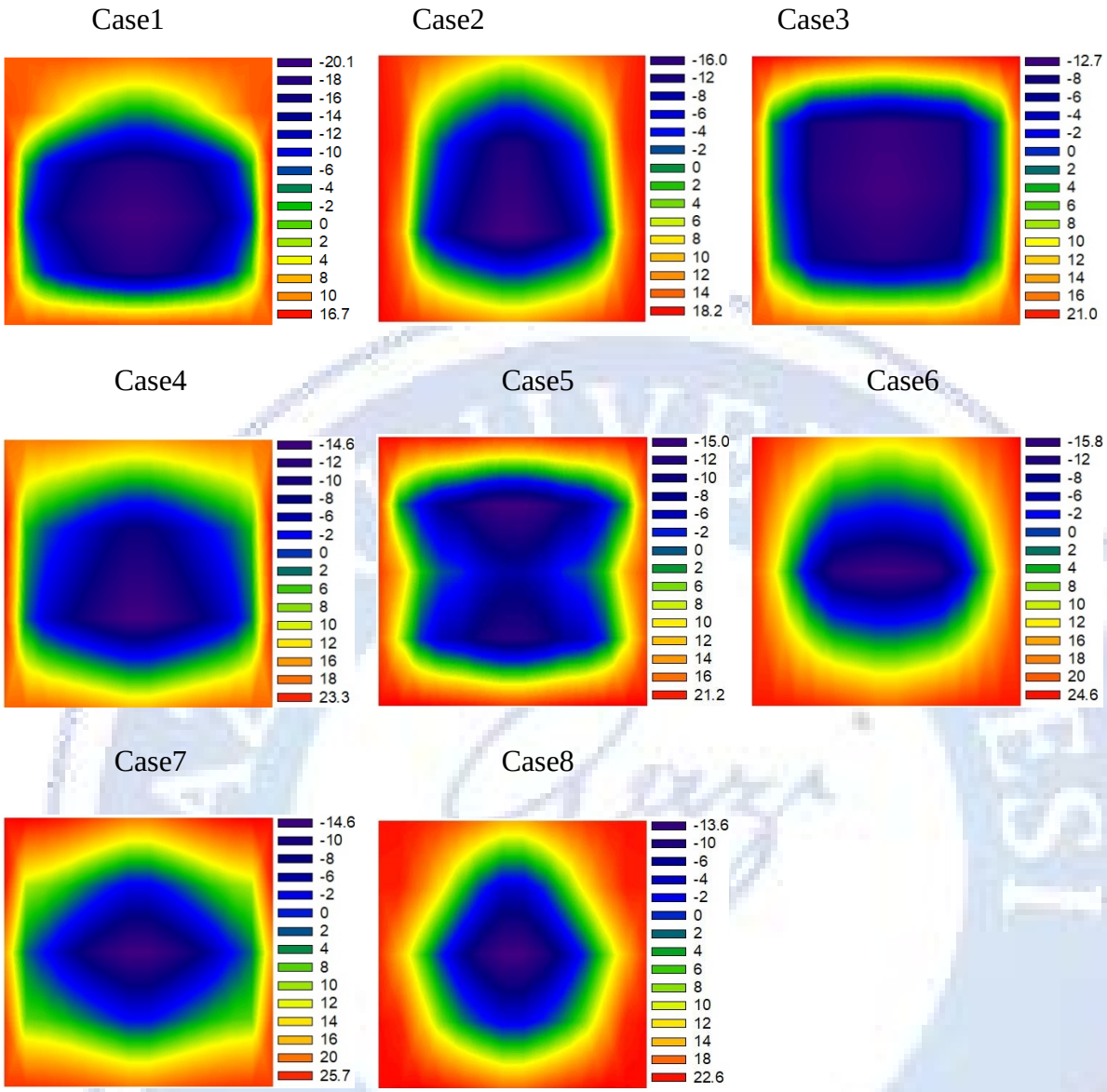


Figure 9. Temperature distributions after 60 seconds for all cases at a mass flow rate of 600 g/min.

To see the effect of mass flow rate on cryo-freezing region, temperature images taken from thermal camera is shown in Figure 10 for a tissue with single vessel after 60 seconds. Cryo-freezing region diameters at 273 K are calculated using thermal camera images. Cryo-freezing region diameters D_{fr} are also given in paranthesis in Figure 10. It is seen that cryo-freezing region diameter decreases with increasing mass flow rate. The highest cryo-freezing region diameter is obtained for the tissue without vessel (Case1) while the lowest cryo-freezing region diameter is obtained at the highest mass flow rate 1200 g/min.

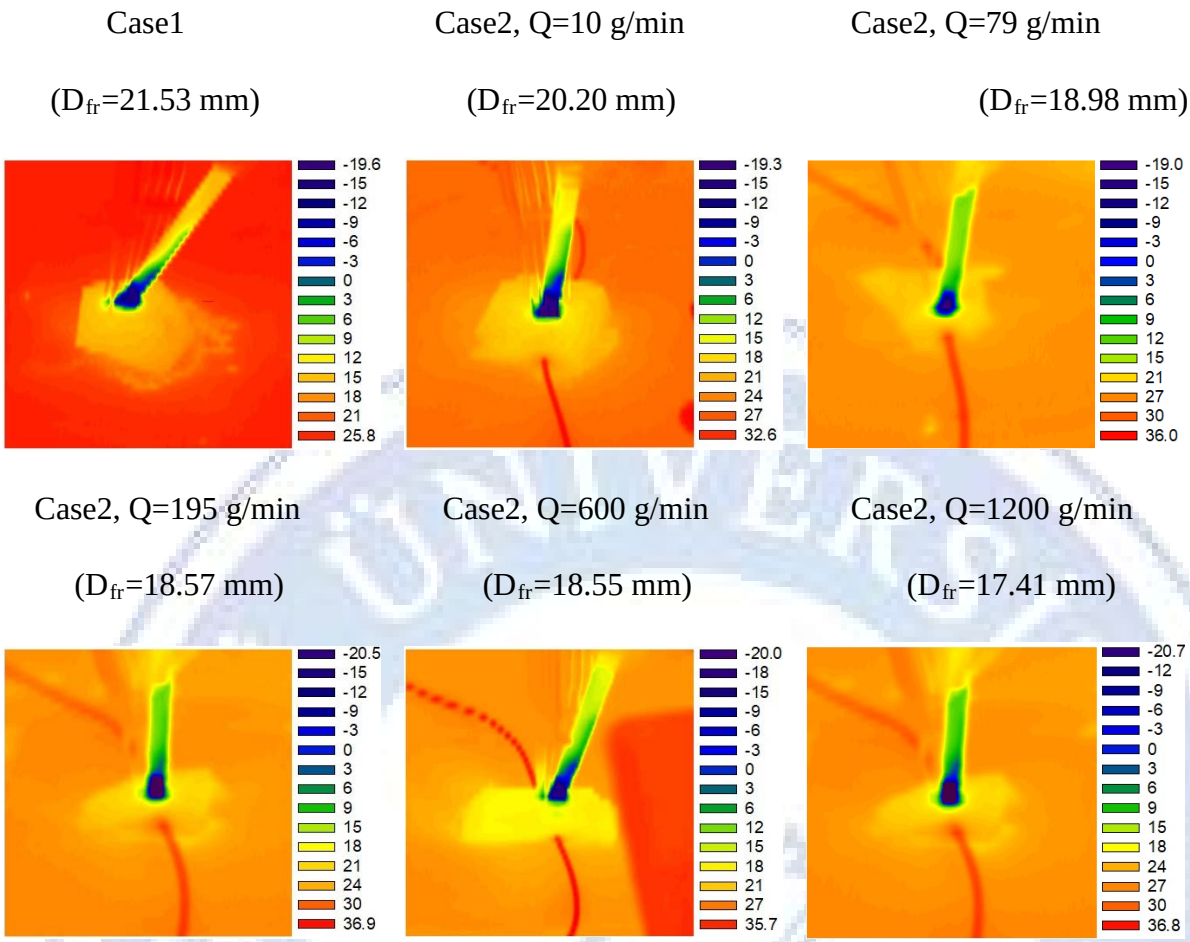


Figure 10. The effect of mass flow rate on cryo-freezing region

In order to see the effect of mass flow rate on cryo-freezing region size, temperature images taken from thermal camera for all cases studied is shown in Figure 11 at a mass flow rate of 600 g/min after 60 seconds. Freezing region diameters D_{fr} are also given in Figure 11 in paranthesis. It is seen that maximum freezing region diameter D_{fr}=21.53 mm is obtained for the tissue without vessel, Case1. And 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 seen that freezing region diameter 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, 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. It is seen that freezing region diameter decreases 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.

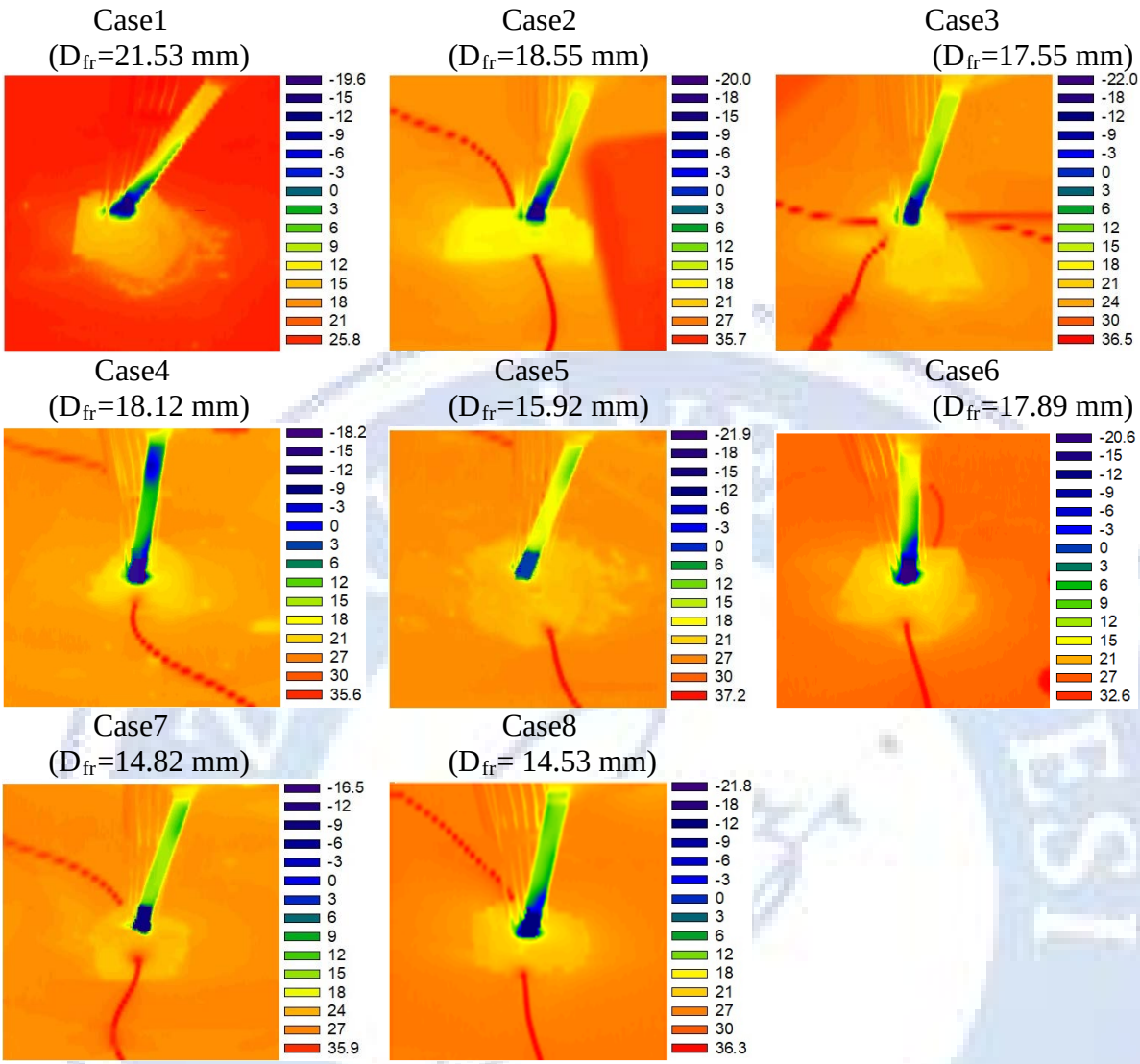


Figure 11. Temperature images taken from thermal camera after 60 seconds for all cases at a mass flow rate of 600 g/min.

Cryo-freezing region diameter is plotted in Figure 12 as a function of time for different cases to see the effect of mass flow rate on cryo-freezing region diameter. It is seen that cryo-freezing region diameter increases rapidly up to 20 seconds, then it continues to increase with increasing time up to 120 seconds. Results show that cryo-freezing region diameter 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 diameter before reaching constant value. This can be interpreted as that cryo-freezing region diameter decreases with increasing mass flow rate of fluid before 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. Cryo-freezing region diameter for tissue without vessel reaches constant value before than that of tissues with vessel.

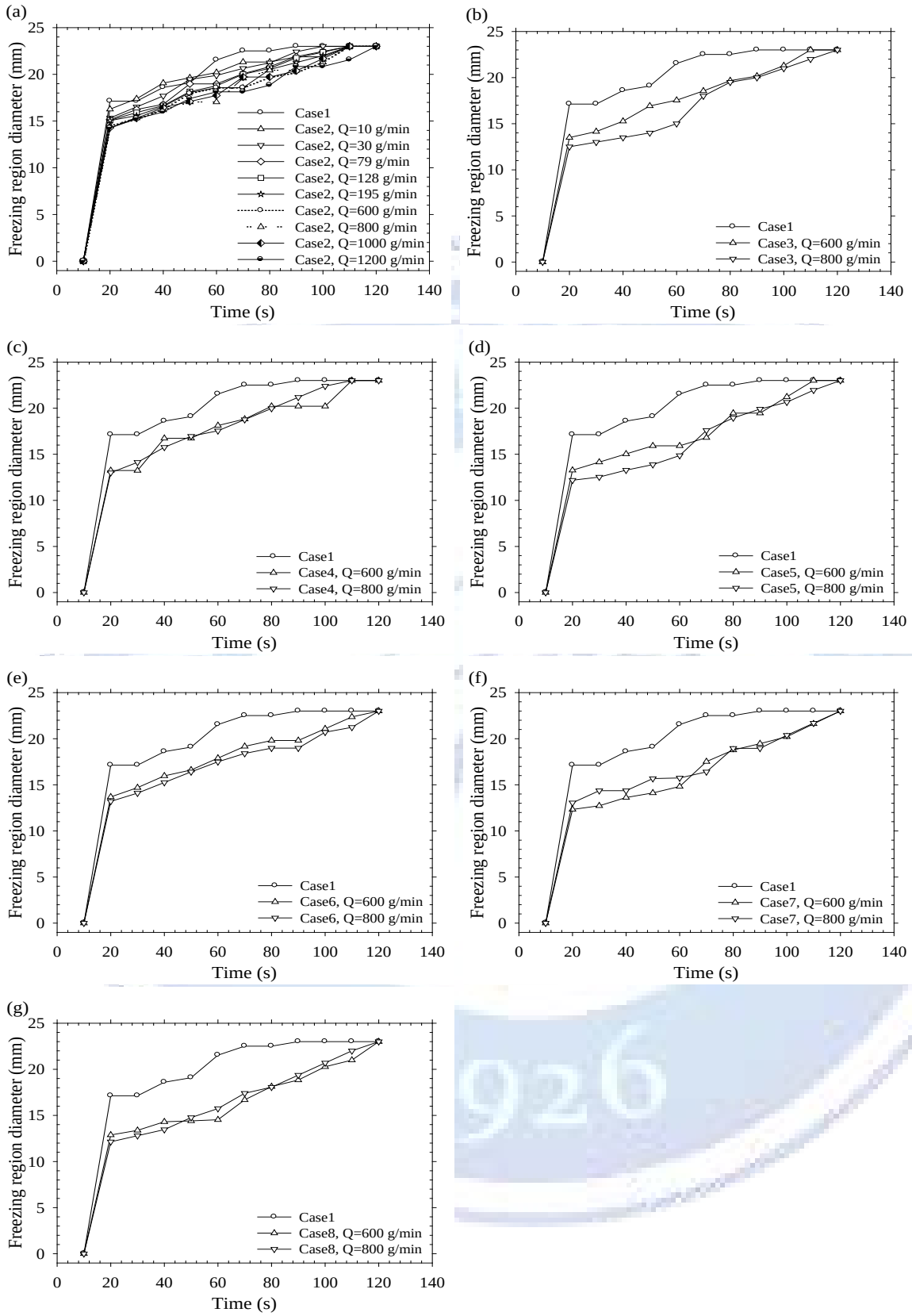


Figure 12. Cryo-freezing region diameters at different mass flow rates for Case2 (a), Case3 (b), Case4 (c), Case5 (d), Case6 (e), Case7 (f) and Case8 (g)

Figure 13 shows the freezing region diameters as a function of time at two different 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 affect 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 the number of vessel due to increasing of bio-heat transfer. Cases 4-6 are compared to see the effect of freezing place in tissue on freezing region diameter. It is seen that less freezing region diameter is obtained when freezing region is the middle of branched vessel and when tumorous tissue is assumed at the middle of branched vessel (Case5). It is interpreted as that 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 Cases 4 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 and freezing procedure is applied to these points.

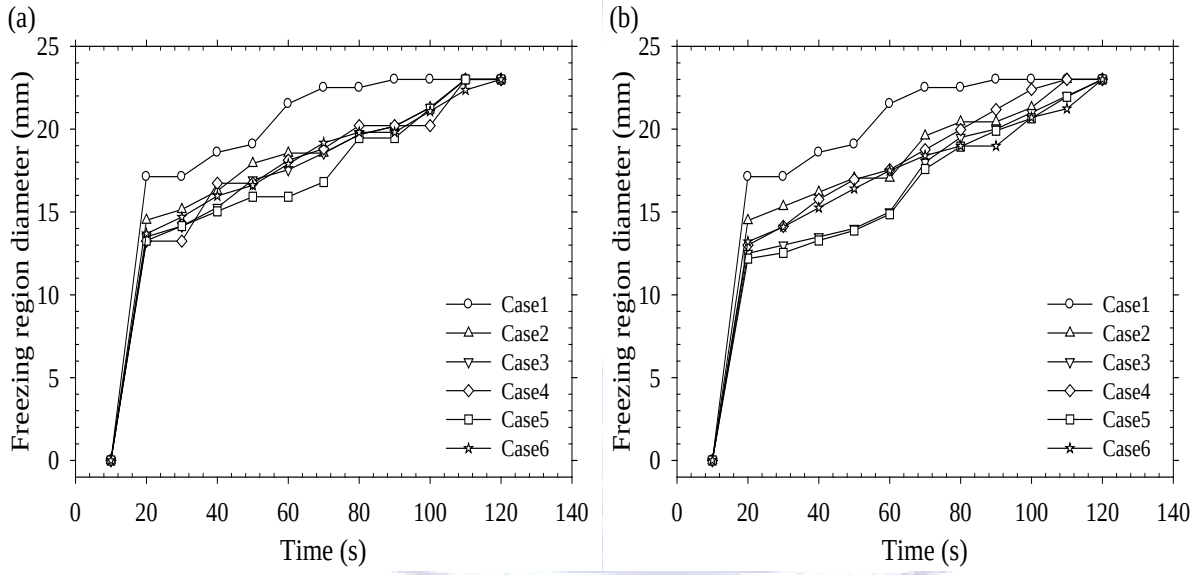


Figure 13. Freezing region diameter versus time; (a) Q=600 g/min and (b) Q=800 g/min

In order to see the effect of the artery diameter in branched vessel, freezing region diameter is shown in Figure 14a and 14b at the mass flow rates 600 g/min and 800 g/min, respectively. Here, 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. The results of tissue without vessel is also given in Figure 14 for the purpose of comparison. It is seen that vessel affects the freezing region diameter. 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.

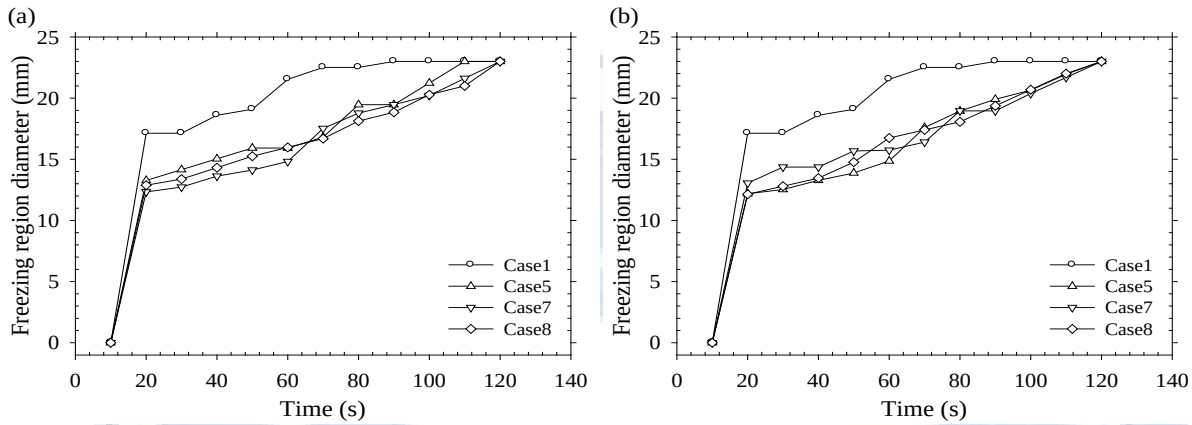


Figure 14. The effect of ID2 on freezing region diameter; (a) Q=600 g/min and (b) Q=800 g/min

4. CONCLUSIONS

The effects of mass flow rate of blood in vessel and the type of the vessel on freezing region are investigated experimentally using cryo-freezing procedure. The temperature regions are obtained from measured thermocouple probes and thermal camera images. Freezing region diameters are given as a function time. It is seen that blood flowing in a vessel and the bio-heat transfer surface area affect the freezing region size. Results show that bio-heat transfer from fluid to tissue increases with increasing mass flow rate and bio-heat transfer surface area. Desired freezing region diameter decreases with increasing bio-heat transfer. Freezing region diameter decreases with increasing mass flow rate of blood in vessel. It is seen that maximum freezing region size is obtained for the tissue without vessel. It is also seen that the location of tumorous tissue for branched vessel affect the freezing region diameter.

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