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**CAROTID ARTERY STENOSIS (CAS)
DISEASE DETECTION BY PASSIVE
AND ACTIVE MEDICAL INFRARED
(IR) THERMAL IMAGING**

ASHISH SAXENA

School of Mechanical and Aerospace Engineering

2020

CAROTID ARTERY STENOSIS (CAS) DISEASE DETECTION BY PASSIVE AND ACTIVE MEDICAL INFRARED (IR) THERMAL IMAGING

ASHISH SAXENA

School of Mechanical and Aerospace Engineering

A thesis submitted to Nanyang Technological University in
partial fulfillment of the requirements for the degree of
Doctor of Philosophy

2020

STATEMENT OF ORIGINALITY

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

Date: 15 Jan 2020

Signature

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SUPERVISOR DECLARATION STATEMENT

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

Date: 15/1/2020.

Signature

Dr. Ng Yin Kwee, Eddie
(Associate Professor)

School of Mechanical and Aerospace Engineering
Nanyang Technological University, Singapore

AUTHORSHIP ATTRIBUTION STATEMENT

This thesis contains material from six papers published in the following peer-reviewed journals in which I am listed as an author.

0 is published as *Ashish Saxena, E.Y.K. Ng, and Lim Soo Teik*. "Imaging modalities to diagnose carotid artery stenosis: progress and prospect." *BioMedical Engineering OnLine* 18.1 (2019): 66 <https://doi.org/10.1186/s12938-019-0685-7>.

As a part of Ph.D. literature review, I initiated the idea of summarizing the progress and prospect in imaging modalities to diagnose carotid artery stenosis in the form of a review paper. I wrote the first draft of the manuscript.

Prof. Eddie Yin Kwee Ng reviewed the draft and provided insight on including the fundamental/advanced technical aspects of imaging modalities included in the review.

Dr. Lim Soo Teik reviewed the manuscript. He provided the medical images and discussion on clinical aspect of the imaging modalities included in the review.

0 is published as *Ashish Saxena, Vedabit Saha, E.Y.K. Ng*. "Skin temperature maps as a measure of carotid artery stenosis", *Computers in Biology and Medicine* (2019): 103548. <https://doi.org/10.1016/j.combiomed.2019.103548>

Ashish Saxena, E.Y.K. Ng, Mrudang Mathur, Chirag Manchanda, and Nehal Amit Jajal, "Effect of carotid artery stenosis on neck skin tissue heat transfer." *International Journal of Thermal Sciences* 145 (2019): 106010. <https://doi.org/10.1016/j.ijthermalsci.2019.106010>

I designed the study protocol, drafted the ethics approval application, came up with the methodology to model the carotid artery geometry, extracting the flow boundary conditions, and stenosis geometry from the ultrasound images, and setup for the computational fluid dynamics and conjugate bioheat transfer simulations to perform the computational study. I performed the qualitative and quantitative result analysis from the computational study, extraction of thermal features from the *in-vivo* thermography measurement, followed by the first manuscript draft write-up.

Mr. Vedabit Saha assisted in executing the designed geometry modeling task, performed data sorting, and running the computational simulations followed by its result extraction.

Prof. Eddie Yin Kwee Ng arranged the patient-specific ultrasound and thermography data that is used in this study. He reviewed the manuscript draft and provided insightful comments to shape the final manuscript.

Mr. Mrudang Mathur performed the initial carotid artery model by extracting the geometrical details from the literature and flow simulation validation.

Mr. Chirag Manchanda performed the mesh independent analysis, running the simulations, and extraction of raw results data.

Mr. Nehal Amit Jajal assisted in extraction of the flow streamlines and temperature contours.

0 is published as Ashish Saxena, E.Y.K. Ng, Soo Teik Lim, "Infrared (IR) thermography as a potential screening modality for carotid artery stenosis", Computers in Biology and Medicine (2019). <https://doi.org/10.1016/j.compbiomed.2019.103419>

I designed the study protocol, drafted the ethics approval application, devised the method to extract thermal features from the thermal images, performed the statistical analysis to select the significant features, executed the sample classification, and result analysis. I wrote the first draft of the manuscript.

Prof. Eddie Yin Kwee Ng arranged the patient-specific thermography data that is used in this study. He reviewed the manuscript draft and provided insightful comments to shape the final manuscript.

Dr. Lim Soo Teik got the ethics approval to perform the study and supervised the ultrasound data collection at the Vascular Lab, National Heart Center, Singapore.

CHAPTER 5 is published as *Ashish Saxena, E.Y.K. Ng, and Vignesh Raman*, “Single Image Reconstruction in Active Dynamic Thermography: A Novel Approach”, *Infrared Physics & Technology* 93 (2018): 53-58. <https://doi.org/10.1016/j.infrared.2018.07.020>

Ashish Saxena, Vignesh Raman, and E.Y.K. Ng. “Study on methods to extract high contrast image in active dynamic thermography”, *Quantitative InfraRed Thermography Journal* (2019): 1-17, Taylor & Francis Online. <https://doi.org/10.1080/17686733.2019.1586376>

I designed the study protocol, drafted the ethics approval application, devised the novel Tissue Activity Ratio (*TAR*) method to quantitatively analyzed the transient thermal image sequence in Active Dynamic Thermography (ADT) procedure, performed the ADT experiment on patients at the National Heart Center Singapore, performed the statistical analysis, formulated the mathematical expression for image transformation and contrast calculation, and result analysis. I wrote the first draft of these manuscripts.

Mr. Vignesh Raman assisted in performing the experiments, data sorting and management, coding the image registration and analysis algorithm, and review of the draft manuscript.

Prof. Eddie Yin Kwee Ng got the necessary ethic approval to perform the study. He reviewed the manuscript draft and provided insightful comments to shape the final manuscript.

CHAPTER 6 is published as *Ashish Saxena, E.Y.K. Ng, Soo Teik Lim*, "Active Dynamic Thermography to Predict the Presence of Stenosis in the Carotid Artery", *Computers in Biology and Medicine* (2020): 103718.

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Ashish Saxena, E.Y.K. Ng, Vignesh Raman, Muhammad Syarifuddin Bin Mohamed Hamli, Mateusz Moderhak, Szymon Kolacz, and Jerzy Jankau. "Infrared (IR) Thermography-based Quantitative Parameters to Predict the Risk of Post-operative Cancerous Breast Resection Flap Necrosis." *Infrared Physics & Technology* (2019): 103063. <https://doi.org/10.1016/j.infrared.2019.103063>

I designed the study protocol, drafted the ethics approval application, devised the novel Tissue Activity Ratio (*TAR*) method to quantitatively analyzed the transient thermal image sequence in Active Dynamic Thermography (ADT) procedure, devised the method to extract region of interest from the reconstructed *TAR* image, performed the statistical analysis, and result analysis. I wrote the first draft of these manuscripts.

Prof. Eddie Yin Kwee Ng arranged collaboration with Prof. Mateusz Moderhak, Dr. Szymon Kolacz, and Dr. Jerzy Jankau to test the method developed on Breast Resection

Flap Necrosis thermography data. He reviewed the manuscript draft and provided insightful comments to shape the final manuscript.

Dr. Lim Soo Teik got the ethics approval to perform the study and supervised the ultrasound data collection at the Vascular Lab, National Heart Center, Singapore.

Mr. Vignesh Raman assisted in data sorting and management, coding the image registration and analysis algorithm, and review of the draft manuscript.

Mr. Muhammad Syarifuddin Bin Mohamed Hamli assisted in executing the image reconstruction through a pre-designed algorithm and computer program to test the devised novel *TAR* method on reconstructed breast flap necrosis active dynamic thermography data.

Prof. Mateusz Moderhak, Dr. Szymon Kolacz, and Dr. Jerzy Jankau are the collaborators who provided the data on reconstructed breast flap necrosis active dynamic thermography to test our devised novel *TAR* method. They all reviewed and approved the manuscript for publication.

Date: 15 Jan 2020

Signature

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ABSTRACT

Background: Carotid artery stenosis (CAS) or atherosclerosis, wherein narrowing of the carotid artery passage occurs as a result of endothelial cell dysfunction and inflammation that leads to thrombosis formation. A complete choke (occlusion) of the carotid artery or dislodging of the atherosclerosis tissue to the brain affects the normal brain functioning and may cause irreversible damage to the brain tissue or leads to a debilitating stroke. Duplex Ultrasound (DUS) is a widely available, low cost, and low-risk carotid artery stenosis (CAS) imaging modality; however, it needs trained personnel to perform and interpret the examination and suffers from inter/intra-observer variability. Therefore, a reliable, non-invasive, cost-effective, and automated alternate CAS screening tool will complement the current clinical CAS imaging and treatment profile. With the presence of stenosis, alterations in the carotid artery hemodynamics bring about changes in the heat transfer to the surrounding tissue, which is expected to translate into resulting temperature maps over the external skin surface (neck and face region); possibly correlates to the presence of stenosis. These abnormal temperature maps could be captured and quantified using non-contact/non-invasive infrared (IR) thermal imaging/thermography.

Materials and Methods: In this study, both passive and active thermographic techniques were used to evaluate the CAS screening potential. Unlike passive thermography, where no external stimulation is applied, active dynamic thermography (ADT) results in a high contrast thermal images with the application of external stimulation. Followed by preliminary computational analysis, prospective clinical research studies were performed

at the National Heart Centre, Singapore. A Duplex Ultrasound (DUS) examination was used to establish the ground truth. Under the computational study, stenosis influenced hemodynamic of the carotid artery and its effect on the bio-heat transfer to the external neck skin surface was studied. A total of 20 carotid artery samples, from 10 study participants with both sides normal (0% stenosis), stenosis (>50%) on one side, and stenosis (>50%) on both sides were studied. A 3-dimensional (3D) carotid artery and jugular vein model, encapsulated with a solid neck tissue phantom resembling the human neck, was used. Incorporating the individual-specific geometrical (depth of artery and stenosis) and flow (peak systolic and end-diastolic inlet velocity) boundary conditions, conjugate bio-heat transfer was studied using a finite volume numerical scheme. Under the passive thermography method, a total of 80 carotid artery samples from 40 study participants were used. A novel parametric thermal feature image extraction method was employed. Image statistical features, viz. correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis, were used to classify the samples by an optimized support vector machine (SVM)-based binary classification model. Upon the application of external stimulation, the presence of stenosis in the carotid artery differs the recovery rate of the external neck skin surface from the case with no stenosis. Using an external non-contact cooling stimulation for 60s, in this study, the ADT procedure was performed on 54 samples from 27 study participants. Analyzing the ADT sequence with a novel quantitative parameter called tissue activity ratio (*TAR*), the study samples were classified using a cut-off value-based binary classification model.

Results: Preliminary computational study and *in-vivo* thermal maps show that the average temperature on the external neck skin surface is significantly higher for normal

samples (32.82 ± 0.53 °C versus 32.00 ± 0.37 °C, $p < 0.001$). Furthermore, the thermal region of interests (TROIs) were extracted from the *in-vivo* thermal images, which both qualitatively and quantitatively distinguish the normal and diseased cases. For the prospective clinical passive thermography study, while for the control samples, the temperature distribution was observed to be more uniform within high-temperature zones (31 °C to 34 °C), for the diseased samples, as a result of presence of stenosis in the carotid artery, the temperature distribution resulted into cold temperature zones (29 °C to 32 °C). The mean temperature was found to have decreased with the increase in the degree of stenosis (30% or more stenosis) in the carotid artery (32.77 ± 0.13 °C versus 32.48 ± 0.18 °C, $p < 0.01$). Classifying the samples with 30% or more stenosis in the carotid artery, the SVM model resulted in a sensitivity, specificity, and accuracy of $89.4 \pm 1.0\%$, $97.3 \pm 0.9\%$, $94.1 \pm 0.5\%$, respectively. For the ADT method, between the two sample groups (30% stenosis cut-off), the value of the *TAR* parameter was found to have depreciated with a significant difference (0.88 ± 0.04 versus 0.75 ± 0.02 , $p < 0.001$). A receiver operating characteristic (ROC) curve analysis was employed to evaluate the optimal cut-off point for the binary classification model, which resulted in a sensitivity, specificity, and accuracy of 100%, 78%, and 85%, respectively.

Conclusions: This study suggests the potential of thermography as a possible screening tool for CAS patients. From this study, no relation between the image feature and the exact location of the stenosis in the carotid could be evaluated. Instead, only the presence of a maximum stenosis degree in the carotid artery can be predicted. This forms the basis for possible future work in the field.

Keywords: Atherosclerosis; Active Dynamic Thermography; Binary Classification; Carotid Artery Stenosis; Conjugate bio-heat transfer; Hemodynamic; Infrared (IR) Thermal Imaging; Medical Thermography; Machine Learning; Tissue Activity Ratio

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I would like to thank the staff of vascular lab (NHCS) and Ms. Siti Aishah Binte Mohd Hassan (Clinical Coordinator, NHCS) who helped with carotid artery duplex ultrasound data collection and patient recruitment assistance, respectively. I would like to acknowledge the contribution of Mr. Vignesh Raman, former Research Associate, NTU, whose experience with infrared thermal cameras, thermography data collection at the hospital, and assistance in developing image processing algorithms played an important role in achieving the most valuable milestones of this thesis. I would like to acknowledge the NTU-India connect program that availed the opportunity to collaborate and work with

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At last, I would like to acknowledge the most important people in my life. First of all, my mother, Late Mrs. Gayatri Saxena, who I lost in an accident during the Ph.D. studies. Though I will never witness the pride in her eyes on this one of the major accomplishments in my career, I believe that her love, warmth, and blessings will always remain with me. There is no word to express my gratitude towards my father, Mr. Ramendra Kumar Saxena, who was always supportive of my higher studies plan and still motivates me to go far and beyond. I would like to convey a special thanks to my sister, Mrs. Akansha Saxena, who was always there through the thick and thin of my life. She is the role model who never stopped believing in me and always reminds me that the sky is the limit. I would like to acknowledge my other two sisters, Mrs. Anju Saxena and Mrs. Divya Saxena, my brothers-in-law, niece, and nephews, who were always a constant source of joy and moral support throughout this journey. A substantial time of my life has culminated in this thesis, that comprises of many colleagues, friends, teachers, technicians, and undergraduate students. A big thanks to all of you.

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LIST OF PUBLICATIONS

Technical Disclosure/Copyright

1. Ashish Saxena, *E.Y.K. Ng, and Lim Soo Teik*. “Neck Thermography for a Non-contact/Non-invasive Screening of Patients with Carotid Artery Stenosis”, NTUitive Pte. Ltd., Singapore (Ref. no.: 2019-046).
2. Ashish Saxena, *E.Y.K. Ng, Vignesh Raman, and Lim Soo Teik*. “Thermography based superficial vein projection system to ease real-time vein puncturing”, NTUitive Pte. Ltd., Singapore (Ref. no.: 2018-150).

Journal

1. Ashish Saxena, E.Y.K. Ng, Soo Teik Lim, "Active Dynamic Thermography to Predict the Presence of Stenosis in the Carotid Artery", *Computers in Biology and Medicine* (2020): 103718. <https://doi.org/10.1016/j.combiomed.2020.103718>
2. Ashish Saxena, *Vedabit Saha, E.Y.K. Ng*, “Skin temperature maps as a measure of carotid artery stenosis”, *Computers in Biology and Medicine* (2019): 103548. <https://doi.org/10.1016/j.combiomed.2019.103548>
3. Ashish Saxena, *E.Y.K. Ng, Vignesh Raman, Muhammad Syarifuddin Bin Mohamed Hamli, Mateusz Moderhak, Szymon Kolacz, and Jerzy Jankau*. "Infrared (IR) Thermography-based Quantitative Parameters to Predict the Risk of Post-operative Cancerous Breast Resection Flap Necrosis." *Infrared Physics & Technology* (2019): 103063. <https://doi.org/10.1016/j.infrared.2019.103063>

4. *Ashish Saxena, E.Y.K. Ng, Soo Teik Lim*, " Infrared (IR) thermography as a potential screening modality for carotid artery stenosis", *Computers in Biology and Medicine* (2019). <https://doi.org/10.1016/j.combiomed.2019.103419>
5. *Ashish Saxena, E.Y.K. Ng, Mrudang Mathur, Chirag Manchanda, and Nehal Amit Jajal*, "Effect of carotid artery stenosis on neck skin tissue heat transfer." *International Journal of Thermal Sciences* 145 (2019): 106010. <https://doi.org/10.1016/j.ijthermalsci.2019.106010>
6. *Ashish Saxena, E.Y.K. Ng, and Lim Soo Teik*. "Imaging modalities to diagnose carotid artery stenosis: progress and prospect." *BioMedical Engineering OnLine* 18.1 (2019): 66 <https://doi.org/10.1186/s12938-019-0685-7>
7. *Ashish Saxena, Vignesh Raman, and E.Y.K. Ng*. "Study on methods to extract high contrast image in active dynamic thermography", *Quantitative InfraRed Thermography Journal* (2019): 1-17, Taylor & Francis Online, <https://doi.org/10.1080/17686733.2019.1586376>
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9. *Ashish Saxena, E.Y.K. Ng, and Vignesh Raman*. "Thermographic Venous Blood Flow Characterization with External Cooling Stimulation." *Infrared Physics & Technology* 90 (2018): 8-19. <https://doi.org/10.1016/j.infrared.2018.02.001>
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1. *Tejas Canchi, E.Y.K. Ng, Ashish Saxena, Sriram Narayanan*, “CFD based post-processing of CT-MRI data to determine the Mechanics of Rupture in Abdominal Aortic Aneurysms” In: Abreu de Souza M., Remigio Gamba H., Pedrini H. (eds) *Multi-Modality Imaging*. 2018, Springer, Cham. https://doi.org/10.1007/978-3-319-98974-7_4
2. *Ashish Saxena, E.Y.K. Ng, Jaya Krishna Devanuri, Jalaiah Nandanavanam, and Parameshwaran Rajagopalan*, “Numerical Investigation of Mixed Convection in a Lid-Driven Square Cavity With and Without Fin” in *Mechanical Engineering for Sustainable Development: State-of-the-Art Research* (eds. Rao, C., Rao, G., Selvaraj, N., Bose, P. & Chandramohan, V.) 483–498 (Apple Academic Press, Taylor and Francis, 2019). <https://doi.org/10.1201/9781351170161>

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1. *Ashish Saxena, Vedabit Saha, E.Y.K. Ng*, “Evaluation of neck tissue heat transfer in case of stenosis in the carotid artery”, 16th UK Heat Transfer Conference (UKHTC), 08-10 Sept 2019, Nottingham, United Kingdom.

2. Ashish Saxena, *E.Y.K. Ng, and Lim Soo Teik*. “Neck skin thermal features as a measure of stenosis in the carotid artery: computational and in-vivo study”, PhD student paper competition finalist at Summer Biomechanics, Bioengineering and Biotransport Conference (SB3C), 25-28 Jun 2019, Seven Springs, PA, USA.
3. Ashish Saxena, *E.Y.K. Ng, and Vignesh Raman*. “A novel approach to analyze transient thermal images in active dynamic thermography of superficial skin tissue”, IUPESM – World Congress on Medical Physics & Biomedical Engineering, 3-8 Jun 2018, Prague, Czech Republic.
4. Ashish Saxena, *E.Y.K. Ng*, “Venous blood flow characterization in a human forearm”, 20th International Conference on Mechanics in Medicine and Biology (ICMMB), 24-25 May 2017, Melbourne, Australia.
5. Ashish Saxena, *Tan Wei long, E.Y.K. Ng*, “Numerical and experimental investigation of temperature map over the superficial skin as a tool for blood flow characterization in the vessels”, 1st International Biophotonics Conference, Singapore, 25-26 Jul 2016.

LIST OF SYMBOLS

A	Area of cross-section (m^2)
C_{Pb}	Specific heat capacity of blood (3600 J/kg°C)
C_{Ps}	Specific heat capacity of skin tissue (3600 J/kg°C)
C_{Pst}	Specific heat capacity of stenosis tissue (4080 J/kg°C)
D	Diameter (m)
h_{NC}	Natural convection heat transfer coefficient ($10 Wm^{-2}°C^{-1}$)
k_b	Thermal conductivity of blood (0.54 W/m°C)
k_t	Thermal conductivity of tissue (0.54 W/m°C)
k_{st}	Thermal conductivity of stenosis tissue (0.48 W/m°C)
l_c	Characteristic length ($4A/P$, m)
m	Variable parameter (non-dimensional)
N	Number of study participants
n	Number of carotid artery samples
P	Perimeter of cross-section (m)
P_g	Gauge pressure (Pa)
q_m''	Volumetric heat generation (33 W/m ³)
Re	Reynolds number ($\frac{Ul_c}{\eta_b}$, non-dimensional)
R_n	Node ratio (non-dimensional)
r	Radial distance from the center of the vessel ($\sqrt{x^2 + y^2}$, m)
T	Temperature at any point in the model (°C)
T_∞	Ambient temperature (21 °C)
T_a	Arterial temperature (37 °C)

T_{mi}	Minimum temperature in the thermal image (°C)
T_{mx}	Maximum temperature in the thermal image (°C)
T_{th}	Threshold temperature (°C)
t	Time (s)
u	Velocity in lateral direction (m/s)
v	Velocity in transverse direction (m/s)
u_{axial}	Velocity in the axial direction of the flow at any area section in the carotid artery (m/s)
U	CCA inlet velocity (m/s)
U_{PSV}	CCA peak systolic velocity (m/s)
U_{EDV}	CCA end diastolic velocity (m/s)
U_{JV}	Jugular vein velocity (m/s)
w	Velocity in streamwise direction (m/s)
W	Contrast factor
x	Lateral coordinate (m)
y^*	Distance between the outer and the dividing wall of the ICA (non-dimensional)
y	Transverse coordinate (m)
z	Streamwise coordinate (m)

Greek symbols

α	Thermal diffusivity of blood ($k/\rho C_p$, m ² /s)
ρ_b	Density of blood (1060 kg/m ³)
ρ_t	Density of skin tissue (1000 kg/m ³)
ρ_{st}	Density of stenosis tissue (920 kg/m ³)
μ_b	Dynamic or absolute viscosity of blood (0.003675 Pa.s)

η_b Kinematic viscosity of blood (μ_b/ρ_b , m²/s)
 ω_b Tissue blood perfusion rate (0.4333 Kg/ms)

Abbreviations

BM Block Matching
CAS Carotid Artery Stenosis
CAD Coronary Artery Disease
CTA Computed Tomography Angiography
CVD Cardiovascular Disease
CWD Continuous-Wave Doppler
CCA Common Carotid Artery
DUS Duplex Ultrasound
DE Doppler Effect
DS Doppler Shift
DSA Digital Subtraction Angiography
ECA External Carotid Artery
IMT Intima Media Thickness
ICA Internal Carotid Artery
MRI Magnetic Resonance Imaging
MRA Magnetic Resonance Angiography
OCT Optical Coherence Tomography

PAT Photoacoustic Tomography

PWD Pulsed-Wave Doppler

ROI Region of Interest

TROI Thermal Region of Interest

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CHAPTER 1 INTRODUCTION

1.1 Introduction

Cardiovascular diseases (CVD) are the medical conditions affecting heart, blood or blood vessels. In clinical medicine, coronary artery disease, carotid artery disease, and peripheral vascular disease are a common manifestation of CVD. Carotid artery stenosis (CAS) or atherosclerosis, wherein narrowing of the carotid artery passage occurs as a result of endothelial cell dysfunction and inflammation that leads to thrombosis formation [1], is of great interest to the scientific medical imaging and clinical communities across the globe. The carotid artery is the primary supplier of oxygenated blood to the human brain. It originates at the aortic arch and moves upwards on either side of the neck as common carotid artery (CCA), which bifurcates into the internal carotid artery (ICA) and the external carotid artery (ECA) – supplying blood to the brainstem and the face, respectively (**Figure 1-1**). The occlusion of the arterial lumen starves the brain of an adequate blood supply leading to an impairment in the brain function. At times, extended periods of reduced blood supply cause permanent damage to the vascular tissue present in the brain. The deposition of stenosis tissue also poses another serious threat, that of a stroke. When this deposition in the arterial lumen is suddenly dislodged, it travels along the internal carotid artery into the brain until it enters a segment of the cerebral vasculature, too narrow for it to pass through. The stenosis tissue is, therefore, lodged in the brain causing a stroke which may lead to death [2,3].

Figure 1-1: Carotid artery anatomy [4]

In 2013, stroke was the second leading cause of deaths globally [5]. According to the American Heart Association (AHA report 2019) [6], in the United States alone, around 795,000 cases of stroke are reported yearly, and on average, every 4 minutes, someone dies of a stroke; consumes 1.7% of national health expenditures, and by 2030, the total annual cost of stroke is expected to increase by 129% [7]. It is estimated that the patients (total of 1840 patients) with 60% or more stenosis have a 16% risk of experiencing a stroke over a period of 5 years [8]. Calculating the age and sex standardized incidence rate of strokes (45 to 84 years age group) from 11 studies (from 1984 to 1995) in 10 different cities of Europe, Russia, Australia, and the United States, it was found out that a higher and lower incidence rate of 627 and 638 per 100,000 people in Russia and France, respectively, while a similar incidence rate of 300 to 500 per 100,000 people for the rest of the regions [9]. The prevalence of moderate/severe CAS increases with age (total participants: 23,706), especially after the age of 50, and affecting men more than women [10] (**Figure 1-2**). Therefore, screening, diagnosis, imaging, and monitoring of CAS play an essential role in the clinical decision making and overall CAS treatment profile.

Figure 1-2: Prevalence of moderate carotid stenosis cases among men and women in various age groups [10]

1.2 Carotid artery stenosis (CAS): Genesis

The structure of an artery, or in most blood vessels like the carotid artery, is composed of three layers of tissue, namely, tunica intima, tunica media, and tunica adventitia or externa [11]. As shown in **Figure 1-3a**, these layers encase over an open space known as the lumen that holds and directs the bloodstream through its designated route. Directly adjacent to the blood flow, the tunica intima contains a monolayer of endothelial cells that forms a sleek surface, facilitating the movement of blood with minimal friction. Surface receptors are embedded into these cells, regulating vascular permeability, platelet aggregation, and resistance to thrombosis. In response to a physical or metabolic injury, the endothelium triggers a biochemical signal for inflammatory cell migration to the damaged site. Recurring damages in this region result in the formation of fatty streaks, leading subsequently to the formation of an atherosclerotic plaque [8]. Lesions inflicted on the arterial wall could be attributed to several factors; hemodynamic, metabolic, environmental, and genetic risk factors which prompts an inflammatory response through

cell proliferation and an eventual plaque progression. The perpetuation of the immune response within the arterial wall leads to formation of an atheroma that protrudes into the arterial lumen causing a reduction in luminal diameter. Further cell repair attempts by the endothelial cells, forming the atherosclerotic plaque, constrict the arterial diameter, progressing into eventual arterial stenosis [12].

Figure 1-3: Schematic of (a) blood vessel structure and its components [4] (b) localized shear stress in carotid artery flow [13]

The carotid artery is the primary supplier of oxygenated blood to the human brain. It originates at the aortic arch and moves upwards on either side of the neck as common carotid artery (CCA), which bifurcates into the internal carotid artery (ICA) and the external carotid artery (ECA) – supplying blood to the brainstem and the face, respectively. The junction of CCA separation into ICA and ECA is known as the carotid bifurcation. Atherosclerotic plaque formation at the carotid bifurcation can be greatly attributed to hemodynamic forces. In a laminar flow of the bloodstream, a gradient of fluid velocities appears increasingly from the wall to the center. Friction induced between the blood flow and wall creates a tangential force on the wall, which is termed as wall shear stress. With the differing velocities from the geometry of the artery, regions of high

and low wall shear stresses are formed (**Figure 1-3b**). In the case of the carotid bifurcation, flow separation occurs when high blood velocities meet the divider, giving rise to secondary flow patterns along the external side of the carotid sinus. Through this separation, high shear stress regions are localized near the inner walls of the bifurcation, with low shear stress regions located nearer to the outer walls. The increase of wall stresses promotes cell elongation and alignment with respect to the flow, while exposure to lower stresses induces rounding of these cells. These surface irregularities in the low-stress regions of the endothelial layer result in the reduction in cell reparability and hence, promoting plaque formation. In addition, the pulsating nature of the blood flow from the cardiac cycle induces varying shear rate, affecting areas with a slower flow such as the carotid sinus and narrowed arteries. These low shear rate areas are prone to atheroma formation [12]. Progressive narrowing of the carotid artery or sudden plaque rupture causing thrombus occlusion or embolization may result in transient ischemic attack (TIA) or stroke.

1.3 CAS Diagnosis

While there exist imaging modalities, viz. Duplex Ultrasound (DUS), Computed Tomography Angiography (CTA), and Magnetic Resonance Angiography (MRA), to visualize and quantify the vulnerable plaque in the carotid artery, potential imaging modalities, viz. Photoacoustic Tomography (PAT) and Optical Coherence Tomography (OCT), are underway to be translated into medical practice [14,15]. In a clinical setting, if the physician detects the presence of carotid bruit, an ultrasound examination or CTA/MRA is then prescribed to confirm the presence and severity of carotid stenosis.

DUS is the most widely available, low cost, and low-risk CAS imaging modality; however, it needs trained personnel to perform and interpret the examination and suffers from inter/intra-observer variability [16]. While CTA has risk associated with X-ray radiation exposure, MRA is not suitable for patients with certain types of implants, viz. cochlear (ear) implants, clips used for brain aneurysms, metal coils placed within blood vessels, older cardiac defibrillators and pacemakers, etc., because of magnetic fields involved [17–19]. In both the modalities (CTA and MRA), contrast usage may lead to adverse allergic reactions or nephropathy [20]. While both CTA and MRA machines need a large area for installation, MRA is a time-consuming procedure, costly, and not readily available [21]. This limits their applicability as a screening tool. While it is established that timely detection and monitoring of the prognosis of symptomatic CAS or atherosclerosis is vital for effective medical treatment response, for asymptomatic cases, there is no conclusive diagnosis yet in place [22,23]. To diagnose asymptomatic cases, mass screening the population under the high-risk category (age, smoking, alcohol, diabetes, etc.) could be a viable solution. However, as per the Society of Vascular Surgery (SVS), using the most readily available and relatively low-cost DUS examination, in the UK alone, such a mass screening will help in preventing only 230 strokes annually, that too at the cost of US\$ 21 million [24]. Therefore, a reliable, non-invasive, cost-effective, automated, fast, and easy-to-use alternate CAS screening tool, that will complement the current clinical CAS imaging and treatment profile, is yet to be fulfilled.

1.4 Medical Thermal Imaging

It is well established that any object above absolute zero temperature emits infrared (IR) radiations. Depending upon the emissivity (ϵ) and temperature (T in K) of the object surface, the total emissive power (E in W/m^2) is calculated [25] as follows:

$$E = \epsilon \sigma T^4 \quad (1-1)$$

where, σ is the Stefan Boltzmann constant with a value of $5.676 \times 10^{-8} \text{ W/m}^2 \text{ K}^4$.

The emissive power provides a measure of temperature when detected with an IR detector, resulting in a thermal map called thermogram. Medical thermal imaging or thermography is a technique for non-contact detection and measurement of variations in the heat emitted by various regions of the body in the form of Infrared (IR) radiations and transforming them into visible signals (temperature) that can be recorded photographically using an IR thermal camera [26]. The application of thermography for various medical disease diagnosis and health monitoring includes fever screening [27], diabetic neuropathy [28], vascular disorders [29], breast cancer detection [30], brain imaging [31], etc. Essentially, thermography can be performed in two ways: passive and active. Unlike passive thermography, where no external stimulation (heat, cold, pressure, etc.) is applied, active dynamic thermography (ADT) results in high contrast thermal images with the application of external stimulation. In ADT, transient temperature maps of the skin surface are captured using an IR thermal camera while the skin surface is stimulated externally followed by a recovery phase.

1.5 Clinical Outlook: Thermography and CAS

In the case of the carotid artery, a conjugate biothermal interaction between three domains: blood, surrounding tissue, and the external ambient environment, exists. It is evident that the convective heat transfer due to blood flow in the carotid artery will lead to the development of a temperature profile at the interface of the carotid artery wall and surrounding tissue. Following this, along with the blood perfusion and volumetric heat generation, thermal diffusion will take place in the tissue, which finally interacts with the external skin surface. Given that the external skin surface is under ambient natural convective boundary condition, a resultant temperature profile will occur. With the presence of stenosis, alterations in the carotid artery hemodynamics bring about changes in the heat transfer to the surrounding tissue. This is expected to be captured in the resulting temperature map over the external neck skin surface; possibly correlates to the presence of stenosis. Upon the application of external stimulation as in the case of ADT, the presence of stenosis in the carotid artery is expected to differ the recovery rate of the external skin surface from the case with no stenosis. Quantifying this difference, a screening tool could be developed.

Currently, there is no temperature-feature based non-invasive and non-contact carotid stenosis screening test available. The proposed thermography-based screening tool offers a fast and easy-to-use diagnostic. On average, a carotid ultrasound takes about 30 minutes that requires a trained sonographer to perform the examination and analyse the results thereafter [32]. While with passive thermography, once the patient is positioned

appropriately, it takes only a few seconds to perform the examination, with active dynamic thermography, this time is about 5 minutes. This time is, however, excluding the 15-minute waiting time to bring the body in thermal equilibrium with the ambient condition [33]. It should be noted that unlike a carotid ultrasound, the patient is not under examination for this 15-minute waiting time. According to the MDsave cost estimation website [34], the cost of carotid ultrasound ranges from US\$217 to US\$700. Though the cost of the thermography-based examination is not estimated yet, intuitively, with no need for a bulky set-up, highly skilled operator, and reduced time of examination, it is expected to be a relatively low-cost examination [35]. Furthermore, only the high-risk patients as detected by the proposed low-cost thermography-based screening shall be prescribed for further investigative diagnostics, hence, complementing the current clinical stenosis diagnosis. Relatively, such a screening examination will be more beneficial to the low and middle-income countries, where both the stroke-related deaths [36] and the patient to medical facilities ratio are high [37–39].

Other than the symptomatic carotid stenosis group of patients, given there is a possible relation between carotid stenosis and postoperative stroke incidences, carotid ultrasound scans are performed before the cardiac surgical procedures like coronary artery bypass grafting [40]. In a study on 295 patients undergoing bypass surgery, only 72 were found to have significant stenosis [41]. Therefore, based on factors like female gender, peripheral vascular disease, history of transient ischemic attack or stroke, smoking, and coronary artery disease, correlations were explored to perform a preoperative carotid ultrasound on high risks patient only [42]. However, this adds to the cost and time burden

on the overall treatment. In such a scenario, thermography could be an alternative carotid screening solution. Additionally, for asymptomatic patients, mass-screening for even high-risk patients (age, smoking, alcohol, diabetes, etc.) is not recommended. According to SVS, screening all 60-year-old high-risk patients with DUS would cost £17 million (US\$21 million). This will result in preventing about 230 strokes annually in the UK, which represents only 0.2% of the annual UK stroke burden [24]. Hence, the cost versus advantage is not justified. However, with the expected low-cost thermography-based screening tool, the cost versus advantage ratio may justify the implementation of such a mass screening.

1.6 Thesis Objective and Scope

As a main objective, this thesis will look at the diagnostic potential of a non-contact/non-invasive IR thermography modality for carotid artery stenosis. Both passive and active thermographic methods are tested. Unlike passive thermography, where no external stimulation is applied, active dynamic thermography (ADT) results in a high contrast thermal images with the application of external stimulation. Accordingly, the scope of this thesis covers the following:

1. Studying stenosis influenced hemodynamic of the carotid artery and its effect on the bio-heat transfer to the external neck skin surface using computational fluid dynamics.
2. Performing *in-vivo* skin temperature measurement and developing an image segmentation method to bring contrast between normal and diseased (carotid artery stenosis) samples.

3. Developing a method to extract statistically distinguishable (between normal and diseased samples) thermal features from the passive thermal images.
4. Performing a prospective clinical passive thermography study to evaluate the classification accuracy of a thermal feature-based carotid artery stenosis detection method using cut-off value-based receiver operating characteristics (ROC) analysis.
5. Developing a protocol to perform ADT procedure for carotid artery stenosis detection and a quantitative parameter to analyze the time-series thermal image sequence in the ADT procedure.
6. Performing a prospective clinical ADT study to evaluate the diagnostic potential of ADT procedure for carotid artery stenosis using cut-off value-based receiver operating characteristics (ROC) analysis.
7. Where cut-off value-based classification results in poor classification performance, a Support Vector Machine (SVM)-based machine learning classification algorithm is employed.

1.7 Thesis Organization

0 provides a review of the imaging modalities which are currently used in clinical settings, their extent of imaging and technical development over time. Furthermore, a comparative analysis among these modalities is outlined, followed by a brief overview of their future development. At last, potential imaging modalities that are either under clinical trial or development are also described. This chapter outlines the carotid stenosis diagnostic space that an IR thermography-based modality could fulfill.

0 presents a study on the effect of carotid artery stenosis on the neck skin temperature maps. In this study, both computational and *in-vivo* measurement techniques were used to qualitatively and quantitatively conceptualize the basis for a temperature feature-based carotid stenosis screening method.

0 evaluates the diagnosis potential of a passive thermography-based screening tool for carotid artery stenosis. This study describes the thermal feature extraction methodology, followed by the application of classification models to report the diagnosis accuracy.

CHAPTER 5 introduces a novel method of quantifying an active dynamic thermography (ADT)-based time-series thermal image sequence. Furthermore, a qualitative and quantitative comparison with the pre-existing methods is reported.

CHAPTER 6 presents the application of the ADT quantitative method, derived in **CHAPTER 5**, in carotid artery stenosis screening. This study describes the data processing methodology, followed by the application of a classification model to report the diagnosis accuracy.

CHAPTER 7 draws the main conclusion of this thesis, followed by a brief reflection on the clinical outlook of a temperature feature-based carotid artery stenosis diagnosis. At last, relating to the limitations of the study, recommendations on the future work are outlined.

1.8 Contribution of the Thesis

Following are the contribution of this thesis:

1. This thesis summarizes a comprehensive technical development in the imaging modalities that are clinically used for diagnosis and imaging carotid artery stenosis, along with a brief note on the potential imaging modalities that could further complement the diagnosis.
2. In contrast to the literature, where the carotid artery was modeled as a cylindrical tube with a standard stenosis geometry and flow conditions, in this thesis work, a computational conjugate bioheat transfer study, on an idealized 3-dimensional (3D) carotid artery model with patient-specific (measured by Duplex Ultrasound examination) stenosis geometry and physiological flow conditions, was performed.
3. For passive thermal images, a novel parametric image thermal feature extraction method is introduced.
4. Using a machine learning-based classification algorithm (Support Vector Machine), on the extracted parametric image thermal features, a highly accurate carotid artery stenosis sample classification is demonstrated.
5. For active dynamic thermography (ADT), where an external cooling stimulation is applied to extract high contrast thermal image sequence, a novel parametric image reconstruction method (*TAR*: Tissue activity ratio) is introduced that qualitatively and quantitatively represents the whole ADT sequence with a reconstructed single image.
6. To correct the motion artifact in the time-series thermal image ADT sequence, an adaptive direct phase substitution algorithm is introduced.
7. Last but not least, using the *TAR* parameter, this thesis reports the diagnosis potential of ADT for carotid artery stenosis.

CHAPTER 2 A REVIEW OF IMAGING MODALITIES TO DIAGNOSE CAROTID ARTERY STENOSIS: PROGRESS AND PROSPECT

2.1 Abstract

In the past few decades, imaging has been developed to a high level of sophistication. Improvements from one-dimension (1D) to 2D images, and from 2D images to 3D models, have revolutionized the field of imaging. This not only helps in diagnosing various critical and fatal diseases in the early stages but also contributes to making informed clinical decisions on the follow-up treatment profile. Carotid artery stenosis (CAS) may potentially cause debilitating stroke, and its accurate early detection is therefore important. In this study, the technical development of various CAS diagnosis imaging modalities and its impact on the clinical efficacy were thoroughly reviewed. These imaging modalities include duplex ultrasound (DUS), computed tomography angiography (CTA) and magnetic resonance angiography (MRA). For each of the imaging modalities considered, imaging methodology (principle), critical imaging parameters, and the extent of imaging the vulnerable plaque are discussed. DUS is usually the initial recommended CAS diagnostic examination. However, for the therapeutic intervention, either MRA or CTA is recommended for confirmation, and for added information on intracranial cerebral circulation and aortic arch condition for procedural planning. Over the past few decades, the focus of CAS diagnosis has also shifted from pure stenosis quantification to plaque characterization. This has led to

further advancement in the existing imaging tools and development of other potential imaging tools like Optical coherence tomography (OCT), photoacoustic tomography (PAT), and infrared (IR) thermography.

2.2 Introduction

In the past few decades, imaging has been developed to a high level of sophistication. Improvement from one-dimension (1D) to 2D images, and from 2D images to 3D models have revolutionized the field of imaging. This not only helps in diagnosing various critical and fatal diseases in the early stages but also contributes to making informed clinical decisions on the follow-up treatment profile. Carotid artery stenosis (CAS) may potentially cause debilitating stroke, and its accurate early detection is therefore important. In this study, the technical development of various CAS diagnosis imaging modalities and its impact on clinical efficacy is thoroughly reviewed. These imaging modalities include Duplex Ultrasound (DUS), Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA). For each of the imaging modalities considered, imaging methodology (principle), critical imaging parameters, and the extent of imaging the vulnerable plaque is discussed. DUS is usually the initial recommended CAS diagnostic examination. Whereas for therapeutic intervention, either MRA or CTA is recommended for confirmation and addition information on intracranial cerebral circulation and aortic arch condition for procedural planning. Over the past few decades, the focus of CAS diagnosis has also shifted from pure stenosis quantification to plaque characterization. This has led to further advancement in the existing imaging tools

and development of other potential imaging tools like Optical Coherence Tomography (OCT), Photoacoustic Tomography (PAT), and Infrared (IR) Thermography.

2.3 X-ray Imaging

X-ray imaging dates to 1895 when Rongten discovered X-rays for imaging the biological tissues. The intensity of the radiation changes due to scattering and attenuation while transmitting through various tissues (different optical properties). This forms a 2D image when falling on a photographic film. The first medical application was in the field of bone (high attenuation for X-ray photons) imaging [43]. To visualize the blood flow in the arteries, X-ray imaging requires an injection of a contrast agent. Contrast agents, like Iodine, Lanthanide, Gold nanoparticle, etc. [44], help in attenuating the X-rays which is measured as contrast density value in Hounsfield units (Hu). This is called X-ray angiography.

2.3.1 Digital Subtraction Angiography (DSA)

DSA or mask mode subtraction is a technique to specifically visualize the vascular system (blood flow in the vessels) with injection of smaller-than-usual quantity of contrast material (compared to conventional quantity) under an X-ray exposure [45]. In DSA, by subtracting the two X-ray images taken before (mask) and after the injection of contrast material (**Figure 2-1**), a blood vessel image with high contrast is obtained. Comparing the visualization of carotid artery with the conventional angiography (in 100 patients), DSA provides a sensitivity, specificity, and accuracy of 95%, 99%, and 97%, respectively [46].

Mask Image Mask with Dye Subtraction Image

Figure 2-1: Subtraction image methodology using mask and dye images in DSA [47]

DSA was used in the randomised studies in the European Carotid Surgery Trial (ECST) [48] and North American Symptomatic Endarterectomy Trial (NASET) [49,50], comparing the surgical carotid endarterectomy (CEA) versus medical therapy in the treatment of patients with moderate (50% to 69%) and severe stenosis (70% to 99%), as defined using the NASCET criteria. Some confusion was introduced to the field because of the different criteria in defining degree of stenosis. NASCET criteria of 50% stenosis is roughly equal to 75% stenosis by ECST criteria (**Figure 2-2**). However, both studies found that compared with medical therapy, there was significant benefit with CEA in symptomatic patients with severe degree of stenosis (NASCET 70-99% stenosis, and ECST 80-99% stenosis). There was only modest benefit in those with moderate degree of carotid stenosis (NASCET 50-69% stenosis, ECST 70-79% stenosis). DSA is also useful in predicting the cerebral hyperperfusion phenomenon (HPP) developed upon carotid interventions. HPP, of low incidence but it can lead to morbidity and mortality, may cause watershed cerebral infarction [51]. Indirectly measuring the cerebral circulation time (CCT), using the time to reach maximum contrast intensity, DSA can predict HPP (prolonged CCT) with a sensitivity and specificity of 75% and 100%, respectively [52].

Figure 2-2: NASCET and ECST measurement of internal carotid artery stenosis
[53]

2.3.2 Computed Tomography Angiography (CTA)

Since the conventional angiography involves acquisition of a 2D image from a 3D body, it superimposes imprints of all the structures across the 3D body as the X-rays pass through it, therefore, a lot of information is not completely revealed. To address this issue, in 1973, the first successful CT scanner, claimed to be 100 times more sensitive as compared to conventional X-ray angiography, was introduced [54]. In CTA, slice-based imaging of the 3D body is done, wherein a series of 2D slice (of defined thickness) images are generated for the whole 3D body. From the 2D slices, a 3D reconstruction can be performed for a better visualization (**Figure 2-3**). The equipment consists of an X-ray source that irradiate a narrow section of the 3D body (called slice) from one side, while the transmitted signals are received by the detector on the other. To perform a complete 360° scan, the set of source and detector rotates around the body to produce slice by slice images. This basic technique to perform CTA has gone through a series of developments in terms of scanning speed, slice to volume scanning, cone-beam scanning, etc. as chronologically summarized in the work of Kalender [55]. Revolutionizing the medical

imaging, CTA has further reduced the quantity of contrast agent needed for the examination as compared to the conventional angiography [56].

Figure 2-3: Carotid artery CTA: (a) 3D reconstruction (b) 2D slice image (credits: National Heart Center Singapore)

With the advancement in the image processing and analysis techniques, semi- and fully-automated 3D CTA analysis programs were developed and tested [57]. In the early attempts, where a semi-automated image processing algorithm is used to segment and trace the target blood vessel, CTA performed poorly as compared to DSA [58] or duplex ultrasound [59]. In semi-automated algorithms, manual identification of the reference point of segmentation and appropriate selection of upper and lower bound of contrast intensity (in Hu) are the necessary steps. Further, with the post-processing manual corrections, semi-automated CTA showed an improvement of 55% in the correlation coefficient (r : 0.53 to 0.82) with respect to DSA [60]. Recently, an operator independent fully-automated CTA showed a carotid artery detection rate of 75% on a small data set of 14 patients [61]. In this method, upon normalizing the original slice images, an automatic identification of the circular region of interest, in the threshold and diameter range of 200-450 Hu and 2-6 mm, respectively, that corresponds to the carotid artery

marking, was performed. Through an inverse approach, where the bone region is first segmented and eliminated before segmenting out the carotid artery, using machine learning based k -NN (k nearest neighbour) classifier model, a full-automated CTA reported an accuracy of 99% [62]. Moving on, it is believed that velocity evaluation can further strengthen the diagnosis efficacy of CTA. The quantification of the visualized blood vessels in terms of blood flow velocity measurement can be done with the help of complex algorithms, viz. tracking and computational methods. These algorithms track the progression of contrast material with respect to time (**Figure 2-4**) [63]. While tracking method tracks a contrast material as it moves inside the vessel within the field of view, computational method employs the mass conservational laws to compute the flow rate.

Figure 2-4: Contrast bolus intensity based time of flight method to estimate velocity with two distal region of interests (ROI) [63]

2.4 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI), where radio frequency pulses are used to stimulate the proton spinning in a tissue (with varied material properties with respect to the

surrounding), is most widely used to achieve high contrast images of the body's internal structures [64]. In principle, when spinning protons experience an external constant magnetic field, they align themselves in the same direction of the applied field, while few protons, possessing high energy state, will align in the direction opposite to applied magnetic field. This gives a resultant magnetization in the longitudinal direction (align with external magnetic field). Further, on the enforcement of a 90° radiofrequency energy pulse at resonance frequency, the protons aligned with external magnetic field absorb the excess energy and change their alignment directions to high energy state. In such a scenario, the spinning of the protons will be in synchronization with each other, which will give a resultant magnetization in the transverse direction to the external magnetic field. On the removal of the radiofrequency signal, the protons will fall back to their original state and releases energy, in the form of magnetic resonance signal, at a rate determined by either T_1 or T_2 relaxation times [65]. As the radiofrequency signal is removed, the spinning protons will start repelling each other, which leads to the decay of net transverse magnetization achieved earlier. This decay processes is measured in terms of T_2 relaxation time (or spin-spin relaxation). On the other hand, the protons in the higher energy state will start falling back to the lower energy state in the direction of external magnetic field, this will lead to the re-growth of the resultant magnetization in the longitudinal direction, which is measured in terms of T_1 relaxation time (spin-lattice relaxation). Based on the molecular structure under study, different T_1 or T_2 times are evaluated, hence, forms the basis for forming an image. This image provides a comprehensive information on internal structures and boundaries.

2.4.1 Magnetic Resonance Angiography (MRA)

In addition to basic MRI technique, registration of flow information led to the development of Magnetic Resonance Angiography (MRA). To bring the image contrast pertaining to the blood movement in the vessels and suppress the static tissue around, MRA projection imaging is used. Methods like temporal subtraction, inversion excitation, stimulating the adjacent regions, and phase shift are used to create projection images [66]. In temporal subtraction, two images are taken and subtracted with a similar static tissue signal and dissimilar moving tissue (blood) signal to produce a contrast enhanced moving tissue image. For instance, in phase contrast (PC) method [67], two images, at the systolic and the diastolic instants of the velocity waveform, are used to create a high contrast image. While the fast-moving blood during systolic instant leads to a signal loss, there will be a relative retaining of the signal for diastolic instant image. On the other hand, signal from static nearby tissue remains consistent. Hence, subtracting the two images results into a bright image of the blood vessel that helps in locating the lesion. Another method is time of flight (TOF) [67] where selective inversion magnetization is applied to the spin of the flowing tissue molecules and the two images with and without inversion are subtracted to leave out the static tissue signal. Alternative to the temporal subtraction method, a similar cancellation technique has also been developed that induces the suppression of the static tissue and selectively exciting the moving tissue to produce the desired projections [68].

Both PC and TOF methods are widely used for the detection of carotid artery diseases. Using these methods, under both NASCET and ECST criteria, the percentage of stenosis

detection (in 55 patients) is found to be higher than DSA [69]. In a study [70], comparing the sensitivity and specificity of TOF, high-resolution (HR) contrast-enhanced (CE), and time-resolved CE MRA techniques in 21 patients, it was found that the sensitivity for all the techniques was 100%, while specificity was highest for TOF MRA (96.7%). Meta-analysis has shown that the overall sensitivity and specificity of TOF MRA to diagnose severe stenosis ($70\% \leq S \leq 99\%$) are 91.2% and 82.3%, respectively [71]. Contrast agents such as gadolinium is also used to produce better quality images for smaller vessels which are likely to be not visible with normal MRA [72]. Further, use of automated vascular segmentation computer programs helps in determining the accurate dimensions of the vessels [73,74]. In an *in-vitro* stenotic phantom-based study, using a waveprop segmentation method, wherein the algorithm calculates the propagation of a virtual wave to segment the vessel upon manual identification of the start and end point of a 3D path line, the semi-automated MRA showed a high correlation coefficient (r) of 0.99 with the true diameter [75]. In an *in-vivo* study (40 carotid arteries), using another semi-automatic MRA, wherein a user-defined volume of interest and a point within the vessel is needed to extract the vessel central axis followed by the detection of the vessel boundaries, a varied degree of agreement with respect to the radiologist's visual inspection was found [76]. While arteries with 0-49% stenosis were detected with 100% agreement, arteries with 50-69% and 70-99% stenosis showed an agreement of 57% and 77%, respectively. In a recent first of its kind attempt, using a hierarchical-tree model along with the application of k -NN supervised classifier to detect the lumen boundary, in both normal (15) and atherosclerotic (20) subjects, a similarity index (Dice overlap), between the software and the manual delineation, of 0.87 was achieved [77].

2.5 Duplex Ultrasound

Being an accurate, non-invasive, yet low-cost mode of diagnostic imaging, Duplex Ultrasound (DUS) has become one of the main assessing methods for carotid diseases. This technique essentially fuses two procedures – traditional B-mode (grayscale) ultrasound, wherein images of the body parts/tissue architect, at rest, are generated from the reflected sound waves, and color-doppler ultrasound that visualizes the motion of the moving parts or fluid (blood) to measure the speed and other flow parameters. B-mode or brightness mode ultrasound is basically a two-dimension (2D) cross-sectional image, generated by the reflected ultrasound waves (echo) from the tissue structure boundaries, upon transmission of short burst or pulse of ultrasound by the transducer placed on the outer surface of the body. This is called pulse-echo principle. The so formed 2D image is composed of several B-mode lines that arises from a respective pulse-echo sequence. A pulse-echo sequence is formed by display of the brightness spot generated by the target that reflects the pulse, located at further depths from the transducer [78].

Figure 2-5: Schematic of Doppler Ultrasound principle

First reported by the Austrian physicist, Christian Doppler, Doppler Effect (DE) or Doppler Shift (DS) found numerous applications in the field of astronomy, radar, flow measurement, satellite communication, etc. Utilizing the basic principle of frequency shift in the sound waves due to relative motion of either the observer or the source of sound travelling in a medium, DS in ultrasound was first discovered in 1957 (**Figure 2-5**). Based on operation and functionality, there are broadly two methods of Doppler ultrasound, namely, Continuous-Wave Doppler (CWD) and Pulsed-Wave Doppler (PWD). As the name suggests, in CWD, a continuous ultrasound wave is emitted and received to scan the whole moving target area, while PWD involves sending short pulse of ultrasound using frequency range gating method [79], and process a small area for velocities at a specific field depth. CWD results in tracking high velocities but at the expense of loss of spatial velocity information, and vice-versa for PWD. The grayscale B-mode image, superimposed with blood flow information, is displayed on the same screen to facilitate a more realistic assessment of the internal anatomy (**Figure 2-6**). The presence of a stenosis consequently appears in the grey scale images with an increase in blood velocity, hence forming a basis/criterion for the non-invasive stenosis evaluation [80]. Characterizing the blood flow in the artery, Doppler ultrasound plays an important role in improving the CAS diagnosis [81], [82]. Additional color flow imaging in conjugation with doppler imaging has revolutionized the visualization of the blood flow velocities in the arteries and veins [83]. In a retrospective study on 1390 patients, DUS has proved to provide a fast screening and surgery decision making within 2 weeks of hospitalization [84].

Figure 2-6: A duplex ultrasound output displaying the B-mode and color flow doppler image side-by-side (credits: National Heart Center Singapore)

Changes in the diameter of the carotid artery, because of plaque formation, is visualized in the B-mode images to diagnose CAS. Intima-media thickness or IMT measurement by B-mode ultrasound, which closely relates to those obtained from the histological results, was the first breakthrough by Pignoli et al. [85] in 1986. Since then, based on B-mode ultrasound IMT evaluation, many studies have been performed on correlation between the occurrences of carotid atherosclerosis versus age, sex, race, diabetes, pulse rate and cigarette smoking, respectively, [86]. Since B-mode diagnosis is dependent on the IMT [87], an accurate marking of the wall boundaries is a critical factor in the diagnosis. To minimize inter- and intra-observer variability in manual IMT identification (by 2 to 4 times), an automated computerized edge detection algorithm, where maximum intensity gradient point in the perpendicular direction of the manual path created along the vessel boundary, was introduced by Selzer et al. [88] in 1994. Thereafter, many such algorithms like dynamic programming procedure, model-based algorithm, match filter algorithm, etc. were developed to more accurately estimate IMT [89]. Using a completely user-

independent deep learning-based highly repeatable and reproduceable arterial layer identification method to segment the IMT, a linear regression between the estimated and ground truth values gives a R^2 value of 0.98 [90]. For an obvious reason, this method is, however, computationally expensive. On the contrary, in a recent study, using a state-space equation-based algorithm, a robust IMT segmentation model gives a R^2 value of 0.92 [91]. Therefore, a trade-off between the computational cost and accuracy is inevitable.

Figure 2-7: Schematic on Block Matching (BM) methodology [92]

Another breakthrough in the diagnosis of the atherosclerosis diseases is the evaluation of the degree of stiffness of the arterial wall as a measure of pathologic condition. Measuring this stiffness factor on 60 left and right post-mortem carotid arteries, ultrasonic phase-locked echo-tracking system, with a correlation factor of 0.68, correlated the stiffness factor and the extent of atherosclerosis [93]. This leads to the development of algorithms, like Block Matching (BM), to perform auto IMT segmentation and arterial wall stiffness analysis. As shown in **Figure 2-7**, BM is done by selecting a block of pixels

or kernel in the current image (reference block) and a similar block (most similar kernel block in terms of intensity [94] that is assumed to be constant over time) is identified in the successive frame [95]. Displacement between these two successive blocks is evaluated to track the motion of the reference block. Since it is expected that the intensity of the reference block (or appearance of the target) will change over time, an Adaptive BM (ABM) method has evolved, whereby, to accurately perform the motion analysis, the reference block is replaced consecutively as the algorithm processes the successive images [96]. Recently, to compute the 2D motion of the carotid wall, BM was applied in conjugation with a state-space equation derived from a linear elastic model of the carotid artery wall [97]. Doing so, a correlation coefficient of 0.98 and 0.95 for the radial and longitudinal motion, respectively, was reported. Further, using a non-linear state-space equation, an improvement to 0.99 in the correlation coefficient was achieved [98].

2.6 CAS diagnosis comparative analysis

Despite being considered as the gold standard to diagnose carotid stenosis, the invasive DSA incurs an increased risk of stroke up to 1.2% [99]. Hence, other non-invasive imaging methods are generally used as the first line screening method. A methodological characteristic comparison between CTA, MRA, and DUS is given in **Table 2-1**. **Figure 2-8** shows the stenosis visualization in various imaging modalities. While DSA, CTA, and MRA provide a full view of the vasculature, DUS only provides a small sectional view of the artery. It can be observed from **Table 2-2** that the sensitivity and specificity of DUS to diagnose $> 70\%$ stenosis increases with the increase in the sample size and age spectrum of the study population. Given the higher prevalence of CAS in the older age

group (> 70 years) [100], the study done by Huston et al. [101], with a wider range of age group (14 to 88 years), provides a higher specificity of detecting patients with no stenosis by DUS. This is further corroborated by the fact that specificity value decreased by 15% as the age group spectrum is shifted towards older age group (39 to 88 years) in the work by Nederkoorn et al. [102].

Table 2-1: Methodological characteristic based comparison among existing imaging modalities [17,20,103,104]

Diagnostic test	Methodology	Advantage	Limitations/ Drawbacks
Computed Tomography Angiography (CTA)	Use of high-dose x-rays to get a detailed picture of the vascular system and its functioning. Patients may also have a dye injected to make it easier to spot blockages.	The examination is quick. 3D results. Able to identify a wide variety of abnormalities.	Risk associated with radiation exposure and contrast use (e.g. allergic reaction, contrast-induced nephropathy). Incidental findings may lead to unnecessary further tests. Presence of vessel calcification leads to an inaccurate stenosis estimation. Large area is needed to house the equipment
Magnetic Resonance Angiography (MRA)	Make use of large magnets and radio waves to take pictures of internal organs like heart and arteries.	Does not involve exposure to ionizing radiation.	Not safe for patients with implants that are not MRI-conditional. Time consuming. Not suitable for patient with claustrophobia. Not widely available. Contrast associated adverse reaction (e.g. nephrogenic systemic fibrosis in patients with kidney impairment).
Duplex Ultrasound (DUS)	To check the blood flow to the brain for a probable plaque formation in the carotid artery.	Reasonable tool in picking up carotid atherosclerosis.	Require trained personnel to perform and interpret. Reflect the presence of systemic atherosclerosis.

Figure 2-8: ICA stenosis visualization with a white marker arrow in (A) DSA image [105], (B) CTA image [105], (C) MRA image [105], and (D) DUS image (credits: National Heart Center Singapore)

CTA and MRA are found to be equally sensitive but differ in specificity; with specificity of CTA being always higher (**Table 2-2**). This could be because of small sample size, for a similar age group, in case of CTA (N = 24 to 40) as compared to MRA (N = 92 to 350). Moreover, MRA suffers from the flow signal loss, mainly in case of turbulent flow and slow flow, leading to an inaccurate measurement of stenosis degree [106]. In such a scenario, contrast enhanced MRA has an advantage. Compared to conventional MRA, contrast enhanced MRA was found to have 7% and 11% higher sensitivity and specificity in diagnosing carotid artery stenosis of 70% or above [107]. Meta-analysis studies of all

the three imaging modalities show that MRA is the most sensitive diagnosis tool for carotid stenosis, followed by DUS, with CTA being the least sensitive. In terms of specificity, both MRA and CTA are reasonably good (in the range of 90% to 95%), followed by DUS [108]. CTA has radiation exposure compared to DUS or MRA. Accounting for the patient convenience, operator's skill requirement, availability, and examination cost, DUS is considered to be the preferred choice for initial screening of CAS.

Table 2-2: Sensitivity and Specificity comparison between Duplex ultrasound, CTA and MRA

Studies	Number of subjects (N)	Age group (Years)	Severity (S)	Sensitivity	Specificity	Remarks
Computed Tomography Angiography (CTA)						
Marks et al. [109]	14	49 – 84	$0\% \leq S \leq 30\%$	86%	-	CTA results were 89% accurate as compared to conventional angiography.
			$30\% \leq S \leq 69\%$	86%		
			$70\% \leq S \leq 99\%$	100%		
Farres et al. [110]	24	48 – 88	$50\% \leq S \leq 99\%$	100%	95.2%	Sensitivity - 95% CI, 15.8% to 100% Specificity - 95% CI, 83.8% to 99.4%
Anderson et al. [111]	40	44 – 83	$50\% \leq S \leq 99\%$	89%	91%	For mild stenosis (0-29%) and occlusion, CTA was found to be almost 100% accurate.
Koelemay et al. [112]	864 (Meta-Analysis)	55 – 73	$70\% \leq S \leq 99\%$	85%	93%	Sensitivity - 95% CI, 95% CI, 79% to 89% Specificity - 95% CI, 89% to 96%
Wardlaw et al. [108]	372 (Meta-Analysis)	-	$70\% \leq S \leq 99\%$	77%	95%	Sensitivity - 95% CI, 68% to 84% Specificity - 95% CI, 91% to 97%
Magnetic Resonance Angiography (MRA)						
Cosottini et al. [113]	92	45 – 82	$0\% \leq S \leq 99\%$	97%	82%	The patients were clinically and ultrasonically tested

						for stenosis sign earlier.
Nederkorn et al. [102]	350	39 – 88	$70\% \leq S \leq 99\%$	92.2%	75.7%	Sensitivity - 95% CI, 86.2% to 96.2% Specificity - 95% CI, 68.6% to 82.5%
Nederkorn et al. [107]	Meta-Analysis	-	$S < 70\%$ versus $70\% \leq S \leq 99\%$	95%	90%	Pooled Weighted Analysis Sensitivity - 95% CI, 92% to 97% Specificity - 95% CI, 86% to 93%
Wardlaw et al. [108]	380 (Contrast Enhanced MRA)	Meta-Analyses	$70\% \leq S \leq 99\%$	94%	93%	Sensitivity - 95% CI, 88% to 97% Specificity - 95% CI, 89% to 96%
	774 (MRA)			88%	84%	Sensitivity - 95% CI, 82% to 92% Specificity - 95% CI, 76% to 97%
Duplex Ultrasound (DUS)						
Huston et al. [101]	621	14 – 88	$50\% \leq S \leq 70\%$	86.4%	90.1%	Peak systolic and end diastolic velocity of 230 cm/s and 70 cm/s, respectively, were evaluated for stenosis $\geq 70\%$.
			$70\% \leq S \leq 99\%$	92.1%	89.5%	
Nederkorn et al. [102]	350	39 – 88	$70\% \leq S \leq 99\%$	87.5%	75.7%	Sensitivity - 95% CI, 82.1% to 92.9% Specificity - 95% CI, 69.3% to 82.2%
Nederkorn et al. [107]	Meta-Analysis	-	$S < 70\%$ versus $70\% \leq S \leq 99\%$	86%	87%	Pooled Weighted Analysis Sensitivity - 95% CI, 84% to 89% Specificity - 95% CI, 84% to 90%
Jahromi et al. [114]	Meta-Analysis	-	$50\% \leq S < 70\%$	98%	88%	Standards for Reporting of Diagnostic Accuracy (STARD) criteria was used for the study.
			$S \geq 70\%$	90%	94%	
Wardlaw et al. [108]	916 (Meta-Analysis)	-	$70\% \leq S \leq 99\%$	89%	84%	Sensitivity - 95% CI, 85% to 92% Specificity - 95% CI, 77% to 89%

2.7 Current trends and prospects

Other than radiation exposure, calcification artefact is another technological drawback with CTA. For this, a computer aided program, that potentially addresses the calcification artefacts issue by selectively removing the bone pixels from the CTA image, can be used [115]. To measure the plaque volume and its association with ulceration, a multi-detector CTA (MDCTA), which comes with a modest interobserver variability, has been evolved [116]. While detection of vulnerable carotid plaque remains an elusive goal and accurate measurement of blood velocity in CTA is still under development, radiation exposure associated with CTA is always a concern. Other than degree of stenosis, plaque characterisation (lipid level, fibrous cap, plaque haemorrhage, calcification, etc.) and progression [21] are important considerations in clinical management decisions. With high sensitivity and specificity, MRA may better characterize the vulnerable plaque due to its apparent ability to produce high contrast images of the soft tissues [117]. However, with the clinically applicable 1.5-Tesla MRI machine, differentiation among various intraplaque tissues is still a challenge due to low signal to noise ratio. Higher field magnet (3-Tesla or 7-Tesla) could possibly improve the signal to noise ratio [118]. In a recent study, intraplaque haemorrhage volume, using a 3-Tesla field strength MRI, was strongly correlated to the histology examination (Cohen's kappa value of 0.76) [74]. This will, however, further increase the cost of the equipment; limiting wide clinical adoption. Imaging the arterial wall at molecular level with the ultra-small superparamagnetic iron oxide particles (USPIO) is a potential method of characterizing the vulnerable plaque through MRI [119]. In such an attempt, a signal loss in MRI due to accumulation of USPIO at the lesion site (high macrophage content), which can be correlated to the

presence of plaque prone to rupture, was shown in the past [120]. However, there is a major drawback in terms of time of accumulation of USPIO at the lesion site, which could go up to 24 hours [121]. As a potential future direction of research, correlation between cerebral damage which can be accurately detected by MRI and presence of high grade carotid stenosis (>50%) could prove to be an efficient method of CAS diagnosis [122].

Deriving the geometry features from the CTA and blood flow parameters from MRI [123], a patient-specific carotid hemodynamic can be studied using computational fluid dynamics (CFD) [124]. In the past, it is shown that CFD-based flow analysis can facilitate an accurate and early prediction of the plaque prone to rupture [125]. Moreover, utilizing the CTA and MRI data, *in-vitro* investigation of the carotid flow in determining the post-stenting success is another prediction-based application in the clinical field [126]. In the era of multi-modality patient-specific imaging data availability, CFD tool is evolving as an important milestone in the clinical decision making [127,128]. Evidence of atherogenesis of the vulnerable plaque linked to the CFD-based hemodynamic parameters such as wall shear stress [129] and pressure gradient [130], was explored in the past. In contrast to the computational cost, the use of an accurate clinically measured inlet boundary condition and calculation of an appropriate outlet boundary condition are, however, very important for the accuracy of CFD-based hemodynamic predictions [131].

Though low cost, low risk and widely available, DUS suffers from inter/intra-observer variability [16]. One way to minimize the variability is the use of computer-aided

algorithms to estimate the carotid intima-media thickness (CIMT) based on pixel contrast value [132]. Improper insonation angle, low blood flow rate, and deeper artery location [133] further introduces difficulty to DUS examination of CAS. Helpful in overcoming these shortcomings is the Contrast-Enhanced Ultrasound (CEUS), where an intravascular contrast agent consisting of microbubbles (1-8 μm) filled with perfluorinated gas (low solubility) is injected to acquire high contrast ultrasonic images of carotid artery [134]. In one of its first long term clinical studies (2 years), CEUS was tested on 85 patients, wherein, compared to conventional carotid angiography, a 100% sensitivity, specificity, and accuracy was achieved [135]. The contraindication of administering an ultrasound contrast agent includes heart failure, acute coronary disease or acute myocardial infarction, ventricular arrhythmias, and unstable respiration. Measuring the plaque strain during the cardiac pulsation, DUS can be correlated to the measure of physical plaque instability that could potentially be more clinically relevant as compared to the measurement of stenosis degree [136]. Either with or without contrast agent, DUS in 2D is highly dependent on the operator's skills with limited planar information. Therefore, a 3D volume based plaque measurement could be an effective tool in establishing the reliability of DUS for an accurate CAS diagnosis [137]. A 3D ultrasound provides a detailed volumetric view of the luminal plaque with high repeatability [138]. As compared to 2D ultrasound, it can easily monitor the progression of the plaque ulceration that substantially affects the treatment decision [139,140]. Moreover, a 3D ultrasound reduces the inter/intra-observer variability to a minimum level [141]. It is expected that an integration of 3D ultrasound with CEUS will further revolutionize the medical imaging.

2.8 Potential Imaging Modalities

2.8.1 Optical Coherence Tomography (OCT)

In principle, OCT is like an ultrasound. However, light is used to produce an image instead of sound waves. The basic phenomenon lies in low-coherence interferometry as described by Fercher [142] through a mathematical model. Because of the different optical properties (refractive index) of various constituents of the human tissue (water, lipids, protein, etc.), the echo time delay of the reflected light waves (emitted by a super luminescent source) is calculated through interferometry and an image is produced as a result of reflected waves' intensity map [143]. Visualizing the microstructures in the arterial wall, the first *in-vivo* imaging of a rabbit aorta, using an intravascular OCT (IVOCT) catheter, showed a reasonable agreement between the imaging results and the histological examination [144]. In one of the very first attempts, OCT was applied during carotid artery stenting on 17 patients, where a successful detection of the fibrous cap disruption, intraluminal thrombus, and plaque protrusion was shown [145]. Later, a successful IVOCT examination without any neurological or vascular complications, on two patients (one aged 78 male, and another aged 83 female), was reported. Unlike carotid angiography, IVOCT provides additional information on ulceration, thin-cap fibroatheroma (TCFA), and intraluminal thrombus that helped in ensuring post angioplasty and stenting success in the patients [146]. Similarly, OCT applied to an 82-year-old male subject, with angiographically proven severe stenosis in the proximal internal carotid artery, showed a lotus root-like appearance at the lesion site, which is formed because of thrombi undergoing recanalization to form lumen [147]. Benefits and

safety (due to its invasiveness) of OCT, for CAS diagnosis and intervention guidance, need further study.

2.8.2 Photoacoustic Tomography (PAT)

Thermal expansion of the human tissue, upon application of a modulated electromagnetic energy, produces an acoustic wave [148]. The energy applied is selectively absorbed by the tissue depending on its absorption properties. This led to tissue expansion due to heating; resulting into an acoustic signal. Detecting these acoustic signals with the help of a transducer, an image is formed using back projection algorithm either in time or frequency domain. This is called photoacoustic tomography (PAT) or optoacoustic (OAT) or thermoacoustic tomography (TAT). The energy source could be a laser, microwaves, optical or radio frequency waves, etc. Application of multi-spectral OAT, using Nd:YAG laser, can be used to visualize the human carotid artery and jugular vein [149]. In an *ex-vivo* study, validated histologically, molecular composition of the tissue (water, collagen, fatty acids, and plaque lipids) is proved to be successfully identified using PAT [150]. Further, a possible method to measure and detect the lipid in carotid artery atherosclerosis, through internal illumination and signal detection from external side of the neck, is shown in **Figure 2-9**. Based on the limited literature findings, a more intensive investigation in the field could result into a strong diagnosis tool in the near future.

Figure 2-9: Proposed PAT method of internally illuminating the carotid artery through pharynx and detecting the acoustic signal from outside using concave transducer array [150]

2.8.3 Infrared (IR) Thermography

Other than the physiological changes at the site of atherosclerosis, an acute inflammatory reaction also takes place at these sites of lesion [151], leading to a rise in the localized temperature [152]. In a histological study on 48 patients, an inverse correlation is found between the plaque fibrous cap thickness and plaque surface temperature [153]. Given that the carotid artery is obstructed (partly or completely), the effective blood perfusion to the facial and forehead skin tissue will be affected in comparison to a normal carotid artery blood flow. This in return affect the skin temperature in the region. In the past, usefulness of plate thermography, wherein a flexible foil coated with specific cholesterol esters that changes the foil color due to temperature oscillations, was examined [154]. Applying the foil on the forehead of the patients, an indirect measure of the decrease in skin blood perfusion (decrease in temperature) was established. Out of 300 patients studied, plate thermography gives positive results (abnormality) in 39 patients against 34

patients using Doppler sonography. In all, both the methods agree for 23 patients, followed by false positive and false negative results in 5 and 3 patients, respectively [154]. To perform a non-contact temperature measurement, facial Infrared (IR) thermography, on 30 patients suffering from angiographically proven carotid stenosis or occlusion, was also used [155]. With a routine IR thermography examination, an abnormal thermal map was found in 57% of the cases as a possible sign of carotid disease. Furthermore, a proactive thermography test, using head clamp to externally occlude the temporal artery flow, resulted in a sensitivity of 83% [155]. In another study, the degree of stenosis was correlated to the ocular temperature on 24 patients ($r = -0.67$) [156]. Therefore, not characterizing the plaque vulnerability, thermography stands a strong potential as a non-contact/non-invasive screening tool. In future, an active thermography method, wherein external stimulation is done to extract maximum thermal features [157,158] could be a potential advancement in the field.

2.9 Summary

Accuracy of CAS diagnosis has substantially increased over the decades with the progressive technological developments. From the measurement of the narrowing carotid artery diameter to the evaluation of the increased velocity field near the obstruction/lesion site, in the carotid artery, increased emphasis has now been on the detection of additional parameters to characterize the plaque vulnerability. Use of computer aided programs has further improved the sensitivity, specificity and accuracy of CAS diagnosis through various imaging modalities. DSA is the gold standard to diagnose CAS but suffers from the X-ray radiation exposure drawback. With optimized X-ray radiation, CTA provides

3D visualization, but inefficient in evaluating the blood flow velocity. MRA is another method, with high accuracy and resolution, that eases the characterization of vulnerable plaque, but the equipment cost is high and not readily available everywhere. DUS is low cost, but its efficacy is operator dependent. Evolution of computer-based diagnosis algorithms and 3D ultrasound systems can potentially address these issues. Intravenous ultrasound contrast brings substantial improvement to the overall performance of DUS. In the parallel imaging technological development, potential imaging modalities like OCT, PAT, and Thermography, are also evolving with time. Through multiple *in-vivo* human subject studies, OCT has already been proven to be a strong potential alternative. Unlike conventional imaging modalities, OCT can detect plaque characteristics more efficiently. Thermography presents a strong CAS screening potential through a correlation between stenosis and ocular temperature, however, limited by the number of clinical studies and accuracy of the screening. Though successfully studied in *ex-vivo* models, PAT must go a long way in the field of CAS diagnosis.

CHAPTER 3 SKIN TEMPERATURE MAPS AS A MEASURE OF CAROTID ARTERY STENOSIS: COMPUTATIONAL AND *IN-VIVO* STUDY

3.1 Abstract

In this study, the effect of carotid artery stenosis on the neck skin temperature maps was investigated. With the presence of stenosis, alterations in the carotid artery hemodynamics bring about changes in the heat transfer to the surrounding tissue. This is expected to be captured in the resulting temperature map over the external neck skin surface; possibly correlates to the presence of stenosis. A total of twenty carotid artery samples, from ten patients with both sides normal (0% stenosis), stenosis (>50%) on one side, and stenosis (>50%) on both sides, were studied. Duplex Ultrasound and infrared (IR) thermography examinations were performed. A computational study, on an ideal 3-dimensional (3D) carotid artery and jugular vein model encapsulated with a solid neck tissue phantom resembling the human neck, was carried out. Incorporating the patient-specific geometrical (depth of artery and stenosis) and flow (peak systolic and end diastolic inlet velocity) boundary conditions, conjugate bio-heat transfer was studied using a finite volume numerical scheme. Simulation results and *in-vivo* thermal maps show that the average temperature on the external neck skin surface is significantly higher for normal patients (32.82 ± 0.53 °C versus 32.00 ± 0.37 °C, $p < 0.001$). Furthermore, the thermal region of interests (TROIs) were extracted from the *in-vivo* thermal images, which both qualitatively and quantitatively distinguish the normal and

diseased cases. This study suggests the potential of thermal feature-based screening of patients with carotid artery stenosis.

3.2 Introduction

External skin surface temperature is a result of conjugate bio-heat transfer between the blood flow in the arteries and veins, tissue perfusion, tissue metabolic heat generation, and external ambient conditions [159], [160]. For the given external ambient conditions, the skin surface temperature is dependent on the internal tissue heat transfer. In case of the neck tissue, blood flow in the large diameter carotid artery and jugular vein can be modelled as a major source of heat transfer [161]. An abnormality in the carotid artery flow, particularly in the presence of stenosis, will affect the overall neck tissue conjugate heat transfer that shall be reflected in the external neck-skin temperature [162]. The narrowing of the carotid artery affects the hemodynamics such that the velocity variation, wall shear stress, and flow separation zones across the stenosis tissue can be used as a measure of stenosis [163–165].

Complex hemodynamics, in the presence of stenosis, can be studied using computational methods, like computational fluid dynamics, to evaluate the wall shear stress and flow separation zones [163–165]. Numerically investigating the unsteady vortical flow in the flow separation zone distal to the stenosis, Bluestein et al. [166] presented a detailed analysis on the vortex shedding in case of 84% area reduction at the throat of stenosis. Covering a wide range of Reynold (Re) numbers, from 300 to 1800, the authors found that the periodic shedding started at $Re = 360$ and continued thereafter for the complete

range of Re studied. However, assuming a tube with reduction in diameter as a stenosis model, is a gross simplification of the flow domain that disregards the geometrical complexity of *in-vivo* stenotic flows. The carotid artery hemodynamics, in a relatively close to *in-vivo* geometry model, was first studied by Bharadvaj et al. [167,168], wherein using patient-specific angiography data, the authors focused on the reconstruction of a fictitious arterial bifurcation model and flow visualization within it. This has been the cornerstone of subsequent numerical studies of carotid artery hemodynamics. Following this, Perktold et al. [169] performed a numerical analysis on the effect of bifurcation angle on the flow. The authors found that the axial velocity approximately doubles as the angle of bifurcation increases from 15° to 50° . The authors utilized Casson's relation to model blood as a non-Newtonian fluid. Given its validity for flow in larger arteries, subsequent numerical studies in the field modeled blood as a Newtonian fluid [170,171]. This has further paved the way for the application of computational methods to study the patient-specific carotid geometry [172–174].

For the given ambient conditions, it is evident that external neck skin surface temperature is the result of bio-heat transfer between the blood flow and the skin tissue [157,159,160,175,176]. Zhu [161] and Dennis et al. [177] numerically studied cooling of the brain, in the event of cerebral ischemia or hyperthermia, through blood flow in the carotid artery upon application of external cooling to the neck skin surface. The authors modelled the carotid artery and jugular vein blood flow as a counter flow heat exchanger system and showed that the external cooling can directly affect the brain cooling. From these studies, it can be posited that the arterial blood flow is strongly related to the

outward heat transfer to the neck skin surface. In the literature, numerical work by Yang and Liu [162] is the only evidence of the effect of carotid stenosis on neck skin temperature contours. The authors have shown that increasing the width of the stenosis (for the same location and thickness of the stenosis tissue), from 3 mm to 8 mm, decreases the temperature on the skin surface by 0.06%, with an increase in the low-temperature region. However, the study is limited by the geometry of the carotid artery, wherein only the common carotid artery (CCA) section of the carotid artery was modelled that too as a cylindrical tube. It is evident that studies based on patient specific carotid artery models are found to be more relevant to draw clinically acceptable conclusions [129,131]. To perform a patient-specific computational study, carotid geometry data from digital subtraction angiography (DSA) or computed tomography angiography (CTA) and flow information from magnetic resonance angiography (MRA) are used [123,128]. However, given the need of intravenous contrast agent and the cost of the examination [20], [21], the patient-specific data is not readily available. As an alternative, measured by DSA, using the average values of length and cross-sectional diameter at various sections of the artery (on 22 normal subjects), an idealized carotid artery bifurcation model can be used to study the hemodynamics [167], [168]. In the author's previous work [178], use of such an idealized carotid artery model was done to numerically study the effect of carotid artery hemodynamics influenced heat transfer to the surrounding neck tissue in the presence of stenosis. Modelling varied degree of carotid artery stenosis in the range of 25%-90%, it was concluded that the presence of stenosis can be quantified with the occurrence of colder region called '*cold feature*' on the outer neck skin surface. Though strongly evident, the results were limited by the use

of an idealized stenosis geometry model based on the occluded internal carotid artery (ICA) diameter [171] and literature-based inlet flow conditions [169].

In this study, in addition to the idealized carotid artery model, a counter flow jugular vein was introduced. To simulate the conjugate bio-heat transfer, the carotid artery-jugular vein model was encapsulated with the neck tissue. Duplex Ultrasound, which is low cost, non-invasive, and readily available [16], was used to measure the individual-specific inlet flow conditions (PSV: peak systolic velocity, EDV: end diastolic velocity) and geometric details like location and dimension of the stenosis tissue in the carotid artery. Given that hemodynamics at the PSV and EDV instants are of clinical relevance in carotid artery stenosis diagnosis [129,179], despite the transient nature of the physiological blood flow in the carotid artery, in this study, flow analysis at the PSV and EDV inlet flow conditions was performed. As established in the previous studies on neck temperature-based pulse measurement [180,181], while the global temperature maps remain the same, the transient physiological cardiac cyclic nature of blood flow in the carotid artery results in a local and infinitesimally small (with noise) temperature perturbation on the external skin surface. Hence, in this study, studying heat transfer at only PSV and EDV inlet flow instants of the cardiac cycle was found to be appropriate. Justified against the computational cost in the author's previous work [178], in this study, a steady conjugate bio-heat transfer computation was performed. Thereafter, an individual sample-specific comparative study, on the resultant external neck-skin surface temperature map in normal and diseased carotid artery models, was computationally performed. Moving on, an *in-vivo* non-contact infrared (IR) thermography-based external skin temperature

measurement was done. Given that the carotid artery is responsible for supplying blood to the face, stenosis in the carotid artery is expected to affect the blood perfusion in the facial region causing low temperature. It is evident that the presence of the stenosis leads to a decrease in the blood flow in the carotid artery, and hence, a lower blood flow to the facial and temporal arteries [182]. Utilizing this, in the past, carotid artery stenosis has been correlated to facial [155], ocular [156], and temporal [154] thermal maps, using contact and non-contact thermographic methods. Unlike in the past studies, wherein either visual observation or mean ocular surface temperature were used, in this study, a thermal region of interest (TROI) extraction method is proposed. Between the normal and diseased thermal map samples, a quantitative method of TROI comparison is discussed.

3.3 Material and Methods

3.3.1 Study participants

Under an approved clinical research study, by Centralized Institutional Review Board, SingHealth, Singapore (CIRB Ref No.: 2017/2119), ten study participants (N=10), in the age group of 49 to 71 years old (mean = 62.7 years and SD = 7.1 years), were recruited. The recruitment was done at the Vascular Lab of National Heart Center Singapore (NHCS), where all the study participants undergo Duplex Carotid Ultrasound examination to characterize the geometrical and flow parameters of the carotid artery on either side of the neck (a total of n=20 samples). Based on the examination, the study participants were categorized into three groups: both sides normal (0% stenosis, N=4, n=8), stenosis on one side ($\geq 50\%$ stenosis, N=2, n=4), and stenosis on both sides ($\geq 50\%$ stenosis, N=4, n=8). **Table 3-1** shows the individual-specific stenosis percentage in the

common carotid artery (CCA), bulb, internal carotid artery (ICA), and external carotid artery (ECA) sections of the carotid artery, and common carotid artery (CCA) geometrical features and inlet flow conditions in all the samples.

Table 3-1: Individual-specific geometrical and flow characteristics measured by Duplex Ultrasound

Sr. no.	Arter y side	% Stenosis				CCA characteristics				Reynolds Number (Re)	
		CCA	Bulb	ICA	EC A	Diamete r (m)	Depth (m)	PSV (m/s)	EDV (m/s)	PSV	EDV
Both sides normal											
N1	Right	0	0	0	0	0.006	0.023	1.14	0.22	2006	387
	Left	0	0	0	0	0.007	0.019	1.04	0.26	1950	487
N2	Right	0	0	0	0	0.007	0.015	1.20	0.31	2354	608
	Left	0	0	0	0	0.007	0.013	1.23	0.30	2590	632
N3	Right	0	0	0	0	0.008	0.015	1.03	0.18	2466	431
	Left	0	0	0	0	0.008	0.015	0.98	0.11	2120	238
N4	Right	0	0	0	0	0.006	0.017	1.01	0.36	1864	665
	Left	0	0	0	0	0.007	0.015	0.92	0.24	1911	498
Stenosis on one side											
ND 1	Right	0	50	20	30	0.009	0.013	0.92	0.19	2388	493
	Left	0	0	0	0	0.009	0.015	0.97	0.21	2462	533
ND 2	Right	0	0	0	0	0.006	0.021	0.93	0.30	1628	525
	Left	0	0	100	0	0.007	0.018	0.53	0.11	1024	213
Stenosis on both sides											
D1	Right	50	35	50	45	0.007	0.020	0.65	0.07	1331	143
	Left	30	45	50	55	0.006	0.016	0.98	0.30	1781	545
D2	Right	30	55	65	70	0.007	0.018	0.82	0.26	1703	540
	Left	30	40	100	40	0.008	0.015	0.88	0.12	2031	277
D3	Right	30	50	45	35	0.008	0.018	0.85	0.18	2010	426
	Left	30	30	30	50	0.008	0.016	0.86	0.18	1984	415
D4	Right	50	20	0	20	0.009	0.017	0.83	0.22	2131	565
	Left	50	25	0	30	0.009	0.019	0.80	0.17	2100	446
CCA: Common Carotid Artery; ICA: Internal Carotid Artery; ECA: External Carotid Artery; PSV: Peak Systolic Velocity; EDV: End Diastolic Velocity											

3.3.2 Model geometry preparation

An idealized 3-dimensional (3D) carotid artery model, derived from literature angiographic geometric data available on 22 study participants in the age group of 22 to 77 years old [167], was reconstructed (**Figure 3-1a**). In the 3D carotid artery model, the

literature-based common carotid artery (CCA) diameter was taken to be 0.008 m, which follows the Duplex Ultrasound measured CCA diameter of 0.007 ± 0.001 m, on 20 carotid arteries, of this study (**Table 3-1**). The jugular vein, running just above the carotid artery with center to center distance between the CCA and jugular vein to be 9 mm, was taken to be of same diameter as the common carotid artery [161]. Using the neck geometric dimension, material, and thermal properties data from the literature [183,184], the carotid artery was encapsulated in a homogenous tissue; resembling a part of the neck tissue around the carotid artery (**Figure 3-1b** to **Figure 3-1f**).

For the diseased group of samples, individual-specific stenosis geometric characteristics, as measured from the Duplex Ultrasound examination, were incorporated in the 3D carotid model. Typically, varied degree of stenosis was found in the CCA, bulb, ICA, and ECA regions (**Table 3-1**). For each of these regions, two Ultrasound images, viz. cross-sectional view and axial view, were used to extract the approximate geometrical details, viz. location, length, and thickness, of the stenosis tissue. Using these geometrical details, the stenosis tissue was created in the 3D carotid artery model such that the percentage diameter occluded matches the Duplex Ultrasound examination (**Figure 3-2**, **Figure 3-3**, and **Figure 3-4**).

Figure 3-1: (a) 3D carotid artery model showing the common carotid artery (CCA), internal carotid artery (ICA), external carotid artery (ECA), dividing wall (DW), and non-dividing wall (NDW) (b) Neck tissue encapsulated model in isometric view (c) Side (d) Rear view (e) Top view (f) Mid-carotid artery sectional view of the neck tissue encapsulated model, respectively.

Figure 3-2: Isometric view with cross-sectional (P1, P2, P3, and P4) and axial planes (P5, P6, and P7) of the 3D carotid artery model with the individual-specific (D1, left carotid artery) stenosis tissue in the common carotid artery (CCA), bulb, internal carotid artery (ICA), and external carotid artery (ECA)

Figure 3-3: Individual-specific (D1, left carotid artery) stenosis tissue modelling at the cross-sectional (P1 and P2) and axial (P5) planes, from ultrasound images, in the common carotid artery (CCA) and bulb region of the carotid artery

Figure 3-4: Individual-specific (D1, left carotid artery) stenosis tissue modelling at the cross-sectional (P3 and P4) and axial (P6 and P7) planes, from ultrasound images, in the internal carotid artery (ICA) and external carotid artery (ECA) regions of the carotid artery

3.3.3 Numerical modelling

The stenosis tissue is considered as a solid, using the material and thermal properties reported in the literature [185]. With constant thermal properties, the 3D carotid artery blood flow was assumed to be Newtonian and incompressible [186]. The fluid flow and heat transfer were modelled by the Navier–Stokes and energy equations [124], respectively, as expressed in the following Cartesian coordinate system:

$$\text{Continuity: } \frac{\partial \rho_b}{\partial t} + \rho_b \left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} \right) = 0 \quad (3-1)$$

$$\text{Momentum in } x - \text{direction: } \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} = -\frac{1}{\rho_b} \frac{\partial p}{\partial x} + \eta \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \quad (3-2)$$

$$\text{Momentum in } y - \text{direction: } \frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} = -\frac{1}{\rho_b} \frac{\partial p}{\partial y} + \eta \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \quad (3-3)$$

$$\text{Momentum in } z - \text{direction: } \frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} = -\frac{1}{\rho_b} \frac{\partial p}{\partial z} + \eta \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) \quad (3-4)$$

$$\text{Energy: } \frac{\partial T}{\partial t} + u \frac{\partial T}{\partial x} + v \frac{\partial T}{\partial y} + w \frac{\partial T}{\partial z} = \alpha \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right) \quad (3-5)$$

$$\text{where, } \eta = \frac{\mu_b}{\rho_b}, \alpha = \frac{k}{\rho_b c_p}$$

Given the carotid artery is encapsulated by the tissue, tissue perfusion was modelled to solve the conjugate bio-heat transfer. Tissue perfusion can be defined as the capillary level blood flow between the circulatory system and the tissue. To mathematically simulate the realistic tissue characteristics, Pennes bio-heat equation (Equation 3-6), that solves the contribution of tissue perfusion (ω_b) and volumetric heat generation (q_m'') to the heat transfer, was used [187].

$$\rho_b c_p \frac{\partial T}{\partial t} + k_t \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right) + [(\rho_b c_{pb} \omega_b) * (T_a - T)] + q_m'' = 0 \quad (3-6)$$

Using the commercially available computational fluid dynamics software FLUENT (version 19.1) by ANSYS Inc, the numerical solution of the governing equations was obtained by a finite volume discretization method. Given the blood flow is assumed to be incompressible (constant blood density), the $\left(\frac{\partial \rho_b}{\partial t} \right)$ term in Equation 3-1 becomes zero.

As justified in Section 1, the Navier-Stokes, energy, and Pennes bio-heat equations were

solved at steady PSV and EDV instants of the cardiac cycle, hence, $\left(\frac{\partial u}{\partial t}\right)$, $\left(\frac{\partial v}{\partial t}\right)$, $\left(\frac{\partial w}{\partial t}\right)$, $\left(\frac{\partial T}{\partial t}\right)$, and $\left(\rho C_p \frac{\partial T}{\partial t}\right)$ terms in Equations 3-2 to 3-6 become zero. Semi Implicit Pressure Linked Equations (SIMPLE) algorithm [188] was used to achieve pressure-velocity coupling and for the spatial discretization of momentum and energy transport equations, a second-order upwind scheme was used. For each of the continuity, velocity components in x, y and z direction, and energy equation, a residual-based convergence criterion of 10^{-10} was applied. Energy and momentum relaxation factors were set to 0.7 and 0.5, respectively, in a laminar viscous model. For all the simulations, within the set maximum number of iterations (100,000), the solution was found to be converged.

3.3.4 Boundary conditions

At the CCA inlet (**Figure 3-1b**), using the individual-specific measured Re value (**Table 3-1**), the model PSV and EDV were calculated and applied to the simulation as a fully developed parabolic velocity inlet $\left(w = U * \left(1 - \frac{r^2}{(D/2)^2}\right), u = v = 0\right)$, along with an isothermal inlet temperature boundary condition ($T = 37^\circ\text{C}$) [189]. For the jugular vein, fully developed parabolic velocity inlet, in the opposite direction of the carotid artery flow, was applied $\left(w = -U_{JV} * \left(1 - \frac{r^2}{(D/2)^2}\right), u = v = 0\right)$. For all the simulations, the value of U_{JV} is calculated using a volume flow rate of 670 ml/min [190]. Taking the *in-vivo* temperature measurement in the work of [191] (on 10 study participants, 47.8 ± 3.6 years) and [192] (on 20 study participants, 70 ± 9 years), an isothermal temperature boundary condition of $T = 35.6^\circ\text{C}$ was used at the jugular vein inlet. At the outlet of the ICA, ECA, and jugular vein, a zero gauge pressure ($P_g = 0\text{ Pa}$) boundary condition was

applied [129]. The lateral side and the bottom body core walls of the neck tissue encapsulation were given an adiabatic $\left(\frac{\partial T}{\partial n} = 0\right)$ and isothermal ($T = 37\text{ }^{\circ}\text{C}$) boundary conditions, respectively, while the top-neck skin surface was given a natural convective boundary condition ($T_{\infty} = 21\text{ }^{\circ}\text{C}$, $h_{NC} = 10\text{ Wm}^{-2}\text{ }^{\circ}\text{C}^{-1}$) [193], [194].

3.3.5 Mesh details and solution validation

To perform the mesh independent study, nine different 3D model meshes with cell numbers in the range of 0.15×10^6 to 12.34×10^6 , were created. In these meshes, tetrahedral and prismatic types of elements were used. An inflation layer of 1mm for the carotid artery and jugular vein walls, which mainly comprises of prismatic elements, was applied. Similarly, an inflation layer of 2 mm, at the top (top-neck skin surface) and bottom (body core) surfaces of the model, was applied. Using the flow conditions as in the study performed by [170], at $Re = 270$, $\mu = 2.9 \times 10^{-3}\text{ Pa.s}$, and $\rho = 1410\text{ Kg/m}^3$, the average velocity at the I00 plane of ICA (**Figure 3-1a**) and top-neck skin average surface temperature are evaluated against the mesh size. From the mesh size of 4.7×10^6 onwards, the relative difference between the average velocity and temperature was found to be less than 1%, hence, this mesh was used to report the validation and simulation results for the normal carotid artery samples (**Figure 3-5**). For this mesh, the average orthogonality, skewness, and aspect ratio were found to be 0.20 ± 0.11 , 1.97 ± 0.78 , and 0.80 ± 0.11 , respectively. For the model with the introduction of varied degree of individual-specific stenosis tissue, a similar mesh density was used. The normalized velocity (u_{axial}/U) profile against the non-dimensional distance (y^*) between the non-dividing (NDW) and the dividing wall (DW) of the ICA planes I05 and I10 (**Figure 3-6**)

and average velocity on all the ICA planes (I00, I05, I10, I15, and I20 in **Figure 3-1a**) were found in agreement with the past experimental and numerical work by [170] and [171] (**Table 3-2**). For a typical mesh size of 4.7×10^6 , an average wall-clock time per iteration, while running on a 12-compute threads of an Intel(R) Xenon(R) CPU E5-1650 v4 3.60 GH computer, was found to be 1.57s.

Figure 3-5: Mesh independent plot for average temperature on the top-neck skin surface and average velocity at the plane I00 in ICA

Figure 3-6: Validation of velocity profile on planes I05 and I10 (DW: Dividing wall; NDW: Non-dividing wall) in the ICA (u_{axial}/U is displaced by a factor of 3 for presentation purpose) with Gisjen et al. [170] and Kashefi et al. [171]

Table 3-2: Numerical simulation validation with benchmark experimental and numerical literature

Studies	Average velocity (m/s) at different planes in ICA				
	I00	I05	I10	I15	I20
Experimental by [170]	0.84	0.66	0.52	0.62	0.90
Numerical by [170]	0.80	0.74	0.65	0.75	0.85
Numerical by [171]	0.69	0.69	0.64	0.68	0.80
This study	0.80	0.65	0.55	0.61	1.06

3.3.6 *In-vivo* IR thermography examination

After the Duplex Ultrasound examination, on the same study participants, an IR thermography examination was performed. Following the body temperature stabilization for 15 minutes, in a thermally controlled environment (23 ± 0.5 °C temperature and 50% relative humidity [195]), a thermal image was captured on either side of the neck (**Figure 3-7**). In this experiment, VarioCAM IR thermal camera by InfraTec, with a temperature resolution of less than 0.1 °C, was used [157,158,175].

Figure 3-7: Thermal image processing: normalizing, masking, segmentation, and thermal region of interest (TROI) extraction.

3.3.7 Thermal image pre-processing

The 2-dimensional (2D) thermal image (rows x columns: 240 x 320 pixels) has neck, face, head, clothes, and background details. To remove the background from this image, the original thermal image was first normalized in grey scale (0-1), and then an image mask was created using Otsu's threshold method [196,197]. Processing the original image with the mask, the background was subtracted. Further, to remove the remaining clothing part in the image, a manual segmentation was performed; resulted into full thermal image (**Figure 3-7**). As explained in **Section 3.1**, given the transient physiological cardiac cyclic nature of blood flow in the carotid artery has no obvious effect on the global thermal maps of the external skin surface [180,181], a thermal image taken at any instant of the cardiac cycle can be used for the analysis.

3.3.8 Thermal image post-processing

Using a temperature threshold value (T_{th} in °C) calculated by Equation 3-7, where T_{mi} and T_{mx} are the minimum and maximum temperature (°C) in the full thermal image, the image was reduced to a usable thermal region of interest (TROI) (**Figure 3-7**).

$$T_{th} = T_{mi} + m * (T_{mx} - T_{mi}) \quad (3-7)$$

The value of ' T_{th} ' is dependent on the value of the variable parameter m that varies from 0.1 to 0.9. To quantitatively differentiate the two groups of image samples (normal and diseased), a node ratio denoted by ' R_n ' (Equation 3-8), defined by the number of non-zero pixels with temperature value $\leq T_{th}$ normalized with the total number of non-zero pixels in the full thermal image, was used.

$$R_n = \frac{\text{number of non-zero pixels with } \leq T_{th}}{\text{total number of non-zero pixels in full thermal image}} \quad (3-8)$$

3.3.9 Statistical data analysis

Average values, of any of the measured or simulated parameters, are reported with standard deviation (SD). Between the simulated and measured quantities, standard error is calculated. Using student's *t*-test, with a significance level of 0.05 (*p*-value), statistical significance of the results is reported (the data is tested for normality using Shapiro-Wilk test [198]). Simulation data post-processing and thermal image data analysis were done in MATLAB toolbox (academic license version: R2019a) by MathWorks.

3.4 Results

In this section, results pertaining to the numerical simulations and IR thermography examination are presented. While statistical tools are used to analyze the significance of the difference in result parameters between the normal and diseased carotid artery samples (*n*=20), one sample from each of the three groups of study participants, viz., both sides normal (N1, *n*=8), stenosis on one side (ND1, *n*=4), and stenosis on both the sides (D1, *n*=8), are used to discuss the hemodynamic, bio-heat transfer, and thermography-based *in-vivo* temperature measurement. **Table 3-3** summarizes the individual-specific (normal and diseased) simulation computed and Duplex Ultrasound measured mass flow rate (kg/s) in the ICA and ECA region. As the inlet blood flow moves in the common carotid artery (CCA), reaches the bulb region and meets the carotid bifurcation divider, secondary flow pattern arises on the external (NDW: non-dividing wall) side of the internal carotid artery (ICA) (**Figure 3-8**). This leads to the localization of the low wall

shear stress (WSS) on the NDW and high WSS on the DW (dividing wall) [13] (**Figure 3-9**). Isolating the stenosis tissue, the peak and average WSS on the rest of the carotid wall region (**Table 3-4**), in the normal and diseased cases, are found to significantly similar ($p > 0.05$). Furthermore, between the peak systolic (PSV) and end diastolic (EDV) inlet flow velocity conditions, the maximum and average WSS values are found to have differed by at least 10 times.

Figure 3-8: Velocity streamlines, at peak systolic velocity (PSV) and end diastolic velocity (EDV) inlet conditions, for the three groups of study participants: both sides normal (N1), stenosis on one side (ND1), and stenosis on both the sides (D1)

To investigate a possible relation with WSS, the average carotid artery wall temperature was extracted [199] (**Table 3-4**). Alike to WSS, the average carotid artery wall

temperature, in both normal and diseased (without stenosis tissue) cases, is found to be significantly similar ($p > 0.05$). Moreover, over the stenosis region, the carotid artery wall shows a low temperature region (**Figure 3-10**). This leads to a lower temperature on the external top-neck skin surface. In **Figure 3-11**, between PSV and EDV inlet flow conditions, a slight change in the length of an elongated ‘cold feature’, at the bottom center of the top-neck skin temperature contour, can be observed. While for the study participants with normal carotid arteries (N1: both sides normal and ND1: normal left side), this change is hardly noticeable, it is more prominently visible in the case of study participants with diseased carotid arteries (ND1: stenosis on right side and D1: stenosis on both sides).

Table 3-3: Mass flow rate (kg/s) from simulation and Duplex Ultrasound measurement in the normal and diseased carotid arteries

Carotid artery groups		Mass flow rate (kg/s)			
		PSV inlet at CCA		EDV inlet at CCA	
		ICA	ECA	ICA	ECA
Normal (n=10)	Simulation	0.022 ± 0.003	0.014 ± 0.002	0.006 ± 0.001	0.004 ± 0.001
	Measured	0.016 ± 0.009	0.020 ± 0.003	0.007 ± 0.003	0.005 ± 0.002
	Standard error	0.009	0.007	0.003	0.002
	<i>p</i> -value	0.062	0.0004	0.376	0.156
Diseased (n=10)	Simulation	0.022 ± 0.004	0.014 ± 0.007	0.006 ± 0.002	0.003 ± 0.001
	Measured	0.028 ± 0.015	0.034 ± 0.016	0.008 ± 0.004	0.005 ± 0.003
	Standard error	0.018	0.022	0.004	0.004
	<i>p</i> -value	0.306	0.005	0.250	0.160
CCA: Common Carotid Artery; ICA: Internal Carotid Artery; ECA: External Carotid Artery; PSV: Peak Systolic Velocity; EDV: End Diastolic Velocity					

Moving on, the IR thermography measurement of the skin thermal map, on the same study participants, indicates the presence of low temperature regions in the cases with stenosis in the carotid artery (**Figure 3-12**). Figure 3-13a shows the average and

maximum temperature in the normal and diseased thermal image samples; higher for normal case. This low temperature region is extracted using the TROI threshold temperature (T_{th} in °C, using Equation 3-7) at different values of variable parameter ‘ m ’. For both normal and diseased samples, as the value of ‘ m ’ increases, the average and threshold temperature of the resultant images are found to have increased with a divergence between the two samples (**Figure 3-13b** and **Figure 3-13c**). The TROI extracted images, at $m = 0.4$, show a high density of lower temperature pixels in the cases with stenosis in the carotid artery (Figure 3-12). Furthermore, quantitatively evaluating the lower temperature pixel density, the value of ‘ R_n ’ (with SD error bars) is plotted against the variable parameter ‘ m ’ (**Figure 3-13d**). It can be observed that the difference between the value of ‘ R_n ’, for normal and diseased cases, first increases and then decreases with the increase in value of ‘ m ’.

Table 3-4: Maximum and average wall shear stress (WSS in Pa) and average carotid wall temperature (°C) in the normal and diseased samples

Simulation parameters	CCA inlet flow condition	Normal (n=10)	Diseased (n=10)		<i>p</i> -value (normal and diseased without stenosis tissue)
			Without stenosis tissue	Over stenosis tissue	
Maximum WSS (Pa)	PSV	41.14 ± 8.37	47.23 ± 12.03	35.89 ± 15.85	0.25
	EDV	4.85 ± 1.82	4.60 ± 1.99	4.47 ± 3.38	0.78
Average WSS (Pa)	PSV	4.20 ± 0.85	4.68 ± 0.94	6.76 ± 2.03	0.29
	EDV	0.63 ± 0.19	0.65 ± 0.23	0.92 ± 0.45	0.85
Average temperature on the carotid wall (°C)	PSV	36.96 ± 0.01	36.96 ± 0.003	36.74 ± 0.26	0.29
	EDV	36.92 ± 0.03	36.92 ± 0.01	36.70 ± 0.27	0.89

3.5 Discussion

An indirect measurement of carotid artery stenosis was investigated. In the presence of stenosis in the carotid artery, the temperature map on the skin surface is expected to differ from the normal case. To confirm the same, a finite volume-based conjugate bio-heat transfer computational study was performed. While using an idealized 3D carotid artery-jugular vein model encapsulated with neck tissue, Duplex Ultrasound-based individual-specific artery depth, stenosis tissue geometrical characteristics, and inlet flow boundary conditions (peak systolic velocity, PSV and end diastolic velocity, EDV) were applied. On the same study participants, an *in-vivo* IR thermography examination was performed. From **Table 3-1**, between study participant groups '*both sides normal*' and '*stenosis on both sides*', while the CCA PSV inlet flow condition (*Re*: Reynolds number) is found to be significantly higher for normal carotid arteries (2158 ± 276 versus 1884 ± 268 , $p=0.03$), the difference in CCA EDV inlet flow condition is found to be insignificant (493 ± 142 versus 420 ± 146 , $p=0.16$). In the '*stenosis on one side*' group, the sample with 100% ICA blockage (ND2) shows a difference of 604 and 303 between the normal and stenosis side, in PSV and EDV *Re* inlet CCA flow conditions, respectively. This difference in PSV *Re* value, in both the study participants (ND1 and ND2), is found to be 1.9 times higher than EDV.

Figure 3-9: Wall shear stress (WSS in Pa), at peak systolic velocity (PSV) and end diastolic velocity (EDV) inlet conditions, for the three groups of study participants: both sides normal (N1), stenosis on one side (ND1), and stenosis on both the sides (D1)

Considering the observation made in the work of Rappitsch and Perktold [200], wherein as compared to steady state solution, the oscillatory nature of the blood flow doesn't affect the transport and deposit of macromolecules on the vessel wall, the steady state analysis in this study concurs the previous studies. On the other hand, use of steady-state carotid artery heat transfer analysis, in the work of [189] and [162], justifies the use of steady Navier-Stokes and energy equations in this study. Following a robust mesh independent study, the governing equation solution, in this study, is validated against the benchmark literature results [170,171] (Table 3-2, Figure 3-5, and Figure 3-6). Furthermore, the mass flow rate, in the ICA and ECA regions of the carotid artery, was

found to be comparable between the numerical simulation and Duplex Ultrasound measurement. Except for the ECA mass flow rate under CCA PSV inlet flow condition, the mass flow rates obtained from the numerical simulation, in both normal ($n=10$) and diseased ($n=10$) carotid arteries, are found to be significantly similar to the measured values ($p>0.05$).

Figure 3-10: Carotid artery wall surface temperature, at peak systolic (PSV) and end diastolic (EDV) velocity inlet conditions, for the three groups of study participants: both sides normal (N1), stenosis on one side (ND1), and stenosis on both the sides (D1)

While in the normal cases, the maximum standard error, between the simulation and measured mass flow rates, is found to be 0.009 kg/s, it is found to be 0.022 kg/s in case of the diseased cases (**Table 3-3**). Observed under PSV inlet flow condition, this error in the measured and simulated mass flow rates could be attributed to the use of an idealized carotid artery geometry model and application of a theoretically acceptable but unrealistic boundary conditions at the outlet of the ICA and ECA [131]. Under EDV inlet flow condition, for both the normal and diseased cases, the measured and simulated mass flow rates are found to be consistent with a maximum standard error of 0.004 kg/s. The flow division ratio (ICA:ECA), between the normal and diseased carotid artery simulations, is found to be significantly different for both CCA PSV ($p = 0.03$) and EDV (p -value = 0.01) inlet flow conditions. Excluding the 100% ICA blockage cases, the ICA:ECA flow division ratio is found to be higher for the diseased (with stenosis) carotid artery models; 2.05 ± 0.32 versus 1.75 ± 0.01 and 2.31 ± 0.35 versus 1.91 ± 0.07 for CCA PSV and EDV inlet flow conditions, respectively. This trend is the result of the higher ECA blockage, in most of the cases, as compared to ICA (**Table 3-1**). In the presence of stenosis tissue, the blood flow passage narrows down that influences the physiological processes, like flow resistance, shear stress, etc., causing a chaotic flow with the formation of pre- and post-stenotic recirculation zones [201]. As a consequence, the increased WSS over the neck of the stenosis tissue makes it vulnerable to rupture; a major cause of stroke upon blockage of the cerebral blood vessels [202]. Moreover, due to the oscillating nature of the blood flow (systolic and diastolic), the WSS also oscillates, which in return complements the stenosis inducing factors causing a further progression of the disease leading to rupture [203]. In this study, the maximum value of WSS is found

to be localized on the bifurcation region of the carotid artery (**Figure 3-9**). On the contrary, over the stenosis tissue, a similar or higher magnitude of WSS concentration is observed (**Table 3-4**). This demonstrates the high rupture vulnerability of the stenosis tissue [204].

Related to WSS, the average carotid wall temperature, over the stenosis tissue region, is found to be significantly lower ($p < 0.02$) as compared to the rest of the carotid artery wall average temperature (**Figure 3-10**). As compared to PSV, the carotid artery wall temperature in EDV is found to be slightly lower for both normal and diseased (without stenosis) cases [205]. The presence of stenosis is found to have a further complementary role in lowering down the temperature over the stenosis region of the carotid wall [178]. This computational observation can be validated from the work of Otani et al. [206], wherein captured during the carotid endarterectomy, the IR thermal image of the carotid artery showed the presence of a cold (low temperature) spot over the stenosis region of the carotid artery wall. This cold spot was found to be disappeared upon successful completion of the carotid endarterectomy procedure. In this study, across the internal (in contact with the blood flow) and external (in contact with the encapsulation tissue) walls of the stenosis tissue, an average temperature difference of $0.23 \pm 0.23^\circ\text{C}$ and $0.21 \pm 0.19^\circ\text{C}$ under PSV and EDV inlet flow conditions, respectively, is observed. Hence, on the external wall of the carotid artery, localized low temperature occurs between PSV and EDV inlet flow conditions, which intensifies with the presence of stenosis tissue in case of diseased carotid arteries (**Figure 3-10**).

Figure 3-11: Top-neck skin surface temperature, at peak systolic (PSV) and end diastolic (EDV) velocity inlet conditions, for the three groups of study participants: both sides normal (N1), stenosis on one side (ND1: right side), and stenosis on both the sides (D1)

As the carotid artery wall temperature interacts with the encapsulation tissue, heat diffusion through Pennes bio-heat transfer comes into play [207]. The localized low temperature zones on the carotid artery wall (**Figure 3-10**) affect the conduction and perfusion term in Equation 3-6 and hence, the effect is propagated up to the top-neck skin via interacting with the counterflow jugular vein. Between normal (n=10) and diseased (n=10) carotid artery models, under both PSV and EDV inlet flow conditions, the average top-neck skin temperature is found to be significantly higher for normal cases ($33.33 \pm$

0.03 °C versus 33.23 ± 0.03 °C, $p < 0.001$). As asserted earlier and shown in the author's previous work [178], with no global change in the top-neck skin temperature, a localized temperature contour difference (shape and size of the *cold feature*) is found to have distinguished the PSV and EDV inlet flow conditions. This is qualitatively observed in **Figure 3-11** as well.

For *both sides normal* group, the *in-vivo* measured IR thermography-based thermal maps are observed to be uniformly high temperature, while this uniformity is not observed for *stenosis on one side* or *stenosis on both sides* groups (**Figure 3-12**). Excluding the study participant D2, as compared to the diseased group of samples ($n=8$), as shown in **Figure 3-13a**, the average temperature in normal group of samples ($n=10$) is found to be significantly higher (32.82 ± 0.53 °C versus 32.00 ± 0.37 °C, $p < 0.001$). Moreover, no significant difference ($p > 0.05$) is found in the maximum temperature values (**Figure 3-13a**). For study participant D2, the average and maximum skin temperature were found to be 34.80 °C and 36.55 °C, respectively. Even with a high degree of stenosis in all parts of both the carotid arteries (**Table 3-1**), it is suspected that the high temperature, in study participant D2, was the result of an unknown pathological condition, hence, this study participant is excluded from the thermal image data analysis. Between the *in-vivo* temperature measurement and simulated model results, though the trend in average temperature value (higher for the normal group of samples) of the skin is same, the actual values differs. This difference is attributed to the fact that the model prediction is done on a geometry which doesn't account for all the complex individual-specific variables, such as inconsistent shape, size, orientation (non-planar), surrounding vasculature, etc. [183].

Figure 3-12: Full IR thermal image and TROI image (at $m=0.4$) for the three groups of study participants: both sides normal (N1), stenosis on one side (ND1: right side), and stenosis on both the sides (D1)

Figure 3-13: (a) Average and maximum temperature (°C) with standard deviation (SD) bar in full IR thermal image (b) Average temperature (°C) (c) Threshold temperature (°C) and (d) Node ratio (R_n) with SD bar versus variable parameter m for TROI images, in normal and diseased IR thermal image samples.

To further quantify the thermal features in the image that relates to the presence of stenosis in the carotid artery, thermal region of interest (TROI) is extracted using Equation 3-7. These images help easing visualization of the stenosis affected thermal zone in the resultant image (**Figure 3-12**). The average temperature values in TROI images (**Figure 3-13b**), at ‘ m ’ value of 0.5 and higher, are found to be have significantly distinguishing ($p < 0.05$) the two groups of samples (normal and diseased). Although the threshold temperature value (T_{th}) is calculated image-specific, this value is found to be significantly similar ($p > 0.05$) at all the variable parameter ‘ m ’ (**Figure 3-13c**). In particular, the TROI extraction method helps distinguishing the thermography results in the study participant ND1. In this case, the qualitative visualization of the full thermal image (**Figure 3-12**) and average skin temperature (Left: 31.97 ± 1.16 °C and Right: 32.01 ± 1.15 °C) do not show obvious differences between the right (with stenosis) and left (normal) side images. With TROI images, this difference is made slightly more obvious (**Figure 3-12**). Further, quantifying the TROI image using node ratio (R_n), the best value of variable parameter (m) is evaluated. Except at $m = 0.7$ and 0.8 , where the value of R_n is found to be significantly similar ($p > 0.05$) between normal and diseased samples, at all other m values, R_n is found to be significantly different ($p < 0.05$). Except at $m = 0.8$ and 0.9 , the value of R_n is found to be lower for the normal samples; implying lower number low temperature image pixels as a result of absence of stenosis in the carotid artery. As shown in **Figure 3-13d**, with no overlap in the values of standard deviation, $m = 0.4$ is found to be the best variable parameter (Normal: 0.17 ± 0.07 versus Diseased: 0.36 ± 0.09 , $p < 0.001$). At $m = 0.4$, the value of R_n , in study participant ND1,

is found to be 0.24 and 0.36 for the normal (left) and diseased (right) side, respectively; quantitatively distinguishing the two sides.

3.6 Summary

From the computational study, it is established that in the presence of stenosis, a relatively lower temperature region occurs on the section of carotid wall over the stenosis tissue. This results in significantly low average temperature on the external skin surface as compared to the carotid artery with no stenosis ($p < 0.001$). A similar observation was observed in the *in-vivo* thermal images. Furthermore, a quantitative method of extracting thermal region of interest (TROI), from the IR thermal images, is introduced. The TROI is found to have distinguished the two groups of carotid artery samples (normal and diseased) both qualitatively and quantitatively. Though the observations are limited by the number of samples ($n=20$), this preliminary study proves to be an important milestone in evaluating the potential of a thermal feature-based carotid artery stenosis screening tool.

CHAPTER 4 EVALUATING THE SCREENING POTENTIAL OF PASSIVE THERMOGRAPHY FOR CAROTID ARTERY STENOSIS

4.1 Abstract

In this study, an infrared (IR) thermal camera was used to map the temperature of the target skin surface, and the resulting thermal image was evaluated for the presence of carotid artery stenosis (CAS). In the presence of stenosis in the carotid artery, abnormal temperature maps are expected to occur on the external skin surface, which could be captured and quantified using IR thermography. A Duplex Ultrasound (DUS) examination was used to establish the ground truth. In each patient, the background-subtracted thermal image, referred to as *full thermal image*, was used to extract novel parametric *cold thermal feature images*. From these images, statistical features, viz., correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis, were calculated and the two groups of patients (control and diseased: a total of 80 carotid artery samples) were classified. Both cut-off value- and support vector machine (SVM)-based binary classification models were tested. While the cut-off value classification model resulted in a moderate performance (70% accurate), SVM was found to have classified the patients with high accuracy (92% or higher). This study suggests the use of IR thermography as a possible screening tool for CAS patients.

4.2 Introduction

It is evident that the occurrence of CAS causes thermal changes, such that the presence of stenosis affects the blood flow (turbulent flow across the lesion) in the carotid artery [173]; alters the heat transfer to the surrounding tissue and the resultant outer skin surface temperature [160,162,178]. In the past, contact-based temperature measurement, called plate thermography, was used to correlate the presence of abnormal temperature map with CAS. Plate thermography, wherein a flexible foil, coated with specific cholesterol ester, changes color due to temperature oscillations, was used to map the forehead temperature in 300 patients; the method showed positive results (abnormality) in 39 patients against 34 patients using Doppler sonography [154]. Thereafter, a non-contact facial temperature measurement, using an infrared (IR) thermal camera [157,158,175], that correlates to the presence of CAS was performed by Capistrant and Gumnit [155]. Of the 30 patients, suffering from angiographically proven carotid stenosis or occlusion, an abnormal thermal map was observed in 57% of the cases. Monitoring the temperature variation among the geometrically symmetrical locations of the human body (ocular, limbs, etc.) could prove to be an indirect cardiovascular disease detection marker [208]. With reference to CAS detection, one such correlation was studied by Morgan et al. [156], on 24 patients, wherein the ocular temperature was correlated ($r = -0.67$) to the degree of stenosis in the carotid artery. Therefore, temperature measurement, especially using IR thermography, could fulfil the need of a desirable CAS screening modality. In the last two decades, however, despite the development of sophisticated image processing, object detection, machine learning, and deep learning algorithms, no IR

thermography-based, highly accurate and clinically proven, CAS detection method has been reported in the field.

Unlike the previous IR thermography-based CAS detection studies [208], [156], wherein the original thermal image and its mean temperature were used to classify the two groups of patients (control and diseased), in this study, using the original *full thermal image*, a novel parametric *cold thermal feature image* extraction method is proposed. Moreover, in the past, the target area of thermal scan in such studies was either the temporal (forehead) or the ocular (eyes) region. The proposed method is taking the IR thermal scan from either side of the neck, including the face region. The *full thermal image* and the extracted parametric *cold thermal feature images* were quantitatively analyzed with the help of statistical features, viz., correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis. While previous studies were limited to cut-off value-based binary classification model, in this study, additionally, support vector machine (SVM)-based binary classification model was applied on the statistically significant features, and the respective classification performance is reported.

4.3 Materials and Methods

4.3.1 Study participants

In this prospective study, 40 study participants (38 males and 2 females) were recruited under the clinical research study approved by Centralized Institutional Review Board (CIRB Ref No.: 2017/2119), SingHealth, Singapore, from September 2017 through March 2018. The study participants were recruited at the Vascular Lab of National Heart

Center Singapore (NHCS). Individuals with a clinical indication for carotid Duplex Ultrasound (DUS) for arterial stenosis detection, as identified by the physicians at NHCS, were approached to participate in the study. Individuals with previously known significant stenosis in the subclavian artery or multiple stenoses or occlusion in cerebral circulation were excluded from the study.

4.3.2 Duplex Ultrasound (DUS) examination

Upon signing the informed consent form, the study participants undergo the standard carotid DUS examination performed by the trained sonographer at NHCS. The stenosis grading, in the Common Carotid Artery (CCA), Internal Carotid Artery (ICA), and External Carotid Artery (ECA), was done using a combined morphological (diameter) and hemodynamic (peak systolic and end-diastolic velocities) criterion [80] as per the standard grading protocol followed at the Vascular Lab, NHCS. Studying the carotid artery on each side of the neck as an individual sample, this study utilized a total of N=80 samples. Based on the outcome of the DUS examination, the left and right carotid arteries of the study participants were labeled with the stenosis grading (either in the CCA, ICA or ECA region of the carotid artery), and hence, the study samples were divided into 4 subgroups, namely, one Control group as 0% (C) stenosis and three Diseased groups with 10%-29% (D1), 30%-49% (D2), and $\geq 50\%$ (D3) stenosis, as shown in **Figure 4-1**. Derived from these four groups, two more groups, namely, extended control (C': 0% - 29% stenosis) and extended diseased (D': $\geq 30\%$ stenosis) groups, were also made.

Figure 4-1: Carotid sample distribution based on stenosis grading by Duplex Ultrasound

4.3.3 Infrared (IR) thermography examination

Following the DUS examination, the study participants were prepared for the IR thermography examination on the same day. As a part of standard medical thermography protocol, the study participants were asked to rest for 15 minutes in a temperature-controlled room maintained at 23 ± 0.5 °C temperature and 50% relative humidity [195]. A passive thermal scan (with no external stimulation), on either side of the neck and face region, was taken using VarioCAM IR thermal camera by InfraTec. The IR thermal camera, equipped with an uncooled microbolometer detector, produces a 2-dimensional (2-D) thermal images (rows x columns: 240 x 320 pixels) with a temperature resolution of less than 0.1 °C. Evident from the studies on neck temperature-based pulse measurement [180,181], the cardiac cyclic nature (systolic and diastolic) of the blood flow in the carotid artery results in a local and infinitesimally small change in the skin temperature with no effect on the global temperature maps, a passive image taken at any instant of the cardiac cycle can be used.

4.3.4 Parametric cold thermal feature image extraction

The original thermal image, taken on either side of the neck, has neck, face, head, cloth, and background details, as shown in **Figure 4-2**. For image noise and background subtraction, the original thermal image, after converting into a grayscale normalized image with intensity value in the range of 0 to 1, was first passed through a 2-D median filter. The resultant image was then used to calculate a global threshold value using Otsu's method [196,197]. The threshold value was calculated as such it minimizes the intraclass variance of the pixels in the image. Using this threshold value, a mask image was created. Masking the original thermal image with the mask image resulted in a background-subtracted image (**Figure 4-2**). Given the temperature of the clothing, on the study participant's body, is higher than the background (surrounding) but lower than the skin temperature, if, at all visible in the original thermal image, it was not masked out entirely in the background-subtracted image. Hence, manual segmentation was performed to remove the clothing part from the image; resulting in a cloth segmented *full thermal image* (**Figure 4-2**). From the *full thermal image*, *cold thermal feature images* were extracted using a parametric threshold temperature method given by Equation 4-1. For a given *full thermal image*, since the threshold value is derived below the mean temperature, at a specific k parameter value, the resultant image is referred to as a *cold thermal feature image* (**Figure 4-2**).

$$T_{ck} = T_m - k(T_m - T_{mi}) \quad (4-1)$$

where, T_{ck} is the cold thermal feature threshold temperature (°C) at the defined k parameter that varies from 0.1 to 0.9 in a step size of 0.1. T_{mi} and T_m are the minimum and mean temperature (°C) value calculated from all the non-zero pixels in the given *full*

thermal image, respectively. For the given k value, all the image pixels with temperature value more than T_{ck} were replaced with zero (**Figure 4-2**). This resulted in a series of nine (for $k=0.1$ to 0.9) *cold thermal feature images*.

Figure 4-2: Thermal image processing: normalizing, masking, segmentation, feature extraction, and classification

Unlike the case of tumor, cervical lymph node metastasis, internal injury, etc. [209], where the presence of pathological condition is defined by a high-temperature region in the thermal image, in this study, a region of lower temperature is expected to be the indication of stenosis in the carotid artery [155]. In the presence of stenosis, changes in the hemodynamics of the carotid artery take place. This results in a lower rate of heat transfer to the external skin tissue surface and hence appears as a low-temperature region in the resultant thermal image [178]. To quantitatively compare the temperature distribution in the thermal image, between the normal and stenosis cases, statistical features were used. In all the thermal scans, from each of the *full thermal image* and its corresponding nine *cold thermal feature images*, nine statistical features, viz., correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis, were calculated (**Figure 4-2**) [210].

4.3.5 Classification Strategy

In clinical settings, accurately screening patients with 30% or more stenosis (vulnerable/unstable: more likely to rupture) is of more importance than less than 30% stenosis [211], such that the false-positive cases are affordable over the false negative ones. To evaluate the classification performance in such a case, in this study, extended groups C' and D' were classified first, and then a sub-classification of groups C' and D' into the group (C and D1) and (D2 and D3), respectively, was performed (**Figure 4-3**).

Figure 4-3: Binary classification flow chart for control (C: 0% stenosis), diseased (D1: 10% - 29% stenosis; D2: 30% - 49% stenosis; D3: ≥ 50% stenosis; and D: ≥ 10% stenosis), extended control and diseased (C': 0% - 29% stenosis; D': ≥ 30% stenosis) groups of samples

4.3.6 Binary classification

Using the significant statistical features, classification of the two groups of samples (control and diseased) was done using the cut-off value and Support Vector Machine (SVM)-based classification models (**Figure 4-2**). For both the classification models, the performance was evaluated with the standard definition (**Equation 4-2 to 4-6**) of

sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

$$Sensitivity = \frac{TP}{TP + FN} \quad (4-2)$$

$$Specificity = \frac{TN}{TN + FP} \quad (4-3)$$

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (4-4)$$

$$PPV = \frac{TP}{TP+FP} \quad (4-5)$$

$$NPV = \frac{TN}{TN+FN} \quad (4-6)$$

where, TP : True positive (diseased patients correctly identified as diseased); FN : False Negative (diseased patients incorrectly identified as normal); TN : True Negative (normal patients correctly identified as normal); FP : False Positive (normal patients incorrectly identified as diseased); PPV : Probability that the subject really has the disease if predicted positive; NPV : Probability that the subject really doesn't have the disease if predicted negative.

4.3.7 Cut-off value-based classification

For each of the extracted significant statistical feature, from each of the nine *cold thermal feature images*, a cut-off value was used to classify the two groups of samples (control and diseased). The optimum cut-off value was defined using the receiver operating curve (ROC) analysis, which is widely used for binary classification problems in medical diagnosis applications [132,212]. In the ROC analysis, at a given cut-off value, the *sensitivity* of the classification is plotted against the $(1 - specificity)$. For a given set

of feature values, from the two groups of samples (control and diseased), several cut-off values are tested and the optimal cut-off value point, from where the distance to the point of ($sensitivity = 1, 1 - specificity = 0$) is minimum [213], is chosen from the ROC curve. The classification sensitivity and specificity are highest at this optimal point. Additionally, the area under the ROC curve (AUC) provides a quantitative measure of classification success: 0.5 is poor, while 1 is the best classification model.

4.3.8 Support Vector Machine (SVM)-based classification

In this study, Support Vector Machine (SVM)-based machine learning classification was used. SVM is widely applied for medical thermography-based disease diagnosis applications such as breast cancer [214,215], cervical lymph node metastasis [195], knee osteoarthritis [216], etc. In SVM, for a given set of feature data from the two group of samples (control and diseased), a hyperplane is introduced such that the closest feature data points in the two classes (called as support vectors), on either side of the hyperplane, are well separated from each other. The objective is to select an optimal hyperplane that maximizes the distance between the hyperplane and the support vectors [217]. Where the feature data set is not linearly separable, a non-linear SVM model is used. In non-linear SVM, the features are mapped into a higher feature space (called *Kernel mapping*), from where a linear hyperplane separation is possible [218]. In this study, non-linear (RBF: radial basis function) SVM model was tested. To entirely utilize the available data, a seven-fold cross-validation SVM model was used [219]. In this model, the samples were randomly divided into seven subsets. At a time, one subset was used for the training while the remaining ones were used for the testing. This process was repeated seven times to ensure the usage of each of the subsets for both training and testing purpose. To

ensure a random mix of the data, in this study, the cross-validation model was iterated ten times. At each iteration, of the generated seven training models, the one with the highest classification error was used to report the classification performance [220]. At the end of the ten iterations, the average values ($\pm$ confidence interval) of the performance parameters, viz. sensitivity, specificity, accuracy, PPV, and NPV, were reported (Equation 4-2 to 4-6).

4.3.9 Statistical data analysis

Extraction of the *cold thermal feature images* from the original *full thermal images*, statistical feature calculation, evaluation of statistically significant features, followed by the classification of samples using cut-off value and SVM-based classification models, (**Figure 4-2**), the processing was done in MATLAB toolbox (academic license version: R2017B) by MathWorks. To determine the statistical significance of the difference in the target skin surface temperature and the calculated statistical features for the *full* and *cold feature thermal images*, between the two groups of samples (control and diseased), student's *t*-test, with a significance level of 0.05 (*p*-value), was used. Shapiro-Wilk test [198] was used to test the data normality. Non-parametric Mann-Whitney U test was applied [221] for data failing normality test. Average values, of any of the measured or calculated quantities, are reported with 95% confidence interval (95% CI).

4.4 Results

In 40 study participants, with a mean ($\pm$ SD) age of 62.70 ± 7.09 years (Male: 61.84 ± 6.94 years and Female: 62 ± 2.83 years), the minimum and maximum age of the participants was found to be 45 and 71 years old, respectively. Of the 40 participants, 34 were found

to have $\geq 10\%$ stenosis in either one or both of the carotid arteries (**Table 4-1**). While only 17% of the participants from the group with no stenosis were found to have a history of smoking, it was found to be in 62% of the participants from the other group. With respect to pre-existing hypertension condition, this distribution, in the two groups, was found to be 50% and 79%, respectively (**Table 4-1**). In this study, the carotid artery on each side of the neck was considered as an individual sample, resulting in a total sample size of $N=80$ carotid artery samples.

Figure 4-4 shows the ultrasound images of the internal carotid artery (ICA), in a single sample from each of the four groups of samples, namely, C, D1, D2, and D3 (**Figure 4-1**), in the increasing order of stenosis degree. Adjacent to the ultrasound images, in **Figure 4-4**, the *full thermal images* are shown. With a qualitative visual inspection, it can be observed that the overall temperature distribution changes from group C to D3. From each of the sample thermal image, using Equation 4-1, nine *cold thermal feature images* were extracted at parametric k values ranging from 0.1 to 0.9. Corresponding to the *full thermal image*, **Figure 4-5** shows the *cold thermal feature image*, for a single sample in each group, at $k = 0.1, 0.4$, and 0.7 . As the k value increases, the region of thermal feature diminishes, while for the same k value, the thermal feature becomes more prominent as the stenosis degree increases from group C to D3. In each sample, from the *full thermal image* and its nine sub-images (*cold thermal feature images* at $k = 0.1$ to 0.9), statistical features, viz. correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis, were extracted. Based on the classification strategy, in **Figure 4-3**, feature statistical significance ($p < 0.05$), between the

classification groups (C' and D'), (C and D1), and (D2 and D3), was evaluated and summarized in **Table 4-2** and **Table 4-3**.

Table 4-1: Passive thermography study cohort characteristics

Parameters	Participants with 0% stenosis on either side	Participants with $\geq 10\%$ stenosis on either or both sides
Number of participants	6	34
Female	2 (33%)	0
Age	58 ± 6.48	62.53 ± 6.69
Height (m)	1.64 ± 0.06	1.65 ± 0.07
Weight (Kg)	70.25 ± 14.71	69.57 ± 10.76
Body mass index (BMI)	25.97 ± 3.68	25.74 ± 3.90
Pulse rate (beats per second)	63 ± 15	72 ± 11
Systolic blood pressure (mmHg)	132 ± 24	129 ± 17
Diastolic blood pressure (mmHg)	69 ± 13	69 ± 9
Hypertension	3 (50%)	27 (79%)
Coronary artery disease	0	5 (15%)
Diabetes mellitus	1 (17%)	19 (56%)
Percutaneous coronary intervention	1 (17%)	7 (21%)
Myocardial infraction	0	6 (18%)
Coronary artery bypass graft	0	0
Smoking	1 (17%)	21 (62%)
Alcohol	0	1 (3%)
Note: Mean data are $\pm$ standard deviation

Figure 4-4: Ultrasound image of the internal carotid artery section (ICA) and corresponding thermal image for a single sample from each of C, D1, D2 and D3 groups

Figure 4-5: Cold thermal feature image (at $k=0.1$, 0.4 , and 0.7) for a single sample from each of C, D1, D2 and D3 group

Considering each of the significantly different statistical features, extracted from the *full thermal image*, the performance of cut-off value based binary classification is summarized in **Table 4-4**. Among the three classification groups, skewness was found to be the only common significant feature that provides the highest classification accuracy. Moving on, the significantly different statistical features, extracted from the *cold thermal feature images*, were used to perform the cut-off value-based classification. For the classification group (C' and D'), of all the statistical features among *cold thermal feature*

images, standard deviation (SD) was found to be the only significantly different feature at all the values of k (Table 4-2 and Figure 4-6).

Table 4-2: List of significant features ($p < 0.05$) between groups C' and D'

k	Features	Feature average value ($\pm 95\%$ CI)		
		C' (N=45)	D' (N=35)	p -value
Full thermal image	Energy	0.53 ± 0.01	0.51 ± 0.01	0.036
	Mean	32.77 ± 0.13	32.48 ± 0.18	0.006
	Skewness	-0.48 ± 0.12	-0.25 ± 0.12	0.004
	Kurtosis	3.44 ± 0.28	2.97 ± 0.28	0.011
0.1	Mean	31.79 ± 0.10	31.57 ± 0.17	0.017
	SD	0.59 ± 0.04	0.52 ± 0.04	0.010
0.2	Entropy	0.57 ± 0.04	0.61 ± 0.04	0.044
	Mean	31.54 ± 0.09	31.37 ± 0.15	0.030
	SD	0.55 ± 0.04	0.48 ± 0.03	0.008
0.3	Energy	0.80 ± 0.02	0.77 ± 0.03	0.032
	Entropy	0.44 ± 0.04	0.50 ± 0.05	0.033
	SD	0.49 ± 0.03	0.44 ± 0.03	0.013
0.4	Energy	0.85 ± 0.02	0.83 ± 0.03	0.042
	SD	0.43 ± 0.03	0.39 ± 0.03	0.028
0.5	SD	0.38 ± 0.02	0.34 ± 0.02	0.008
0.6	SD	0.31 ± 0.02	0.28 ± 0.02	0.004
0.7	SD	0.24 ± 0.01	0.21 ± 0.01	0.003
0.8	SD	0.16 ± 0.01	0.14 ± 0.01	0.0005
0.9	SD	0.08 ± 0.004	0.07 ± 0.01	0.002
C': 0% - 29% stenosis; D': $\geq 30\%$ stenosis				

Choosing the best performance feature, Table 4-5 summarizes the results of cut-off value-based classification and Figure 4-7 shows its corresponding ROC curve. While the group (C' and D') was found to have best classified using the *full thermal image* itself, use of *cold thermal feature images*, at $k = 0.2$ and 0.9 , was found to have performed better for the sub-classification of groups (C and D1) and (D2 and D3). Even though the features are significantly different, the performance of the cut-off value-based classification was found to be poor; therefore, in this study, the SVM-RBF model was applied to perform the classification. Using all the significant features (Table 4-2 and Table 4-3) from the *full thermal image* and its sub-images (*cold thermal feature images*), Table 4-6 summarizes the outcome of the SVM classification.

Table 4-3: List of significant features ($p<0.05$) for sub-classification groups (C and D1) and (D2 and D3)

k	Features	Feature average value ($\pm$ 95% CI)					
		C and D1			D2 and D3		
		C (N=20)	D1 (N=25)	P -value	D2 (N=23)	D3 (N=12)	P -value
Full thermal image	Mean	32.90 $\pm$ 0.21	32.67 $\pm$ 0.16	0.042	-	-	-
	Skewness	-0.64 $\pm$ 0.15	-0.36 $\pm$ 0.16	0.008	-0.31 $\pm$ 0.15	-0.10 $\pm$ 0.15	0.029
0.1	SD	0.63 $\pm$ 0.06	0.55 $\pm$ 0.05	0.040	-	-	-
0.2	Homogeneity	0.973 $\pm$ 0.004	0.968 $\pm$ 0.003	0.028	-	-	-
	Contrast	1.52 $\pm$ 0.21	1.81 $\pm$ 0.19	0.028	-	-	-
	SD	0.58 $\pm$ 0.05	0.52 $\pm$ 0.05	0.039	-	-	-
0.3	Homogeneity	0.979 $\pm$ 0.003	0.973 $\pm$ 0.004	0.022	0.974 $\pm$ 0.004	0.968 $\pm$ 0.005	0.035
	Contrast	1.21 $\pm$ 0.15	1.50 $\pm$ 0.23	0.022	1.45 $\pm$ 0.21	1.77 $\pm$ 0.26	0.035
	SD	0.52 $\pm$ 0.05	0.47 $\pm$ 0.04	0.043	-	-	-
0.4	SD	0.46 $\pm$ 0.04	0.41 $\pm$ 0.03	0.032	-	-	-
0.5	SD	0.40 $\pm$ 0.03	0.36 $\pm$ 0.02	0.038	-	-	-
0.8	SD	0.169 $\pm$ 0.012	0.155 $\pm$ 0.009	0.040	-	-	-
	Kurtosis	-	-	-	1.97 $\pm$ 0.11	1.83 $\pm$ 0.05	0.011
0.9	SD	0.086 $\pm$ 0.006	0.079 $\pm$ 0.005	0.032	-	-	-
	Skewness	-0.02 $\pm$ 0.06	-0.10 $\pm$ 0.05	0.025	-0.16 $\pm$ 0.06	-0.03 $\pm$ 0.06	0.003
C: 0% stenosis; D1: 10% - 29% stenosis; D2: 30% - 49% stenosis; D3: $\geq$ 50% stenosis							

4.5 Discussion

As per clinical DUS evaluation, using both the B-mode and color doppler 2-D ultrasound images, the original and the reduced (due to stenosis) blood vessel diameter boundaries were marked (**Figure 4-4**). While the peak systolic blood flow velocity in these single samples, from group C, D1, D2, and D3, was found to be 71, 55, 60, and 33 cm/s, respectively, the end-diastolic blood flow velocity was found to be 21, 13, 17, and 4 cm/s, respectively. The average ($\pm$ 95% CI) peak systolic velocities, in group C, D1, D2, and

D3, were 61.1 ± 8.5 , 57.8 ± 4.7 , 67.7 ± 11.3 , and 117 ± 53.5 cm/s, respectively, and the average end-diastolic velocities were 22.5 ± 3 , 20.9 ± 2.2 , 23.4 ± 4.3 , and 39.3 ± 21.7 cm/s, respectively. Given the group D3 has a wide range of stenosis degree cases (from 50% to near occlusion) and presence of multiple location stenosis in the CCA, ICA, and ECA region, it resulted in a high 95% CI velocity value. With the reduction in the diameter, from group C to D3, the blood flow velocity tends to increase, which is accompanied by the formation of recirculation zone past the stenosis and reduction in the adequate blood volumetric flow [124,222,223]. This affects the surrounding tissue heat transfer, which is expected to result in variational temperature features on the outer skin surface [178,182]. To quantify this temperature change, in this study, thermal images were used and the classification performance, among the groups of control and diseased samples, was evaluated as illustrated in **Figure 4-3**.

In **Figure 4-4**, while for the group C sample thermal image, the temperature distribution is observed to be more uniform within high-temperature zones (31 °C to 34 °C), for group D1 to D3, as a result of presence of stenosis in the carotid artery, the temperature distribution resulted into cold temperature zones (29 °C to 32 °C). The mean ($\pm$ 95% CI) temperatures, in group C, D1, D2, and D3, were found to be 32.90 ± 0.21 °C, 32.67 ± 0.16 °C, 32.52 ± 0.23 °C, and 32.39 ± 0.27 °C, respectively; mean temperature decreases with the increase in degree of stenosis in the carotid artery [156]. As per the proposed classification strategy (**Figure 4-3**), the mean temperature in extended classification group (C' and D') was found to be significantly higher for group C' (C': 32.77 ± 0.13 versus D': 32.48 ± 0.18 , $p=0.006$). For the sub-classification groups (**Table 4-3**), while

the mean temperature was significantly different in (C and D1), it was insignificant in the group (D2 and D3). Therefore, in addition to the mean temperature feature, more statistical features were extracted from the *full thermal images*.

Table 4-4: Performance of the cut-off value-based binary classification model for various groups of samples using significant features from full thermal images

Groups	Thermal feature cut-off value	Sensitivity (%)	Specificity (%)	AUC	Accuracy (%)	PPV (%)	NPV (%)
C' and D'	Energy: 0.51	64	53	0.57	58	50	67
	Mean: 32.69	61	62	0.67	62	54	68
	Skewness: -0.42	79	62	0.68	69	60	80
	Kurtosis: 3.12	70	60	0.64	64	56	73
C and D1	Mean: 32.83	64	65	0.64	64	70	59
	Skewness: -0.45	56	75	0.68	64	74	58
D2 and D3	Skewness: -0.19	80	65	0.67	70	50	88
C: 0% stenosis; D1: 10% - 29% stenosis; D2: 30% - 49% stenosis; D3: $\geq$ 50% stenosis; C': 0% - 29% stenosis; D': $\geq$ 30% stenosis; AUC: Area under the receiver operating characteristics (ROC) curve							

In the classification group (C' and D'), Energy, Skewness, and Kurtosis features were also found significantly different. Moreover, while in the classification group (C and D1), Skewness feature was also found significant, in the classification group (D2 and D3), only Skewness was found significant (**Table 4-2** and **Table 4-3**). Using these significant features, the cut-off value-based classification of groups (C' and D'), (C and D1), and (D2 and D3) yielded the highest accuracy of 69%, 64%, and 70%, respectively, for the Skewness feature (**Table 4-4**). Using the Skewness feature, in this study, the sensitivity of classifying the samples with $\geq$ 50% stenosis (group D3), using cut-off value-based binary classification model, was found to be 80%, which is around 40% and 864% better

than the one achieved using mean temperature in the work of Capistrant and Gumnit (57%) [155] and Morgan et al. (8.3%) [156], respectively.

Table 4-5: Performance of the cut-off value-based binary classification model for various groups of samples using significant features from full and cold thermal feature images

Groups	k	Thermal feature cut-off value	Sensitivity (%)	Specificity (%)	AUC	Accuracy (%)	PPV (%)	NPV (%)
C' and D'	Full thermal image	Skewness: -0.42	79	62	0.68	69	60	80
C and D1	0.2	Contrast: 1.54	72	65	0.68	69	72	65
D2 and D3	0.9	Skewness: -0.09	80	65	0.76	70	50	88
C: 0% stenosis; D1: 10% - 29% stenosis; D2: 30% - 49% stenosis; D3: $\geq 50\%$ stenosis; C': 0% - 29% stenosis; D': $\geq 30\%$ stenosis; AUC: Area under the receiver operating characteristics (ROC) curve								

To further enhance the classification, in this study, the proposed *cold thermal feature image* extraction method was applied (Equation 4-1). For the classification group (C' and D'), at all the k values, though SD feature was found to be significantly different (**Table 4-2**), except at $k=0.4$, the feature value overlap, between the two groups of samples, was found to have decreased with the increase in k value. This is further corroborated from the AUC curve that shows an increasing trend (linear regression, $R^2 = 0.68$) with the k value increment (**Figure 4-6**). A lower R^2 value is the result of the catastrophic change in the AUC value at $k = 0.4$ and 0.8 . While at $k=0.4$, the lower AUC is the result of the high overlap in the feature values that resulted in a high p -value of 0.028, at $k=0.8$, a high value of AUC is the result of the low overlap in the feature values that resulted in a lower p -value of 0.0005 (**Table 4-2**). For the SD feature, the highest AUC value of 0.72, at $k = 0.8$ *cold thermal feature image*, resulted in a sensitivity and specificity of 73% and 63%, respectively. On the other hand, with slightly lower specificity, the skewness feature,

extracted from the *full thermal image*, resulted in an improvement of 8% in the sensitivity of the classification (**Table 4-4**).

Table 4-6: Performance ($\pm 95\%$ CI) of the SVM-RBF binary classification model for various groups of samples using all the significant features

Groups	Number of features	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
C' and D'	19	89.4 ± 1.0	97.3 ± 0.9	94.1 ± 0.5	95.8 ± 1.3	93.0 ± 0.6
C and D1	14	96.4 ± 1.8	87.8 ± 1.9	92.6 ± 0.7	90.8 ± 1.2	95.3 ± 2.2
D2 and D3	5	80.3 ± 5.0	97.6 ± 1.5	92.7 ± 1.2	93.8 ± 3.9	92.7 ± 1.7
C: 0% stenosis; D1: 10% - 29% stenosis; D2: 30% - 49% stenosis; D3: $\geq 50\%$ stenosis; C': 0% - 29% stenosis; D': $\geq 30\%$ stenosis						

In the sub-classification groups, (C and D1) and (D2 and D3), *cold thermal feature images* at $k = 0.2$ and 0.9 , respectively, provided the highest classification performance (**Table 4-5**). In contrast to the cut-off value-based binary classification model, the SVM-RBF model resulted in a better performance. Given that the SVM-RBF was tested using cross-validation, an average value ($\pm 95\%$ CI) of the classification performance is reported in **Table 4-6**. For the extended group classification (C' and D'), the sensitivity to classify samples with $\geq 30\%$ stenosis in the carotid artery (D') was found to be 89%, which is 10% higher than the best cut-off value-based model. With an improvement of 56% from cut-off value model, the specificity of SVM-RBF model classification (classify sample with $<30\%$ stenosis) was found to be 97%. In the sub-classification groups, compared to the cut-off value model, while SVM-RBF model resulted in a substantial improvement in the sensitivity and specificity of classification in the group (C and D1),

with a similar sensitivity of 80%, specificity improvement of 33% is observed in the group (D2 and D3).

Figure 4-6: Standard deviation feature versus k for extended groups C' and D' and its binary classification performance in terms of area under the receiver operating characteristics (ROC) curve (AUC)

For all the three groups, while the cut-off value-based classification model resulted in an accuracy of around 70%, the accuracy of the SVM-RBF classification model was 92% or higher (Table 4-5 and Table 4-6). Given that the SVM-RBF model has utilized all the significant features (Table 4-2 and Table 4-3) to perform the classification by mapping the features in a high-dimensional feature space, on the contrary to the cut-off value model, SVM-RBF model resulted in high classification performance. Though justified against the literature [220,224–226], the results of this study are limited by the number of samples. In the past studies on medical thermography-based disease diagnostic applications, utilizing cross-validation technique, high dimensional features extracted from small sample sizes of 50 (25 in each class) [210,214] and 90 (45 in each class) [195] were used to perform the SVM-based binary classification. Given the use of SVM model

for thermography-based disease diagnostic applications in the past studies, to prove the potential of improving the classification performance from the cut-off value-based model for carotid stenosis detection [155], this study is limited to the use of SVM-based machine learning model only. With the demonstrated high performance with the SVM model, this study paves the path for the future studies on the evaluation of the best machine learning-based classification model, along with the application of deep neural network-based classification [227–229].

Figure 4-7: ROC curve to evaluate optimum classification cut-off value point for groups (C' and D'), (C and D1), and (D2 and D3) for features skewness, contrast, and skewness, respectively, from full and cold thermal feature images

4.6 Summary

In this study, infrared (IR) thermography images were used to evaluate the presence of stenosis in the carotid artery. The intended sample classification study was performed on three classification groups, namely, (C': 0% -29% stenosis and D': $\geq 30\%$ stenosis), (C: 0% stenosis and D1: 10%-29%), and (D2: 30%-49% and D3: $\geq 50\%$ stenosis). From the background-subtracted original thermal image (referred to as *full thermal image*), using a novel parametric thermal feature extraction method, *cold thermal feature images* were extracted. Using the significant statistical features from both the *full* and *cold thermal feature images*, the binary classification problem was solved using the cut-off value and SVM-RBF classification models. With the demonstrated high sensitivity, specificity, and accuracy of the SVM-RBF classification model, this preliminary study suggests the potential of an IR thermography-based fast, non-contact, and non-invasive screening test for carotid artery stenosis disease.

CHAPTER 5 ACTIVE DYNAMIC THERMOGRAPHY: QUANTITATIVE PARAMETER FOR ANALYSIS

5.1 Abstract

In this study, a novel single thermal image reconstruction method, from the transient image series in active dynamic thermography (ADT), is proposed. ADT was performed with an external stimulation in the form of cooling, over the forearm skin tissue of a human subject, and the resulting transient images (due to thermal recovery) were captured using a non-contact Infrared (IR) thermal camera. A unique tissue activity ratio (*TAR*), the ratio of thermal recovery rate to excitation rate, was calculated at each pixel, and hence, a single thermal image (called *TAR* image) was reconstructed. Existing parametrized image reconstruction methods, viz. Tau time (τ), dT_{norm} , and t_{90-10n} , were used for a comparative study. To perform a quantitative comparison, among the image reconstruction methods, the image contrast value was evaluated. While sequentially subtracted image provided a high contrast image in non-parametrized image reconstruction methods, for parametrized image reconstruction methods, it was *TAR*. Among all the methods considered, *TAR* provided the best contrast image followed by τ image method.

5.2 Introduction

Active dynamic thermography (ADT), wherein transient sequence of images result upon application of an external thermal or pressure excitation, is one of the most useful quantitative thermography methods in medical diagnosis [230]. Since a diseased tissue

responds differently to the external excitation as compared to a normal tissue, ADT proves to be an efficient tool in diagnosing various diseases, such as breast tumor detection, Raynaud's disease, burn wounds, etc. [231–233]. While external excitation improves the image contrast that eases the target feature extraction, it also leads to the generation of a large amount of sequence image data to be analyzed. Moreover, the contrast of the image sequence decreases as the recovery phase progresses upon removal of the excitation source [234]. Therefore, reconstruction of a single synthetic image, which is both qualitatively and quantitatively advanced (feature contrast and diagnosis parameter) as compared to the whole image sequence, is needed. To do so, application of various image reconstruction algorithms, to ADT problems, is summarized hereafter.

It is well known that the original sequence images have a lower signal to noise ratio (SNR). SNR can be improved by deriving phase and amplitude images using Fourier transformation (FT) [235,236]. In such an attempt, Boue et al. [237] evaluated the diameter of the superficial vein using thermographic amplitude images, of which the contrast is found to be comparatively better than the transient sequence images. Using fast Fourier transform (FFT), Liu et al. [238] showed that the large sub-cutaneous veins can be distinguished from microvasculature and skin tissue without the blood vessel, respectively, in the frequency range of 0.005 to 0.06 Hz. Given that an adequate contrast enhancement cannot be achieved in all the patients, application of thermographic signal reconstruction (TSR) method, which is conventionally used in the field of material characterization and defect detection by ADT [239–242], is shown in the work of Liu et al. [243]. The authors have applied a 5-minute cuff-based occlusion, followed by

transient thermal image acquisition during the reactive hyperaemia. At each pixel, the coefficient values are derived from the first derivative of the logarithmic equation fit to the temperature response over time, and a synthetic image is reconstructed. The authors have shown a substantial improvement in SNR that helps in clear visualization of the angioarchitecture in the synthetic image.

Since ADT involves a transient process of recovery to normal state post external excitation, to reconstruct the synthetic image, pixel specific quantitative parameters pertaining to thermal recovery can also be extracted. One such parameter is the thermal time constant (called Tau time, ' τ ') that quantifies the thermal activity of the tissue. Given the apparent difference in heat transfer rate between the skin tissue with and without vein, it is imperative that the τ time evaluation would differentiate the two; hence, brings out the contrast in the resultant τ image. This image can be used to diagnose skin tissue with pathological conditions as described in the work of Foerster et al. [244], wherein the authors have developed a τ image based tool to diagnose Raynaud's phenomenon (RP). Further, to estimate the τ value more accurately, a non-linear regression-based exponential curve fitting to the experimental data can be done. This method is applied to monitor the cardiosurgery [245–247], evaluation of burn wound healing [248–250], vascular disease diagnosis [251], etc. Recently, Moderhak et al. [252] described a dynamic thermography method, wherein 60 seconds of thermal excitation and 180 seconds of recovery time is used, to quantitatively determine the success of breast reconstruction procedure by skin flap perfusion assessment. The authors have used a Simplified Magnitude-Temporal Parametrization method (SMTP) to define two

unique parameters: dT_{norm} and t_{90-10n} [253], at each pixel, to reconstruct a single image from the ADT sequence, respectively. With the help of the improved contrast images, reconstructed using these two parameters, the authors have shown that the two groups of patients, who will either develop post-surgery necrosis complications or not, can be diagnosed at an early stage.

From the literature, it is evident that ADT is both qualitatively and quantitatively useful in medical diagnosis, however, the decision to evaluate the best contrast image, within the sequence or sequentially subtracted images, is operator dependent. To analyze the ADT data both qualitatively and quantitatively, single image reconstruction methods are used. Given the development of this single image reconstruction method is still at a premature stage, in this study, a novel tissue activity ratio (TAR) method is proposed to reconstruct a single thermal image that would qualitatively and quantitatively represent the transient thermal image sequence in ADT. With the application of cooling excitation, ADT sequence was captured, on the forearm of a human subject, to visualize the superficial vein with high contrast. Pre-existing single image reconstruction methods, viz., τ , dT_{norm} , and t_{90-10n} , were used to perform a comparative study with the proposed TAR method. To quantitatively compare the images obtained from each of the image reconstruction methods studied, a contrast factor (W) is used.

5.3 Materials and Methods

5.3.1 Experimental Setup

In-vivo human subject tests were carried out on 3 male subjects (age: 24 ± 1 years), under an approved ethical study, at Nanyang Technological University, Singapore (IRB: SHS-NTU/014/2016). In this experiment, a continuous cooling was applied on the left forearm of each subject for 30 seconds. The cooling application was done with the help of a cooling pad [157] recirculated with ice water at a temperature of 5 ± 0.5 °C (**Figure 5-1**). After the removal of cooling, 90 seconds of sequential thermal images were captured by an Infrared (IR) thermal camera (VarioCam by InfraTec) at a rate of 2 frames per second (**Figure 5-2**). To statistically analyze the results, in each subject, 3 repetitions were performed. Experiments were performed after allowing the subject to sit for 15 minutes in a controlled temperature environment of 22 ± 0.5 °C. In each subject, the average value of temperature with standard deviation ($\pm$ SD), over the skin tissue (within the cooling stimulation zone) at 5s after the start of the experiment, after the removal of cooling (40s), and end of rewarming (130s), is summarized in **Table 5-1**.

Table 5-1: External cooling stimulation details

Subject Studied	Average temperature within the cooling stimulation zone (°C) $\pm$ SD		
	Before cooling (t=5s)	After cooling (t=40s)	End of rewarming (t=130s)
Subject-1	33.53 ± 0.12	8.53 ± 3.5	27.27 ± 1.87
Subject-2	33.52 ± 0.19	9.53 ± 1.98	28.55 ± 1.68
Subject-3	32.82 ± 0.33	9.42 ± 1.03	25.09 ± 2.90

Figure 5-1: Experimental setup: 1) Infrared thermal camera 2) Tripod to fix the camera 3) Human subject forearm 4) Cooling pad to apply the external stimulation

5.3.2 Parametric image reconstruction methods

a) Tau (τ) Image:

The natural rewarming of the skin tissue, to the cooling excitation, can be analyzed using lump capacity analysis model, wherein a uniform rewarming is assumed under the influence of ambient convection thermal boundary condition [254]. This process can be characterized with the help of thermal time constant (called Tau time, ' τ ') which is equal to the time required for a system response to decay to zero [255]. Further, as shown in the work of Dupuis [233], Foerster et al. [244], Jankovic et al. [251], Meffert et al. [256], Merla et al. [257], etc., the rewarming process closely resembles to an exponential response curve described by the transient first order response as given by Equation 5-1.

$$T(t) = T_o + \Delta T(1 - e^{-t/\tau}) \quad (5-1)$$

where, $T(t)$ is the temperature ($^{\circ}\text{C}$) at any time instant, t (s), T_o is the initial temperature ($^{\circ}\text{C}$), ΔT is the total temperature change ($^{\circ}\text{C}$), and τ is the Tau time (s). When the rewarming process reaches the τ time, the temperature of the system attains $(1 - 1/e)$ times of total temperature difference between the initial and post excitation temperature (dT_{excite} in $^{\circ}\text{C}$), which is equal to 63% of dT_{excite} (**Figure 5-2**). At each pixel, Tau time (τ) was calculated (**Figure 5-3**), followed by replacing the original sequence image pixel value with the evaluated τ value, and thereby, a τ image was reconstructed. This τ image is an equivalent representation of the whole thermal image sequence.

Figure 5-2: Cooling-rewarming curve in active dynamic thermography depicting curve variables ($T_{\text{Core}}=37^{\circ}\text{C}$)

b) dT_{norm} and t_{90-10n} Image:

As defined in the work of Moderhak et al. [252], dT_{norm} and t_{90-10n} is calculated as follows:

$$dT_{\text{norm}} = \frac{dT_{\text{recovery}}}{dT_{\text{excite}}} \quad (5-2)$$

$$t_{90-10n} = \frac{t_{90-10}}{t_{recovery}} \quad (5-3)$$

where, $dT_{recovery}$ is the temperature difference (°C) between the start and end of the allowed experimental thermal recovery, dT_{excite} is the temperature difference (°C) between the start and end of the thermal excitation, t_{90-10} is the difference in time (s) to reach 90% and 10% of the $dT_{recovery}$, respectively, ($t_{90-10} = t_{90\% \text{ of recovery}} - t_{10\% \text{ of recovery}}$), and $t_{recovery}$ is the total experimental time (s) of the thermal recovery (**Figure 5-2**).

c) *Tissue Activity Ratio (TAR) Image*

In this method, a novel approach to reconstruct a unique image, based on the individual pixel's thermal activity, is used [158]. On removal of the external cooling, it is evident that pixel just above the blood vessel will show a higher thermal activity as compared to the other pixels; hence forms the basis for a qualitatively and quantitatively advanced image. Using Equation 5-4, the thermal activity during the rewarming phase, at each pixel, can be quantified with the help of a ratio called as Tissue Activity Ratio (*TAR*). *TAR* accounts for both the rewarming as well as the excitation phase. First, a reference recovery temperature (T_r in °C), for all the pixels within the excitation zone, is evaluated. As shown in **Figure 5-2**, T_r is defined as the temperature to reach 50% of the total temperature difference from the instant of removal of cooling to the end of rewarming/recovery phase ($dT_{recovery}$). The selected T_r value ensures that all the pixels will reach at least this temperature within the acquired recovery duration (90s in the present study). Using this T_r value, at each pixel, the time of rewarming (t_r in s), to rewarm from the temperature at the end of cooling (T_c in °C) to T_r , is evaluated and thus,

the rate of rewarming (RR in $^{\circ}\text{C/s}$) is calculated (Equation 5-5). Further, the rate of cooling (RC in $^{\circ}\text{C/s}$), at each pixel, is calculated (Equation 5-6) by subtracting the temperature at the end of the cooling (T_c in $^{\circ}\text{C}$) from the initial temperature (T_i in $^{\circ}\text{C}$) before application of cooling, and dividing the resultant temperature difference by the total duration of application of cooling (t_c in s). Unlike the value of t_r in the rewarming phase, the time for cooling (t_c) will be same for all the pixels. The mathematical formulation to calculate TAR , at each pixel, within the cooling zone is given below:

$$TAR = \frac{RR}{RC} \quad (5-4)$$

$$\text{where, } RR = \frac{T_r - T_c}{t_r} \quad (5-5)$$

$$RC = \frac{T_i - T_c}{t_c} \quad (5-6)$$

Computing TAR value at each pixel, a unique TAR image is reconstructed (**Figure 5-3**).

Figure 5-3: Parametric image reconstruction of transient thermal image sequence from standard forearm ADT experiment

5.3.3 Image Contrast Analysis

To compare and evaluate the quality of an image, a contrast factor (W) is evaluated. The contrast factor defines the relative strength of an image target parameter with respect to the background. In this study, the feature of interest (target) is the superficial vein around the skin tissue (background). A high value of W refers to a better visibility of the superficial vein in the image. Using the Weber's formula [258], W is defined as follows:

$$W = \left| \frac{I - I_b}{I_b} \right| \quad (5-7)$$

where, I and I_b are the image parameter over the skin tissue with (target) and without superficial vein (background), respectively. In this study, average values of I and I_b are taken from the reference sampling locations (black and red-dashed rectangular boxes) as shown in **Figure 5-3**. While I is taken over the superficial vein (target), I_b is taken from the neighboring skin tissue (background). These reference sampling locations, in each subject, are consistently used for all the images extracted from the various image reconstruction methods studied.

In Equation 5-7, the value of I_b is essentially less than the value of I [258], therefore, the value of W provides a measure of difference in the image parameter, between the two regions (target and background), with respect to the minimum of the image parameter over the two regions. By default, it is considered that the background will have the minimum image parameter value as compared to the target ($I > I_b$), however, this is not true in all the cases. For comparison purpose, if all the images, resulting from different image reconstruction methods, provide a trend of either $I > I_b$ or $I < I_b$ consistently, the

resultant contrast comparison is balanced. However, if any of the images deviate from the adopted consistent trend, the resultant contrast comparison is imbalanced. In this study as well, $I > I_b$ is adopted as a consistent trend. To perform a balanced comparison, irrespective of $I > I_b$ or $I < I_b$ trend in the images, the Weber's formula (Equation 5-7) should be modified (W') such that the minimum of I or I_b should be used in the denominator (as given by Equation 5-8).

$$W' = \left| \frac{I - I_b}{\min(I, I_b)} \right| \quad (5-8)$$

On the other hand, to maintain the standardized usage of the Weber's contrast formula (Equation 5-7) and present a balanced comparison among the adopted ($I > I_b$) and deviating ($I < I_b$) trend images, the deviating trend images can be transformed using the following inversion formulation:

$$\phi'_{ij} = \left(\frac{1}{\phi_{ij}} \right) * \phi_{ij_{max}} \quad (5-9)$$

where, i and j are the number of row and column, respectively, to locate the target pixel, ϕ'_{ij} and ϕ_{ij} are the transformed and original image parameter, respectively, and $\phi_{ij_{max}}$ is the maximum image parameter value of all the pixels in the original image. Using Equation 5-9, the value of I and I_b (where, $I < I_b$) can be transformed as follows:

$$I' = \left(\frac{1}{I} \right) * \phi_{ij_{max}} \quad (5-10)$$

$$I'_b = \left(\frac{1}{I_b} \right) * \phi_{ij_{max}} \quad (5-11)$$

The proposed transformation results into an equivalent image as the original image but with an inverted scale (inverse proportionality), which provides the desired $I' > I'_b$ trend.

Given the multiplication with $\phi_{ij_{max}}$ in Equations 5-10 and 5-11, the resultant I' and I'_b are dimensionless in nature. Using the standard Weber's contrast formula (Equation 5-7), the contrast for the transformed image (with I' and I'_b) can be calculated as follows:

$$W = \left| \frac{I - I'_b}{I'_b} \right|, \text{ where } I' > I'_b \quad (5-12)$$

Replacing the value of I' and I'_b from Equations 5-10 and 5-11, Equation 5-12 will result into Equation 5-13.

$$W = \left| \frac{I_b - I}{I} \right|, \text{ where } I < I_b \quad (5-13)$$

Since Equation 5-13 follows the generic nature defined by the modified Weber's contrast formula in Equation 5-8 (using minimum of I or I_b in the denominator for a balanced comparison among the adopted ($I > I_b$) and deviating ($I < I_b$) trend images), the contrast calculated from the standard Weber's formula (Equation 5-7), using a transformed value of I and I_b (where, $I < I_b$), will provide a balanced comparison with the images following the adopted $I > I_b$ trend.

5.4 Results

5.4.1 Transient image sequence

After the removal of the external stimulation (cooling), before reaching the original thermal equilibrium with the ambient surroundings, the skin tissue undergoes a transient recovery phase. The thermal activity of the skin tissue, due to blood perfusion and blood flow in the superficial vein, determines the rate of the recovery process. It is evident that the skin tissue over the superficial vein will recover faster as compared to the surrounding

skin tissue with no such vein. This brings out the contrast in the visibility of the superficial vein. However, the dynamic sequence images do not hold a consistent clear visibility of the blood vessel as the recovery progresses further. Given the rate of recovery is directly proportional to the temperature difference, due to a continuous decrease in the temperature difference, the rate of recovery slows down as the recovery progresses. Therefore, the visibility of the superficial vein with reference to the nearby skin tissue region first increases and then decreases. To quantify this characteristic, using Equation 5-7, the contrast of the superficial vein, in all the sequence images, was calculated. Plotting the superficial vein contrast, in all subjects, against time, **Figure 5-4** corroborates with the fact that the visibility of the superficial vein changes dynamically throughout the recovery phase.

Figure 5-4: Contrast versus time after removal of cooling for the original sequence of thermal images

5.4.2 Best contrast image from the sequence

Marking the peak of the contrast curve in **Figure 5-4**, the maximum contrast point ($W_{max.}$) is determined, which is in the range of 0.2 to 0.6 in the three subjects studied.

Using the W_{max} point, a single high contrast image, from the transient sequence of images, can be selected. In each subject, **Figure 5-5** shows the image corresponding to W_{max} point. A contrast value of less than 1 suggests a poor visibility of the superficial vein. It is to be noted that the occurrence of W_{max} point differs in all the subjects. This is because of the different morphological and hemodynamic characteristics, like thickness of the skin tissue, diameter of the superficial vein and its blood flow velocity, skin tissue blood perfusion rate, etc., which bring varied intensity of thermal activity in each subject and hence, either speed-up or delay the occurrence of W_{max} point. In Subject-2, the W_{max} point occurs much later ($W_{max} = 0.21$ at 40 s) as compared to Subject-1 ($W_{max} = 0.56$ at 22 s) and Subject-3 ($W_{max} = 0.61$ at 26.5 s).

Figure 5-5: Original sequence and sequentially subtracted thermal images at the maximum contract value (W_{max})

5.4.3 Sequential image subtraction

To further enhance the contrast of the sequence images, a primitive noise subtraction technique can be used [157], wherein the very first image after the removal of the cooling (external thermal excitation) is subtracted from the subsequent images in the recovery

phase. Analogical to DSA (**0, Section 2.3.1**), given the image to be subtracted is always the same, it is imperative that the contrast of all the subsequent images will increase by a same fraction. Hence, in each subject, to evaluate the highest enhancement in the contrast, the subtracted image corresponding to the W_{max} point in the original sequence images is selected. From **Figure 5-5**, it can be observed that the qualitative visibility of the superficial vein in the subtracted images, in all subjects, is better than the corresponding original sequence images. Quantitatively, the contrast of the subtracted images, in all the three subjects, is found to be improved by 52%, 76%, and 28%, respectively, as compared to the corresponding sequence images.

5.4.4 Parametric image reconstruction

The quantitative parameters used to reconstruct the single thermal image are τ , dT_{norm} , t_{90-10n} , and TAR , of which the resultant images, in each subject, are shown in **Figure 5-6**. As defined in **Section 5.3.2**, of the four quantitative parameters, τ has a unit of seconds (s), while the other three are dimensionless. Given the recovery rate is higher over the superficial vein, the τ value is lower and vice-versa for the tissue with no superficial vein. Therefore, to calculate the contrast value (W), a transformed τ image is used as explained in **Section 5.3.3**. A similar image transformation is performed for t_{90-10n} images. Except for Subject-2, the τ image in other two subjects provide a contrast value of more than 1 (**Figure 5-7**), which can be corroborated from the visual inspection of the images (**Figure 5-6**). For each subject, comparing among the image reconstruction methods considered, the value of contrast (W) is found to be highest for TAR method along with a high-quality image. While the TAR method provides the highest contrast

value, dT_{norm} and t_{90-10n} methods provide the least. In all the cases, TAR is found to provide a higher contrast as compared to τ image method; an average contrast difference ($\pm$ Standard Error) of 0.54 ± 0.19 and 0.22 ± 0.11 , and 0.28 ± 0.17 , in Subject-1, 2, and 3, respectively.

Figure 5-6: Parametric images from various image reconstruction methods

5.5 Discussion

Reconstruction of a single image, from ADT sequence, not only provides a qualitative representation, but also includes quantitative information. This quantitative information, at each pixel, provides the heat flow characteristics. To do so, quantitative parameters, during the rewarming phase, can be defined. The basis for any of these parameters is the quantification of thermal activity of the tissue, which can be defined as the measure of degree of responsiveness to the external stimulation. This responsiveness, in terms of heat transfer, is the result of the tissue blood perfusion. In this study, other than the skin tissue perfusion, presence of a superficial vein, which acts as an additional heat source, leads to a higher responsiveness to the external stimulation as compared to the tissue with no such superficial vein. Evaluated using a quantitative parameter, this higher responsiveness brings contrast to the visibility of target superficial vein in the image.

Figure 5-7: Parametric image contrast (W with SD error bars) from various image reconstruction methods

In a numerical study by Moderhak [253], on comparison of parametrization methods applied to ADT on a skin flap model with blood vessel perforator, the contrast value, for

the first order τ , dT_{norm} , and t_{90-10n} images, was found to be 0.05, 0.11 and 0.06, respectively. For the τ and t_{90-10n} images, it should be noted that the contrast is calculated without any image transformation. Using the proposed transformation in this study (Equation 5-9), the new value of contrast, for τ and t_{90-10n} images in [253], is calculated to be 0.06 and 0.08, respectively. The contrast value for dT_{norm} and t_{90-10n} images in both the studies is found to be less than 1. Given the ADT procedure and the skin tissue model used are different, comparison among the same kind of parametric images, between the two studies, is not possible. For the case of dT_{norm} and t_{90-10n} , the superficial vein part of the reconstructed images, in all subjects, is found distorted and blurred (**Figure 5-6**) which is reflected in the lower value of contrast as well (**Figure 5-7**). Being one of the parametric methods that depends on the tissue recovery rate, the lower value of contrast in case of dT_{norm} and t_{90-10n} images is possibly because of the inclusion of data until the end of recovery phase as per the definition of these parameters (**Equations 5-2 and 5-3**).

It is imperative that as the recovery process approaches towards the end, the temperature difference, between the current skin tissue recovery temperature and the initial temperature (T_i), decreases, which leads to a reduction in the rate of recovery (**Figure 5-2**). Hence, the contrast between the tissue with and without vein also decreases, which affects the overall quality of the image; resulting into blurred and distorted images (dT_{norm} and t_{90-10n} images in **Figure 5-6**). Therefore, to satisfy both the conditions, viz. use of rate of recovery as a parameter while considering the data from the initial stages of the recovery process, the TAR parameter is used. This is done by defining a reference

recovery temperature value (T_r), within the total recovery phase duration, for all the pixels in the cooling zone. Given the fact that the tissue with superficial vein will rewarm to T_r temperature with a lower value of t_r , while a higher value of t_r for the same T_r over the tissue with no superficial vein, the resulting TAR value will have a higher contrast between the two regions. Visual inspection of the TAR images (**Figure 5-6**), in all the subjects, reveals a high qualitative visibility of the superficial vein. Applied to ADT procedure performed post (after 24 hours) breast reconstruction surgery to predict the risk of flap necrosis, the novel quantitative TAR parameter was found have significantly distinguished the normal and diseased study participants ($p<0.05$); resulted in a sensitivity, specificity, and accuracy of 89%, 83%, and 84%, respectively [259].

5.6 Summary

Active dynamic thermography (ADT) was performed on the forearm of three human subjects, using cold thermal stimulation, to produce high contrast image of the superficial vein with the application of single image reconstruction methods. A ratio, called tissue activity ratio (TAR), based on the tissue rewarming and excitation rate, was defined. Using the defined ratio value, a single image was reconstructed, which is the best contrast image as compared to the original image sequence. To validate the pre-eminence of the proposed method, a qualitative and quantitative comparative study was performed with the Tau (τ) time, dT_{norm} , and t_{90-10n} image methods found in the literature. With visual inspection, it can be concluded that the visibility of feature of interest (blood vessel) is much clearer in the TAR image. Furthermore, the parameterized TAR image reconstruction method provides the best contrast image, followed by Tau time (τ) image

method. Using this quantitative parameter (TAR), clinical studies can be performed to test the efficacy of TAR image in a medical ADT procedure.

CHAPTER 6 PREDICTION OF CAROTID ARTERY STENOSIS USING ACTIVE DYNAMIC THERMOGRAPHY

6.1 Abstract

Unlike passive infrared (IR) thermal imaging/thermography, where no external stimulation is applied, active dynamic thermography (ADT) results in a high contrast thermal image. In ADT, transient thermal images of the skin surface are captured using an IR thermal camera while the skin surface is stimulated externally, followed by a recovery phase. Upon the application of external stimulation, the presence of stenosis in the carotid artery is expected to differ the recovery rate of the external neck skin surface from the case with no stenosis. In this prospective study, using an external cooling stimulation, the ADT procedure was performed on a total of 54 (N) samples (C: N=19, 0% stenosis; D1: N=17, 10%-29% stenosis; D2: N=18, $\geq 30\%$ stenosis using Duplex Ultrasound). Analyzing the ADT sequence with a parameter called tissue activity ratio (TAR), the samples were classified using a cut-off value: C versus (D1+D2) and (C+D1) versus D2. As the degree of stenosis increases, the value of the TAR parameter depreciates with a significant difference among the sample groups (C: 0.97 ± 0.05 , D1: 0.80 ± 0.04 , D2: 0.75 ± 0.02 ; $p < 0.05$). Under the two classification scenarios, classification accuracies of 90% and 85%, respectively, were achieved. This study suggests the potential of screening CAS with the proposed ADT procedure.

6.2 Introduction

Infrared (IR) thermal imaging or thermography, where either with (active) or without (passive) the use of an external stimulation (heat, cold, pressure, etc.), temperature maps or thermal images are captured in a non-contact and non-invasive manner, could be a potential low-cost, automated, and easy-to-use screening modality for carotid artery stenosis [14,157]. With the occurrence of stenosis in the carotid artery, there is a reduction in the blood flow in the region (neck and face); this is reflected in the low temperature on the external skin surface [178]. In **0**, the performance of a passive thermography-based CAS disease screening modality has been demonstrated [260]. With the use of external stimulation, called active dynamic thermography (ADT), a substantially higher signal to noise ratio of the thermal images captured during the recovery process is achieved [234]. This could work in favor of developing a more reliable CAS screening modality as a stenosed artery shall result in a lower rate of thermal recovery. However, the ADT procedure produces large data from a series of transient thermal images, which makes the analysis complex and computationally expensive. Therefore, a quantitative parameter that integrates the ADT sequence into a single value, hence, forming a single synthetic image that qualitatively and quantitatively represents the whole ADT sequence, is used [175].

In the past, ADT was applied to medical applications like diagnosing the occupational disease called vibration-induced white finger (VWF) [233], Raynaud's phenomenon (RP) [244], to monitor the open-heart surgical interventions [245], to determine the need of

surgical intervention in case of burn wounds [248], predicting necrosis in breast reconstruction procedure [252], etc. In these studies, various quantitative parameters like tau time (τ), dT_{norm} , t_{90-10n} , etc., were used. As described in **CHAPTER 5** and reported in author's previous studies on ADT, a novel parametric ADT image sequence registration and quantification method (*TAR*: tissue activity ratio) was devised [158,175]. Tested for potential applications like high contrast superficial vein imaging and reconstructed breast necrosis prediction, this method is claimed to be the most superior in the active medical thermography field [259]. The goal of this study is to test the performance of the ADT procedure, using an external cooling stimulation, in predicting the presence of stenosis in the carotid artery. To do so, a prospective ADT study was carried out on both control and diseased samples. Using the quantitative *TAR* parameter, the ADT sequence was analyzed by a single synthetic image. Applying a cut-off value-based classification model, the performance of ADT for CAS screening is reported.

6.3 Materials and Methods

6.3.1 Study participants

In this prospective study, 27 participants (24 male and 3 female) were recruited at the Vascular Lab of National Heart Center, Singapore (NHCS) from February 2019 through September 2019. The study was approved by the Centralized Institutional Review Board (CIRB Ref No.: 2017/2119), SingHealth, Singapore. study participants with previously known significant stenosis in the subclavian artery or multiple stenoses or occlusion in cerebral circulation were excluded from the study. Performed by the trained sonographer at NHCS, the study participants undergo the standard carotid duplex ultrasound (DUS)

examination upon signing the informed consent form. Using a combined morphological (diameter) and hemodynamic (peak systolic and end-diastolic velocities) criterion [80], the stenosis grading, in the Common Carotid Artery (CCA), bifurcation bulb, Internal Carotid Artery (ICA), and External Carotid Artery (ECA), was done as per the standard grading protocol followed at the Vascular Lab, NHCS.

6.3.2 Active dynamic thermography (ADT) data collection

As shown in **Figure 6-1**, the ADT experiment protocol adopted in this study involves the external cooling stimulation of the target skin surface (either side of the neck and face region) for 60s, and then, the skin was left to rewarm naturally. Cooling stimulation was done using a cold air blower device (Gymna CryoFlow ICE-CT endorsed by Health Science Authority, Singapore for the study purpose) as shown in **Figure 6-1a**. In this device, the cold air is delivered by means of a fan incorporated with a nozzle outlet which was positioned at least 30 cm away from the target skin surface. In this study, the cold air flow was set to 1000 lit/min. This device was earlier used in other ADT related research studies on monitoring cardiosurgery interventions, reported in the work of Kaczmarek et al. [245] and Nowakowski et al. [246]. Thermal images were captured for the whole duration (250s) of the experiment using a FLIR E8 IR thermal camera. At a frame rate (number of frames per second) of 5.5, the thermal camera produces 2-dimensional (2-D) thermal images (rows x columns: 240 x 320 pixels) with a temperature resolution of less than 0.06 °C. Prior to the cooling stimulation, thermal images were captured for 30s. Post the cooling stimulation, thermal images were captured for a duration of 160s during the rewarming process. The experiment was performed in a temperature-controlled room maintained at 23 ± 0.5 °C temperature and 50% relative humidity [195], where the study

participants were asked to sit for 15 minutes prior to the examination as a part of standard medical thermography practice. As concluded in the past studies on neck temperature-based pulse measurement [180,181], the pulsating blood flow (systolic and diastolic cycle) in the carotid artery has a local and infinitesimally small effect on the external skin temperature. Therefore, the overall cooling or rewarming process is assumed to have no relation with the pulse rate of an individual subject under study.

Figure 6-1: (a) Experimental setup (b) Schematic of active dynamic thermography (ADT) experiment temperature curve

6.3.3 Pre-processing of the ADT data

In medical thermography applications, given the measurement accuracy is dependent on the natural motions introduced by unrestrained subjects, the sequence image data preprocessing for motion artifact correction is a critical step [261]. If the ROI is a superficial blood vessel, such as in the case of cardiac pulse rate measurement, the simplest and most effective method is to segment the blood vessel in all the sequence images to perform the temporal measurement analysis [262]. If there is no obvious blood vessel present in the ROI, use of an external marker such as an aluminum foil, that shows a consistently lower temperature as compared to the skin, helps tracking the body motion [263]. However, the use of an external marker may hinder the ROI measurement or question the non-contact nature of the thermography examination itself, which may not be appreciated by the patients. Another method is to use conditional density propagation tracker [264], which makes use of tracking the high-temperature body part boundaries on the lower temperature background [181]. These methods are, however, suitable for passive thermal image sequence, wherein the temporal change in the temperature of the ROI is quite small along with a large difference in temperature with respect to the background. In ADT sequence, with the application of external stimulation (heating or cooling), the magnitude of change in the temperature of ROI is in the range of 5-10 °C [175]. With such a magnitude of change in temperature, use of above-mentioned motion artifact correction algorithms is not applicable, which is the case in this study.

Given that the ADT procedure was prolonged (a total of 250s), body movement was inevitable, therefore, a direct phase substitution (DPS)-based image-matching motion

artifact correction algorithm was used [265]. In this method, applying Fast Fourier Transformation (FFT), first, the amplitude and phase components of the reference and distorted images were extracted. While the amplitude component contains image intensity information (temperature in thermal images) corresponding to the image's frequency sub-band, the phase component contains the spatial distribution information of those frequency sub-bands. The geometrical relation, between two consecutive thermal images in a sequence, is related by the translational property of FFT [266].

Figure 6-2: Adaptive direct phase substitution (DPS) image matching for motion artifact correction

By combining the amplitude component of the distorted image with the phase component of the reference image (phase substitution), a complex spectrum is created. Calculating the inverse FFT of this complex spectrum results in a geometrically matched image. In addition to the requirements like small translational movement, the region of interest (ROI) to be in the center of the image, and no rotation or scaling of the ROI, no large step changes in the intensity of the image is inevitable in the ADT image sequence. If the very first image is taken as the reference image, due to a continuous change in temperature

throughout the excitation and recovery phases in ADT, the conventional DPS image matching algorithms fails. To solve this problem, in this study, similar to adaptive block matching described in **0 Section 2.5**, an adaptive DPS image matching algorithm was used, whereby, instead of using a fixed reference image, the reference image is replaced consecutively as the algorithm processes the successive images (**Figure 6-2**) [259]. Using this technique, the ADT thermal image sequence was corrected for any linear translation movement in x (horizontal) or y (vertical) direction of the thermal image.

6.3.4 Post-processing of the ADT data

Upon correcting the images for any possible motion artifacts, the ADT sequence was quantified by reconstructing a single synthetic thermal image called tissue activity ratio (TAR) image as reported in **CHAPTER 5**. Calculated at each pixel, TAR_{ij} is a dimensionless ratio of the rate of rewarming (RR_{ij} in $^{\circ}\text{C/s}$: during rewarming phase) to the rate of cooling (RC_{ij} in $^{\circ}\text{C/s}$: during external cooling stimulation phase) as given by Equations 6-1 to 6-3).

$$TAR_{ij} = \frac{RR_{ij}}{RC_{ij}} \quad (6-1)$$

$$\text{where, } RR_{ij} = \frac{T_{ij}^r - T_{ij}^c}{t_{ij}^r} \quad (6-2)$$

$$RC_{ij} = \frac{T_{ij}^i - T_{ij}^c}{t_{ij}^c} \quad (6-3)$$

Here, i and j are the numbers of rows and columns, respectively, to locate the target pixel in the image. T_{ij}^i , T_{ij}^c , and T_{ij}^r are the initial (before application of cooling), end of cooling, and reference temperature ($^{\circ}\text{C}$), respectively, at each pixel. t_{ij}^c is the total time (s)

of cooling at each pixel. t_{ij}^r is the total time of rewarming to temperature ' T_{ij}^r ' after the removal of cooling at each pixel. As shown in **Figure 6-1a**, the value of ' T_{ij}^r ' is defined as the 50% of the total temperature difference from the instant of removal of cooling to the end of rewarming/recovery phase ($dT_{recovery}$) [259].

To segment out the region of interest (ROI) from the reconstructed TAR image, a mask image was developed using the image before and after application of the external cooling stimulation (**Figure 6-3**). It is to be noted that the TAR value calculated over the region where only effective cooling was performed (ROI) is of interest for further analysis. To do so, the image taken at the end of the cooling stimulation was subtracted from the image taken before the cooling. In doing so, the region of effective cooling was extracted. The subtracted image was then processed through Ostu's method to remove the background from the image [196,197]. Manually removing the region with no skin surface (chair headrest, clothing, etc.) from the image, a manually segmented image was extracted (**Figure 6-3**). In this image, all the non-zero-pixel values are replaced with 1, while the rest becomes 0; hence, it forms the mask image for ROI extraction from the TAR image. Thereafter, from the ROI image, an average TAR value is reported.

Figure 6-3: Active dynamic thermography (ADT) sequence data processing flow diagram

6.3.5 Cut-off value-based classification

Using the average *TAR* value from the two groups of samples, several cut-off values were used to perform the classification [132,212]. The optimum cut-off value of classification was evaluated using a receiver operating curve (ROC) analysis [132,212]. For the optimum cut-off classification, the classification performance is reported in terms of sensitivity, specificity, accuracy, area under the ROC curve (AUC), positive predictive value (PPV), and negative predictive value (NPV) [259,260].

6.3.6 Statistical data analysis

Average values are either reported with a 95% confidence interval value (95% CI) or standard deviation (SD) value. To evaluate the statistical significance between the two

groups of samples (normal and diseased), using the significance level of 0.05 (p -value), a student's t -test was performed. Using the Shapiro-Wilk test, data normality was tested [198]. Non-parametric Mann-Whitney U test was used for the set of data found not in compliance with the normality requirement [221]. Image processing, synthetic image reconstruction, data analysis, etc. were performed in Python (open source) and MATLAB toolbox (academic license version: R2019a) by MathWorks.

6.4 Results

In 27 study participants, with a mean ($\pm$ SD) age of 60.23 ± 5.94 years (Male: 60.10 ± 6.32 years and Female: 60.67 ± 6.66 years), the minimum and maximum age of the participants was found to be 49 and 70 years old, respectively. Of the 27 participants, 20 were found to have $\geq 10\%$ stenosis in either one or both of the carotid arteries (**Table 6-1**). While 57% of the participants from the group with no stenosis were found to have a history of smoking, it was found to be in only 35% of the participants from the other group. In both the groups, none of the participants had a history of alcohol. In this study, the carotid artery on each side of the neck was considered as an individual sample, resulting in a total sample size of $N=54$ carotid arteries. Of the CCA, bifurcation bulb, ICA, and ECA, taking the maximum stenosis (evaluated through DUS), the samples ($N=54$) were divided into three subgroups, namely, one Control group with 0% (C, $N=19$) stenosis and two Diseased groups with 10%-29% (D1, $N=17$) and $\geq 30\%$ (D2, $N=18$) stenosis. In the D2 group, only two carotid artery samples were found to have stenosis $\geq 50\%$.

Table 6-1: Active dynamic thermography study cohort characteristics

Parameters	Participants with 0% stenosis on either side	Participants with $\geq 10\%$ stenosis on either or both sides
Number of participants	7	20
Female	1 (14%)	2 (10%)
Age	58.71 ± 6.63	60.79 ± 5.76
Height (m)	1.70 ± 0.07	1.67 ± 0.07
Weight (Kg)	86.14 ± 28.36	68.48 ± 12.05
Body mass index (BMI)	30.06 ± 10.29	24.64 ± 4.52
Pulse rate (beats per second)	74 ± 12	73 ± 10
Systolic blood pressure (mmHg)	126 ± 21	126 ± 22
Diastolic blood pressure (mmHg)	74 ± 8	71 ± 11
Hypertension	5 (71%)	12 (60%)
Coronary artery disease	1 (14%)	7 (35%)
Diabetes mellitus	3 (43%)	8 (40%)
Percutaneous coronary intervention	1 (14%)	4 (20%)
Myocardial infraction	1 (14%)	3 (15%)
Coronary artery bypass graft	0	0
Smoking	4 (57%)	7 (35%)
Alcohol	0	0
Note: Mean data are $\pm$ standard deviation		

Figure 6-4 shows the *TAR* images for a single sample in each group. Qualitatively, the *TAR* image is found to have distinguished the three groups of samples (**Figure 6-4**). Quantitatively, in **Figure 6-4**, the *TAR* image for the control sample (C: 0% stenosis) provides an average *TAR* value ($\pm 95\%$ CI) of 1.09 ± 0.18 , which is slightly higher than the diseased group (D1: 25% stenosis) sample (0.96 ± 0.20) and 1.4 times higher than the

diseased group (D2: 45% stenosis). Within the diseased group D2, as the stenosis changes from 45% to 75% (**Figure 6-4**), the value of average *TAR* changes by only 1.13 times (from 0.78 ± 0.11 to 0.69 ± 0.08). Collectively, the mean ($\pm$ 95% CI) *TAR* values, in group C, D1, and D2, were found to be 0.97 ± 0.05 , 0.80 ± 0.04 , and 0.75 ± 0.02 , respectively; mean *TAR* value depreciates as the stenosis goes higher. As shown in **Figure 6-5**, while the mean *TAR* value for the control group (C) was found to be significantly higher ($p < 0.001$) compared to both the diseased groups (D1 and D2), given a relatively higher overlap in the sample values, a significant but lower p -value was found between the diseased groups D1 and D2 ($p = 0.02$).

In a practical classification scenario, the detection of control carotid artery samples (C) versus diseased carotid artery samples (D1+D2) is of high clinical interest. In this study, the *TAR* value for the control group (C) versus diseased groups (D1+D2) was found to be significantly different (0.97 ± 0.05 versus 0.77 ± 0.03 , $p < 0.001$), hence, using a cut-off value-based classification model, sample classification was performed (**Table 6-2** and **Figure 6-6**). Given that the occurrence of 30% or more stenosis, especially the irregular plaques with lipids content in 40% or more stenosis, is clinically vulnerable to rupture [211], an accurate detection or monitoring of such cases is vital in the treatment profile. Therefore, in this study, while in the first scenario, the control group samples (C) were classified against all the diseased samples (D1+D2), in the second scenario, using the quantitative *TAR* parameter, the samples with $\geq 30\%$ stenosis (D2) were classified against the samples with $< 30\%$ stenosis (C+D1). The value of *TAR* parameter for the group (C+D1) was found to be significantly higher than the group D2 (0.88 ± 0.04 versus

0.75±0.02, $p<0.001$). The results of the classification are summarized in **Table 6-2**, along with the ROC curve in **Figure 6-6**.

Table 6-2: Performance of the cut-off value-based binary classification model for the groups of samples

Groups	Study	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	Accuracy (%)	PPV (%)	NPV (%)
C and (D1+D2)	This study (TAR)	0.83	88	95	0.95	90	97	82
	Head clamp: temperature difference [155]	0.7 °C	83	92	NA	NA	NA	NA
	Contact cooling: temperature difference [155]	0.7 °C	81	84	NA	NA	NA	NA
(C+D1) and D2	This study (TAR)	0.81	100	78	0.86	85	67	100
	Passive thermography: mean temperature [260]	32.69 °C	61	62	0.67	62	54	68
	Passive thermography: Skewness [260]	-0.42	79	62	0.68	69	60	80
C: 0% stenosis; D1: 10% - 29% stenosis; D2: ≥ 30% stenosis; AUC: Area under the receiver operating characteristics (ROC) curve; PPV: Positive predictive value; NPV: Negative predictive value; TAR: Tissue activity ratio

Figure 6-4: Representative original and ROI (region of interest) segmented TAR (tissue activity ratio) images in each group of samples

Figure 6-5: TAR (tissue activity ratio) value in each group of samples with 95% CI (confidence interval) bars

6.5 Discussion

In this study, external cooling stimulation was used to actively excite the skin tissue that resulted in a transient thermal recovery. For all the experiments performed in this study, external cooling stimulation for 60s resulted in a mean temperature difference (before and after cooling) of 10.61 ± 0.56 °C . In clinical settings, Gymna CryoFlow ICE-CT device is used for a duration of 10 min to 15 min with a target skin temperature range of 12 °C to 15 °C to treat achillodynia [267]. For a given ambient room temperature of 22 °C to 24 °C, the body skin temperature varies from 30 °C to 34 °C [159], therefore, the cryotherapy treatment could lead to a temperature difference of up to 22 °C. Since the cooling application duration and the target skin temperature difference were relatively less than the usual cryotherapy treatment procedures, the ADT protocol adopted in this study is deemed to be within the comfort limit of the subject under study.

For the constant ambient thermal conditions, the recovery phase is dependent on the internal tissue heat transfer. Given the presence of stenosis results in an apparent reduction in blood flow in the region (neck and face), the recovery process is expected to differ from the case with no stenosis [260]. By definition, the reconstructed *TAR* image from the ADT sequence quantifies the recovery processes [259]; hence, it forms an indirect measure of presence of stenosis in the carotid artery. A normalized measure of skin rewarming with respect to the skin cooling compensate for the individual geometrical complexities in the ADT process [252,268]. In the work of Capistrant and Gumnit [155], for the two different types of ADT procedure, namely, using a head clamp to occlude the temporal artery and application of a soft rubber bag filled with crushed ice on the forehead, the temperature asymmetries during the recovery phase were recorded and the sample classification was done. While for the head clamp method, sensitivity and specificity of 83% and 92%, respectively, were achieved, it was found to be 81% and 84%, respectively, for the cooling method. In this study, using a non-contact method (cold air blower) of application of external cooling stimulation and a quantitative parameter to analyze the ADT sequence (*TAR* parameter), with an overall classification (C versus (D1+D2)) accuracy of 90%, an improvement of 6% and 3% in the sensitivity and specificity, respectively, was achieved as compared to the head clamp method in the work of Capistrant and Gumnit [155].

Figure 6-6: Receiver operating curve (ROC) for the cut-off value-based sample classification

As reported in 0, using passive IR thermography examination (with no external stimulation), cut-off value-based classification of the carotid artery samples with $\geq 30\%$ stenosis was reported; sensitivity and specificity of only 61% and 62%, respectively, were achieved using the mean temperature feature. While the use of the skewness feature resulted in an improvement of 18% in the sensitivity, there was no improvement reported in the specificity of the classification [260]. Compared to the use of the skewness feature in 0, in this study, with an overall accuracy of 85%, use of a quantitative parameter (*TAR*) with the application of ADT procedure resulted in an improvement of 27% and 26% in sensitivity and specificity, respectively. It is to be noted that given a high rate of false positive prediction rate, the classification in this t study resulted in a poor positive

predictive value of 67%. In a clinical setting, where thermography is proposed to be used as a screening tool, a high false positive rate is more affordable as compared to false negative rate. Furthermore, as in case of the study reported in 0, with the use of a machine learning-based classification model (support vector machine), with an overall accuracy of 93%, sensitivity and specificity of 89% and 97%, respectively, were achieved, it is expected that the application of an appropriate machine learning-based classification model, on significant features from a large set of *TAR* image data, will result in an improved classification performance with a lower false positive rate. Additionally, from this study, no relation between the *TAR* image feature and the exact location of the stenosis in the carotid could be evaluated. Instead, only the presence of maximum stenosis degree in the carotid artery can be predicted. Hence, ADT is proposed to be only used as a screening tool.

6.6 Summary

In the summary, this study demonstrates the potential of an active dynamic thermography (ADT) procedure, comprised of application of external cooling stimulation (60s) of the neck and face region skin surface followed by the rewarming phase, in differentiating the samples with and without stenosis (atherosclerosis) in the carotid artery. The ADT sequence was qualitatively and quantitatively represented using a single synthetic image reconstruction method called tissue activity ratio (*TAR*) image. The *TAR* parameter was used to differentiate the samples into three known (from Carotid Duplex Ultrasound examination) groups, namely, C: 0% stenosis, D1: 10%-29% stenosis, and D2: $\geq 30\%$ stenosis. Furthermore, cut-off value-based sample classification was performed. Though

limited by the number of samples, the study results hold promise for screening CAS related cases using ADT.

CHAPTER 7 CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

The work described in this thesis is an attempt to evaluate the potential of medical thermography in detecting carotid artery stenosis (CAS) disease. Both passive and active methods of thermography examination were tested. First, the clinical diagnostic space that a thermography-based tool could fulfill was identified. Reviewing the CAS diagnostic landscape, it can be concluded that the diagnosis has shifted from simply measuring the percentage blocking of the carotid artery section to detecting additional parameters that characterize the plaque vulnerability. Given the technological advantages, viz., non-contact, non-invasive, fast, and easy-to-use, which medical thermography offer, it can be used as a complementary screening modality. Its clinical evaluation is, however, either limited by the number of studies or the performance of screening. This is corroborated from the fact that the last clinical research study in this field was reported in the late '90s. In these earlier attempts, for passive thermography, a classification sensitivity of only 57% was reported in 1973. In the same study, the classification sensitivity was found to have increased to 83% with the use of an external head clamp pressure application-based active thermography. This clinical research-based thesis work was, therefore, adopted to study the problem using advanced computational, image processing, and classification algorithm tools. Duplex Ultrasound (DUS) examination was used to establish the ground truth labelling of the samples.

To start with, a computational bioheat transfer study, on 20 carotid artery samples, was performed to form a conceptual basis for the intended temperature-feature based screening tool. In this study, patient-specific stenosis geometry and flow conditions were simulated in a carotid artery-jugular vein model encapsulated with neck tissue phantom. The resultant external skin temperature maps, between a normal (0% stenosis) and diseased (50% or more stenosis) carotid artery model, show a statistically significant difference (33.33 ± 0.03 °C versus 33.23 ± 0.03 °C, $p < 0.001$). Compared to the simulation results, while a similar trend was observed in the *in-vivo* neck and face region temperature measurement using passive thermography (32.82 ± 0.53 °C versus 32.00 ± 0.37 °C, $p < 0.001$), the temperature values were found to be different. This observation attributes to the over-simplification of the simulated model geometry that does not account for the complex individual-specific geometrical and metabolic differences. In this study, a thermal region of interest (TROI) extraction technique was used to show a quantitative and qualitative contrast, in the temperature maps, between the two groups of samples.

Based on the TROI criteria, a parametric thermal image (*cold thermal feature image*) extraction method was utilized to perform the sample classification. For this, a cohort of 80 carotid artery samples was studied. As determined by the DUS examination, these samples come from various groups, namely, C (0% stenosis), D1 (10%-29%), D2 (30%-49% stenosis), and D3 ($\geq 50\%$ stenosis). The classification was first performed to screen samples $< 29\%$ stenosis (C') from samples $\geq 30\%$ stenosis (D'), then a sub-classification of groups (C and D1) and (D2 and D3) was performed. To perform the classification,

image features, viz., correlation, energy, homogeneity, contrast, entropy, mean, standard deviation (SD), skewness, and kurtosis, were calculated from the background-subtracted original thermal image (*full thermal image*) and *cold thermal feature images*. Of the three classification groups (C' and D'; C and D1; D2 and D3), optimized by receiver operating curve (ROC), the cut-off value-based classification model resulted in a maximum accuracy of only 70% using all the statistically significant features between any two groups of samples. Therefore, a machine learning classification algorithm was adopted. Using a Support Vector Machine (SVM)-based classification model, the three classification groups resulted in an accuracy of $94.1 \pm 0.5\%$, $92.6 \pm 0.7\%$, $92.7 \pm 1.2\%$, respectively, and sensitivity of $89.4 \pm 1.0\%$, $96.4 \pm 1.8\%$, $80.3 \pm 5.0\%$, respectively. For passive thermography, the reported classification performance is not only better than the one reported in the literature, but it is also comparable to the one achieved after using head clamp occlusion-based active thermography method.

Given that the active thermography method or active dynamic thermography (ADT) results in high contrast thermal images, in addition to the passive thermography technique, in this study, an ADT technique was also tested to perform CAS screening. Unlike the head clamp-based occlusion method used in the literature, the ADT procedure adopted in this thesis work comprised of an external non-contact cooling stimulation (cold air). Upon removal of the external stimulation, a temporal response-based sequence of a large number of thermal images is produced. Analyzing these images individually is not only troublesome but also time-consuming and complex in nature, therefore, in this thesis work, a novel method of quantifying the ADT sequence was developed. This was

achieved by a separate classical *in-vivo* experimental study. In this study, an ADT procedure was performed on the left forearm of three human subjects with three repetitions in each of the subjects. The aim of the study was to extract a single high contrast thermal image of the superficial blood vessel, from the dynamically changing contrast of the thermal image sequence, captured during the recovery phase upon application of the external cooling stimulation. This is attributed to the fact that the part of skin tissue with the superficial blood vessel as a heat source will rewarm faster compared to the part with no such superficial blood vessel. This was done by combining the whole ADT sequence, at a pixel level, by using a quantitative parameter called tissue activity ratio (*TAR*). *TAR* is defined as the ratio of the rate of rewarming to the rate of cooling in the ADT procedure. Compared to the existing parametric single image reconstruction methods (τ , dT_{norm} , t_{90-10n}), the *TAR* method was found to have provided a qualitatively and quantitatively high contrast single thermal image of the superficial blood vessel. With respect to the second-best high contrast τ image method, *TAR* image method resulted in an average contrast difference ($\pm$ Standard Error) of 0.54 ± 0.19 and 0.22 ± 0.11 , and 0.28 ± 0.17 , in Subject-1, 2, and 3, respectively.

Analogical to the presence of blood vessels as a heat source, a well-perfused skin tissue (normal) will result in a faster rewarming as compared to a poorly perfused skin tissue (diseased). In case of the neck and face region skin tissue, given the main source of tissue perfusion is the carotid artery, an anomaly in the carotid artery blood flow, as in the case of stenosis, will result in a slower recovery response to the external stimulation in the form of cooling. In this thesis, using the *TAR* parameter in the ADT procedure, this

difference was quantified and a cut-off value-based sample classification was performed. A sample size of 54 carotid arteries, grouped as C (0% stenosis), D1 (10%-29% stenosis), and D2 ($\geq 30\%$ stenosis), was utilized. To segment the ROI from the reconstructed *TAR* image, a novel masking method was devised. In this method, the mask image was prepared by subtracting the thermal image captured before and after the application of cooling stimulation; resulting in an image with a region of high cooling. Masking the *TAR* image with this mask image, an ROI segmented *TAR* image was extracted. Quantifying this ROI segmented *TAR* image in terms of average *TAR* value, the sample groups were found to have differed significantly (C: 0.97 ± 0.05 , D1: 0.80 ± 0.04 , and D1: 0.75 ± 0.02 , $p < 0.05$ between any two groups). The classification was performed in two scenarios: C versus (D1+D2) and (C+D1) versus D2; resulted in a classification accuracy of 90% and 85%, respectively. This cut-off value-based classification performance is comparable to the one achieved using SVM classification-based passive thermography. It can be concluded that both the passive and active thermography methods, studied within the limited number of samples in this thesis, suggest a strong potential of screening CAS.

7.2 Recommendations for Future Work

7.2.1 Patient-specific carotid artery geometry

In this thesis work (0), a computational bioheat transfer study was performed. Since only Duplex Ultrasound (DUS) data was available, an idealized 3D carotid artery model was used from the literature that was derived from the angiographic data. From the DUS data, the patient-specific stenosis geometry and physiological flow conditions were extracted and incorporated in the idealized 3D carotid artery model to perform the computational

study. Though this study presents a substantial advancement in the field of carotid artery bioheat transfer analysis, it is limited by the use of patient-specific carotid artery geometry. In future studies, this can be mitigated by using a patient-specific carotid artery model derived from either Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) imaging data.

7.2.2 Number of samples

It is imperative that the use of a passive thermography method with a machine learning-based classification model (0) is relatively more preferable to be implemented in a clinical setting over an active dynamic thermography (ADT) procedure with external cooling stimulation (**CHAPTER 6**). In this thesis work, though passive thermography-based CAS screening suggests a strong clinical potential, this particular conclusion of the thesis is drawn on the basis of a limited sample size of 80 carotid arteries. A larger cohort of patient groups must be investigated to generalize the proposed classification model. Since data labeling using DUS is a major roadblock in such a study, instead of a supervised machine learning model as used in this thesis work, a semi-supervised model could be an advancement in the field.

7.2.3 Effect of ambient conditions

As an inherent limitation of medical thermography, it is difficult to replicate the same controlled environment in every clinical setting. This may differ the threshold value of skin temperature distinguishing normal and diseased cases; resulting in poor performance of the classification model. If there is any such correlation between the environmental condition and threshold temperature, a correction factor to the threshold value could be

introduced in the classification model. This requires a systematic clinical study in the future.

7.2.4 Degree and location of the stenosis

Though this thesis work presents a proof-of-concept of accurate detection of CAS related cases using medical thermography in both passive and active form, the study is limited to only predicting the range of maximum stenosis in the carotid artery. For instance, in **0**, various sample groups were defined, namely, C (0% stenosis), D1 (10%-29%), D2 (30%-49% stenosis), and D3 ($\geq 50\%$ stenosis). While it is demonstrated that an accurate prediction of these groups is possible, the prediction of exact location and degree of stenosis is not covered in the scope of this thesis. This shall be focused in future work.

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