Carotid Artery Reactivity Measurement among Healthy Young People based on Optimized Ultrasound Images

Mohd A. Jamlos, Eko Supriyanto

***Abstract*—**Carotid artery (CA) reactivity measurement is required to detect the sign of Alzheimer Diseases (AD) in the early stage. Ultrasound (US) has been proposed to be used as the best modality candidate for this measurement due to its safety, cost effectiveness and easiness. US however has limitation in term of resolution and noises. This will lead the inaccuracy and irreproducibility of measurement. In order to solve this problem, an optimized carotid artery ultrasound images are required. This includes the application of thresholding technique, points filtering and hole fulfilling for segmentation. 320 US images from young female and male have been captured using 3D ultrasound machine before and after stimulation. The developed method then applied to the captured images for carotid artery diameter measurement. The result shows that the method can be used successfully to measure the CA reactivity with good accuracy. This is very useful to be used in early detection of AD that gives only carotid artery diameter changes in few millimeter lengths.

***Keywords*—**Alzheimer disease, image segmentation, ultrasound machine, carotid artery (CA), threshold, carotid artery reactivity (CAR)

I. Introduction

ALZHEIMER disease (AD) is a progressive neurodegenerative disorder associated with disruption of neuronal function which is the most common cause of dementia in the elderly [2]. Within the period of 25 years, efforts done to have more understanding on basic principle of AD are based on two independent lines of research. The first line is the study on molecular level of the protein deposits in order to obtain the identification of their major components while the second line is the study on rare and inherited disease [24]. AD has a widely variety of presentation and clinical course made it among one of the heterogeneous disorder disease. Because of that, it is quite difficult to measure the severity of AD as the cognitive decline rate is different among AD patient [3]. Among the biggest risk factors to get AD are age, insulin resistance or diabetes and genetic [25].

However, all these factors do not ensure in increasing the rate of AD progress as a lot of patients experienced either slow or fast rate without any present of those risk factors [3]. As mentioned before, age is always related as the main risk factor for almost all neurodegenerative diseases especially AD. Due to the expectation of increasing in life span particularly in developed countries' citizens, more people will have higher risk and potential to get AD [4]. Early detection among potential individuals to get AD is very essential in order to reduce the risk of AD where it has affected 24.3 million people worldwide in 2010 with increment around 4.6 million yearly [5]. In Malaysia only, it is estimated that there are currently about 50,000 people with this disease. However, most of them are not diagnosed due to relatives think that the symptoms displayed are a normal part of growing old and lack of awareness about the dangerousness of AD [6].

Nowadays, it is very hard to detect AD at early phase. Thus, a lot of methods have been invented to detect AD as earliest as possible. In order to do that, structural and functional brain has to be evaluated first. Fundamentally, single photon emission tomography (SPECT) and positron emission tomography (PET) are used for brain functional imaging while computed tomography (CT) and magnetic resonance imaging (MRI) are used for brain structural imaging. SPECT and PET will show reduced neuronal function in human brain such as altered cerebral glucose and altered cerebral blood flow while CT and MRI will show tissue atrophy due to loss of synapses and neurons because of AD process [8,18]. However, the developed methods are either high risk due to radiation utilization for PET, SPECT and CT scan meanwhile high cost or consume long scanning duration for MRI. Hence, ultrasound machine is utilized in order to replace those conventional methods since this modality is quickly, safely, accurately and cost effectively in capturing images related AD.

Treatment in the early stage is very efficient in treating AD especially before any clinical symptoms shown [7]. Ideally, with the early detection of Alzheimer, it should be possible to diagnose AD earlier or at a stage at which neurons are not irreversibly impaired by the disease process yet and have the potential to be treated efficiently with specific treatment [8].

It has been proven before that AD could be accurately detected by analyzing carotid artery structure. This is due to vascular abnormalities have the great potential to lead to

Manuscript received August 30, 2011

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vascular dysfunction which able to stimulate synaptoxic protein accumulation in the brain considered as the central process for AD formation [9,17]. This kind of protein is known as amyloid-like filaments that formed plaques and tangles of AD. Amyloid-like filaments are made up of Amyloid-b (AB) and tau where they are normally soluble proteins at the beginning [24]. The problem rises when overproduction of beta-amyloid occurred and the brain fails to dispose it at the same time. It will cause excess jams signaling at the synapses, blocking information flow and the worst is leading to brain cell death [13].

Thus, a lot of new techniques have been explored to study vascular function including diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), arterial spin labeling (ASL) and blood oxygenated level dependent (BOLD) [10]. However, 3D imaging scan technique using ultrasound machine is the most suitable one compared to other method since this modality has been used safely, accurately, cost effectively and quickly in evaluating carotid artery reactivity [1]. In vitro studies found that one of the best methods to evaluate vessel function is on its contractility through measurement of carotid artery reactivity (CAR) [13]. Hence, it is very important to have good and clear ultrasound image of carotid artery's structure and condition first before its being further analyzed through carotid artery reactivity (CAR). Determining the CAR value could be done with comparing the minimum carotid artery diameter under normal (rest) condition and maximum carotid artery diameter under stimulated (exercise) condition. In order to confirm that carotid artery reactivity can be used to detect AD in early stage, characterization of carotid artery 3D structure in healthy people need to be obtained first so that it can be compared and analyzed with Alzheimer patient later.

Ultrasound images captured from existing ultrasound machine have however very strong noise and limited resolution. Since the carotid artery diameter difference before and after stimulation is just few milimeters, an optmized ultrasound images are required. The optimization should involve image enhancement and segmentation.

Currently, varieties of methods have been used for image segmentations including robust edge detection algorithm, contour tracking algorithm, watershed algorithm. However, all these methods have their own weaknesses such as low contrast image, blur image, less accurate and need common point to complete wall segmentation [26]. Thus, segmentation method has been selected for image processing due to it does not blur the image, no need to set a common point and can be applied for other parts of human body [19-23].

Once the carotid artery wall is successfully segmented, it will be further analyzed to determine its reactivity value. CAR indicates the capacity of blood vessels to dilate when being stimulated by several particular stimuli where the bigger the dilation, the better the condition of carotid artery (CA) [11]. Well-functioned carotid artery has the ability to dilate for reserve capacity reacted towards any dilatory stimulus is a very essential method in regulating and maintaining constant cerebral blood flow in healthy human. It has been suggested that in order to have a continuous physiologic blood supply for brain, CAR must be in normal range of reading for healthy human [12]. The developed optimization method then has been applied to measure the CAR of healthy subjects. All the subjects have undergone adequate exercise to stimulate carotid artery reactivity under hypertension condition. In this study, a significant value has been acquired for normal carotid artery reactivity among young healthy people. This value can be used as a reference value to categorize the subject having Alzheimer disease or not.

II. Materials and Methods

This study is divided into two different parts which are carotid artery wall segmentation and carotid artery wall reactivity measurement. Carotid artery wall segmentation had been done first followed by carotid artery wall reactivity measurement. Wall segmentation was done in order to provide good and clear image of carotid artery wall to be used for reactivity measurement. There are a few steps for carotid artery wall segmentation which consist of images or data collections, algorithm for image processing and segmentation method. A software using MATLAB is developed particularly for that purpose. On the other hand, reactivity measurement is done to observe dilation capability of carotid artery under hypertension condition (exercise condition). Human subjects' carotid artery consist of 10 each of male and female being scanned using 3D ultrasound scan technique during normal (rest) and stimulated (exercise) condition.

A. Data acquisition

In this study, we collected carotid artery ultrasound images from 20 patients with different sex and age. The captured images are shown in figure 1 and figure 2.

3D ultrasound scan is used in this study to evaluate carotid artery reactivity. It provides 3D carotid artery structure image of its lumen and wall. 3D scan is done due to it is able to display the image within three different imaging views which are coronal, saggital and transverse [28]. It is also able to record images within slices form as thin as 0.5 mm [27]. Slices consist of the smallest diameter under rest condition and the largest diameter under exercise are selected to be analyzed within three different views. This is due to measure the dilation of the carotid artery in order to find its carotid artery reactivity value.

3D structure of carotid artery is being scanned using Toshiba Diagnostic Ultrasound System machine (Aplio MX SSA-780A). The probe used is PLT-1204 MV 3D linear transducer. The 12-MHz transducer is placed at the middle right of the subject neck to obtain the desired images. The transducer has to be in contact with subject neck and remain static during the recording and reconstructing process for about 5 seconds. The highest signal is determined at depth ranging from 1 to 2 cm and gain of 80 dynamic range (DR). The slice thickness chosen for the image is 0.5 mm which is the thinnest slice possible.

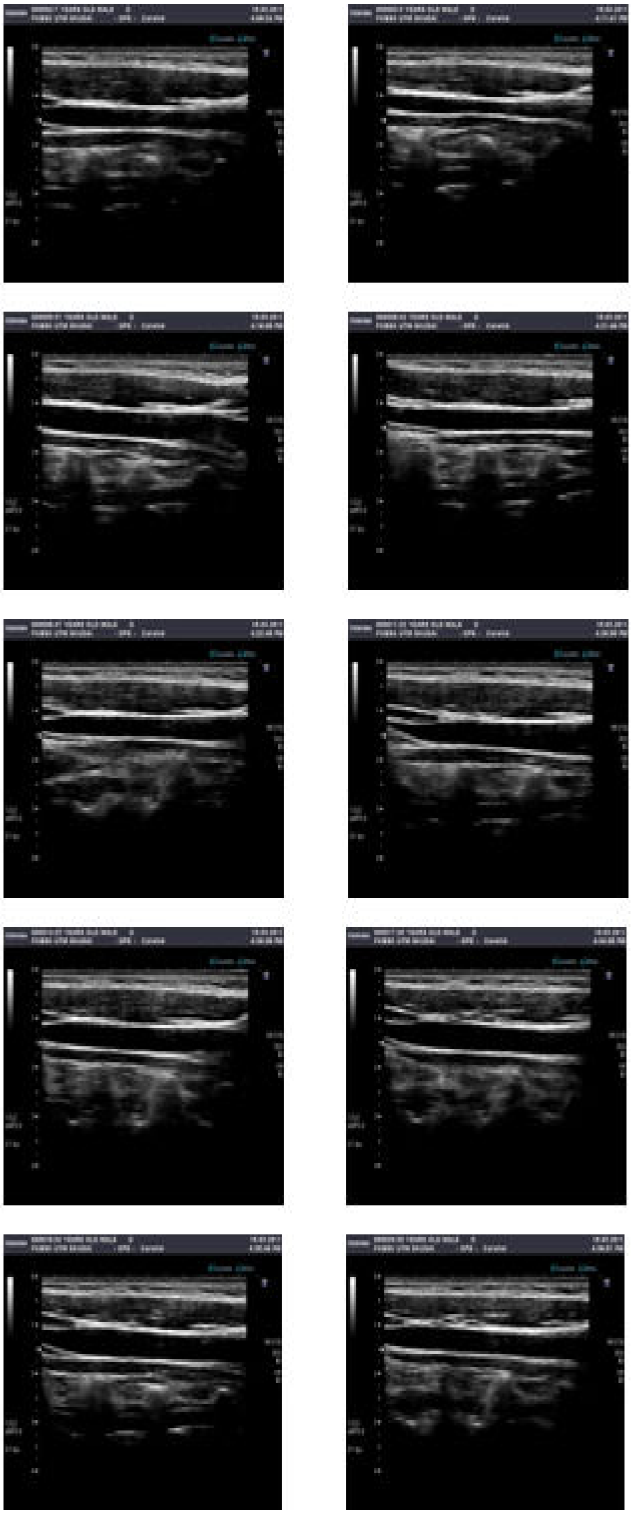


Fig. 1: Ten male carotid artery ultrasound images

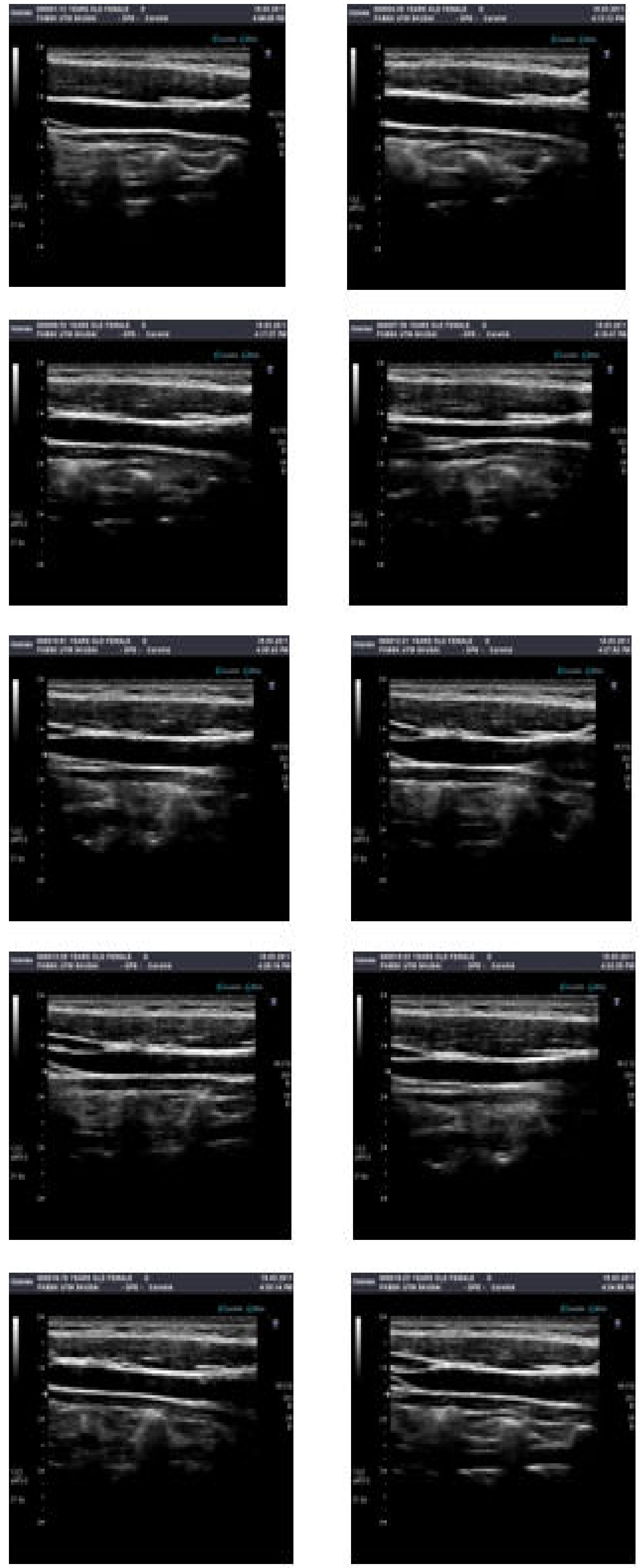


Fig. 2: Ten female carotid artery ultrasound images

B. *Algorithm for image processing*

For the algorithm of software, there are some steps have to be done before the carotid artery wall could be segmented. Figure 3 shows the flow chart of software algorithm.

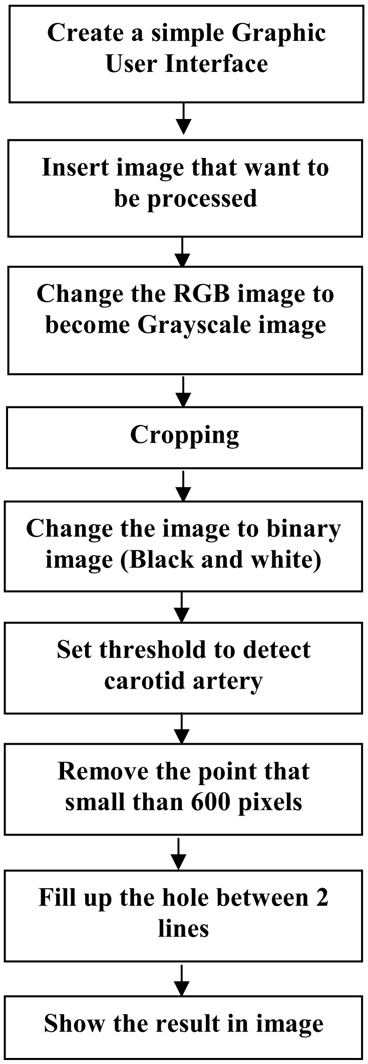


Fig. 3: Flow chart of image processing

MATLAB has been used to create a simple Graphical User Interface (GUI) so that it is friendlier towards the users. First of all, there is a button to press to insert the images that need carotid artery automatic detection. Next, the RGB image is changed from RGB to gray scale image. After that, we need to set a rectangular cropping area for the image so that the software system can detect the carotid artery more accurate. Furthermore, the image is changed to become binary image. The suitable threshold value is found and set to the software system. Then, points which smaller than 600 pixels are removed from the image. After that, the column (hole) between 2 lines is filled up. This process is called points segmentation. Lastly, the carotid artery is ready for next segmentation process and shown in the Graphical User Interface (GUI).

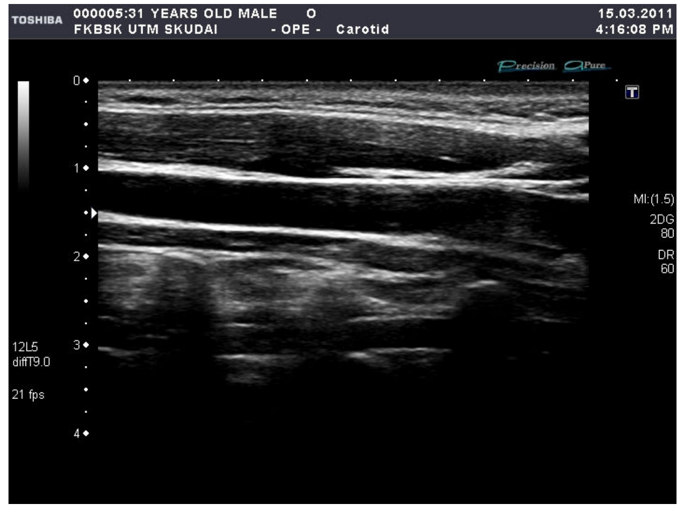


Fig. 4: Original ultrasound image

Figure 4 show the original image selected to be processed using segmentation method. The image above is the ultrasound carotid artery image of 31 years old male subject. After cropping, the image will become like figure 5. The area that not included in the crop area will be erased automatically and set to become black colour. The area remain in the image is the region of interest (ROI).

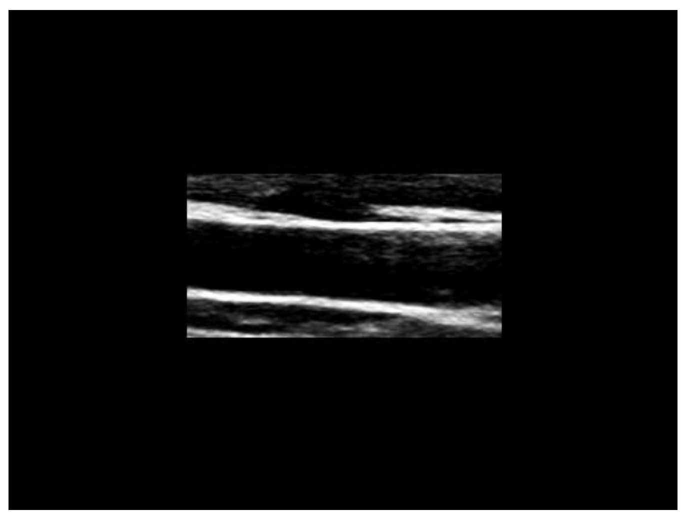


Fig. 5: Ultrasound image after cropping

Next, the ultrasound image is changed to binary image and the threshold set to be 0.6. The carotid artery is shown but still have a lot of other parts are included in the image. These other parts are unwanted parts and need to be removed from the ultrasound image. To remove all these parts which are not related, some testing need to be done to check what is the biggest point of these parts and the amount of its pixel number.

Fig. 6: Ultrasound image after thresholding

After that, the parts which are not the carotid artery have been identified consist of below than 600 pixels. Hence, the parts which are smaller than 600 pixels are set to be automatically removed. Figure 7 shown the image after filter the parts that smaller than 600 pixels. From the image, we can see the carotid artery wall is almost been segmented. However, there are some holes in the middle of the line of carotid artery. These holes need to be filled up so that a perfect carotid wall outline is shown out.

Fig. 7: Ultrasound image after removing parts smaller than 600 pixels

After set the software system to fill up the hole in the middle of carotid artery lines, a perfect carotid artery lines of wall is shown in figure 8. A carotid artery wall segmentation system is successfully developed.

Fig. 8: Ultrasound image of carotid artery wall after successfully being segmented

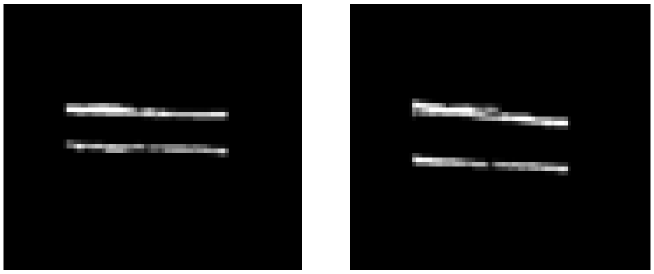
C. Segmented Wall Reactivity Measurement

The successfully segmented of carotid artery wall reactivity are being measured in this part. The measurement results are considered as the normal carotid artery wall reactivity value. In this study, 10 healthy subjects of male and female each are selected to be participated for data collection. The subjects are below than 30 years old, non-smoker, free from any vascular disease and have normal blood pressure. Before start data collection, their details such as name, identity card number, age, weight, height, blood pressure and oxygen concentration are taken. Personal interview between the subject and the researcher also done to ensure the subjects are really fit and suitable to participate in this study. Table 1 shows the average value for subject details.

Table 1: Details of subjects

Characteristics	**Average Value**
Mean age	22.5 ± 3.3
Mean weight	70 kg ± 8.5
Mean height	165.7cm ± 5.4
Mean blood pressure	125/83 mm Hg ± 8.4/6.2
Mean oxygen concentration	99% ± 1.5

Figure 9 shows the data acquired which is images ultrasound carotid artery during rest and exercise.



(Rest) (Exercise)

Fig. 9: Segmented carotid artery wall ultrasound image

Meanwhile figure 10 show the flow chart of carotid artery characterization process in human.

This measurement is done with two different parts which are under rest condition (normal) and under exercise condition (stimulated). After being explained by the researcher, the subject started the process of the experiment. The heart rate and carotid artery diameter under rest condition are taken simultaneously. Heart rate reading is taken using patient monitor while ultrasound machine with 3D imaging technique have been utilized to record the carotid artery diameter. Figure 11 shows how diameter of carotid artery being determined.

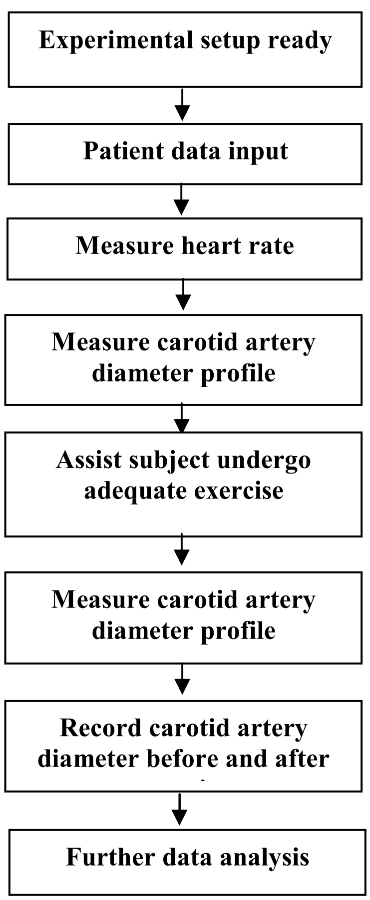


Fig. 10: Flow chart of carotid artery characterization

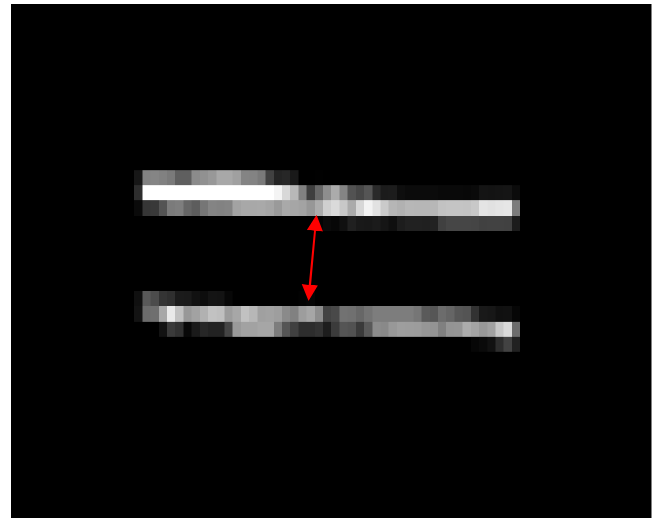


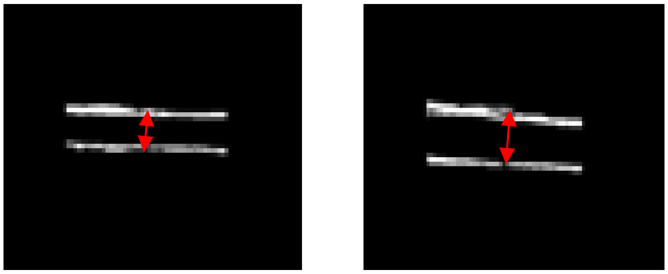
Fig. 11: Diameter of carotid artery

Heart rate and carotid artery diameter are recorded in beat per minute and millimeter respectively. When all the required data are taken, subject asked to have adequate exercise on the treadmill. The period of the exercise and the speed of the treadmill are not fix as long as the heart rate of the subject achieve 85% of maximal heart rate. Adequate exercise has been used as the stimulator to create carotid artery reactivity. The reactivity state could be achieved when the subject heart rate reach 85% of its maximal heart rate after having adequate exercise [16]. Maximal heart rate (MHR) is calculated in beat per minute (bpm) and determined with specific formula [15]. The formulas are shown as followed:

Male MHR : 220 – age (1)
Female MHR : 200 – age (2)

Subjects asked to warm up their body first to avoid any injury during the exercise period. The subject heart rate is being observed during all the time of exercise and once the subject achieves the target heart rate, he or she will be scanned immediately using ultrasound machine to record his or her carotid artery wall structure. This is because to avoid decline of the subject heart rate in order to remain the target heart rate during the recording process of carotid artery structure. Subjects are asked to have rest first and being ensured they are in good condition before leaving examination room.

The reactivity of carotid artery could be determined through the dilation of the carotid artery wall structure. The bigger the carotid artery wall, the more the carotid artery reacted. The more the carotid artery reacted, the better the condition of the carotid artery. Figure 12 shows the image of normal (rest) and dilated (exercise) carotid artery image. The normal image has smaller diameter while the dilated image has larger diameter.



Normal (rest) Dilated (stimulated)

Fig. 12: Carotid artery diameter comparison

In this study, unharmed exercise method has been selected as the stimulator for the carotid artery to react or dilate as big as possible. Hence, the minimum carotid artery diameter before exercise and maximum carotid artery diameter after having exercise will be compared and analyzed to find the increment percentage and at the same time find the normal carotid reactivity among young healthy people. This normal value could be used to compare with the value belong to Alzheimer patient so that it could be used as the main indication to categorize healthy people and Alzheimer patient. The normal carotid reactivity value could be obtained through below formula:

$$\Delta D = \frac{D_{CAS} - D_{CAN}}{D_{CAN}} X100 \qquad (3)$$

Where ΔD= percentage of increment, D_{CAS}= Stimulated carotid artery diameter, D_{CAN}= Normal carotid artery diameter

$$\Delta D = D_{CAS} - D_{CAN} \qquad (4)$$

Where ΔD= Increment value, D_{CAS}= Stimulated carotid artery diameter, D_{CAN}= Normal carotid artery diameter

III. Result and Analysis

A. Test Result

After complete the software development, the software is tested on 20 carotid artery ultrasound images to check the accuracy of automatic detection. Results are shown in figure 13 and 14. Then, the optimization step is taken to improve the software so that the accuracy level will be increased.

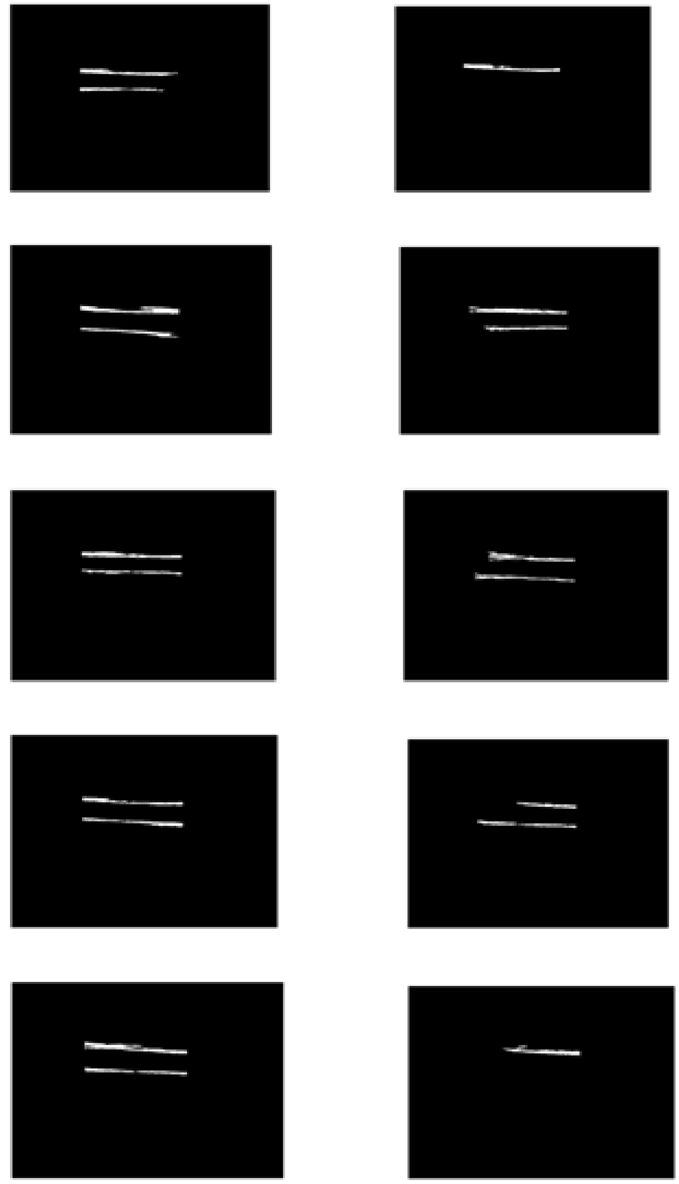


Fig. 13: Results of 10 males carotid artery ultrasound images

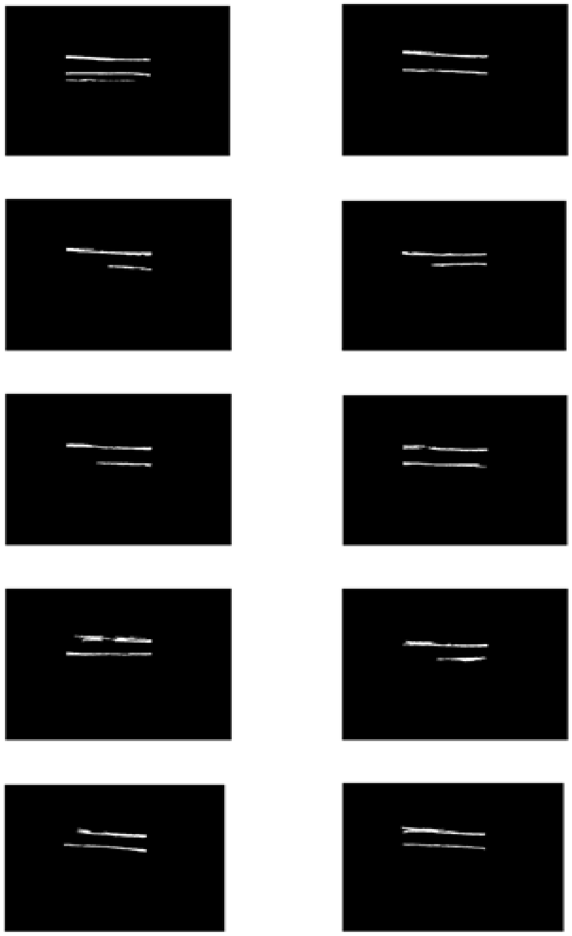


Fig. 14: Results of 10 females carotid artery ultrasound images

B. *Analysis of accuracy and error*

To check the reliability of the software, some analyses need to be done. From the analysis, we can know how accurate the software in segmenting the carotid artery wall.

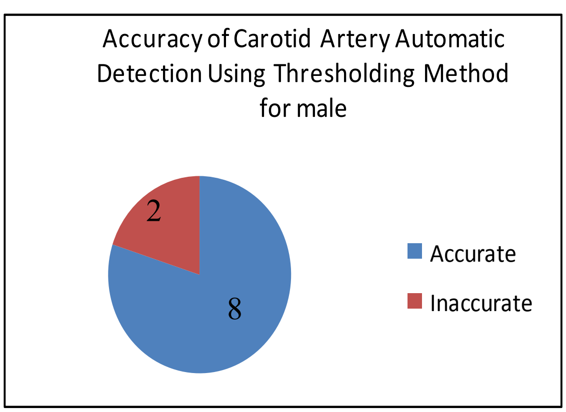


Fig. 15: Pie Chart of accuracy of carotid artery wall segmentation for male.

Fig. 15 shows the accuracy of carotid artery wall segmentation. From the pie chart, eight out of ten male carotid artery images show the accurate result in carotid artery wall segmentation. While only two of the images for male are not accurate. It means that 80 percent of the male's carotid artery walls can successfully being segmented.

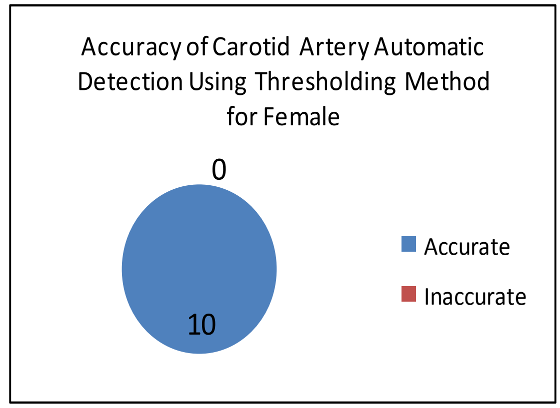


Fig. 16: Pie Chart of accuracy of carotid artery wall segmentation for female.

On the other hand, figure 16 shows the accuracy of carotid artery wall segmentation for female. From the pie chart, ten out of ten of the result are accurate whereby the carotid artery wall is successfully segmented. It means the software 100 percent effectively segment the carotid artery wall of female subjects.

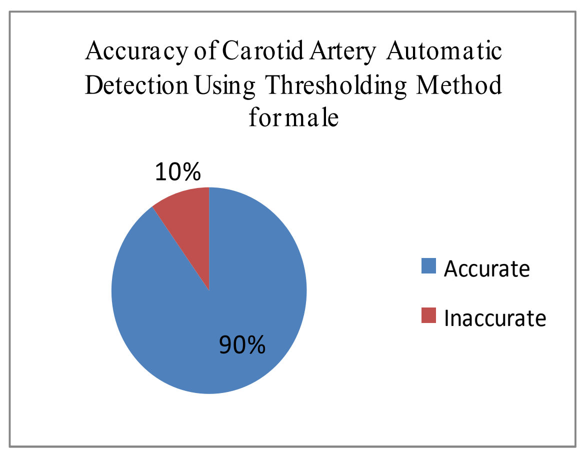


Fig. 17: Pie Chart of overall accuracy of carotid artery wall segmentation

Figure 17 shows the overall accuracy result of the carotid artery wall segmentation. From the pie chart, 90% of the result shows that the carotid artery wall segmentation is accurate whereas only 10% shows otherwise. This analysis shows that the developed software using segmentation method is very accurate and reliable for carotid artery wall segmentation.

C. Segmented Wall Reactivity Measurement

The results of segmented wall reactivity are shown in this part. The reactivity values show the ability of the carotid artery wall to dilate under hypertension technique. It includes the readings of carotid artery diameter and subject heart rate which are taken during rest and exercise state.

Table 2: Carotid artery diameter changes of male subject

n^{th} subject	Rest (normal)(mm)	Exercise (stimulated)(mm)
1	6	8
2	7	8
3	7	9
4	7	9
5	7	8
6	7	9
7	8	10
8	8	10
9	8	9
10	9	11
Average value	7.5	9.1

Table 2 shows the result for 10 male subjects. The results show the reading carotid artery diameter (mm) during rest (normal) and exercise (stimulated) condition. From the result, the lowest diameter for rest condition is 6 meanwhile the highest one is 9. The average diameter for rest condition is 7.5 mm. On the other hand, the lowest diameter for stimulated condition is 7 meanwhile the highest one is 11. The average diameter for stimulated condition is 8.8 mm.

Table 3: Carotid artery diameter changes of female subject

n^{th} subject	Rest (normal)(mm)	Exercise (stimulated)(mm)
1	5	6
2	5	6
3	6	7
4	6	7
5	6	8
6	6	7
7	6	7
8	6	7
9	7	9
10	7	8
Average value	6	7.2

Table 3 shows the result for 10 female subjects. The results show the reading carotid artery diameter (mm) during rest (normal) and exercise (stimulated) condition. From the result, the lowest diameter for rest condition is 5 meanwhile the highest one is 7. The average diameter for rest condition is 6 cm. On the other hand, the lowest diameter for stimulated condition is 6 meanwhile the highest one is 8. The average velocity for stimulated condition is 7.3.

D. Analysis carotid artery diameter and heart rate increment

The increment values which are the target data consist of normal carotid artery reactivity percentage are shown in these following tables.

Table 4: Carotid artery diameter increment in male

n^{th} subject	Increment value(mm)	Increment percentage (%)
1	2	33.3
2	1	14.3
3	2	28.6
4	2	28.6
5	1	14.3
6	2	28.6
7	2	25
8	2	25
9	1	12.5
10	2	22.2
Average value	1.7	23.2

Table 4 shows the lowest increment value among male subjects is 1 mm while the highest one is 2 mm. The average increment value is 1.7. On the other hand, the lowest carotid artery diameter increment percentage is 12.5% while the highest one is 33.3%. The average for this increment percentage is 23.2%.

Table 5: Carotid artery diameter increment in female

n^{th} subject	Increment value (mm)	Increment percentage (%)
1	1	20
2	1	20
3	2	16.7
4	1	16.7
5	1	33.3
6	2	16.7
7	1	16.7
8	1	16.7
9	2	28.6
10	1	14.3
Average value	1.3	20.0

Table 5 shows the lowest increment value among female subjects is 1 mm while the highest one is 2 mm. The average increment value is 1.3 mm. Apart from that, the lowest carotid artery diameter increment percentage is 14.3% while the highest one is 28.6%. The average for this increment percentage is 20.0%.

Table 6: Heart rate increment in male subject

n^{th} subject	Increment value (bpm)	Increment percentage (%)
1	59	79
2	77	88
3	71	102
4	82	127
5	87	128
6	83	139
7	90	139
8	99	140
9	82	149
10	111	179
Average value	82	127

Table 6 shows the lowest heart rate increment value among male subjects is 59 while the highest one is 111. The average increment value is 82 bpm. On the other hand, the lowest heart rate increment percentage is 79% while the highest one is 179%. The average for this increment percentage is 127%.

Table 7: Heart rate increment of female subject

n^{th} subject	Increment value (bpm)	Increment percentage (%)
1	58	70
2	61	71
3	60	75
4	63	77
5	69	78
6	66	79
7	70	88
8	65	105
9	85	119
10	84	121
Average value	69	88

Table 7 shows the lowest heart rate increment value among female subjects is 58 while the highest one is 85. The average increment value is 69 bpm. On the other hand, the lowest heart rate increment percentage is 70% while the highest one is 121%. The average for this increment percentage is 88%.

E. Correlation between heart rate and carotid artery diameter

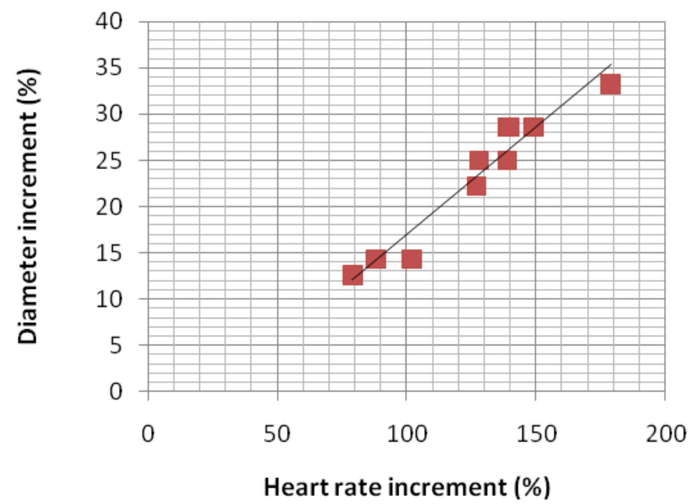


Fig. 18: Correlation between heart rate and CA diameter in male subjects

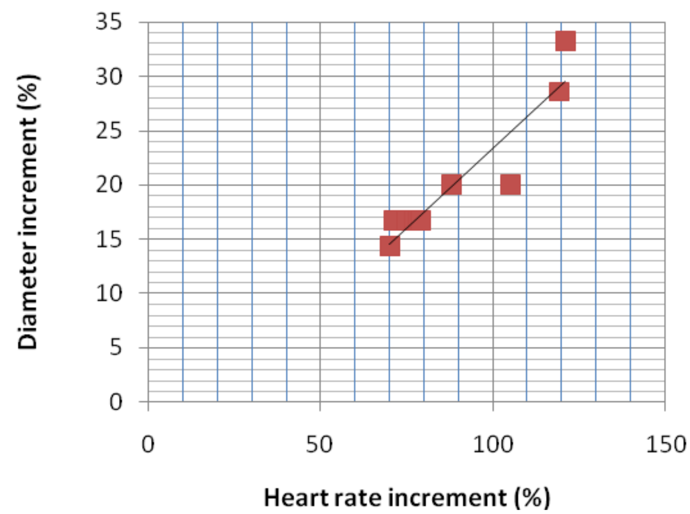


Fig. 19: Correlation between heart rate and CA diameter in female subjects

Figure 18 and 19 represent the correlation between heart rate and carotid artery blood flow velocity for male and female respectively. Both scatter plot show that the carotid artery blood flow velocity is directly proportional to heart rate since both diameter increment and heart rate values together formed a line of identity. The entire plots located close toward the line and almost equal in number between both sides of the line. Hence, the higher the heart rate, the more the carotid artery dilates. This is due to compensate the faster and higher amount of blood flow from heart towards brain to fulfill high metabolic demands of neural activity.

F. Comparison between male and female on carotid artery characterization

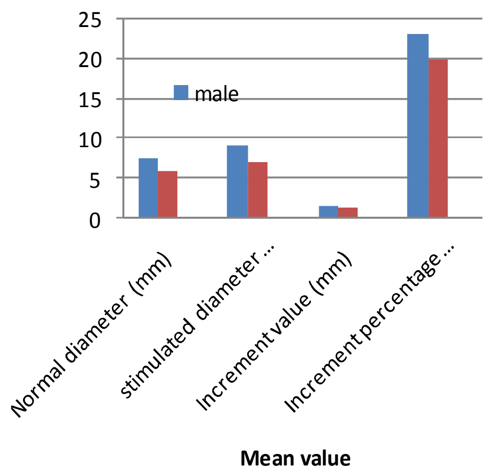


Fig. 20: Overall comparison between male and female carotid artery characterization.

Figure 20 shows that male will have higher value than female in all parameters which are normal carotid artery diameter, stimulated carotid artery diameter and carotid artery diameter increment value. This might be due to male is stronger, bigger and tougher in nature compared to female. This could be seen when the average normal diameter of carotid artery in male is larger (7.5 mm) compared to female (6 mm). Another factor could be male subject achieved higher target heart rate compared to female subject where male average heart rate increment is higher (82 bpm) compared to female (69 bpm). Male subject experienced higher heart rate increment might because of they did heavier exercise by running faster on the treadmill compared to female subject. This factor made the carotid artery among male subjects to dilate more where average stimulated diameter of carotid artery in male subject is 9.1 mm meanwhile in female subject is 7.2 mm.

IV. CONCLUSION

A new method for human carotid artery reactivity measurement has been successfully developed. This includes the 3D ultrasound image optimization for segmentation purpose. Test result shows that the optimized images are very suitable to improve of accuracy and reproducibility of CA diameter measurement. This can be used to measure the changing of CA diameter, which is only 23.3 % for male and 20 % for female. This normal carotid artery reactivity value is very useful to be used as an indicator to evaluate the risk to get AD in the early stage.

V. ACKNOWLEDGEMENT

This work is fully support by Ministry of Science, Technology and Innovation (MOSTI) Malaysia under grant of Science Fund Vot No. Q: J130000.7136.00H25. The authors would like to thank to Research Management Centre (RMC), Biotechnology Research Alliance (RA), and Faculty of Health Science and Biomedical Engineering, Universiti Teknologi Malaysia (UTM) for their support.

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