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Determination of the effect of glucose and cholesterol on the flow velocity of Blood Mimicking Fluid in a Common Carotid Artery Wall-less Phantom

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Abstract

Objective: *In this research, we have shown how increase in glucose and cholesterol levels in a blood mimicking fluid (BMF) influenced the peak systolic velocity (PSV) and end diastolic velocity (EDV) in the common carotid artery wall-less phantom.* ***Methodology:*** *The BMF was prepared and mixed with D(+)-glucose and cholesterol powders at different levels from 50 mg/dl to 500 mg/dl. A multi-lumen diameter common carotid artery (CCA) wall-less phantom was used to carry out measurements of flow velocity of the BMF using a Hitachi HI Vision ultrasound scanner.* ***Results:*** *The PSV and EDV of the BMF are inversely related to the concentration (level) of glucose and cholesterol in the BMF. The PSV and EDV decreased by a maximum of about 3.0 cm/s across the 8 lumen diameters, while they decreased by a maximum of 4.0 cm/s with increased in glucose and cholesterol levels respectively.* ***Conclusion:*** *This suggests that no matter the concentrations of glucose or cholesterol in the BMF samples, the flow parameters were similar to those for healthy arteries. Therefore, we conclude that hyperglycemia and hypercholesterolemia does not influence the flow velocity in the CCA, but trigger other risk factors at advance stages of atherosclerosis.*

Key Words: Common Carotid Artery; Blood Mimicking Fluid; Carotid Flow Velocity; Cardiovascular Risk Factors; Doppler Ultrasound.

1.0 Introduction

The common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) form a major supply route for blood to the brain (Piotr & Joshua, 2006). Therefore, they are a subject of a lot of clinical investigations (Barnett et al., 1998; Ferguson et al., 1999). Researchers have studied blood flow velocity because it is considered as an important tool to assess hemodynamic parameters that can give good idea about cardiovascular disease such as stroke (Manisha & Vilas, 2019; Melanie *et al.*, 2020; Mete Özdikici, 2020; Thea *et al.*, 2020). The measurement of resistivity index (RI) is independent on the Doppler angle, but measurements of other hemodynamic indices require that the Doppler angle should be within the range 30^0 to $60^0$with very accurate measurements taken at 60^0. This is because at angles greater than 60^0, the velocity measurements will substantially change leading to much errors and inaccuracies (Lee, 2013). Blood flow within a vessel does not have the same velocity at any given time. It is faster at the centre of the vessel and slow near the vessel wall

due to viscous drag exerted by the walls causing the fluid at wall to become stationary. This difference in the flow velocity across the vessel is referred to as velocity profile.

As a homogeneous fluid enters a long tube with a steady flow, it moves from a blunt flow profile with all the fluid moving with the same velocity to a parabolic flow (Caro et al., 2012). The distance over which the velocity profile transits from blunt to parabolic flow is dependent on the diameter of the vessel and velocity of the fluid, but the velocity is usually several times the tube diameter. The same difference in velocity profile is observed in several vessels in the human body, for instance, flow profile up the aorta is blunt while it is parabolic in the normal mid superficial femoral artery even though the shape of the velocity profile can be complicated by the pulsatile nature of blood flow (Peter *et al.,* 2019). In arteries, blood flow is pulsatile and the velocity profile varies over time, therefore, for normal common femoral arteries and common carotid arteries, there is no reverse flow except during diastole where reverse flow is observed in the common femoral artery. There have been no much studies on the relationship between carotid artery hemodynamic indices and ischemic stroke. PSV, EDV and RI in the carotid artery have been found to be associated with ischemic stroke (Chyi-Huey *et al.,* 2007; Chuang *et al.,* 2011). Age is a major risk factor associated with stenosis of the carotid artery. Elderly people have low PSV and large CCA diameters, while high systolic blood pressure and diastolic blood pressure increase PSV (Homma *et al.,* 2009; Toru *et al.,* 2005; Arkadiusz *et al.,* 2012; Azhim et al., 2011; Pam *et al.,* 2015a). Because cholesterol is an insoluble particle in the blood, its movement within blood vessels like arteries makes it a risk factor of cardiovascular disease known as atherosclerosis or hardening of the artery wall by cholesterol deposits (stenosis) (Vasudevan & Sreekumari, 2013). A real human blood contains glucose as part of the components of its plasma and serum, the presence of high level of glucose in the blood plasma ($\geq 130 mg/dl$) makes it hyperglycaemic (diabetic) and a risk factor of cardiovascular disease (Rita *et al.,* 2015; Flora & Nayak, 2019; Hamid et al., 2019). Obese humans are known to have large CCA lumen diameter and decreased flow velocity, pointing to early stage of atherosclerosis (Hüseyin *et al.,* 2015; Pam *et al.,* 2015b).

There are no known studies on the effect of high or low glucose and cholesterol levels on the hemodynamic blood flow in the carotid artery of the human being. Even though high glucose and total cholesterol levels in the blood plasma have been indicated as risk factors of atherosclerosis and ischemic stroke, there is no information on how they influence flow velocity indices in the carotid artery. In this research, the effect of different levels of glucose and cholesterol in the BMF on flow velocity in a multi-lumen diameter CCA wall-less phantom has been discussed.

2.0 Materials and Methods

This experiment was approved by Physics department, Universiti Sains Malaysia. There was no need seeking for consent or approval from the ethics committee or Institution Review Board as this research does not involve human or animal participants.

2.1 Blood Mimicking Fluid Preparation

The BMF was prepared by a combination of 70% w/w of distilled water, 5% w/w of propylene glycol, 25% w/w of polyethylene glycol and 0.8% w/w of poly (4-methylstyrene) (Sigma Aldrich, Germany) scatters (Oglat et al., 2018a). This was followed by adding 2 drops of benzalkonium chloride to serve as a preservative against bacterial manifestation. The prepared BMF was then mixed with 50 mg/dl to 500 mg/dl of glucose and cholesterol separately to find out their effects on the flow velocity measurements. The pumping of the BMF was actualized using a 50130 centrifugal multi-flow pump produced by the German Society for Applied Medical Physics and Technology (GAMPT), capable of delivering up to 10 liters/minute. Care was taken to ensure that the BMF was not left inside the phantom after use to avoid settling of the scatter particles. The phantom was flushed with glycerol solution to remove the BMF completely and avoid changing the composition of the

TMM while it is being stored at room temperature.

2.2 Preparation of Tissue Mimicking Material (TMM) Wall-less Phantom

The TMM composition for the wall-less phantom was adopted from research conducted by (Ammar et al., 2018). It was made up of 84% distilled water, 0.53% of silicon carbide, 0.96% of aluminum oxide (3.0 μm size), 0.89 % of aluminum oxide (0.3 μm size), 0.92% of gelatin, 1.5% of konjac powder, 1.5% of carrageenan powder, 0.7 % of potassium chloride and 9.0% of glycerol. About 5 cm^3 of benzalkonium chloride solution was added as an ant-fungal agent. The Prepared TMM was cast inside a plastic rectangular box with 8 different straight metal rod of diameters 8.0 mm. 7.5 mm, 7.0 mm, 6.5 mm, 6.0 mm, 5.5 mm, 5.0 mm and 4.5 mm placed inside the box (figure 1a). When the TMM had cooled to about 40^0C, the metal rods were removed gradually to provide 8 lumens which were attached to rubber tubes for connection to a gear pump.

2.3 Measurements of Density and Viscosity

The densities of the BMF fluids were measured using a portable Density Meter

(DMA 35, Firmware Version, V1.79, Austria) at 37^0C. The strip attached to the meter was pressed down and dipped inside the fluid, then it was released to draw up the fluid inside the strip by suction pressure, while the density reading was recorded automatically by the meter in just few seconds.

About 700 cm^3 of each BMF fluid was required for the viscosity measurements using the electronic rotational viscometer (ERV) (Software Version 1.2, Fungilab, Barcelona, Spain). The spindle L1 was selected for viscous liquid, it was fixed to the ERV and then lowered into the fluid while the ERV was switched on (figure 1b). The spindle rotates inside the liquid for few minutes until a steady value of the viscosity was recorded due to the viscous resistance from the fluid (Kim et al., 2015; Chunhwa et al., 2020).

2.4 Measurements of speed of sound, Attenuation and Backscatter power

The speed of sound was measured by pulse echo (PE) method using Ultrasonic echoscope GAMPT-scan machine (German society for Applied Medical Physics and Technology, GAMPT Ultrasonic solutions, Hallesche Strabe, Merseburg, Gamany). The arrangement for this measurement is shown in (figure 1c) where the time of flight (TOF) between the highest two peaks of the transmitted and reflected waves was measured, the values for the speed of sound of the liquids were calculate using the equation:

$$\text{Speed of sound} = \frac{2x}{t} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

Where x is the distance between the walls of the vessel containing the liquid and t is the time of flight

The amplitudes of the highest two similar peaks were also measured and the attenuation coefficients (α) were also calculated using the attenuation equation:

$$\alpha = \frac{2\times0.868}{x}\ln\frac{A_2}{A_1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 3$$

Such that A_1 and A_2 are the amplitudes of the two highest but similar wave peaks respectively and x is the distance.

The backscatter power of the BMF was measured at different radio frequency signals by calculating the average power spectrum through applying the fast Fourier transform (FFT) generated by the A-scan GAMPT software at 5 MHz. This was done to find out if the BMF simulates the real human blood.

(a)

(b)

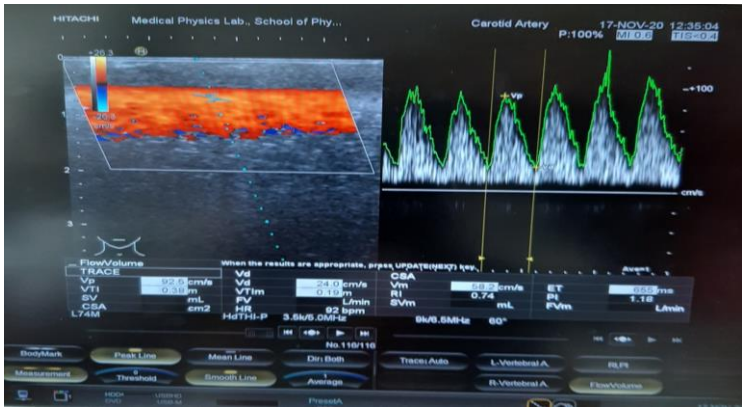
(c)

Figure 1: (a) casting of the TMM inside the phantom box, (b) Rotational Viscosity Meter measuring the viscosity of the mixture fluids, (c) Measurement of the acoustic properties of solutions using the A-scan Gampt technique

2.5 Doppler Ultrasound Measurement of Flow Velocities

A digital clinical Hitachi ultrasound scanning machine (HI VISION Avius, Hitachi Medical Corporation, Tokyo, Japan) connected with a linear array transducer (probe) EUP-L74M with frequencies ranging from 5 to 13 MHz was used to get an image of the wall-less flow phantom. The phantom was placed on a flat table and connected to a 50130 centrifugal multi-flow pump (German society for Applied Medical Physics and Technology, GAMPT mbH, Hallesche Strabe, Merseburg, Gamany) with the aid of plastic tubes to pump the BMF (figure 2a). This fluid was pumped through the lumen at a flow rate of 1500 ml/min (for both steady and pulsed flow) and B-mode images of the lumen and the BMF were displayed on the screen of the scanning machine. Measurements of peak systolic velocity (PSV) and end-diastolic velocity (EDV) were carried out by color Doppler and Pulse- wave (PW) Doppler systems (figure 2b). The angle of beam (insonation angle) was set at the center of the flow at 60^0 with the required sample volume and a minimum entrance length of about 5 cm.

(a)



(b)

Figure 2: (a) Ultrasound measurements of hemodynamic parameters using the Hitachi ultrasound scanner, (b) Colour Doppler measurements of peak systolic and end diastolic velocity.

3.0 Results

The BMF prepared has a density of 1.040±0.02g/cm^3, viscosity of 4.40±0.03 mPa.s, speed of sound of 1595±1.2 m/s and attenuation of 0.055±0.002 dB/cm at 5 MHz. The values for these physical and acoustic properties increased slightly as 50 mg/dl to 500 mg/dl of glucose and cholesterol were added to the BMF. This increase in the values of the BMF properties did not affect its effectiveness to be used as a fluid for Doppler ultrasound flow measurements. The TMM multi-lumen diameter CCA wall-less phantom has a speed of sound of 1548±0.07 m/s while the attenuation was 0.5±0.02 dB/cm at 5 MHz frequency. Results for the peak systolic and end diastolic velocities of 50 mg/dl to 500 mg/dl of glucose and cholesterol in the BMF are shown in table 1 and table 2 respectively.

Table 1: Results for the Effects of Change of Glucose concentration (level) in milligram per deciliter (mg/dl) on the Peak Systolic velocity (V1) and End Diastolic Velocity (V2)

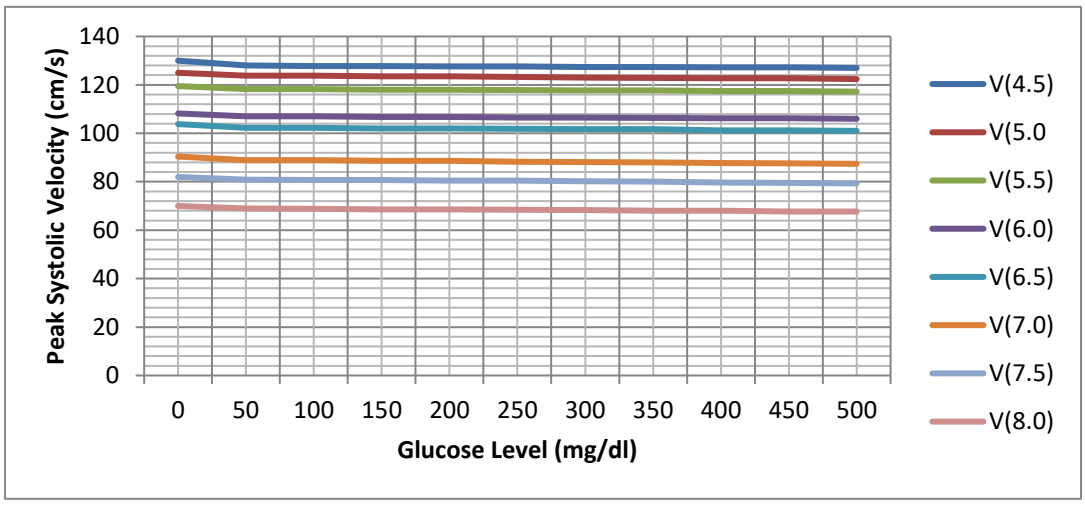
Conc. of Glucose (mg/dl)	**4.0 mm**		**5.0 mm**		**5.5 mm**		**6.0 mm**		**6.5 mm**		**7.0 mm**		**7.5 mm**		**8.0 mm**	
	V1	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**
0	130.0	36.7	125.0	31.0	119.5	28.4	108.2	27.5	103.8	26.5	90.4	22.0	82.0	21.2	70.0	19.9
50	128.0	35.4	123.8	29.7	118.3	27.0	107.0	26.0	102.2	24.9	88.9	20.8	80.8	20.9	68.9	18.0
100	127.8	35.2	123.8	29.7	118.3	27.0	107.0	26.0	102.2	24.7	88.9	20.6	80.7	20.4	68.8	18.0
150	127.8	35.2	123.6	29.5	118.0	26.9	106.7	25.8	102.0	24.5	88.6	20.6	80.7	20.4	68.6	17.7
200	127.6	35.0	123.5	29.5	118.0	26.6	106.7	25.6	102.0	24.5	88.6	20.5	80.4	20.1	68.6	17.5
250	127.6	35.0	123.3	29.3	117.8	26.6	106.5	25.5	101.8	24.4	88.3	20.4	80.4	20.0	68.4	17.3
300	127.4	34.8	123.0	29.3	117.7	26.4	106.5	25.4	101.7	24.3	88.1	20.2	80.2	19.7	68.3	17.3
350	127.4	34.7	122.9	29.1	117.7	26.2	106.3	25.4	101.7	24.3	88.0	20.2	80.0	19.7	68.0	17.0
400	127.2	34.7	122.7	29.0	117.5	26.2	106.2	25.2	101.2	24.0	87.7	19.9	79.6	19.5	68.0	17.0
450	127.2	34.5	122.7	29.0	117.5	25.9	106.2	25.0	101.2	24.0	87.6	19.6	79.5	19.5	67.7	16.8
500	127.0	34.2	122.4	28.7	117.2	25.5	106.0	25.0	101.0	23.9	87.4	19.6	79.3	19.2	67.7	16.6

Table 2: Results for the Effects of Change of Cholesterol (CHO) concentration (level) in milligram per deciliter (mg/dl) on the Peak Systolic velocity (V1) and End Diastolic Velocity (V2)

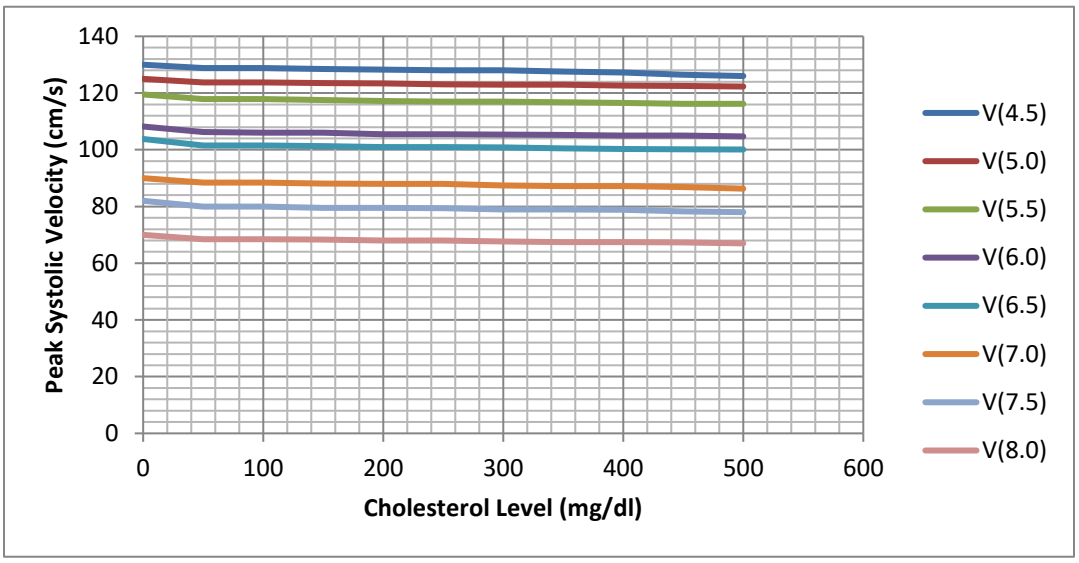
Conc. of CHO (mg/dl)	**4.0 mm**		**5.0 mm**		**5.5 mm**		**6.0 mm**		**6.5 mm**		**7.0 mm**		**7.5 mm**		**8.0 mm**	
	V1	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**

0	130.0	36.7	125.0	31.0	119.5	28.4	108.2	27.5	103.8	26.5	90.0	22.0	82.0	21.2	70.0	19.9
50	128.8	35.0	123.7	29.6	117.9	26.7	106.3	25.7	101.5	24.8	88.4	20.6	80.0	19.9	68.4	17.8
100	128.8	35.0	123.7	29.6	117.9	26.7	106.0	25.5	101.5	24.5	88.4	20.6	80.0	19.2	68.4	17.0
150	128.5	34.8	123.5	29.5	117.5	26.5	106.0	25.3	101.3	24.5	88.1	20.3	79.5	19.0	68.3	17.0
200	128.3	34.8	123.4	29.3	117.2	26.5	105.5	25.3	101.0	24.2	88.0	20.3	79.5	18.5	68.0	17.0
250	128.0	34.5	123.1	29.0	117.0	26.4	105.5	25.0	101.0	24.2	88.0	20.0	79.4	18.5	68.0	16.8
300	128.0	34.2	122.9	29.0	117.0	26.2	105.4	25.0	100.8	24.0	87.4	20.0	79.0	18.3	67.7	16.5
350	127.6	34.0	122.9	28.7	116.8	26.2	105.2	24.6	100.5	24.0	87.2	19.6	79.0	18.1	67.4	16.0
400	127.2	33.6	122.6	28.7	116.5	26.0	105.0	24.5	100.3	23.7	87.2	19.5	78.8	18.0	67.4	16.0
450	126.4	33.4	122.5	28.4	116.2	26.0	105.0	24.3	100.2	23.4	86.9	19.0	78.3	17.5	67.3	15.5
500	126.0	32.5	122.3	28.3	116.2	25.6	104.7	24.0	100.1	23.4	86.3	18.6	78.0	17.5	67.0	15.5

50 mg/dl of glucose or cholesterol means mixing 0.05g of glucose or cholesterol in 100 cm^3 of the BMF, while 500 mg/dl means mixing 0.5g in 100 cm^3 of the BMF. The PSV and EDV of the BMF are inversely related to the concentration (level) of glucose and cholesterol in the BMF. These results show that increase in glucose and cholesterol levels have no significant effect on the velocity of BMF flow in the wall-less phantoms because only a maximum decrease of about 3.0 cm/s of Peak systolic and end diastolic velocity were observed across the wall-less phantoms as the glucose level was increased from 0 -500mg/dl in the BMF. Similarly, a maximum decrease of about 4.0 cm/s was observed as the cholesterol level was increased from 0 -500mg/dl in the BMF. Graphs showing the correlations between glucose and cholesterol levels with the Peak systolic and end diastolic velocities are seen in figures 3, 4.

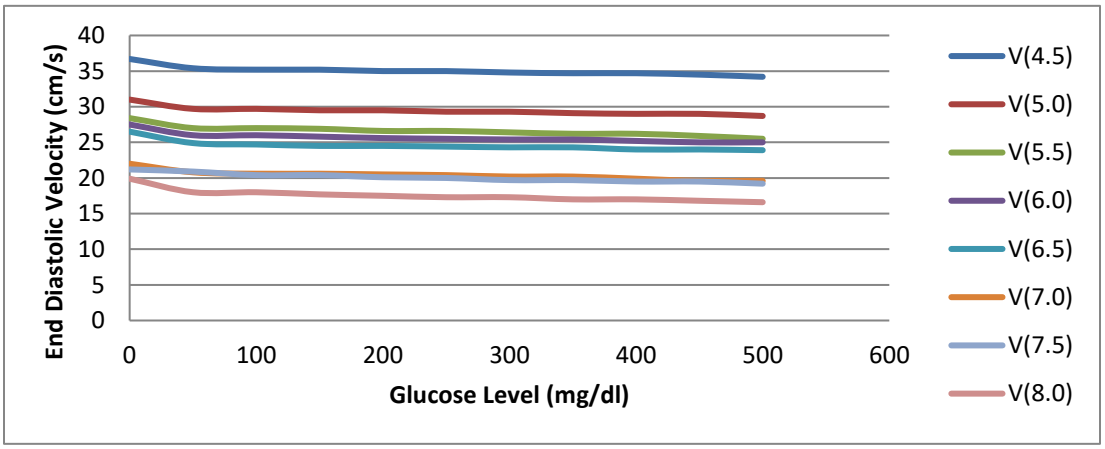


(a)

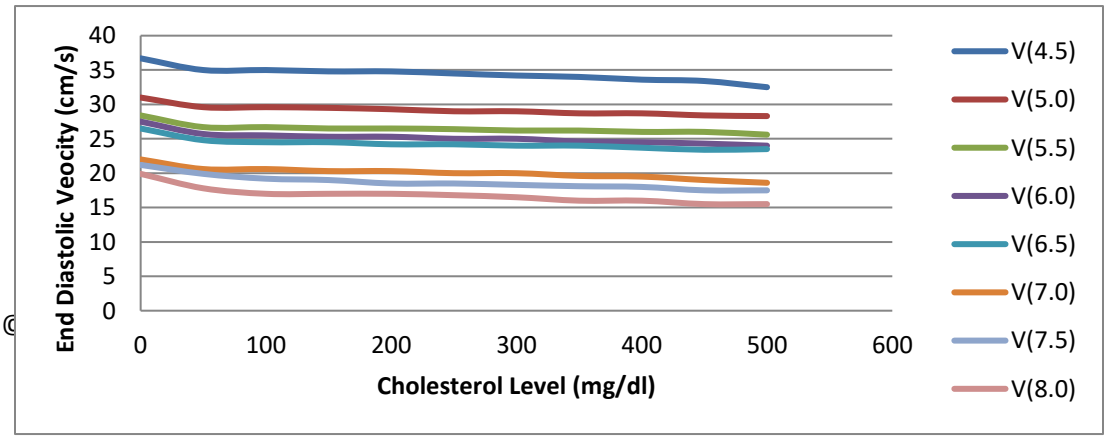


(b)

Figure 3: (a) Variations between Peak Systolic Velocity and glucose level across the lumen diameters from 4.5 mm to 8.0, (b) Variations between Peak Systolic Velocity and cholesterol level across the lumen diameters from 4.5 mm to 8.0 mm



(a)



(b)

Figure 4: (a) Variations between End Diastolic Velocity and Glucose level across the lumen diameters from 4.5 mm to 8.0 mm, (b) Variations between End Diastolic Velocity and Cholesterol level across the lumen diameters from 4.5 mm to 8.0 mm

4.0 Discussion

Atherosclerosis, or hardening of the arteries, developed when too much cholesterol clogged arteries with fatty deposits called plaques. When blood vessels became completely blocked, heart attacks and strokes occur. Diabetes (high blood glucose or sugar) on the other hand increases high blood pressure, which in turn damages the carotid artery walls and making it prone to plagues development (Francine K. Welty, 2013; Minsu *et al.*, 2017; Niki & Dimitri, 2020). The effect of high glucose and cholesterol levels in the blood is a long time effect and does not have any immediate influence on the blood flow velocity in the carotid artery. Hypercholesterolemia, hyperglycemia, high blood pressure and other cardiovascular risk factors cause arterial stiffness, plague formation, increased ITM and increased chances of arterial blockage (Vasudevan *et al.*, 2013; Alvim *et al.*, 2017; Alessandro *et al.*, 2019). The narrowing of carotid lumen diameter by accumulated plaques is the major factor that affects the blood flow velocity and volume flow. This accumulated plaque caused by cholesterol and fatty substances takes years to happen leading to a narrowed lumen (Leticia *et al.*, 2017). The results in this research suggest that high blood glucose and cholesterol levels do not have any significant influence on the velocity of flow in the carotid artery at different lumen diameters since the results of the PSV and EDV values are within the range of acceptable standards (Oqlat, et al., 2018b). Therefore, high glucose or cholesterol levels in the blood (hyperglycemia and hypercholesterolemia) cannot be classified as independent risk factors of stroke because they influenced other major risk factors such as hypertension and atherosclerosis (Virani et al., 2011; Kozakova & Palombo, 2016; Minsu *et al*, 2017).

5.0 Conclusion

In conclusion, this research results suggest that no matter the concentrations of glucose or cholesterol in the BMF samples, the flow parameters were similar to those for healthy arteries. This is because the real human artery is not only affected by glucose and cholesterol concentrations in the blood, but also by their long time effects on the walls of the artery combined with other cardiovascular risk factors.

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Conflicts of interest

There are no conflicts of interest.

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