A Review of Carotid Artery Phantoms for Doppler Ultrasound Applications

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Abstract

Ultrasound imaging systems need tissue-mimicking phantoms with a good range of acoustic properties. Many studies on carotid artery phantoms have been carried out using ultrasound; hence this study presents a review of the different forms of carotid artery phantoms used to examine blood hemodynamics by Doppler ultrasound (DU) methods and explains the ingredients that constitute every phantom with their advantages and disadvantages. Different research databases were consulted to access relevant information on carotid artery phantoms used for DU measurements after which the information were presented systematically spanning from walled phantoms to wall-less phantoms. This review points out the fact that carotid artery phantoms are made up of tissue mimicking materials, vessel mimicking materials, and blood mimicking fluid whose properties matched those of real human tissues and vessels. These materials are a combination of substances such as water, gelatin, glycerol, scatterers, and other powders in their right proportions.

Keywords: Blood mimicking fluid, common carotid artery, Doppler ultrasound, tissue mimicking materials, vessel mimicking materials

INTRODUCTION

Carotid artery structure and function

The human carotid artery is an elastic vessel found on both sides of the neck originating from the brachiocephalic trunk. Each common carotid artery (CCA) bifurcates into the external and internal carotid artery (ICA) (with a bifurcation angle of about 50°), respectively supplying the face and brain with oxygen and nutrients. Blood supply to the face and the brain ensures their normal functions to avoid complications such as stroke and other cardiovascular diseases. The ICA usually has no branching vessels in the neck and supplies oxygen rich blood to the brain, while the external carotid artery (ECA), which supplies the facial musculature, has multiple branches in the neck. The left and the right CCA varies among individuals particularly at the point where the left CCA arises from the aortic arch and the position of the carotid bifurcation located at the fourth or fifth cervical vertebra.[1,2] Like other arteries, the carotid artery is made up of three layers namely: Tunica intima, media and the adventitia, while its relative tissue makeup is about 8% endothelium, 32% elastic tissues, 44% smooth muscle cells, and 16% fibrous tissues.[3,4] The diameters of a healthy human CCA, ICA, and ECA are 6.0 mm, 4.2, mm and 3.5 mm, respectively, with a normal range of 4.3 mm–7.7 mm for the CCA, but women have higher artery diameters compared to men.[5-8] The length of the carotid artery from the aortic arch to the skull base is about 22.2 cm on the right neck and 20.8 cm on the left, while that of the CCA is 13.6 cm on the right and 12.4 cm on the left. Both the CCA and ICA are longer in men than in women most especially in people over 60 years of age.[9] The intima media thickness (IMT) of the carotid artery for a healthy human has a value from 0.5 mm to 0.7 mm while a value ≥1.0 mm is associated with increased risk of cardiovascular complications.[10,11]

Hemodynamics and complications of the carotid artery system

Blood flow information in the carotid artery such as the peak systolic velocity (PSV), end diastolic velocity (EDV),

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resistivity index, pulsatility index, and shear stress are very important indices for assessing a normal or abnormal artery. [12-14] Carotid artery disease occurs when fatty deposits (plaques) clog the blood vessel (carotid artery) that deliver blood to the brain and head, this disease is referred to as atherosclerosis or stenosis. Atherosclerosis is a systemic disease characterized by thickening of the arterial wall with accumulation of cholesterol in the intima which later leads to calcifications. The blockage increases the risk of stroke, a medical emergency that occurs when blood supply to the brain is interrupted or seriously reduced.[15,16] Notable among the risk factors of carotid atherosclerosis are; bad lipids (high low density lipoproteins, triglycerides and low high-density lipoproteins), hypertension, smoking, obesity (high body mass index values), diabetes, physical inactivity, age and recently, snoring.[17,18] These risk factors lead to high value of carotid IMT of >1 mm as a result of formation of calcified plagues within the intima and media of the carotid wall.[19] The plaques keep accumulating and at a certain moment, the growth cannot be compensated anymore resulting in the narrowing of the carotid lumen. A new set of vulnerable plaques then develops containing lipids and calcifications with a thin fibrous cap. When mechanical forces in the cap due to blood pressure and blood flow exceed the maximal strength of the cap, it will rupture leading to thrombus formation into the intracranial circulation. This rupture of the atherosclerotic plague of the carotid artery can result in neurological events such as the transient ischemic attack or ischemic stroke.[20]

Carotid artery phantom

Phantoms are test tools used to simulate different parts of the human systems. They can also be used to test the effectiveness of an ultrasound system, in tutoring ultrasonographers and in conducting researches on new methods of investigating carotid artery diseases.[21-23] The design and construction of a carotid artery phantom takes into consideration, the properties of real human vessels and tissues.[21,24,25] This means that the tissue mimicking material (TMM) and the blood mimicking fluid (BMF) that make up a carotid artery phantom must have values of speed of sound, viscosity, density, attenuation, and backscatter properties close to the internationally accepted standards by the International Electrochemical Commission IEC 6168.[26] Any far departure from this international standard can make the Doppler systems unable to capture the images of stationary, moving objects and fluids.[21,27,28] This study provides a review of relevant carotid artery phantoms used for Doppler ultrasound (DU) measurements which will serve as a quick summary for researchers interested in getting good information on carotid artery phantom fabrications for ultrasound medical applications. The advantages and disadvantages of each phantom have also been reviewed with respect to the above applications.

Search strategy

The search of relevant information on the topic was carried out using research databases such as the Google scholar, PubMed, Web of sciences, and world's largest ebook library (Z-Library). Key words including TMM, vessel mimicking material (VMM), BMF, DU, walled phantoms, and wall-less phantoms were searched using these databases to get recent and vital information on the topic from journals and books after which the information were reviewed. The search was limited to carotid artery phantoms of large and small animals for both CCA and arteries with bifurcations.

WALLED CAROTID ARTERY PHANTOMS

Walled phantoms for DU studies are made up of TMM, BMF, and VMM with acoustic properties close to soft tissues, blood, and vessel wall, respectively.[29-31] This means that for a walled phantom, the BMF flows through the VMM. Flow phantoms developed initially were made up of straight tubes designed using shrinking tubes, tapers, or rods.[32-37]

Straight-tube phantoms

Straight-tube phantoms simulate the CCA of big and small arteries for human beings and animals.

Phantom for velocity error estimation

An example of a flow test simulator was constructed to represent a nonstenosed CCA which used a tube of internal diameter of 7.9 mm with wall thickness of 0.1 mm placed inside a 15 mm TMM medium depth.[38] This phantom was designed to study maximum velocity errors linked with measurements using DU systems. The BMF used has a density and viscosity of 1.02 g/cm³ and 3.6 cs at room temperature, respectively[37] mixed with nylon scatterers of 5 mm diameter.[39] The BMF was passed through the test phantom at a steady flow rate of 7.31 ml/s.[34] The maximum velocity estimation error[40] was calculated using the formula:

$$v_{est-max} = \frac{v_{d-max} - v_{t-max}}{v_{t-max}} \times 100\% \qquad (1)$$

Where v_{d-max} is the highest velocity, while v_{t-max} is the real peak velocity. A positive and negative values for $v_{est-max}$ represents an overestimation error and an underestimation error, respectively. Results from this research suggest that the effects of Doppler angle and intrinsic spectral broadening are the major sources of DU errors and should be the focus of future efforts to improve the accuracy of flow measurements. They found out that the effect of transducer focal depth, intra-transducer, intra-machine, inter-machine, and beam-steering did not significantly contribute to maximum velocity estimation errors. Apart from Doppler angle and spectral broadening as major sources of velocity estimation errors, we suggest that human inexperience in carrying out US measurements could be a major source of error estimation.

Phantom for assessment of wall motion of the artery

A walled phantom was designed to be applied in ultrasound assessment of wall motion of the artery.[41] This phantom was made up of a straight tube representing the CCA and built with a polyvinyl alcohol cryogel (PVA-C) as the VMM enclosed by a TMM made from gelatin. The VMM and TMM were contained in a Perspex tank of length 320 mm,

breadth 100 mm, and width 100 mm connected at the inflow and outflow with a polyvinyl chloride tube, 9.5 mm internal diameter. The BMF was pumped through the phantom with the aid of a magnetic gear pump. The TMM was a combination of 82.3% water, 13.1% gelatin, 3.4% glycerol, and 0.87% CA24 preservative.[42] A Philips HDI 5000 ultrasound scanner was used to obtain tissue Doppler imaging measurements. Results showed that the elastic modulus, acoustic velocity, and attenuation coefficient varied from 57 kPa, 1543 ms^{-1} and 0.18 dBcm^{-1} MHz^{-1} for one freeze-thaw cycle to 330 kPa, 1583 ms^{-1} and 0.42 dBcm^{-1}MHz^{-1} for 10 freeze-thaw cycles respectively. All distension curves exhibited a rapid rise to a peak followed by a decrease in distension as the vessel wall contracted. The results mean that the elastic modulus, speed of sound, and attenuation of the vessel is a function of the number of freeze-thaw cycles. A good vessel made of PVA-C can be obtained at a freeze-thaw cycle numbers from 1 to 10 since the characteristics of the vessel are within acceptable standards.[43-45] However, the effect of viscoelasticity on wall motion of the PVA-C phantom was not measured because the research was to produce physiologic distension waveforms only. The vessel in this research was made of only one layer unlike real human arteries that contains 3 layers since wall motion is centered on the wall at interface with the blood.

Phantoms to test the suitability of different plastics as vessel mimicking material

Another research was conducted by[46] on five plastic materials to find out which of them is more suitable to be considered as a VMM. These materials are Teflon, Urethane-90A, Urethane-75D, Polyethylene of high density and polyethylene with high molecular weight. The acoustic properties of the 5 materials were determined by a pulse–transmission technique[47] at a frequency of 5 MHz. The vessel geometry chosen was a normal CCA with internal diameter of 8.0 mm and 50% stenosis at the bulb area as prescribed by the North American Symptomatic Carotid Endarterectomy (NASCET) criteria.[48-50] The experimental results revealed that Teflon was more suitable to be used as plastic material for flow phantoms because it had the best values for the speed of sound (137 ± 40 ms^{-1}) and attenuation (1.30 ± 0.03 dBcm^{-1} Hz^{-1} at 5 MHz) compared to the other four plastics. Speed of sound is the primary acoustic property while attenuation is a secondary consideration in phantom fabrication.[51] This explains the reason for selecting Teflon over other plastic materials even though its attenuation is higher compared to other materials. Plastic materials with very high speed of sound compared to international standard value (1540 ms^{-1}) results to phantoms with high refraction problems during ultrasound examinations. The phantom fabricated with Teflon in this experiment shows that Teflon provides the best combination of rigidity, reproducibility, and DU compatibility, making it a suitable choice for the fabrication of rigid flow phantoms using a direct-machining method. The Teflon phantom also has the added advantage of an accurate and rapid fabrication process.

Phantoms for assessment of the impact of vessel stiffness on flow dynamics

In this study, three phantoms were made from PVA-C with different stiffness[52] fabricated to have properties of a rubber from cryogel. The solution was made from a combination of 10% PVA powder, 87% deionized water, and 3% of scatterers. The vessel had 6 mm inner diameter, 10 mm outer diameter, and 16 cm length. The phantoms were made by applying 3, 5, and 8 freeze-thaw cycles on the vessels molds to produce 3 phantoms of different stiffness. The speed of sound and attenuation for the 3 phantoms were (1543.2 ms^{-1}, 1.31 dBcm^{-1} MHz^{-1}), (1550.8 ms^{-1}, 1.61 dBcm^{-1} MHz^{-1}), and (1552.1 ms^{-1}, 1.70 dBcm^{-1} MHz^{-1}) for the 3, 5 and 8 freeze-thaw cycles, respectively. These acoustic properties are closed to those of normal arteries.[53,54] Measurements of the PSV and EDV were found to have magnitudes of 55.0 cm/s and 12.3 cm/s, 50.0 cm/s and 13.4 cm/s, and 44.9 cm/s and 14.8 cm/s in ascending order of stiffness. The results show that the acoustic properties and EDV increased with increase in the vessel stiffness, while the PSV decreases. Therefore, the design and fabrication process simulates blood flow in the artery properly. The use of test phantoms with different stiffness actually suggests that arterial stiffness has an impact on flow dynamics such as wall distension, flow pressure, time-dependent flow velocity, and wall share stress. A decrease in wall shear rate was observed for a stiffer vessel, which may result to the pathological development of the endothelial cells in real vessels. The time to achieve peak systolic pressure in the pressure waveform coincided with the time to achieve maximum inner diameter in the wall distension waveform. This indicates that the wall motion and flow pressure occurred at the same time and frequency. For the pulsatile flow, the vessels underwent cyclic dilation and contraction during one cardiac cycle; the time-dependent curves of inner diameter increased from a minimum at end diastole to a maximum at peak systole, and then declined to the minimum. The recorded vessel wall distension waveform of the vessel is similar to that of an asymptomatic CCA.[41] However, the use of micro-bubbles in aqueous solution as working fluid had lesser values of physical properties such as density and viscosity compared to real tissues thereby, influencing the distribution of the velocity flow and the wall share stress.

Walled phantoms with bifurcations (branches)

Phantoms with bifurcations represent arteries that branches into the ICA and ECA from the CCA.

Anthropometric atherosclerotic phantom for ultrasound images

A more robust method for fabricating atherosclerotic phantom was done using better ingredients for producing TMM and BMF.[55] Computer-aided manufacturing (CAM) software was used to realized a 3-D carotid artery phantom from which a mold was modeled consisting of an outer vessel mold (ABS plastic) and an inner core (soluble filament) to produce the artery lumen. This method was used to produce two other

phantoms with hyper echoic or hard plaques (30% stenosis) and hypo echoic or soft plaques (65% stenosis). The composition of the VMM, TMM and BMF are summarized in Tables 1-3. The TMM ingredients were cooked until at 96 ± 3°, then allowed to cool down to 42°C before, it was poured in a box containing the vessel phantom and left to solidify at about 20°C.[7] Brightness-mode (B-mode) images of the longitudinal and radial sections of the healthy, hard and soft plaque phantoms properly simulate the lumen diameter of the real CCA, IMT and other hemodynamic indices comparable to normal arteries. This method of fabrication of anthropometric walled phantoms is very flexible, reproducible, less expensive, allows the study of cardiovascular diseases and provides extremely realistic ultrasound-based investigations.

Silicone-cellulose vessel phantom

A phantom was constructed with silicone as the VMM[47] while cellulose particles were added as scatterers to test for the acoustic properties with ultrasound B-mode technique. The TMM was a combination of aluminum oxide (Al_2O_3) and silicon carbide (SiC) to achieve the attenuation and backscatter properties,[7,56] a high-gel strength agar[37] and formaldehyde as a preservative.[50,57] The BMF used in this

work was the one described by Ramnarine and others.[39] The vessel geometries used in fabricating this phantom were to simulate a carotid artery with bifurcation established by[49] which consisted of a lost-material casting technique to create two molds with the required carotid dimension.[50,58] The plaques were introduced by injecting more elastic polymer around the bulb of the ICA where soft and hard plaques were achieved by changing the quantity of scatterers in relation to the TMM and VMM. These procedures produced healthy or normal phantom and a stenos phantom with 60% stenosis at the ICA bulb. Both the TMM and VMM had acoustic attenuations of 0.56 dB cm^{-1} MHz^{-1} and 3.5 dB cm^{-1} MHz^{-1} at 5 MHz respectively, with nearly linear frequency dependence. Their acoustic velocities were 1539 ± 4 ms^{-1} and 1020 ± 20 ms^{-1} respectively. The phantoms showed excellent physical stability over time with no gross changes observed over a 2-year period with no swelling, bulging, or sagging in the silicone vessels. The major advantage of this method is that it allows for the fabrication of various levels of plaques and flexible to being modeled with different shapes and sizes. The phantom is robust, durable and provided good ultrasound measurements that matched that of the human carotid arteries.

Table 1: Percentage composition of substances used to prepare vessel mimicking material and their uses in anthropometric atherosclerotic walled phantom

Name of substance	Percentage composition	Role of substance
De-ionized water	79.5	To serve as a solvent
PVA powder	10.0	For gel formation
Glycerol	10.0	To increase sound speed
Aluminum oxide powder	2.0	To serve as scattering particles
Benzalkonium chloride	0.05	To serve as anti-fungal agent

PVA: Polyvinyl alcohol

Table 2: Percentage composition of substances used to prepare tissue mimicking material and their uses in anthropometric atherosclerotic walled phantom

Name of substance	Percentage composition	Role of the substance
De-ionized water	82.97	To serve as a solvent
Glycerol	11.21	To measure the acoustic properties of the tissue
High gel-strength agar	3.0	For gel formation
Silicon carbide	0.53	To serve as scatter particles
Aluminum oxide (3 μm)	0.94	To serve as scatter particles
Aluminum oxide (0.3 μm)	0.88	To serve as scatter particles
Benzalkonium chloride	3.0	To serve as a preservative

Table 3: Percentage composition of substances used to prepare blood mimicking fluid and their uses in anthropometric atherosclerotic walled phantom

Name of substance	Percentage composition	Role of substance
Distilled water	83.86	Mimic the water component of blood
5μm Orgasol particles (2001 UDNAT1 Orgasol, ELF Atochem)	1.82	Used as scatters
Glycerol	10.06	To ensure appropriate density and speed of sound
Sigma D4786 dextran of average mw 150000D	3,36	To increase the solution viscosity
Synperonic A7 surfactant (Croda Health Care)	0.9	To serve as surfactants

Phantom for the study of wall motion and flow dynamics

Walled carotid artery phantoms for studying vessel wall motion and flow dynamics were fabricated with the aid of a computer and printing technology.[59] The geometry consisted of CCA with 6-mm diameter, ICA with 4.2-mm diameter and ECA with 3.5-mm diameter taking on a tuning fork model[50] with a thickness of 1.5 mm. The vessel branch parameters were defined such that they were in line with the mean carotid artery diameter of adults.[5] The vessel cores for carotid bifurcation models were made up of healthy and diseased geometries (25%, 50%, and 75% stenosis). The VMM mixture consisted of 86.7% distilled water, 10% PVA powder, 3% graphite with particle diameter <20 μm, and 0.3% potassium sorbate, which served as an antimicrobial agent. The mixture was prepared in solution form at 90°C under a double-boiler configuration and left to cool and settle for at least 12 h for easy degassing. The TMM was composed of 94.45% distilled water, 1.5% agar, 3.75% gelatin, and 0.3% potassium sorbate preservatives. This mixture was made in solution form at 90°C and after cooling to about 45°C; it was poured into an open volume of the phantom box and allowed to set at room temperature for 6 h to form a congealed slab. The BMF was a solution of nylon scatterers.[39] Test results conducted using the phantoms showed that the materials used in the fabrication process exhibit strong acoustic and physical compatibility for use in ultrasound imaging experiments more than the previously discussed phantoms. The speed of sound and attenuation for the TMM and VMM were 1510 ± 1.3 ms^{-1}, 0.145 ± 0.027 dBcm^{-1} MHz^{-1} and 1535 ± 2.4 ms^{-1}, 0.229 ± 0.032 dBcm^{-1} MHz^{-1}, respectively. The phantom can suitably be used to carry out imaging of wall motion and flow dynamics using ultrasound methods. Several other studies on *in vitro* blood flow took their methods for fabricating walled human carotid artery phantoms from the above discussed methods[60-63] with the aid of CAD and 3-D printing technology. More applications of PVA-C and agar-based mixture for VMM, TMM, and BMF are found in arterial phantoms with regional variations in wall stiffness and thickness.[64,65]

WALL-LESS CAROTID ARTERY PHANTOMS

Unlike walled phantoms, wall-less phantoms have their TMM in direct contact with the BMF.[7] They have the advantage of low attenuation coefficients and eliminating problems associated with different values of impedance between the tissues involved.[66] However, wall-less vessels may be exposed to changes when the TMM is exposed to air or water.

Phantom constructed to solve problems of high absorption, reflection, and scattering associated with walled phantoms

A wall-less test object was fabricated[37] to solve the problems of high rate of absorption, reflection and scattering common with walled phantoms. To achieve the purpose of this research, two types of vessel were investigated: A wall-less vessel and latex rubber tubing. The wall-less vessel phantom was formed by sliding an aluminum mandrel (outside diameter of 0.63 cm)

inside the inlet and outlet tubes. Molten TMM was then poured into the Plexiglas box and allowed to harden before the mandrel was removed. The TMM was a mixture of distilled water with 3% (by mass) of high strength agar gel, Glycerol and 50μm cellulose scatterers were used instead of graphite to provide the desired acoustic attenuation.[67] The BMF was made up of 50% distilled water and 50% machine cutting fluid to increases the viscosity of the blood mimic and also serve as a lubricant for the pump. Nylon particles, with a mean diameter of 10 m were added to provide ultrasonic scattering sites. The acoustic attenuations of the TMM, VMM (latex rubber) and BMF were 4.8 ± 0.1 dBcm^{-1} MHz^{-1}, 42.5 ± 1 dBcm^{-1} MHz^{-1} and 2.0 ± 0.05 dBcm^{-1} MHz^{-1} respectively. The speeds of sound were respectively 1535 ± 2 ms^{-1}, 1550 ± 5 ms^{-1}, and 1560 ± 1 ms^{-1} for the TMM, VMM, and BMF. B-mode images of the vascular phantoms showed lack of bright reflections on the top and bottom of the wall-less vessel which indicates that the impedances of the blood mimic and tissue mimic are closely matched. In addition, there was no any shadowing due to excess attenuation. However, the latex-wall vessels showed a large degree of shadowing due to the attenuation of the latex as well as bright spots on the top and bottom of the vessels between the VMM and BMF interfaces, indicating an impedance mismatch. These observations mean that the wall-less phantom had no artifacts problems while the severe shadowing observed in the thin-wall and thick-wall latex phantoms was an indication of artifacts problems. Therefore, wall-less phantoms solved the problems of absorption, reflection, scattering, and impedance mismatches common with walled phantoms.

Agar-based common carotid artery wall-less phantom

About 20 years ago, advancements in the methodology for creating wall-less phantoms were carried out. One of such flow phantoms was designed with an agar-based TMM.[7] It was made up of 82.97% water; 11.21% glycerol; 0.46% Benzalkonium Chloride; 0.53% 400 grain SiC powder; 0.94% of 3 mm Al_2O_3 powder; 0.88% of 0.3 mm Al_2O_3 powder; and 3.00% Struers agar for rigidity. These components were heated in a double boiler at 96°C for about an hour and then allowed to cool down to 42°C with continuous stirring before finally pouring it into the container holding an 8-mm diameter straight rod. Reticulated foam of pore size 1–2 mm was fixed using Araldite adhesive around the inside and outside of the large inlet and outlet acrylic tubes. This was done to prevent the BMF from leaking and to provide good rigid support to the small acrylic tubes for attachment to the flow circuit tubing. After the casted TMM had set and cooled, the rod was carefully removed allowing a hollow lumen for passage of the BMF (1.82% of 5 m Orgasol particles; 83.86% of pure water; 10.06% of glycerol; 3.36% of Sigma D4876 dextran 185000D; and 0.9% surfactant). All measurements of flow rates, velocities, attenuation, and back scatter properties of the TMM and BMF using this phantom made the standard requirements by the International Electrochemical Commission.[26] With continuous flow for some days, there

was no leaking observed except for high backscatter signals possibly due to air bubbles and improper mixing during the preparation process. However, agar-based wall-less phantoms suffered from the limitation of rupture at high flow rates because of their shallow depths.

Konjac-carrageenan-based tissue mimicking material wall-less phantom

Studies on the use of konjac and carrageenan as constituents for preparing TMM was carried out by.[68] They found these powders suitable for gel formation with applications in both walled and wall-less phantoms at high frequencies of 5–60 MHz. This new recipe was used to construct phantoms with femoral artery (1 mm diameter) and CCA (2 mm diameter) of rats.[69] Other components of the TMM are summarized in Table 4. The prepared TMM with acceptable velocity of sound and attenuation was poured into the container of dimensions 10 cm × 10 cm × 23 cm and allowed to set very well. A BMF[39] was pumped through the phantom using a gear pump. Acoustic properties were characterized using two methods; a broadband reflection substitution technique using a preclinical ultrasound scanner (Vevo 770, FUJIFILM VisualSonics, Toronto, ON, Canada), and a dedicated high-frequency ultrasound facility developed at the National Physical Laboratory (NPL, Teddington, UK), which employed a broadband through transmission substitution technique. The mean speed of sound across the measured frequencies was found to be 1551.7 ± 12.7 ms^{-1} and 1547.7 ± 3.3 ms^{-1} for the two methods respectively. Attenuation was found to increase as a function of frequency fitting the polynomial functions $0.01024f^2 + 10.3639f$ ($R^2 = 0.99$) and $0.009787f^2 + 0.2671f$ for the two methods. The phantom was suitable and useful for preclinical ultrasound applications.

A similar research was conducted using konjac-carrageenan (KC) recipes in fabricating wall-less phantoms for DU imaging.[70] They produced two phantoms; the first one is made of potassium chloride while the second consists of agar for the TMM preparation with diameters of a Rat (1 mm) and a Mouse (0.5 mm), respectively. The test phantoms were characterized to give good values of speed and attenuation. These values matched those of soft tissue, arterial wall, and blood which are relevant considerations for studies involving measurements of diameter, maximum velocity, mean velocity, wall shear rate, and volumetric flow.[69] The KC-TMM has a limitation of not being used for a long time because anti-fungal agent could not be added as its application affected the acoustic properties of the TMM.

Konjac-carrageenan-gelatin-based tissue mimicking material wall-less phantom

An improvement on the KC-based TMM test phantom was put forward by adding gelatin from bovine skin to form KC-gelatin-based phantom which resulted to a speed of sound and attenuation of 1533 ± 2 m/s and dB/cm. MHz respectively.[71] This wall-less test object simulates the CCA of a healthy human with a diameter of 8 mm produced from a straight, hard metallic rod mold inserted is a transparent acrylic box (260 mm × 120 mm × 90 mm). The new TMM composition is well explained by[72] while the new BMF used was as discussed by.[73] The phantom is very flexible, robust, elastic and strong; it can be used and stored for a very long time because addition of anti-fungal agent did not affect the acoustic properties of the TMM. The acoustical properties (speed of sound and attenuation) of the TMM were 1533 ± 2 ms^{-1} and 0.2 dBcm^{-1}. MHz^{-1} respectively which agreed with the IEC 61685 standards. In addition, the velocity percentage errors decreased with increase in the Doppler angle in which the lowest % error (3%) was recorded at 53°. The gelatin from bovine skin was a good match with KC that enhanced the strength of TMM without rupture at high flow of 2000 ml/min. PVA-cryogel has also found important applications in producing wall-less TMM phantoms even though the phantoms may not be as robust as KC-based and KC-gelatin based wall-less phantoms.[74] The KC-gelatin based wall-les phantom has found useful applications involving simulating the human CCA (8 mm diameter) to carry out research using DU Color-Mode and MotionMode systems.[75]

COMMERCIAL DOPPLER FLOW PHANTOMS

Commercial phantoms are specially designed to test for the efficiency and efficacy of imaging systems and other medical ultrasound applications. They can be used in the investigation of flow-field velocity data and associated phenomena using particle image velocimetry (PIV) and laser Doppler anemometry. Validation of flow-field data obtained using medical imaging such as the magnetic resonance imaging (MRI) and ultrasound to measure blood velocity

Table 4: Constituents of Konjac-Carrageenan based tissue mimicking material for wall-les phantom

Name of substance	Percentage composition	Function
De-ionized water	84.0	Serves as a solvent
Silicon Carbide	0.53	Serves as scatters
Al$_2$O$_3$ powder (3 μm)	0.96	Serves as scatters
Al$_2$O$_3$ powder (0.3 μm)	0.89	Serves as scatters
Konjac powder	1.5	For gel formation
Carrageenan powder	1.5	For gel formation
Potassium chloride	0.7	To fertilize the TMM
Glycerol	10.0	To mimic the acoustic properties of the tissue

TMM: Tissue mimicking material

and associated quantities can be carried out with the aid of commercial flow phantoms. These phantoms are made as straight tubes with and without tissue equivalents, planar bifurcations with and without tissue equivalents and nonplanar bifurcations with and without tissue equivalents.[76] Majority of phantoms constructed for sale are used in the quality control application while in-house phantoms are fabricated by research groups to meet specific experimental and development purposes. In both cases, TM materials are most likely to be based on gelatin materials, from recipes that have been empirically found to control sound speed, attenuation, and backscatter properties.[77] Table 5 shows a summary of both

Table 5: Summary of locally and commercially made Doppler flow phantoms with their fabrication materials, geometry, pathology and flow rates

Authors	VMM composition	TMM composition	BMF composition	Flow rare	Pathology	Geometry	Wall	Origin
Hoskins *et al.*, 1998[78]	Shrink tube	-	Water, glycerol, sephadex	1.37 ml/min	Healthy	PS	TW	CM
Tewart 2001[79]	Rubber tube	-	Blood analog fluid	-	Healthy	AG	TW	CM
Evan and James1988[80]	Latex rubber	Water-based gel, graphite	Degased water, glycerol, polystyrene microsphere	500 ml/min	Healthy	PS	TW	CM
Rickey *et al.*, 1995[37]	Latex rubber	Water, high strength agar, cellulose particles	Water, machine cutting fluid, nylon	6.825 ml/s	Healthy	PS	TW, wall-less	HM
Guo and Fenser 1996[35]	-	Water, high strength agar, glycerol, cellulose particles	Water, machine cutting fluid, Pulverised nylon	2-18 ml/s	Stenosis	PS	Wall-less	CM
King *et al.*, 2010[81]	Plastic tubing	Agar-based	Water, glycerol	-	Stenosis	PS	TW	CM
John and Kevin 2010[82]	Electronic phantom	-	-	-	Healthy	AG	-	CM
Steinman *et al.*, 2001[38]	Latex tube	Water, high strength agar, cellulose particles	Water, machine cutting fluid, nylon	7.31 ml/s	Healthy	PS	TW	HM
Dineley *et al.*, 2006[41]	PVA-C	Water, glycerol, gelatin,	Water, glycerol, dextran, surfactant	320 ml/min	Healthy	PS	TW	HM
Wong *et al.*, 2008[46]	Teflon	-	Water, glycerol, dextran, surfactant	5 ml/s	Healthy, stenosis	PS	TW	HM
Qian *et al.*, 2014[52]	PVA-C	Synthetic tissue	Aqueous micro bubbles	15 ml/s	Healthy	AG	TW	HM
Galluzzo *et al.*, 2015[55]	PVA-C	Agar-based	Water, orgasol, glycerol, dextran, surfactant	-	Stenosis	PS	TW	HM
Poepping *et al.*, 2002[58]	Silicone, cellulose	Agar-based	Water, glycerol, dextran, surfactant, nylon	24 ml/s	Stenosis	PS	TW with BF	HM
Chee *et al.*, 2016[59]	PVA-C, graphite particles	Agar-gelatin based	Nylon scatter solution	6.5 ml/s	Healthy, stenosis	PS	TW with BF	CM
Ramnarine *et al.*, 2001[7]	-	Agar-based	Water, orgasol, glycerol, dextran, surfactant	2000 ml/min	Stenosis	PS	Wall-less	HM
Kenwright *et al.*, 2015[69]	-	Konjac-carrageenan	Water, glycerol, dextran, surfactant, nylon	-	Healthy	AG	Wall-less	HM
Zhou *et al.*, 2017[70]	PVA-C	Agar-based, Konjac-carrageenan	Water, glycerol, orgasol, dextran, Synperonic N	-	Healthy	AG	TW, wall-less	HM
Ammar *et al.*, 2018[70]	-	Konjac, carrageenan and gelatin from bovine skin	Water, propylene, polyethylene glycol, polystyrene microsphere	2000 ml/min	Healthy	AG	Wall-less	HM

AG: Average geometry, PS: Patient specific, HM: Homemade, CM: Commercial, TW: Thin walled, TMM: Tissue mimicking material, VMM: Vessel mimicking material, BMF: Blood-mimicking fluid

commercial and locally made or homemade Doppler flow phantoms with their fabrication materials, geometry, pathology, flow rates, and manufacturing process.

In vitro researches using carotid artery phantoms for studying the degree of stenosis have concentrated their studies on the use of PSV in the ICA as one of their primary considerations for plaque assessment. Future researches should involve the CCA PSV to estimate the degree of stenosis by fabricating a multi-lumen diameter CCA phantom to establish a relationship between PSV and lumen diameter of the CCA. This relationship can be used to estimate the level of stenosis using PSV in the CCA at whatever level of lumen reduction. A human blood has cholesterol and glucose as part of the components of its plasma and serum. Previous *in vitro* studies using BMF does not involve cholesterol and glucose as part of the chemical items needed in its preparation; hence, the need to have a new BMF with these substances for DU analysis of blood flow in the carotid artery is important. Furthermore, future *in vitro* research should consider BMF that are hyperglycemic and hypercholesterolemic to find out the effects of hyperglycemia and hypercholesterolemia on the hemodynamic indices of flow in the carotid artery. Not many wall-less carotid artery phantoms with bifurcations have been found in the course of this review. Hence, future wall-less phantom fabrications should include bifurcation into the ICA and ECA for good comparison with walled phantoms. The TMM composition for walled and wall-less phantom reviewed involved the use of aluminum oxides, silicon carbide, gelatin, conjac roots, carrageenan powder, glycerol and other usual items. More research is needed to include new and available chemicals such as superdex and other chemicals as scartterers.

This study has limitations. Our search was limited to articles published between 1999 and 2020, although we are aware that the development and use of carotid artery phantoms date further back. The review only discusses carotid artery phantoms involving walled and wall-less phantoms, mostly for DU applications. It does not involve phantoms of other types of arteries and those for MRI, PIV and computed tomography applications. The review focuses on fabrication methods, chemical material items for the production of TMM, VMM, BMF, phantom molds, and box. It is limited to DU applications on carotid artery assessment of arthrosclerosis using flow information by simulations.

Conclusion

This review provided concise information on the items and processes of fabricating carotid artery phantoms for DU measurements. A summary on how to construct walled and wall-less carotid artery phantoms have been discussed ranging from substances such as TMM, VMM, BMF, and other materials required to produce the phantom box and molds. A complete carotid artery phantom must be made up of these three substances that closely mimic real tissues, vessels and blood with their acoustic and physical properties meeting the approved internationally accepted standards.

Conflicts of interest

There are no conflicts of interest.

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