**A review of arterial phantom fabrication methods for flow measurement using PIV techniques**

**Running title: Fabrication techniques for haemodynamic PIV flow measurement**

Mr Sina G. Yazdi; BSc, MSc

PhD candidate, Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand

Email: sina.ghafoorpooryazdi@pg.canterbury.ac.nz

Dr P. H. Geoghegan; MEng, PhD

Lecturer, School of Life & Health Sciences, Aston University, Birmingham, England

Email: p.geoghegan@aston.ac.uk

Dr P. D. Docherty;BE, PhD

Senior Lecturer, Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand

Email: paul.docherty@canterbury.ac.nz

Corresponding author Mechanical Engineering

University of Canterbury

Private Bag 4800

Christchurch 8140

New Zealand

Phone: +64 3 3692230

Dr Mark Jermy;BSc MSc PhD

Associate Professor, Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand

Email: mark.jermy@canterbury.ac.nz

Dr Adib Khanafer; MBBS, FRCS, FRCS

Specialist, Vascular, Endovascular, & Renal Transplant Unit, Christchurch Hospital, Christchurch, New Zealand

Email: Adib.Khanafer@cdhb.health.nz

**Abstract**

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in the western world. In the last three decades, fluid dynamics investigations have been an important component in the study of the cardiovascular system and CVD. A large proportion of studies have been restricted to computational fluid dynamic (CFD) modelling of blood flow. However, with the development of flow measurement techniques such as particle image velocimetry (PIV), and recent advances in additive manufacturing, experimental investigation of such flow systems has become of interest to validate CFD studies, testing vascular implants and using the data for therapeutic procedures. This article reviews the technical aspects of *in-vitro* arterial flow measurement with the focus on PIV. CAD modelling of geometries and rapid prototyping of moulds has been reviewed. Different processes of casting rigid and compliant models for experimental analysis have been reviewed and the accuracy of construction of each method has been compared. A review of refractive index matching and blood mimicking flow circuits is also provided. Methodologies and results of the most influential experimental studies are compared to elucidate the benefits, accuracy and limitations of each method.

**Key words:** Particle image velocimetry; manufacturing; in vitro experimentation; experimental fluid dynamics; haemodynamics; cardiovascular disease

# Introduction

The cardiovascular system pumps blood through a complex network of blood vessels that extend throughout the body transporting nutrients and oxygenated blood [64](#_ENREF_64). Despite considerable clinical development and public education, cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the western world [168](#_ENREF_168). According to the world health organization (WHO), 17.5 million people died from CVD in 2012, representing 31% of all global deaths [177](#_ENREF_177). The leading cause of CVD is atherosclerosis [160](#_ENREF_160). Atherosclerosis is the accumulation of fatty substances such as cholesterol and fibrin within the arterial wall (the intima) forming a “plaque” which leads to a narrowing of the lumen and reduction in the arterial compliance (increased arterial stiffness). Progression of atherosclerosis and plaque rupture can cause arterial occlusion and thus organ failure due to hypoxia. Coronary artery occlusion inhibits blood flow to the heart and causes potentially fatal myocardial infarction. The loss of blood supply to the brain causes a stroke, which is also potentially fatal [171](#_ENREF_171). Treatments for atherosclerosis include change in lifestyle, medications, stenting, endarterectomy and-or bypass surgery [16](#_ENREF_16), [50](#_ENREF_50), [185](#_ENREF_185).

Fluid dynamics has played an important role in investigating the flow characteristics in the cardiovascular system to provide insight into the disease condition, disease progression and therapeutic optimisation [34](#_ENREF_34), [41](#_ENREF_41), [78](#_ENREF_78), [91](#_ENREF_91), [97-99](#_ENREF_97), [118](#_ENREF_118), [124](#_ENREF_124), [125](#_ENREF_125). Lumped parameter modelling, computational fluid dynamics (CFD), *in-vitro* experiments, high resolution computerized tomography (CT) scans and magnetic resonance imaging (MRI) all have been utilised to further knowledge of CVD [2](#_ENREF_2), [46](#_ENREF_46), [55](#_ENREF_55), [158](#_ENREF_158). However, although these methods are currently under investigation and recent outcomes have been promising [32](#_ENREF_32), much research is needed to further establish and validate their use as a standard practice. There lacks consensus on the optimum ways to treat CVD, and thus treatment can vary significantly across clinicians [130](#_ENREF_130), [167](#_ENREF_167). Quick optimisation of implant design and model-based algorithms for hemodynamic control could potentially be achieved via *in-vitro* analysis of modelled arteries.

To date, there have been many *in-vitro* studies of hemodynamics [24](#_ENREF_24), [28](#_ENREF_28), [42](#_ENREF_42), [49](#_ENREF_49), [66](#_ENREF_66), [83](#_ENREF_83). *In-vitro* studies use a physical representation of the artery with measurements of forced flow to capture key hemodynamic properties. There are many methods for manufacturing the physical representations and many measurement techniques used. However, manufacturing and measurement limitations in *in-vitro* studies lead to compromises that limit the applicability of the outcomes for clinical use. In particular, assumptions regarding flow behaviour, boundary condition stiffness, simplified blood rheology and inaccurate vessel geometry mitigate clinical value of many findings or recommendations. Therefore, the aim of this article is to review different aspects of *in-vitro* flow visualization studies of the cardiovascular system that use PIV and ultrasound methods.

PIV and stereoscopic PIV (SPIV) have been used extensively and successfully to investigate medical and physiological phenomena such as arterial haemodynamics and respiratory mechanics. In particular, PIV has been used to successfully investigate the haemodynamics of stented and non-stented aneurysms [40](#_ENREF_40), [139](#_ENREF_139), [182](#_ENREF_182). [Deplano, et al. 40](#_ENREF_40) noted the benefit of compliant phantoms to capture physiological flow fields and [Raschi, et al. 136](#_ENREF_136) used PIV to validate CFD analysis of a cerebral aneurysm. SPIV has also been used to provide insight into flow fields generated by high flow therapy on the geometrically complex nasal cavity [156](#_ENREF_156), [157](#_ENREF_157). [Augsburger, et al. 6](#_ENREF_6) studied the influence of different commercial haemodynamic flow diverters using PIV. [Roszelle, et al. 144](#_ENREF_144) used SPIV for the investigation of the flow characteristics in a cerebral aneurysm and the effect of stenting. Haemodynamics during cannulation and the effect of cannula position on haemodynamics have also been investigated with PIV [79](#_ENREF_79), [90](#_ENREF_90), [105](#_ENREF_105), [107](#_ENREF_107). Charonko investigated four drug-eluting stents XIENCE V® (Abbott Vascular), TAXUS® Liberté® (Boston Scientific), Endeavor® (Medtronic), and Cypher® (J&J Cordis) and a bare-metal stent VISION® (Abbott Vascular) in a compliant model of the coronary artery using Time-Resolved PIV [28](#_ENREF_28). Further experimental haemodynamics studies conducted using different PIV techniques can be found in Table 1 and Table 2.

The objective of this article is to review the state of the art in geometry construction and preparation from medical imaging, rapid prototyping of the rigid and compliant phantom, flow circuit mimicking, and experimental analysis.

# Phantom Construction

Generally the fabrication of phantoms can be subdivided in to three major steps:

1. Definition of a 3D model
2. Mould manufacture and casting
3. Extraction and commissioning

The methods used to undertake these steps vary significantly across studies. Therefore the feasibility, application and accuracy of different techniques will be investigated.

## Geometry construction

The first step of any computational or experimental study of hemodynamics, is to have a 3D model which mimics the blood domain. Two approaches can be used to prepare the 3D model: idealised or patient specific.

### Generalized geometries

Blood vessels are not homogeneous in diameter or wall thickness. Furthermore, bifurcations provide additional geometric complexity. In many computational and experimental studies, simplified geometries of the arterial system have been considered. Common simplifications include, isotropy, constant diameter, reduced or eliminated curvature, constant wall thickness, adjustment of bifurcation angle and elimination of bifurcations [27](#_ENREF_27), [93](#_ENREF_93), [170](#_ENREF_170). For instance, [Shipkowitz, et al. 150](#_ENREF_150) conducted numerical simulation of the abdominal aorta considering constant diameter defined by the average measured diameter in the vessel. [Paul, et al. 120](#_ENREF_120) considered a rectangular channel to investigate flow in a stenosis. This approach enables modulation of certain characteristics to allow generalizable understanding of certain flow phenomena. For example, [Nguyen, et al. 113](#_ENREF_113) investigated the effect of the carotid geometry on blood flow using an idealized model and showed that out-of-plane angle and bifurcation angle resulted in a reduction of wall shear stress (WSS) and increased the risk of plaque formation. Different CAD software can be utilized for designing ideal geometry such as, SolidWorks, CATIA, Geomagic, Amira etc. While many studies took advantage of medical images for construction of the patient specific geometry, simplified models are also used for experimental flow modelling and experimentation. The detail of the studies that used idealized or patient specific geometries, different segmentation software and medical imaging techniques is reviewed in Table 1 and Table 2.

### Patient specific geometry

Different medical techniques for extracting patient specific geometries have been previously reviewed by [Geoghegan, et al. 56](#_ENREF_56) including MRI and CT scanning. It was found that after image post-processing, MRI scan data provides the best image contrast when extracting arterial geometries. The first stage in extracting a 3D arterial geometry is segmentation and surface interpolation. Segmentation uses pixel intensity to differentiate between different types of human tissue in each 2D image slice obtained using MRI. Manual segmentation is possible, but it is time consuming and subject to operator variability. Therefore, automatic methods are preferable [31](#_ENREF_31). A complete review of different segmentation techniques can be found in [Withey and Koles 174](#_ENREF_174).

Once segmentation is complete on each slice, an interpolation is performed between segmented regions in neighbouring slices to produce a 3D geometry. Medical image segmentation and interpolation is possible via various software packages such as Materialise Mimics®, AMIRA, 3D-Doctor. The final reconstructed geometry is likely to have a course wall surface which is an artefact of the resolution quality of the MRI. Different software can be used to improve the surface quality, i.e. Materialise 3MaticTM, MeshLabTM and MeshMixer. [Geoghegan, et al. 56](#_ENREF_56) used both 3Matic and MeshLab for their surface enhancement and reported that 3Matic was faster and produced smoother surfaces. When the geometry is free of all observable defects, it is converted to a standard STereoLithography (stl) file and can be used in additive or subtractive computer aided manufacture.

## Cast manufacture

Aycock et al. [7](#_ENREF_7) recently showed that rigid phantoms can be directly printed with an inkjet 3D printer using transparent resin. However, most transparent 3D printing resins have a relatively high refractive index (RI) (~1.47-1.51) and thus require uncommon, high-RI working fluids to avoid the need for numerical correction [154](#_ENREF_154). The resins are also generally stiff and thus cannot generate compliant geometries that accurately mimic haemodynamics [154](#_ENREF_154).

The most common current method for arterial phantom manufacture is lost core casting. In lost core casting, silicone or similar can be formed around a sacrificial male mould for a rigid model, or thin walled compliant phantoms can be manufactured.

### Male mould construction

For *in-vitro* experimentation, phantoms are often constructed from silicone that is shaped using moulds. A male mould forms the lumen of the vessel. The phantom material is generally applied to the male mould surface in liquid form and sets to a solid. The male mould is typically destructively removed once the phantom material has cured.

After construction of the 3D model, the next step is mould prototyping. In general, many rigid or compliant phantom fabrication studies have a negative mould of the lumen geometry prototyped from the 3D model. Negative (male) moulds can be constructed utilizing 3D printer techniques. Different printer types such as Selective Laser Sintering (SLS), Laminated Object Manufacturing (LOM), Fused Deposition Modelling (FDM), Polyjet/Solid Ground Curing (SGC), Three dimensional printing (3DP) and Ink Jet printing techniques [30](#_ENREF_30) can be used for this process. All of these methods use a layering approach to develop the model. Polyjet/SGC, and SLS use light to fuse plastic and metal particles, respectively to successful layers of the model. LOM glues successive layers of shaped plastic to form the model. Inkjet printing uses adhesive to bind layers of powder to form the model. 3DP covers a range of practices where layers of the models are developed via deposition of various working mediums including plaster, glue, starch, epoxy, etc. FDM is a subset of 3DP which uses polymer deposition. A comparison of different additive manufacturing techniques is given by [Gross, et al. 63](#_ENREF_63) and [Kalpakjian, et al. 77](#_ENREF_77).

In the FDM printer, the model is fabricated by extrusion of a semi-molten thermoplastic filament or wax material through a nozzle and the cross sectional geometry is plotted layer by layer with typical thickness of 0.25 mm. The nozzle has a heater that keeps the build material above melting point ensuring easy flow. Once the material is deposited, it hardens promptly. Different materials are available for FDM printing, including ABS (Acrylonitrile Butadiene Styrene), polycarbonate (PC), polyphenylsulfone (PPSF), PC-ABS blends, wax blends, and PC-ISO [115](#_ENREF_115). FDM requires a scaffolding material to support the build material. In general, two types of support material are available; mechanically removed materials and dissolvable materials. Mechanical removal of material can often require heating and mechanical force that can lead to damage of the build structure [161](#_ENREF_161). For dissolvable materials, a tank and solution of heated water or acetone is required. One of the common water soluble support materials for Stratasys® FDM printing machines is WaterWorks. Some applications have used WaterWorks as build material and ABS as scaffold [173](#_ENREF_173), [180](#_ENREF_180). This facilitates the removal process without damaging the phantom.

The advantage of FDM rapid prototyping is that it is less expensive than other forms of 3D printing. However, the FDM resolution along the z-axis is low (0.25 mm) when compared with other additive manufacturing techniques [176](#_ENREF_176). Therefore, the final printed model has a layering affect that can cause unacceptable surface roughness in the final phantom (Figure 1), requiring surface refinement post-print.



Figure 1. Surface ripples of the FDM printed model.

Polyjet printers, are similar to the inkjet printing system. A photopolymer build material exits the printer on a build tray and is cured with UV light. Model support is provided by a gel type material, which is removed with a water jet with a smooth final surface finish [151](#_ENREF_151). The final resolution is higher than FDM with a layer thickness of 16-30 µm and in-plane resolution of 42 *µ*m [54](#_ENREF_54). This technology offers a wide range of materials and the ability to mix different materials together. [Murugesan, et al. 110](#_ENREF_110) compared the accuracy of three different rapid prototyping techniques: Polyjet, FDM, and 3DP, determining that the model fabricated with Polyjet techniques had the highest accuracy (0.133%, compared with 1.67 % and 1.73 % for 3DP and FDM, respectively). Additive manufacturing of 3D skull models was performed with different techniques giving a dimensional error of the Polyjet model of 0.18 ± 0.12 % compared with 0.79 ± 0.26 % and 0.67 ± 0.43 % for SLS and 3DP, respectively [145](#_ENREF_145). The discrepancy in 3DP accuracy is most likely attributable to difference in 3D printer quality, settings, or working material.

Inkjet printing uses different types of fine powders like plaster or starch (systems e.g., by Z Corporation Burlington, MA, USA). A layer of powder is deposited and then an adhesive is added to specific regions. The adhesive cures with the powder creating a solid. The uncured powder is discarded, leaving the final model [138](#_ENREF_138). [Geoghegan, et al. 56](#_ENREF_56) utilized plaster powder for the male mould construction (Figure 2). This material is porous therefore requires a layer of PVA (Polyvinyl acetate) to stop infusion of silicone during casting. PVA also provided a smooth model surface, which was enhanced by sanding with increased grade of sandpaper (200-1600). PVA also increased the structural rigidity of the model. Different mixtures of PVA-water, 90:10 and 80:20, gives an increase in diameter of 0.03 and 0.01 mm, respectively, which can be accounted for in the rapid prototyped model. Cross-sectional area error of 5 to 16% is noted for the final silicone phantom due the application of PVA. [Cao, et al. 24](#_ENREF_24) applied the same method for surface refinement via a varnish coating. In their later work, the accuracy measurement of their moulds and phantom showed 3.5-4.3% relative error in diameters attributed as a result of 3D printing and surface refinement [25](#_ENREF_25).



Figure 2. Plaster model with PVA coating of the carotid artery bifurcation

Further options of wax, gelatine and chocolate were also examined [56](#_ENREF_56). It was found that although they reproduce fine detail, they were susceptible to shrinkage when cooled. Low melting point alloys (60 °C) were also investigated. [Hoi, et al. 66](#_ENREF_66) and [Smith, et al. 152](#_ENREF_152) used Cerro® alloy, however it was also susceptible to shrinkage and can also leave residue when the melting process is completed which can be hard to remove in complex vascular geometries.

[Doutel, et al. 44](#_ENREF_44) used both wax and sucrose for their sacrificial mould in construction of compliant polydimethylsiloxane (PDMS - silicone) phantoms. The sucrose mould was removed with water at room temperature but the wax mould was removed by melting at 80 °C. They used scanning electron microscopy (SEM) and energy dispersive X-Ray spectroscopy (EDS) to investigate the contaminants on the surface of the phantom and the chemical composition difference of the surface from that of PDMS, respectively. They reported the model fabricated with the lost-sucrose casting method provided better model transparency.

Plaster can be dissolved in water leaving a clear phantom, but can be hard to handle as a material, as it is brittle and plaster printers are not always readily available. A recent study by [Huetter, et al. 70](#_ENREF_70) suggested ABS plastic, which has an improved layer resolution (0.17 mm) and is structurally tougher. The surface of the ABS can be smoothed before casting with the application of acetone to the surface. After casting, acetone is used to dissolve the ABS and remove the mould [4](#_ENREF_4), [20](#_ENREF_20), [71](#_ENREF_71), [109](#_ENREF_109). [Aplin, et al. 4](#_ENREF_4) noted that soaking the final silicone model in acetone can lead to a yellowing of the silicone phantom which harms optical performance. This can be prevented by curing the silicone for at least seven days before acetone is applied for ABS removal. It is noted that the yellowing did not affect the RI index or optical access for PIV analysis. Rapid prototyping systems material and removing processes from different experimental studies are compared in Table 1 and Table 2.

Table 1 Summary of some experimental in-vitro studies of hemodynamic using rigid phantoms

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Article | Arterial region | Geometry | Software | RP system | RP material | Wax removal | Mould polishing | Cast material | Blood-analogue | Surrounding fluid | Physical  properties | RI | Analysis Method |
| [Minakawa, et al. 106](#_ENREF_106) | Aortic arch | P-C | Mimics | laser experimentation system | Epoxy resin |  |  | Glass | W | water |  |  | PIV |
| [Kaufmann, et al. 79](#_ENREF_79) | Aortic arch | P-C-M | Mimics, 3-matics | Objet Eden500 (PJ) |  |  |  | Silicone |  |  |  |  | SPIV |
| [Minakawa, et al. 107](#_ENREF_107) | Aortic arch | P-C | Mimics | laser experimentation system | Epoxy resin |  |  | Glass | W | W |  |  | PIV |
| [Minakawa, et al. 105](#_ENREF_105) | Aortic arch | P-C | Mimics | laser experimentation system | Epoxy resin |  |  | Glass | W | W |  |  | PIV |
| [Huang, et al. 69](#_ENREF_69) | Aortic arch | I |  |  |  |  |  | Glass | W-G |  |  |  | PIV |
| [Büsen, et al. 22](#_ENREF_22) | Aortic arch | P-M | Mimics, 3-matics | Eden 350V (PJ) | FullCure720 | Mechanical | polyvinyl alcohol coated | silicone (RT601) | W-G (43.6-56.4) |  |  | 1.403 | SPIV |
| [Laumen, et al. 90](#_ENREF_90) | Aortic arch | P-M | Mimics | Eden 350V (PJ) | acrylic-based photopolymer |  | water-soluble ﬁnish coated | silicone (RT601) | W-G (58-42) | W-G (58-42) |  |  | SPIV |
| [Zhu, et al. 186](#_ENREF_186) | vertebral basilar  artery | P-C | Mimics, Geomagic |  | Resin | Heating |  | Silicone  (Sylgard 184) | W-G |  | *ρ =* 1157 kg·m-3,  *µ =* 10.6 cP, *Re=*300, 500 |  | PIV |
| [Ford, et al. 49](#_ENREF_49) | vertebral basilar artery aneurysm | P-A |  | Stratasys FDM 1650 | ABS |  |  | Silicone  (Sylgard 184) | W-G 50:50 and 5% salt by volume |  | *µ =* 6.2 mm2·s-1 |  | PIV |
| [Kefayati and Poepping 83](#_ENREF_83) | Carotid | P |  |  |  |  |  | Silicone  (Sylgard 184) | W-G-NaI (7.3 -36.94 -15.68%) |  | μ = 4.31±0.03 | 1.4140±0.0008 | SPIV |
| [Hoi, et al. 66](#_ENREF_66) | Cerebral aneurysm | I |  |  | Cerro alloy |  |  | Silicone  (Sylgard 184) | W-G 40:60 |  |  |  | PIV |
| [Stamatopoulos, et al. 159](#_ENREF_159) | AAA | P-C | Open source | 3D Printer |  | Water |  | Silicone  (Sylgard 184) | W-G 40:60 |  | ν = 7.583 cSt |  | PIV |
| [Kefayati, et al. 82](#_ENREF_82) | Carotid | P |  |  |  |  |  | Silicone  (Sylgard 184) | W-G-NaI (7.3, 36.9 and 15.7%) |  | μ = 4.31 mPa·s | 1.4140±0.0008 | SPIV |
| [Kefayati, et al. 81](#_ENREF_81) | Carotid | I |  |  |  |  |  | PDMS | W-G-NaI (7.3, 36.94 and 15.68%) |  | μ = 4.3160.03 cP  ρ=1.244 g·ml-1 | 1.4140±0.0008 | SPIV |
| [Sherman, et al. 149](#_ENREF_149) | Cerebral basilar | P-CA |  |  | Wax | Heating |  | Silicone  (Sylgard 184) | W 75% G 25% |  | 2.45 cP  ρ=1059 kg·m-3 |  | Optical imaging |
| [Van Ooij, et al. 169](#_ENREF_169) | Intracranial aneurysm | P-A |  |  |  |  |  | Glass | W 60% G 40% |  | ν = 2.95 mm2·s-1 | 1.471 | PIV |
| [Ionita, et al. 72](#_ENREF_72) | cerebral | I |  |  | Cerro alloy | Hot water |  | Silicone  (Sylgard 184) | W 40% G 60% |  | μ = 10.8 cP |  | PIV |
| [Kim, et al. 87](#_ENREF_87) | basilar | P-M |  | Fortus 400mc, Stratasys (FDM) | ABS | Acetone |  | PDMS | W 40% G 60% |  |  | 1.413 | SPIV |
| [Nemati, et al. 112](#_ENREF_112) | Carotid | P-C |  |  | Wax |  |  | PDMS | W-G |  |  | 1.413 | PIV; LASCA |

I: Idealized; P: Patient specific; C: CT-Scan images; M: MRI images; PJ: Polyjet Technology; A: angiography; ABS: acrylonitrile butadiene styrene; PIV: particle image velocimetry; SPIV: stereoscopic PIV; AAA: abdominal aortic aneurysm; A: angiography; W: water; G: glycerin; NaI: sodium iodide; LASCA: laser speckle contrast analysis

Table 2. Summary of some experimental in-vitro studies of hemodynamic using compliant phantoms

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Article | Arterial region | Geometry | RP system | RP material | RP material removing | Mould polishing | Cast material | Blood-analog | Surrounding fluid | Physical  properties | RI | Analysis Method | Wall Thickness (mm) | Manufacturing Method |
| [Cao, et al. 24](#_ENREF_24) | Carotid | I; P-M | Multi-jet Experimentation (InVision® XT) | Wax | Melting and hot water | Sandpaper & varnish | RTV 3040 | W-G |  |  |  | PIV | 1 | 3PM |
| [Pielhop, et al. 123](#_ENREF_123) | Aorta | I |  |  |  |  | RTV 615 | W-G | SB |  |  | TRPIV |  |  |
| [Suh, et al. 162](#_ENREF_162) | Coronary | P-C | Z-printer |  | Water |  | Silicone | W-G | SB |  |  |  |  | 3PM |
| [DiCarlo and Poepping 42](#_ENREF_42) | Carotid | I |  |  |  |  | Sylgard 184 | W-G-NaI (47.38, 36.94, 15.68%) | SB | µ= 4.31 cP  ρ= 1.244 kg·m-3 | 1.414 | SPIV | 1 |  |
| [Arcaute and Wicker 5](#_ENREF_5) | Various geometries | P-M-C | FDM | WaterWork | water | Sandpaper & soldering | Silicone |  |  |  |  |  | varied | Coating |
| [Brunette, et al. 17](#_ENREF_17) | Coronary | I |  | Aluminum |  |  | Silicone (T-2 silastic) | W 40% - G 60% | SB | µ= 1.45 mPa·s  ρ=1114 kg·m-3 | 1.43 | PIV |  | 3PM |
| [Geoghegan, et al. 55](#_ENREF_55) | Carotid | I | ZPrinter 310 Plus & Spectrum Z510 | Plaster | Water | Sandpaper & PVA glue | Sylgard 184 | W-G 39:61 | SB | µ= 10.2 × 10-6 | 1.417 | TRPIV | 1.3 ± 0.05 | 3PM |
| [Sulaiman, et al. 163](#_ENREF_163) | Aortic arch | P-M | Polyjet | Epoxy resin |  |  | silicone |  |  |  |  |  | 2 | 3PM |
| [Yip, et al. 180](#_ENREF_180) | Aortic arch | P-M | FDM | WaterWorks | Water |  | Sylgard 184 | W 57% - G 43% | SB |  | 1.414 | PIV |  | Coating |
| [Tanné, et al. 165](#_ENREF_165) | Left heart | P-C | 5-axis milling | Aluminum |  |  | Silicone | W 60% - G 40% | SB | ρ=1130kg·m-3,  µ= 4.0 mPa·s | 1.38 | PIV |  |  |
| [Deplano, et al. 39](#_ENREF_39) | AAA | I |  |  |  |  | polyurethane | W 60% - G 40% | SB | ρ=1130kg·m-3,  µ= 4.0 mPa·s |  | PIV |  | Coating |
| [Yagi, et al. 179](#_ENREF_179) | Cerebral aneurysm | P-C |  | wax |  |  | Silicone | W-G | SB | ρ=1160kg·m-3,  µ= 5.3 mPa.s | 1.4096± 0.002 | SPIV | 1.0 ± 0.3 | Coating |
| [Meyer, et al. 103](#_ENREF_103) | AAA | I |  | Glass |  |  | Estane®5714 (polyurethane, ) | W-G |  |  |  | SPIV |  | Coating |
| [Deplano, et al. 40](#_ENREF_40) | AAA | I |  |  |  |  | polyurethane | W 60% - G 40% | SB | ρ=1083 kg·m-3  µ= 3.9 mPa.s |  | PIV |  |  |
| [Charonko, et al. 28](#_ENREF_28) | AAA |  |  |  |  |  | Sylgard 184 | W 60% - G 40% | SB | ρ=1099 kg·m-3  µ= 3.7×10-6 m2·s-1 |  | TRPIV | 0.4 |  |
| [Deplano, et al. 38](#_ENREF_38) | AAA | I |  |  |  |  | Estane®5714 | XG-Na-W-G; Na-W-G | SB |  |  | PIV |  |  |
| [Deplano, et al. 37](#_ENREF_37) | AAA | I |  |  |  |  | Estane®5714 | XG-Na-W-G | SB |  |  | SPIV | 0.2 |  |
| [Hütter, et al. 71](#_ENREF_71) | Aortic arch | I | FDM | ABS | Acetone | Sandpaper and acetone | Sylgard 184 |  |  |  |  |  | 1.01 | 3PM |

W: water; G: glycerin; XG: Xanthan gum; NaI: sodium iodide; I: Idealized; P: Patient specific; SB; Same as blood-analog; C: CT-Scan images; M: MRI images; AAA: abdominal aortic aneurysm; TR: time-resolved; SPIV: Stereo PIV; PIV: planar PIV; Note the reported viscosity values were measured at various temperatures; 3PM: 3 piece mould

## Rigid phantom construction

Many studies used lost-core casting techniques to construct rigid phantoms [49](#_ENREF_49), [56](#_ENREF_56), [66](#_ENREF_66), [129](#_ENREF_129), [152](#_ENREF_152), [186](#_ENREF_186). The male mould is placed in a casting box (Figure 3). The casting box can be manufactured from Polymethylmethacrylate (PMMA) [56](#_ENREF_56), [142](#_ENREF_142), [152](#_ENREF_152), glass [35](#_ENREF_35), and even various resins or polymers have been proposed [21](#_ENREF_21). PMMA is popular as it is transparent, easily machined and can provide a rigid surface for fixing other elements of the flow circuit. Sacrificial casting boxes can also be used, but generally require an adhesive bond between the phantom and the flow circuit, which can be a point of failure.

PDMS silicone such as Sylgard® 184 is poured into the casting box and forms around the male mould. PDMS silicone is used as it has a low RI that is easily matched with water-glycerol solutions [57](#_ENREF_57), [72](#_ENREF_72), [84](#_ENREF_84). RI matching ensures that curvature in the geometry does not distort optical flow measurement techniques.

The silicone is a two part mixture that requires vigorous agitation to mix. This agitation induces a large quantity of air bubbles in the solution and thus, it must be degassed in a vacuum chamber. Once degassing is complete, the PDMS is poured into the casting box and cured. Once curing is complete the casting box is removed and the male mould is removed (Section 2.2). The general methodologies employed by a number of rigid phantom studies are presented in Table 1.

The casting box surfaces should be flat and parallel to the fields of interest. This orientation will generate minimal optical distortion in the images acquired. However, this strategy may also require expensive volumes of silicone. The design of the casting box should involve careful consideration of the cost to achieve image capture in the various potential planes of interest. For example, the lateral planes of the nasal cavity were of primary interest in the study of the phantom shown in Figure 3. Hence, the lateral surfaces of the phantom casting box were flat. In contrast, anterior planes were not considered critical and thus, the casting box had discontinuities that reduced silicone volume in that plane (Figure 3).



Figure 3 Male mould of the nasal cavity in PMMA casting box

## Compliant phantom prototyping

Accurately mimicking the compliance of the arterial wall is a challenge when capturing fluid-structure interaction. Failing to mimic the arterial compliance reduces the precision of the model [55](#_ENREF_55) and restricts the potential benefits of the results for clinical use and therapeutic optimisation.

Female moulds are often used to enable thin walled phantoms that mimic arterial wall compliance. The female mould defines the outer surface of the compliant silicone model. It can be modelled by extruding the 3D model of the lumen using CAD software and fabricated via additive or subtractive manufacture. The male mould must be located accurately within the female mould. Silicone is poured into the cavity and cured. The male and female moulds are then removed. The male mould can be removed using the same processes used for rigid phantoms. Female moulds are usually just unbolted, and do not require destructive removal.

The fabrication of the moulds is not trivial. Many manufacturing artefacts influence the efficacy of the resultant phantom. Two main factors dictate the phantom quality: surface finish and distortion. For compliant phantoms, the wall thickness is typically very small and thus, geometric distortion has a large effect on the phantom efficacy. In particular absolute errors in wall thickness cause disproportionately large changes in compliance of the phantom (Equation 1). [Sulaiman, et al. 163](#_ENREF_163) fabricated a compliant model of the aortic arch for endovascular prosthesis assessment using epoxy male and female moulds. Comparison of the STL file with internal dimensions of the phantom showed less than 0.52 mm variance at four key positons. [Geoghegan, et al. 56](#_ENREF_56) fabricated a compliant model of the carotid artery with a symmetric stenosis using aluminium CNC milling for the female mould and 3D printed plaster for the male. The silicone was injected from the bottom of the mould to prevent air bubbles trapping in the silicone during pouring. The fidelity of the phantom was assessed by dissecting the phantom and digitally measuring cross-sectional slices. The comparison of the geometry with the initial STL file showed 3-5% cross-sectional area error. [Cao, et al. 24](#_ENREF_24) constructed compliant silicone phantoms of the carotid artery, including internal and external branches. A single mould was printed in the form of a male core and female shell. Since the gap between the connected moulds was small, surface smoothing was undertaken using high pressure water containing abrasive particles. Hence, ensuring an adequate surface finished with this method is difficult. Dilation and contraction of the phantom was tested using echography. The results showed lumen dilation of 28.3% of the diameter. They achieved Young’s modulus of 0.52±0.15MPa and 0.3±0.9MPa with 4:1 and 1:0 ratios of RTV 3040 silicone and hardener respectively. These Young’s modulus values are close to human physiology (Table 3A).

Mould Dipping is a simple method for compliant phantom production. A male mould is printed and then dipped in silicone or latex liquid several times to allow a full coating. This process shapes the lumen [180](#_ENREF_180). This technique does not require a female mould but wall thickness is difficult to control. The variation in thickness can have a major effect on experimental results [180](#_ENREF_180). Dip-spin coating mitigates the variation in wall thickness by spinning the mould after dipping to achieve a more consistent wall thickness. [Arcaute and Wicker 5](#_ENREF_5) developed a technique of dip-spin silicone coating for fabrication of compliant arterial phantoms including the aortic arch, abdominal aorta and bypass graft. They spun the mould with a two-axis mechanism. A dip-spin-cure process was repeated until the desired wall thickness was achieved. They determined that horizontal dipping produced more uniform thickness compared with vertical dipping. Results from [Arcaute and Wicker 5](#_ENREF_5) demonstrated that the wall thickness increased on smaller mould diameters. Their results showed 0.60±0.13 mm (accuracy±precision) and 0.58±0.23 mm of vertical and horizontal thickness variation respectively, for different diameter locations. Since dipping methods require a large quantity of silicone that is 80-90% discarded, the methodologies are relatively expensive.

[Deplano, et al. 39](#_ENREF_39) and [Meyer, et al. 103](#_ENREF_103) used a glass coating method for phantom fabrication. Glass phantoms of the arterial geometry were manufactured by pressure induced radial expansion (blowing) of molten glass into a CNC milled female mould. The interior surface of the glass was coated repeatedly by polyurethane until the desired thickness was achieved. The authors did not specify how the mould is removed. However, it may be presumed that the glass mould is destructively removed from the phantom. It is reported that polyurethane shows viscoelastic behaviour similar to real artery and a Young’s modulus of 5.16 × 105 was obtained.

The artery wall is not monolayer. [Brunette, et al. 17](#_ENREF_17) fabricated a multilayer compliant transparent phantom of a stenosed coronary artery for PIV investigation. It was accomplished by multistage mould injection casting to create an arterial layer and occlusion with different material properties. A male and five female moulds with increasing diameter were machined in aluminium. Casting was performed in 5 stages of moulding and curing. Three steps were used to embed the occlusion and two steps for media and adventitia. [Pazos, et al. 121](#_ENREF_121) constructed a compliant multilayer phantom for the purpose of mechanical testing and intravascular imaging. It was designed for use in Echo-PIV therefore did not require optical access. The artery was fabricated in three stages, using two moulds. Between moulding steps, a mixture of lard, water and sodium was poured in the region of the stenosis. The material used for the arterial wall was Polyvinyl alcohol (PVA) cryogel. The material was prepared by mixing PVA powder (10 wt %) with room temperature tap water. The solution was heated in a sealed container for complete dissolution of the powder, and then cooled to room temperature to eliminate bubbles. This material shows nonlinear elastic behaviour and can mimic soft biological tissues. The two mould layers underwent 4 and 3 thermal curing cycle respectively from+10 oC to -20 oC over 40 hours. [Fromageau, et al. 51](#_ENREF_51) showed that there is an increase in Young's moduli with number of freeze-thaw cycles. In addition, [Surry, et al. 164](#_ENREF_164) reported that the speed of sound increases as the number of freeze-thaw cycle increases which is an important factor for MR imaging. The inner layer had an average thickness of 0.41 ± 0.8 mm, which mimicked the intima-media and a second layer of 0.64 ± 0.16 mm mimicking the adventitia. The phantom withstood large deformation with a 29.5% increase in lumen diameter during expansion. This method seems to be efficient for mimicking mechanical behaviour of the artery, but it is not suitable for PIV experimentation since PVA is not transparent.

[Qian, et al. 133](#_ENREF_133) fabricated a series of phantoms with different stiffness (60.9-310.3 kPa) by curing the mould with different freeze-thaw levels, similar to the process seen in [Pazos, et al. 121](#_ENREF_121). The male and female moulds were made from steel and authors do not mention how the moulds were removed. However, it can be presumed that the steel male mould would not have been destructively removed. Thus, difficult axial removal of the male mould, or rolling the phantom from the mould would have been necessary. The freeze-thaw cycles, were 12 h of freezing at -20 oC and 12 h of thawing at 20 oC, with the Young’s modulus increasing during freeze-thaw cycles. The waveform morphology for the flow pressure and wall dilation was influenced by stiffening the vessel.

[Ionita, et al. 73](#_ENREF_73) directly constructed the artery using a 3D Polyjet printer. This method was utilised for complex arterial geometries with the purpose of testing catheter-based cardiovascular interventions. Rigid and flexible phantoms were fabricated. While the rigid material was transparent, the flexible phantom was only semi-transparent (TangoPlus). To verify the accuracy of prototyping, the phantoms were scanned by angiography and compared with the initial patient specific geometries. Distance analysis showed an average difference of 120 μm between the phantom and initial model. The choice of employing this method seems efficient for production of phantoms for PIV studies. However, further studies are needed to check the RI of both the rigid and elastic material. The modulus of elasticity was not reported for the TangoPlus material. However, it is reported that it has tensile strength of 5.5 -10.3 kPa and elongation at break of 170-220%. [Dalaq, et al. 36](#_ENREF_36) investigated the mechanical properties of TangoPlus and found that it has Young’s modulus of 0.34 MPa during a compression test. It was noted that the printing direction affected the elastic anisotropy of the specimen. [Biglino, et al. 12](#_ENREF_12) directly 3D printed phantoms using TangoPlus material with a PolyJet 3D to assess distensibility and feasibility of this material for the use in *in-vitro* cardiovascular experimentation. They noted a non-linear stress-strain behaviour and that the range of distensibility values observed in TangoPlus FullCure was a good surrogate of *in-vitro* arteries. [Biglino, et al. 12](#_ENREF_12) also found elastic anisotropy due to printing orientation.

Many works have made the assumption that the walls of the artery can be treated as rigid (Table 1). However, it has been shown that this assumption can lead to an over estimation in WSS. [Geoghegan, et al. 59](#_ENREF_59) experimentally investigated the effect of wall compliance on flow field and WSS and noted that there was 61% maximum relative difference in peak WSS between rigid and compliant phantoms. [Perktold and Rappitsch 122](#_ENREF_122) numerically showed that WSS is 25% lower in compliant arteries. This contrast is very important as WSS is a critical element of research into stenosis formation [95](#_ENREF_95), [184](#_ENREF_184) and endothelium structure [29](#_ENREF_29). [DiCarlo and Poepping 42](#_ENREF_42) performed PIV studies on rigid and compliant phantoms. Their outcomes showed that compliant walls result in slightly lower overall velocity than rigid walls. They also determined that higher wall stiffness caused an increase in maximum average turbulent intensity. Furthermore, flow separation and recirculation occurred in different regions when compliant models that mimicked physiological conditions were compared to rigid models. [Alishahi, et al. 3](#_ENREF_3) showed that the pressure magnitude is 15% lower in compliant arteries compared to rigid.

Arteries are high pressure blood vessels, which transfer blood from the heart through the body. Except for the capillaries, blood vessels are composed of three layers: tunica adventitia, tunica media and tunica intima all separated by elastic lamina. The outer layer, adventitia, is composed of fibrous and connective tissue that serves to support the vessel. The media is largely composed of a smooth muscle that controls the arterial diameter by contracting and expanding. The intima is comprised of a layer of endothelial cells, which deposit locally acting chemical mediators that influence the elastic state of the vessels smooth muscles and is supported by an internal elastic lamina. To simplify experimental and numerical studies, it is common to assume arteries are isotropic and passive with a constant wall thickness. However, *in-vivo* blood vessels are anisotropic, active-responsive and have a variable wall thickness [119](#_ENREF_119).

There is a large variation in the Young’s modulus of the aorta as it is affected by age, sex and diseases such as atherosclerosis and aneurysm (Table 3A). [Ozolanta, et al. 117](#_ENREF_117) found that Young’s moduli increased with age (1 to 80 years), from ~1.06 to 2.85 MPa and from ~1.06 to 3.3 MPa in men and women respectively (*post-mortem* right coronary artery). [Xiong, et al. 178](#_ENREF_178) measured a peak Young’s moduli of 9.14±3.31 MPa in an abdominal aortic aneurysm (AAA) from autopsy. It was shown that the maximal strain of the AAA was considerably less than the non-aneurysmal abdominal aorta. A comparison of studies investigating the elastic modulus of human arteries in healthy and disease conditions had a range of 0.5 105 – 1.5 105 MPa (Table 3A). Furthermore, arteries have non-linear, anisotropic elastance [65](#_ENREF_65), [67](#_ENREF_67), [68](#_ENREF_68), [75](#_ENREF_75), [135](#_ENREF_135). Non-linear elasticity is caused by the wavy collagen ﬁbrils within the artery wall which also lead to the anisotropic behaviour of the artery [114](#_ENREF_114), [141](#_ENREF_141). However, arterial phantoms are typically manufactured from isotropic materials with linear elasticity at operational conditions. For an elastic tube, the incremental Young’s modulus can be calculated from the lumen compliance [171](#_ENREF_171):

(Eq.1)

Therefore,

(Eq.2)

wwhere *C* is the compliance, *A* is the cross sectional area, *P* is pressure, *r* is the arterial radius and *h*is the vesselthickness.

Physiologically realistic arterial wall motion is important when performing experimental and numerical investigation of haemodynamics. Hence, elasticity is an important factor, which is dominated by the Young’s modulus. Table 3B compares the elastic modulus of studies that fabricated arterial phantoms for flow visualization. It can be seen that values vary amongst studies.

Table 3.Comparison of theelasticity modulus of different arterial regions and conditions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Author** | **Structure** | **Experiment Condition** | **Young’s Modulus (N.m-2)** |
| A | [**J. Thubrikar 75**](#_ENREF_75) | AAA | In vitro (Tensile Test) | L:4 106  C: 1.5 106 |
| [**Isnard, et al. 74**](#_ENREF_74) | Aortic arch | In vivo | H: 1.071 105  N: 0.526 105 |
| [**MacSweeney, et al. 94**](#_ENREF_94) | PAD, AA | In vivo | Atherosclerosis: 1.6 105  Aneurysm: 3.13 105  In thirty’s: 0.4 105  Middle age: 1.04 105  Elderly: 1.4 105 |
| [**Kupari, et al. 89**](#_ENREF_89) | Aorta | In vivo | Ascending: 0.572 105  Descending: 0.436 105  Thoracic: 0.508 105 |
| [**Blacher, et al. 13**](#_ENREF_13) | Carotid | In vivo | Young: 4.1 105  Elderly: 7.1 105 |
| B | [**Cao, et al. 24**](#_ENREF_24) | Carotid | Sampling | 5.2 105, 3 105 |
| [**Pielhop, et al. 123**](#_ENREF_123) | Aorta | Sampling (tensile test) | 2.17 106 |
| [**Suh, et al. 162**](#_ENREF_162) | Coronary | Calculated from compliance | 6-32 106 |
| [**DiCarlo and Poepping 42**](#_ENREF_42) | Carotid | N.M | 1.3 106 |
| [**Qian, et al. 133**](#_ENREF_133) | Carotid | Sampling (tensile test) | 1.65 105  2.505 105  3.103 105 |
| [**Biglino, et al. 12**](#_ENREF_12) | Aortic arch | Pressure and volume measurement | ------ |
| [**Geoghegan, et al. 55**](#_ENREF_55) | Carotid | Sampling (tensile test) | 1.2 106 |
| [**Yagi, et al. 179**](#_ENREF_179) |  | Sampling (tensile test) | 0.96 ± 0.115 106 |
| [**Meyer, et al. 103**](#_ENREF_103) |  | Tensile test | 17.5 106 |
| [**Deplano, et al. 39**](#_ENREF_39) |  |  | 5.16 105 |

AAA: abdominal aortic aneurysm; L: longitudinal; C: circumferential; H: hypertensive; N: normative; PAD: peripheral arterial disease; AA: aortic aneurysm; N.M: not mentioned

Another important parameter for characterising compliant phantoms is the wave propagation length, which corresponds to the artery walls longitudinal response to the pulse pressure wave. For a particular period (T), the input oscillatory pressure completes one cycle in time and the pressure inside the tube completes one cycle in space [183](#_ENREF_183). The propagation wavelength *λ* can be calculated using the following equation:

(Eq.3)

Where *B* is the dispersion coefficient and *c0* is the propagation speed in inviscid flow which can be obtained from:

(Eq.4)

For precise compliant analysis it is important to calculate the minimum model length by matching the ratio of the model length *Lmodel* and *λmodel* to the real-world values, which is:

(Eq.5)

### Material

Different types of materials were observed in literature for the construction of a compliant phantom. PDMS is a silicone-based polymer that is extensively used as an elastic material for phantom fabrication (Table 2). TangoPlus [12](#_ENREF_12), [73](#_ENREF_73), polyvinyl alcohol (PVA) and cryogel [121](#_ENREF_121), [133](#_ENREF_133) have also been used. [Millon, et al. 104](#_ENREF_104) showed that it is possible to produce an anisotropic material with PVA, which makes the method desirable for mimicking the non-linear anisotropic mechanical properties of the vessel. However, PVA is not transparent. The major advantages of PDMS is that it is optically transparent through the visible spectrum down to 240 nm, it is inexpensive, it has a low shrinkage rate, and fast simple fabrication [102](#_ENREF_102). Sylgrad 184 has also been used for compliant phantom fabrication as it has good elastic properties. However, its mechanical properties are significantly affected by different parameters such temperature and cross-linking agent.

[Fuard, et al. 53](#_ENREF_53) examined the influence of curing time and different mix-ratios of curing agent on the Young’s modulus of PDMS. It was shown that increasing the curing duration from 10 to 1000 minutes at 100 oC, increases the Young’s modulus. Their samples were maintained at 20 oC and atmospheric pressure after preparation for 5 months. Samples cured for less than 5 hours had a Young’s modulus increase 50% over 5 months. In contrast, samples cured for more than 10 hours showed no signiﬁcant change in elastance. [Johnston, et al. 76](#_ENREF_76) investigated the relationship between the mechanical properties of PDMS (Sylgard 184, Dow Corning) over a range of curing temperatures. They observed that Young’s modulus almost doubled linearly from 1.32 106 N.m-2 to 2.97 106 N.m-2 over the curing temperature range tested (25-200 oC). The stress-strain curve showed a linear relation up to a strain of 40 %, followed by a non-linear trend before rupture. They also showed that the maximum strain of their samples was inversely proportional to the curing temperature. [Geoghegan, et al. 56](#_ENREF_56) reported the rising trend of modulus of elasticity associated with curing temperature for their carotid phantom fabrication (Table 4). This relation is not quantified in manufacturer product information [45](#_ENREF_45).

The manufacturers recommend a 1:10 mixing ratio for various PDMS products such as Sylgrad 184, RTV 615, RTV 3040. [Sollier, et al. 153](#_ENREF_153) measured the effects of different mixing ratios of curing agent and PDMS silicone on the stiffness of the resultant material. The elastic modulus of PDMS varied from 0.8 to 2.5 MPa for ratios between 1:20 and 1:5 respectively. The commonly recommended ratio of 1:10 results in a modulus of 2.5 MPa. [Khanafer, et al. 85](#_ENREF_85) determined that Young’s modulus peaks at a mixing ratio of 1:9. The experiment was conducted on tensile test specimens with different crosshead speed (strain rate). The Young’s modulus calculated was different for the same mixing ratios but different crosshead speed.

Table 4. Variation of the Young’s modulus of Sylgard 184 at different temperature

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Temperature ºC | 20 | 25 | 50 | 100 | 125 | 150 | 200 |
| Young's Modulus (MPa) | 1.25 ± 0.12 [56](#_ENREF_56) | 1.32 ± 0.07 [76](#_ENREF_76) | 1.8 ± 0.18 [56](#_ENREF_56) | 2.05 ± 0.12 [76](#_ENREF_76);  2.23 ± 0.22 [56](#_ENREF_56) | 2.46 ± 0.16 [76](#_ENREF_76) | 2.59 ± 0.08 [76](#_ENREF_76);  2.70 ± 0.26 [56](#_ENREF_56) | 2.97 ± 0.04 [76](#_ENREF_76) |

RTV 615 takes a longer time to cure whereas Sylgard 184 is stiffer and chemically inert to acids and bases [52](#_ENREF_52). [Schneider, et al. 148](#_ENREF_148) performed tensile tests to investigate the mechanical properties of two silicone elastomers, Sylgard 184 and RTV 615. They found that Sylgard 184 has 20% higher elastic modulus compared with RTV 615 (Table 5). A compliant phantom of stenotic arteries constructed using RTV 615 yielded a Young’s modulus of 2.17 106 N·m-2 [123](#_ENREF_123). RTV-3040 is a translucent elastomer with less than 0.1% linear shrinkage during cure and a high tensile strength of 6.3 MPa. The curing process of RTV 3040 takes 16-24 h at room temperature. However, in the material catalogue description, it is mentioned that curing at 40-65 oC accelerates the process, but is not recommended as heating may lead to shrinkage [140](#_ENREF_140). [Cao, et al. 24](#_ENREF_24) used RTV 3040 for phantom fabrication with a mixing ratio of 1:10. They achieved a Young’s modulus of 0.53 MPa by curing at room temperature for 24 hours. Sylgrad 184 seems to be the most extensively used silicone elastomer in PIV experimentation. In particular, the Glycerine-water working fluid that can be RI-matched with the Sylgrad 184 and RTV is safer to handle compared with other working fluids.

Table 5. Elastic modulus of the Sylgard 184 and RTV 615 for different concentration of the hardener; test samples are cured at 150 ºC for 15 min.

|  |  |  |
| --- | --- | --- |
| Hardener concentration % | Sylgard 184 (MPa) | RTV 615 (MPa) |
| 0 | 1.820 ± 0.091 | 1.528 ± 0.055 |
| 5 | 1.546 ± 0.018 | 1.455 ± 0.075 |
| 10 | 1.407 ± 0.085 | 1.197 ± 0.055 |

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# Blood Analogues

Blood is a complex mixture that contains plasma, proteins, platelets, white and red blood cells. Blood is a non-Newtonian liquid and is approximately 3-4 times more viscous than water at high shear rates, and even more viscous at low shear rates. The viscosity of the blood varies across gender, age, health and shear rate [88](#_ENREF_88). [Mayer 100](#_ENREF_100) measured human blood viscosity in a wide range of healthy and chronic coronary heart disease subjects. The results showed that viscosity varies between 2.96 ± 0.19(SD) mPa.s in healthy children to 3.72 ± 0.02 mPa.s for healthy men between 21-26 years. However, in patients with chronic coronary heart disease, the measured viscosity was 3.98 ± 0.35 and 3.60 ± 0.33 mPa.s in male and female participants, respectively. Rosenson et al. [143](#_ENREF_143) measured blood viscosity from 126 male and female healthy adults. Shear rates of 100, 50 and 1 s-1 illustrated viscosity of 3.26 ± 0.43, 4.37 ± 0.60, and 5.46 ± 0.84 mPa.s, respectively. Polaschegg noted that patients with acute hemolysis receiving haemodialysis had a lower red blood cell count leading to lower hematocrit [131](#_ENREF_131). This leads to lower hemodynamic viscosity [80](#_ENREF_80). Some important physical properties of blood and the equivalent properties of candidate analogues are detailed in Table 6.

Table 6. Physical properties of blood and some blood analogues (\*due to high haematocrit, capillary blood viscosity tends to be higher than larger artery blood or arteriole blood)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| fluid | Ratio | RI | *ρ* (kg·m-3) | Dynamic viscosity (mPa.s) |
| Blood | ------ | ------ | 1060 @ 37 ºC | 2.9-4.37\* |
| Water @ 20 ºC | ------ | 1.333 | 998.2 | 1.0016 |
| Glycerine @ 20 ºC | ------ | 1.474 | 1261.08 | 1.76 |
| Water-Glycerol-NaI | 47.38-36.94-15.68 % by weight | 1.414 | 1244 ± 2 | 4.31 |
| Water-Glycerol | 61:39 | 1.417 | 1156.6 | 10.6 |

[Najjari, et al. 111](#_ENREF_111) reported different aqueous solutions of glycerine with and without NaCl (sodium chloride) or NaI (sodium iodide) and aqueous solutions of NaI and potassium thiocyanate (KSCN) as possible solutions to mimic the non-Newtonian nature of blood.

The RI of the blood analogue is an important factor to consider when performing optical experimentation in models of the arterial system. Optical refraction occurs at each interface of the model and liquid. This refraction can cause distortion when viewing the internal fluid leading to degradation of the experimental results. This issue can be mitigated by matching the RI of the phantom and the fluid. However, it is often difficult to find a mimicking fluid with both appropriate RI and dynamic viscosity. Phantom RI is generally defined by material selection and curing process [22](#_ENREF_22), [56](#_ENREF_56). [Schneider, et al. 147](#_ENREF_147) analysed the mechanical and optical properties of RTV 615 and Sylgard 184 in microelectromechanical systems. They measured RI values of 1.4295 to 1.4483 for Sylgard 184 and 1.4282 to 1.4470 for RTV 615 across wavelength from 405 to 635 nm.

A water glycerol solution is commonly used to match the RI of Sylgard 184 [60](#_ENREF_60), [66](#_ENREF_66), [72](#_ENREF_72). Changing the ratio can tune the RI of the working fluid with a range of 1.311 for pure water to 1.459 for pure glycerol [33](#_ENREF_33). A ratio by weight of 39:61 of water to glycerol was found to match the RI of Sylgard 184 [18](#_ENREF_18), [19](#_ENREF_19), [44](#_ENREF_44), [56](#_ENREF_56), [58](#_ENREF_58).

[Yousif, et al. 181](#_ENREF_181) proposed an alternative blood analogue solution to match the RI of Sylgard 184 (RI = 1.414) and mimics human blood viscosity (4.4±0.6 mPa.s). The working fluid was composed by weight 47.38% of water, 36.94% of glycerol and 15.68% of NaI salt and has been used in subsequent studies [84](#_ENREF_84). Furthermore, this solution can be matched for different RI index silicone by maintaining water-glycerol ratio and changing NaI concentration to match the RI. [Bai and Katz 8](#_ENREF_8) conducted a study on RI of NaI solution for index matching in PIV. They have reported that NaI solution can cover an RI range of 1.333-1.51. Further details regarding temperature dependency and solubility can be found in their study. However, NaI is corrosive and it can degrade components in the flow system over time.

The viscosity of blood reduces to a plateau level at high shear rates and is thus a non-Newtonian fluid. [Brookshier and Tarbell 15](#_ENREF_15) proposed an aqueous solution of xanthan gum (XG) to mimic the non-Newtonian characteristics. [Walker, et al. 172](#_ENREF_172) utilised aqueous xantham gum to capture transitional flow through a phantom of a stenosis using PIV. The results indicated that aqueous XG solutions can provide an appropriate whole blood mimicking fluid in transitional environments. Aqueous polyacrylamide (PAA) has also been proposed as a non-Newtonian blood-analogue which has higher elastic characteristics compared with XG [155](#_ENREF_155). [Mann and Tarbell 96](#_ENREF_96) investigated the effect of non-Newtonian rheology on WSS with different blood-analogues. They indicated that the elasticity of PAA is higher than blood and does not provide a good model of blood under oscillatory conditions, especially for reversed WSS. Care must be taken to ensure that the non-Newtonian characteristics of the working fluid scale appropriately with the model and match the Reynolds and Womersley numbers of arterial flow (Equations 6 and 7) at all locations. This may be difficult in locations where the non-Newtonian shear-rate dependence of blood viscosity are pronounced (shear rates <100/s). Such regions are inevitable in flows with stagnation, although the affected regions may not necessarily influence neighbouring regions noticeably. Achieving correct shear thinning at all locations and times, simultaneously with Reynolds and Womersley matching, may be impossible with known transparent working fluids. In such cases, interpretation of findings must be undertaken with care.

[Campo-Deaño, et al. 23](#_ENREF_23) developed four distinct polymer solutions as viscoelastic blood analogues. These analogues had a refractive index range of 1.38 to 1.43 thus suited PDMS arterial phantoms. They reported that the XG-sucrose and XG-DMSO (Dimethyl sulfoxide) solutions have shear thinning behaviour similar to blood. [Oates 116](#_ENREF_116) proposed a mixture of powdered nylon (5-15 µm) suspended in water-glycerine as a blood analogue for Doppler ultrasound experimentation of arterial phantoms. Concentrated liquid detergent was added to obtain a range physiological viscosity. It was reported that at low shear rates the fluid shows non-Newtonian behaviour due to aggregation of nylon powder.

To match the RI, sodium thiocyanate (NaSCN) can be added to the aqueous solution of xanthan gum [14](#_ENREF_14). A recent study by [Najjari, et al. 111](#_ENREF_111) demonstrated adding NaSCN or NaI to xanthan gum, substantially reduced the viscoelastic and shear thinning behaviours of the solution. Therefore, the RI of the fluid cannot be easily matched by changing the concentration of NaSCN and NaI.

# Flow mimicking circuit

## Flow signal generation

The pulsatile pressure waveform of blood varies as it travels through the arterial tree from the aortic arch to the arterioles (Figure 4) [43](#_ENREF_43), [88](#_ENREF_88). Arterial compliance, vascular resistance, cardiac output and arterial geometry affect the pressure waveform. Predominantly, pressure wave reflection and inductance influence the shape of the waveform as it travels to the periphery. The high resistance to flow in the arterioles diminishes pressure pulsations in small downstream vessels but augments upstream arterial pressure pulses due to wave reflection. As pressure waves travel from the aorta and large arteries to the narrower, less compliant distal arteries, they travel at a greater speed. The ascending part of the wave becomes steeper and the maximum systolic pressure tends to increase [108](#_ENREF_108).

Figure 4 pressure and velocity waveform at different regions of arterial tree [26](#_ENREF_26)

Two dimensionless numbers are important to consider in the study of pulsatile biological flow to ensure dynamic similarity. The Womersley number (α) represents the ratio of the pulsation frequency to viscosity [175](#_ENREF_175).

(Eq.6)

where *r* is the tube radius, *ν* is the kinematic viscosity and *ω* is the angular frequency.

When *α* is low (), the flow is quasi-steady and the cross sectional velocity profile has a parabolic shape and the centreline velocity oscillates in phase with the driving pressure gradient. In this case, viscous forces are dominant and inertial forces can be neglected. At higher range of α (1-3), the instantaneous flow rate lags behind instantaneous pressure gradient. For higher magnitudes of α () high inertial forces prevail instead of viscous forces. Hence, the velocity profile is flat in the centre and the phase lag increases (Figure 5) [101](#_ENREF_101). Values of α vary from aorta to capillaries due to diameter changes (See Eq.7). Values of α for different arterial sizes in canine subjects are shown in Table 7.

The second dimensionless number is Reynolds number (Re), which relates inertial to viscous forces.

(Eq.7)

where is the time averaged velocity and *D* is the inlet diameter (or any characteristic linear dimension). Reynolds number ranges between approximately 0.1 and 4000 in small and large arteries, respectively (Table 7) [88](#_ENREF_88).

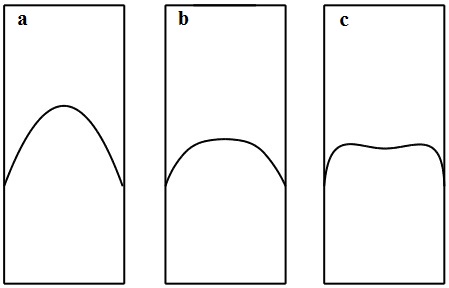


Figure 5. Schematic view of the effect of Womersley number on velocity profile shape. Womersley value increases from case **a** to **c**.

Table 7. Some parameters of canine cardiovascular system; Re: Reynolds number; di internal diameter [88](#_ENREF_88)

|  |  |  |  |
| --- | --- | --- | --- |
| **Arterial region** | ***di* (mm)** | **α (assuming heart rate 2Hz)** | **Re (peak)** |
| Ascending Aorta | 15  10 - 24 | 13.2 | 4500 |
| Descending Aorta | 13  8 – 18 | 11.5 | 3400 |
| Abdominal Aorta | 9  5 – 12 | 8 | 1250 |
| Femoral Artery | 4  2 – 8 | 3.5 | 1000 |
| Carotid Artery | 5  2 - 8 | 4.4 | Not reported |
| Typical Arteriole | 0.05  0.01 - 0.08 | 0.04 | 0.09 |
| Typical Capillary | 0.006  0.004 - 0.008 | 0.005 | 0.001 |
| Typical Venule | 0.04  0.01 - 0.075 | 0.035 | 0.035 |

## Steady flow studies

Although blood flow is pulsatile, some experimental and numerical studies consider steady conditions stating that arterial blood flow can be considered quasi-steady. However, this assertion has proven controversial. [Taylor and Yamaguchi 166](#_ENREF_166) numerically simulated the blood flow in an abdominal aortic aneurysm for both steady and unsteady cases. It was shown that the transient flow field had different vortex locations from the steady case. Furthermore, during pulsatile flow, the greatest pressure was observed at the aneurysm inlet. In contrast, the greatest pressure was at the aneurysm outlet region for the steady flow. [Liu, et al. 92](#_ENREF_92) numerically investigated the effect of pulsation and non-Newtonian behaviour on LDL concentration and oxygen flux in the aorta. Their results showed that pulsatile blood flow induced oxygen flux that was considerably higher than the equivalent flux of steady flows in most regions of the aorta. The numerical study by [Finol and Amon 48](#_ENREF_48) on abdominal aortic aneurysms showed that the WSS and WSS gradient were significantly higher in pulsatile flow in comparison with steady flow. [Banerjee, et al. 9](#_ENREF_9) reported that the unsteady flow consideration produced a higher pressure drop than the steady flow in a stenosed artery. The experimental study of [Geoghegan, et al. 55](#_ENREF_55) revealed that the strength of the vortices in the shear layer downstream from a stenosis not only depends on the instantaneous flow rate, but also the rate of change of flow rate. [Razavi, et al. 137](#_ENREF_137) numerically investigated the pulsatile flow in a stenotic artery. They reported that the steady assumption leads to 6-12% error in calculation of the separation length of the recirculation region compared with pulsatile flow. These studies show that inducing pulsatile flow in the phantom is necessary to capture certain clinically relevant characteristics of pulsatile flow.

## Flow circuit

Many PIV physical phantom studies of haemodynamics utilise pumped fluid circuits to mimic and capture the flow fields. The circuits typically include a piston or pump, pressure transducers, flow meters, head tank and reservoirs (Figure 6) [123](#_ENREF_123), [133](#_ENREF_133), [162](#_ENREF_162). A reciprocating piston connected to a motor (Figure 7) is programmed to drive the fluid from a temperature controlled reservoir through the phantom in the desired waveform. An electromagnetic flow meter was placed at the entrance of the phantom to measure real-time flow rate and send feedback to the computer controlling the piston pump. Header tanks can be used to control the exit pressure and-or mimic extramural pressure. To ensure Poiseuille flow profiles enter the experimental region, a honeycomb flow straightener can be used [55](#_ENREF_55), [69](#_ENREF_69), [186](#_ENREF_186) (Figure 8).

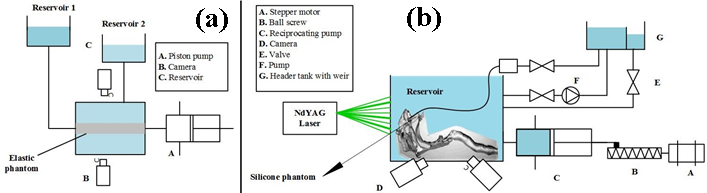


Figure 6. Flow circuit configuration; (a) [123](#_ENREF_123); (b) [156](#_ENREF_156)

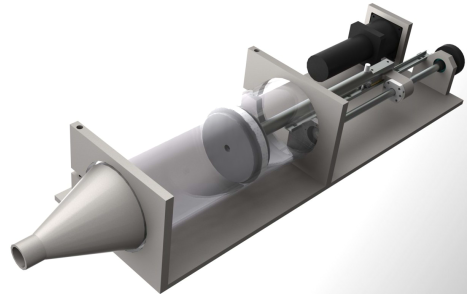


Figure 7. Reciprocating piston and stepper motor setup for fluid waveform generation

Most PIV studies use stepper motors due to their high control resolution. However, some studies use pulsatile pumps to fully mimic the flow characteristics at certain regions of the arterial system (Model 55-3305, Harvard, USA) [133](#_ENREF_133), [162](#_ENREF_162). In other flow visualization experiments, the waveform generation was achieved with ventricular assisted devices (VAD) (Figure 9), ball valves [24](#_ENREF_24), [112](#_ENREF_112), or electronically controlled pumps. Some studies utilise resistive elements at the inlet and outlet of the phantom to mimic physiological flow patterns [11](#_ENREF_11), [22](#_ENREF_22), [38](#_ENREF_38). Needle valves, butterfly valves or fixed washers can be used as resistance elements (Figure 8). To mimic Windkessel effects of the downstream arteries, a liquid-air compliance chamber can be used.

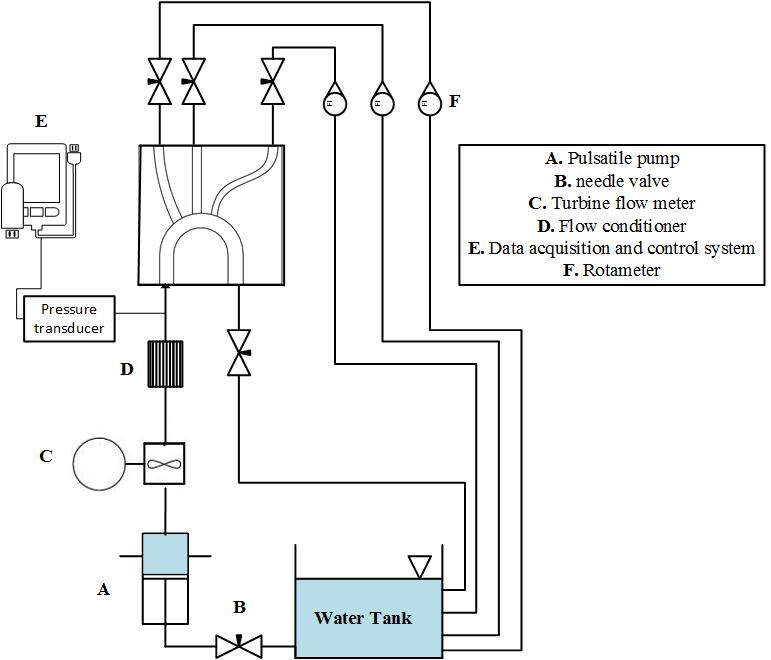


Figure 8. Flow circuit configuration including different elements [69](#_ENREF_69)

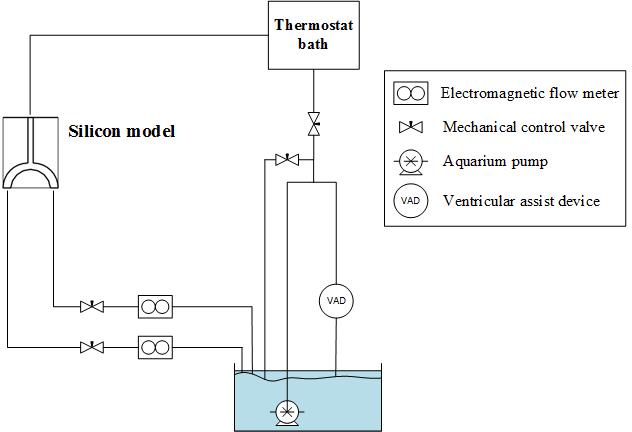


Figure 9 configuration of using VAD [112](#_ENREF_112)

In compliant phantom studies, the phantom is typically placed in a tank that is filled with the same fluid as the working fluid. This allows control of the distensibility of the compliant model and replicates the effects of the surrounding biological tissue [37](#_ENREF_37). It also minimises the buoyancy forces [123](#_ENREF_123) and prevents optical distortion from diffraction [55](#_ENREF_55).

## PIV image capture

PIV is a laser based optical measurement technique to capture fluid velocity fields. The PIV method uses a high intensity light source to illuminate small tracer particles across a plane of interest within the phantom. The light source is often a laser beam that has passed through a series of lenses to produce a thin light sheet. Two or more instances of tracer particle location in the illuminated region are captured via digital photography. The elapsed time between images must be appropriate to observe particle motion. Various statistical methods such as autocorrelation, cross correlation and/or Fourier analysis are used to determine a velocity field. A detailed description of PIV can be found in Grant, et al. [62](#_ENREF_62) and Raffel, et al. [134](#_ENREF_134).

Planar PIV uses one camera to capture a two dimensional plane with two components of velocity (2D2C). Stereoscopic PIV (SPIV) allows the acquisition of the third component of velocity (2D3C) by directing the second camera to the illuminated plane from a different angle, allowing the reconstruction of the out of plane velocity component. By measuring multiple planes, a 3D flow field can be reconstructed by interpolating between the acquisition planes during post processing [132](#_ENREF_132). Tomographic PIV (tomoPIV) uses multiple cameras to obtain a velocity volume (3D3C) [47](#_ENREF_47). TomoPIV is more expensive in initial setup costs and computational complexity and processing time.

## Ultrasound image capture

Ultrasound based imaging techniques present an alternative to PIV that do not require transparent phantoms. The pulse wave Doppler method is usually employed to achieve 1-D time-dependent blood ﬂow velocity information [1](#_ENREF_1). However, many recent studies have shown that it is possible to capture the velocity profile using an ultrasound imaging system [61](#_ENREF_61), [128](#_ENREF_128), [133](#_ENREF_133). Echo-PIV, ultrasonic speckle velocimetry [146](#_ENREF_146) and ultrasonic perpendicular velocimetry [10](#_ENREF_10) do not have the Doppler ultrasound limitation such as angle dependence and can determine 2D velocity profiles. [Poelma, et al. 127](#_ENREF_127) employed ultrasound PIV to study 3D flow in a curved tube. The error level (0.5–1.5%) was comparable to conventional PIV, without the requirement of optical access to the geometry. However, typical ultrasound frame rates and frame sizes limit the peak speeds that can be captured. In particular, Kheradvar et al. [86](#_ENREF_86) noted peak velocity measurement capability of 0.3m/s and 0.7m/s at 35Hz and 80Hz, respectively. Poelma [126](#_ENREF_126) notes that in most ultrasound imaging investigations of haemodynamics, the upper limit for accurate velocity measurement is between 0.5m/s and 0.8m/s which is inversely dependent on the scale of the experiment. Ultimately, these velocities are too low to capture some inner lumen kinematics that occur in some haemodynamic flows.

# Conclusion

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality. *In-vitro* experiments that simulate haemodynamic dysfunction could provide the foundation for model-based algorithms to treat CVD, implant design, and validating the outcomes of CFD studies. There are various methodologies and many different steps in *in-vitro* experimentation. This level of choice makes it difficult for researchers to come to a consensus on the optimal approach. In this article, various *in-vitro* experimental simulation techniques to describe arterial haemodynamics were reviewed with the focus on using PIV flow imaging techniques. In particular, the relative benefits and costs of various experimental options regarding geometric reconstruction, prototyping, rigid and compliant phantom casting, flow mimicking, RI matching and experimental setups were presented and brief comparisons were assessed. This review shows that high accuracy *in vitro* experimental simulation of haemodynamics is difficult with current manufacturing and imaging processes. However, the review also shows that the current state of the art in haemodynamic modelling is capable of interpreting and mimicking haemodynamic dysfunction and ultimately can be used to optimise CVD treatment and the design of the vascular implants (stents and stent grafts).

**Statements:**

The authors declare that they have no conflict of interest with respect to the work presented.

SGY was supported during this research by the University of Canterbury Doctoral Scholarship scheme.

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