Physiological fluid mechanics research: A special Issue with a taster of forefront research

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Physiological fluid mechanics has been a research area for more than half a century with attempts to develop diagnostic techniques and biomarkers that differentiate between healthy and pathological circulatory states. In arterial hemodynamics, initially, from the 50's of the 20th century, techniques generally described arterial pressure and velocity waves as sinusoidal wavetrains running into long tubes. These were usefully expanded by the introduction of the impedance analysis in the late 60's and early 70's; the technique was borrowed from electrical engineering disciplines, presented arterial resistance, pressure and flow as an electrical circuit and the results were presented in the frequency domain.

Further development has been presented in the late 80's, described arterial waves as infinitesimal wavefronts and with the introduction of wave intensity analysis, the results were presented as a function of time, making the link between physiological events and time within the cardiac cycle possible. The analysis of wave intensity provided a positive step change in hemodynamics but 20 years after its introduction clinical uptake remained limited due to the invasive requirement of using the measured pressure and flow velocity. Therefore, it was important to reproduce the results using noninvasive measurements. With advances in ultrasound technologies, a successful attempt was introduced in the early 21st (2010) century to reproduce the wave intensity results using Doppler velocity and ultrasound M-mode diameter. Traditional wave intensity and impedance analyses considered the changes in pressure and velocity waveforms are entirely due to the travelling waves. A new, yet still controversial concept was introduced early this century (2003), with the reservoir-wave analysis, which accounted for the pressure developed due to stroke volume ejected into the arterial system as well as the waves generated by ventricular contraction. The concept is still debated and illustrates that a seemingly trivial biomarker as blood pressure, encompasses a level of complexity that will require advanced modelling and physiological experimentation to be fully understood.

The substantial advances in computer capacities in terms of speed and memory with the onset of the 21st century, in silico arterial models have become a popular research area. The computational simulations encompassed normal, young, old and pathological models to investigate the hemodynamics of various organs/vascular locations (i.e. cardiac, coronary artery, aorta, cerebral, kidney and liver) along the arterial system, including anatomical features such as tapering and congenital diseases. As well as regional level investigations, local simulations using 3D computational fluid dynamics studies were also popular attempting to uncover the association between localised geometrical and fluid mechanical features such as flow separation and recirculation near bifurcations and the development of certain pathologies, namely atherosclerosis.

The objective of introducing this Special Issue is to produce a taster of the latest advances in theoretical and experimental physiological fluid mechanics with potential clinical applications. The goal was to gather a collection of manuscripts that reflects research at the fore front of hemodynamics at various scales (0D, 1D and 3D), using different analytical techniques (wave intensity analysis, reservoir-wave analysis, and artificial intelligence) and applied to a variety of vascular territories and organs (coronary artery, cerebral circulation, and Arteriovenous fistula). The following is a brief commentary that is thought of as an enticing invitation to studying the manuscripts presented in this special issue, which we hope that will generate further discussions and research in the most exciting area of physiological fluid mechanics.

Since the observation that atherosclerosis, a focal disease, primarily develops in the immediate vicinity of bifurcations, branches and bends, wall shear stress (WSS) must be the most widely investigated biomechanical parameter in cardiovascular fluid mechanics research, with many studies demonstrating associations between shear stress patterns and disease development. Also in this special issue, Feng et al. (REF) use computational fluid dynamics (CFD) models of lesion specific and idealized coronary bifurcation models to investigate the effect of the bifurcation angle on the flow patterns and WSS distributions. Interestingly, while simulations in idealized models showed a significant correlation between WSS and bifurcation angle, such relation was not found for lesion-specific simulations. Caution is thus warranted when interpreting data from idealized models.

Fluid dynamics, and in particular wall shear stress, is also believed to play a critical role in the success and maturation for an arterio-venous fistula (AVF), a surgically created direct connection between an artery and a vein in patients with kidney failure. The fistula, bypassing the microcirculation, serves as an access site ensuring a high enough blood flow during dialysis sessions. Unfortunately, fistula creation often leads to complications and morbidity in these patients. Colley et al. (REF) have revised the literature and outline the proposed mechanisms for both AVF maturation and AVF failure. Authors conclude that neither clinical, animal nor computational studies have not yet shown a definitive link between any investigated metric and disease development. To reveal the possible role of biofluid dynamics in AVF maturation and failure, it will be paramount to collect data from patient-based longitudinal studies, which has become feasible using combined CFD modelling and 3D non-invasive imaging.

While the previous studies report on and/or apply well established and widely used wall shear stress metrics, the contribution of Calo' et al. (REF) is of a more fundamental fluid mechanics nature. Rather than seeking to grasp and quantify the complexity of blood flow in a single parameter like the time averaged wall shear stress or the oscillatory shear index – most convenient for statistical analysis though -, they embrace the complexity of the flow field and characterize time-histories of WSS magnitude and WSS projection along the main flow direction and orthogonal to it. The method is demonstrated in a CFD study on a dataset of ten left anterior descending pig coronary arteries. Authors conclude that a combined effect of low WSS magnitude and of the shape of the WSS-based descriptors time-histories could trigger atherosclerosis at its earliest stage, and they call for new experiments to provide a clearer determination of the WSS phenotype which is at the basis of the so-called arterial hemodynamic risk hypothesis in coronary arteries. Food for thought, at least.

Biofluid mechanics studies often address biofluid (or air) flow in larger vessel structures. These larger tubular structures, however, only ensure the transport of biofluids to sites of nutrient or gas exchange at cellular level and represents only about roughly 20 to 30% of the extracellular fluid (and just a fraction of total body water). Plasma leaks out of capillaries into the interstitium and ultimately finds its way back into the circulation, possible via drainage via the lymphatic circulation. It wasn't until very recently that a dedicated lymphatic system was discovered in the brain (called the glymphatic circulation) as an evacuation route of cerebrospinal fluid. Modelling interstitial flow is complex, and should not only account for the permeability and porosity of tissues, but ideally also for the fact that these tissues can undergo dynamic pressure and volume changes in response to instantaneous imbalances between mass in- and outflow. In this special issue, Vardakis et al. (REF) outline a novel multiporoelastic solver that allows for the coexistence of a multitude of interconnected compartments with varying properties, and apply the solver to study brain perfusion and the neurovascular unit in a 3D anatomically accurate brain geometry. They acquire novel, biomechanistically inspired biomarkers that capture the sophisticated nature of the neurovascular unit and the glymphatic system.

Amid all computation-based contributions in this special issue, the guest editors are most pleased to also have received one experimental study that made it through the peer review process. This may have to do with the specific topic of the study, namely on ventricular assist devices, a field where the value of hydraulic bench testing is still widely recognized and an essential component of the long road from device design to clinical applications. Highly performant and miniaturized rotary blood pumps have been introduced for a long time and are used for short term support of the circulation, but the absence of flow pulsatility forms a barrier for long-term applications. In their study, Wu et al. (REF) have tested a third-generation blood pump with pulsatile operation control algorithm isolated under pulsatile mode at various speeds, amplitudes, and waveforms, followed by experiments in a mock circulation system. Results show that the hemodynamic performance of pulsatile operations is promising, but susceptible to phase shifts, which seems plausible given that the pump interacts with a still contracting ventricle and an afterload system with its own characteristics.

With part of our community focusing on fluid dynamics, there is still considerable interest in the physics and mechanisms that shape the pressure (and flow) waveform, which is obviously the result of wave propagation and reflection in a complex 3D arterial network with branching non-uniform vessels, permanently changing size, composition and mechanical properties. While "downstream" reflections in the systemic or pulmonary arterial tree are relatively well understood, it is much less clear what happens at the ventricular-arterial interface. It may be assumed that the aortic/pulmonary valve acts as a total reflector in diastole when valves are closed, but less well known is the faith of backward propagating waves in systole, when the heart is contracting. Anyhow, what is clear is that the paradigm of the pressure and flow wave being composed of the forward and backward component blurs a much more complex reality where re-reflected backward waves add to the forward wave, whose reflections add to backward wave, and so on. A deeper insight into these mechanism may change our interpretation and view on the importance of reflection, and may especially force us to look differently towards the forward wave, which may be much more shaped by reflections than assumed now. The importance of re-reflection is addressed by Hametner et al., (REF) who established a model that enables the simulation of re-reflection at the aortic valve. The results show that the model is capable to provide physiological pressure curves only if re-reflections are assumed to be present during the whole cardiac cycle and authors conclude that re-reflections should be incorporated into models of wave transmission and may also be considered in methods of arterial pulse wave analysis.

Another aortic pressure wave feature associated with wave travel and reflection is the dicrotic notch, the "signature" of aortic valve closure in the pressure waveform, although no physical mechanism for the formation of the dicrotic notch seems to be generally accepted. In this special issue, Mazen et al. (REF) explore a mechanism based on the reflection of a backward wavefront from the aortic valve at the time of closure, but authors reject this hypothesis on the basis of experimental evidence. A hypothesis that holds more firmly involves the acceleration of the aortic valve apparatus at the time of valve closure.

Arterial pressure and flow waves were for a long time studied in the frequency domain, with waves seen as a superposition of a steady component and sinusoidal harmonics. While the technique is perfectly suited for system identification purposes and allows for wave separation analysis, frequency based methods are often perceived as less tangible or intuitive. An additional and complementary tool became available when Wave Intensity Analysis (WIA) was introduced for analysis of cardiovascular hemodynamics by Parker and Jones, adopting the concept from gas dynamics. At a given location, instantaneous changes in pressure (dP) and flow velocity (dU) combine into dI=dP.dU, the wave intensity (energy flux in W/m²). It allows for a most elegant analysis and interpretation of pressure and flow waves present at any moment during the cardiac cycle and allows for further exploration and wave separation analysis. A drawback of the original formulation, however, is the necessity of pressure and flow (velocity) waveforms, complicating implementation of the method into the clinic and clinical routine. Al alternative, based on diameter and velocity, has been formulated by one of the co-authors of this editorial (Ashraf W Khir) which can be applied non-invasively using ultrasound measurements of diameter and velocity. Ryan et al. (REF) have tested the magnitude of the disagreement between the invasive and non-invasive formulation using a 1D arterial network model through which they generated an age-stratified virtual population. They investigated how the two dominant nonlinearities - viscoelasticity and strain-stiffening - cause the two formulations to differ and found strong agreement between the pressure-velocity and diameter-velocity methods, particularly for the systolic wave energy, the ratio between systolic and diastolic wave heights, and older subjects.

An important consideration when processing measured signals for some sort of analysis is the accuracy of the measured data, and whether the process of the measurement itself may have an impact on the data. This concern applies to the specificities of the measurement setting (to what extent are measurements representative for the normal physiology? Clearly, highly invasive open chest experiments under anesthesia are unlikely to be representative, but what about measurements at rest in supine conditions) but also to performing the measurement itself. Does the instrumentation by itself have an effect on the measurements? Such question was addressed by Mynard et al. (REF), who investigated what effect the presence of a perivascular flow probe may have on the measurement of flow and pressure, and subsequent wave intensity analysis. The study was conducted using a 1D model of the sheep aorta and fetal lamb, animal models frequently used by the group. Results are reassuring, demonstrating a mostly minor effect of probe constraint on the intensity and pressure effects of the three major waves, and no impact on pressure reflection indices.

We are extremely happy to have received a contribution by one of the founding fathers of the widely accepted wave intensity theory and of the somewhat more controversial reservoir-wave concept. In its original formulation, the arterial pressure waveform is seen as of the superposition of a spatially invariant reservoir pressure, and an excess pressure attributed to waves. Since the original paper, the reservoir-wave concept has been refined and in a novel paper, Hughes and Parker (REF) present their latest insights on the modified arterial reservoir. A major refinement to the concept is the explicit recognition of the wave nature of both reservoir (Pres) and excess pressure (Pxs). The mathematical derivation and methods for estimating Pres in the absence of flow velocity data are described. Authors also discuss the zero-flow pressure (Pzf), the pressure at which flow through the circulation ceases and how it relates to the asymptotic pressure ($P\infty$) as estimated by the reservoir model.

The asymptotic reservoir pressure is also the topic of a paper by Pomela et al. (REF) co-authored by the guest editors. Still using the original reservoir-wave formulation, the concept was applied to a subset of the Asklepios population study, comprising over 1000 non-invasively measured carotid pressure and flow velocity waveforms in middle-aged healthy subjects. Different fitting techniques to the diastolic decay of the measured arterial pressure were used to determine the asymptotic pressure decay, which in turn was used to determine the reservoir pressure waveform. The corresponding wave speed was determined using the PU-loop method, and wave intensity parameters were calculated and compared. It was found that different fitting methods resulted in significant changes in the shape of the reservoir pressure waveform, but not in its peak and time integral. Although peak and integral of excess pressure, velocity components and wave intensity changed significantly with changing the diastolic decay fitting method, wave speed was not substantially modified.

1D arterial network models provide an elegant and efficient way to study arterial hemodynamics. Models used are most often based on generic, published datasets in humans, mainly addressing the systemic circulation. In their paper, Chambers et al. (REF) employ an appealing semi-automated methodology based on directed graphs and structured tree models that allows to construct subject-specific 1D arterial network models from micro-CT images of the pulmonary vasculature in mice leading to models incorporating several thousands of segments. The method is applied to control animals and a mouse model of pulmonary hypertension. Fluid dynamics predictions show that in addition to changed network geometry, vessel stiffness is higher in the hypertensive animal models than in the control models. Given that vessel stiffness and pulsatile hemodynamics are increasingly used in diagnosing patients with pulmonary hypertension, exploiting anatomical and functional information that can be acquired using MRI, the methodology may be transferrable to the human setting.

Detailed analyses of the intra-arterial flow field and wall shear stress distributions or a better understanding of the arterial pressure waveform and the circulation improve our understanding of the pathophysiology of the cardiovascular system and may contribute to a better diagnosis, treatment and follow up of patients, but have relatively little acute impact for the patient. Nor do we provide data that helps clinicians in acute care, where decisions on whether or not to intervene may make a difference between life and death. One such critical variable is cardiac output, i.e., the blood volume circulated by the heart within one minute. It is somewhat surprising that to date, there is still no generally accepted, reliable method that allows for a trustworthy and permanent monitoring of cardiac output in patients. In this special issue, Papaioannou et al. (REF) tested the Mobil-O-Graph for that purpose, a brachial oscillometric cuff-based ambulatory blood pressure device with on-board algorithms that provide waveform-derived physiological data, including cardiac output. The study demonstrates that non-invasive, automated, oscillometric, cuff-based apparatus is reproducible with a similar precision as thermodilution and a fairly acceptable accuracy, but it remains to be demonstrated that the technology can also detect acute changes in cardiac output which is vital in the intensive care unit, and the purpose of monitoring.

It has become hard to escape from artificial intelligence (AI) in science, and AI will not be absent in this special issue thanks to the work of Carson et al. (REF) who applied artificial intelligence strategies for the estimation of coronary fractional flow reserve (FFR), the clinical golden standard to assess the severity of coronary stenosis. To measure FFR, an invasive intracoronary pressure recording is required, distal to the stenosis after induction of maximal vasodilation. FFR is then calculated as the ratio of mean distal to proximal pressure, with a value below a certain threshold indicating intervention. Since a few years, CFD-based FFR predictions have been introduced, whereby the pressure drop over the stenosis (and thus FFR) is calculated from CFD simulations set up from CT-scans. Here, Carson et al. go one step further and trained different AI models on a database of synthetic data, generated using a 1D blood flow model set up on CT-scans. The aim of the AI model is to bypass the CFFD simulations and get the pressure drop and FFR from features extracted from the CT-scan. It is concluded that the Feed Forward Neural Network shows promise in successfully predicting FFR in real patients, and could be a viable option if trained using a large enough data set of real patients.

Finally, we both have had a long standing interest in physiological fluid mechanics and we have discussed producing this Special Issue in 2019. Despite the undesirable tide with COVID-19, it has been a real pleasure to see this Special Issue come to fruition. So it is with much gratitude that we thank all our contributors to this edition, both authors and reviewers. We sincerely hope that the content of this Special Issue will stimulate further research with the ultimate goal in mind to better understand the nature and characteristics of travelling fluids inside the human body, and developing clinical biomarkers that could be used as bedside tools and an aid to assist clinical decisions.

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