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In vitro validation of measurement of volume elastic modulus using photoplethysmography

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ABSTRACT

Arterial stiffness (AS) is one of the earliest detectable symptoms of cardiovascular diseases and their progression. Current AS measurement methods provide an indirect and qualitative estimation of AS. The purpose of this study is to explore the utilisation of Photoplethysmography (PPG) as a measure of volumetric strain in providing a direct quantification of the Volume Elastic modulus (E_v). An *in vitro* experimental setup was designed using an arterial model to simulate the human circulation in health (*Model 2*) and disease (*Model 1*). Flow, pressure, and PPG signals were recorded continuously under varied conditions of flow dynamics. The obtained E_v values were validated with the gold standard mechanical testing techniques. Values obtained from both methods had no significant difference for both models with a percent error of 0.26% and 1.9% for *Model 1* and *Model 2*, respectively. This study shows that PPG and pressure signals can provide a direct measure of AS in an *in vitro* setup. With emerging noninvasive pressure measurement methods, this research paves the way for the direct quantification of AS *in vivo*.

1. Introduction

Cardiovascular diseases (CVD) are the foremost cause of death globally, with numerous risk factors such as diabetes, hypertension, hypercholesteremia, smoking and obesity associated with their development and progression [1–3]. Many studies have reported that the presence of these factors is related to a change in the mechanical properties of the arterial wall and an increase in Arterial Stiffness (AS) [4–8]. AS describes the reduced capability of an artery to expand and contract in response to pressure changes. Its clinical relevance is due to its fundamental role in pulsatile haemodynamic forces, as one of the earliest detectable symptoms of structural and functional changes within the vessel wall. AS is emerging as the most important determinant of increased systolic and pulse pressure in our ageing community. Therefore, AS is a root cause of cardiovascular complications at an early stage and is associated with accelerating Atherosclerosis (ATH) [9,10]. An increase in AS can be related to two major factors: (1) an increase in Intima Media Thickness (IMT) due to calcification, plaque formation, inflammation and rupture of elastin and collagen fibers [11,12]; (2) hypertension and hence an increase in the Circumferential Stress (CS) affecting the vessel wall which is associated with further cardiovascular complications and plaque rupture [13,14].

It is only recently that significant attention has been given to providing a precise measurement of AS. There has been an increased interest in the development of innovative non-invasive methods and devices for the diagnosis of CVD at an early stage in an effort to prevent further complications, and monitor pharmacological and non-pharmacological treatments [15,16]. In recent papers, we addressed the role of haemorheology in the photoplethysmographic waveform [17], and the relationship between the photoplethysmographic signal and transmural pressure values [18]. Further waveform analysis has been used for non-invasive estimations of AS [19–21].

Photoplethysmography (PPG), is a non-invasive optical technique commonly used for the measurement of arterial blood oxygen saturation in pulse oximetry [22]. It is widely accepted that the optical pulsations detected by a PPG system are modulated at the heart pulse rate due to arterial blood volumetric changes. The PPG signal, as is commonly referred, can be obtained at any vascular tissue surface using optical sensors, operating in either reflection or transmission mode [23,24]. The choice of the light sources used in pulse oximetry sensors varies between the visible and the near infrared range in accordance with the absorption spectra of oxy and deoxyhaemoglobin. The light transilluminates the tissue, and undergoes multiple stages of reflection, absorbance, and scattering. The photodetector, which is an integral part of the PPG sensor, captures the travelling light, where the current variations

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are electronically processed, amplified and finally recorded. The PPG signal comprises two components, the pulsatile AC, and they non-pulsatile DC component. The origin of the signal and the question of what does PPG actually measures has attracted wide interest from the research community over the last decades [25–28]. Besides the major application of PPG in pulse oximetry, the signal is believed to contain further chemo-mechanical information related to the circulation [25,29,30]. For example, there were studies where the PPG was used to monitor blood pressure non-invasively [31–33]. Others have developed methods for the estimation of respiratory behaviour [34,35].

In relation to arterial stiffness, a host of indices derived from PPG and pulse pressure signals have been introduced to quantify AS [4,20,21,36–39]. When multiple indices exist, it is expected that none has proved any superiority, and all have problems in measurement and interpretation. Noninvasive measurement of AS entails measurement of parameters that are intrinsically associated with stiffness. The most widely used method is Pulse Wave Velocity (PWV), used for the estimation of AS by the Stiffness Index (SI) [21,40,41]. Further studies have explored the possibility of using the PPG pulse counter analysis and provide the augmentation index (AIx) [39,42]. AIx is the measure of the contribution that the wave reflection makes to the systolic arterial pressure, and is obtained by measuring the reflected wave coming from the periphery to the centre. It is defined as the ratio of the height of the late systolic peak to that of the early systolic peak in the pressure pulse. The second derivative of the PPG signal (SDPTG) has been utilised for the detection of the diastolic, systolic and inflexion points in the PPG for the estimation of arterial stiffness using AIx or the Reflection Index [21,43].

The PWV method measures the pulse propagation speed between two measurement sites. The parameter relevance to AS has been described in the late 19th century by Moens–Korteweg equation:

$$\mathrm{PWV} = \sqrt{Eh/(2r\rho)} \tag{1}$$

and is determined by E, the *elastic modulus*, arterial geometry (h = thickness, r = radius) and blood density, ρ. The assessment involves measurement of two quantities: transit time of arterial pulse along the analysed arterial segment, and distance on the skin between both recording sites. A practical problem that arises in the measurement of PWV is when convenient points of measurement are not in the same line of travel. Moreover, inaccuracies are highly expected in determining the actual arterial distance between recording sites from measurements on the surface of the body [40]. PWV in large central elastic arteries such as the aorta increases markedly with age, whereas in upper limb arteries PWV does not increase. Furthermore, fundamental limitations still occur with PWV measurement due to ignoring some of the major variables in the circulation. Such factors include the pumping power of the heart, blood rheology, and the resistance of the microcirculation. All such factors are associated with changes in the thickness of the arterial wall (h), the arterial radius (r) and blood density (ρ), which will directly affect PWV, and hence a change in PWV might not necessarily reflect only stiffness changes in all cases [44–46].

Pulse pressure, pressure AIx and ambulatory arterial SI have been widely used in the identification of large AS. Over the age of 60 years, pulse pressure is expected to increase and is associated with a dominant rise in AS. However, in young subjects, pulse pressure increase at the peripheral site may lead to misinterpretations of hypertension. Thus, pulse pressure may not be a very accurate marker for assessing AS [47].

All indices suggested are known to be qualitative and indirect in principle. Clarenbach et al. reported a study comparing PPG with tonometry [20]. This study concluded that AIx and SI weakly correlated in patients with the chronic pulmonary disease or obstructive sleep apnoea. Such correlation was not observed at all when patients with low cardiovascular risk were included in the analysis. Moreover, AIx did not differentiate between patients with intermediate and high cardiovascular risks. Jerrard et al. demonstrated that in a hypertensive population, there was a poor agreement between PWV, AIx and pressure pulse methods. Following adjustment for age and gender, no correlation was observed [38]. Some other studies have shown IMT and PWV to be positively correlated, however, such relations were relatively weak and some studies have shown no relation [10,12]. Zureik et al. found no association in 564 subjects after adjusting for age and blood pressure [48]. Compared with the original reports there is sufficient evidence in the literature suggesting a poor correlation between those parameters in hypertensive patients whether treated or untreated, to the extent that all correlations were lost following adjustment for age and gender. The current understanding is that there is a disparity in the ability of these measures to predict future vascular events.

The *Volume Elastic modulus* (E_v) is estimated from the regional Pressure–Volume (P–V) relationship. This parameter provides comprehensive information on the arterial wall properties regarding the global effect of the circulation. A higher value of E_v suggests increased stiffness. Currently, there are no studies in the literature reporting on the precise and direct measurement of E_v of the arterial wall using non-invasive methods.

In this study, we have developed a new method to measure E_v using the PPG and pressure signals. We validated the method in an *in vitro* model of human circulation in health and disease. During an *in vivo* scenario, many factors can influence the dynamics of the flow. This includes the vassal tone, the specific biochemical content, and the endothelial activity. Such factors also vary from one participant to another and can be altered in the same participant throughout the day. To overcome some of these limitations and develop a better understanding of the quantitative analysis of the PPG, an *in vitro* setup was developed. This allowed validation of the proposed method with the gold standard elasticity method of extension testing and generating the true stress-strain curve, a merely unfeasible practice for *in vivo* studies. In this paper, we present *in vitro* results, highlighting the capability of using the PPG components as a measure of AS which could contribute further in the diagnosis of complications related to biomechanical abnormalities in the arterial wall and the endothelium.

1.1. Theoretical method

Consider a circular tube with an initial volume (V_1); suppose the inner surfaces of the tube are exposed to transmural pressure (P); forces of radial stress are perpendicular to and act on all surfaces uniformly as seen in Fig. 1(a). The response of the object to this uniform stress is an expansion of volume to V_2.This behaviour can be characterised using the bulk modulus or the Volume Elastic modulus (E_v) which can be expressed with the following relationship:

$$\left(\frac{dV}{V}\right).E_v = dP \tag{2a}$$

where dP, is the change in the transmural pressure signal, and dV is the change in the volumetric signal. In the presence of pulsatile flow conditions, the side view of the tube can be represented as seen in Fig. 1(b) and the pulsatile transmural pressure (P) and Volume (V) signals are out of phase ($\emptyset$), as seen in Fig. 1(d). Due to the time-dependency of the pulsatile flow, Eq. (2a) can be derived with respect to time and expressed with Eq. (2b). This is illustrated in the linear approximation in Fig. 1(c). Here, the flow is assumed

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