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## Distinguish the Stable and Unstable Plaques Based on Arterial Waveform Analysis

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### Abstract

The rupturing of unstable plaques, formed by atherosclerosis, is the main factor contributing to the stroke event. According to stroke association in 2017, the stroke is the fourth leading cause of death in the UK. The percentage of plaque composition plays an important role for plaque stability and can be considered as important information to determine whether the patients need surgery or not. The main aim of this work is to determine the relationship that exists between plaque composition and arterial waveform for distinguishing stable and vulnerable plaques. An *in-vitro* experiment, representing the arterial system, is used to investigate the effect of the composition of the atherosclerosis on the propagation of the arterial waveforms. Different types of the artificial plaque, fabricated manually, were implemented into the artificial carotid artery. The pressure, velocity and arterial vessel wall movement were measured simultaneously proximal to the site of the arterial plaques. Wave intensity analysis (WIA) was used to separate the waves into forward and backward waves to identify how the plaque compositions will affect the reflected arterial waveforms. Our results indicated that stable plaques caused the stronger reflected waves, leading to the higher amplitude of the arterial diameter waveform. In general, this study demonstrated that the arterial waveforms are strongly associated with the compositions of the arterial plaques, implying the arterial waveform could provide the information to characterize the types of the plaques, then leading to a novel approach to stratify the atherosclerosis patients and determine if the interventional vascular surgery is needed.

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*Keywords:* Stable plaque; Vulnerable plaque; Wave Intensity Analysis;

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### 1. Introduction

Cardiovascular diseases (CVD) cause a death for almost 30% in the worldwide and could even lead to disability (Kohno et al., 2018). Stroke is the fourth largest causes of death in England and Wales, and the third in Scotland where approximately 100,000 stroke events occur in the United Kingdom (Stroke Association, 2018). The atherosclerosis plaque in the carotid arteries is considered the main cause of a stroke and it is

initiated by inflammatory processes in the endothelial cells of the artery, which is associated with retained low-density lipoprotein (LDL) particles. The LDL, therefore, will pass through the endothelium, which build up the so called ‘*Plaque*’ (Johri et al., 2017).

There are several types of plaques, and some of them are more likely to rupture than the others. The stable plaques are less likely to rupture because they have a thick fibrous cap with a small lipid core (LC) area (van der Wal, 1999). While unstable and vulnerable plaques have been characterized by several studies which indicate that they have a thin fibrous cap ( $< 65 \mu\text{m}$ ) and its LC is substantial (Libby, 2001; Andrews et al., 2018). If plaque ruptures in the carotid artery, it will either block the oxygenated blood from reaching the brain or bleed, which will lead the brain cells to die (Li et al., 2019).

In recent years, Magnetic Resonance Imaging (MRI) has played an important role in assessing the health of blood vessels. One of the MRI studies investigated the macrophages by using Polymeric Nanoparticle PET/MR Imaging to detect atherosclerotic plaques. That study proved that this technique can be used as a non-invasive method to assess the inflammation plaques and can play an important role in the therapy purposes (Majmudar et al., 2013). However, one of the limitations of this technique is that the acquisition data is not simultaneous, which may lead to creating incorrect results (Cuadrado et al., 2016). In addition, the negative sides of MRI are relatively high cost and require breath holds, which may not be suitable with some patients. The composition of plaque and its vulnerability were examined by Naim et al. (2013) to evaluate the ability of non-invasive vascular electrography (NIVE) by applying high MRI resolution. Although this study success to detect the present of lipid core in the significant stenosis, it fails to detect precisely the vulnerability of plaque.

Jashari et al. (2015) used Cone Beam Computed Tomography (CBCT) in conjunction with ultrasound to detect the atherosclerotic calcification in the carotid artery. It is true that this study identifies the volume and the presence of calcification, but does not show the detection of LC and the progress of plaque in the early stages. Sigovan et al. (2017) applied 3D black blood Magnetic Resonance Angiographic (MRA) of the carotid blood vessel to investigate intra - plaque hemorrhage (IPH) and the stenosis, which showed reliable measurements in the stenosis of the carotid vessel, although overestimation has been detected through comparison with 3D contrast-enhanced angiography. The pulse wave imaging has been used in recent study with stenosis degree between 50% and 80% in order to identify the plaque properties (Li et al., 2019). This study gives an optimistic view that it is possible to differentiate between plaques. However, the results of this study, to large extent, are not accurate because the data was not adequate due to complex waveform. To date, a novel technique, being able to distinguish the compositions of the plaques and providing the accurate information to the vascular surgeons to clarify the types of the plaques, is still lacking. Therefore, the main aim of this paper is to use the wave intensity analysis (WIA) techniques to separate the arterial waveform into the forward and backward components to characterize the difference between stable and unstable plaques.

## 2. Theoretical background

WIA technique was introduced by Parker and Jones to enable the measured waveform to be separated into the forward and backward components (Park and Jones, 1990). WIA needs the knowledge of wave speed,  $c$ . In this paper, the wave-speed,  $c$ , is determined by simultaneously measurement of the diameter and velocity using the methods of  $\text{Ln DU-loop}$  (Eq (1)) (Feng et al., 2010),

$$c = \pm \frac{1}{2} \frac{dU}{d \ln D} \quad (1)$$

where:  $dU$  is the change of velocity and  $d \ln D$  the change of logarithm of diameter. The separation of  $U$  and  $D$  depends on the  $c$  and the changes of  $U$  and  $D$ . Their calculations are illustrated in the following equations:

$$dD_{\pm} = \frac{1}{2} \left( dD \pm \frac{D}{2c} dU \right) \quad (2)$$

$$dU_{\pm} = \frac{1}{2} \left( dU \pm \frac{2c}{D} dD \right) \quad (3)$$

where: (+) refers to the forward wave and (-) to the backward wave; the  $dD_{\pm}$  is the change of the forward and backward diameter,  $dU_{\pm}$  is the change of the forward and backward of velocity;  $D$  is the measured diameter. Then, the forward and the backward diameter and velocity can be calculated by the following equations:

$$D_{\pm} = \sum_{t=0}^T dD_{\pm} + D_0 \quad (4)$$

$$U_{\pm} = \sum_{t=0}^T dU_{\pm} + U_0 \quad (5)$$

where:  $T$  is the period total time,  $D_0$  and  $U_0$  are the integration constants and taken arbitrarily as zero. The forward and backward waves in arteries are caused by heart and reflection, respectively. Thus using this technique could give important information in arterial system especially with a plaque.

### 3. Methodology

This study attempts to distinguish between stable and unstable plaques based on arterial waveform. Two types of plaques were fabricated and their characteristics are illustrated in Table 1. The *in-vitro* experimental setting (Fig. 1) consists of the pulsatile pump (Harvard Apparatus, USA), reservoirs and latex penrose tubing (Kent Elastomer, UK). The measurement devices include: Digitimer (Sonometric Corporation, Canada) for diameter, perivascular flow probe (Transonic, USA) for flow rate. The artificial plaques, possessing the features of the human carotid plaques, were prepared based on the clinical findings by Butcovan et al. (2016). The artificial plaque in this study consisted of gelatin (from bovine skin, type B, Sigma – Aldrich, St. Louis, MO) and a collagen (from human placenta, type III, Sigma – Aldrich, St. Louis, MO) for fibrous cap, calcium chloride hexahydrate (Sigma – Aldrich) for calcification and soybean oil for LC (Guo et al., 2013). The fibrous cap was firstly prepared and left for 24 hours. The calcium, collagen and soybean oil were filled into the fibrous cap and left for 48 hours.

Table 1. The compositions of two types of arterial plaques: stable (FC) and vulnerable plaques (TCFA)

Plaque type	Fibrous cap thickness	LC % of plaque volume	Ca % of plaque volume
FC	0.27 mm	46.86 %	6.23 %
TCFA	0.02191 mm	25.90 %	0 %

Note: FC, fibro-calcified plaque; TCFA, thin-cap fibroatheroma.

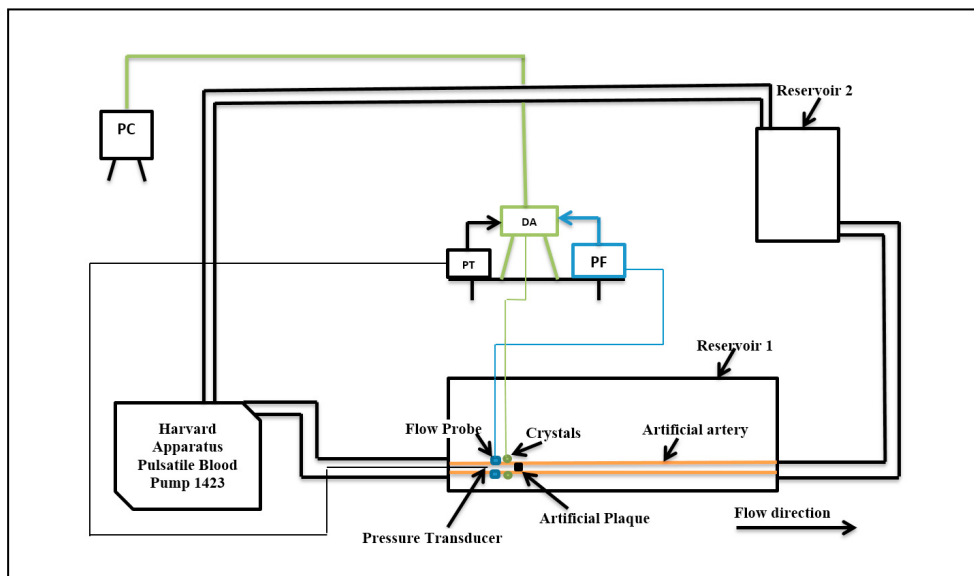


Fig. 1. The experimental set-up consists of the pulsatile blood pump, two reservoirs and artificial arterial system. The measurement sensors include flow probe, pressure transducer and sonometric crystals. The measurements were taken at the site of 5mm before the plaque.

Abbreviation of measurement equipment: PT for pressure transducer bridge amplifier, PF for perivascular flow meter, DA for data acquisition and PC for personal computer.

The setting of pulsatile pump which represents the heart was as follows: heart rate at 70 RPM and the stroke volume was at 17 c.c. The tube system was adjusted by applying different compliance in order to obtain the healthy carotid waveform. The pressure transducer, flow probe and crystals were close to each other and their distance between one to another were less than 5 mm. The pressure, flow rate and change of diameter reading

were firstly collected with no plaque as a healthy case and the measurements were taken proximal to the plaques. The flow rate and wall movement data were collected simultaneously and sent it to the computer. These data were analyzed by Matlab version 16.

## 4. Results

### 4.1. The measured diameter and velocity

The measured velocity and diameter for the healthy one (no plaque), unstable plaque and stable plaque are shown in Fig.2 a and b, respectively. It is clear that the higher amplitudes of diameter waveforms were generated in the arteries with the plaques attached, while healthy artery with no plaque has the lowest amplitude of the diameter waveforms. As is expected, the stable plaque generated the highest amplitude of the arterial waveform, while the amplitude of the diameter waveform in the artery with the unstable plaque is less than that with the stable plaque. Similar pattern was also found for the velocity arterial waveform although the difference between three types of arterial system is not very significant.

### 4.2. The forward diameter and velocity

WIA is used to separate the measured pressure, velocity and diameter into the forward and backward components for three types of arterial-plaque system (Fig.3). The forward velocity amplitude of the stable plaque that generated from the heart (ventricle) is slightly higher than that of unstable plaque (0.553 m/s via 0.533 m/s). Similarly, the forward diameter amplitude of stable plaque is also slightly higher than that of unstable plaque (1.04 mm via 0.96 mm).

### 4.3. The backward diameter and velocity

The backward waves which produced from the reflections are shown in Fig. 4 a and b. It was observed from the figures that the backward velocity and diameter of soft plaque are higher than those for hard plaque are. This phenomenon is opposite to our prediction as the hard plaque should have higher backward reflection than the soft plaque because of their stiffness.

## 5. Discussion

This study investigated two types of plaques: the FC and TCFA plaques, which represent the hard plaque and soft plaque, respectively. Configuration of these two artificial plaques were referred from the previous studies regarding the plaque characteristics and properties by Guo et al. (2013), Teng et al., (2014) and Butcovan et al. (2016). The data was collected after five minutes of starting the experiment. Each plaque was tested three times in order to ensure the reproducibility. It is as expected that the stable plaques with the higher proportions of Ca is linked with the higher amplitude of the measured diameter, whereas the unstable plaques with the more percentage of lipid core is related to the lower amplitude of the measured diameter. The visible differences of the measured velocity waveforms were observed for two types of the arterial-plaques system with the lowest velocity amplitude occurring at the arterial system with the stable plaque. This means that stable plaques generated the stronger reflected waves, leading to the higher amplitude of the arterial diameter waveform and lower amplitude of the velocity waveforms.

The observations from Fig. 3a shows that the forward velocity in hard plaque is slightly higher than soft plaque. This observation could be explained as the further reflection of the reflected wave was occurring at the inlet of the system, which led to the increase of the velocity. Likewise, the forward diameter amplitude (Fig. 3b) in hard plaque is slightly higher than in soft plaque with the same reason.

The amplitude of backward waveform in the arterial system with hard plaque is expected to be higher than soft plaque because the stiffness of the arterial hard plaque is higher than soft plaque which supposed to produce higher reflection. It has been observed that the backward reflection amplitude of the soft plaque in velocity and diameter is higher than hard plaque (Fig. 4 a and b). These results do not meet our expectation. The reason of this phenomenon could be from further re-reflections from the inlet tube or because the material properties of the artificial artery of the hard plaque is different from the one that used in the soft plaque which do need further investigations.

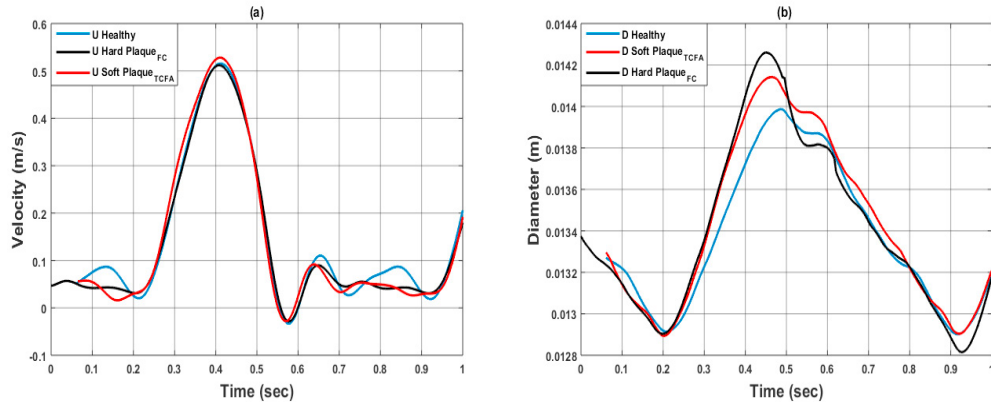


Fig. 2. The measured velocity (a) and diameter (b) waveforms in three types of the arterial system: healthy one (blue), and with hard plaque (black) (FC) and soft plaque (TCFA) (red). The amplitudes of the velocity waveform are close to each other. The hard plaque caused the highest amplitude of the diameter, while the lowest amplitude of diameter was observed in the healthy arterial system.

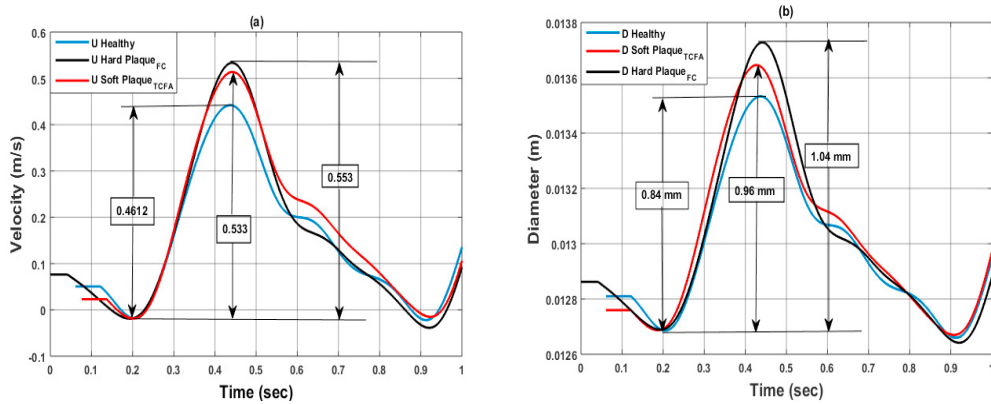


Fig. 3. (a) The forward velocity of healthy (blue), hard plaque (black) (FC) and soft plaque (TCFA) (red). The amplitude of velocity for hard plaque is higher than that for soft plaque; (b) The forward diameter of the healthy, hard and soft plaques. The amplitude for hard plaque is higher than that for soft plaque. The double- arrow lines demonstrate how the amplitude is measured.

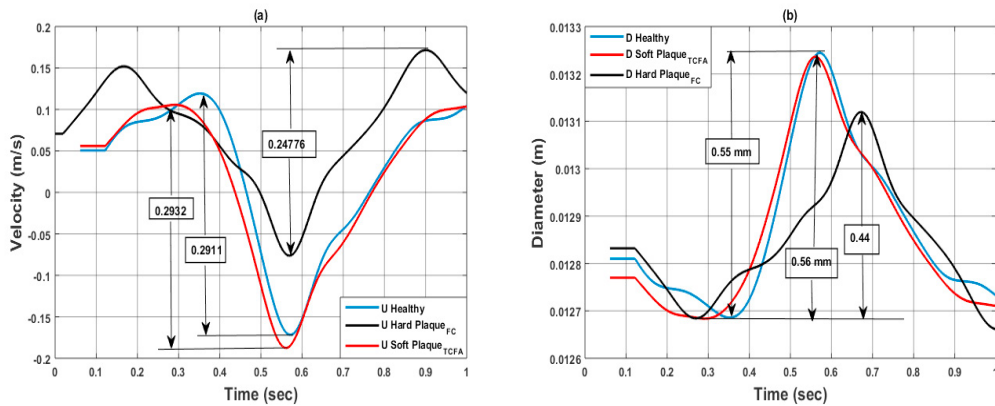


Fig. 4. (a) The backward velocity of healthy (blue), hard plaque (black) (FC) and soft plaque (TCFA) (red). The amplitude for soft plaque is higher than that for hard plaque; (b) The backward diameter of the healthy, hard and soft plaques. The amplitude for soft plaque is also higher than that for hard plaque. These results are not expected and further investigations are needed.

Finally, the limitation of this study is the fact that other types of plaque should be investigated. This may increase the capability of using this technique. Furthermore, the artificial plaque characteristics were fabricated as the same as the real plaque in terms of compositions and dimensions. However, its shape was uniform, which is different from the human carotid arterial plaques observed from clinical studies.

## 6. Conclusion

This study demonstrates that the arterial waveform could provide useful information about different types of plaques. The compositions of the plaque are directly related to the waveform properties, which could lead to characterize between stable and vulnerable plaques. Using WIA to separate the waves into forward and backward waves has the potential to distinguish between stable and unstable plaques. Our findings notify that the forward velocity and diameter amplitude in hard plaques is higher than soft plaques. The fact that the backward velocity and diameter amplitude in soft plaque is higher than hard plaque is not expected and needs more investigations. The outcome might assist to distinguish between hard and vulnerable plaques and help the vascular surgeons to make decision precisely.

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