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Review

Photoplethysmogram second derivative review: Analysis and applications

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Photoplethysmogram (PPG) and its second derivative of the photoplethysmogram (SDPTG) are simple and low cost optical techniques for detecting and tracking blood volume changes. The PPG waveform and its SDPTG have been used by many scholars to obtain valuable information about heart and cardiovascular system. Since PPG and SDPTG reflect blood volume changes, much work has been done on its application as a diagnostic tool for screening arterial structure and its related diseases and disorders. In this article, we first provide a short review of the effects of atherosclerosis in losing arterial elasticity. Secondly, we introduce the PPG waveform and discuss in details the analysis methods and applications of its SDPTG waveform. Finally, we demonstrate links between elastic properties of arteries, atherosclerosis, PPG and SDPTG. The main focus of the review is on the analysis methods and applications of SDPTG.

Key words: Photoplethysmogram (PPG), second derivative of the photoplethysmogram (SDPTG), atherosclerosis, aging, arterial stiffness, distensibility, morphological changes, endothelial function.

INTRODUCTION

The underlying cause of cardiovascular (CV) disease is atherosclerosis. Atherosclerosis can occur because of fatty deposits on the inner lining of arteries or thickening of muscular wall of the arteries from chronically elevated blood pressure (Joachim et al., 2015). Atherosclerosis does not usually produce any symptoms until a cardiovascular disease (CVD) occurs. Therefore the prediction of atherosclerosis might contribute a lot to disease stratification and risk prevention. Mainly, atherosclerosis starts with oxidation of low-density lipoprotein (LDL) particles in the arterial wall (Hanna et al., 2011). Oxidative modified LDL (oxLDL) damages the endothelium of the artery – a pathophysiology similar to that of vascular erectile dysfunction (ED) (Stocker and Keaney, 2004; Kirby et al., 2005). As a result, the elasticity of the arteries deteriorates. Impaired arterial elasticity and increased levels of circulating oxLDL as well as elevated fibrinogen and resting heart rate associate with subclinical atherosclerosis and increased risk of CVD events (Cooney et al., 2010). The development of atherosclerosis prevents endothelial cell from regulating blood flow. Moreover, the accumulation of atherosclerosis affects the propagation of blood which can be detected by the recording the PPG signal. A great

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contribution to PPG research and development has been provided by Allen (2007). This article aims to extend the contribution by providing a topical review on the second derivative of PPG (SDPTG). The SDPTG can be used to reflect arterial characteristics. The changes of its five-waves (namely 'a', 'b', 'c', 'd', and 'e') can be utilized to study changes in vascular system and arterial elasticity. In addition, the SDPTG is used by many scholars to ease the detection of peaks, valleys, and inflection point on the original PPG waveform. This topical review seeks to bring SDPTG's analytical methods and applications in one pool to ease and facilitate linking and building of ideas and thoughts of SDPTG applications and utilizations.

PHOTOPLETHYSMOGRAM (PPG)

Several decades before the arrival of pulse oximetry, the simple PPG was used as a measure of tissue blood volume (Challoner, 1979). It is related to plethysmograph, the measurement of pulsatile tissue volume. The plethysmograph measures the volume changes in any and all blood vessels (Andrew et al., 2008). Arterial pulsations are the most significant (Whitney, 1953). The PPG is an optically obtained plethysmograph, which is a volumetric measurement of an organ. It can be used to detect blood volume changes in the microvascular bed of tissue (Challoner, 1979). The PPG is often obtained by using a pulse oximeter which illuminates the skin and measures changes in light absorption (Shelley and Shelley, 2001). The contour of the pulsatile component of the PPG signal has been found to include content descriptive of vascular health (Brumfield and Andrew, 2005). PPG pulse signals can be easily obtained from the tissue pads of the ears, fingers and toes where there is a high degree of superficial vasculature (Allen and Murray, 2003). It has widespread clinical application, with the technology utilized in commercially available medical devices, for example in pulse oximeters, vascular diagnostics and digital beat-to-beat blood pressure measurement systems (Allen, 2007).

The use of PPG's signal derivatives are developed actually to facilitate the accurate recognition of the PPG's points of interest and to ease the interpretation of the original PPG waveform. The use of PTG to study vascular aging, arterial stiffness, atherosclerosis, endothelium dysfunction and erectile dysfunction is highly appreciated. Aging is accompanied by increased stiffness of large elastic arteries, leading to an increase in pulse wave velocity (PWV) (Peskin and Rowen, 2010). Premature arterial aging, as determined by an elevated aortic PWV, is now recognized as a major risk factor for ischemic heart disease (Laurent et al., 2001). Vascular aging influences the contour of the peripheral pressure and volume pulse in the upper limb (O'Rourke and Kelly, 1993). Arterial stiffness can be measured noninvasively by the use of PPG technique (Qawqzeh et al., 2012).

TOPICAL REVIEW BACKGROUND

The second derivative of the PPG wave has characteristic contours (waves) that facilitated the interpretation of the original PPG waves (Takazawa et al., 1998). Therefore, the SDPTG was developed as a method allowing more accurate recognition of the inflection points and easier interpretation of the original plethysmogram wave (Elgendi, 2012). The SDPTG wave patterns is determined by the proportions of the b, c, d, and e waves to the 'a' wave. The second derivative of the finger PPG waveform is used to stabilize the baseline and enable the individual features to be visualized and detected easily (Elgendi, 2012). However, this topical review tries to provide a reference document for researchers interested in finding a promising screening tool based on the analysis of PPG waveform and it's SDPTG.

PPG SECOND DERIVATIVE (SDPTG)

The length of the vascular system and the inner diameter and wall thickness of vessels may modify the SDPTG wave pattern in the growth period. Thereafter, as the effects of these factors decrease, the increase in intravascular pressure and decreasing wall elasticity due to aging may affect the wave pattern (Iketani et al., 2000).

Toshiaki et al. (2007) sought to elucidate independent determinants of the SDPTG among various cardiovascular risk factors in middle-aged Japanese men. They observed no independent association between the SDPTG indices and blood leukocyte count or serum C-reactive protein levels. Raveendranadh et al. (2012) utilized the SDPTG to assess aortic stiffness and wave reflection in their study of cardiovascular effects of caffeine in healthy human subjects. Takazawa et al. (1998) performed a drug administration study to evaluate the clinical application of the SDPTG of the fingertip PPG waveform. They extracted an aging index (AI = b-c-d-e/a) based on SDPTG five waves. The developed aging index had a higher value for women than for men. Moreover, they concluded that the aging index might be useful for evaluation of vascular aging and for screening of arteriosclerosis. Takazawa et al. (1998) and Imanaga et al. (1998) observed that the effect of angiotensin on the value of b/a was contrary to that of nitroglycerin and the value of b/a was clearly affected by atherosclerosis indications.

However, a study by Toshiaki et al. (2006) described the association of SDPTG indices, the risk of CHD and Framingham risk score. They recorded SDPTG from a community without apparent atherosclerotic disorders. Their findings showed that SDPTG indices significantly correlated with the Framingham risk score in both genders, as well as several coronary risk factors. Figure 1 demonstrates the characteristics of PPG and its

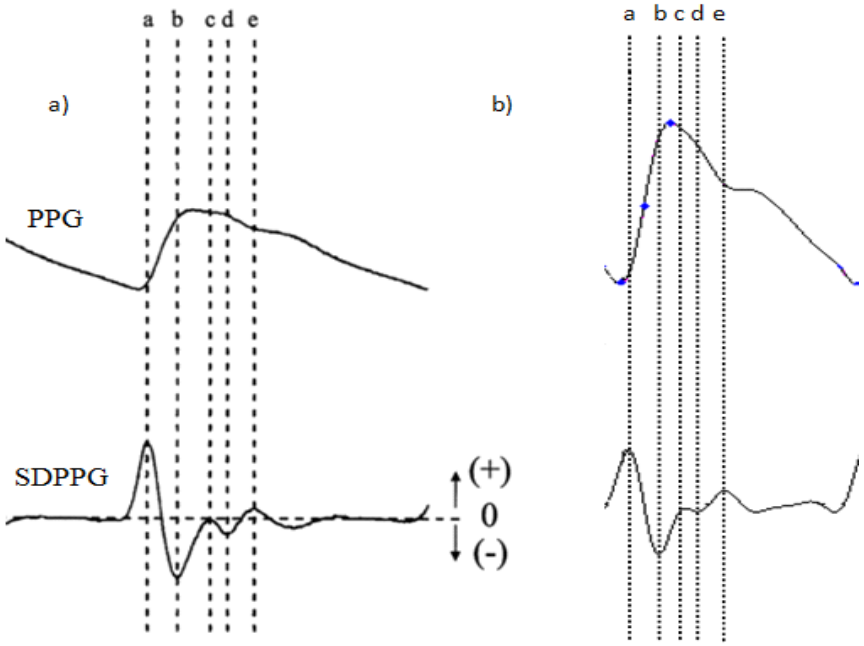

Figure 1. The characteristics of SDPTG. Part (a) represents SDPTG waves by Toshiaki et al. (2006). And part (b) represents the recorded PPG and its SDPTG by Qawqzeh (2011).

SDPTG.

Rubins (2008) described a novel algorithm based on SDPTG for analyzing simultaneously measured ear and finger photoplethysmography (PPG) signals. The developed algorithm separated the systolic wave and the diastolic wave of the PPG and fits each of them with the sum of two Gaussian functions. Tomoyuki and Toshiaki (2013) categorized SDPTG indices in combination with age, and they concluded that SDPTG indices differed in characteristics from components of MetS or inflammatory markers. Qawqzeh et al. (2014) utilized SDPTG to develop a statistical model for the assessment of high-risk atherosclerosis. Their analysis facilitates the recognition of PPG points of interests, in specific, the detection of PPG's diastolic peak and inflection valley.

Alberto (2002) used SDPTG for the assessment of arterial properties. Imanaga et al. (1998) utilized SDPTG to assess arterial distensibility. Šimek et al. (2005) utilized SDPTG for the assessment of arterial elastic properties. They concluded that early systolic indices discriminate independently between subjects with essential hypertension and healthy controls. SDPTG analysis facilitates the distinction of 5 sequential waves, called a, b, c, d, and e waves. The relative heights of these waves (b/a, c/a, d/a, and e/a ratios) have been related to age, atherosclerosis, arterial blood pressure, arterial stiffness, and the effects of vasoactive drugs. The b/a ratio has been related to aging and carotid distensibility (Peskin and Rowen, 2010). Following analysis of the correlation of the b/a, c/a, d/a, and e/a ratios with age, a more complex index “aging index (SDPTG-AI)” was defined as [(b–c–d–e)/a]. In a study to assess arterial distensibility in adolescents, the d/a ratio identified individuals at increased risk of developing atherosclerosis (Millasseau et al., 2006; Hyun et al., 2007) analyzed SDPTG to estimate vascular aging.

Luiz et al. (2000) compared SDPTG indices to pulse wave velocity (PWV) for the assessment of vascular aging and atherosclerosis in hypertensive patients. However, they claimed that SDPTG might be used for the assessment of vascular aging and atherosclerosis in hypertensive patients. Kristjan et al. (2014) developed a new algorithm to estimate arterial stiffness in diabetes patients using the SDPTG. They concluded that SDPTG-AI can be used to differentiate subjects with increased arterial stiffness from healthy subjects. In their study to clarify the role of blood lead level (Pb-B) as one of the cardiovascular risk factors (Orawan et al., 2010) the SDPTG was used to evaluate the cardiovascular risk. These results suggest that Pb-B is possibly an independent cardiovascular risk factor for bus drivers exposed to lower level of lead. Kan-ichiro et al. (2003) utilized the analysis of SDPTG indices to determine whether migraine is accompanied by peripheral blood circulation disorder.

In a study by Qawqzeh et al. (2012) they developed an algorithm that can detect the desired points of interest in the original waveform based on the utility of PPG's first

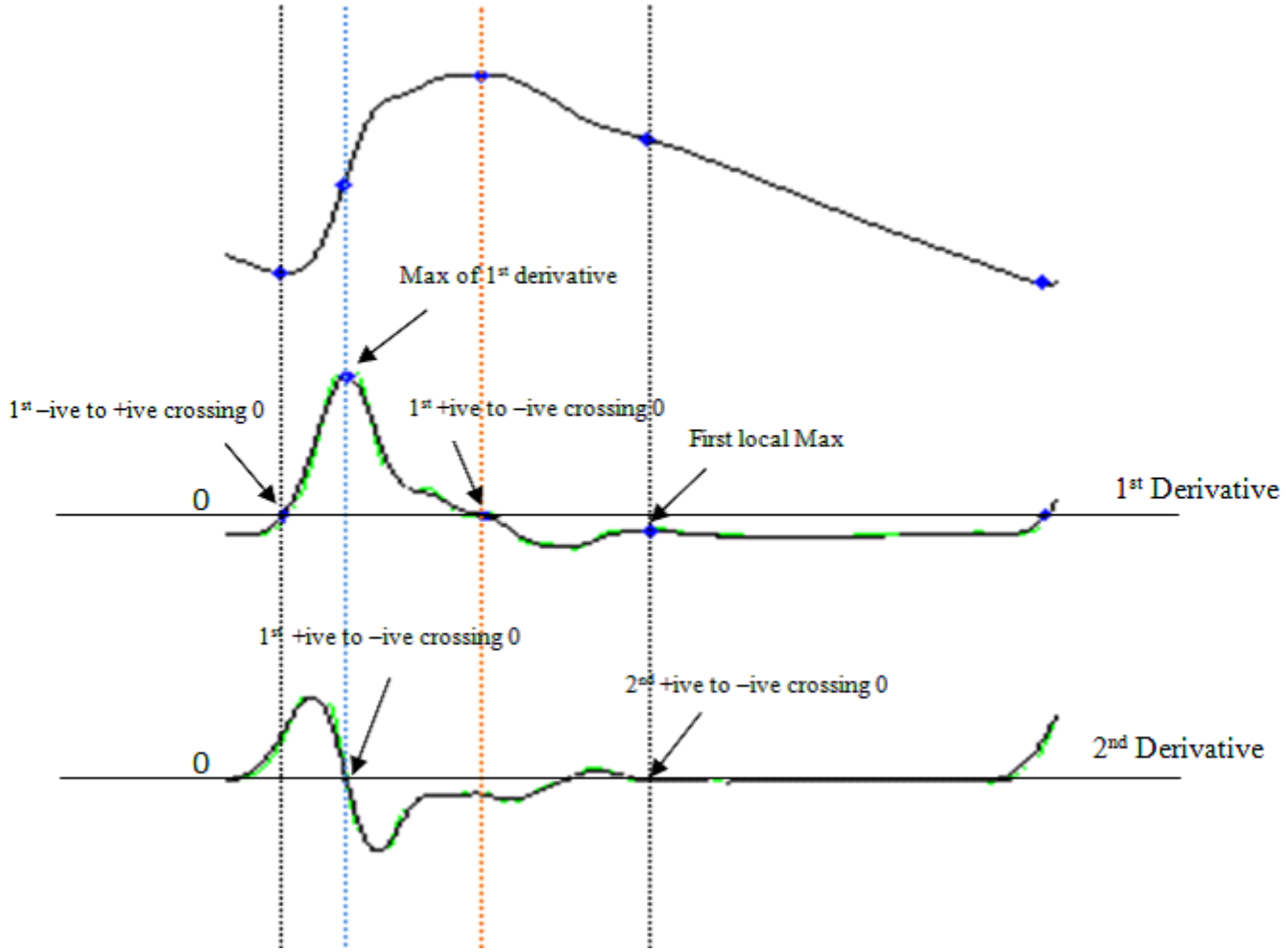

Figure 2. Description of the process of locating points of interest from PPG waveform and its first and second derivatives (Qawqzeh et al., 2012).

derivative and SDPTG. Figure 2 illustrates the method of locating points of interest based on the proposed algorithm. They concluded that the increases in thickness of the intima and media of the carotid artery, as measured by CIMT, are directly associated with a decreased of b/a index values and increased of PP values.

Hashimoto et al. (2002) tried to clarify the factors influencing two measures of arterial stiffness, pulse wave velocity (PWV) and the (SDPTG), and to evaluate their relationship in treated hypertensive subjects. Their findings indicated that the two measures of arterial stiffness, namely PWV and SDPTG, are regulated at least in part through different mechanisms, and that the one is not capable of acting as a surrogate marker of the other. This may be explained partly by the hypothesis that PWV and SDPTG reflect different arterial properties at central and peripheral sites. An algorithm has been developed by Chan et al. (2007) for the automatic beet-to-beet detection of left ventricular ejection time (LVET) based on the SDPTG. They concluded that the correlation between the PPG-Pow derived LVET and the aortic flow derived LVET was high and significant. Atsushi et al. (2012) claimed that SDPTG analysis enables the evaluation of atherosclerosis and cardiovascular aging. In their study Mohamad et al. (2012) the aging index of the SDPTG (SDPTG-AI) was used for monitoring the arterial condition. They claimed that vascular response in resistance arteries plays an important role in blood pressure and the SDPPG-AI can be used to evaluate the vascular aging and screening of atherosclerotic patients.

A new algorithm has been introduced by Elgendi et al. (2014) for the detection of a waves and b waves from the SDPTG. They compared nine algorithms based on fixed thresholding, and they claimed that their new algorithm improved the detection rate using a testing set of heat stressed PPG signals containing a total of 1,540 heart beats. The SDPTG was utilized by Pilt et al. (2012) to characterize the changes in forehead's PPG signal,

Table 1. Some applications of PPG and SDPTG.

Application domain	Applications	References
Monitoring applications	Monitoring arterial condition	Hyun et al., 2007; Mohamad et al., 2012
Assessment and measurement applications	Assessment of high-risk atherosclerosis, Assessment of carotid distensibility, Assessment of Arterial elastic properties. Assessment of migraine	Qawqzeh et al., 2012, Peskin and Rowen, 2010; Šimek et al., 2005; Kan-ichiro et al., 2003
Evaluation applications	Atherosclerosis evaluation Evaluation of cardiovascular risk, Evaluation of hypertension	Atsushi et al., 2012; Orawan et al., 2010; Hashimotoa et al., 2002.
Estimation/prediction applications	Detection of the directional change LEVT, Estimating arterial stiffness, Aging index.	Chan et al., 2007; Kristjan et al., 2014; Takazawa et al., 1998; Imanaga et al., 1998; Luiz et al., 2000.

which might be caused by the stiffness of blood vessels. They normalized SDPTG's waves (a wave to e wave) and correlated them with age. They concluded that the changes in the forehead vascular bed can be described with SDPTG signal normalized amplitudes b/a and d/a.

DISCUSSION ON SDPTG APPLICATIONS AND POSSIBLE CATEGORISATION

This topical review tries to bring-together most of analytical techniques and sought applications for SDPTG in clinical settings. The philosophical analysis used by several scholars in this field is addressed. However, characterizing and utilizing the great usages of PPG waveform and its SDPTG still not fully understood. For the purpose of understanding and discussion the SDPTG applications can be divided into four domains namely: (1) Monitoring applications, (2) Assessment and Measurement applications, (3) Evaluation applications, and (4) Estimation/prediction applications. Table 1 demonstrates these categories and the applications of PPG and SDPTG that come under its umbrella.

B/A INDEX

However, the analysis of SDPTG indices revealed that b/a index is the most promising index in the assessment of arterial health. It was affected by atherosclerosis indications (Alberto, 2002); It used to assess aortic stiffness and wave reflection (Chan et al., 2007); It used by Tomoyuki and Toshiaki (2013) to predict high-risk atherosclerosis. It utilized by Millasseau et al. (2006) to assess atherosclerosis and related arterial distensibility; It used by Pilt et al. (2012) to assess arterial elastic properties; It has been declared by Toshiaki et al. (2007) that b/a is related to aging and carotid distensibility. In addition, Tomoyuki and Toshiaki (2013) claimed that b/a has a negative relationship with atherosclerosis, the more the value of b/a index, the less the risk of atherosclerosis. It was independently associated with dyslipidemia (Alberto, 2002).

Therefore, the b/a index are found to be important factor in the study of arterial stiffness. It was illustrated that the b/a index reflects increased arterial stiffness, (Takazawa et al., 1998). It claimed by Imanaga et al. (1998) that the magnitude of b/a index is related to the distensibility of the peripheral artery. Moreover, Qawqzeh et al. (2014) demonstrated that b/a index reflects the existence of atherosclerosis.

C/A AND D/A INDICES

In addition, c/a index is used to discriminate independently between subjects with essential hypertension and healthy controls (Pilt et al., 2012). It found to reflect decreased arterial stiffness, (Takazawa et al., 1998). However, in regards to d/a index, it found to reflect decreased arterial stiffness as c/a index. It was utilized by Atsushi et al. (2012) to assess the risk for the development of metabolic components.

CONCLUSIONS

This topical review has introduced the technique of

SDPTG. It illustrated its main research activities by many scholars in the field. In addition, it demonstrated the great potential of SDPTG for use in different clinical measurements. PPG and its SDPTG technologies can be found in a wide range of medical devices that are available in clinical settings. The ability of measuring oxygen saturation, blood pressure, cardiac output, assessing autonomic function, detecting peripheral vascular disease, and also predicting the high-risk atherosclerosis reflects the important of these techniques in providing useful diagnostic tools. Many challenges remain with the technology, including the standardization of PPG measurements, data collection, indices quantification, improving repeatability, and establishing comprehensive normative data ranges for comparison with patients and for evaluating responses to therapy. However, the ability to bring PPG and its SDPTG as a diagnostic tool to clinical settings would be advance in science and therapy.

Conflict of Interest

The authors have not declared any conflict of interest.

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