Wave intensity analysis in the ventricles, carotid and coronary arteries – What has been learnt during the last 25 years?: Part 2

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Abstract

Wave intensity analysis (WIA) was introduced 25 years ago for the study of arterial wave travel and has since been established as a powerful tool for the investigation of cardio-vascular interaction. Despite the complex mathematical derivation of the method, the implementation is simple. As a time-domain technique, WIA enables the direct association between waves and events during the cardiac cycle. Furthermore, it enables the separation of the pressure (or diameter), velocity and wave intensity waveforms into their forward and backward components, and provides a means for the determination of the timing and magnitude of waves of different origins. Hemodynamic questions at several locations along the vascular tree have been investigated with WIA. Part 2 of this review will focus on the physiological and clinical findings to which WIA has contributed, through clinical and in vivo studies in the ventricles and in the coronary and carotid arteries.

Introduction

The temporal changes in pressure and flow generated during every cardiac cycle are inextricably linked and propagate as waves along the vascular tree. These waves get reflected at sites where changes in vascular geometry and/or elastic properties occur. Wave intensity analysis (WIA) was introduced approximately 25 years ago for the study of arterial wave travel[1-3], and has since been established as a powerful tool for the decomposition of pulsatile flow into its wave components[4-8]. Waves contain embedded information about their origin and blood vessels through which they propagated; hence they can provide insight into the dynamic interaction between the various components of the cardiovascular system. For example, WIA in the ascending aorta provides information about the interaction between the left ventricle (LV) and the systemic arterial tree[2, 9]. Likewise WIA in the root of the pulmonary artery provides information about the interaction between the right ventricle (RV) and the pulmonary circulation[9, 10].

We provided an overview of the WIA methodology in Part 1 of this review, where we thoroughly explained the basics of the technique[9]; it could be useful for readers who may not be well acquainted with this tool to peruse that article for further theoretical details. Briefly, WIA requires local measurements of pressure (P) and flow velocity (U) (or vessel diameter (D) and U, or alternatively vessel cross-sectional area (A) and U), and enables the separation of P (or D or A), U and wave intensity into forward and backward components, usually originating from the heart and from reflection sites along the arterial bed, respectively. The prominent peaks discernible in the time-varying separated wave intensity profiles represent the dominant forward- and backward-travelling waves during the cardiac cycle. As well as their direction of travel, waves can be characterised according to the blood pressure changes that accompany them; compression waves are associated with an increase in pressure and expansion waves with a decrease in pressure. Consequently, there are four types of waves: forward compression (FCW) and backward expansion (BEW) waves, that cause flow acceleration, and forward expansion (FEW) and backward compression (BCW) waves, that cause flow deceleration.

Because WIA is a time-domain technique, each wave is time-stamped and can be easily associated with events during the cardiac cycle. In the aorta, for example, a FCW (FCW_{ao}) generated by the contraction of the LV in early systole is followed first by a BCW (BCW_{ao}) that is produced by the reflection of the FCW_{ao} at the periphery in mid-systole, and next by a FEW (FEW_{ao}) that is generated as the rate of myocardial shortening is reduced in late systole. A second FCW (FCW_{ao_2}) might be occasionally observed during aortic valve closure.

In Part 1 of this review we provided a detailed account of the physiological and clinical findings to which WIA has contributed over the past 25 years from measurements in the aorta, pulmonary arteries and pulmonary veins. In the second part of this review we will extend this account to include findings from studies in the ventricles, coronary and carotid arteries (Figure 1).

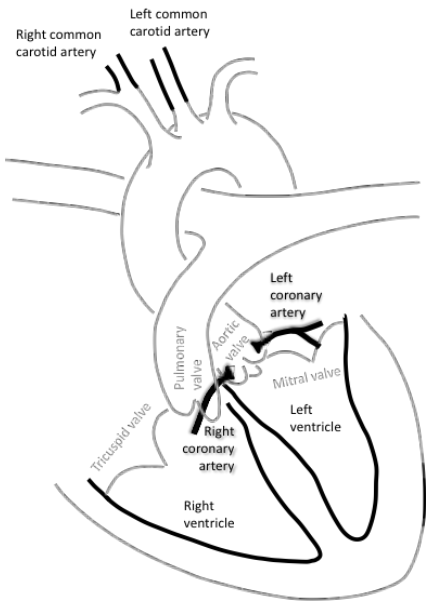

Figure 1: Schematic representation of the anatomical sites (in black) at which WIA will be discussed in this review.

Ventricular wave intensity studies

The complex and time-varying geometry of the ventricular cavities is likely to give rise to three-dimensional (3D) intra-ventricular flows and variable wave speeds during the cardiac cycle. Therefore, the assumption that the ventricle is a one-dimensional (1D) compliant vessel with time-invariant elastic properties may not be valid throughout the cavity. To avoid these limitations, the measuring location selected for ventricular WIA applications is commonly the plane of the mitral valve or tricuspid valve, where concerns about 3D flow and variations in cross-sectional area are less pertinent[11].

Recent ventricular WIA studies assume ventricular inflow velocities to be positive and ventricular outflow velocities to be negative[12-14]. According to this approach, waves generated by ventricular contraction during systole and propagating towards the aortic root or the main pulmonary artery are presented as backward waves in the resulting ventricular wave intensity profile, but are at the same time presented as forward waves in the corresponding aortic and pulmonary wave intensity profiles, as discussed in Part 1[9]. Perhaps a modification to the above approach can resolve this ambiguity, by taking into account the convention of forward direction of wave travel being the direction of mean blood flow and backward direction of wave travel being the opposite direction. According to this modification, during diastole waves travelling through the mitral or tricuspid valves towards the ventricular apex would be considered forward, and waves travelling from the apex towards the base would be backward, in agreement with the current ventricular WIA studies. During systole the direction of mean blood flow is towards the aortic or pulmonary valves and waves travelling from the ventricular apex towards the aorta or the pulmonary artery would be forward, while waves travelling from the periphery towards the ventricles would be backward, in agreement with all aortic and pulmonary WIA studies.

Left ventricle

WIA applied in measurements of LV cavity pressure and mitral valve blood flow velocity recorded from healthy dogs, through its ability to separate left atrial (LA; upstream) from LV (downstream) events, provided useful mechanistic insight into the interactions that generate the atrio-ventricular pressure gradient during the phase of LV filling[11, 13]. The occurrence of a BEW (BEW_{LV}) during early ventricular diastole was consistent with the notion of the LV actively aspirating blood from the LA, through a mechanism similar to that generating the preceding FEW_{ao}[11, 13]. Further study indicated that the energy carried by the BEW_{LV} depended inversely both on the rate of LV elastance decrease and on the completeness of the previous LV ejection[11,13]. However, this active LV contribution to early LV filling was somewhat disputed when the WIA equations were adapted to account for the time-varying elastic properties of the LV wall during relaxation, and according to this modification early-diastolic LV filling appeared not to be due to the aforementioned BEW_{LV}, but due to a FCW generated by the LA[15]. LV wave intensity has also been derived from LV pressure-volume measurements obtained with a conductance catheter from patients with heart disease[16].

Right ventricle

The right ventricle (RV) has not been investigated extensively with WIA. A BEW (BEW_{RV}) generated by the right ventricle after the opening of the tricuspid valve indicated that the RV tends to refill itself during early diastole; the energy of this wave depends inversely on both the rate of elastance decrease and on the completeness of the previous RV emptying[12].

Coronary wave intensity studies

The coronary circulation is unique among systemic circulations in that it is predominantly perfused in diastole, since during systole the coronary microvasculature, which is largely intramural, is compressed by the contracting myocardium. Coronary blood flow is restored in diastole, as the intramural vascular bed is decompressed during ventricular relaxation. As a consequence of this distinctive anatomy, waves are actively generated on both ends of the coronary tree, with LV ejection being the source of forward waves, and intramural vessel compression/decompression generating backward waves. The potential of WIA to interrogate the dynamic ventricular, epicardial and microcirculatory interactions taking place in the coronary circulation was recognised early[17, 18], but the sensor-equipped guidewire technology that made possible the acquisition of the necessary intracoronary measurements on a routine basis became widely available only recently. The lack of a suitable technique for the measurement of coronary wave speed has also somewhat hindered the wide applicability of this analysis because of the ensuing limitations on wave separation[19]. In fact, a method for obtaining coronary wave speed from simultaneous P and U measurements has been developed[20], but its applicability is hampered by the windkesselness of the coronary arteries[21].

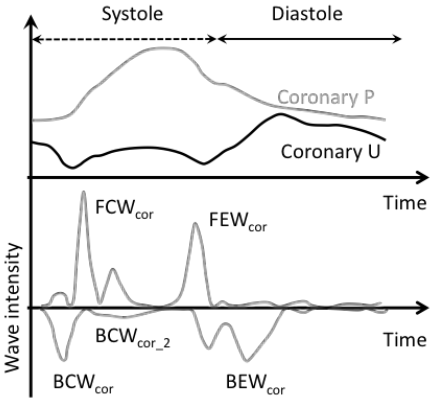

Figure 2: Schematic representation of the P, U and separated wave intensity profiles that are typically encountered in angiographically normal coronary vessels over the cardiac cycle.

Coronary wave intensity in health

Coronary wave intensity is typically characterised by at least four main waves (Figure 2)[17,19, 22, 23]. A BCW (BCW_{cor}) is generated in the microcirculation during isovolumic contraction, as the intramural vessels are compressed by the contracting myocardium and blood is squeezed out of them, and creates a pushing effect at the distal end of the coronary tree that travels towards the coronary ostium and decelerates coronary blood flow. Upon aortic valve opening the FCW_{ao} is transmitted into the epicardial arteries (FCW_{cor}) and propagates downstream, where it can rapidly give rise to a second BCW (BCW_{cor_2}) through distal reflection[22]. The BCW_{cor_2} contributes to the BCW_{cor}, and may well be indistinguishable from it. At this phase of the cardiac cycle the increased elastance of the ventricular wall protects the intramural vessels from further compression and neutralises the BCW_{cor} source; as a result, the FCW_{cor} is dominant during this period and accelerates coronary blood flow[19]. This wave sequence during early systole is promptly followed by the transmission of the FEW_{ao} in the epicardial arteries (FEW_{cor}) and subsequent deceleration in blood flow through the resulting proximal aspiration action. As ventricular relaxation progresses, the intramural vessels are decompressed and aspire blood volume, generating a BEW (BEW_{cor}) in the

microcirculation which propagates upstream and increases coronary blood flow[22]. In essence, ventricular function both drives (proximally) and impedes (distally) coronary perfusion in early systole, with the pattern reversed during late systole. The transmission of the FCW_{ao_2} in the epicardial arteries (FCW_{cor_2}) completes the coronary wave sequence[22]. Several of these waves largely overlap in time and thus wave separation is essential for the accurate interpretation of the wave intensity profile.

In healthy animals, the BCW_{cor} was augmented both by increased contractility and vasodilation, while a close association found during changes in cardiac contractility and coronary resistance between the energy carried by the BCW_{cor} and coronary systolic flow impediment (CSFI) suggested that the BCW_{cor} is the mechanistic cause of CSFI[24]. Intracoronary measurements obtained during cardiac catheterisation from unobstructed left (LC) and right (RC) coronary arteries, revealed that the lack of diastolic predominance in RC blood flow, and oppositely the occurrence of this striking pattern in LC blood flow, was associated with the presence of a smaller BEW_{cor} in the RC compared to the LC artery[25]. This smaller BEW_{cor} was accounted for by the well-known fact that RV pressure is lower than LV pressure and consequently the microvascular bed supplied by the RC artery experiences lower cardiac compressing/decompressing force[25]. This finding also fortified conclusions from studies emphasising that the BEW_{cor} is the major determinant of diastolic coronary blood flow[22]. However, the mechanisms underlying wave generation and heart perfusion, although undoubtedly connected, are nonetheless not necessarily one and the same[26]. Under conditions of dynamically changing cardiac function (using the Valsalva manoeuvre as a paradigm for the stimulation of rapid hemodynamic changes in the cathlab), a certain amount of decoupling between coronary blood flow velocity changes and wave energy changes measured in angiographically normal coronary vessels with intact autoregulation, indicated that there is more in cardiac-coronary interaction than meets the eye[26].

Coronary wave intensity in disease

Invasive studies in patients with LV hypertrophy and normal coronary angiograms uncovered a pronounced reduction in the size of the BEW_{cor}, suggesting that pathological hypertrophic growth can have a detrimental effect on myocardial relaxation and microvascular decompression, and thereby undermine the wave that primarily drives diastolic coronary flow[22]. Also during cardiac catheterisation, patients post non-ST elevation myocardial infarction presented after revascularisation a strong inverse correlation between the BEW_{cor} measured in the artery supplying the infarcted territory and indices of infarct size, an association that is a likely indicator of the sensitivity of the BEW_{cor} to underlying microvascular dysfunction[27]. Moreover, the size of the BEW_{cor} strongly predicted regional LV recovery, bringing to light the potential of WIA as a tool for the assessment of myocardial viability in this clinical setting[27]. The effect of warm-up angina has also been studied with WIA in patients with coronary artery disease and symptoms of exertional angina prior to revascularisation. Triggered by the first exercise, beneficial adaptive changes in the systemic and coronary circulations and augmentation in the size of the BEW_{cor} acted jointly to improve vascular-cardiac coupling and myocardial perfusion during second exercise[28]. The instantaneous wave-free ratio (iFR), is an adenosine-independent index of stenosis severity for use in the cathlab that has been derived from coronary WIA[29], and its capacity as a substitute for fractional flow reserve is currently being evaluated and vigorously debated[30-33].

Changes in the BEW_{cor} feature among the coronary wave intensity abnormalities observed in patients with aortic stenosis during transcatheter aortic valve insertion[34-37]. A prominent increase in the BEW_{cor} in the presence of an aortic stenosis was considered a marker of severe LV pressure loading and excessive wall stress[35]. Furthermore, a progressive fall in the size of this wave with increasing heart rate in the presence of the stenosis and immediate reversal of this pattern post-implantation were interpreted as suggestive of an aortic stenosis-induced decoupling of the mechanisms normally regulating coronary perfusion[34, 35]. The gradual reduction in the energy of the BEW_{cor} could be revealing of reduced coronary reserve under exercise conditions, and could explain the anginal symptoms often presented by these patients, who otherwise have normal coronary vessels[34, 35]. An unknown beneficial effect of biventricular pacing in patients with heart failure and left bundle-branch block (but unobstructed coronary arteries) was shown with coronary WIA in the form of improved coronary perfusion driven by an increase in the size of the BEW_{cor}, which was in turn a manifestation of the positive lusitropic effect achieved by the restoration of LV synchronisation[38].

Carotid wave intensity studies

The common carotid artery lends itself to non-invasive investigation, because of its anatomical location[39]. The measurements required for the derivation of carotid wave intensity, typically consist of Doppler blood flow velocity and either time-varying arterial diameter obtained with ultrasound echo-tracking[40-42] or applanation tonometry[43], after suitable calibration of the latter signals for the derivation of blood-pressure-equivalent waveforms.

Forward waves in the carotid artery arrive from the aorta and backward waves from the cerebral microvasculature. A FCW ($FCW_{carotid}$) in early systole and a FEW ($FEW_{carotid}$) in late systole that are prominently present in a typical carotid wave intensity profile, are in effect the FCW_{ao} and FEW_{ao} after being transmitted from the aorta to the carotid artery. Mid-systole is typically occupied by up to three waves with magnitudes substantially smaller than those of the FCWcarotid and FEWcarotid: a BCW ($BCW_{carotid}$) followed by a second FEW ($FEW_{carotid\_2}$) which is in turn followed by a second FCW ($FCW_{carotid\_2}$) just before the onset of the $FEW_{carotid}$[44, 45]. This mid-systolic wave sequence received relatively little attention in the first published carotid WIA studies[40, 46-48], presumably because without wave separation and due to their small size they can be easily overlooked as noise. The $BCW_{carotid}$ is attributed to the distal reflection of the $FCW_{carotid}$ at the vascular bed supplied by the carotid artery[44, 45]. The $FEW_{carotid\_2}$ is considered to be the subsequent proximal “open-end” type reflection of the $BCW_{carotid}$, due to the considerable increase in cross-sectional area it encounters as it travels towards the heart and reaches the aortic arch (left common carotid) or the brachiocephalic artery (right common carotid)[44, 45]. The $FCW_{carotid\_2}$ is likely the BCW_{ao} after being transmitted from the aorta to the carotid artery[44, 45].

Carotid wave intensity in health

In healthy volunteers, a reduction in the energy carried by the $BCW_{carotid}$ during a hypercapnia challenge, which is known to cause cerebral vasodilation, provided evidence that the $BCW_{carotid}$ originates from the cerebral vascular bed and showed its diagnostic potential in the assessment of acute changes in cerebral vasomotor tone[49]. Carotid WIA was also implemented in a study on the effects of caffeine and nicotine, both commonly identified as heart failure

risk factors, on LV function[50]. An increase in the size of the $FCW_{carotid}$ was found after caffeine consumption, suggesting sympathomimetic effects on LV function, while smoking did not affect the carotid waves, although it did increase local arterial stiffness[50]. Oppositely, within the context of a study that aimed to investigate the cause of sudden cardiac events during fire-fighting duty, a reduction in the magnitude of the $FCW_{carotid}$ in young fire-fighters was observed after training drills, which may indicate suppressed systolic LV function, while the accompanying decrease in $BCW_{carotid}$ could indicate concomitant changes in vasomotor tone potentially resulting from mental stress[51]. WIA in healthy carotid arteries has revealed that in the presence of a prominent $FEW_{carotid\_2}$, the shape of the pressure waveform is such that it leads to misinforming negative augmentation index values[52, 53], whereas a reflection index based on wave intensity did not exhibit the same shortcoming[53]. The effect of hot hydrotherapy on wave reflections has also been studied with carotid WIA and the findings show a delay in the arrival of the $BCW_{carotid}$ with respect to the $FCW_{carotid}$ post-bath[54].

Carotid wave intensity in disease

The first carotid WIA study was conducted in patients with mitral valve regurgitation and a striking decrease in the size of the $FEW_{carotid}$ compared to normal volunteers was reported[47]. The size of the wave was restored after surgery. The authors attributed these findings to the LV not being efficient in decelerating and stopping myocardial shortening, possibly as a result of the continuation of LV ejection into the LA after the closure of the aortic valve[47]. Studies in patients with chronic heart failure report impairment in the ability of the LV to generate a $FCW_{carotid}$[43, 55]. Concurrent increased wave reflections, as suggested by an increase in the size of the $FCW_{carotid\_2}$, could place an additional hemodynamic load to the failing heart[43]. Moreover, the $FEW_{carotid}$ showed good association with exercise capacity in these patients and thus potential for clinical use[56]. Hyperthyroid patients exhibited a considerable increase in $FCW_{carotid}$, $FEW_{carotid}$ and $BCW_{carotid}$ and prolonged ejection period compared to healthy subjects, while no echocardiographic differences in LV function were found between the two groups[57]. In the light of the good correlations between the above wave intensity parameters and serum levels of free triiodothyronine, it was proposed that WIA might be able to provide sensitive biomarkers of cardiac function in hyperthyroid patients[57].
In patients with Fontan physiology, comparison with age-matched control subjects revealed several deviations in the carotid wave intensity profile that were suggestive of impaired cerebral perfusion in this pathological condition[58]. Increased wave reflections, quantified as the wave energy ratio WRI = $(BCW_{carotid} + FCW_{carotid\_2}) / FCW_{carotid}$, predicted cardiovascular events in patients with treated hypertension independently of blood pressure and other risk factors[59]. However, it could not be determined whether this was directly due to the detrimental effect of reflected waves on cardiac function or due to the pathological changes that gave rise to increased reflections[59]. Lately, the $FEW_{carotid}$ in particular, but also the $BCW_{carotid}$, both showed ability to distinguish between patients with non-obstructive hypertrophic cardiomyopathy from patients with left ventricular hypertrophy secondary to systemic hypertension[60]. The $FCW_{carotid}$ and $FEW_{carotid}$ have also shown differences in magnitude between different geometries of remodelled hypertensive hearts[61].
Carotid WIA has also found a role in the assessment and comparison of antihypertensive medication beyond brachial blood pressure monitoring, via probing the underlying mechanisms through which the various drugs yield altered pressure waveform morphology[62]. A comparison between amlodipine and atenolol in hypertensive patients, showed that, despite no differences in brachial blood pressure, a larger reduction in carotid systolic blood pressure was present in patients treated with amlodipine; this dissimilarity was associated with smaller WRI, likely resulting from superior vasodilator action of amlodipine and thus less impedance mismatching[45]. In addition, in patients with well-controlled hypertension, those receiving atorvastatin (lipid lowering agent) showed less carotid blood pressure augmentation and less reflections transmitted from the aorta ($FCW_{carotid\_2}$) compared to patients receiving placebo, potentially due to the beneficial effects of statin treatment on endothelial function. Patients with essential hypertension treated with doxazosin presented increased $FCW_{carotid}$ and $FEW_{carotid}$, but the efficacy of doxazosin as antihypertensive medication was explained by the decreased $BCW_{carotid}$ and the good correlation of the reduction in the size of this wave with the corresponding reduction in mean blood pressure, attributed to reduced peripheral vascular resistance[63]. On the other hand, in patients with newly diagnosed hypertension, there was evidence that after 6 months of vasodilator therapy with barnidipine and successful reduction in central blood pressure, there was a reduction in pressure augmentation index, which however was not accompanied by significant changes in wave intensity or intrinsic arterial stiffness[64].

Conclusions

In conclusion to both Part 1 and Part 2 of the review, WIA has been used over the past 25 years both at the left and right sides of the circulatory system, and proved to be a useful technique in studying wave travel at various anatomical sites. The greatest advantage of this method is that it is a time-domain technique, allowing for events during the cardiac cycle to be directly associated with the time, intensity, direction and type of waves that cross the measuring locations. WIA allows for the separation of the P, U and D waveforms into their forward and backward components, and also for the separation of the resulting wave intensities. It has thus been established as a powerful tool for the investigation of cardio-vascular interaction under a wide range of pathophysiological conditions. The technique has a great potential for use at the bedside. The recently-introduced WIA formulations that require vessel D and U rather than P and U may unlock the full non-invasive potential of the method, using ultrasound measurements.

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