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Pulse Waveform Analysis: Is It Ready for Prime Time?

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Abstract
Purpose of Review Arterial pulse waveform analysis has a long tradition but has not pervaded medical routine yet. This review aims to answer the question whether the methodology is ready for prime time use. The current methodological consensus is assessed, existing technologies for waveform measurement and pulse wave analysis are discussed, and further needs for a widespread use are proposed.
Recent Findings A consensus document on the understanding and analysis of the pulse waveform was published recently. Although still some discrepancies remain, the analysis using both pressure and flow waves is favoured. However, devices which enable pulse wave measurement are limited, and the comparability between devices is not sufficiently given.
Summary Pulse waveform analysis has the potential for prime time. It is currently on a way towards broader use, but still needs to overcome challenges before settling its role in medical routine.

Keywords Pulse wave reflection · Augmentation index · Wave separation analysis · Pulse wave intensity · Arterial Windkessel

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Introduction

Pulse waveform analysis has a long tradition dating back to ancient times, and the pulsatility of arterial pressure and flow has inspired health professionals and scientists since then [1]. Progress was made in the understanding of the human physiology as well as in the formulation of mathematical concepts to describe fluid dynamics and wave transmission, linking these two together, developments in engineering lead to better measurement techniques of arterial pressure and flow. Most progress could be achieved when these disciplines joined forces, as can be seen in the example of a short but very fruitful collaboration of Donald McDonald and John Womersley [2].

Over the years, different basic concepts like pulse wave reflection and the arterial Windkessel were introduced, leading subsequently to methods for pulse wave analysis. Finally, different parameters trying to capture changes in pulse wave morphology and relating them to physiological changes were proposed and applied in a variety of clinical studies [2]. Differences between concepts, methods and parameters have been and still are lively discussed in the scientific communities [3, 4]. Nevertheless, up to now, all these approaches, and thus pulse waveform analysis as a whole, are still in a niche of scientific and especially clinical routine. Therefore, the aim of this review article is to give a brief overview about the different waveform analysis methods, to describe the current consensus in the scientific field about them, and to judge them for their readiness for prime time use.

Different Methods in Pulse Waveform Analysis

In this chapter, we briefly introduce several methods for pulse wave analysis. This overview does not claim to be complete but rather tries to present classic concepts along with newer approaches which might have the potential for widespread use.

A historical important concept in the understanding of arterial haemodynamics is the class of Windkessel models. According to the number of parameters incorporated in an ordinary linear differential equation of the first order, they are classified as 2-, 3- or 4-element Windkessel model, following the number of components in an analogue electrical circuit [5, 6]. Usually, flow is used as input to the system and a corresponding pressure wave can be obtained as output. A modification, which can be applied to all of these Windkessel models, is the introduction of a nonzero asymptotic pressure level [7]. This originates from the concept of the arterial reservoir theory, which tries to combine the reservoir behaviour of the arterial system with wave travel characteristics [8]. Originally, pressure and flow need to be known in order to calculate excess and reservoir pressure; however, a pressure-only version has also been introduced and applied [9, 10].

Another concept relying on both pressure and flow is the idea of wave separation. Here, the measured pressure and flow are separated in their forward and backward travelling waves. This can either be achieved in the frequency domain or in the time domain. The term "wave separation analysis" (WSA) is generally used for the frequency domain method, although this is not clear per se by the wording. To perform the separation, either characteristic impedance has to be estimated from input impedance over a specific frequency range or wave speed has to be determined in a potentially reflection-free period at the beginning of systole (PU-loop method) [11]. The latter was introduced together with the concept of wave intensity analysis (WIA) [12]. Here, forward and backward waves can be identified using their intensity obtained by the product of differences of pressure and flow or the respective forward or backward components. To overcome the measurement of flow, approaches with different levels of complexity have been introduced and tested in connection with WSA [13–18].

Other methods depend solely on the measurement of arterial pressure waves. The most prominent one, and for sure an important driver of the field for the last decades, is the augmentation index AIx. Here, the basic idea is that the forward travelling wave coming from the heart is reflected more distally and the pressure wave at the aortic root is augmented by this reflected wave, which is visible by an inflection point during systole [2]. As the AIx has been widely studied, it is now known that it not solely depends on wave reflections but also on several other cofounders including heart rate and ventricular contraction [19•, 20, 21]. Also, other pressure-only approaches of waveform analysis exist; several researchers have used Gaussian functions for the separation of waveforms [22, 23]. Another alternative for wave separation is the method of empirical mode decomposition, which can be seen as an alternative to Fourier analysis [24].

Methodological Consensus and Its Implications for Current Pulse Waveform Methods

In this section, we want to highlight certain aspects of a recently published consensus document which we feel that are relevant for this review and relate them to the readiness of pulse waveform analysis for clinical practice [25•]. Beyond this short extract, we would like to encourage the readers to go through the full consensus document including all comments from participants of the consensus group in the original publication. The consensus paper was published by the Association for Research into Arterial Structure and Physiology (Artery Society). After a workshop in 2016, consensus statements were formulated and an online vote was held among the workshop participants to evaluate the extent of agreement on the statements. Furthermore, all voters could state personal comments which were published as well. Below, a list of citations from the consensus statements is presented, while quotations at the bottom of this chapter are taken from additional comments by the workshop participants [25•].

- "The heart is a pulsatile pump, and blood pressure is the result of waves travelling back and forth in the arterial system. […] the pressure decay in the diastole can be explained on the basis of re-reflection of forward waves. […] Any particular arterial pulse […] contains a contribution from previous beats. […] there is no such thing as a reflection-free period."
- "There is no single or limited number of discrete reflection sites in the arterial tree. Wave reflection takes place wherever there is a change in characteristic impedance".
- "Impedance analysis, based on Fourier-transformed pressure and flow waves, is a valid characterization of the arterial system." One important restriction is that it "relies on the assumption that the system is in steady state".
- "Wave intensity analysis represents a very elegant technique to analyse the timing and nature of waves, and is suitable to analyse transient states and phenomena". Drawbacks are that this method is "susceptible to noise" and it is important to notice that it "emphasizes rapid changes in pressure and flow and tends to underestimate slowly changing signals".
- "Wave separation analysis can be done either in the time or frequency domain" and "all forward and backward waves are summed, which implies that the forward and backward components also include re-reflections".
- "As full wave analysis implies knowledge of pressure and flow (or velocity), it is difficult to get accurate information on the timing of wave reflections based on pressure or flow signals alone."
- "Windkessel models are zero dimensional, lumped parameter models and cannot account for any wave travel/reflection".

- "The reservoir-wave model is a conceptual model/paradigm" and "as for all simplified models, it has limitations. […] The excess pressure should not be used in conjunction with measured flow to analyse wave dynamics".

Together with the first statement, which is basically saying that it is all about waves, the last statements could be interpreted in a way that Windkessel models should not be applied for analysing arterial dynamics. But when looking deeper (e.g. also in a couple of comments of the consensus document), this should not be the key message, as Windkessel models have proven to be very useful for different aspects describing the cardiovascular system and describing the relation of pressure and flow. Although they do not explicitly describe wave travel, they implicitly incorporate wave phenomena. When Windkessel models are combined to a tree-like structure, one can even deduce this model mathematically from a one-dimensional model based on wave transmission [26]. Due to the reduced complexity of Windkessel models—only a number of parameters are needed—they represent a simple dynamical description of the arterial system, which is generally favourable for methods in a widespread use.

The reservoir-wave concept was strongly discussed within the last years and general agreement about its validity despite this consensus statement is still not found. This currently hampers its readiness for a general use [27]. The determination of excess and reservoir pressure was introduced based on pressure and flow measurements. In order to make it better applicable and, at least, a potential method for prime time use, a pressure-only approach relying on additional assumptions was developed. Under which circumstances these assumptions hold, a question which eventually is related to the site of measurement still needs to be investigated [28•]. Important to note is that under certain assumptions, the reservoir pressure equals two times the backward pressure from wave separation. Thus, when leaving conceptual differences behind, both methods contain approximately the same information and are comparably valuable for risk stratification [29].

Several statements support the methods of wave separation in the time and frequency domain and subsequently WSA and WIA. But at the same time, they oppose the widespread use of pulse waveform analysis, as two different biosignals have to be incorporated in the analysis, which can hardly be captured with one device in a convenient way. As mentioned above, several flow models have been developed to overcome these circumstances. However, the consensus document does not make any explicit statement on such an approach or on the validity of any of the flow models. Without operator-independent and cost-effective methods for flow measurement being available right now, flow models seem to be the only chance to bring WSA and WIA into prime time. Beyond the capabilities of wave separation to quantify forward and backward travelling waves, the consensus document implies that a calculation of pulse wave velocity from time differences between forward and backward travelling waves obtained by wave separation (both in the frequency and in the time domain) is not feasible [30, 31].

Although there is a clear statement supporting the validity of wave separation in the frequency domain, it is restricted to steady-state conditions. Nevertheless, such a necessity of periodicity of the waveforms is not a major restriction, as for most use cases in clinical or pre-clinical practice, the cardiovascular system will be in a quasi-steady-state during measurement. A notable and thus a method-relevant pressure change within a few beats can only be expected in special cases such as change of body position, acute changes of physical load or critical care situations.

The consensus document generally favours the use of WIA for pulse waveform analysis. As it is a time-domain method, the alignment of pressure and flow is crucial for an exact analysis, especially for the determination of wave speed by the PU-loop method [32]. WIA was originally introduced via pressure and flow differences based on a specific discrete grid in time, which is usually identical to the sampling frequency of the signals. This leads to interrelation between absolute WIA values and sampling frequencies hindering the comparability between devices. Making this method ready for prime time, a consensus on the step size or on an alternative formulation without this dependency has to be found. Another alternative is to look at ratios of WIA parameters, where the step size cancels out [33].

Windkessel-related methods as well as transmission line methods need to deal with the topic of re-reflections and the duration until waves are mostly damped—both issues have been mentioned in the consensus document. By means of mathematical simulations it is possible to "separate contributions from previous beats by prolonging the diastolic decay" [34]. The RC-time obtained from Windkessel models or from an exponential fit during diastole enables as well an estimation of the influence of previous heart beats on the actual waveform [5]. It will influence the RC-time, whether the exponential decay is prolonged to a zero or to a positive value, as proposed by the reservoir theory [7, 34]. Especially, the first statement is questioning methods relying on wave-free periods at the beginning of systole such as the PU-loop method for time-domain wave separation. A quantification of methodological deviation and a potential need for correction of methods needs to be determined [32]. With this regard, it is also important to notice that the amount of reflections being present at a certain point in time depends also on the location of the measurement. This has to be incorporated in the decision for the most appropriate measuring site and whether a carotid measurement or a distal measurement in combination with a transfer function is the better surrogate for an aortic pressure wave. Whatever approach is taken, for clinical purposes (i.e. for prime time) it is necessary to identify the relevant reflections, which should then also be identified by the methods applied. A comment states that "reflections in diastole remain unimportant compared with end-systolic reflections".

The consensus is in contradiction with methods relying on a single reflection site and those which are trying to estimate reflection times from such a site. This is the case for the augmentation index AIx and the timings connected to it [35]. Nevertheless, this should not lead to an abundance of AIx, as this index has shown its predictive value in different cohorts [36]. Instead, the dependency of AIx on covariates additional to wave reflections needs to be further investigated. Especially, the relation of AIx to ventricular function and ventriculo-arterial coupling could lead to new insights [20, 21, 37].

The consensus document is an important step in bringing pulse waveform analysis into practice; although not all aspects are included in this consensus, as a comment on the definition of a wave indicates "This question […] suffers from the lack of a clear definition of what is meant by a wave. […] much of the confusion about different methods of analysis in arterial haemodynamics reduced to confusion about these different, usually implicit, definitions of wave." Also, mechanisms additional to wave effects should not be forgotten, as it still needs to be recognized that local changes in cross-sectional area "correspond to changes in blood volume, which are determined by the blood flow distribution along the arterial pathway and local arterial compliance", as also mentioned in a recent viewpoint paper [38].

Usability of Concepts for Prime Time Use—A Question of Devices

Besides the scientific soundness of a method and the ability of a parameter to serve as biomarker [39], additional requirements have to be met for prime time use. In this context, arterial waveform analysis can only be achieved in a non-invasive setting. Commercially available devices combining suitable hardware as well as algorithms are inevitable for this purpose. Additionally, methods should be easy to handle and, in best case, operator-independent. Essential for a widespread use is cost-effectiveness and the incorporation into health insurance refunding schemes.

Only a very limited number of devices fulfil these criteria to a broader extent [40]. Some of them rely on measurements at the carotid artery; others use measurements at more distal superficial arteries in combination with a transfer function. Either way, these approaches try to obtain an estimate for an aortic waveform. Additionally, several devices exist that estimate absolute central pressure values from brachial or radial measurements without an aortic waveform, thus having only the possibility to provide distal waveform analysis. For the determination of augmentation index, an increasing number of devices exist, following the pioneering path of the SphygmoCor device (Atcor Medical, West Ryde, Australia). However, comparability between devices is not always given, since, for instance, some devices report a peripheral AIx instead of a central one [41]. The SphygmoCor device also allows wave separation analysis based on a pressure-only approach in connection with a flow model [15, 42]. Using an alternative flow model, this is also possible with devices using the ARCSolver® algorithms (AIT Austrian Institute of Technology, Vienna, Austria), best known from the Mobil-O-Graph plus PWA ambulatory blood pressure monitor (I.E.M., Stolberg, Germany).

For other methods, users are currently forced to apply their own algorithms to the raw data obtained with one of the existing pulse wave measurement devices. This naturally can only be done for research purposes and hinders the widespread use of such methods.

Overall, there is still a need for additional devices performing reliable pulse wave analysis. However, new devices need to be tested and validated firstly before they are ready for prime time. Currently, a lot of new devices dedicated to mobile or cuffless measurements are coming on the market. Here, a differentiation needs to be done between medical devices following given standards and newcomers yielding to be rather a lifestyle product.

Necessities on The Way to Prime Time

On the way to bring pulse waveform analysis from a niche application into prime time, several tasks have to be accomplished. These involve the following issues:

- Many physiological processes connected to the cardiovascular system leading to the specific and individual shape of the arterial waveform are still unknown. Thus, physiological studies are needed beyond existing ones to clarify basic principles as well as the exact mechanisms leading to a certain parameter value, including the influence of arterial compliance, wave reflections, fluid shifts, ventricular function and ventriculo-arterial coupling. [43–46]. This need can exemplarily be deducted from the consensus statements cited above, which say that there are many reflection sites in the body, but does not give any information about the quantity of wave reflections related to a certain location and subsequently on the influence of certain reflection sites on the overall wave shape.
- Consensus has to be reached not only on a scientific methodological level, but also on a more applied level. Questions that should be discussed are as follows: What are target groups for pulse waveform analysis methods? Do different use cases allow different level of accuracies and subtleness of given parameters (screening vs. decision

making)? Which measurement locations are suitable (peripheral vs. central, carotid vs. transfer-function-derived aortic)? Is there a relevant diurnal change in waveform parameters? Subsequently: When and how often should it be measured?

- Existing methods of pulse waveform analysis focus on the determination of arterial properties and especially wave reflections. However, the dependency of waveform features on the input into the system, i.e. preload effects, the contractility of the heart and the ventriculo-arterial coupling needs to be understood better [20, 33, 37, 47].
- The role of re-reflections from the heart has been mentioned in the consensus document in several statements and has been highlighted in a recent paper [48•]. However, the exact impact of re-reflections on the different methods needs to be investigated further. It could be a key point to understand the differences and similarities between the proposed methods, e.g., for the relation between the backward wave from WSA and the reservoir pressure.
- For a widespread use, the relation of waveform features and gender have to be investigated more closely, i.e. sex differences and ethnicity factors [49, 50].
- Existing methods should be critically judged and revised where appropriate, and the field should be open minded to new ideas, which naturally have to undergo critical control from the scientific community before they can enter the pathway to prime time [51–53].
- Guidelines for the validation of devices incorporating pulse wave analysis are currently not available and should be formulated. For methods incorporating pressure values, such as wave separation, they could follow guidelines for peripheral or central blood pressure measurement. A proven comparability between devices will be necessary for an interchangeable use, being another prerequisite for a broad application.

Conclusion

Arterial pulse waveform analysis has a long tradition but has not yet pervaded medical routine. Different methods of waveform analysis coexist, all having their pros and cons. Recently, a step towards a methodological consensus was undertaken by the Artery Society in formulating consensus statements. Although no clear consensus could be found for every approach, a strong favour for methods relying on both pressure and flow can be deviated. Especially, wave separation analysis seems to be widely accepted as a tool being ready for prime time use. Unfortunately, not many devices are available to perform such an analysis. Already existing devices rely on model-based estimations of flow rather than measurements, and the validity of the different flow models for specific patient groups still needs to be determined. Overall, there are only a small number of devices performing adequate and effective pulse waveform analysis which hinders widespread use.

To conclude, pulse waveform analysis has the potential for prime time. It is currently on a way towards broader use, but still needs to overcome challenges before settling its role in medical routine.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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