TOWARDS A CONSENSUS ON THE UNDERSTANDING AND ANALYSIS OF THE PULSE WAVEFORM: RESULTS FROM THE 2016 WORKSHOP ON ARTERIAL HEMODYNAMICS: PAST, PRESENT AND FUTURE

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on behalf of the Participants of the 2016 Workshop on Arterial Hemodynamics: past, present and future (listed below).

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Introduction

The Association for Research into Arterial Structure and Physiology (Artery Society) is proud to count some "*eminence grises*" among its active members, including Michael O'Rourke, Nico Westerhof and Kim Parker. All three have been honoured by the society over the past few years with McDonald lectures.[1-3] It was on one of these occasions (the 2013 annual meeting in London), that we realized that the legacy of these giants should be preserved. In addition to their books and numerous papers on hemodynamics and cardiovascular function, seen as reference works in the field, we thought it would be valuable to record audio-visual material, reflecting their viewpoints and contributions to modern hemodynamics and cardiovascular mechanics, which would produce valuable material available not only for the scientific community but also for teaching and graduate and postgraduate training.

Commented [AlunH1]: Are these the correct references for Michael and Nico?

It still took us a couple of years to finally organize a workshop entitled A*rterial hemodynamics: past, present and future* held in London on June 14 and 15, 2016. We also felt that, together with the recognition for the work of Nico, Michael and Kim, the workshop would also offer an opportunity to discuss some contentious aspects of our field that have remained unresolved despite years of research. In particular, the importance of waves and wave reflections in shaping the arterial pulse, and the Windkessel-like behaviour of the arterial system in diastole have been the subject of debate.[4-9] In this special issue of Artery Research, Michael O'Rourke, Kim Parker and Nico Westerhof present summaries of their views and contributions. [refs to be added] The audio-visual recording of their talks in London can also be found at the Artery

Society website (http://www.arterysociety.org/arterial-hemodynamics-download-videos-from-meeting/).

In this manuscript, we sought to evaluate whether a degree of consensus could be achieved on some of the topics covered by O'Rourke, Westerhof and Parker. To do this we formulated a list of potential consensus statements informed by discussion at the meeting in London. However, rather than simply positing these statements, we felt it might be more interesting, relevant and fair to quantify the degree of agreement and invite comments from the participants of the workshop to be included in this manuscript.

Methods

Following the London meeting, all attendees were contacted by e-mail on November 17th, 2016 and invited to participate in an internet survey, with a deadline set on December 1st, 2016. We did not invite responses from O'Rourke, Westerhof and Parker since their views and insights are provided at length elsewhere in this special issue. Participation to the survey was coupled with co-authorship on the manuscript, and hence was not anonymous, although participants were permitted to make unattributable comments for inclusion in the manuscript, or comments not for publication. The internet survey was created in Google Forms and participants were asked to what extent they agreed with each of 9 statements using a Likert scale (a score of 1 indicating full agreement, and a score of 5 indicating full disagreement). Comments have been presented verbatim, except for corrections of spelling or other typographical errors and reformatting of references for consistency.

Results

30 participants out of 50 attendees at the meeting responded to the survey. The number of comments on each statement ranged between 6 and 15. Of the 30 respondents, 3 requested that their comments be unattributable and 2 requested that their comments not be published.

Statement 1. It’s all about waves!

The heart is a pulsatile pump, and blood pressure is the result of waves travelling back and forth in the arterial system. Diastole is therefore not a wave-free period, although the intensity of waves in diastole is generally small or undetectable. Waves persist in systole and diastole, and the pressure decay in diastole can be explained on the basis of re-reflection of forward waves, including reflection of cardiac compression and expansion waves. Any particular arterial pulse is the result of wave dynamics generated in that particular beat, but also contains a contribution from previous beats. Strictly speaking, there is no such thing as a reflection-free period (not even early systole) although the intensity of the waves varies throughout the cycle.

Most respondents fully agreed with the statement (Figure 1). Nevertheless, despite the strong overall consensus that wave dynamics are fundamental to arterial hemodynamics, several pertinent comments or qualifications were made regarding the conceptual framework (supplementary table S1). Notably, some respondents questioned the importance of the contribution of previous heart beats to the current pulse waveform (supplementary table S1). At the same time, it was noted that numerical modelling supported the idea that previous beats contribute to the current pulse (supplementary table S1).

2. Wave reflection is continuous and diffuse

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, which implies reflections at branching points, along tapering tubes, etcetera.

The majority of respondents fully agreed with this statement (Figure 2); however, commentators raised issues regarding the location of reflection sites, the concept of ‘effective’ reflection sites and the importance of reflection at the aortic root (supplementary table S2).

Statement 3. Impedance analysis is a valid way to analyse the arterial system

Impedance analysis, based on Fourier-transformed pressure and flow waves, is a valid characterization of the arterial system. Drawback of impedance analysis, however, is that it is performed in the frequency domain, which is somewhat abstract. It also relies on the assumption that the system is in steady state, making the method unsuitable for the analysis of transient states and phenomena.

The majority of responders fully agreed or agreed (Figure 3). Comments included noting linearity as an assumption of Fourier analysis, criticism of the use of the term ‘valid’, and questioning the use of the term ‘somewhat abstract’ (Supplementary table S3).

Statement 4. Wave intensity analysis is a valid way to analyse wave dynamics.

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. The method can be performed in the time domain and is more intuitive than impedance analysis, but calculation of wave intensity involves multiplication of derivatives of pressure and flow which renders the method very susceptible to noise and might potentially introduce spurious waves when signals are not adequately filtered and/or time aligned. Wave intensity analysis emphasizes rapid changes in pressure and flow and tends to underemphasize slowly changing signals.

A large majority of responders fully agreed or agreed with this statement (Figure 4). Comments are shown in supplementary table S4. These drew attention to mainly technical issues related to the high frequency content of wave intensity signals, timing and alignment of pressure and velocity signals, sampling frequency, and the determination of wave speed. In addition, the use of the term ‘very elegant’ was criticised as unscientific.

Statement 5. Wave separation analysis

Wave separation analysis can be done in either the time or frequency domain, results are essentially identical. In wave separation analysis, all forward and backward waves are summed, which implies that the forward and backward components also include re-reflections. The separation of pressure (and flow) waves into one compound forward and backward wave does not imply that the compound backward wave is the result of the reflection of the compound forward wave at a given discrete “effective” reflection site. The “self-cancelling” flow waves in diastole are not in contradiction with physics.

The majority of responders fully agreed or agreed with the statement. Comments (supplementary table S5) related to the interpretation of ‘effective reflection site’, ‘self-cancelling’ waves the ratio of backward to forward waves and the inability to distinguish reflected from re-reflected waves. It was noted that wave separation analysis had advantages over use of augmentation index.

Statement 6. Timing of wave reflections should be based on pressure and flow/velocity

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. Assessment of the timing of reflection should be based on high-fidelity pressure and flow waveforms, e.g. using wave intensity analysis. Timing based on identification of fiducial points on signals derived from transfer functions may be inaccurate.

Most responders fully agreed or agreed with the statement (Figure 6). Comments (Supplementary table S6) generally agreed with the limitations of (generalized) transfer functions, but some noted that estimates using generalized transfer functions broadly agreed with more direct measures and that the combination of pressure and flow analysis have never been proved to be better than pressure-alone approach for predicting long-term outcomes in population-based studies.

7. Windkessel models

Windkessel models are zero dimensional, lumped parameter models and cannot account for any wave travel/reflection. They are, by definition, limited in capturing the physics of the arterial system, no matter how many parameters they contain.

Most responders fully agreed or agreed (Figure 7). Commentators (supplementary table S7) were critical of the term " the physics of the arterial system" and questioned the evidence that Windkessel models could capture wide dynamic changes in hemodynamics, or how the statement took account of distal flow and resistance. Other comments related to pros and cons of the Windkessel model, and one respondent noted the relationship of Windkessel models to 1-dimensional models.

Statement 8. Tube and T-tube models

Tube and T-tube models do account for wave travel and reflection, but assume one or two discrete reflection sites and are, by definition, limited in representing the behaviour of the arterial tree. They can be an unreliable basis for physiological or pathophysiological interpretations.

Most responders fully agreed or agreed with this statement (figure 8) and this statement elicited fewest comments - six (Supplementary table S8). No respondent expressed strong disagreement but some noted the historical significance of these models.

9. The reservoir-wave concept

*The reservoir-wave model is a conceptual model/paradigm, just as the Windkessel, uniform tube and T-tube models. As for all simplified models, it has limitations. The reservoir pressure travels and displays wave-like properties. In the aorta in the absence of large intensity backward waves, the excess pressure (Pexcess) equals Q*Zc, with Q the flow and Zc aortic characteristic impedance. In diastole, the reservoir pressure equals 2Pb, with Pb the backward wave as obtained from wave separation analysis. The excess pressure should not be used in conjunction with measured flow to analyse wave dynamics. Some parameters such as the excess pressure integral do seem to have prognostic value. It is not clear whether this is because of the paradigm or despite the paradigm.*

The majority of respondents fully agreed or agreed with this statement (Figure) but approximately one third of responders were neutral, which was greater than for any of the other consensus statements. This statement evoked the largest number of comments (fifteen). Respondents made a number of conceptual and technical criticisms (supplementary table S9).

Discussion and conclusions

Overall the responses and comments show a high measure of quantitative agreement with the various proposed ‘consensus’ statements. This is consistent with a more qualitative analysis (Figure 10) showing that the words ‘agree’ and ‘useful’ featured commonly in comments. Consequently, these statements seem a useful basis for proceeding with a more detailed and comprehensive consensus document on the current understanding and approaches to analysis of the pulse waveform. Future efforts should be directed at identifying remaining areas of dispute and future topics for research.

References

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Acknowledgements

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Conflicts of interest

None.

Figures

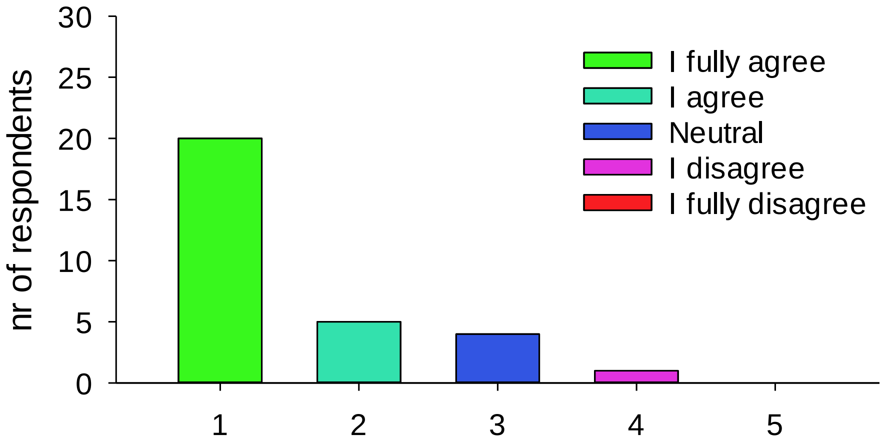

Figure 1. Summary of responses to statement 1. It’s all about waves!

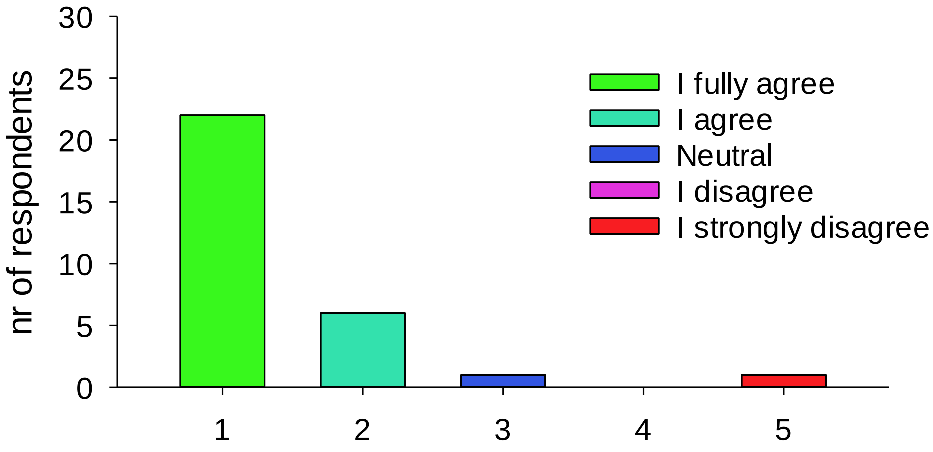

Figure 2. Summary of responses to statement 2. Wave reflection is continuous and diffuse.

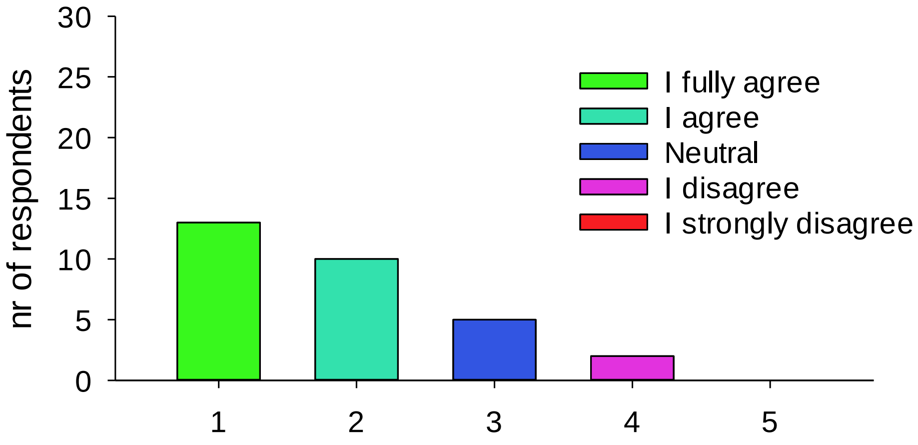

Figure 3. Summary of responses to statement 3. Impedance analysis is a valid way to analyse the arterial system.

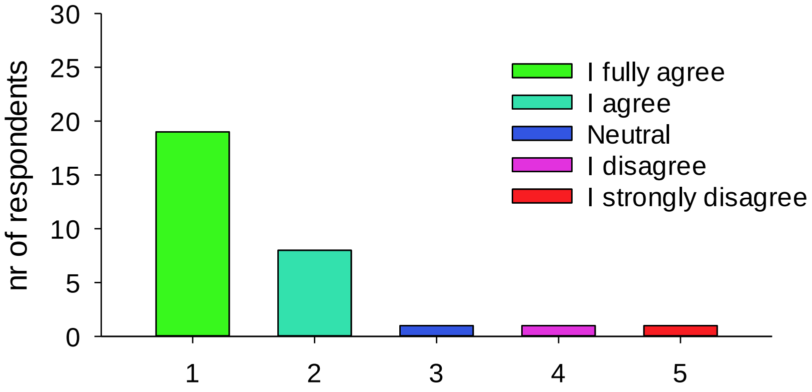

Figure 4. Summary of responses to statement 4. Wave intensity analysis is a valid way to analyse wave dynamics.

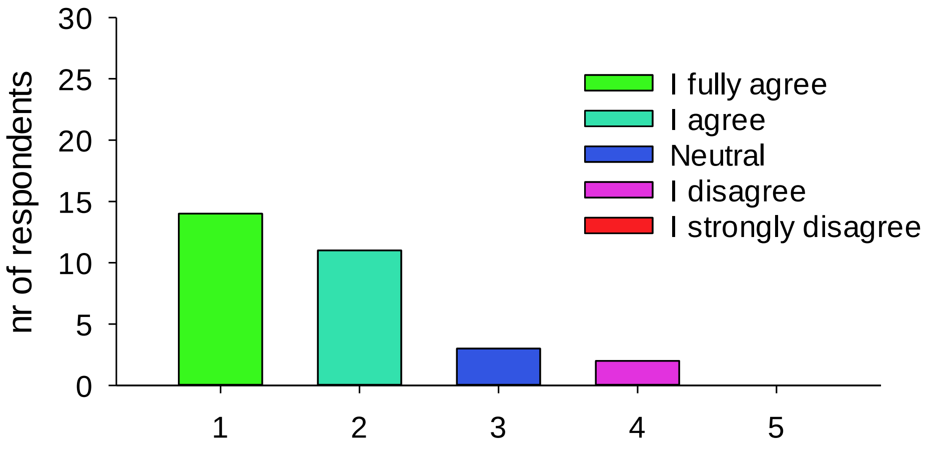

Figure 5. Summary of responses to statement 5. Wave separation analysis.

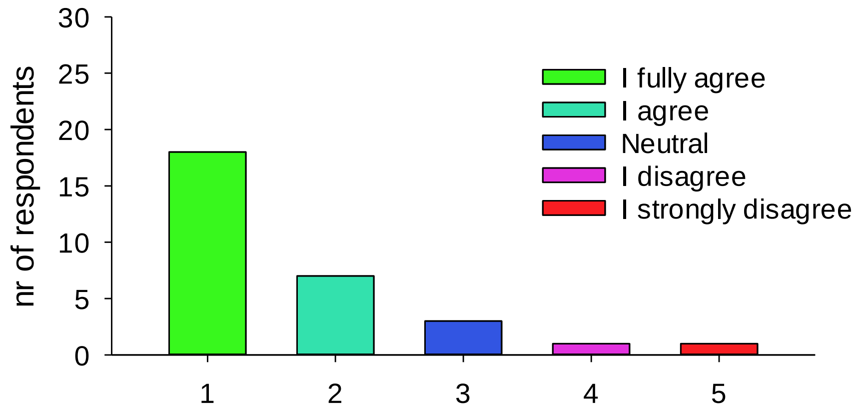

Figure 6. Summary of responses to statement 6. Timing of wave reflections should be based on pressure and flow/velocity.

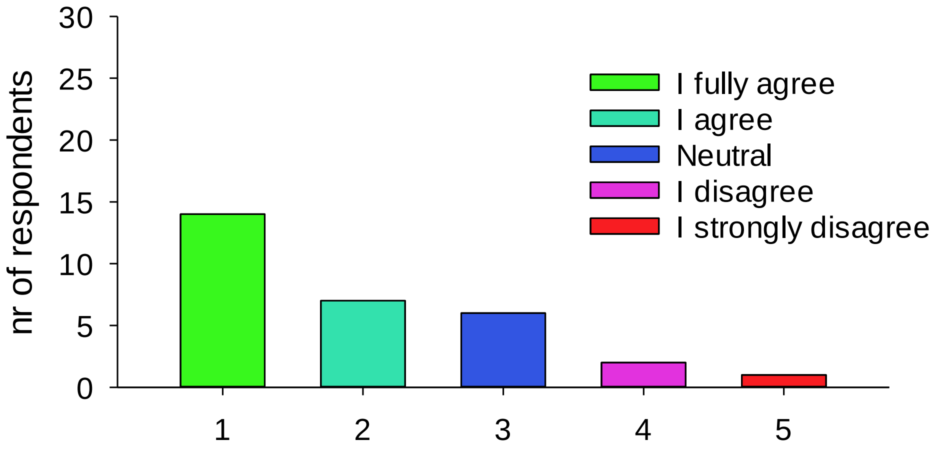

Figure 7. Summary of responses to statement 7. Windkessel models.

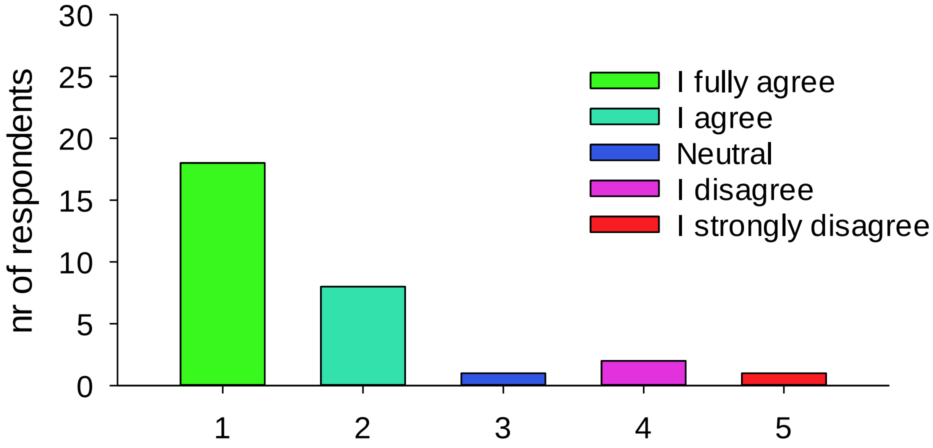

Figure 8. Summary of responses to statement 8. Tube and T-tube models.

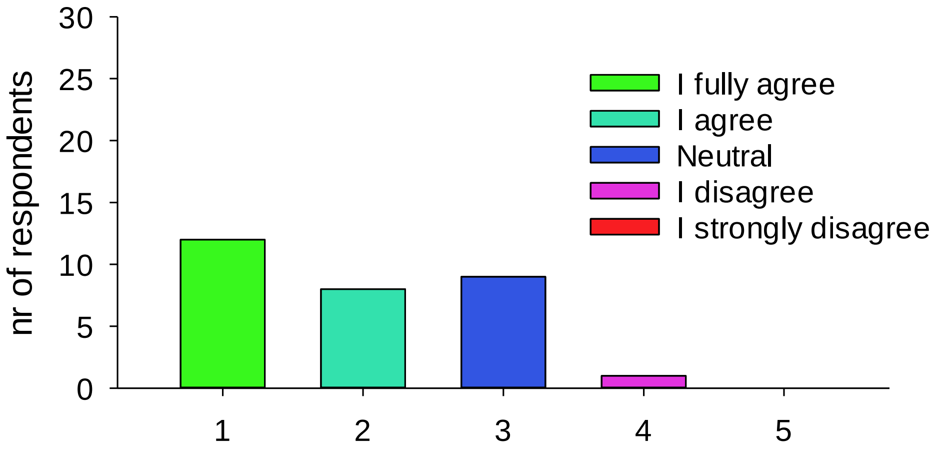

Figure 9. Summary of responses to statement 9. The reservoir-wave concept.

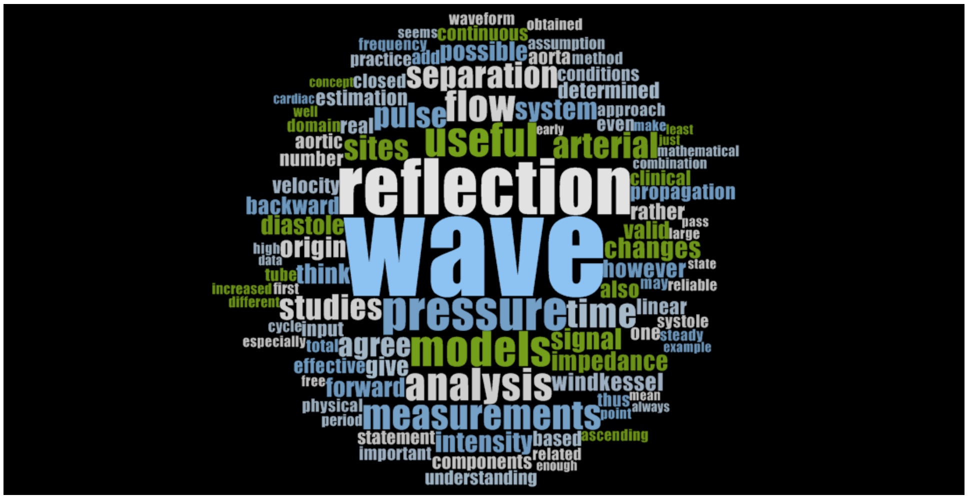

Figure 10. Word cloud derived from comments received in response to consensus statements.

SUPPLEMENTARY TABLES

Supplementary table S1

"… this begs the (semantic) question of what one defines as 'a wave': an incremental wave front versus the entire waveform over the cardiac cycle versus sinusoidal components. Mostly only short wavelength/duration disturbances can be observed in measurements and long wavelength/duration aspects kind of defy the telecommunications definition of a wave ('wavelength much shorter than the waveguide's length itself') otherwise things get pretty complicated". (Reesink).
"This statement is based on the analogy of the arterial tree to a system of electrical transmission lines, where wave propagation depends on the line properties and not on the source. Hence, systole and diastole are only secondary constructs related to the operation of the source and so not relevant to wave propagation in the line. This also assumes a linear and time-invariant system, where any time-varying signal can be transformed into sinusoidal waves, so diastole is a component of the whole composite waveform, which is completely defined in a single cardiac cycle under steady state conditions." (Avolio)
"I fully agree with the first part of the statement, at least up to "Waves persist in systole and diastole"… but I would add that the Windkessel approach of regarding diastolic decay as the discharge of a capacitor through a resistor is extremely useful, even though it says nothing about wave propagation. It is a powerful conceptual tool which is of value to non-purists, clinicians and others lacking a strong background in engineering or physics because it helps to reveal the link between increased large arterial stiffness and increased systolic pressure. At the risk of aggrandising a mere biomechanical sticking point, one might regard the wave versus Windkessel approach as being analogous to the wave/particle duality in quantum physics. Neither model fully explains the observations but one can freely choose either to aid understanding of (some of) the observations…" (Greenwald)
"Diastole may not be wave-free, but the predominant "diastolic wave" (the forward expansion wave) is initiated by the onset of untwisting and ventricular suction before aortic valve closure. If arterial wave intensity during diastole is undetectable, then the hypothesis that there are multiple continuing small waves may be theoretically attractive but impossible to prove or disprove. For clinical purposes, when studying ventricular-arterial coupling, reflections in diastole remain unimportant compared with end-systolic reflections; and the ventricle itself is very important since within a closed system the intensity of the forward compression wave generated during ejection contributes the most to the intensity or energy of the reflected waves" (Fraser).
"… This statement does not seem to convey that the backward waves remain important in generating pressure, especially in early diastole... "(Izzo)
A general comment for the whole form if I may - I believe the focus is on pressure waves (pulses) here and not say vascular optic measurements, e.g. PPG pulses that assess the

microvascular bed. Techniques such as PPG can have features that link to arterial haemodynamics. Similarly scope on the topic of pulses could include Impedance plethysmography too. (Allen)
"… I also think that in practice, waves from previous beats are negligible due to attenuation by visco-elastic damping and frictional losses… (Greenwald)
"I'm quite convinced that the intensity of reflected wave is low enough in early systole that its contribution to the wave amplitude can be neglected (at this time point, at least). This is particularly helpful when dealing with a mathematical model that requires a reflected wave–free period, such as the technique for the assessment of the local PWV obtained by processing the pressure-flow loop." (Faita)
Because the reflection coefficients at junctions and bifurcations in the backward direction are much larger than those found in the forward direction, the magnitude of reflected wave travelling back towards the heart would be greatly diminished. Therefore, it is reasonable to expect a period during early systole with only forward waves in the ascending aorta. It also follows that the reflection-free period is location dependent. (Khir)
"It is possible to separate contributions from previous beats by prolonging the diastolic decay of the pressure waveform from the previous cardiac cycle into the current cycle [1]. Estimation of PWV by the PU-loop provides evidence that waves persist in diastole: aortic PWV estimates in the rabbit improved when only the portion of the aortic pressure waveform generated in the current cardiac cycle was combined with aortic flow velocity [2]. (Alastruey) 1. Willemet M, Alastruey J. Arterial pressure and flow wave analysis using time-domain 1-D hemodynamics. Ann Biomed Eng 2015;43:190-206. 2. Alastruey J, Hunt AAE, Weinberg PD. Novel wave intensity analysis of arterial pulse wave propagation accounting for peripheral reflections. Int J Numer Meth Biomed Eng 2014;30:249-79.

Supplementary table S2

Several studies have shown that it’s difficult to pinpoint an exact location of an effective reflection site and thus there is likely multiple sites and an ever compounding number of waves (in both directions) in the system at any given time or location. Certainly, it is clear that a single, discrete reflected wave cannot return from a site in the periphery to augment BP centrally. Indeed, reflected waves appear to become trapped by a series of reflections and re-reflections in the periphery. Surely, the CV system is designed to favour the forward movement of blood? (Schultz)
See comment [in Supplementary table S1]. (Izzo)
The discretization of reflection sites could be a good (simplifying) starting point to be used in some wave propagation mathematical models. However, these models seem to be more accurate when the number of reflection sites is increased and their position is widened, thus approaching the concept of continuous and diffuse reflection sites. (Faita)
Although there is no single or limited number of discrete reflection sites in the arterial tree, it is sometimes useful to consider an “effective” reflection site considered to be in the abdominal aorta which presumably arises from the combination of multiple reflections and re-reflections from multiple sites. This can be used to provide a graphic, if only qualitative explanation of the shape of the pressure wave in the ascending aorta and how this changes with age-associated increases of large arterial stiffness and or blood pressure. However, I acknowledge that the explanation does break down when one looks quantitatively at the timing of the reflected wave. (Greenwald)
This is based on an extension of the comment in Topic 1 [Supplementary table S1].. (Avolio)
I do agree but I would just add that some sites of reflections are more preponderant than others and studies have highlighted the potential of “effective” reflection sites accounting for the bulk of reflections[1,2]. (Vennin) 1. Mitchell G F, Parise H, Benjamin E J, Larson M G, Keyes M J, Vita J A, Vasan R S and Levy D 2004 Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham heart study Hypertension 2004; 43: 1239–45. 2. Nichols W, O’Rourke M. McDonald’s Blood Flow in Arteries Theoretical, Experimental and Clinical Principles. 2005, Ed. H Arnold (USA: Oxford University Press)
I think it is important to highlight the role of the reflection site at the aortic root. Mathematically, the aortic root can be understood as a major reflection site, where the reflection coefficient changes with time: during systole, it is larger than 1, it becomes smaller than 1 when the valve is closing, and it is equal to 1 when the valve is closed [1]. (Alastruey) 1. Alastruey J, Parker KH, Peiro J, Sherwin SJ. Analysing the pattern of pulse waves in arterial networks: a time-domain study. J Eng Math 2009; 64:331–351.

Supplementary table S3

The Fourier method also assumes linearity, which of course is not strictly valid. e.g. the pressure dependence of wave speed etc is neglected. With time domain methods, it is possible to perform a non-linear wave separation analysis (although this is infrequently performed, since the pressure-area relation must be known). (Mynard)
I agree, though impedance and phase at higher harmonics are difficult to interpret. Studies up until now have been limited in terms of dealing with frequency-resolution, measurement noise (particularly stemming from flow-measurements) and use of measured input signals in computational models instead of model-generated (deterministic) input signals/boundary conditions. (Reesink)
Linearity is also required (Westerhof)
I would change the word valid to "convenient" (Izzo)
An important assumption of impedance analysis is that the system being studied is linear (or behaves linearly). The arterial system clearly does not behave linearly. This nonlinearity has been shown to distort the measured arterial input impedance. [1] (Spronck) 1. Stergiopulos N, Meister JJ, Westerhof N. Scatter in input impedance spectrum may result from the elastic nonlinearity of the arterial wall. Am J Physiol 1995; 269: H1490-5.
I agree that the lower acceptance rate of this theory (especially) from the medical community and the small number of available clinical studies showing impedance analysis can be ascribed to the difficulties related to frequency domain representation. However, I believe that main limitations of the impedance analysis technique are mainly due to the assumption of stationarity of the cardiovascular system (which is not always correct), rather than the mathematical complexity. (Faita)
Continuing my pragmatic approach to your most stimulating questions, I would change the word “valid” to “useful”. I don’t believe the frequency domain is “somewhat abstract” – again it provides a complementary view to analysis in the time domain. I think most people are quite happy with the idea that a complex time varying signal can be represented in the frequency domain, especially when this is expressed as a discrete Fourier series. I agree with the last sentence that the method does not deal well with transient phenomena and would add the obvious point that it involves the implicit assumption of linearity, which is of course always questionable. Thus in many instances WIA is to be preferred. (Greenwald)
It is valid as a concept and has been useful, but now in comparison with newer techniques it is uninformative for clinical application. (Fraser)
An analysis in the frequency domain is probably “somewhat abstract” for most of the people who are not familiar with classic signal analysis. But it seems to be very natural to people from this field of (electrical) signal analysis, which was presumably the background of many researchers who developed methods for pulse wave analysis. The term “steady

state” has different meanings in different fields (physiology, signal analysis, stability theory…) and could therefore be misleading in this statement. I would rather argue that the Fourier Transform relies on a periodic signal. (Hametner)
The impedance concept is not abstract. It is determined by the physical (real!) properties of the system. The impedance spectrum can be determined either by the system in steady state oscillation (regular heart beat) on in unsteady oscillation (irregular heart beat), and both give the same spectrum (as long as the arterial pressure does not change, to then change the arterial properties, which will then yield a different impedance). [Note: the proposal is somewhat ambiguous in relation to the response. I fully agree that impedance is a valid characterization of the system, but do not agree that it is abstract and that the assumptions do not hold for a robust analysis. So the bias is towards not agreeing. Maybe some thought to be given as to how these responses (also applies to other questions) are scored or weighted according to the comments provided by the respondents]. (Avolio)

Supplementary table S4

WIA is considering high-pass filtered signals, hence, yes/by definition, lower frequency content is progressively not considered. Time-alignment of real measured signals is critical. System delays and phase response should be fully known and measurement of pressure of flow/velocity should be co-local, otherwise absolute timing and wave shape will be artefactual. However, in real studies, by keeping recording/processing settings equal and positioning constant, changes between groups or time-points are interpretable. (Reesink)
Perhaps the most readily comprehensible and physiologically relevant method to analyze pulse wave dynamics - certainly from a clinical perspective. Its application in humans has provided new and novel insights, not captured by other models/paradigms. (Schultz)
May be more intuitive than impedance analysis, the use of derivatives is also less direct than the original forward and backward waves. (Westerhof)
Expand on the limitations of wave intensity analysis. (Izzo)
Before the last sentence I would add an additional one stressing the fact that Wave Intensity Analysis relies on accurate estimation of Pulse Wave Speed, which is to date still a challenge. (Rivolo)
Wave intensity analysis is very similar to wave separation analysis. Wave intensity analysis, however, uses derivatives of the pressure and flow waves. This differentiation (acting as a high-pass filter) emphasises fast changes in pressure and flow and correspondingly suppresses slow changes. This has previously led to conclusions about a “wave free period”, which could be more appropriately called “fast-wave free period” or “high frequency wave-free period”. (Spronck) 1. Westerhof N, Segers P, Westerhof BE. Wave Separation, Wave Intensity, the Reservoir-Wave Concept, and the Instantaneous Wave-Free Ratio: Presumptions and Principles. Hypertension 2015; 66: 93-8.
Wave intensity analysis is definitely an innovative and easy to understand approach. Moreover, the possibility to carry out wave intensity analysis by means of ultrasound image analysis only (using diameter-velocity loop to estimate local PWV) could represent an additional benefit, which makes this tool an interesting option for diagnostic and prognostic clinical studies. (Faita)
I think the description of the question you give excellently summarises the pros and cons of WIA and I have little to add, except that the supposed “wave-free period” in diastole, implied by WIA appears, as Westerhof and Segers argue, to be a result of multiplying two small quantities together and may not reflect the reality of non-negligible forward and backward travelling waves cancelling each other out. This would be easy to verify experimentally if it were not for the fact that the aorta (as most other arteries) contains a large number of discrete potential reflection sites (junctions) plus an infinity of reflection sites due to geometric taper and a ‘continuous’ increase in stiffness along its length. (Greenwald)

"Very" elegant sounds rather too enthusiastic and unscientific - wouldn't just "elegant" be more than enough? Also, the "spurious waves" could be waves or noise so what about calling them instead "spurious signals interpreted as waves"?

The technique is possibly too sensitive for application in routine clinical practice since waves can change on a beat-by-beat basis. Measured waves demonstrate continuous physiological changes, as well as noise related to measuring the product of the rates of change of two variables.

That makes it a good research tool when measured with careful technique, but its reproducibility (e.g. coefficients of variation of 25% or even more) is insufficient for clinical studies in individual patients. (Fraser)

As already argued in the last comment, I would agree that a time domain analysis is more intuitive to many people, but I would not generalize this statement. I think intuition should not be a major evaluation criterion for a (mathematical) method, but rather its validity and the results that can be achieved. It is also important to notice that the sampling frequency must be sufficiently high to perform reliable computations in the time domain, e.g. numerical differentiation. (Hametner)

Yes, wave intensity is useful, but susceptible to noise (as is determination of characteristic impedance due to low power of sinusoidal waves at high frequencies). (Avolio)

Supplementary table S5

I agree, but should the statement read "does not imply that the compound backward wave is the result of the reflection of the compound forward wave at a given discrete (actual single) reflection site"? My understanding is that the use of the term "effective" implies that we are not talking about an actual reflection site, but something that is "as though there were a discrete reflection site". Thus it is just a way of summarising something about the bulk nature of reflection, just like we say "mean pressure" even though it doesn't really exist (it is a calculation that helps us summarise something that is complex). Much of the confusion in this area seems to stem from a misreading of "effective reflection site" as "actual single reflection site". (Mynard)
Self-cancelling flow waves in diastole are not a physical entity. (Aguado-Sierra)
Calculation of forward-backward ratios is valid, but interpretation of changes or differences therein in terms of PWV or distal reflection site/coefficient without establishing the latter independently are erroneous. (Reesink)
In my opinion, one of the main advantage of WSA is the possibility to directly evaluate the impact of backward waves on aortic pulse pressure, instead of using augmentation index, which is a rather unreliable measurement. (Faita)
I agree with this. I suppose one drawback of WSA is that, as far as I understand it, there is no possibility of investigating the magnitude or indeed the existence of re-reflections. (Greenwald)
The statement "all forward and backward waves are summed" could mean that they are all added to make one net wave intensity signal, whereas I think you intend it to mean "all simultaneously occurring forward waves are summed and all backwards waves are summed"... (Fraser)
This is consistent with the assumption of linear, time-invariant system in steady state. While strictly not entirely true, the correspondence of impedance with steady and unsteady oscillations suggests that the assumptions are physically robust, and consequently so is all that follows, such as the method and conceptual articulation of wave separation. (Avolio)
In diastole, self-cancelling forward and backward flow waves at the aortic root are the result of a full reflection against a closed aortic valve. The backward pressure (Pb) is totally reflected at the closed valve, so that the forward pressure (Pf) and Pb are equal in magnitude. Given that Pf-Pb is proportional to the flow [1], Pf=Pb at the closed valve yields zero flow. I think it is important to note that because the forward and backward components also include re-reflections, both components are misleading indicators of the proximal (from the heart) or distal (from the periphery) origin of reflected waves. This is particularly important when quantifying cardiac and peripheral contributions to the pressure waveform. The idea can be illustrated using a uniform tube model with reflective inflow and outflow boundaries. Propagation of a single pulse from the inlet generates multiple pulses reflected successively at the outlet (the periphery in this model) and inlet. The peripheral origin of

reflected pulses is not identified by the forward and backward components of pressure, since reflected pulses originating at the outlet contribute to the forward component once they are re-reflected at the inlet (see Fig. 7 in [2]). According to multi-branched 1-D modelling, the aortic pressure waveform during diastole is made up mostly of reflected waves originating at peripheral sites. However, the forward and backward components of aortic pressure are similar, leading to a misleading interpretation of the origin of the reflected waves that make up aortic pressure during diastole: the origin is mainly peripheral, however wave separation analysis predicts the origin to be half cardiac and half peripheral.

1. Alastruey J. On the mechanics underlying the reservoir-excess separation in systemic arteries and their implications for pulse wave analysis. Cardiovasc Eng 2010; 10:176–189.
2. Willemet M, Alastruey J. Arterial pressure and flow wave analysis using time-domain 1-D hemodynamics. Ann Biomed Eng 2015;43:190-206.

Supplementary table S6

This is ideal. However, the combination of pressure and flow analysis have never been proved to be better than pressure-alone approach for predicting the long-term outcomes in population-based studies. (Cheng)
Any pre-determined transfer function will 'shape' the input signal according to the primary modulus-phase characteristics of the input-output signals it was derived from. Most transfer functions [TF] are used to estimate amplitude, not phase. Fiducial points are all about phase. Use of TFs will lead to regression to the mean (of the TF cohort!), hence will not provide subject-specific values. (Reesink)
I only partially agree about the inaccuracy of timing data assessment obtained by analysis of pressure or flow signals alone. In some conditions, the accuracy and reliability is good enough. As an example, in epidemiological studies characterized by high number of enrolled subjects, it is possible to adopt this approach to obtain fiducial time points which, in turn, would be used to measure (other) vascular biomarkers. Moreover, the feasibility of epidemiological studies could be only assured by adopting this simplified approach. (Faita)
I agree that in practice, high fidelity pressure and flow recordings are preferable to the uncertain identification of fiducial points (especially shoulders) and transfer functions, although it is remarkable that the transfer function works as well as it seems to. I also think the statement is incomplete because timing of reflections can be obtained in other ways. Firstly, as shown in a number of old experiments (I haven’t the references to hand but could find them) reflection information can be obtained, in principle at least, from 2 point measurements not only of pressure/flow, but also pressure/diameter or flow/diameter. These experiments can in practice be tricky and do not lend themselves well to human studies. Also I believe there are at least two reports in the old literature where refection coefficients were derived from three equally spaced pressure measurements. I believe the method was proposed by MG Taylor in the 60s. Secondly, there are total occlusion, methods as reported by Nico Westerhof and David Newman and thirdly there are impulse response experiments (David Newman and others) where a short duration pressure pulse can be tracked as it moves along the aorta. If the impulse is short enough it can be seen in isolation from its reflection. (Greenwald)
If flow can be used instead of velocity, then once validated and given appropriate circumstances and conditions a calibrated diameter could also be used, as a surrogate for pressure - at least for clinical research studies. We should remember that what we really want to measure non-invasively in clinical practice and in pathophysiological studies is wave travel, amplitude and timing, in the ascending aorta - but currently this is impossible with current technology. Consecutive rather than simultaneous acquisitions of velocity and pressure at the common carotid are still a "surrogate" in the sense that waves in the carotid vessels may be strongly influenced by cerebrovascular tone. So any combination of sufficient signals may be usable, as long as they have been validated. (Fraser)

We have agreed in topics 1 and 2 [supplementary tables S1 & S2] that there are many superimposed waves in the arterial system. Thus, it is very difficult to achieve reliable timing information of specific waves even with knowledge of pressure and flow. (Hametner)

True in theory and in general. However, estimates can be made from waveform features that give measures that have broad agreement with physical measurements. (Avolio)

I haven't studied this problem and cannot comment much about it. (Alastruey)

The arrival time of reflected wave to the ascending aorta using wave intensity analysis in both human and large animals is always found to occur in mid-systole in a large age range. Therefore, it is important to ascertain that the notion of reflected wave arriving back in early diastole in the healthy and young, and arriving earlier to mid-systole in the elderly is incorrect. For example, let us examine a conservative case where the average wave speed between the ascending aorta and the aorta-iliac bifurcation is 5m/s, and the distance between the two sites is approximately 50cm. Then, making the hypothetical assumption that the wave will be first reflected at the aorta-iliac bifurcation, an estimated arrival time of the reflected wave to the ascending aorta is approximately 200ms; that is well within the systolic period. (Khir)

Supplementary table S7

" the physics of the arterial system" is not clear. Arterial stiffness is a major component of the physical property of the arterial system. (Chen)
To first statement: agree fully. To second: there is still limited evidence of Windkessel models in their ability to capture (without fitting to data) wide-dynamic changes in hemodynamics. Here, as first order model understanding changes in non-linear resistance and compliance WK models may be very useful, especially in clinical physiology. (Reesink)
Yes, but the elements of the Windkessel represent real and useful parameters. (Westerhof)
See 1 [supplementary table S1]. If the flow "runoff" and arterial pressure dissipation from a proximal Windkessel are affected by distal flow/resistance, how can this statement be true? (Izzo)
Windkessel models are indeed zero-dimensional, lumped models. However, their behaviour may mimic the integrated effect of wave dynamics at a certain point in the circulation. For example, if a four-element Windkessel model is used to describe total arterial input impedance [1] using it to convert arterial input flow to input pressure yields a realistically shaped pressure waveform. In reality, this waveform is a result of wave travel/reflection, a phenomenon that is not described by the Windkessel model. However, still, Windkessel models can yield a realistic description of e.g., arterial input impedance. (Spronck) 1. Stergiopulos N, Westerhof BE, Westerhof N. Total arterial inertance as the fourth element of the windkessel model. Am J Physiol Heart Circ Physiol 1999; 276: H81-H8.
Windkessel models have played a fundamental role in hemodynamics. Nowadays, they have an educational role for people who would like to start studying vascular blood flow and pressure wave propagation theories. (Faita)
Agreed, although I think the Windkessel approach is useful as mentioned in my comment on Q1 [supplementary table S1]. (Greenwald)
I'm being non-committal since I could not stand up in court to explain this satisfactorily! I'd need advice from a physicist / fluid mechanics expert. (Fraser)
Obviously there is no spatial component in the Windkessel models, thus they cannot directly represent wave phenomena. Nevertheless, they can account for total effects of wave reflections, as they have shown to represent the overall wave shape quite well. (Hametner)
If the parameters do not contain the dimension of "length" it is not possible to obtain associated information involving time (e.g. wave speed). However, depending on how they are used, they can describe volume and pressure changes with time, such as estimation of a value for total compliance of the system. (Avolio)
They do make sense though energy-wise and the absolute values (MBP, SBP) are usually accurate. This approach is more “top-level” than the wave theory but can produce

significant insights about the state of the cardiovascular system if we defined the Windkessel components as “broad” physiological parameters. (Vennin)

I agree with the statement if we only consider a stand-alone Windkessel model. However, it has been mathematically demonstrated that a finite number of Windkessel models, each containing three elements (compliance, inductance and resistance), discretrise at first-order accuracy in space a linear continuous 1-D model arterial segment [1]. Based on this result, numerical and electric analog models have been produced to simulate pulse wave propagation in the arterial tree (e.g. [2]). (Alastruey)

1. Milisic V, Quarteroni A. Analysis of lumped parameter models for blood flow simulations and their relation with 1D models. Mathem Mod and Num Analysis 2004; 38:613–632.
2. Westerhof N, F. Bosman, de Vries CJ, Noordergraaf A. Analog studies of the human systemic arterial tree. J Biomech 1969;2:121–143.

Supplementary table S8

Whilst a useful conceptual model, it appears an oversimplification of pulse wave dynamics and is hard to find a pure physiological relevance with in vivo application. (Schultz)
Indeed unreliable and giving rise to confusion. (Westerhof)
I completely agree about poor informative content of tube and T-tube models. This is the reason why I believe that these models unlikely would be useful in clinic (for design of prevention and/or diagnosis studies). (Faita)
Agreed. They were valuable though, in early work, on understanding the relationship between the arterial pulse wave and its reflections, in animal models at least. But, their days are long past. (Greenwald)
Tube models can be reliable in obtaining a reduced representation of the arterial load downstream. In fact, transmission line models are a form of tube models, with many tubes connected in series and parallel. (Avolio)
Taken alone, those models can’t give any significant insights into wave phenomena. On the other hand, when they give similar results to clinical data, they add strength and a medium to understand phenomenon. For example, a protocol to turn flow into pressure in the ascending aorta has been established using numerical 1-D tube models and then confirmed, as a proof-of-concept, with experimental data [1]. It has also been shown that one could downsize the arterial tree to a single tube accurately [2]. (Vennin) 1. Vennin S, Mayer A, Li Y, et al. Noninvasive calculation of the aortic blood pressure waveform from the flow velocity waveform: a proof of concept. Am J Physiol Heart Circ Physiol 2015; 309: H969-76. 2. Epstein, S., Willemet, M., Chowienczyk, P. J., & Alastruey, J. Reducing the number of parameters in 1D arterial blood flow modeling: less is more for patient-specific simulations. Am J Physiol Heart Circ Physiol 2015; 309: H222-H234.

Supplementary table S9

"While a model can never be “truth,” a model might be ranked from very useful, to useful, to somewhat useful to, finally, essentially useless"-George E. P. Box. All conceptual models have to be tested for its utility in real world, the clinical practice. The reservoir-wave concept may not be inferior to the conventional impedance analysis. (Cheng)
The statement "In diastole, the reservoir pressure equals 2Pb" is incorrect and misleading. The amplitude of the reservoir pressure may approximate 2 amplitudes of Pb. However, the waveform of the reservoir pressure is different from that of the Pb. "In diastole" is also not correct, since the peak of the reservoir pressure is well within the systole. (Chen)
Since reservoir pressure is essentially equal to 2Pb, statements such as "systolic pressure augmentation is caused by the reservoir pressure and not wave reflection" are incorrect since wave reflection underlies reservoir pressure. There would be no reservoir pressure if there were no wave reflections. It is also important to recognise the difficulty of calculating reservoir pressure when there is no clear exponential pressure decay during diastole, which may frequently occur in some settings (particularly younger individuals and/or at high heart rates). Hence one might expect the prognostic value of 2Pb and Q*Zc to be better than reservoir/excess pressures if the former are more robustly calculated (since these don't rely on an exponential decay); however, this needs to be tested. (Mynard)
Reservoir pressure has also provided relevant information regarding hypertension and excess pressure can provide useful information regarding arterio-ventricular coupling. (Aguado-Sierra)
The pressure-difference across the proximal impedance Z in 3-element (or R//L in 4-element) WK models equals Q*Zc too. In that sense the R-W model is much like a WK model. If one calculates the R-W components at distal locations than at aortic input, OF COURSE the reservoir travels forward too. (Reesink)
Whilst controversial, this model surely cannot be dismissed solely on the basis of some potential 'mathematical limitations' because' it has been consistently demonstrated to hold prognostic value beyond conventional BP parameters and provides physiologically plausible explanations for changes in BP associated with such things as ageing and exercise. (Schultz)
Not sure if there is a general consensus on how to fit the reservoir wave. (Westerhof)
We need a good up to date topical review on modern Pulse Wave Analysis. It seems now that there is good healthy debate on the pulse and what it is, how to describe and understand it, and how to extract useful clinical information from it reliably. (Allen)
(not sure what the actual proposition is here to agree/disagree with). In my opinion, we are studying haemodynamics to improve our understanding of phenomena such as arterial stiffening. Generally, a theoretical framework (e.g., a Windkessel model or the reservoir-wave concept), with several assumptions, is applied to data to yield an interpretation. In the reservoir-wave case, the framework used seems a bit

arbitrarily chosen. Of course, it can always be the case that a result appears to have prognostic value, but do we learn something from that? (Spronck)

Despite the limitation of being a purely conceptual model, the (partially, at least) proved and published possibility to provide prognostic biomarkers (independent from the standard ones) encourage to keep working on this theory. Moreover, new prospective studies with biomarkers derived from the reservoir-wave concept should be designed and started. (Faita)

I don’t have any direct experience of using the reservoir pressure concept to “analyse flow wave dynamics” so cannot comment on that part of your statement. However, I think that, in spite of its limitations, the reservoir pressure hypothesis is a powerful explanatory tool (just as is the Windkessel). I am uneasy though about your statement that it “travels and displays wave-like properties” given that on the one hand it is regarded as independent of the pressure that drives the pulse wave (i.e. the wave pressure). As I understand it the reservoir pressure as explained by Kim Parker is spatially uniform throughout diastole, i.e. it shows no evidence of progressing along the aorta during this time and is not therefore behaving like a wave. (Greenwald)

I don't think that the last sentence here will be clear to the uninitiated.
I'll be interested to see the summary of responses but please note that the way that they are stated will provoke a biased response towards agreement; maybe that's what you intended!
Thank you. (Fraser)

I cannot follow the statement that the “absence of large intensity backward waves” implies P_ex=Q*Zc and I would be happy to see calculations supporting this statement.
To my knowledge it holds that P_ex=Q*Zc, when one of the two following assumptions is taken:
(1) P = P_3WK with P_3WK is the arterial pressure modelled by a 3-element Windkessel, which also implies that P_res=2*Pb
(2) it is directly assumed that P_res=2*Pb. (Hametner)

Generally agree with the concept as being a model representation but not so much with the separation aspect of excess pressure. However, the consistency of the findings could be due to some type of circular redundancy in the paradigm. (Avolio)

In its usual definition, the reservoir pressure behaves as a travelling wave and, under certain conditions, it is twice the backward pressure and, hence, not uniform in space. However, it is possible to obtain a reservoir-like 0-D approximation to the pressure by linear analysis of the 1-D formulation. Unlike the classic reservoir pressure, this alternative 0-D pressure is not a travelling wave and can be used at any location of the arterial network, providing a very good fit during diastole. It is space-independent and determined by the distributed parameters of the arterial network. Nevertheless, there is no evidence that the corresponding excess pressure provides any relevant physical information [1]. I like to think of the Windkessel model as an approximation to the 1-D model, as the 1-D model is an approximation to the full 3-D formulation in compliant vessels. (Alastruey)

1. Alastruey J. On the mechanics underlying the reservoir-excess separation in systemic arteries and their implications for pulse wave analysis. Cardiovasc Eng 2010; 10:176–189.