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SPECIAL ISSUE - REVIEW ARTICLE

Time domain analysis of the arterial pulse in clinical medicine

Michael F. O'Rourke

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Abstract The arterial pulse at any site is created by an impulse generated by the left ventricle as it ejects blood into the aorta, together with multiple impulses travelling in the opposite direction from reflecting sites in the peripheral circulation. The compound wave at any site depends on the pattern of ventricular ejection, the properties of large arteries, particularly their stiffness (which determines rate of propagation) and the distance to and impedance mismatch at reflecting sites. Physicians are familiar with waveform analysis in the time domain, as in the electrocardiogram (ECG) where the principal features are explicable on the basis of atrial depolarisation followed by ventricular depolarisation, then repolarisation. Effects of cardiac functional and structural disease can be inferred from the ECG. It is more difficult to make similar interpretations from the pulse waveform and clinicians usually use this only to count heart rate, extremes of the pressure pulse to express systolic and diastolic pressure, and (sometimes) time from wave foot to incisural notch to measure time of systole and diastole. More information can be gleaned from the shape of the arterial pressure wave through consideration of the factors which create it—on stiffening of large arteries with age, effects of drugs on smallest arteries, and changes in such arterial properties on left ventricular load and function. Such is a major challenge to future physicians. It is aided by better and more accurate methods for measuring flow and diameter as well as pressure waveforms, and by appropriate use of other analytic techniques such as analysis of the pulse in the frequency domain.

Keywords Arterial haemodynamics · Waveform analysis · Wave reflection · Augmentation index · Pressure pulse

1 Introduction

From my perspective as a clinician and physiologist, the modern era in arterial haemodynamics began with the collaboration between Donald McDonald and John Womersley some 60 years ago, and which introduced steady-state analysis to the study of pressure gradient and flow waves in arteries [30]. My mentor Michael Taylor was the principal offspring of this group, and his contributions to the study and interpretation of vascular impedance, wave travel and reflection surpassed those of his mentors [49, 50]. I first met Taylor in 1962, and saw an approach which had the prospect of giving new insight into atherosclerotic disease, then an even greater scourge than now. But I had to "know the ropes". This involved a different process than now. Original works—sometimes first editions of classic articles—needed be read, instruments made if they did not exist, and instrumental accuracy scrutinised in the steady and dynamic state. I read Harvey, Hales, Wiggers, Gregg and Hamilton, and heard gloomy words on contemporary authorities in the USA who would not stray beyond analysis of the pulse in the time domain [43]. Through Harvey's work and his clash with Riolan from Paris (best illustrated in the first pages of "de Circulatone

Michael F. O'Rourke is a founding director of AtCor Medical, manufacturer of systems for analysing the arterial pulse.

M. F. O'Rourke
St. Vincent's Clinic, University of New South Wales,
Victor Chang Cardiac Research Institute, Sydney, Australia

M. F. O'Rourke (✉)
St. Vincent's Clinic, Suite 810, 438 Victoria Street,
Darlinghurst, NSW 2010, Australia
e-mail: m.orourke@unsw.edu.au

Sanguinis" [6], I first became aware of real scientific controversy, and realised that I would likely be embroiled in the same through the debate that was brewing between the McDonald camp who would only view the arterial pulse in the frequency domain, and the Remington group in the USA who would only view the pulse in the time domain [43]. Mercifully, both of the groups had been trained in classical physiology, so that artefacts in pressure and flow waves were not a source of distraction.

Taylor was fastidious about accuracy—in measurement, reporting and discussion. He was so obsessive that data recording on FM tape was done with a zero voltage channel always, so that subtle changes in tape speed would be apparent and correctable. The first task assigned me was to dismiss previous assurance on the dynamic accuracy of the electromagnetic flowmeter, and check this myself through use of a sinusoidal pump and harmonic resolver through pumping saline and/or blood through arterial segments. We managed to show that flow could be accurately measured if this was axisymmetric, and that frequency distortion was attributable to the flowmeter's electronic filter [33].

My experimental works in second and third years with Taylor were some of the most productive and satisfying of my life. In 1963, he had acquired state of the art digital processing facilities, and had access to Sydney's first computer in the School of Physics at Sydney University. My animal experiments by day were followed by computer analysis by night, then interpretation through modelling experiments designed next day. Together we found that the concept of vascular impedance did work, and did describe the wave propagation into and wave reflection from various vascular beds in a host of different animals—studied deliberately so as to test the theoretic models of different vascular size, length and branching patterns [30, 49, 50].

Michael Taylor as a pupil of Donald McDonald had "inherited" his views on analysis of the pulse waveforms in the frequency domain. I worried about this because, as a simple clinician I was more comfortable with pulse in the time domain, and needed to explain mechanisms in terms of the waveforms as well as impedance or other transfer functions. I managed to win over Taylor, somewhat grudgingly, if only by convincing him that I could better identify artefact in the time domain during an experiment, rather than from results of a transfer function, available from the computer next day. But I could not convince Donald McDonald, who when faced with tracings which showed evidence of strong wave reflection and rereflection in the arterial tree would not concede such a possibility but would refer to amplitude and phase of the nth harmonic. My first paper to show analysis of the pulse waveforms in both time and frequency domains was reviewed by John Remington [43] who revealed himself in an encounter with Bill Milnor who had been asked by Phillip Dow to arbitrate on behalf of the journal. Remington disliked the paper, and so did McDonald, yet it was published [34].

Memories such as the above seem relevant in this journal issue, since the same types of dispute remain, are fired by human nature and a disinclination to consider another point of view. The same concerns still exist about instrumental accuracy, and are now perhaps all the more important when we utilise non-invasive measurements of pressure and flow to interpret the effects of ageing and disease in humans.

2 Clinical practice: link between frequency and time domain analysis

My brief is to discuss time domain waveform analysis in clinical medicine. It is important for readers to appreciate that I entered this field through a frequency domain analysis path, and have a profound respect for such analysis. My entry into human clinical haemodynamics was at Johns Hopkins with Bill Milnor, whose prime clinical interest was the pulmonary circulation. At the time Donald McDonald was in Philadelphia, en route to Birmingham, AL, and Nico Westerhof was in Philadelphia with Bram Noordergraf. Eugene Braunwald was in Bethesda conducting clinical and experimental cardiovascular studies. When Chris Mills, Ivor Gabe and John Shillingford visited Bethesda we were invited to see the new catheter tipped electromagnetic flowmeter used in the catheterisation laboratory [24]. This opened a new field, but data quality was often poor, especially for the flow waveforms, while frequency response of the fluid-filled catheter system was marginal. Huntley Millar then introduced a superior high fidelity pressure sensor together with electromagnetic flow sensor mounted below an extended catheter tip; this was intended to stabilise the catheter in the proximal aorta. Murgo and colleagues [28, 29] conducted studies of ascending aortic impedance with this catheter, as did Merillon, Gourgon and colleagues in France, Nichols in Gainesville and Yin in Baltimore and Taiwan, and Yaginuma in Tokyo [30]. We did limited studies and reverted to collecting data with an electromagnetic sensor around the ascending aorta of patients at cardiac surgery [36]. None of the above clinical researchers were happy with use of the electromagnetic flow catheter sensor, since different flow patterns were regularly seen, and could be explained on the basis of jets and secondary flows in the ascending aorta. Yin's [60] careful work could only be completed on a fraction of patients originally studied, and Yaginuma came to measure pressure and flow in the proximal descending aorta where flow was more stable. With time, use of the electromagnetic flow catheter was

abandoned for measuring ascending aortic impedance, and such studies are now conducted non-invasively with Doppler flow from the left ventricular outflow tract and with pressure determined by carotid tonometry [25], or synthesised from the radial artery, using arterial tonometry and a generalised transfer function which corrects for distortion of the pressure pulse in the upper limb [30, 37].

Achievements in impedance analysis are discussed by Mitchell in chapter 8 of this supplement. We do have concerns about the results and interpretations of this work, since there is little consideration of sources of error in measurement of flow in the left ventricular outflow tract and ascending aorta [39, 40]. The same problems of secondary flows (jets and eddies) that bedevilled invasive measurement of flow at cardiac catheterisation with the Mills or Millar pressure/electromagnetic flow catheter are apparent in the Doppler flow waves as a wide envelope. The encircling electromagnetic flow probe that we used in animal and clinical studies appears to have been less influenced by these flow problems, presumably because flow was measured in the ascending aorta, and secondary flows were largely axisymmetric. With this instrument one invariably got a sharp forward flow wave in systole, with its peak around 100 ms after the foot (in humans) and no flow in diastole. With the electromagnetic flow catheter, considerable difference is seen in published flow waves, even sequential waves. My assessment of this experience was largely influenced by my training with Michael Taylor. There was error in flow recordings that was explicable but could not be controlled. I all but abandoned flow wave analysis and sought to analyse the pressure pulse wave alone, and non-invasively.

My approach to time domain analysis of the pulse was heavily influenced by the superb work done by Murgo and colleagues at the Brooke Army Medical Centre in San Antonio, using Millar pressure/velocity catheters. Murgo drew attention to the different patterns of pressure wave that he saw with ageing and disease, and linked these to different patterns of impedance and to difference in timing of reflection. It seemed that as in different experimental animals [30], the pattern of aortic flow waves was similar in different patients, so one did not need the flow waves or the impedance patterns to interpret wave reflection and vascular load, and could get most of the clinical information from the pressure waves alone. (This is only partially true particularly in the presence of systolic LV dysfunction, as discussed below). But this was the simple practical compromise we adopted, and sought to make the process non-invasive through introduction of a Millar sensor on a hand-held tonometer over the carotid or radial artery [9, 10]. Most of the early work in my department was undertaken by the late Ray Kelly with Alberto Avolio, Chris Hayward and David Gallagher. We followed similar work in Tokyo by Yaginuma's pupil Kenji Takazawa [48]. Takazawa's principal interest was to seek sources of information and error in the invasively recorded left ventricular and aortic pressure waveforms, and their relationship with pressure waves in peripheral arteries such as the carotid and radial, and the finger volume plethysmograph. His work broadly supported the view that in contrast to flow waves, the aortic pressure waveform measured by Millar micromanometer was little influenced by secondary flows.

Such non-invasive studies were guided by the principles espoused by Michael Taylor—history, hierarchy, accuracy and frequency domain analysis. We also belatedly became aware that we were travelling the same path as nineteenth century physicists and physicians such as Etienne Marey [21] and Frederick Mahomed [35] who had introduced sphygmograms to measure the radial pulse waveform so as to recognise hypertension, premature arteriosclerosis and high risk of cardiovascular events [5]. The characteristic feature of the radial artery waveform in such persons, and in the aged, apparently well, was a secondary peak in late systole. Mahomed showed that this corresponded to high augmentation of the pulse in a central (carotid) artery [35]. Journal articles and textbooks of the late nineteenth and early twentieth century were liberally illustrated with radial pulse wave tracings [19], as was the first edition of the *Journal of the American Medical Association.*

Kelly's work [9] with arterial tonometry showed that this could accurately measure the pressure waveform features, but not the actual pressure values. This was supported by work from Yin, Kass and others at Johns Hopkins [2, 60]. Possibly the most important and certainly the most controversial work by Kelly and our group in Sydney was to show that the transmission of the pressure pulse through the upper limb to the brachial or radial artery could be characterised by a generalised transfer function whose properties were little affected by age, vascular disease or even by vasoactive drugs in normal clinical doses [8]. This finding was suggested by the simple observation of cardiac catheterisation (Fig. 1) that there is a fixed relationship between pressure waves in the aorta and radial artery before and after sublingual nitroglycerine, such that change in the aortic pressure wave could be inferred from the radial [11]. Importance of this finding was that aortic and left ventricular systolic pressure could fall by as much as 20 mmHg without this being detected in the upper limb by conventional recording—even by intra-arterial catheter.

Our views on use of a generalised transfer function process for generation of the central aortic pressure waveform was met with incredulity. Our colleagues (Yin, Kass, Chen et al.) at Johns Hopkins repeated the process and obtained substantially similar results [3, Fig. 2]. They, like we, concentrated on invasively recorded waveforms from matched

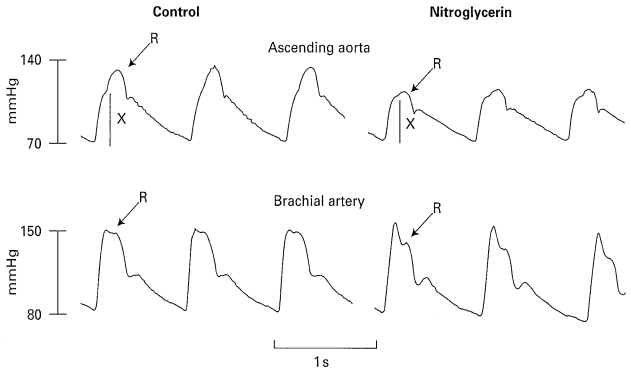

Fig. 1 Pressure waves recorded in the ascending aorta (*top*) and brachial artery (*bottom*) at short time intervals apart during diagnostic cardiac catheterisation with a Millar micromanometer. Recordings at *left* were taken under control conditions. Recordings at *right* were taken several minutes after administration of nitroglycerin 0.3 mg sublingually (after Kelly et al. [10]). In this middle aged man, the peak of the aortic pressure wave was created by the secondary late systolic reflected wave whereas in the brachial artery, the initial wave generated the pressure peak. Reduction in wave reflection by the arterial vasodilator nitroglycerine reduced amplitude of the secondary wave. This reduced aortic systolic pressure but not the peak of the pressure wave in the brachial artery. This same effect has been shown with calcium channel blocking drugs (CCBs), angiotensin converting inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) as well as nitrates, and accounts for the superior effect on blood pressure lowering as compared to the effect measured directly from pressure waves or by sphygmomanometric cuff in the upper limb

catheter/tonometer systems so that there was no distraction from calibration to sphygmomanometer cuff values. This became a focus for criticism by other clinicians who apparently were unaware of the marked differences between invasive and non-invasive pressure measurement even when taken simultaneously [30]. The US FDA was so aware, since this is the agency's "bread and butter" through comparison of different sphygmomanometric systems. The FDA passed the SphygmoCor device which incorporates the generalised transfer function for measurement of the central aortic from the radial pressure waveform under K002742 and K012487. Use and stability of the generalised transfer function under different conditions and in models of upper limb arteries have confirmed our initial claims and even our most vocal critics now grudgingly agree, though one group has based their analysis on flawed mathematics as pointed out by Segers and colleagues [45].

We have favoured use of tonometry on the radial artery with use of a generalised transfer function to generate the aortic pressure wave [30]. The principal option is to use carotid tonometry [2, 25, 46] which provides a waveform closer in amplitude and contour to the aortic pressure wave even without use of an appropriate transfer function. We do this because the radial waveform can be recorded more accurately, more comfortably, and more safely than the carotid wave, and because it is hallowed by time and history [5, 21, 34]. The carotid waveform is an option, and we use this for recording when there is difficulty or uncertainty with one or other radial arteries. There is a predictable relationship between pressure waves in the aorta, carotid and radial arteries [10, 30, 58].

3 Explanation of aortic pressure and flow waveforms

Relative simple explanations can be given for the patterns of pressure and flow waves in the ascending aorta—and for the change in travel to peripheral arteries. The typical flow waveform [30] is shown in Fig. 3, with rapid rise to early systolic peak at about 100 ms after the wave foot, and with a convex pattern to the right down to end systole at around 300 ms, a little backflow and then no flow during diastole. This pattern does change with heart rate, and with ageing and ventricular weakening. As heart rate accelerates, duration of diastole decreases more than systole. The peak remains at about 100 ms after the wave foot, and the fall to end systole is more linear. With ageing and ventricular weakening, and at normal heart rate, the flow during late systole falls with a concavity rather than a convexity to the right [27, 30, Fig. 3]. In ventricular failure due to predominantly systolic dysfunction, ejection duration is shortened whereas in failure due to diastolic dysfunction, ejection duration may be lengthened [30]. These changes in the left ventricular ejection (aortic flow) with age are relatively subtle, and have not been noticed in many analyses [15, 33]. In contrast, changes in the aortic pressure wave are striking [11, 26, 28, 30, 38, 46].

The pressure wave in a young adult human (Fig. 3 right) shows an early peak which occurs about 100 ms after the wave foot and corresponds to the peak of the flow wave. After this peak, pressure falls to the incisura which corresponds to aortic valve closure. Between the early peak and incisura there may be an inflection which corresponds to the foot of the reflected wave from peripheral sites. This wave is, however, more prominent throughout diastole and causes pressure to undulate rather than falling in an exponential fashion such as one would expect to see if there were no wave reflection. The features of the aortic pressure wave—its foot, its initial peak, its late systolic inflection corresponding to the return of wave reflection, and the incisura, caused by aortic valve closure—can be identified from differentials of the pressure wave. These are so utilised in the SphygmoCor reports [30, 38, Figs. 4, 5].

4 Change in waveforms with age

While changes in the aortic flow wave with age are subtle [27, 30], as described above, change in the pressure wave

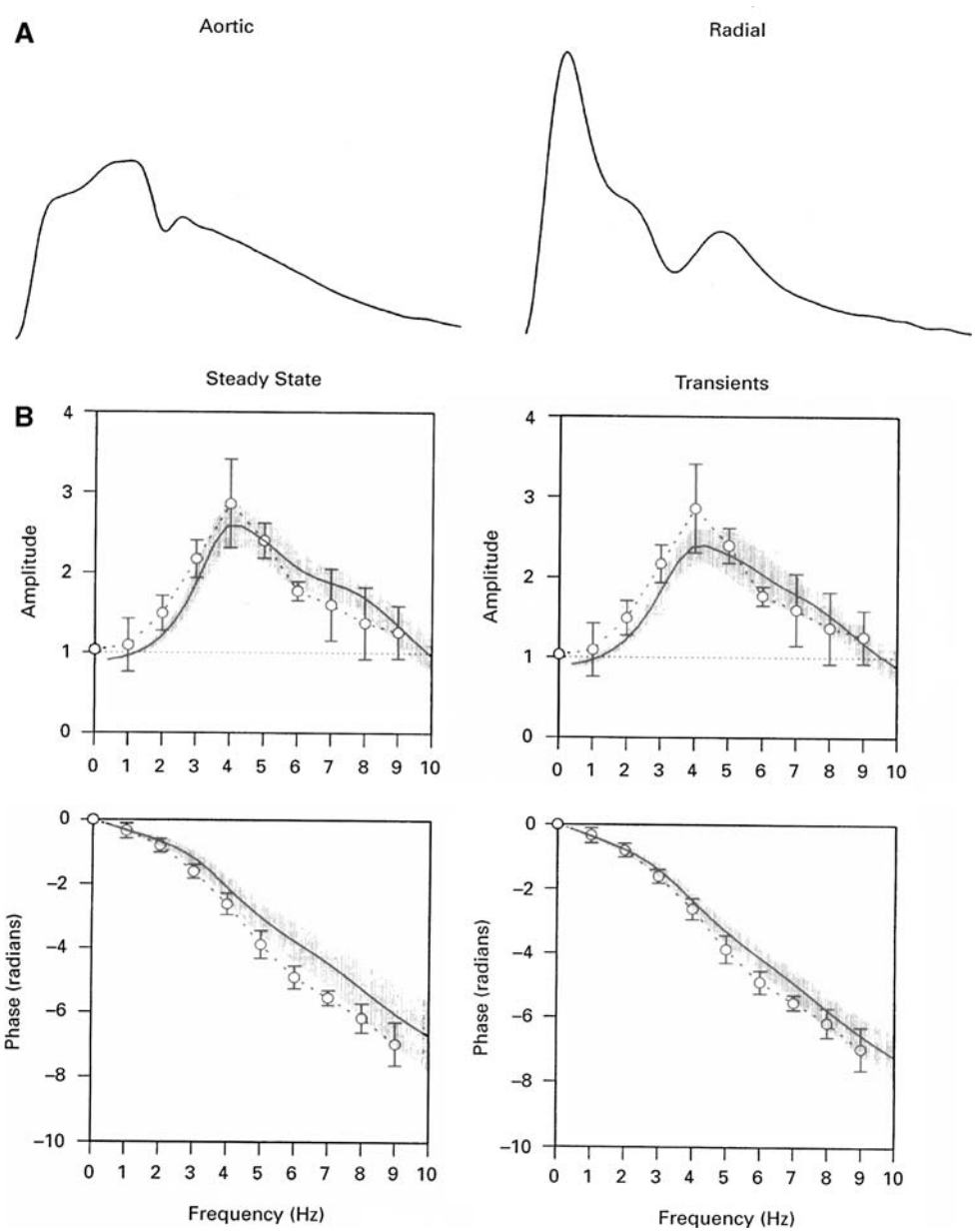

Fig. 2 Pressure waveforms in the ascending aorta (*left*) and radial artery (*right*) together (*below*) with their relationship described in terms of transfer functions using two different techniques (*left* steady state, *right* transients). Data from Karamanoglu et al. 1993 [8] and Chen et al. 1996 [2] showed similar patterns of modulus and phase. After Chen et al. [2]

are more marked (Fig. 3, right). The initial peak of the pressure wave remains at about 100 ms after the wave foot, but pressure continues to rise after this to a peak in late systole, before falling to the incisura, then decreasing almost exponentially during diastole. Close inspection of the pressure wave change shows that the first peak still corresponds to the peak of flow, but that the beginning of the second peak corresponds to the late systolic inflection in the younger subject, and the late systolic peak corresponds to the diastolic pressure surge in the younger person. As in the younger person, the features can be detected by differentials of the pressure wave. In the elderly, the inflection corresponding to return of the reflection wave, (identified by differentials as a concavity to left on the original wave) comes so close to the initial wave peak at around 100 ms that it merges, and no separate shoulder or inflection may be seen at all [31]. A consequence of the change in the aorta wave shape is that augmentation of the wave—the rise from the first shoulder or peak to second peak—increases progressively with age at least up to 60 years [22, 58]. Rise at older ages is less steep; this may be due to change in shape of the aortic flow wave and attributable to decreased left ventricular output at high pressure in late systole, to reduction in wave reflection from the lower body as aortic wave velocity increases to match values of wave velocity in the iliac and femoral arteries [26], or to the difficulty in identifying the shoulder from which augmentation is measured [30, 38].

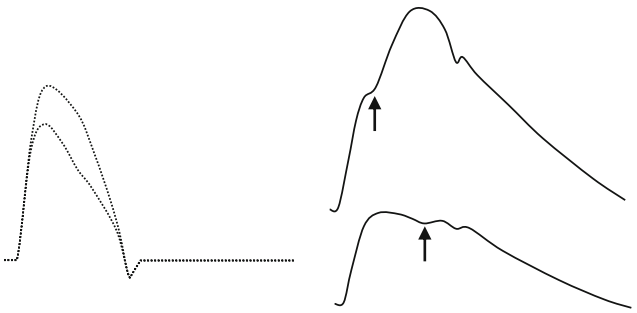

Fig. 3 Schematic flow (*left*) and pressure (*right*) waves in the ascending aorta of a young and old person. In the young person, peak flow velocity is higher and the late systolic part of the flow waves is convex to the right. In the older person peak flow velocity is lower (aortic diameter is greater) and the flow pattern after the peak shows initial concavity to the right. In the young person amplitude of the pressure wave is lower, and the peak is seen early in systole. Return of wave reflection is apparent as an inflection (indicated by an *arrow*) shortly before the notch which represents aortic valve closure. In the older person, amplitude of the pressure wave is greater on account of a higher initial pressure rise to an early systolic shoulder together with return of the reflected wave (whose beginning is indicated by an *arrow*) and which causes pressure to rise further to a late systolic peak

Support for these interpretations comes readily from clinical observations, as in an elderly patient with slow or rapid heart rate (Figs. 4, 5), or in a patient with atrial extra systoles where there is great variation in ejection period (Fig. 6). Changes in the wave shape at least up to age 60 can only be explained on the basis of wave travel and strong wave reflection.

5 Change in waveforms with heart failure

Characteristic pressure waveforms in (systolic) heart failure were described almost a century ago by Thomas Lewis [17], one of the founders of British cardiology and the first editor of "Heart". Lewis described a characteristic dicrotic (twice-beating) pulse; such is typical in patients with severe heart failure as in intensive care following cardiac surgery, in cardiogenic shock following myocardial infarction, and in patients with cardiomyopathy awaiting transplantation [4, 30, 32]. In such patients, ascending aortic impedance is similar to that in normal subjects [14, 30] indicating that vascular properties are similar, that wave reflection is strong, and the principal cause must be cardiac. The characteristic feature is indeed shortened left ventricular ejection, such that wave reflection is seen after the aortic valve shuts as an exaggerated diastolic wave [3, 14, 17, 30, 32]. Further study of this phenomenon suggests, however,

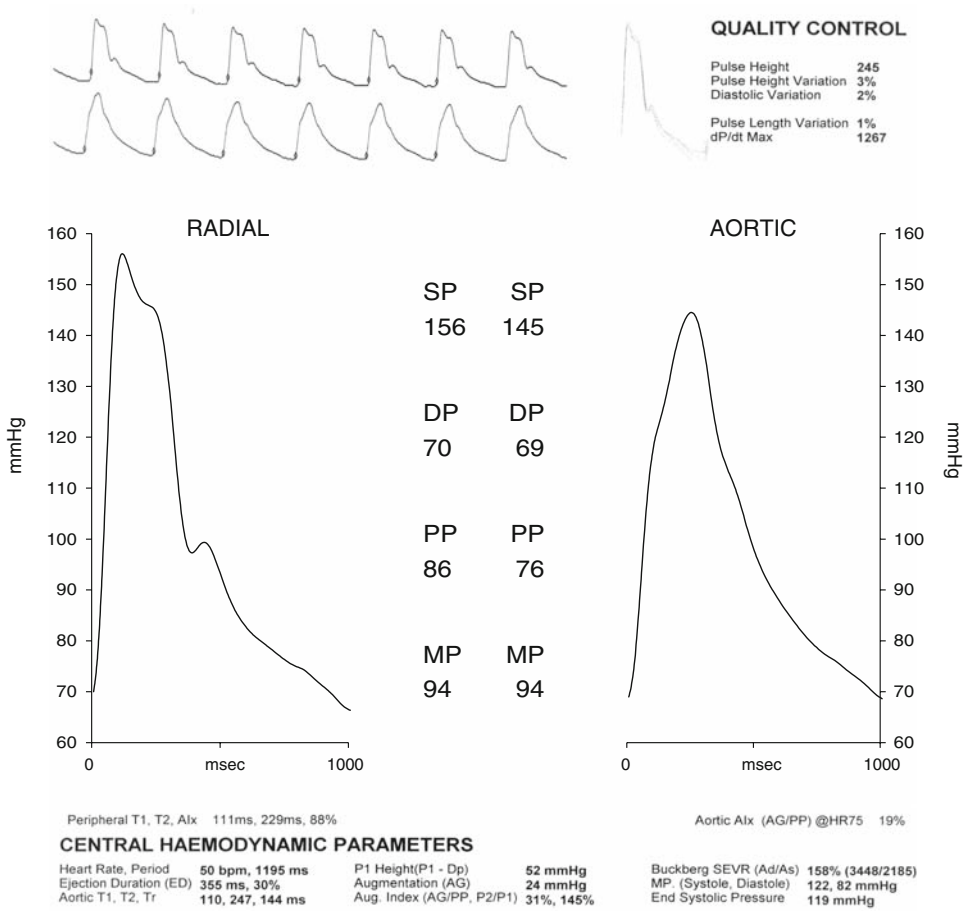

Fig. 4 Segment of a SphygmoCor report in an 87-year-old man, showing (*at top*) a series of pressure waves recorded over 10 s from the radial artery by applanation tonometry together with (*immediately below*) the corresponding series of aortic pressure waves synthesised from application of the transfer function process shown in Fig. 2. Quality control parameters for the radial pressure waves are inset at *upper right*. The two waves at *bottom* are (*at left*) the ensemble-averaged radial wave from data above, calibrated to values of systolic and diastolic pressure measured by brachial cuff, and (*at right*) the ensemble-averaged aortic pressure wave set to the same mean pressure as determined for the radial artery. Timing intervals and central haemodynamic parameters are set out below. *SP* peak systolic pressure, *Dp* lowest diastolic pressure, *PP* pulse pressure (Sp-Dp), *MP* integrated mean pressure in the radial artery

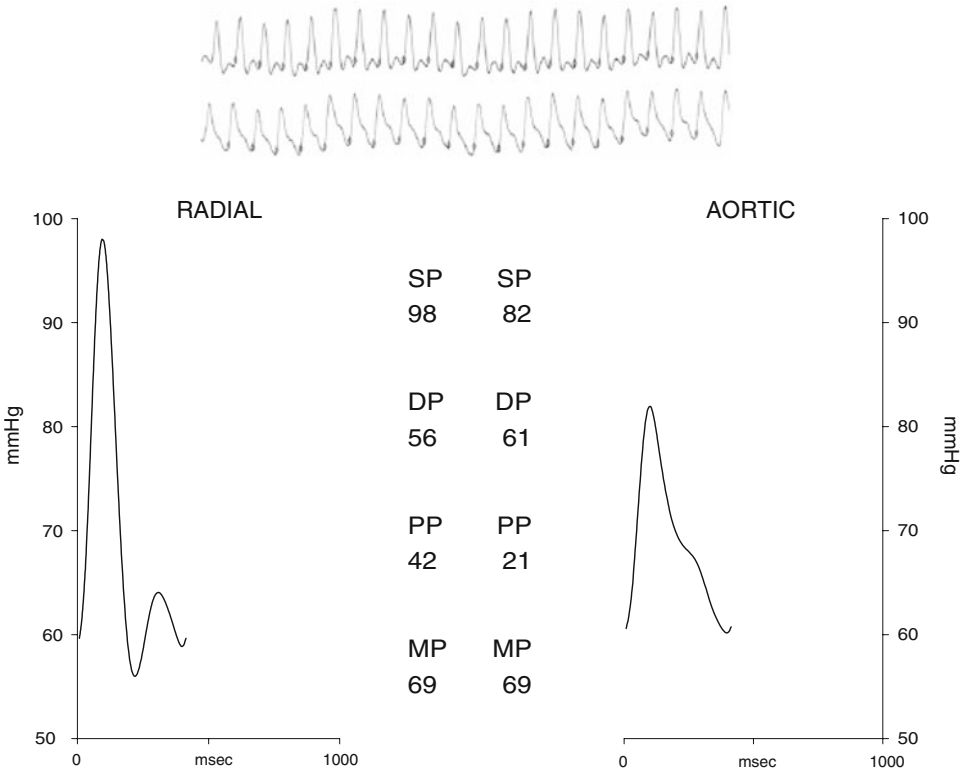

Fig. 5 Segment of SphygmoCor report in the same man as shown in Fig. 4 during an episode of junctional tachycardia. As a consequence of shortened ejection period, wave reflection causes a boost to pressure in diastole rather than during late systole

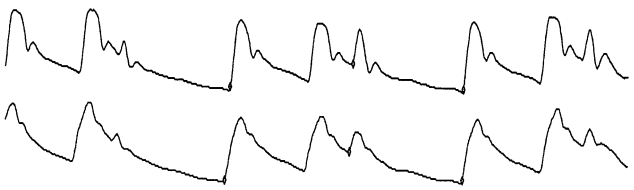

Fig. 6 Ten-second segment of SphygmoCor report from a 60-year-old man with extra systoles showing the differences seen in Figs. 4 and 5, but in successive beats

that the cardiac phenomenon is a consequence of the vascular phenomenon—a consequence of wave reflection [54]. When ventricular contraction is weakened, the ventricle acts as a pressure source, with ejection limited by and terminated prematurely by return of wave reflection. The simplest demonstration of this mechanism is administration of a vasodilator agent which reduces wave reflection; this prolongs ejection duration and increases cardiac output. Vasodilator therapy is the principal treatment of such patients—for acute and chronic use, and its benefit is readily explained on the basis of reducing wave reflection [30].

There is another form of heart failure, typically seen in older persons, usually women, with longstanding elevation of arterial pressure and left ventricular hypertrophy. In these patients, left ventricular contraction paradoxically is strong; heart failure is due to delayed relaxation and impaired ventricular filling in diastole, i.e. to diastolic heart failure [52]. The left ventricle of the patients acts as a flow source—it ejects strongly against the reflected wave, which is seen as augmentation of pressure in late systole. Ejection fraction of the left ventricle is not reduced; ejection duration may be lengthened [30, 52].

In clinical practice, heart failure is often a mixture of systolic and of diastolic dysfunction [30, 42]. This develops gradually with ageing, is attributable to increasing left ventricular systolic load from arterial degeneration, and is characterised by decreasing exercise capacity, and breathlessness on exertion. The principal feature of this condition appears to be a consequence of the effects of load on the ventricle. Ejection duration may be normal or prolonged, but flow is reduced in late systole, just as it is in the pulmonary circulation with the development of pulmonary hypertension [12, 30].

6 Change in waveforms with hypertension

Change in pressure waveforms in hypertension are similar to those seen with ageing, and are explicable on the same basis—of increase in arterial stiffness with early return of wave reflection [30]. These features of the waveform were first used for identification of hypertension in young subjects by Frederick Mahomed some 135 years ago, well before introduction of the cuff sphygmomanometer [5, 35]. We now know that hypertension ultimately leads to left ventricular failure if other complications do not supervene

[16], and that associated left ventricular weakening leads to reduction in late systolic ventricular ejection, so that the degree of late systolic augmentation of the pressure wave progressively decreases [30]. So called "burnt out hypertension" is associated with a lesser degree of pressure augmentation than previously present.

7 Change in waveforms with vasodilator drugs

Vasodilator drugs are widely used in clinical practice, for treatment of elevated arterial pressure, for treatment of cardiac failure (both "systolic and diastolic"), and for management of ischaemic heart disease [30]. The most effective such drugs and the most effective doses are those that have predominant effect on muscular arteries, rather than veins or arterioles, i.e. that do not cause venous pooling or reduction in peripheral resistance. Benefits are attributable to reduction in early wave reflection (Fig. 1).

When the left ventricle acts as a flow source as it normally does [54], contracting powerfully against pressure, reduction in wave reflection with such drugs is apparent as decrease in late systolic pressure augmentation. In the aorta and left ventricle, this is apparent as reduction in systolic pressure and benefit is obvious. However, when pressure is measured in the brachial or radial artery, the augmented wave is in late systole and usually does not constitute the peak of the wave. Hence systolic pressure fall is underestimated [7, 11, 30]. Studies such as REASON [18] and CAFE [57] have confirmed that the superiority of vasodilator drugs for reducing cardiovascular events in hypertension is attributable to greater reduction in central systolic pressure, i.e. to benefits beyond the brachial artery, rather than beyond blood pressure.

When the left ventricle acts as a pressure source, with contraction weak and flow limited by pressure, reduction in wave reflection by vasodilator drugs has its greatest effect on flow rather than pressure [30, 54]. This is apparent as an increase in ejection duration, and in cardiac output [14]. Arterial pressure and the arterial pressure wave may not appear to change significantly, and the subtle change in ejection duration may be overlooked.

8 Problems in clinical assessment of the pulse in the time domain

Accuracy of measurement is the principal problem, and has been emphasised throughout this article. There are extreme difficulties in accurate measurement of ascending aortic flow in all circumstances with invasive and non-invasive methods. These are a consequence of jets, turbulence, secondary flow in the inlet to the arterial system where the pathway narrows at the aortic valve, annulus, dilates at the sinuses of Valsalva, then narrows again before curving around to the descending aorta. Our approach has been to be very careful of flow estimates particularly during early systole, and of measures which depend on flow patterns such as impedance. We base our analyses on relative constancy of the flow pattern under different conditions, but with appreciation of how flow contour can be altered by reduction of ventricular contractility when output during late systole becomes highly dependent on pressure.

Analysis of the pressure pulse depends on the accuracy of the recording method. Problems of low frequency response of fluid-filled catheter systems are well known [30], but are often overlooked by clinicians, particularly those undertaking cardiac catheterisation procedures. Accurate tonometry requires careful applanation (flattening) of the surface of the artery [2, 9, 30]. This is harder to achieve consistently in the carotid than radial site on account of the artery being further from the skin and poorly supported laterally, with tendency of the whole artery to move, kink, or flip [15].

A particular problem arises with measurement of pressure augmentation or augmentation index, since this requires identification of the first peak or shoulder which corresponds to the peak of flow in the artery [10, 26]. (This shoulder needs be distinguished from the subsequent inflection which corresponds to the foot of the reflected wave [41]). Both of these may be influenced by a Venturi effect in the ascending aorta, which can result in the point being measured around 4 mmHg lower in the aorta than in the left ventricle [41, 48]. Inflections on the wave such as this shoulder, but also the foot and incisura are composed of high frequency components of the waves, and depend on capacity to adequately record frequencies up to at least 12 Hz [3], and not to filter these in instruments or through use of an inappropriate transfer function [45].

Problems in identification of a shoulder on the central pressure wave can explain many anomalies in present literature [41, 46, 47].

Use of transfer functions are better accepted now than in the past [37], and are apparent in description of vascular impedance by Mitchell in Chap. 8 of this supplement. However, use of a generalised transfer function for generating aortic pressure waveforms from radial waveforms has taken longer [38, 45]. It is possible to use these inappropriately when phase is not properly expressed and/or when harmonics are compared rather than absolute frequencies [45].

9 Apparent anomalies

Research would lose its interest if it did not throw up new challenges. One of these challenges is that augmentation

index (AIx) of the pressure wave in the aorta, radial and carotid arteries does not increase progressively with age, flattening off over age 60 [10, 22, 58], and does not over 60 years correlate with cardiovascular events [51] whereas, aortic PWV (an accepted measure of stiffness) does increase progressively with age [15, 22, 30] and does correlate with events at all ages [15]. Related to this is that in diabetic subjects under age 60, with known greater risk of cardiovascular events, and with greater aortic PWV often have lower AIx than normal subjects [13]. Another related possibility is that persons with abdominal adiposity whether they have diabetes or not often have lower AIx than normal subjects of the same age [20]. Contrary results have been reported [59].

The probable explanation is intriguing, and exposes a possible wider value of pulse wave analysis. AIx in the aorta cannot exceed 50%. The reflected wave cannot exceed the amplitude of the incident wave. Values over 50% are suspect. But the incident wave has similar pattern to the aortic flow wave which generates it. Declining LV function with age causes a change in shape of the aortic flow wave such that ejection in later systole is reduced. This will affect the amplitude of the reflected wave and of the resultant compound wave. The phenomenon has been described earlier in this article. The plateau or decline in AIx with age is partly attributable to development of cardiac weakening and incipient heart failure. It is also partly attributable to reduction in aortic wave reflection as proposed by Mitchell [26]. Separation of compound waves into incident and reflected waves was first described by Westerhof et al. in 1972 [55]. The same group has shown early return of wave reflection as the cause of increase in augmentation with age [53].

Most studies of diabetic subjects show higher values of aortic AIx than control [1, 56] but some show lower values [13]. The explanation of diabetes follows from this. Diabetic cardiomyopathy is well known as a cause of premature left ventricular weakening due to impaired fatty acid metabolism in the heart with generation of toxic metabolites [23, 44]. Lower AIx in some diabetics may be a manifestation of this, and may be a reason for introducing early therapy for cardiac failure. Recent studies [23] have shown a similar problem in persons with abdominal obesity—with evidence of abnormal lipid accumulation in the heart.

Previous commentary on this issue has focussed on lower than anticipated AIx being a manifestation of altered wave reflection [20, 26] or as a fault of the technique. It may be neither, but something even more important—a manifestation of another problem (incipient left ventricular failure) which may warrant early or intensified treatment.

10 Summary

Time domain analysis of the pulse in clinical medicine stretches back to the times of Marey, Mahomed and Mackenzie when diagnoses were made, therapy planned and prognosis assessed on the basis of the radial pulse waveform. Modern advances follow recognition of limitations and shortcomings of brachial cuff blood pressure analysis, and depend on better instruments for recording arterial pressure and flow pulses, better understanding of arterial haemodynamics and ventricular/vascular interaction, and greater appreciation of artefact. Modern analysis of the pulse in the time domain supports the conventional historical views, and those that emerge from other analyses, and emphasise the importance of arterial stiffening with age, and of wave reflection, their effects on the heart and their modification with therapy.

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