

Use of Generalised Transfer Function in Clinical Studies

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Important recent studies using SphygmoCor draw attention to the basic assumptions of the process to derive the aortic pressure waveform from the radial artery waveform. These assumptions are reviewed in this report.

The CAFE substudy of ASCOT trial used the SphygmoCor transfer function to generate aortic systolic pressure from the radial artery waveform (calibrated with brachial cuff pressure), and showed that aortic systolic pressure was significantly lower (by 4mmHg) than brachial systolic pressure in patients treated on an amlodipine strategy compared to those on an atenolol strategy¹. Lower aortic pressure was sufficient to explain fewer cardiovascular events in the CAFE substudy, and in the full ASCOT trial.

A perceived flaw in this study was that the two drug regimens may have different effects on the transfer function, and that such difference may explain published results. Such a criticism was not raised by reviewers of *Circulation*, possibly because this had been considered by the FDA before endorsement of the SphygmoCor process, with requirement that upper limb transfer function must remain constant during use of vasoactive drugs. Respect for the FDA in American institutions may explain acceptance of the method in the US, but queried outside from persons who are less aware of the background of transfer function techniques. Studies performed before and after CAFE have shown similar results from tonometric carotid pressures^{2,3}, and directly measured aortic pressures^{4,5,6}. Direct examination of the radial artery waveform permits central aortic systolic pressure to be measured by another (non transfer function) method. This gives identical results when drug effects are compared⁷. There is thus no support for a view that results of CAFE were influenced by any effect of the two drug regimens on the generalised transfer function process used in the SphygmoCor system.

Criticism of the transfer function process in the literature has generally come from persons who are not familiar with background concepts, or the detailed literature. It is true that the original transfer function used in SphygmoCor was obtained in just 14 persons studied at cardiac catheterisation before and after use of nitroglycerine. But this was consistent with data obtained previously in 106 patients at cardiac catheterisation and 119 subsequently at catheterisation and cardiac surgery, and with data obtained non-invasively from the carotid and radial arteries in 439 subjects. All published work at 2003 was summarised by Gallagher *et al.*⁸, and included modelling studies^{9,10} which showed similar patterns to those determined in vivo, and minor effects of simulated vasodilation. The non-invasive studies of carotid to radial transfer function by Gallagher *et al.* in 439 subjects confirmed little effect of age and of arterial pressure on the transfer function itself.

All studies of transfer function in the upper limb have shown progressive increase in modulus from 0-5Hz, corresponding to amplification of the pressure wave in the limb. None have showed any absence of amplification; hence use of a transfer function is necessary to allow for distortion of the pressure pulse in the arm, and to infer aortic pressure. From the original study, Chen *et al.*¹¹ from Johns Hopkins emphasised the value of a generalised transfer function as compared to a transfer function for an individual, noting that the generalised transfer function yielded 96% improvement in the fit between measured and estimated central aortic pressure waveform ($p < 0.001$) while the individualised transfer function improved the fit by just another 3%. A further update is given in the 5th edition of McDonald's *Blood Flow in Arteries*, 2005¹².

The general concepts of transfer function to describe physiological phenomena were introduced by McDonald and Taylor in the 1950s^{13, 14}. These were vigorously challenged on the basis of artificiality of Fourier series for describing pulsatile phenomena, and of non-linear physical properties of the arterial tree. Such challenges evaporated over the subsequent two decades when studies showed the value and consistency of the techniques, and when it was accepted that non-linearities, while present, are sufficiently small to be neglected to a first approximation. Contributions of McDonald and Taylor to physiological and medical research are well recognised in their obituaries^{15, 16}. Taylor showed the value of transfer functions of pressure measured at different sites (as in the SphygmoCor process) through experimental and theoretical modelling studies¹⁷, but is better known for the concepts of impedance that he introduced through relating pressure and flow in the frequency domain from measures taken at the same site¹⁸.

Studies of transfer function of pressure/pressure and pressure/flow required meticulous care of instrumentation to eliminate or control artefact, and the factors that may degrade frequency response and dynamic accuracy of flow meters and manometers. They also had to take into account the low amplitude of signals at frequencies over 5 Hz, and the errors that could arise from measurements and calculations from pressure and flow components that were within the “noise” level. Introduction of catheter tipped manometers by Huntly Millar were a major advance, and were crucial for establishing differences in contour of the pressure pulse waveform with age. This advanced further with introduction of Millar’s tonometer for non-invasive use. In human catheterisation laboratories, these issues of accuracy are less well known than in the physiology departments which inherited the traditions of McDonald and Taylor; it was these centres in Amsterdam, Sydney and Baltimore which performed the initial studies on transfer function utilisation for calculation of aortic pressure from upper limb pressure in humans.

In considering the SphygmoCor submission from AtCor Medical, the FDA was well aware of the physiological, theoretic and practical background stemming from McDonald and Taylor, as well as the inaccuracies in current cuff sphygmomanometry. The FDA required a prospective trial (conducted at Wake-Forest), which included challenge with intravenous nitrate in therapeutic dose. It required confirmation from independent centres and modelling data to support. Validation was determined from criteria used for comparison with clinical manometer systems (American Association for the Advancement of Medical Instrumentation, SP10 criteria) by White *et al.*¹⁹. Ultimately the process was accepted as equivalent to the comparator – measurement of pressure in the ascending aorta with a catheter system. The validation studies were published by Pauca *et al.*²⁰, O’Rourke & Pauca²¹, as well as in the 2005, 5th edition of the McDonald book²².

The most objective independent published comparison of the SphygmoCor system as used in clinical practice was by Smulyan *et al.*²³. Two problems dominated this study. The first, recognised only after the study was done, related to direct measurement of aortic pressure while the second related to accuracy of the cuff sphygmomanometer. An electrical filtering system had been installed in the laboratory catheterisation equipment and this degraded frequency response of the Millar catheter to the point where it was difficult or impossible to identify any inflection point or shoulder of the aortic pressure wave and thereby calculate pressure augmentation. The inaccuracy of the cuff method resulted in diastolic pressures often being calculated as 15mmHg higher than recorded. This study raised the possibility that measures of the pressure waveform, independent of cuff calibration – such as augmentation index (radial or aortic), amplification of the wave, and time intervals, may be more useful and accurate than measures that included values of systolic and especially diastolic cuff brachial pressure.

Colleagues in Melbourne^{24, 25, 26} have re-examined the calculation of transfer function data obtained at cardiac catheterisation and raised queries on applicability of the transfer function process. These included the possibility of transfer functions being different for diabetics and normal subjects and from males compared to females and came from analysis of the same data with a different transfer function proposed for each situation. This group had the same problems as did Smulyan *et al.*²³ with cuff pressure calculation.

It is not easy to directly compare data published by Hope *et al.* with our own since this is displayed in the inverse (i.e. aortic \div radial pressure rather than radial \div by aortic), and in one article as a function of frequency and in the other in terms of harmonic number. But when appropriate adjustment is made (Figure 1), the data correspond very well with that used in SphygmoCor and published by others, at least up to 5 Hz. Variability of all results over 5 Hz is attributable to the low amplitude of pressure components at high frequency, and also to the resonance of Hope's fluid-filled manometer system used in the first study.

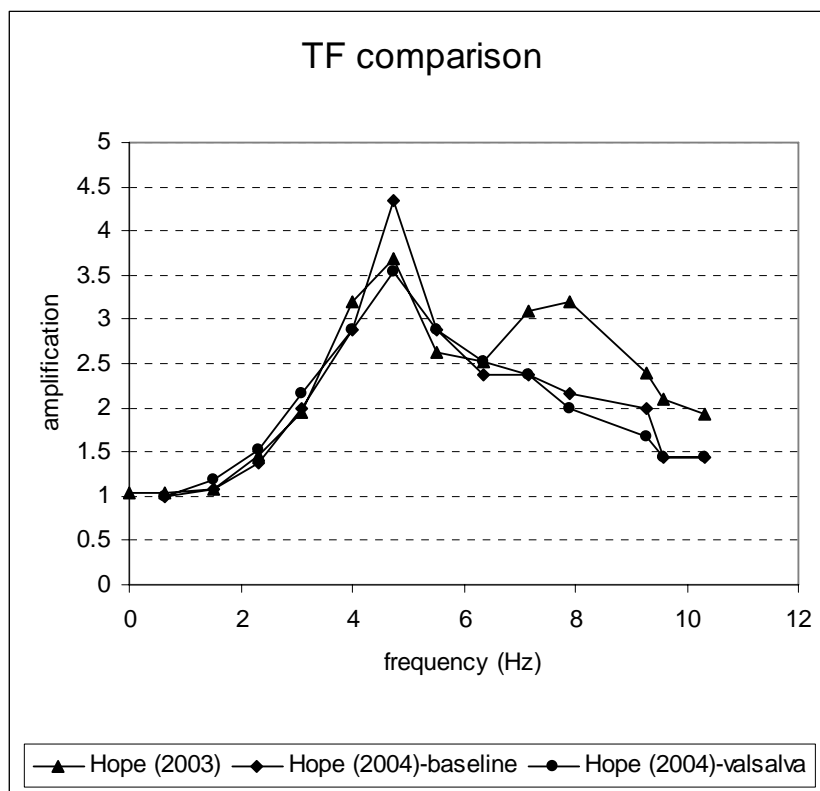


Figure 1. Comparison of transfer functions from data published by Hope *et al.* in *J Hyertens*²⁴, and *Heart, Lung and Circulation*²⁶. Y axis is amplification (radial \div aortic) calculated by inverting data as published. X axis is Hz for 2003 paper²⁴, and Hz calculated from harmonic number in 2004 paper and assuming same average heart rate as in 2003 paper²⁶. All transfer functions peaked between 4 to 5 Hz (or 6th to 7th harmonics).

Figure 2 compares values of the transfer function with energy in the pressure waves from which they were calculated. The very low power above 5Hz accounts for variability of calculated transfer functions, but also has another implication – that the benefit of utilising the transfer function resides in values of pressure components less than 5Hz, not those above, since the higher frequencies above 5 Hz just provides detail of notches and inflections. These may become important in measurement of augmentation, but not peak systolic pressure, as used in CAFÉ. This point was made by Chen *et al.* in the first independent validation of the SphygmoCor process¹¹.

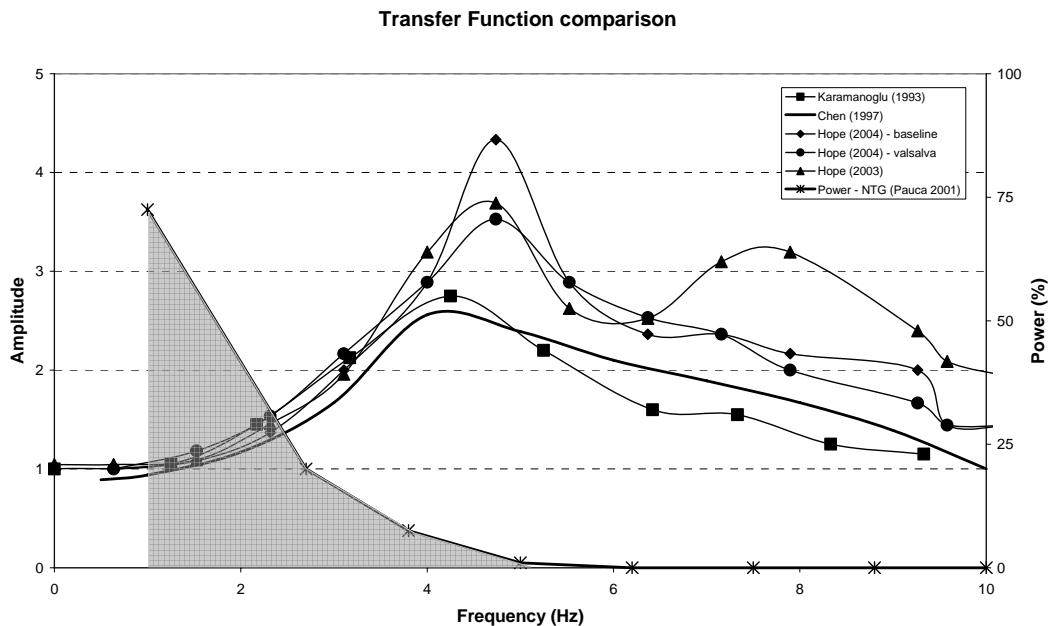


Figure 2. Transfer function calculated for published data from Hope *et al.* (see fig 1) compared to transfer function published by Karamanoglu *et al.*²⁷ and Chen *et al.*¹¹. Also shown is power calculated for pressure wave harmonics from 1-10 Hz in data of Pauca *et al* during IVI nitroglycerine infusion (when higher pressure frequency components are most apparent)⁸.

We are comfortable with the results of Hope *et al* and look forward to full publication of data obtained with Millar manometer systems in due course. These data all emphasise the need for use of a transfer function process since all results deviate strongly from unity. Indeed, the Hope data show a greater deviation from unity than data previously published, and so provide a strong argument for correction of upper limb pressure waves. They do approximate the values published previously and as used in the SphygmoCor instrument - a maximum amplitude of 2.5-3 Hz at around 5Hz.

The most recent validation of the SphygmoCor process was undertaken before and during exercise by Sharman *et al.*²⁸. Difference between simultaneously recorded direct aortic systolic and radial systolic pressure was substantial (mean difference at rest 16.3 ± 9.4 mmHg and during exercise 15.5 ± 10.4 mmHg) but difference between synthesised aortic and directly measured aortic pressure was small (-1.3 ± 3.2 mmHg at rest and -4.7 ± 3.3 mmHg during exercise).

In the Sharman paper, correlation between invasive and non-invasive aortic pressure for rest and exercise combined was 0.995. Values are within AAMI SP10 criteria and are in accord with those previously accepted by FDA.

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