Measurement of Ambulatory Central Aortic Pressure in Clinical Trials using the BPro™ Device.

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Introduction:
Blood pressure (BP) plays a key role in the development of cardiovascular disease. Conventionally, BP is measured using a sphygmonanometer (manual or automated) over the brachial artery in the “office setting”. This has remained the “gold standard” for BP measurement in clinical trials. Infrequent isolated BP readings in a seated position in an office setting are unlikely to be comprehensive in assessing the full impact of cardiovascular interventions, particularly BP-lowering drugs therapies in clinical trials. Consequently, more recently, ambulatory BP monitoring (ABPM) has increasingly been incorporated into trials as sub-studies. Traditionally, ABPM also uses a cuff device to measure BP over the brachial artery at pre-set intervals throughout the day and night. The assumption with all of these measurements is that the pressure being measured over the brachial artery is representative of the pressure in the central circulation, i.e. the aorta. Whilst this assumption be reasonable for the trial population as a whole, it is not accurate and for individual patients, in whom there may be marked differences in their central pressure, especially their systolic pressure, despite similar brachial pressures. Moreover, this differential relationship between brachial and central aortic systolic pressure (CASP) may be further modified by the effects of drug therapy. These observations are important because they suggest that brachial BP measurements are not always providing an accurate representation of central pressures in individual patients, or the potential effects of BP-lowering drugs on their central pressures.

Why is central aortic pressure different from brachial BP?
Whilst diastolic pressure is largely unchanged across the main arteries, i.e. from aorta-to-brachial, systolic pressure (and thus pulse pressure) differs markedly. This is due to pressure amplification as the pressure waves moves from the heart to the periphery. Thus, systolic pressures are higher at the periphery than they are centrally. This difference can be very substantial, amounting to 30mmHg or more in younger, healthy individuals. The differences between central aortic systolic pressure and brachial systolic pressure diminish with age but the two pressures are rarely ever the same. The diminution in pressure amplification from aorta-brachial with ageing reflects deterioration in the performance of large conduit arteries, especially the aorta with ageing and disease. This is mainly due to a loss of the aorta’s elastic properties due to fragmentation of elastin and its replacement by inelastic collagen. This is further compounded by two processes; i) post-translational modification of the collagen by the accumulation of advanced glycation end-products, a process that it accelerated in people with diabetes; and ii) vascular wall calcification. The resultant stiffening of the aorta adversely effects the characteristic impedance of the aorta thereby increasing left ventricular work and increasing pulse wave velocity (PWV). In westernised societies, PWV typically doubles from age 20yrs to 80yrs. This increase in PWV is of major importance because it results in faster forward wave propagation after systole and earlier pulse wave reflection from distal reflection sites. This earlier pulse wave reflection means that the reflected wave returns earlier, towards the end of systole (rather predominantly in diastole in healthy people) and leads

Figure 1: Radial and corresponding central aortic pressure wave-forms from a young (top panel) and older (bottom panel) man. The reflected wave in the younger male return predominantly in diastole, i.e. after the incisura, whereas in the older man it returns earlier and augments the central aortic pressure.
to augmentation of central aortic pressure, further increasing left ventricular work. The augmentation of central systolic pressure diminishes the normal differential between central aortic and brachial systolic BP (figure 1). Importantly, these dramatic changes in pulse wave morphology and central aortic systolic pressure cannot be appreciated by the simple measurement of brachial BP.

Controversy over the mechanism accounting for the increased central aortic systolic pressure with ageing and disease;

There has been much debate about the aforementioned mechanism accounting for the elevation of the central aortic systolic pressure with ageing. Some have suggested it is less dependent on wave reflection and more dependent on the increased characteristic impedance of the stiffened proximal aorta, for which the increased PWV is a surrogate. Others have argued that the aforementioned changes to wave reflection and enhanced systolic augmentation are more important. Whilst this debate is of academic interest, it should not distract from the unanimous agreement that central aortic systolic and pulse pressures rise relative to brachial pressures with age and are likely to be a major factor accounting for increased risk of cardiovascular morbidity and mortality with ageing.

Central Aortic Systolic and Pulse Pressures and Cardiovascular Disease Risk;

Evidence is now emerging to support the view that this sinister but unmeasured relentless rise in central aortic systolic and pulse pressure is a key driver of target organ damage, cardiac dysfunction and enhanced risk of heart disease and stroke with ageing. Moreover, this change is enhanced in those at risk of developing early aortic damage, notably, those with i) hypertension, ii) diabetes, and iii) renal impairment, and especially severe in those with a combination of all three. Recent data suggesting that central aortic systolic and pulse pressure might be better predictors of clinical outcome than brachial BP is consistent with this hypothesis. Furthermore, modulation of the relationship between brachial and central pressures might be an important protective action of cardiovascular drugs as highlighted by the CAFE study but has been otherwise been poorly studied. It is indeed remarkable that the main read-out for the action of BP-lowering drugs in clinical trials has been the measurement of seated brachial BP! It is even more remarkable when one considers that the various drugs evaluated often have different mechanisms of action and the potential to influence the relationship between brachial and central aortic pressures in different directions and by different orders of magnitude. In this regard, brachial BP has never been and will never be an adequate surrogate for the differential actions of drug therapies on the circulation.

Based on these observations, it seems very likely that the measurement of central aortic pressure would provide a more accurate read-out of the effects of drug therapies on the circulation, and more importantly, on target organ damage and clinical outcomes.

The Non-invasive Measurement of Central Aortic Pressures from Radial Pulse Wave Analysis:

To be practical for routine clinical use and for use in clinical trials, central pressure has to be measured simply, accurately and non-invasively. Experience in clinical trials thus far has been limited; i) largely by a lack of suitable technology, ii) compounded by a lack of appreciation of the potential importance of central aortic pressures, iii) poor recognition of the differential effects of drugs on central pressures, and iv) a general assumption/complacency that traditional brachial BP measurements tell us all we need to know. Where central aortic pressures have been assessed non-invasively, this has mainly been done by the technique of pulse wave analysis. This is performed by applying a tonometer to the skin overlying the radial artery to record a radial wave-form in a patient seated and at rest. This radial wave form can then be calibrated by imputing the readings from the brachial BP (measured contemporaneously in the same arm using a standard validated BP device) to generate a pressure-wave form (the assumption being that the pressures in the brachial artery are little different from those at the radial artery). The SphygmoCor™ device (used in the CAFE study) uses this approach. In this application, the radial pressure wave-form is then transformed to generate a central aortic pressure wave form using a validated generalised transfer function. The central aortic pressures are then derived from the central aortic pressure wave form. This approach can be used to derive central aortic pressures and other central hemodynamic indices at routine clinical trial visits. However, this is still only recording a static seated pressure reading and provides no information about the ambulatory profile of central pressure. This latter point is important because fluctuations and variability in central aortic systolic pressures are greatest when the patient is ambulant. Moreover, such variability is likely to be even greater in those with stiffer conduit arteries and higher pressures. Thus, seated central aortic pressure readings are likely to greatly underestimate the effect of drug therapies on ambulant central aortic pressures.
The BPro™ Watch:
The BPro™ device is different to other devices for measuring ambulatory BP and ambulatory central aortic pressure. It has a high fidelity tonometer incorporated into a watch strap. The watch is worn with the tonometer positioned and fixed over the radial artery (figure 2). The tonometer samples the radial wave-form in up to 96 x 10 second blocks of time, over 24hrs. When the watch is first placed onto the patient, the radial wave-form is calibrated to the brachial BP, measured conventionally using a standard validated electronic BP monitor. This calibration then allows the radial wave form to be transformed into a pressure wave form, providing measurements, equivalent to brachial blood pressure every time the radial wave form is sampled. Thus, the pressure wave form recorded from the radial pulse wave, by virtue of its calibration to the brachial pressure, is now recording ambulatory brachial BP. Thus the BPro™ device can be used as an unobtrusive device to measure 24hr ambulatory BP, calibrated to the brachial pressure measured in clinical trial conditions. The BPro™ is comfortable to wear and the patient simply wears it as a wrist watch for 24hrs. Thereafter, the watch is connected to a computer to down-load the wave form data. The BPro™ has been validated against the AAMI and ESH protocols and passed both validations. It carries a CE mark and is approved for clinical use by the FDA.

Figure 2: The BPro™ watch showing the tonometer integrated into the watch strap. The diagram shows the tonometer positioned over the radial artery when the watch is worn for recording ambulatory radial wave-forms calibrated to brachial pressure.

Measurement of Ambulatory Central Aortic Systolic Pressure (CASP) using BPro™:
Unlike conventional BP monitoring devices, the BPro™ records pressure wave forms calibrated to the brachial BP. Thus, in addition to using the waveforms to measure brachial BP, it seemed feasible to utilise this abundant wave-form data to derive central aortic systolic pressure (hereafter terms CASP) from the pressure wave forms records. The basis of the “generalised transfer function” used by the Sphygmocor™ device to generate a central aortic wave-form and derive central pressure indices was unpublished and thus unknown to us. We thus considered a novel approach to develop a new method to derive central aortic pressures from the radial artery pressure wave form. We used an “n-point forward moving average” (NpMA) method and experimented with a number of sampling frequencies. We applied the NpMA method to the wave forms recorded by BPro™ (where n = ¼ sampling rate of the tonometer) to derive the maximum value from the wave-form array, which we hypothesised should equate to CASP. To further evaluate this novel approach, we utilised the radial wave forms from the CAFE study data base. These wave-forms had been captured with the Sphygmocor™ device and we wanted to determine whether application of the NpMA method to the radial wave-forms would generate similar CASP measurements to those generated by the Sphygmocor™ device for the CAFE study. We used our NpMA method in a blinded study of 5,366 brachial pressure calibrated radial wave-forms from the CAFE study. We derived CASP using this method and then compared the CASP result using the NpMA method with the central pressure data derived from the Sphygmocor™ generalised transfer function (figure 3). The correlation was r²=0.993. This confirmed the applicability of the NpMA method to derive CASP directly from the radial pressure wave form.

Figure 3: The relationship between central aortic systolic pressure derived from the radial artery wave-forms of patients in the CAFÉ-study using the Sphygmocor™ generalised transfer function and the BPro™ n-point moving average method.

In-vivo Validation of BPro™ NpMA method to derive central aortic systolic pressure (CASP):
We then went on to undertake a direct in-vivo validation of this approach in humans in collaboration with Dr. Peter Yan at the Gleneagles medical Centre in Singapore. 20 patients undergoing routine cardiac catheterisation provided their informed consent to participate in this study. At the end of their diagnostic cardiac catheterisation, the central aortic pressures were recorded at the aortic root using a Millar’s SPC-454D tonometer (Millar’s instruments, Texas U.S.A).
Simultaneously, the patients were wearing a BPro™ watch calibrated to their brachial BP measured using a conventional (MC3100) automatic BP monitor. The BPro™ provided real-time derivation of the CASP from the calibrated radial pressure wave-form using the NpMA method. This was compared with the simultaneous real-time direct in-vivo aortic measurement of CASP using the Millar’s tonometer. The correlation between the BPro™ readings of CASP and the direct measurement of aortic CASP was \( R^2=0.9835, r=0.9917 \) (Figure 4).

**Figure 4**: relationship between central aortic systolic pressure (CASP) derived from the radial artery wave-form using BPro™ and the direct simultaneous measurement of CASP at the aortic root in-vivo at cardiac catheterisation in humans.

These two validation steps for the NpMA method to derive CASP, i.e. i) cross validation with the CAFE data set, and ii) direct in-vivo measurement of central pressure in humans, confirms that the BPro™ device can be used to record both; i) the brachial ambulatory BP (as the radial wave form is calibrated to the brachial pressure) and ii) ambulatory central aortic systolic pressure or CASP.

Thus, with the BPro™ technology we now have the potential to make the first detailed recordings of ambulatory central aortic pressures. In addition, because the BPro™ records 96 x 10 second blocks of wave forms per 24hrs, there is also the potential to obtain data on heart rate changes and to detect paroxysmal arrhythmias. Moreover, there is the potential to perform further off-line processing of the wave form data to determine the effects of disease and therapeutic intervention on a wide range of wave form characteristics.

**Implications for Clinical Trials:**
There is an urgent need to learn more about the effects of BP-lowering drugs and other cardiovascular interventions on hemodynamics from two perspectives; i) their impact on BP in an ambulatory setting, rather than just a static isolated clinic setting, and ii) their impact on central aortic pressures. It is likely that both parameters will be seen to be more important than conventional office brachial BP measurements as a predictor of target organ damage and clinical outcomes. It is also likely that potentially beneficial effects of drug interventions on these parameters, by virtue of both their mechanism of action and their duration of action, are being overlooked.

**Implications for Specific Trials Settings:**

**Patients with diabetes / diabetic nephropathy:** Patients with diabetes have accelerated ageing of their aorta, with enhanced stiffening. This process is accentuated in patients with co-existing renal disease who form the highest risk group. In addition, these patients also have disturbances to their circadian rhythms such that nocturnal pressures are higher and BP variability is greater. Furthermore, aortic stiffening means that the resulting wider fluctuations in pressure and higher central aortic pulse pressures are likely to be transmitted deeper into the circulation – this allied to the impaired blood flow autoregulation of these patients makes them especially vulnerable to small vessel injury. It is conceivable that much of the beneficial effects of ACE-inhibition, ARBs and Direct Renin inhibition on renal, cardiovascular and heart failure outcomes in these patients relate to favourable effects central aortic systolic pressures over 24hrs – effects that are not fully appreciated by simple measurement of clinic BP at the end of the dose interval.

**Patients with Hypertension:** Hypertension accelerates aortic ageing and predisposes to higher central aortic pressures relative to brachial pressures, greater BP variability and potentially higher nocturnal central pressures. As indicated above, we have already shown in the CAFE study that different types of BP-lowering treatment can influence central pressures in different ways. The prospect of incorporating ambulatory central aortic pressure measurements into major clinical outcomes trials in hypertensive patients is very exciting and would provide important and novel data relating central pressures to intermediate and hard clinical outcomes and drug effects on pressures and these outcomes.

**Patients with Atherosclerosis:** There have been many recent studies of patients using intravascular ultrasound (IVUS) to quantify coronary atheroma progression and regression. It seems likely that the pressure modifying effects of drugs could have a
major impact on the evolution of atheroma. It is also logical to assume that pressure in the central aorta, rather than pressure in the brachial artery is more relevant to this process. Thus, it would be very interesting to define the impact of drug related changes in central aortic pressure (both absolute changes and qualitative circadian rhythm changes) with regard to the evolution of atheroma.

**Patients with Heart failure:** Ventricular:vascular coupling is a key determinant of systolic and diastolic function. We spend much time studying the heart as a pump but too little time considering the huge importance of the aorta as the conduit. Pulse wave characteristics are potentially very important in heart failure but have been poorly studied. The impact of acute or chronic heart failure on central aortic pressure profiles over 24hrs, the impact of drug therapies on these parameters, and their impact on outcomes, has never been established. The recent data showing impressive falls in plasma NT-proBNP in patients with heart failure receiving direct renin inhibition is consistent with a significant beneficial effect of the intervention on central aortic pressures and improved ventricular:vascular coupling.

**Conclusions:** Technology is now available that has the potential to provide much added value to ongoing clinical trials by providing the first detailed recordings of ambulatory central aortic pressures and a repository of arterial pulse wave form data that could be further analysed for other key indicators of large artery function and the impact of specific drug therapies. The standard clinic brachial BP reading has provided an important but crude read-out of the impact of drug therapies on the arterial circulation and pressures. There is a clear need to move to the next level to better appreciate the mechanism of action of modern drug interventions and inform the development of even more effective drug interventions in the future.

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**Arterial Pulse Waveform Analysis**

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**Arterial Pulse Waveform**

**Average Arterial Pulse Waveform**

Sample BPro™ report of a single 10 second radial wave form capture showing the brachial BP and corresponding central aortic systolic pressure (CASP) measurements.