

## Use of Radial Artery Applanation Tonometry and a Generalized Transfer Function To Determine Aortic Pressure Augmentation in Subjects With Treated Hypertension

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**Objectives.** The purposes of this study were to investigate the use of radial artery applanation tonometry and a generalized transfer function for the assessment of central aortic pressure augmentation in subjects taking commonly used antihypertensive agents (angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, Ca<sup>2+</sup> antagonists, diuretic therapy).

**Background.** Applanation tonometry of the radial artery with a generalized transfer function has been proposed as a means of assessing central aortic blood pressure. Recently, a commercial apparatus based on this technique has become available; we therefore examined the effect of a generalized transfer function on derived central aortic pressure compared with measured brachial blood pressures and also investigated the potential of this technique to assess the influence of differing drug therapy.

**Methods.** Two hundred and sixty-two hypertensive patients on stable medication were studied using the PWV Medical Blood Pressure Analysis System (version 2, DAT-1).

**Results.** In univariate analysis, augmentation index showed association with age, sex, height and heart rate. In multivariate analysis, diastolic blood pressure and age (positively), height and heart rate (negatively) and sex were significantly associated. After adjustment for these variables, pressure augmentation was not associated with any antihypertensive treatment investigated. Linear relationships were demonstrated between brachial blood pressures and corresponding central pressures derived by transfer function methods.

**Conclusions.** Our findings suggest that if adjustment for central-peripheral pressure difference is necessary, simple linear relationships may be sufficient. Age, heart rate and height but not the class of antihypertensive medication affected the degree of pressure augmentation observed using this technique.

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The mechanical characteristics of the systemic vasculature are a major influence on cardiac afterload and coronary perfusion. Indices of arterial distensibility and compliance have therefore been proposed as a therapeutic target (1). Augmentation index (AI) assessed in the proximal aorta is a means of quantifying the distensibility of the aorta through the effect of mechanical properties on the timing of the reflected pressure wave and hence of magnitude of augmentation of central pressure. The AI has been used to define age-related vascular changes (2,3), to show an association of decreased pulse wave velocity (PWV) with increasing aerobic fitness (4) and has been shown to be associated with the presence of left ventricular hypertrophy (5).

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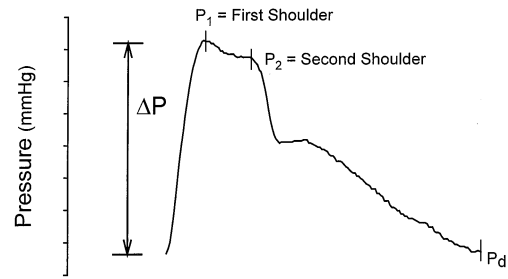
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In view of the potential for epidemiologic and clinical use, a number of groups have recently used the noninvasive technique of arterial applanation tonometry to obtain pressure waveforms with a view to assessing aortic properties as determined by the AI. Initially, carotid artery applanation was used (2-5), with Chen et al. (6) showing good approximation of results from noninvasively determined carotid pressure waveforms with invasively determined central aortic waveforms. Use of radial artery applanation with derivation of a surrogate central aortic pressure waveform by use of a generalized transfer function (TF) was initially reported by Karamanoglu et al. (7). Chen et al. (8) recently found good association between this technique (using their own TF) and results based on directly recorded central pressure waveforms, although in general their TF technique underestimated the derived AI compared to the invasively recorded case.

The use of radial rather than carotid artery applanation to obtain a pressure waveform has been proposed as preferable on the basis that it is an easier technique and more amenable to adequate applanation (9). The drawback of this approach has been the established differences in temporal pressure wave shape between the two sites; however, the recent innovation of

**Abbreviations and Acronyms**

- ACE = angiotensin-converting enzyme
- AI = augmentation index
- AP = augmentation pressure
- DBP = diastolic blood pressure
- PWV = pulse wave velocity
- SBP = systolic blood pressure
- TF = transfer function



**Figure 1.** Illustration of AP and inflection points used in analysis.  $P_1$ ,  $P_2$  and  $P_d$ , are the BP at the first and second shoulders and at end diastole, respectively.

$$AI = \frac{100(P_2 - P_d)}{P_1 - P_d}, AP = (P_2 - P_1).$$

the use of TF techniques borrowed from control-system engineering theory is proposed to overcome this drawback.

Central pressure augmentation is dependent on the relative timing of the arrival of the reflected pressure wave back at the point of measurement in the aortic root within the same cardiac cycle that generated it, and hence is related to the mechanical stiffness of the vasculature through the PWV. Assessment of the AI from analysis of the central aortic pressure wave provides an indication of the degree of impedance mismatch at distal reflection sites and of the magnitude of the PWV within the thoracic and, to a lesser degree, abdominal aorta. It provides an indication of the cardiac afterload (2) and is fundamental to the pathogenesis of systolic hypertension (10). Hypertension is considered to be associated with increased vascular stiffness (11,12) and it is generally considered that a less stiff systemic vasculature, associated with a lower PWV, represents a beneficial state. A number of local neuroendocrine factors, including the renin-angiotensin system, have been postulated as potentially affecting vascular stiffness (13). Different antihypertensive agents are known to affect arterial properties differently. Angiotensin-converting enzyme (ACE) inhibitors and calcium channel blocking agents have been shown to increase both brachial and central arterial compliance (14). Beta-adrenergic blocking agents have mixed effects and diuretic agents show little or no direct effect on mechanical properties when used alone (15). We therefore investigated in a cross-sectional study whether, as derived from radial artery applanation tonometry and a generalized TF, a discernible effect on central pressure AIs is associated with current use of common antihypertensive treatment regimens, in particular treatment with ACE inhibition or calcium channel blockers. The potential for use of radial artery sphygmography has been discussed by O'Rourke (9) and further advanced by Chen et al. (8); however, we believe this to be the first report of the use of a commercially available automated system (PWV Medical Blood Pressure Analysis System, version 2, DAT-1, PWV Medical, Sydney, Australia) in a large, unselected, patient group. The availability of commercial systems to perform TF-based assessment of central AI requires further information on at least two issues. First, does the information obtained aid clinical decision making and, second, is a "generalized" TF applicable to the usual population of hypertensive patients presenting for management. This report is an initial step to addressing these questions.

In the current version of the PWV Medical SphygmoCor device, AI as defined here is labeled as  $AI_{P_2/P_1}$ . If the reported AI is greater than 100, then  $P_2 > P_1$ , that is the pressure at the second systolic shoulder, is greater than at the first. In terms of the classification of Murgu et al. (17), this corresponds to a type "A" waveform, whereas if  $P_2 < P_1$ , a type "C" waveform results. Kelly et al. (2) calculated AI as  $AI = (P_1 - P_2)/\Delta P$ , that is, AP divided by pulse pressure. This formula gives both positive and negative values of AI.

## Methods

**Subject recruitment.** All subjects were taking long-term antihypertensive medication at the time of study and were recruited from hospital inpatients and those attending hypertension outpatient clinics at two metropolitan teaching hospitals. Patients were included as they became available irrespective of therapy or concurrent medical condition, the only entry criterion being the presence of stable antihypertensive treatment. This investigation was performed in accordance with the requirements of the Alfred Hospital and Monash Medical Centre Human Ethics Committees.

Augmentation index was originally defined by Kelly et al. (2) as the ratio of augmentation pressure (AP) (difference in pressure between the early and late systolic shoulders) and pulse pressure expressed as a percentage. In this study we have reported values as given using the PWV Medical Blood Pressure Analysis System. This device automates the assessment of the AI as the ratio of the difference between the pressure at the first systolic shoulder and diastolic blood pressure to that between DBP and the pressure at the second inflection point ( $AI = 100 \times (P_2 - DBP) / (P_1 - DBP)$ ) (16), see Fig. 1). Although numerically different values are obtained (including no negative values) a one-to-one mapping occurs between the two definitions and both provide a quantitative expression of pressure wave contour. A quantitative AP, defined as the pressure difference between the late and early systolic shoulders, is also provided by automatic analysis. In use, the PWV Medical device employs applanation tonometry of the radial artery (16), with the obtained waveform subsequently scaled from brachial artery blood pressure recordings and converted to represent the central aortic pressure wave by use of a proprietary TF relating peripheral to central

**Table 1.** Descriptive Statistics of Study Subjects and Characteristics of Monotherapy Groups

Treatment Group	Number	Mean (SD)						
		Age (yr)	AP (mm Hg)	AI (%)	Heart Rate (min <sup>-1</sup> )	Height (cm)	SBP (mm Hg)	DBP (mm Hg)
ACE inhibitor	33	55 (17)	12 (11)	138 (26)	74 (11)	168 (11)	134 (23)	82 (15)
Ca <sup>++</sup> antagonist	28	60 (14)	14 (9)	140 (21)	74 (14)	168 (9)	139 (30)	82 (13)
Beta-blocker	14	64 (10)	16 (8)	144 (18)	57 (10)	168 (7)	135 (19)	76 (10)
Diuretic	14	66 (9)	14 (10)	148 (18)	71 (13)	162 (10)	134 (19)	77 (9)
All	262	59 (13)	13 (9)	137 (30)	70 (13)	167 (10)	143 (25)	80 (13)

Abbreviations: ACE inhibitor = angiotensin-converting enzyme inhibitor; AI = augmentation index; AP = augmentation pressure; Ca<sup>++</sup> antagonist = calcium antagonist; DBP = diastolic blood pressure; SBP = systolic blood pressure.

waveforms. The AI and pressure reported are obtained from the transformed and scaled waveform that are taken as representing the central aortic blood pressure.

**Statistics.** Statistical analysis was performed using SigmaStat for Windows Version 1 (Jandel Corp., Chicago, Illinois). Significance for group comparison and multiple regression analysis was taken as  $p = 0.05$ . Multiple linear regression was performed using a forward stepwise procedure, alpha value of 0.05, with results reported as partial regression coefficients of predictor variables. One-way analysis of variance (ANOVA) with Student–Newman–Keuls pairwise comparison was used to compare the characteristics of monotherapy groups. For comparison of treatment, only subjects on monotherapy for their hypertension were included; all subjects were included in correlative analyses unless otherwise specified. To allow for the effect on AP of the known pressure dependence of vascular compliance (18), only DBP was used in multiple regression analysis. The reason for this is that minimum distending pressure is a more appropriate index of pressure dependence than either systolic blood pressure (SBP) or mean BP, which are themselves contributed to by AP and hence are not independent predictors.

## Results

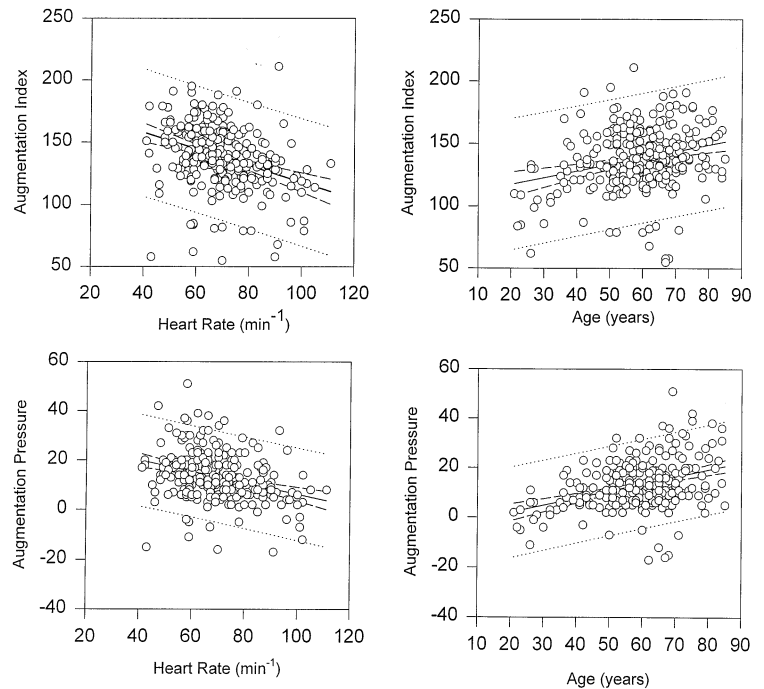
**Subject characteristics.** Subject inclusion was not limited to monotherapy. Two hundred and sixty-two subjects (128 men, mean age 57 years [range 21 to 85] and 134 women, mean age 60 years [range 26 to 84], characteristics shown in Table 1) were assessed, of whom 121 were taking an ACE inhibitor, 106 a calcium channel blocker and 64 a beta-blocker. Eighty-nine subjects were on monotherapy, with 14 of these taking a beta-blocker, 33 an ACE inhibitor, 28 a calcium channel blocker and 14 a diuretic as their only antihypertensive medication.

**Univariate and multivariate associations with APs.** There was the expected close association (all subjects,  $n = 262$ ; Fig. 2) between AI and AP ( $r = 0.78$ ,  $p < 0.001$ ) and also strong association between both indices and heart rate (AI:  $r = -0.33$ ,  $p < 0.001$ ; AP:  $r = -0.32$ ,  $p < 0.001$ ). Significant positive correlation was shown between augmentation parameters and the quantitative variables age, SBP and mean BP,

with negative association demonstrated with heart rate and height. Augmentation parameters were also correlated with the categorical variable sex. Results of univariate correlations with AI for the individual treatment groups are shown in Table 2. The association of AI and heart rate and AI and DBP was investigated separately for men and women, with results shown in Figure 3. The significant inverse relationship between AI and heart rate was maintained in both sexes; however, the AI was uniformly less in men at any given heart rate while a significant positive association between AI and DBP was found only in the male group. Men exhibited a lower AI than women at a given value of DBP over the range of DBP in the study. In view of significant association among the univariate correlates, multiple regression analysis was performed. In stepwise multiple regression, the strongest predictors were height and heart rate (see Table 3). Sex remained a significant contributor, along with age and DBP, but the strong association of sex and height make differentiation of individual contribution difficult. Inclusion of categorical treatment groups did not improve prediction of measured central AP.

When AI was normalized for age (all subjects,  $n = 262$ ), significant correlation with height ( $r = -0.43$ ,  $p < 0.001$ ), sex ( $r = 0.31$ ,  $p < 0.001$ ) and heart rate ( $r = -0.32$ ,  $p < 0.001$ ) was maintained but association with DBP lost. In stepwise regression employing age-corrected parameters, only height and heart rate were significant predictors of AI. For the 89 subjects on monotherapy, ANOVA of age-corrected AI by treatment group showed no significant difference between groups.

The lack of identified association of AI with the monotherapy groups was confirmed by comparison of the slope and intercept of the individual regression lines versus age. The numbers of subjects using only one antihypertensive medication were small in this study; however, there was no statistical difference in either slope or intercept between the ACE inhibitor, calcium channel blocker or diuretic groups, and consequently these were combined in a single regression. While the calculated regression for the beta-blocker group was significantly different from the other three, the AI in this group was widely scattered versus age and, in fact, tended towards an inverse association (probably associated with lowered heart rate; see Discussion) but did not fall outside the expected range associated with the other treatment groups (Fig. 4). This



**Figure 2.** Univariate association (95% confidence interval of the line and 95% prediction interval) of AI and AP with heart rate and age.

study was of cross-sectional design, and assessment of AI pretreatment was not available; however, on the basis of a single measurement in groups of stable hypertensives, no difference in central AI could be demonstrated between the defined groups using the techniques described.

**Comparison of measured brachial and derived central BPs.**

Figure 5 shows the relationship between brachial BP measured oscillometrically and the assigned (posttransformation) values representing central aortic pressures. The slopes of the association between measured peripheral and derived central diastolic and mean BP do not differ significantly from unity; however, the derived DBP was consistently greater than that measured (mean difference 1.84 mm Hg, Standard Error of Difference [SED] 0.120) while the derived mean BP was consistently less than measured (2.62 mm Hg, SED 0.140). The difference between derived and measured SBP increased as measured SBP increased.

**Discussion**

Overall, in a large general patient group, a significant positive univariate relationship was shown between augmenta-

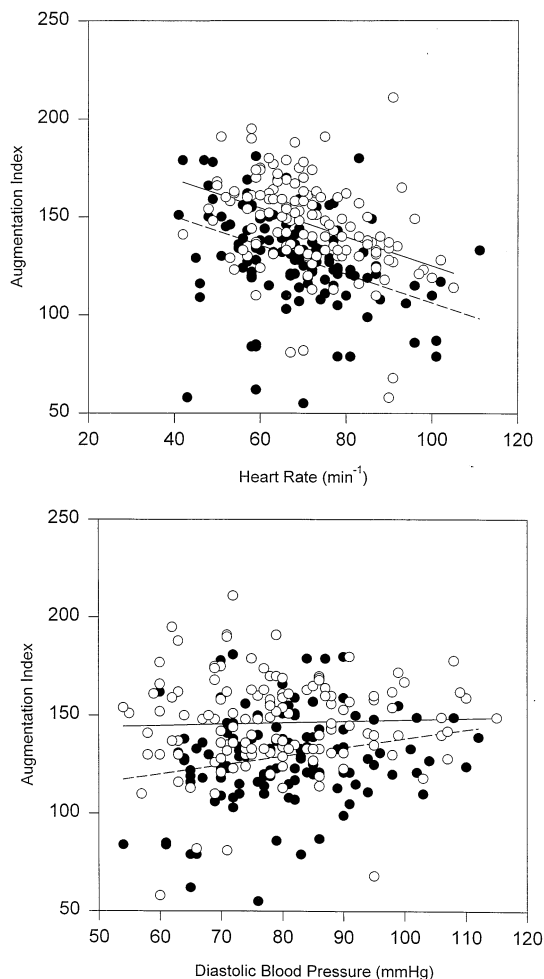
tion parameters and age with a negative relationship between AP and both height and heart rate. Association was also shown with the categorical variable sex, which is consistent with a previous report from London et al. (19) using manual analysis of carotid waveforms. When analyzed by multiple regression DBP, age (positively) and sex were related with AP while heart rate and height retained significant negative association. Neither ACE inhibition nor any of the other forms of treatment investigated was associated with the degree of AP observed when adjusted for the confounding effects of heart rate, age and other covariates. Although the ACE inhibitor monotherapy group was younger than the remaining monotherapy subjects (analysis of variance), there were no significant pairwise differences and, in fact, comparison with a younger group would tend to increase a drug-dependent association rather than obscure it. The number of subjects on monotherapy in this study was small and whether our cross-sectional findings associated with individual drug groups are representative of larger clinical usage may require further prospective study.

**Mechanisms.** It is clear from consideration of the mechanism involved that a reflected pressure wave returning to the aortic root earlier in the cardiac cycle will be associated with

**Table 2.** Univariate Correlation of Augmentation Index (Correlation Coefficient, p Value)

Treatment	Heart Rate (min <sup>-1</sup> )	DBP (mm Hg)	SBP (mm Hg)	Height (cm)	Age (yr)
ACE inhibitor	-0.55, <0.001	0.08, 0.68	0.58, <0.001	-0.63, <0.001	0.32, 0.07
Ca <sup>++</sup> antagonist	-0.48, 0.02	-0.01, 0.99	0.23, 0.27	-0.42, 0.04	0.32, 0.12
Beta-blocker	0.22, 0.45	0.50, 0.07	0.25, 0.39	-0.55, 0.05	-0.24, 0.41
Diuretic	-0.28, 0.35	0.22, 0.47	0.68, 0.01	-0.215, 0.50	0.28, 0.36
All subjects	-0.33, <0.001	0.09, 0.14	0.27, <0.001	-0.34, <0.001	0.26, <0.001

Abbreviations as in Table 1.



**Figure 3.** Linear regression of central aortic AI with heart rate (**top panel**) and DBP (**lower panel**) for males (**solid circle, dashed line**) and females (**open circle, solid line**) analyzed separately. The regression equations are: AI (males) =  $179.37 - 0.73 \times (\text{HR})$ , ( $r^2 = 0.134$ ,  $p = 0.000$ ); AI (females) =  $198.70 - 0.74 \times (\text{HR})$ , ( $r^2 = 0.159$ ,  $p = 0.000$ ); AI (males) =  $93.02 + 0.45 \times (\text{DBP})$ , ( $r^2 = 0.034$ ,  $p = 0.04$ ); AI (females) versus DBP, ( $r^2 = 0.002$ , nonsignificant).

greater augmentation of central aortic pressure than if return is delayed until later in systole or early in diastole. Earlier return is associated with a slower heart rate, an increased PWV at a given heart rate or with a lesser distance of travel to and from principle reflection sites. The unifying thread in these mechanisms is the underlying dependence of AP on duration of the cardiac cycle and pressure PWV. As with all other mechanical indices reported, our results clearly show the association of AP with aging, presumably acting through the accepted association of increased vascular stiffness with increased PWV. These results also suggest that this dependence may be different for men and women but, importantly, highlight the dependence of the measurement on height and underlying heart rate.

The validity of the TF in arterial measurement depends not only on the applicability of the method in general but also on

**Table 3.** Partial Regression Coefficients (All Subjects,  $n = 262$ ) for Forward Stepwise Linear Regression for Dependent Variables Augmentation Pressure and Augmentation Index\*

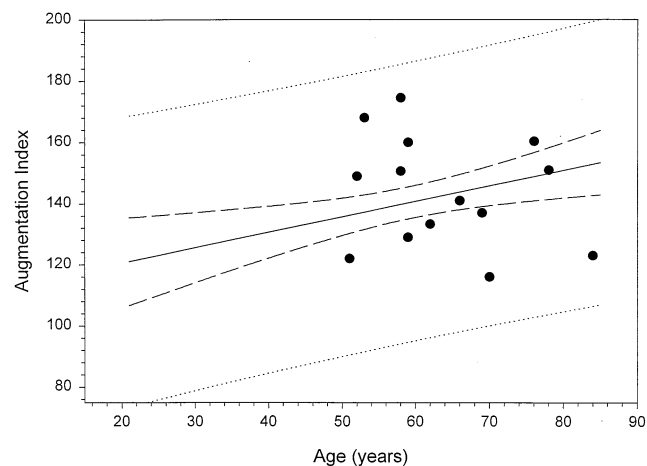
Predictor variable	Forward Stepwise Linear Regression	
	Partial Regression Coefficient	Partial Regression Coefficient
Constant	AP	AI
Age (yr)	33.37	221.34
Sex	0.22	0.34
Diastolic BP (mm Hg)	4.32	10.68
Heart rate ( $\text{min}^{-1}$ )	0.22	0.48
Height (cm)	-0.29	-0.83
	-0.22	-0.59

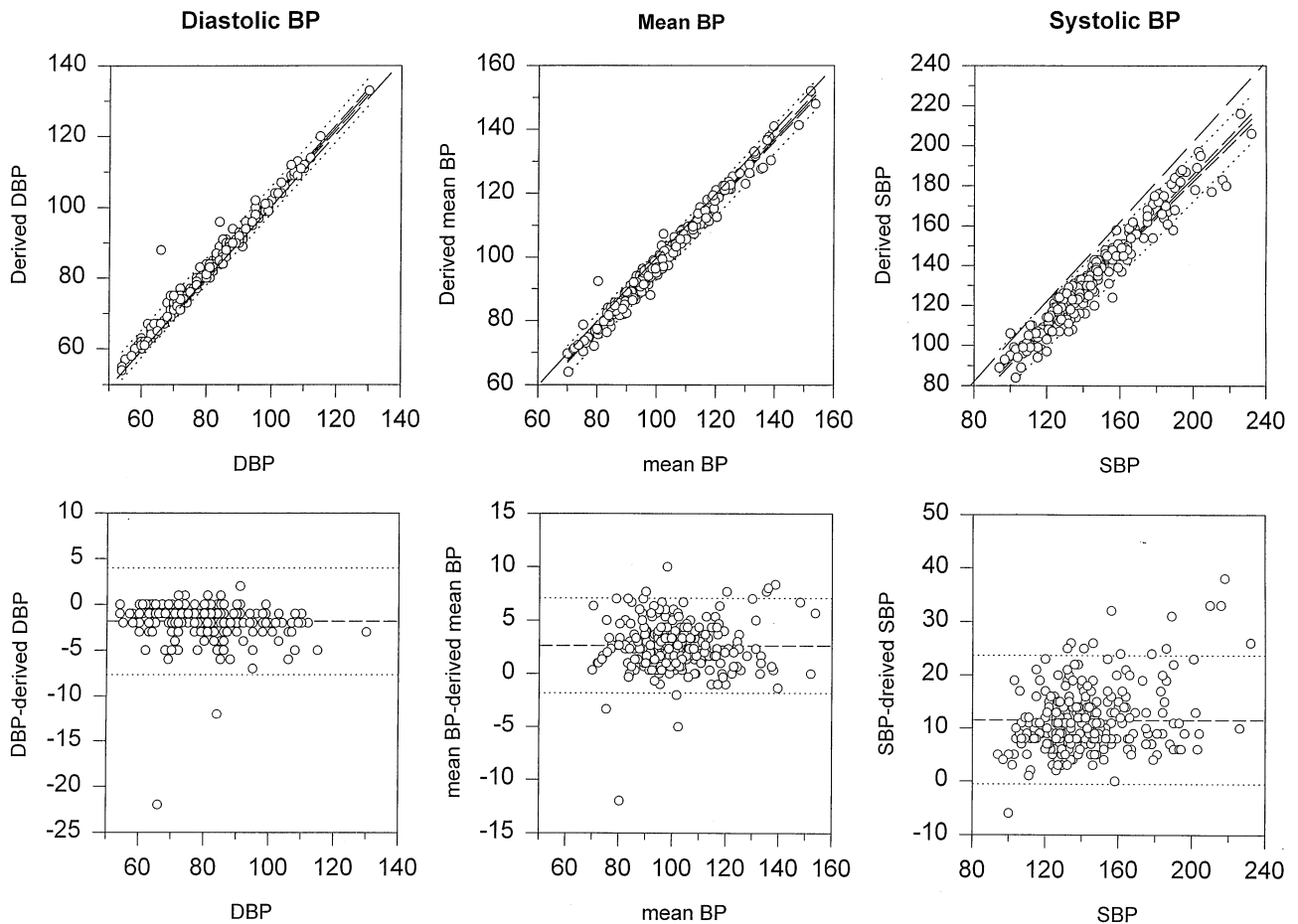
\*All  $p$  values  $< 0.01$ . AI = Augmentation index; AP = augmentation pressure; BP = blood pressure.

the specific function adopted. As yet, the two TFs reported for radial to central transfer have been obtained from relatively small numbers of subjects [14 subjects (7) and 16 subjects (8)]. In the case of the device used in this study, the TF is based on results obtained from normotensive subjects undergoing invasive procedures for presumptive coronary heart disease and it is yet to be established whether generalized TFs obtained in a particular patient group are applicable over a wide range of patient types.

This is the first reported use of a commercially available device for the measurement of augmentation parameters. We therefore looked in detail at the manner in which the peripheral to central transformation affects the outcome. Mean BP does not vary in the large conduit arteries and transformed results obtained were consistent with this fact. Systolic blood pressure is amplified with peripheral progression but the magnitude and significance of the effect between brachial and central aortic pressures is disputed (12,20-22). In the current study, the differences in mean and diastolic BP fall within the range of measurement resolution and are inconsequential. The

**Figure 4.** Combined regression line for the ACE inhibitor, calcium channel blocker and diuretic groups (95% confidence and prediction intervals shown) with beta-blocker group (**solid circles**) superimposed.





**Figure 5.** Upper three panels, comparison of derived central pressures versus measured brachial pressures. Lower three panels, error plots (mean difference and 95% confidence intervals) of the comparisons.

strong relationship between derived and measured SBP implies that, in the practical case, equivalent results may be obtained by assessment of the pressure waveform from the carotid or subclavian artery with use of directly measured brachial pressures adjusted, if necessary, using the linear regression equation obtained. This would obviate the need for waveform transformation. Alternatively, SBP may be dispensed with entirely, and the carotid pressure waveform scaled by linear interpolation using the brachial DBP and mean BP values (3,23). Also, since there is clear association between AP and the dimensionless AI, use of AI (2,4) may be preferable as numerical scaling is not required. In this case the benefit of use of the radial artery relies solely on the ease of applanation, a factor which may be significant if ambulatory techniques become available.

**Generalized TF.** In the system used, the scaled and transformed central pressure waveform is obtained via passage of the radial waveform through a proprietary TF. Using differing techniques, both Karamanoglu et al. (7) and Chen et al. (8) found very similar generalized TFs. Although neither group of

authors provided the precise mathematical form of their TF, the PWV Medical device relies on the technique and validation studies described by Karamanoglu et al. (7) as the basis of its procedure. Theoretically, use of TF techniques require a linear, time-invariant system (24). The basic transmission parameters of the vasculature (pressure–volume relationship) are accepted as nonlinear, and by definition time invariance is negated by any effective intervention, including non–steady-state drug therapy. Since by definition a generalized TF is applied to all subjects, this would appear to be inconsistent with the TF approach; however, the magnitude of the effect of this assumption is unknown and cannot be determined by the current study. As discussed by Chen et al. (8), the assumption of a uniform TF may be tenable in certain instances—for example, in assessing group responses—but it must be carefully considered when assessing individual responses, and further work is required here. Interventions that differentially affect the more muscular brachioradial compared to the elastic aorta may also affect the applicability of a generalized TF.

**Effect of heart rate on AP.** The dominant variables in analysis of augmentation parameters in this study were height and heart rate. In comparison studies, therefore, it would be necessary to adjust for height as well as any variation in heart rate at the times of assessment. In general, women might be

expected to have lower PWVs than men of similar age; despite this, AI at any given heart rate or DBP was greater in women compared to men (see Fig. 3). The likely explanation for these differences is the decreased distance of travel to the principle reflecting site in women due to their relatively shorter stature. It may therefore also be necessary to control for significant height differences in future studies using augmentation parameters.

**Conclusions.** Assessment of pressure augmentation using the technique described is noninvasive and a relatively easy measurement to perform. In this study, the increase in AI with age has been confirmed. The major new findings arising from the present study were the heart rate dependence of AI and the close linear association between brachial and central BPs as assessed by the generalized TF. Also of interest was the lack of discrimination of AI by class of antihypertensive therapy. Although it is now generally accepted that particular antihypertensive classes, especially the ACE inhibitors, have beneficial effects on muscular arterial mechanical properties, as well as lowering BP, a differential effect was not able to be demonstrated in this study using radial artery applanation. Whether this is a real lack of antihypertensive drug class effect on change in arterial function as seen at the level of the central aorta, or a limitation of radial applanation tonometry for the use proposed, or of the cross-sectional nature of the study could not be determined. To resolve the presence or absence of a true drug effect would require a prospective controlled study and would require invasive studies, negating the proposed benefit of noninvasive applanation tonometry.

**Summary.** Derivation of central AI via radial artery tonometry is a relatively simple, noninvasive procedure for which a commercial device is available. In the present study, we were not able to demonstrate that use of a generalized TF altered practical assessment of central aortic BP, nor could we demonstrate any difference in the age-related dependence of derived AP due to the common antihypertensive drug classes. Further studies are required to ascertain the clinical place of measurement of augmentation parameters and the use of radial artery applanation.

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