

Use of Arterial Transfer Functions for the Derivation of Central Aortic Waveform Characteristics in Subjects With Type 2 Diabetes and Cardiovascular Disease

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OBJECTIVE— Optimal blood pressure control in subjects with diabetes reduces cardiovascular complications. There is theoretical benefit in the assessment of central aortic waveforms including the augmentation index, which is taken as a putative index of stiffness. Transfer functions may be used to reconstruct aortic from radial pressure waveforms; however, a single generalized transfer function may not be appropriate for all patients. We aimed to evaluate the technique in subjects with diabetes.

RESEARCH DESIGN AND METHODS— Simultaneous invasive central aortic and noninvasive radial waveforms were acquired in 19 subjects with type 2 diabetes, and a diabetes-specific transfer function was derived. Similar data were acquired from 38 age- and sex-matched subjects without diabetes. Central waveforms were reconstructed using a generalized transfer function in all patients and the diabetes-specific transfer function in individuals with diabetes.

RESULTS— There was no difference between groups in measured central pressures. The error in generalized transfer function–derived systolic pressure was greater in individuals with diabetes (6 ± 7 mmHg) (mean \pm SD) than without diabetes (2 ± 8 mmHg) ($P < 0.05$). Errors in other parameters were no different. The diabetes-specific transfer function reduced the error in derived systolic pressure to 0 ± 7 mmHg in individuals with diabetes—no different than that with the generalized transfer function in individuals without diabetes. The central augmentation index reconstructed by either transfer function was unrelated to that directly measured.

CONCLUSIONS— A generalized transfer function is inappropriate for the derivation of central waveforms in subjects with type 2 diabetes. Errors in subjects with diabetes might be reduced with a diabetes-specific transfer function.

Diabetes Care 27:746–751, 2004

Cardiovascular disease is the major cause of mortality and morbidity in western societies (1). Diabetes, reaching epidemic proportions in some populations, is an important risk factor for cardiovascular disease, augmenting the effects of coexistent risk factors such as hypertension (1). Optimal blood pres-

sure control in subjects with diabetes and hypertension significantly reduces risk of cardiovascular complications and death (2). Thus, potential benefit from improvements in the recognition and treatment of hypertension may be even greater for patients with diabetes than without.

The central aortic pressure waveform

is thought to represent the sum of a forward traveling wave, the product of cardiac contraction, and a backward traveling wave, due to wave reflection from the periphery (3). The timing, and potentially the magnitude, of wave reflection in the ascending aorta is influenced by arterial mechanical properties that change early in the course of diabetes (4,5) and may adversely affect the relationship between cardiac workload and myocardial blood supply (3). With increasing appreciation of the potential contribution of wave reflections to central aortic blood pressure and cardiovascular risk, it has been proposed that hypertension may be better recognized and managed on the basis of central aortic pressure waveform characteristics than on the basis of simply brachial artery systolic blood pressure (sBP) or diastolic blood pressure (dBP) (6). Characteristics proposed as of potential value include not only central aortic sBP, but also characteristics of waveform morphology, particularly the augmentation index (Fig. 1) (7).

Because central waveforms are not usually directly accessible, noninvasive methods for their estimation have been developed. Commercial devices are available that use a generalized arterial transfer function to reconstruct central aortic from radial pressure waveforms. An arterial transfer function describes the relationship between pressure waveforms from two arterial sites. If this relationship is known and data are collected from one site, the pressure waveform at the other site may be deduced. The radial artery has been proposed as the best site for noninvasive assessment because optimal applanation may be easier to achieve than at other sites (8,9). Transfer function approaches are attractive because they are easy to use and are increasingly used in both research and clinical practice, despite very modest data validating the technique for use with noninvasively acquired radial waveforms (8–13). Additionally,

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Received for publication 22 May 2003 and accepted in revised form 20 October 2003.

Abbreviations: dBP, diastolic blood pressure; sBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 831.

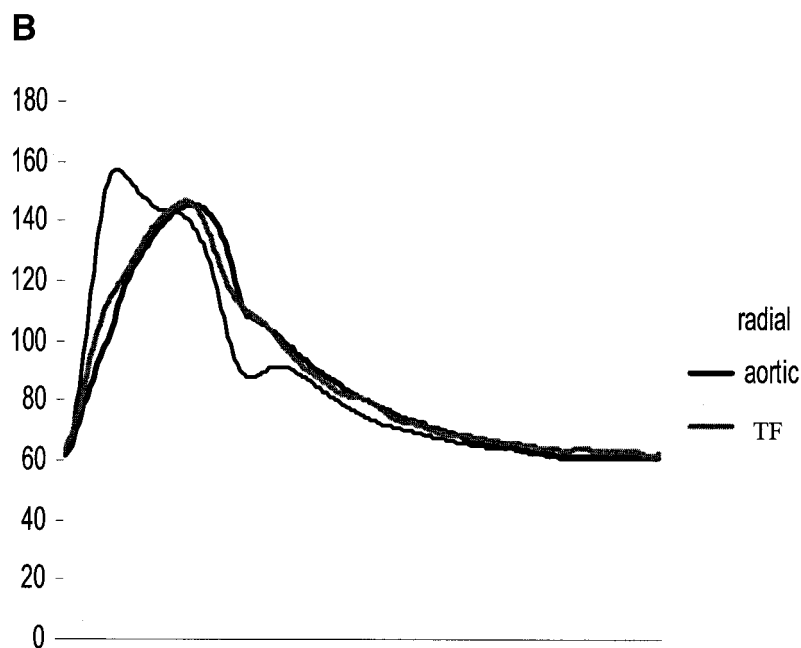
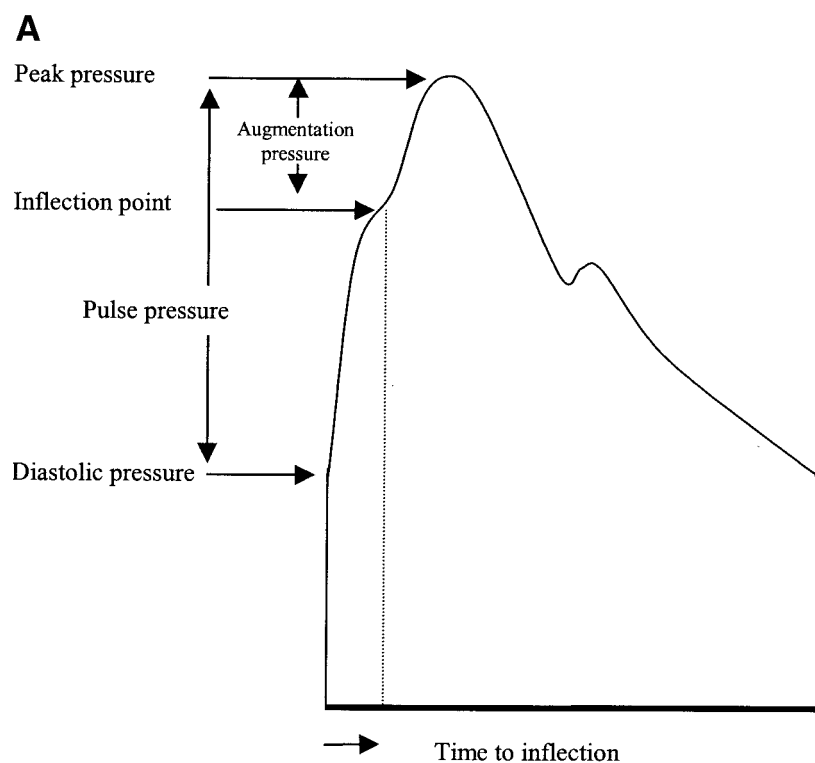


Figure 1—A: Representation of central aortic pressure waveform. Augmentation index = augmentation pressure/pulse pressure \times 100%. B: Three-way comparison of measured central aortic, generalized transfer function-derived central aortic, and applanated radial artery pressure waveforms. TF, generalized transfer function.

all these studies suggest significant limitations of the technique (8–13), with no published data supporting the contention that a single generalized transfer function

is equally valid in subjects with and without diabetes. This issue has previously been raised as a concern (14), and there is evidence suggesting that important differ-

ences may exist between subject groups with different characteristics, for example, different sex (12). We therefore aimed to compare a generalized with a diabetes-specific transfer function in subjects with and without diabetes for the derivation of central waveform parameters proposed as of potential clinical value.

RESEARCH DESIGN AND METHODS

The study was approved by the institutional Human Research and Ethics Committee and performed in the cardiac catheterization laboratory of Monash Medical Centre. Participants gave informed consent. A total of 19 diabetic subjects were studied during clinically indicated coronary angiographic procedures. Subjects were fasted overnight in accordance with standard practice. All 19 had type 2 diabetes, 9 were using oral hypoglycemic agents alone, 2 were using insulin alone, 3 were using oral hypoglycemic agents and insulin, and the remainder were treated by diet. The interval since diagnosis of diabetes was 9.5 ± 10.7 years (means \pm SD) (13 subjects had suffered a previous acute coronary syndrome). All subjects were known or suspected to have coronary artery disease. A total of 38 age- and sex-matched subjects without diabetes, but with a similar burden of coronary artery disease, were also studied.

Data collection and waveform analysis

Invasive central aortic pressure (low compliance fluid-filled catheter) and noninvasive radial pressures (Millar Mikro-tip tonometer; Millar Instruments) were measured simultaneously as previously described (12). A generalized transfer function (12) was used to reconstruct central from radial waveforms of all subjects and was compared with a diabetes-specific transfer function, derived by the same method (12) in individuals with diabetes.

Measured radial and both measured and transfer function-derived aortic waveforms were analyzed for sBP and dBP, augmentation pressure, augmentation index (augmentation pressure/pulse pressure \times 100%), and the time to the inflection point (Fig. 1).

The burden of coronary artery disease was assessed from the coronary angiographic study according to standard

Table 1—Demographic features of subjects with and without diabetes

	Diabetes	No diabetes
n	19	38
Age (years)	66 ± 11	65 ± 10
Male sex	14 (74)	28 (74)
Height (cm)	169 ± 9	169 ± 9
Weight (kg)	81 ± 15	79 ± 12
BMI (kg/m ²)	28.4 ± 5.3	27.9 ± 4.0
>25 kg/m ²	16 (84)	30 (79)
>30 kg/m ²	9 (47)	9 (24)
Current smoking*	4 (21)	1 (3)
Hypertension	11 (58)	22 (58)
Hypercholesterolemia	17 (89)	32 (84)
Family history of coronary artery disease	9 (47)	14 (37)
Coronary artery disease on angiography	16 (84)	33 (87)
Heart rate (bpm)	72 ± 10	69 ± 12

Data are means ± SD or n (%). **P* < 0.05 for difference between subjects with and without diabetes. See Table 2 for central aortic blood pressures.

criteria as smooth arteries, minor irregularities, and single, double, or triple vessel disease. An experienced cardiologist blinded to waveform parameters performed this assessment.

Statistical analysis

Data were assessed for normality. Continuous variables are presented as means ± SD. Demographic features, waveform parameters, and errors in derived parameters were compared between subjects with and without diabetes by unpaired *t* tests or χ^2 tests. Measured central and radial waveforms were compared using paired *t* tests. Pearson's correlation coefficients were calculated and compared for the relationships between the measured

central aortic and both the radial and transfer function–derived waveform parameters. Statistical analyses were performed using SPSS 10.0 for Windows (SPSS) and Microsoft Excel 2000 (Microsoft Corporation), and the significance was taken as *P* < 0.05. The study was powered at >0.80 with *P* < 0.05 to detect a mean error or a difference between transfer functions of ≥ 5 mmHg in sBP, a level considered to be of clinical significance (15).

RESULTS— Subject demographic features are detailed in Table 1. The prevalence of current smoking was greater in the diabetic group (*P* < 0.05). More subjects with diabetes than without were

on diuretic medication (7 [37%] vs. 3 [8%] [*P* < 0.01]) and Nicorandil (3 [16%] vs. 0 [*P* < 0.05]). There was no difference between groups in other cardiac medications.

Measured central aortic and radial waveforms

Measured central waveform parameters were similar in both groups, with a difference only in time to inflection point (*P* < 0.05) (Table 2), which was shorter in individuals with diabetes. Central and radial blood pressures were correlated in subjects both with and without diabetes (*P* < 0.001). Neither central augmentation index nor time to inflection point was correlated with its respective radial counterparts in either group. Correlation coefficients did not differ between individuals with and without diabetes.

Transfer function–derived waveforms

Individual measured aortic applanated radial and reconstructed aortic pressure waveforms are illustrated in Fig. 1. Despite small mean errors (Table 2), neither transfer function–derived augmentation index nor time to inflection point correlated with the corresponding measured aortic parameter using either generalized or diabetes-specific transfer functions.

Using the generalized transfer function in individuals without diabetes, derived central and measured radial parameters were correlated (*r* = 0.91 [augmentation index, *P* < 0.001] and *r* = 0.36 [time to inflection point, *P* < 0.05]).

Table 2—Central aortic waveform characteristics of subjects with and without diabetes and errors in transfer function–derived waveform characteristics

	No diabetes			Diabetes				
	Measured	Generalized transfer function		Measured	Generalized transfer function		Diabetes-specific transfer function	
		Values	Errors		Values	Errors	Values	Errors
sBP (mmHg)	134 ± 23	132 ± 22	2 ± 8§	133 ± 22*	127 ± 19	6 ± 7	133 ± 20	0 ± 7
dBP (mmHg)	70 ± 10*	62 ± 10	9 ± 2	68 ± 11†	60 ± 10	8 ± 2	64 ± 10	5 ± 2
Augmentation pressure	8 ± 7*	15 ± 9	−7 ± 8	12 ± 7	14 ± 8	−4 ± 7	13 ± 7	−3 ± 7
Augmentation index (%)	13.1 ± 9.8*	20.6 ± 9.7	−7.1 ± 12.9	18.0 ± 10.2	21.3 ± 9.5	−4.9 ± 12.9	18.7 ± 7.2	−1.4 ± 11.6
Time to inflection point(s)‡	0.163 ± 0.033*	0.146 ± 0.010	0.014 ± 0.034	0.144 ± 0.030	0.148 ± 0.036	−0.006 ± 0.035	0.146 ± 0.010	−0.002 ± 0.026

Data are means ± SD. **P* < 0.05 for difference between measured parameters and generalized transfer function–derived parameters (measured minus transfer function–derived values). †*P* < 0.05 for difference between measured parameters and diabetes-specific transfer function–derived parameters. ‡*P* < 0.05 for difference in measured parameters between subjects with and without diabetes. Significant differences from generalized transfer function errors in subjects with diabetes: §*P* < 0.05, ||*P* < 0.001. Significant differences from generalized transfer function errors in subjects without diabetes: *P* < 0.001.

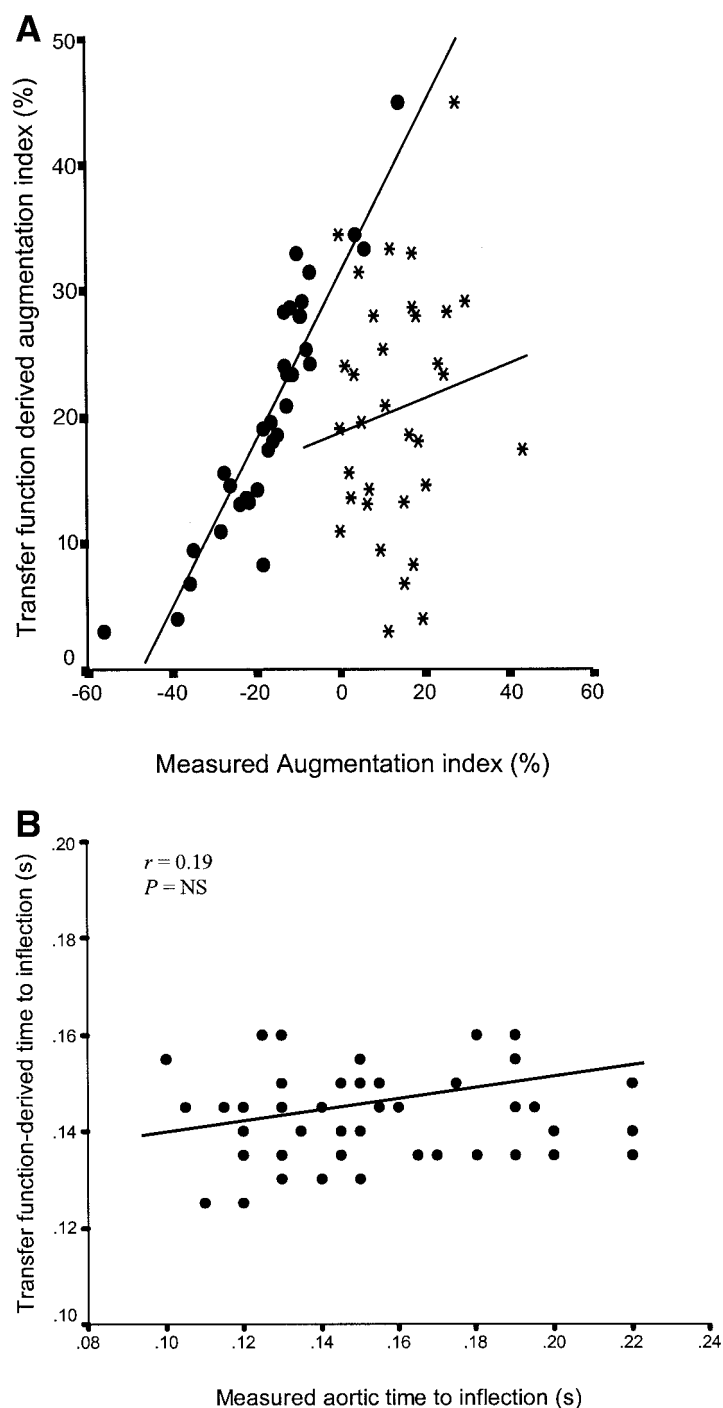


Figure 2—A: Relationship between generalized transfer function–derived augmentation index and measured central aortic and radial augmentation index. ●, Generalized transfer function and measured radial augmentation index; $r = 0.91$ ($P < 0.001$). *Generalized transfer function and measured central aortic augmentation index; $r = 0.15$ ($P = 0.40$ not significant). B: Relationship between generalized transfer function–derived and measured central aortic time to inflection point.

In individuals with diabetes, using the diabetes-specific transfer function, correlations were $r = 0.89$ ($P < 0.001$) and $r = 0.72$ ($P < 0.01$), respectively (Fig. 2).

Diabetes was associated with greater

error in derived central sBP using the generalized transfer function (6 ± 7 and 2 ± 8 mmHg, with and without diabetes, respectively) ($P < 0.05$) (Fig. 3), but there was no difference in errors in any other

parameter. The diabetes-specific transfer function yielded smaller errors in derived sBP (to 0 ± 7 from 6 ± 7 mmHg [$P < 0.001$]), such that the error was no different from that using the generalized transfer function in the group without diabetes. There was also improvement in the error in derived dBP ($P < 0.001$) in individuals with diabetes.

The error in sBP derived using the generalized transfer function was positively associated with the measured sBP; for example, the greater the central sBP, the greater the error in the derived sBP ($r = 0.32$ [$P < 0.01$]). Despite improvements in error, this trend remained with the substitution of diabetes-specific transfer function–derived values in individuals with diabetes ($r = 0.39$ [$P = 0.1$]). Improvements in error with the diabetes-specific transfer function were not associated with changes in correlation between measured and derived parameters.

CONCLUSIONS— Noninvasive assessment of central waveforms is appealing with theoretical clinical benefit. Applanation tonometry of the radial artery together with a transfer function is also appealing because it is technically easy, quick, and reproducible (16). Despite the previous application of this technique to subjects with diabetes (17,18), lack of data in this group has been a topic of concern (14). This study is the first to address whether the technique is valid in individuals with diabetes.

Apparent wave reflection is influenced by arterial mechanical properties. Diabetes is associated with changes in arterial mechanical properties with increased arterial stiffness before discernible vascular complications (4,5). These changes may be caused by structural changes in arterial walls caused by abnormal glycation and functional changes associated with insulin resistance (4). We found a shorter time to the inflection point and a trend toward a greater augmentation index in measured aortic waveforms of subjects with type 2 diabetes, despite a similar prevalence and extent of atherosclerotic coronary artery disease, as expected in a group with stiffer arteries and higher pulse wave velocity. That neither the generalized nor diabetes-specific transfer function demonstrated the difference between groups in the time to the inflection point suggests that transfer functions may not adequately differenti-

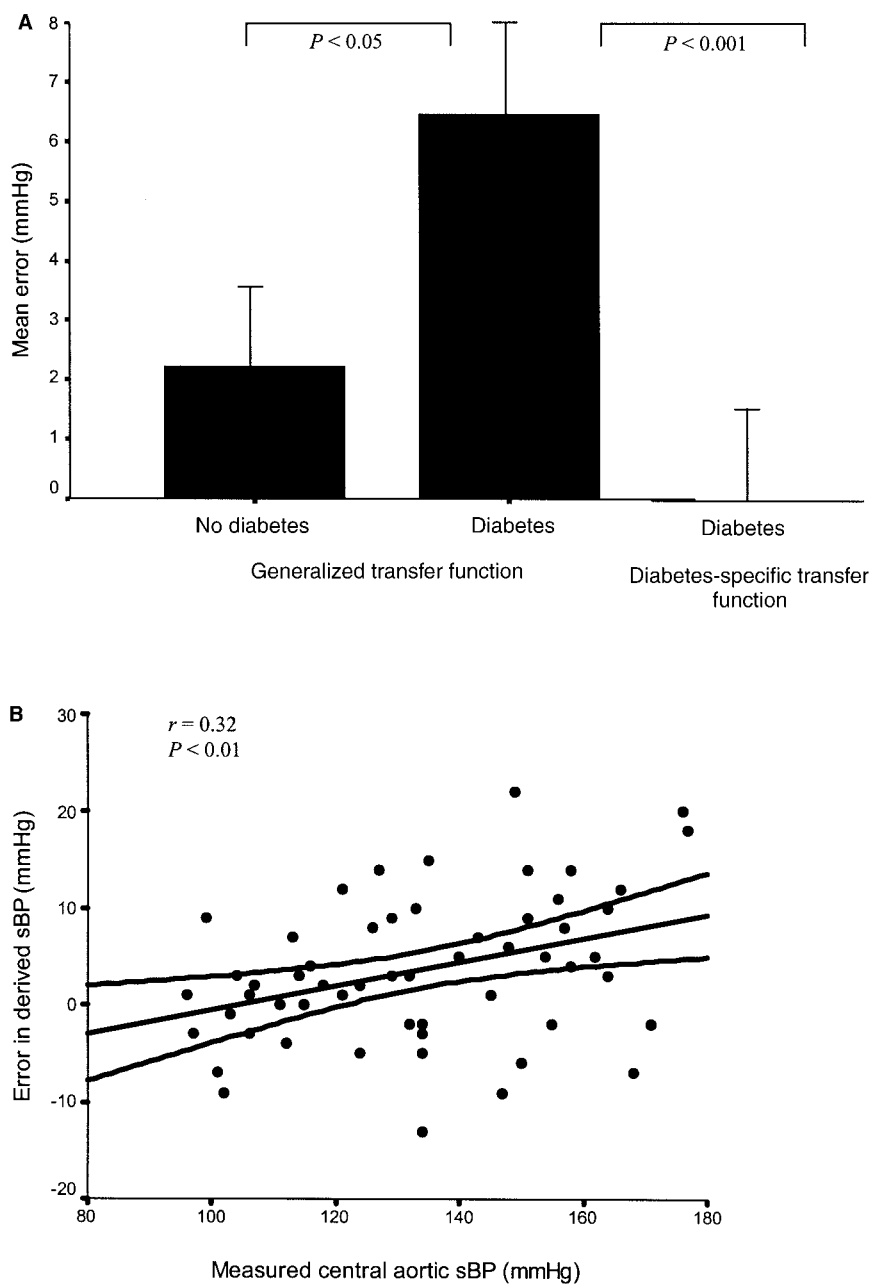


Figure 3—A: Mean error between measured and transfer function–derived sBP in subjects with and without diabetes. Error is measured aortic minus reconstructed value. Bars represent SE. B: Relationship between error in sBP and measured central aortic sBP.

ate groups with altered mechanical properties at increased risk of cardiovascular complications.

We, and others, have explored the accuracy of reproduction of central aortic sBP by the application of a generalized transfer function to radial waveform data obtained noninvasively by applanation tonometry (8–10). In subjects with diabetes, the error in estimating central sBP using a generalized transfer function ex-

ceeded international recommendations (15). Use of the diabetes-specific transfer function improved the error to within acceptable limits.

We found similar errors in the reproduction of central augmentation pressure (used in the calculation of augmentation index) in both groups, with a magnitude consistent with previous studies (19). The error was unaltered by application of the diabetes-specific transfer function. The

derived augmentation index remained closely correlated with the radial. The transfer functions reconstructed the augmentation index so poorly that derived estimates were statistically unrelated to measured values. Our findings are consistent with the limited data in the literature (10,20), suggesting that transfer functions may not reproduce the central augmentation index with sufficient accuracy to be of any clinical value.

In common with others, this study is limited by the application of transfer functions to subjects from whom they were derived; therefore, the data cannot validate the technique for use in other groups (21). Mean error using a transfer function that has been derived from a population mean might be expected to be small; however, our results are likely to represent the minimum individual variability that might be seen, and errors in a different group with type 2 diabetes may be substantially larger. Additionally, concerns may be raised regarding the use of fluid-filled rather than micromanometer-tipped catheters for the measurement of central pressures. However, previous assessment of our system, and the similarity between our generalized transfer function and that of Fetis and colleagues (9,10), support the conclusion that frequency response characteristics of our system are adequate (12,20). This study is limited by recruitment of subjects only with a clinical indication for coronary angiography, a limitation shared by all reported studies deriving arterial transfer functions because it is an inevitable ethical limitation of this type of invasive study.

Whereas we did not aim to validate the transfer functions prospectively, the study raises important questions regarding their use in clinical practice. Currently, all epidemiological data on the cardiovascular risks of hypertension and risk reduction by control of blood pressure are based on conventional noninvasive brachial artery blood pressure measurements, with as yet no evidence to support the contention that hypertension may be better managed with knowledge of derived central pressure waveform characteristics. Given this, in patients with diabetes, who have much to gain by optimal blood pressure control by conventional criteria, it seems premature to suggest that greater credence should be given to derived central waveform characteristics than to conventional pressure

measurements, particularly if, as suggested by this study, this group of patients may be subject to greater error in the estimation of central pressures than lower-risk groups without diabetes. It can only be assessed by prospective validation studies whether, in other subjects with diabetes, the use of a diabetes-specific transfer function may produce an estimate of central blood pressure to within clinically acceptable limits. In common with previously published data, we found poor estimation of the central augmentation index, suggesting that clinicians should be circumspect before allowing any clinical decision to be influenced by transfer function–derived estimates of this parameter. Particular caution should be exercised when using a transfer function in a patient group in which it has not been appropriately validated.

Summary

The error in the estimation of central aortic systolic pressure by the application of an arterial transfer function to noninvasively obtained radial pressure waveform data might be reduced in subjects with type 2 diabetes by the use of a diabetes-specific transfer function. However, arterial transfer functions appear unreliable for the estimation of the central aortic augmentation index. Our findings suggest caution should be exercised when applying a generalized arterial transfer function to a subject group in which it has not been evaluated, in particular, for the derivation of central waveform characteristics for which it has not been evaluated appropriately in any subject group.

Acknowledgments—S.A.H. is supported by Medicine International and Faculty Postgraduate Research Scholarships from Monash University and a Cardiovascular Research Centre PhD Scholarship from Monash Medical Centre.

We gratefully acknowledge the constructive comments of Associate Professor Richard O'Brien.

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