Comparison of generalized and gender-specific transfer functions for the derivation of aortic waveforms

SARAH A. HOPE,1 DAVID B. TAY,2 IAN T. MEREDITH,1 AND JAMES D. CAMERON1
1Cardiovascular Research Centre, Monash Medical Centre and Monash University, Melbourne 3168; and 2La Trobe University, Melbourne, Victoria, 3083 Australia

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There is considerable evidence (3, 5, 18, 21, 22) that changes in arterial mechanical properties are associated with both risk factors for and the presence of cardiovascular disease. The central arterial pulse wave is determined by the sum of a forward traveling pulse wave and a reflected wave. The characteristics of the reflected wave are altered according to the net effect of changes affecting both intrinsic arterial wall properties and arterial geometry, both of which change with age and the presence of cardiovascular disease (3, 17, 22, 28, 30, 34, 35). The adverse cardiac effects are likely related to the changes in the central arterial pulse; consequently, methods for the noninvasive acquisition of central aortic pulse wave data by applanation tonometry of accessible peripheral arteries have been developed (1, 6–9, 14). Although noninvasive assessment of waveforms in arteries close to the central aorta give acceptable estimates of central aortic waveform characteristics [carotid (6, 8) and subclavian (1)], the radial artery is often proposed as the preferred site for applanation tonometry because optimal applanation may be easier to achieve (7). However, the waveform contour is substantially different from that in the ascending aorta and therefore requires further manipulation before adequately approximating the central aortic waveform shape (7). Arterial transfer functions (TF) have been promoted for this purpose (7, 14).

This technique is becoming increasingly utilized in research for the derivation of a range of central aortic waveform characteristics in both men and women. Indeed, the technique has been used to describe differences between men and women (39). However, the published data (7, 14, 33) on which the technique is based remains small, with no published data to support the contention that a single generalized arterial TF is equally valid for both genders. With differences in both the physical and mechanical properties of the arterial tree between men and women potentially influencing the relationship between peripheral and central waveforms, the use of a gender-appropriate TF (GATF) may be essential (3, 4, 10, 11, 25, 34). Therefore, our study aimed to characterize the differences in central aortic waveform characteristics between men and women and to compare the use of a generalized arterial TF with gender-specific TF in both men and women for the derivation of a range of central aortic pressure waveform parameters that could potentially have clinical value.

METHODS

This study was performed in the cardiac catheterization laboratory of Monash Medical Centre. The study was approved by the Institutional Human Research and Ethics Committee and the participants gave informed consent. Seventy-eight patients (61 male and 17 female) undergoing elec-
Coronary angiography or percutaneous coronary intervention were studied.

Central aortic pressure was recorded invasively via a low-compliance fluid-filled catheter positioned in the ascending aorta simultaneously with noninvasively obtained radial artery waveform data acquired via a tonometer (Millar Mikro-tip, Millar Instruments). Waveforms were recorded at 200 Hz with the use of Chart for PowerLab (ADInstruments) to a personal computer. A 4,096-point sequence was selected for analysis with due regard for artifactual baseline variability of the radial waveform. The peripheral tonometric waveforms were scaled to measured aortic mean and diastolic pressures by linear interpolation as previously described (7).

A single-input/single-output model was used to calculate linear time-invariant TFs between applanated radial and directly measured central blood pressure waveforms. All calculations were done with MatLab version 6R12 (MathWorks) with only the first 14 harmonics (11 Hz) included in the final spectra (7). The 4,096-point data sequence was used to derive individual TFs for each subject by two methods. For method 1, input and output spectra were calculated via fast Fourier transformation using 256-point Hanning windows with 128-point overlap to obtain ensemble average spectra. A complex TF was obtained as the quotient of output spectrum to input spectrum. For method 2, the same data sequence was initially segmented into corresponding individual cardiac cycles and aligned at identical start-systolic points (local maxima of the first derivative), and ensemble-averaged pressure cycles were obtained. A single 256-point fast Fourier transformation was performed on these cycles and a TF obtained by division. From the individual TFs, ensemble-averaged TFs were obtained for the group as a whole (ensemble-averaged TF method 1, eTF1) and for both genders individually (male-averaged TF method 1, male-averaged TF method 2, female-averaged TF method 1, and female-averaged TF method 2). Reverse transformation was performed with the use of each ensemble-averaged TF applied to the radial artery data for each subject.

Waveform analysis was undertaken using custom-designed software to identify on both measured aortic and TF-derived waveform parameters proposed to be of potential clinical value, and parameters of importance in their calculation. These include the peak systolic blood pressure (SBP), time to peak pressure (T_p) and time to the end of systole (T_s), diastolic pressure time integral (A_d), and systolic pressure time integral (A_s), and the A_d-to-A_s ratio, known as the subendocardial viability index (SVI) (Fig. 1) (13). Time intervals were measured from the onset of the SBP upstroke for each waveform. The software identified an inflection point [the first zero crossing from positive to negative of the fourth derivative of the pressure (16)] on the SBP upstroke, when present, and hence also the time to this inflection point (T_i), the pressure at the augmentation point (P_i), the augmentation pressure (AP) (SBP - P_i), and augmentation index (AI) (AP/pulse pressure × 100%).

The burden of coronary artery disease was assessed from the clinical angiographic study and categorized into five groups: 1) angiographically smooth arteries; 2) minor irregularities only; 3) single vessel disease, with a stenosis of ≥70% in one vessel; 4) double vessel disease, with a stenosis of ≥70% in one vessel and a stenosis of ≥50% in a second vessel; 5) triple vessel disease, with a stenosis of ≥70% in one vessel and a stenosis of ≥50% in both other major coronary arteries.

The waveform parameters of the measured central aortic waveforms were characterized and compared between men and women using unpaired Student's t-tests. Parameters of the gender-specific TF-derived surrogate central waveforms for the group as a whole, both gender-appropriate and -inappropriate [gender-inappropriate TF method 1 (GNTF1) and gender-inappropriate TF method 2 (GNTF2)], were compared with the generalized TF-derived waveform parameters. Mean values were compared by analysis of variance with

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Fig. 1. Representation of central aortic pressure waveform.
repeated measures and within-subject contrasts, with the generalized TF-derived values as the reference values. Comparisons were also made with the measured central aortic waveform parameters. Comparisons were made between correlation coefficients for the relationships between the measured aortic parameters and those derived from both the gender-specific and ensemble-averaged TFs. Regression slopes were compared with the line of unity. Continuous variables are expressed as means ± SD, and demographic differences between men and women were assessed with the use of t-tests and \( \chi^2 \)-tests as appropriate.

A secondary analysis was undertaken comparing the reconstructed central waveforms of the female group with a subgroup of males matched for measured SBP to assess whether differences between generalized and gender-specific TFs could be explained simply by the difference in measured central waveform parameters between the genders.

A value of \( P < 0.05 \) was considered statistically significant. Statistical analyses were performed using SPSS version 10.0 for Windows and Microsoft Excel 2000.

**RESULTS**

Subject demographic characteristics are detailed in Table 1, and cardiovascular risk factors in Table 2. The incidence of angiographic coronary artery disease was the same in men and women; however, there was a greater incidence of double and triple vessel disease in the men (\( P < 0.05 \)). Drug treatments are typical of a group with established coronary artery disease, and do not differ between men and women (Table 3).

**Measured central aortic parameters and gender.** Unpaired t-tests that compared measured central aortic parameters in men and women revealed significantly higher SBP, \( P_i \), and \( A_\alpha \) in females, with significantly lower SVI (Table 4). These findings remained unchanged in a multiple stepwise linear regression model when height, weight, heart rate, and age were also considered. In addition, a longer \( T_s \) was significantly associated with female gender after heart rate was considered.

By simple linear regression, all time intervals were associated with heart rate. Both increased AP and AI were associated with shorter \( T_i \), consistent with an increased pulse wave velocity. This relationship was retained in a multiple stepwise linear regression model including heart rate, but there was no association with gender. Larger \( A_\alpha \) was associated with longer \( T_s \), but was additionally independently associated with both increased heart rate and female gender. Increased \( A_\alpha \) was associated with slower heart rate, with no association with either gender or \( T_s \). Higher SVI was significantly associated with a slower heart rate. In a multiple stepwise regression model it was additionally significantly associated with male gender, but this association was not independent of \( T_s \), which preferentially entered the model. In this group, AI was not associated with heart rate, gender, or height (see **DISCUSSION**).

**Method 1.** Derived AI was not significantly correlated with the directly measured (AI), and was therefore not further analyzed. There were statistically significant differences between the measured and derived mean values of the other parameters assessed, but no significant differences between the values derived by the generalized or GATF (Table 5). There were no significant differences between the correlation coefficients for the relationship between the measured and derived waveform parameters for the generalized and gender-appropriate TFs.

There were significant differences in derived mean values for most parameters when the generalized TF was compared with the GNTF (SBP, \( T_p \), \( A_\alpha \), \( A_d \), \( T_i \), AP, and \( P_i \)). For some parameters, the mean difference from measured was smaller with GNTF than the generalized TF, but for no parameter was the correlation significantly stronger. For SBP, diastolic blood pressure (DBP), and \( P_i \), the correlation was significantly stronger with the generalized TF. Correlation coefficients for these parameters were also stronger with the GATF than GNTF, but the difference did not reach statistical significance. The presence of coronary artery disease was not significant when included as a covari-
The burden of coronary artery disease reached borderline statistical significance for DBP only. Comparison of the regression slopes for the relationships between GATF-derived and measured aortic parameters with those for the relationships between the generalized TF-derived and measured aortic parameters revealed significant differences for SBP, Pi, and Ti only. GATF produced regression slopes significantly nearer to unity for SBP and Pi, and did not differ significantly from unity for SBP. Comparison of the regression slopes for the relationships between GNTF-derived and measured aortic parameters with those for the relationships between the generalized TF-derived and measured aortic parameters revealed a significant difference only for Ai, with that for the generalized TF being closer to unity.

Method 2. Derived Ai and Ti were not significantly correlated with the measured (Ai and Ti), and were therefore not further analyzed. There were statistically significant differences between the measured and derived mean values of a number of the other parameters assessed (Table 6). Where differences existed between

Table 4. Comparison of mean measured aortic parameters in men and women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Male</th>
<th>Mean Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>127 ± 21</td>
<td>146 ± 19b</td>
</tr>
<tr>
<td>Tp, s</td>
<td>0.239 ± 0.031</td>
<td>0.231 ± 0.035</td>
</tr>
<tr>
<td>Ts, s</td>
<td>0.321 ± 0.027</td>
<td>0.328 ± 0.038</td>
</tr>
<tr>
<td>As, mmHg/s</td>
<td>34.8 ± 6.8</td>
<td>40.0 ± 4.9a</td>
</tr>
<tr>
<td>As, mmHg/s</td>
<td>48.4 ± 12.9</td>
<td>45.4 ± 7.8</td>
</tr>
<tr>
<td>SBI</td>
<td>1.4 ± 0.3</td>
<td>1.2 ± 0.2a</td>
</tr>
<tr>
<td>AL, %</td>
<td>15 ± 11</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>Ti, s</td>
<td>0.160 ± 0.034</td>
<td>0.165 ± 0.037</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>9 ± 6</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>Pi, mmHg</td>
<td>118 ± 21</td>
<td>137 ± 18b</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68 ± 10</td>
<td>72 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SD. SBP, systolic blood pressure; Tp, time to peak pressure; Ts, time to end of systole; As, systolic pressure time integral; Ai, diastolic pressure time integral; SBI, subendocardial viability index; AI, augmentation index; Ti, time to inflection point; AP, augmentation pressure; Pi, pressure at inflection point; DBP, diastolic blood pressure. aP < 0.01, bP < 0.001 for difference between men and women.

Table 5. Relationships between transfer function-derived and measured aortic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GATF</th>
<th>GNTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>128a</td>
<td>135c,d</td>
</tr>
<tr>
<td>Tp, s</td>
<td>0.246b</td>
<td>0.231d</td>
</tr>
<tr>
<td>Ts, s</td>
<td>0.347c</td>
<td>0.344c</td>
</tr>
<tr>
<td>As, mmHg/s</td>
<td>36.3</td>
<td>38.6</td>
</tr>
<tr>
<td>SBI</td>
<td>43.3c</td>
<td>46.5c</td>
</tr>
<tr>
<td>AL, %</td>
<td>19.3b</td>
<td>14.5d</td>
</tr>
<tr>
<td>Ti, s</td>
<td>0.147b</td>
<td>0.10</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>113c</td>
<td>114c</td>
</tr>
<tr>
<td>Pi, mmHg</td>
<td>61c</td>
<td>61c</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>97c</td>
<td>97c</td>
</tr>
</tbody>
</table>

eTF1, ensemble-averaged transfer function (TF) method 1; GATF, gender-appropriate TF method 1; GNTF, gender-inappropriate TF method 1; r, correlation coefficients of derived with measured parameters. aP < 0.05, bP < 0.01, cP < 0.001, difference between derived and measured mean values. dP < 0.05, difference from eTF1-derived mean values or correlation coefficients.

*Correlation was significantly better with the generalized TF than the GNTF for Ts, As, SBI, and SBI. Correlation coefficients for these parameters were also better with the gender-appropriate than the GNTF, but reached statistical significance only for As, SBI, and SBI.

Comparison of the regression slopes for the relationships between GATF derived with measured aortic parameters with those for the relationships between the generalized TF-derived and measured aortic parameters revealed significant differences for Tp and Pi only. The GATF produced a regression slope significantly nearer to unity for Pi. Comparison of the regression slopes for the relationships between GNTF derived with measured aortic parameters with those for the relationships between the generalized TF derived and measured aortic parameters revealed significant differences for As, SBI, and Tp, with those for the generalized TF being closer to unity.

Subgroup analysis. Matching the female group with a group of males by measured SBP yielded groups with values derived by the generalized and GATFs, with the exception of DBP, for which the generalized TF was significantly better, the GATF was statistically significantly closer to the measured (AP and Pi), or the differences were less than the limits of measurement (SBP and Tp). There were significant differences between the correlation coefficients for the relationship between the measured and derived waveform parameters for the generalized and GATFs for both Ad and As, with the generalized TF being significantly stronger.

There were significant differences in derived mean values for all parameters when the generalized TF was compared with the GNTF. With the exception of AP and Pi, the mean differences were smaller with the generalized than the GNTF. For AP and Pi there were no significant differences in the correlation coefficients, and the mean differences from measured were still smaller with the GATF, although not reaching statistical significance. Neither the presence nor the burden of coronary artery disease was significant when included as covariates.
no difference in any measured central waveform parameters with gender. Analysis of the findings in these groups confirmed that significant differences remained between waveform parameters derived by the use of generalized and gender-specific TFs. The GATF1 yielded results significantly closer to the measured than the generalized eTF1 for SBP, DBP, Aa, and Pi, and GATF2 yielded results significantly closer to the measured than the generalized eTF2 for SBP, Ti, Tp, AP, and Pi.

**DISCUSSION**

The central pulse wave characteristics are determined both by a forward traveling pulse wave together with a reflected wave. The timing of the reflected wave is dependent on the pulse wave velocity, which is dependent on arterial mechanical properties, together with the distance to the putative peripheral reflection sites, both of which may be influenced by gender (3, 10, 17, 20, 30).

We have demonstrated differences in measured central aortic waveform parameters between men and women. As with other studies (10, 13), we have demonstrated longer $T_p$, or left ventricular ejection time, and lower SVI in women. The lower SVI in women, thought to represent an adverse relationship between left ventricular workload and coronary blood flow, has been proposed to contribute to the relatively poorer outcomes in women with cardiovascular disease (13).

Although there is some discrepancy in the literature, there appear to be differences in the mechanical properties of arteries between men and women (2–4, 10–13, 12–25, 26, 28, 31, 34, 38, 39). The discrepancies are probably in part due to different study populations, the use of different methods of assessment, assessment of different parts of the arterial tree, and consideration of different covariables during statistical analysis. The differences between men and women in both mechanical properties and arterial geometry may also be influenced by age, and menopausal status in women (15, 17, 20, 24, 28, 30, 32, 34–36). Changes in these physical properties will be responsible for changes in pulse wave velocity, with differences in different parts of the arterial tree resulting in different regional changes in pulse wave velocity which may differ between men and women (17, 20, 30). The changes in geometry may also

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### Table 6. Relationships between transfer function-derived and measured aortic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measured Mean</th>
<th>$eTF_2$ Mean</th>
<th>$eTF_2$ r</th>
<th>$GATF_2$ Mean</th>
<th>$GATF_2$ r</th>
<th>$GNTF_2$ Mean</th>
<th>$GNTF_2$ r</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>129</td>
<td>130</td>
<td>0.95c</td>
<td>130d</td>
<td>0.95c</td>
<td>132d</td>
<td>0.95c</td>
</tr>
<tr>
<td>$T_p$, s</td>
<td>0.226</td>
<td>0.247b</td>
<td>0.70a</td>
<td>0.231a-d</td>
<td>0.59c</td>
<td>0.221c-d</td>
<td>0.50c</td>
</tr>
<tr>
<td>$T_s$, s</td>
<td>0.310</td>
<td>0.346c</td>
<td>0.53c</td>
<td>0.344b</td>
<td>0.32b</td>
<td>0.436c-d</td>
<td>0.16d</td>
</tr>
<tr>
<td>Aa, mmHg</td>
<td>34.5</td>
<td>37.8c</td>
<td>0.85c</td>
<td>38.2b</td>
<td>0.67c-d</td>
<td>46.8d</td>
<td>0.41d</td>
</tr>
<tr>
<td>$A_s$, mmHg</td>
<td>52.0</td>
<td>46.2c</td>
<td>0.96c</td>
<td>45.8d</td>
<td>0.89d</td>
<td>37.5c-d</td>
<td>0.65d</td>
</tr>
<tr>
<td>SVI</td>
<td>1.54</td>
<td>1.24c</td>
<td>0.79c</td>
<td>1.26a</td>
<td>0.70c</td>
<td>0.897c-d</td>
<td>0.22-d-c</td>
</tr>
<tr>
<td>AI, %</td>
<td>14.4</td>
<td>18.6b</td>
<td>0.18</td>
<td>14.1d</td>
<td>0.18</td>
<td>15.4d</td>
<td>0.17</td>
</tr>
<tr>
<td>$T_v$, s</td>
<td>0.161</td>
<td>0.151</td>
<td>0.13</td>
<td>0.154</td>
<td>0.15</td>
<td>0.154a</td>
<td>0.37b</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>8.8</td>
<td>11.6c</td>
<td>0.29a</td>
<td>8.4d</td>
<td>0.21</td>
<td>9.8d</td>
<td>0.42</td>
</tr>
<tr>
<td>Pi, mmHg</td>
<td>122</td>
<td>116c</td>
<td>0.92c</td>
<td>122d</td>
<td>0.93c</td>
<td>123d</td>
<td>0.92c</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>69</td>
<td>69b</td>
<td>0.97c</td>
<td>72-d-d</td>
<td>0.98c</td>
<td>74-d-d</td>
<td>0.96c</td>
</tr>
</tbody>
</table>

$eTF_2$, $eTF$ method 2; $GATF_2$, GATF method 2; $GNTF_2$, GNTF method 2. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for difference between derived and measured mean values. *$P < 0.05$ for difference from $eTF_2$-derived mean values or correlation coefficients. *$P < 0.05$ for difference from $GATF_2$-derived correlation coefficients.
result in changes in the distance to peripheral reflection sites.

All of these factors may contribute to important differences in the relationship between peripheral and central pulse wave characteristics between men and women, which may necessitate the use of gender-appropriate arterial TFs if this technique is to be of value.

This is the first study to address the merits of the use of gender-appropriate arterial TFs. We have demonstrated, with the exception of DBP for TFs derived by method 2, that a GATF yields similar, or, for several parameters, better results for the derivation of central waveform characteristics than a generalized TF. In addition, regression slopes of unity are desirable because this will result in similar mean error across the physiological range encountered, rather than an overestimate at one end and underestimate at the other end of the scale; regression slopes with the GATFs were closer to unity than with the generalized TFs. The GATF and GNTF values were derived by averaging fewer individual TFs for the 17 women and 61 men than by averaging 78 for the generalized TFs. The averaging of a larger number of TFs may reduce the residual error and therefore increase the power to demonstrate significant differences in correlation between the two groups. Significant differences persist between different TFs when blood pressure-matched groups are considered, and the presence or burden of coronary artery disease has little, if any, effect on the findings.

We have not found in our study population the previously described association between AI and either height or heart rate (20, 29, 37). This may not be surprising. The studies demonstrating these associations have been noninvasive studies, whereas our study population was selected on the basis of a clinical indication for invasive coronary artery studies or intervention. Our population may therefore have effectively been selected on the basis of their central waveform characteristics, thus obscuring any association between waveform characteristics and demographic features. In addition, in our population, an increased heart rate may reflect impaired cardiac function, which would be expected to occur in those with the most severe cardiovascular disease and the most impaired arterial mechanical properties. Hence, the elevation in AI related to arterial mechanical properties might have obscured any inverse relationship with heart rate on a group basis. Such a relationship would still be expected to occur in the individual.

Study limitations. There are potential limitations in this study due to the possible loss of high-frequency data from the invasive arterial pressures measured by a fluid-filled catheter system rather than an intravascular micromanometer. However, observations in our own laboratory (Fig. 2) suggest that the frequency response characteristics of fluid-filled catheter systems and an intravascular micromanometer may be very similar in the clinical setting over the required frequency range. Although there is clearly more variation at the top end of the frequency response, which may affect individual waveform parameters predominantly dependent on high-frequency components (in particular AI), the fluid-filled catheter system appears overall to have an adequate response for the purpose of this study, and its use is unlikely to have significantly influenced the reported results.

Loss of high-frequency data from the peripheral arterial waveforms may be an inherent problem of the technique of tonometry (27). The loss of high-frequency data would be expected to particularly affect AI, which was so poorly reproduced on the derived central aortic waveforms as to bear no statistically significant relationship to that of the measured waveform and was therefore not analyzed further in this study. This is not inconsistent with studies (7, 9) that have reported mean differences between measured and derived waveforms, but have not addressed the degree of correlation between the two.

Despite being substantially larger than any previously published study, the numbers, particularly of women, remain small, which limits the statistical power to demonstrate significant differences between different TFs for any but the most closely correlated parameters. In addition to the small number, the study has not taken account of the menopausal status of the women. This may be important because there is evidence to suggest that changes occur in arterial mechanical properties that are specifically associated with menopause (15, 24, 32, 36). This may result in the need for different TFs for pre- and postmenopausal women.

As with previous studies (7, 14, 19), this study does not permit any comment on the generalizability of these TFs to other subject groups because the TFs were applied only to the radial data that were used in their derivation.

In summary, we have demonstrated significant differences between men and women in a number of central arterial waveform characteristics. We have compared the central waveform parameters derived by the use of gender-appropriate arterial TFs with those derived by the use of generalized TFs and demonstrated statistically significant differences between them, with, in most cases, GATFs yielding results more closely related to the measured parameters. Generalized arterial TFs may not be universally applicable to both genders across all waveform parameters of interest, with GATFs potentially being more appropriate.

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