Four-Limb Blood Pressure Measurement
A Research Tool Looking for Clinical Use

Christopher E. Clark

See related article, pp 1155–1160

References to the difference in blood pressure (BP) measurements between arms can be traced back through more than a century of reports. International BP guidelines consistently recommend that BP is measured in both arms at initial assessment, and that accurate measurement of BP is important in both diagnosis and management. An interarm difference has been implicated in delay in the diagnosis of hypertension and is associated with a higher prevalence of poor control in hypertension. Patients with systolic or diastolic interarm differences are encountered in cohorts with hypertension, diabetes mellitus, chronic kidney disease, or peripheral arterial disease. Findings are largely derived from white European populations, but differences are also reported in African and Far-Eastern cohorts.

A reduced ankle-brachial index is a proven predictor of increased all-cause mortality, and fatal or nonfatal cardiovascular events. A systolic interarm difference is also associated with peripheral arterial disease, cerebrovascular disease, and increased cardiovascular and all-cause mortality. The data supporting the interarm difference findings are largely derived from populations at elevated cardiovascular risk and modest sample sizes, therefore the linked cohort study from Sheng et al is to be welcomed as a representative community–based study.

Sheng et al’s study enrolled >3000 participants aged ≥60 years and followed them for a median of 4 years. At recruitment, BP was measured simultaneously in all 4 limbs using a dedicated device (Omron Colin VP-1000), allowing estimation of ankle-brachial index, interarm and interankle BP differences. Diagnosis was based on a single set of simultaneous measurements, whereas repeated simultaneous measurements are conventionally recommended to avoid overestimation of BP differences. The 4-limb technique has not been assessed against this gold standard; nevertheless, the prevalence figures for interarm differences reported by studies using it seem consistent with the best previous estimates.

After adjustment for covariates, interarm differences remained a significant predictor of total but not cardiovascular mortality. We and others have found a trend to higher hazard ratios for cardiovascular than that for total mortality. The reason for this difference is not clear, but there are no other published survival series from Asian populations, so ethnicity may be relevant. We have previously presented a meta-analysis of published hazard ratios for all-cause mortality. Updating this with data from the current study and our new analysis of a large (n=3350) Scottish cohort free of cardiovascular disease at recruitment followed for 8.4 years shows hazard ratios consistent with our previous findings of 1.4 (1.0–1.9) for cardiovascular mortality and 1.6 (1.2–2.1) for all-cause mortality, based on pooled data for almost 8500 subjects (Figure).

Absolute BP was not predictive of mortality. We have made similar observations in our cohort studies and found the interarm difference enhanced risk prediction over the Framingham score alone. This emphasizes the importance of identifying subclinical atherosclerosis by other means, such as these interarterial indices to refine calculated vascular risks from intermediate to lower or higher risk categories. The interankle pressure difference seems to have an additional predictive value to ankle-brachial and interarm differences. No previous studies have examined interankle BP differences, and the value of such an index will require further study, because its derivation requires the use of a 4-limb machine that must still be regarded as a research tool. Conversely, interarm difference can be cheaply and easily detected with a pair of standard sphygmomanometers as easily as with more sophisticated and expensive devices.

Differences in BPs between arms are assumed to be attributable to peripheral arterial disease, but we only have direct radiological evidence to support this from a subset of patients with established cardiovascular disease and large (≥35 mm Hg) differences in BPs between arms. Arterial stiffness is associated with increased variability of BP (a potential confounder of interarm difference, especially without repeated measures). Su et al have recently shown an association of a systolic interarm difference ≥10 mm Hg with elevated brachial-ankle pulse wave velocity, suggesting increased arterial stiffness as the cause, and it may be that all indices based on a difference in BPs between limbs (ankle-brachial, interarm, and interankle) are associated with increased mortality by representing measures of generalized arterial stiffness or arteriosclerosis. Further imaging work in unselected populations and assessment of markers of arterial stiffness is needed to fully explain the pathogenesis of differences and their relationship to increased mortality. An understanding of the underlying pathology is a prerequisite to any intervention. Presence of an interarm difference

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predicts increased mortality, and is independently associated with higher prevalences of peripheral arterial disease, increased left ventricular mass, and arterial stiffness. Antiplatelet and statin therapy are of proven benefit in secondary prevention of cardiovascular events, but not in primary prevention or in asymptomatic peripheral arterial disease. Risk stratification with interarm and interankle pressures has been demonstrated, but until intervention studies based on these techniques exist, we have no evidence to guide drug therapy. Lifestyle interventions, such as smoking, dietary, and exercise advice, may seem sensible given what we already know, but without studies and cost-effectiveness data even this statement goes beyond the current evidence base. Therefore, although the demonstration of the association of an interankle BP difference with mortality is novel, and may hint at better noninvasive assessment of generalized arterial disease, its clinical applications seem limited until adequately powered intervention studies are undertaken. This is where future research efforts should concentrate.

Disclosures
None.

References

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hazard Ratio Random effects [95% CI]</th>
<th>Hazard Ratio [95% CI]</th>
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<tbody>
<tr>
<td><strong>Simultaneous measurements</strong></td>
<td></td>
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<tr>
<td>Sheng et al 2013</td>
<td>2.47 [1.24, 4.92]</td>
<td></td>
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<tr>
<td>Aboyans 2007 (cohort A)</td>
<td>1.38 [0.84, 2.25]</td>
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<tr>
<td>Aboyans 2007 (cohort C)</td>
<td>1.28 [0.87, 1.90]</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td><strong>1.50 [1.07, 2.09]</strong></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.36 (P = 0.02)</td>
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<tr>
<th>Sequential measurements</th>
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<tr>
<td>Clark 2012</td>
<td>3.10 [1.60, 6.00]</td>
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<tr>
<td>Aboyans 2007 (cohort B)</td>
<td>1.77 [1.10, 2.82]</td>
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<tr>
<td>Clark 2013</td>
<td>1.08 [0.62, 1.43]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td><strong>1.70 [0.98, 2.93]</strong></td>
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<tr>
<td>Test for overall effect: Z = 1.89 (P = 0.06)</td>
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| Total (95% CI) | **1.58 [1.18, 2.13]** | |
| Test for overall effect: Z = 3.05 (P = 0.002) | | |
| Test for subgroup differences: Ch² = 0.14 (P = 0.70), I² = 0% | | |

Figure. Meta-analysis of published hazard ratios for all-cause mortality with and without a systolic interarm difference (sIAD) ≥15 mmHg. CI indicates confidence interval.

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