A Comparison of Colour Duplex Ultrasonography, Papaverine Testing and Common Femoral Doppler Waveform Analysis for Assessment of the Aortoiliac Arteries

Y. J. Sensier¹, A. J. Thrush¹, I. Loftus², D. H. Evans¹ and N. J. M. London*²

Departments of ¹Medical Physics and ²Vascular Surgery, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX, U.K.

Objective: to study the “accuracy” of aortoiliac colour duplex ultrasonography.

Design: prospective study.

Setting: vascular laboratory, University Hospital.

Methods: a total of 25 aortoiliac stenoses were studied in 23 patients. For each iliac segment, colour duplex ultrasound, papaverine testing, hyperaemic common femoral Doppler waveform analysis and hyperaemic testing using a thigh pressure cuff were performed. A velocity ratio of two was used to indicate a significant 50% diameter-reducing stenosis, but the velocity differences across stenoses as well as various characteristics of the hyperaemic common femoral waveform were also studied. Retrospective receiver–operator characteristics and Kappa values were used for analysis.

Results: the Kappa agreement between ultrasonography and papaverine testing was 0.12 using peak systolic velocity ratios and 0.8 using hyperaemic peak systolic velocity differences. Hyperaemic common femoral pulsatility (PI) and resistance index (RI) both gained a Kappa level of 0.60. The reactive hyperaemia produced by a thigh cuff was more pronounced than that produced by papaverine.

Conclusion: although the velocity ratio did not appear to perform well against the papaverine test, its apparent over-sensitivity calls into question the sensitivity of papaverine testing itself. The hyperaemic velocity difference at the stenosis or the hyperaemic PI or RI at common femoral level appear useful, non-invasive indicators of significant aortoiliac arterial disease.

Key Words: Duplex scanning; Doppler; Arterial disease; Aortoiliac disease.

Introduction

Colour duplex ultrasonography is now widely used to image the femoropopliteal segment.¹⁻¹¹ However, its value in the aortoiliac segment remains controversial because it can be difficult to obtain an adequate angle of insonation¹¹ and because of patient obesity or bowel gas. For these reasons, relatively few authors propose aortoiliac ultrasonography as the sole imaging modality prior to endovascular or surgical treatment.²⁻⁴⁻¹⁵ Many authors consider arteriography to be the “gold standard” for imaging the aortoiliac segment.¹,²,⁶,¹⁷⁻¹⁹ However, arteriography tends to underestimate aortoiliac disease²⁰⁻²⁴ and for this reason papaverine testing is considered to be the real “gold standard”. Papaverine testing offers a quantitative technique and, when performed under hyperaemic conditions, enables milder forms of disease to be exposed. The aims of this study were to compare colour duplex with papaverine testing²⁵ and, in particular, to investigate whether scanning under hyperaemic conditions improved the sensitivity of duplex.

Given the relative ease with which severely diseased or completely “disease-free” iliac arteries can be distinguished,²² it was decided to focus on moderate aortoiliac lesions. Previous studies have shown that an angiographic 50% diameter reduction correlates to a two-fold velocity increase on duplex, and stenoses with a velocity ratio around two were therefore selected.⁵,¹⁷⁻¹⁹,₂⁶,₂⁷

In order to compare a hyperaemic ultrasound assessment with papaverine testing, consideration was given to determining velocity ratios under hyperaemic conditions.²⁸ Because velocity ratios do not change with increased flow,²⁸ the hyperaemic peak systolic velocity difference across the stenosis was chosen as an alternative.²⁶,³⁰,³¹ However, it proved too difficult to obtain reproducible results in the short period of optimum hyperaemia response available and, as a
compromise, the velocity change recorded by a continuous wave Doppler ultrasound probe at common femoral level during hyperaemia was used to predict velocity changes at the stenosis site.

Common femoral Doppler waveform analysis is a well-researched technique for non-invasive aortoiliac assessment and several studies have analysed the waveform during a hyperaemic response. Various features from the hyperaemic common femoral Doppler waveforms were extracted and compared to papaverine testing.

In an attempt to develop a totally non-invasive method of assessing the aortoiliac arteries, hyperaemia induced by an inflated thigh cuff and by papaverine injection were compared in order to assess the utility of an entirely non-invasive assessment.

Materials and Methods

Patients found to have iliac disease associated with at least a 1.5 increase in velocity during routine ultrasound were considered for inclusion. Selection was biased towards moderate disease.

For each aortoiliac stenosis under study, ultrasound and a papaverine test, with continuous monitoring of the common femoral Doppler waveform were performed, followed by a secondary hyperaemic test using the thigh cuff.

Following previous work, a cut-off velocity ratio of two-fold was used to indicate a significant 50% diameter-reducing stenosis. Retrospective receiver-operator characteristics (ROC) analysis was used to determine the optimum cut-off points both for the hyperaemic velocity difference and for the various features of the common femoral waveforms. The Kappa statistic, sensitivity and specificity values were used as a measure of agreement. Correlation coefficients were used to compare the reactive hyperaemia created by the thigh cuff and papaverine injection.

Ultrasonography

Aortoiliac ultrasound scans were performed by a single operator (YS) using a Diasonics Spectra System (Diasonics, Bedford, U.K.) and a 3.5-MHz curved array probe. Proximal and stenotic peak systolic velocity (PSV) were used to calculate the PSV ratio and PSV difference. Proximal readings were taken from the nearest disease-free segment, PSV were taken from the site of true maximum velocity. Hyperaemic values were calculated using the maximum percentage change in PSV observed at common femoral level, during papaverine-induced hyperaemia.

Papaverine testing

Radial (RA) and common femoral arteries (CFA) were cannulated, and pressures monitored via a two-channel chart recorder system (Manufacturer: Gould) before and after a 20-mg dose of papaverine hydrochloride. Maximum effects occurred typically 10–15 s after papaverine injection and the percentage pressure gradient was calculated as follows:

\[ \text{CFA pressure drop} - \text{RA pressure drop} / \text{CFA resting pressure} \]

Cut-off points ranging from 15 to 18% have been suggested to indicate a significant, i.e. 50%, diameter-reducing lesion of the aortoiliac tract during papaverine testing. In this study a threshold of 18% was chosen, as this appeared most representative of the literature.

Recording and analysis of common femoral Doppler waveforms

The purpose of monitoring common femoral Doppler waveforms was two-fold. First, to convert the velocity measurements taken from the stenosis site at rest into equivalent hyperaemic values, and second, to analyse the characteristics of the hyperaemic common femoral Doppler waveform in relation to the significance of upstream disease.

A 4-MHz continuous wave Doppler probe (Vasaflo) was positioned proximal to the common femoral artery cannula and tilted towards the head at an angle of approximately 60°. Doppler signals and the intrarterial pressure measurements were recorded continuously onto digital audiotape (DAT). This allowed post-papaverine hyperaemia to be accurately compared with common femoral Doppler waveforms. Recordings began with the patient at rest and were maintained throughout hyperaemia until pressure readings had returned to “at rest” levels.

Common femoral Doppler waveform analysis

A maximum of 10 waveforms were selected for averaging from each patient during the period of maximum hyperaemic effect, typically 15 s post-papaverine injection. This created a normalised
Aortoiliac Ultrasonography

Fig. 1. Common femoral Doppler wave-form analysis. t = duration of systolic acceleration; c = end-diastolic velocity; pulsatility index (PI) = (a–b)/mean; resistance index (RI) = (a–c)/a.

Sample mean record (SMR) of 6.25 ms resolution and 700 ms duration, from which various calculations were drawn. This included the percentage change in PSV (for adjusting the resting velocity measurements around the stenosis) and waveform characteristics; namely, systolic acceleration duration, end-diastolic velocity, pulsatility and resistance index (Fig. 1). 

Reactive hyperaemia using a pressure cuff

Following a complete return to “normal” pressure levels after papaverine testing, hyperaemia was further induced using an inflated pressure cuff around the top of the thigh of the affected limb. An inflation pressure 20 mmHg above systemic systolic pressure (obtained from the radial line measurement) was used and, if tolerated by the patient, sustained for a period of 3 min. Following deflation of the pressure cuff, percentage pressure drops after reactive hyperaemia were calculated in the same way as for post-papaverine measurements above.

Results

Twenty-three patients (18 males, five females), of median (range) age of 69 (57–82) years were studied. Two patients had bilateral examinations. Fourteen lesions were in the common iliac, 11 in the external iliac artery, and the majority (52%) producing velocity ratios of between 1.5- and 2.5-fold.

Ultrasoundography and papaverine studies were completed successfully for all stenoses. In three cases, papaverine injection produced a <100% change in common femoral velocity. The thigh cuff produced a >100% change in CFA velocity in all but one patient. Although tolerated well, in seven instances the thigh cuff produced such excessive skin movement on deflation that intra-arterial readings from the common femoral line were lost. This left 18 cases for comparison. Doppler recordings from the CFA during hyperaemia proved too noisy for three patients, leaving a total of 22 for analysis.

Velocity ratio

Figure 2 compares post-papaverine pressure drops with the greatest detectable velocity ratio. Stenoses associated with a velocity ratio of >4 were all confirmed as being haemodynamically significant. Fifteen iliac stenoses associated with a ≥ two-fold velocity increase failed to produce significant post-papaverine pressure drops. Consequently, despite a sensitivity of 100%, ultrasonography proved specific in only 21% of cases (Table 1).

Velocity difference during hyperaemia

The absolute velocity difference during hyperaemia predicted significant post-papaverine pressure drops with a sensitivity of 100% and a specificity of 89%, using a cut-off threshold of 5.7 m/s (ROC analysis). The corresponding Kappa agreement level (95% CI) demonstrated substantial agreement at 0.80 (0.54–1.0) (Table 1).

Common femoral Doppler waveform analysis

Pulsatility (PI) and resistance indices (RI) of the common femoral Doppler waveform, post-papaverine,
Table 1. The ability of the resting velocity ratio and hyperaemic velocity difference, to identify significant aortoiliac stenoses.

<table>
<thead>
<tr>
<th>Velocity parameter at the stenosis site</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Kappa level (confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity ratio (at rest)</td>
<td>≥ 2.0</td>
<td>100</td>
<td>21</td>
<td>0.12 (0.00–0.40)</td>
</tr>
<tr>
<td>Velocity difference (hyperaemic)</td>
<td>≥ 5.7 m/s</td>
<td>100</td>
<td>89</td>
<td>0.80 (0.54–1.00)</td>
</tr>
</tbody>
</table>

Table 2. The ability of parameters from the hyperaemic common femoral waveforms to identify significant aortoiliac disease.

<table>
<thead>
<tr>
<th>Hyperaemic CF waveform parameter</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Kappa level (confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsatility index</td>
<td>≤ 1.3</td>
<td>100</td>
<td>76</td>
<td>0.60 (0.24–0.96)</td>
</tr>
<tr>
<td>Resistance index</td>
<td>≤ 0.6</td>
<td>100</td>
<td>76</td>
<td>0.60 (0.24–0.96)</td>
</tr>
<tr>
<td>End-diastolic velocity</td>
<td>≥ 38 m/s</td>
<td>60</td>
<td>71</td>
<td>0.26 (0.00–0.71)</td>
</tr>
<tr>
<td>Acceleration duration</td>
<td>≥ 23 ms</td>
<td>60</td>
<td>65</td>
<td>0.20 (0.00–0.65)</td>
</tr>
</tbody>
</table>

CF: common femoral.

Proved the most useful. Using a threshold of 1.3 for PI and a 0.6 RI (ROC analysis), the sensitivity and specificity of both parameters were 100% and 76% respectively, when compared to post-papaverine pressure drops (Table 2). A Kappa value of 0.60 (0.24–0.96) was achieved for both indices.

**Reactive hyperaemia using a pressure cuff**

Hyperaemia induced by the thigh cuff was more pronounced than that produced by papaverine. The resulting percentage pressure is contrasted in Figure 3. Only a moderate degree of correlation was observed ($r = 0.65$, $p < 0.01$, $n = 18$, two-tailed test) with papaverine testing.

**Discussion**

The majority of studies examining the aortoiliac segment compare ultrasonography with angiography and relatively few compare ultrasonography with hyperaemic pressure studies. Those who have, report that a velocity ratio cut-off between 2 and 3 produces a level of aortoiliac ultrasonography sensitivity between 62% and 76%.

Although the sensitivity of duplex in the present study was 100%, the specificity was only 21%. Although it would be possible to improve the specificity by changing the velocity ratio threshold to 4, there is no logical reason why the velocity ratio threshold equating to an angiographic 50% diameter reduction should be 4 in the aortoiliac segment and 2 in other arterial segments. It is appreciated that ultrasound and papaverine testing are two quite different tests; ultrasonography concerning single-site lesions and papaverine testing the net flow over an entire segment. However, our results beg the question as to whether duplex is too sensitive or whether papaverine testing is too insensitive.

Although papaverine testing is considered a “gold standard”, a range of techniques and criteria exists among the literature. We did not use a “pull-through” technique to measure the hyperaemic pressure drop, because a previous study has shown that the radiofemoral technique is less prone to error. The criteria used for papaverine testing have ranged from 50 mg of papaverine and a pressure drop of 10 mmHg to 30 mg and a post-papaverine pressure gradient of 15%. In addition, the original studies compared papaverine testing with angiography, a method that we now know can miss iliac lesions.

Although papaverine testing is not susceptible to subjectivity, to a certain extent its accuracy will therefore reflect that of arteriography. In particular, the difficulty in distinguishing aortoiliac stenoses in the 50–75% range angiographically is said to be reflected by the variable pressure gradients and extent of thresholds applied to this subgroup. Interestingly, in one recent study of...
153 aortoiliac segments only 63% of patients with an abnormal papaverine test required a subsequent operative or endovascular procedure, resulting in only moderate correlation between papaverine testing and the treatment performed. As Udoff et al. state, the level of pressure reduction at which surgery is required will only be obtained through comparison to surgical outcome.

Iliac arteries are often difficult to visualise on ultrasound due to obesity and bowel gas. Klean-Prep bowel preparation may overcome some of these difficulties. However, alternative non-invasive techniques, such as hyperaemic common femoral PI or RI, may be more appropriate.

The difference in peak systolic velocity across the stenosis during hyperaemia produced a sensitivity of 100%, and a specificity of 89%. Elsman et al. and Currie et al. produced sensitivities and specificities of around 100% and 82% respectively, but used thresholds (Elsman et al., 1.6 m/s and Currie et al., 2.4 m/s) at least half that found to be optimum in the current study (5.7 m/s). This is presumably due to differences in techniques. Currie et al. performed an in vitro study, whereas Elsman et al. used a bicycle ergometer. Both assessed hyperaemic stenotic velocities directly as opposed to deriving them from common femoral readings. Interestingly, Elsman et al. also reported that the optimum significance threshold remained the same between studies at rest and those undertaken during hyperaemia. Although the velocity difference appears a valuable parameter, it lacks the comparative qualities of a ratio, due to its sensitivity to flow, which some remark may require flow-rate compensation.

This may prevent it from implementation as a first-line approach.

Previous assessments of hyperaemic common femoral Doppler waveforms are relatively scarce and only two used direct, hyperaemic pressure testing as their gold standard. Of these two studies, both found that a combination of indices produced the best results. Currie et al. found that a combination of the post-hyperaemia EDV and PI. at 70 and 40 s, respectively, produced sensitivities and specificities of >85%. Asten et al. found combining acceleration and deceleration times with the resistance index during hyperaemia brought the best results, though it produced a sensitivity of only 67%. In the present study, despite the emphasis on moderate disease, significantly diseased aortoiliac segments were detected with an accuracy of 82%, and, more importantly, a sensitivity of 100% using either PI or RI. Previous studies on common femoral Doppler waveforms at rest have identified the pulsatility index (PI) as the most discriminating, though some authors recommend a "grey area" of thresholds ranging from 3 to 5.5. During the current, hyperaemic study, a pulsatility index of ≤1.3 or a resistance index of ≤0.6, proved optimum cut-off points.

The remaining common femoral waveform parameters of acceleration duration and end-diastolic velocity demonstrated results comparable to simple femoral pulse palpation. The success of Currie et al. in using end-diastolic velocities during recovery from hyperaemia could not be reproduced. Likewise, the prediction of significant upstream disease using the duration of the systolic upstroke was inferior to both Asten et al., one of the few studies to examine hyperaemic waveforms, and Burnham et al. whose comparison with angiography (and an acceleration time of 144 ms, at rest) achieved a sensitivity of 82% and a specificity of 97% in predicting >75% lesions. Breslau et al. produced an accuracy of 71% (not dissimilar to the current study) in contrasting resting acceleration components with papaverine testing, though they reported a bias towards false negatives. Each concluded that the systolic element of the waveform is the most important, and prolonged accelerations are particularly indicative of upstream rather than downstream disease.

For the 18 patients successfully monitored, cuff-induced reactive hyperaemia recorded alterations in flow that were at least equal to that produced by papaverine injection and a response in pressure that was more often than not (68%) greater than that created by papaverine. If this technique is used in conjunction with either the velocity difference at the stenosis or the pulsatility at common femoral level, a potentially powerful non-invasive tool is produced. However, further investigation into its technical success rate is warranted. In the current study, common femoral Doppler recordings from 12% of patients proved too noisy to enter analysis and, although not the case here, others have reported that around 10% of patients may not tolerate the thigh cuff.

In conclusion, the findings from the present study can either be interpreted as showing that colour duplex is too sensitive or papaverine testing too insensitive for the detection of 50% diameter-reducing iliac artery lesions. Although papaverine testing is traditionally considered a 'gold standard', it was originally calibrated by comparison to angiographic studies and it is known that angiography is relatively insensitive for the detection of iliac disease. This, along with the range of criteria used and evidence suggesting that papaverine testing is unreliable, calls its role into question. With respect to colour duplex, there does...
not appear to be a reason why the velocity ratio threshold of two-fold should not be applicable across the entire lower limb, since velocity ratio relates only to changes in cross-sectional area and not to the status of flow of the segment under study. Testing against clinical or surgical outcome appears the only remaining gold standard for the aortoiliac arteries. A recent publication has addressed such a comparison17 and no significant differences were found in the reliability of ultrasound and angiographic preoperative assessments. Of the 22 patients in the arteriography group, four had unexpected findings during surgery as opposed to two patients from a total of 22 in the corresponding ultrasonography group. Despite this, angiography was recommended where ultrasound proved equivocal.

To summarise, ultrasonography certainly appears an accurate method of delineating high-grade aortoiliac arterial lesions. For borderline cases, or in circumstances where adequate angles of insonation are impossible and visualisation is difficult, assessment may benefit from the added measurements of either velocity difference across the stenosis, or common femoral pulsatility, during cuff-induced hyperaemia.

Acknowledgement

The authors also wish to thank Stefan Nydahl for his invaluable help with this study.

References


Accepted 11 January 2000