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The Ability of Non-invasive Physiological Tests to Detect Arterial Occlusions in the Lower Extremity

An ROC study with particular regard to recruitment of patients for clinical trials

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ABSTRACT

In the prerandomization phase of a clinical trial it is essential to be able to exclude, in a non-invasive way, patients who cannot be randomized into the trial. The ability of routine non-invasive physiological examinations to detect arterial occlusion in the lower extremities was investigated in 182 patients with hypercholesterolaemia. Ankle blood pressure measurement, pulse oscillometry, digital pulse plethysmography and treadmill and cycle exercise tests were performed as part of the prerandomization phase of the Probucol Quantitative Regression Swedish Trial (PQRST). The PQRST was designed to compare the antiatherosclerotic effect of two different lipid-lowering regimens. Before randomization the patients also underwent aorto-femoral arteriography, which was used as 'gold standard'. The results were analysed with ROC methodology. Ankle blood pressure measurement (ABP) and inclination time (IT), measured with digital pulse plethysmography, without significant mutual difference, were the variables, best able to detect occlusions. For ABP, the A_z-values were 0.85, 0.82 and 0.94 in detection of right-sided,

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left-sided and bilateral occlusion, respectively. The corresponding figures for IT were A_z= 0.86, 0.91 and 0.93. If a bilateral occlusion was predicted in a patient with an ABP value of $\leq$0.98, a specificity of 0.90 and a sensitivity of 0.87 were obtained, using arteriography as reference method. For IT, with a critical value of 320 ms, sensitivity and specificity were 0.83 and 0.90, respectively.

INTRODUCTION

Arteriography is still the standard method for mapping atherosclerosis in the lower extremity. In most situations, however, atherosclerosis-related non-invasive physiological methods are used for initial assessment of the degree of atherosclerosis in the lower extremities. In the prerandomization phase of a follow-up trial, designed to monitor progression/regression of peripheral atherosclerosis, and in which repeat femoral angiography is to be performed, it is desirable to be able to detect non-invasively and exclude individuals with very little atherosclerosis and those with both femoral arteries occluded. The aim of this study was to assess the ability of certain routine physiological tests, used in patients with symptoms of peripheral vascular disease (PVD), to identify occlusions in the iliac or femoral arteries, using arteriography as a reference method. Doppler ultrasound, which is now increasingly used for screening purposes in PVD patients, was introduced in clinical practice after the start of the present study, and has therefore not been included.

MATERIAL AND METHODS

During the years 1986-89, 342 patients (195 men, 147 women), underwent aorto-femoral arteriography as baseline investigation in the Probucol Quantitative Regression Swedish Trial (PQRST). PQRST, a three-year double-blind randomized study was designed to compare the anti-atherosclerotic effect of probucol + cholestyramine + diet versus that

of placebo + cholestyramine + diet. The primary end-point of the trial was change in atheroma volume, as estimated by repeat quantitative arteriographic assessment of the lumen volume of the right or left femoral artery. A detailed description of the design and main results of the trial have been reported elsewhere (12, 13, 5, 9). The patients were recruited from the Stockholm and Linköping areas and.were between 27 and 69 years old (mean age 55). All had hypercholesterolaemia with total serum cholesterol $\geq$6.88 mmol/l, LDL cholesterol $\geq$4.53 mmol/l and total triglycerides $\leq$4.53 mmol/l. 68 patients had symptoms of PVD, as defined by use of Rose's questionnaire (11), while 274 were asymptomatic. The arteriographies were performed at the Departments of Diagnostic Radiology of the University Hospitals in Linköping and Uppsala. Within 2 weeks before arteriography, the patients had undergone a set of non-invasive physiological examinations: ankle blood pressure measurement (2), pulse oscillometry (4), digital pulse plethysmography (7) and treadmill and bicycle exercise tests.
Plethysmography and blood pressure measurement were used to identify and exclude individuals with probably normal femoral arteries: patients with inclination time $\leq$13 ms or a blood pressure fall of <20 mmHg from arm to ankle bilaterally were not randomized into the trial, and thus did not undergo angiography. No corresponding criteria were used to exclude patients with severe aorto-femoral atherosclerosis, but patients who at angiography appeared to have bilateral occlusion in the lower extremities were then excluded from the trial. 160 of the patients lacked results from one or several of the physiological tests. This study was based on the remaining 182 patients who had undergone all six physiological tests.
Arteriography Standard angiographic equipment was used, with a nominal focal spot size of 0.2 x 0.2 mm. Film size was 35 x 35 cm. Aorto-femoral arteriography was carried out without premedication, via a right- or left-sided transfemoral catheterization, depending on which side was the more likely, on the basis of the physiological tests, to exhibit visible

atherosclerosis in the superficial femoral artery (SFA) - but not a complete occlusion. If the patient did have a complete occlusion somewhere in the route, common iliac artery - external iliac artery - common femoral artery - superficial femoral artery on the punctured side, another puncture was made contralaterally. In the event of bilateral occlusion, the patient was excluded from the trial. In patients without bilateral occlusion, magnification arteriography of a 20 cm segment of the superficial femoral artery was performed for quantification purposes (9).

Physiological test methods The physiological investigations were performed 1-2 weeks before the arteriography. The patients were examined after 10-15 min rest and had been instructed to refrain from smoking and drinking coffee or tea for 12 h.

1. Ankle systolic blood pressure (ABP): ABP was measured in both the right and the left ankle simultaneously with the arm pressure and expressed as an ankle/arm ratio (2). The ratio was expressed with two decimals.

2. Oscillometry Blood pressure cuffs, 5 cm wide, were applied on both legs at four levels: proximally and distally on the thigh, 50 cm apart, around the widest part of the calf and at the ankle. The cuffs were connected to an Infraton OS 3 pulse oscillograph (Siemens-Elema, Stockholm). The pulse curve was recorded during continuously falling cuff pressure on a Mingograph 34 (Siemens-Elema) and calibrated by reference to standardized test volumes. For each of the cuff levels, the maximum pulse amplitude (MPA) was measured (4). The ratio between the MPA in the distal part of the thigh and that in the proximal part of the thigh was calculated with two decimals.

3. Digital pulse plethysmography The room temperature was kept at 22-24^{o}C. Recordings were made from the big toe of each foot, after vasodilatation to a skin temperature on the toe exceeding 28^{o}C. Vasodilatation was accomplished either by heating the trunk under a heat cradle at 70^{o}C or by direct heating of the feet in water at 38^{o}C for 15 min. Occasionally, a lower skin temperature was accepted if the pulse curves were technically

satisfactory. The arterial volume pulsations of the digit were measured with a strain gauge around the toe. The pulse curves were recorded on a Mingograph 34 (Siemens-Elema, Sweden) at a paper speed of 100 mm/s, simultaneously with an ECG. From the pulse curve the inclination time (IT) and the propagation time (PT) were calculated. IT = the interval (in ms) from the intersection of the tangent to the steepest part of the ascending limb of the pulse curve with the base and the top line. PT = the interval (in ms) from the peak of the R-wave of the ECG (lead II) to the start of the upstroke of the pulse curve (7).

4. Treadmill test (TM) The patient started walking with the treadmill in the horizontal position at a speed of 1 m/s. The load was then increased at 1 min intervals, by tilting the treadmill. If the patient tolerated more than 170 W, the load was increased by accelerating the treadmill speed by 0.2 m/s every minute to avoid an uncomfortably steep slope. The test was terminated if chest or leg pain occurred, or when the patient was unable to continue for other reasons. The maximum work load, expressed in W, was noted. ECG (6 chest-head leads) was recorded continuously.

5. Cycle test (C) The patient sat on an electrically brakable ergometer cycle (EM 370, Siemens-Elema, Sweden). The same procedure for load increase and ECG recording was used as in the treadmill test. The maximum work load was determined.

Statistical methods The diagnostic performance of each physiological test with regard to arterial occlusion was determined with ROC methodology (8). For each possible value τ of a physiological variable V, measured in the right leg, the following diagnostic test was devised:

if $V \leq \tau$ the test is considered positive, i.e. a right-sided occlusion is indicated; if $V > \tau$ the test is negative.

τ is said to be the critical value of the test.

In the case of left-sided occlusion, the same test was used with V measured in the left leg. For bilateral occlusion the test is considered positive when the larger value from right and left sides is $\leq \tau$. For IT and PT the tests are instead considered positive when $V \geq \tau$. The sensitivity or true-positive fraction (TPF) of the test is set = the number of patients with a positive test and arteriographically verified occlusion, divided by the number of patients with arteriographically verified occlusion. The specificity of the test is set = 1 - the number of patients with positive test and without occlusion at arteriography divided by the number of patients without arteriographically verified occlusion. The false-positive fraction (FPF) is set = 1 - specificity. For each τ, FPF = $x(\tau)$ and TPF = $y(\tau)$ were calculated. The binormal ROC-curve fitting to the points $(x(\tau), y(\tau))$ is plotted within the unit square. The area beneath the curve, the A_z-index, is taken as a measure of the overall accuracy with which the variable V can detect an arterial occlusion. Comparison of two A_z-values was made by use of a two-tailed correlated Student's *t*-test (3), taking into account the fact that all the tests in this study were performed on the same set of patients. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

The results of the physiological tests are given in Table 1. There were 14 patients with bilateral occlusion, 9 with unilateral right-sided occlusion and 9 with unilateral left-sided occlusion. The ROC curves for the six physiological tests are shown in Fig. 1. In the detection of right-sided occlusion (Fig.1 a) the highest A_z-values were obtained for IT, SBP and MPA, with no significant differences between them (A_z= 0.86, 0.85 and 0.77 respectively). For left-sided occlusion (Fig. 1 b) IT had again the highest A_z-value = 0.91, which was significantly greater than the second highest value = 0.86 (p=0.04), obtained in the treadmill test. The corresponding

Table 1. Ankle/arm blood pressure ratio (ABP), maximum pulse amplitude (MPA) at oscillometry (ratio distal/proximal part of the thigh), propagation time (PT), inclination time (IT) and max load in treadmill (TM) and cycle (C) tests in 182 patients with hypercholesterolaemia. The results are given separately for patients with and without occlusion along the route common iliac artery - external iliac artery - common femoral artery - superficial femoral artery [mean value (min to max; standard deviation)].

1a: Right side

	No occlusion (*n*=159)	Occlusion (*n*=23)
ABP ratio:	1.09 (0.58 to 1.45, SD=0.16)	0.82 (0.53 to 1.19, SD=0.21))
MPA ratio:	0.59 (0.22 to 1.09, SD=0.15)	0.45 (0.16 to 0.68, SD=0.16
PT (ms)	293 (210 to 350, SD=26.1)	300 (250 to 350, SD=28.5)
IT (ms)	146 (90 to 280, SD=32.7)	213 (120 to 450, SD=64.2)
TM (W)	204 (40 to 540, SD=92.7)	127 (30 to 300, SD=67.2)
C (W)	158 (60 to 330, SD=56.3)	119 (40 to 220, SD=49.6)

1b: Left side

	No occlusion (*n*=159)	Occlusion (*n*=23)
ABP ratio:	1.10 (0.39 to 1.33, SD=0.15)	0.89 (0.39 to 1.30, SD=0.21)
MPA ratio:	0.59 (0.25 to 1.08, SD=0.14)	0.45 (0.18 to 1.03, SD=0.21
PT (ms)	296 (220 to 400, SD=26.1)	294 (240 to 360, SD=28.5)
IT (ms)	146 (90 to 360, SD=37.1)	210 (150 to 290, SD=42.8)
TM (W)	208 (40 to 540, SD=90.2)	99 (30 to 180, SD=49.1)
C (W)	160 (65 to 330, SD=56.2)	105 (40 to 165, SD=34.3)

values for ABP and MPA were 0.82 and 0.80. In the detection/exclusion of a bilateral occlusion (Fig. 1 c) ABP and IT had the highest A_z-values, 0.94 and 0.93 respectively, without significant difference. Both values were significantly greater (in both tests p=0.02) than the third largest (0.85) obtained for TM.

Table 2 lists for ABP and IT the sensitivity values obtained at specificity = 0.80, 0.90 and 0.95 respectively:

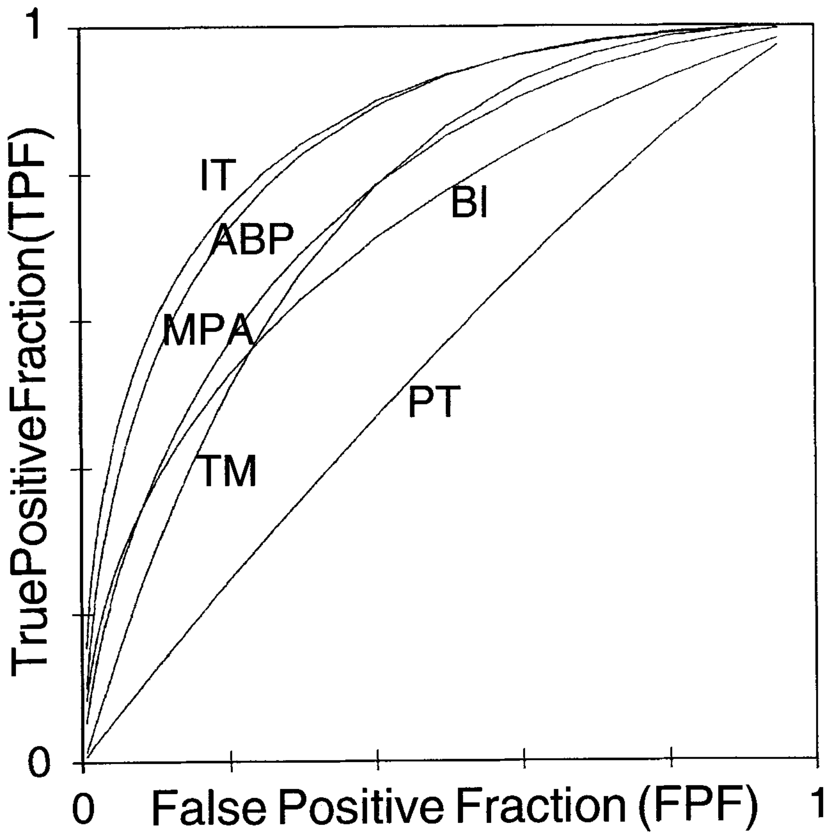
Ankle blood pressure (ABP): if a specificity of 0.80 is required, a unilateral occlusion is said to be diagnosed when the ABP ratio $\leq$0.99 (right side) or $\leq$1.00 (left side). The sensitivity is then = 0.85 (right side) and = 0.73 (left side). At higher values of specificity the sensitivity will become markedly lower. For bilateral occlusion the diagnostic value is higher: at a specificity of 0.95 the sensitivity will be 0.83 (critical value 0.91).

Inclination time (IT): if a specificity of 0.80 is required a unilateral occlusion is said to be diagnosed when inclination time (IT) $\geq$340 ms. The sensitivity is then = 0.85 (right side) and = 0.82 (left side). At higher values of specificity the sensitivity will be $\leq$0.77. For bilateral occlusion the obtained pairs of specificity-sensitivity are 0.80 to 0.88, 0.90 to 0.83 and 0.95 to 0.73 (critical values IT = 350, 320 and 300 ms respectively).

DISCUSSION

The present study refers to a situation occurring in clinical trials where quantitative femoral arteriography has to be performed at baseline without being clinically motivated. It is desirable that the baseline arteriography is preceded by a set of non-invasive examinations, arranged in such a way that patients need not undergo arteriography only to find that both femoral arteries are occluded and therefore be excluded from the trial. There is an obvious need for tests having high sensitivity with regard to arterial occlusion. On the other hand the tests also need to be highly specific: the

Fig. 1. ROC curves demonstrating the ability (A_z-value) of six different non-invasive physiological tests to detect/exclude a right-sided (1a), left-sided (1b) and bilateral (1c) arterial occlusion in the lower extremity. A_z= area under the curve.



<u>1a</u>: for IT (inclination time), ABP (systolic blood pressure, ankle/arm ratio), MPA (maximum pulse amplitude at oscillometry, ratio distal/proximal thigh), TM (treadmill test), C (cycle test) and PT (propagation time) the A_z-values were 0.86, 0.85, 0.77, 0.75, 0.72 and 0.55 respectively. The A_z-values for IT, ABP and MPA did not differ significantly, but the values for IT and ABP were significantly higher than those for TM, C and PT (two-tailed Student's *t*-test). The test values of IT, ABP , MPA and PT refer to measurement in the right side of the body.

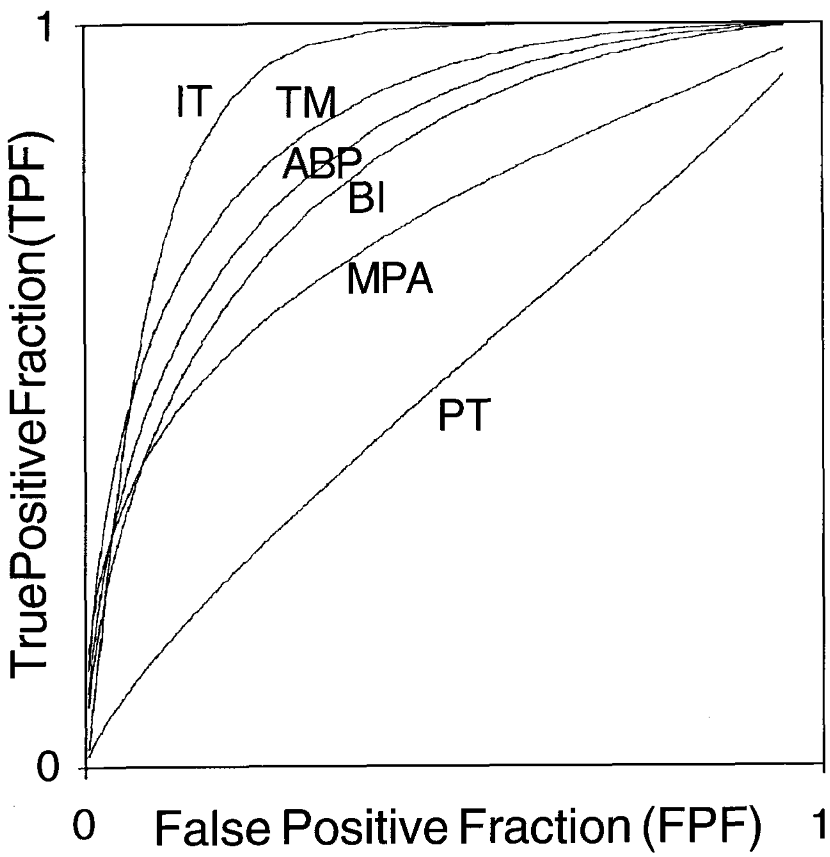


Fig. 1b (left-sided occlusion): The A_z-values for IT, TM, ABP, C, MPA and PT are 0.91, 0.86, 0.82, 0.80, 0.73 and 0.52 respectively. IT was significantly better than all other methods.

recruitment of patients into a trial is expensive, and patients who have passed the prerandomization phase must, if possible, be able to complete the trial. As indicated by the wide spread of values for several physiological variables (see Table 1) the patient material in this study covered a broad range of atherosclerotic disease. The physiological test results from the right and left body half were similar. Also, not unexpectedly, the values of ABP ratio, MPA ratio at oscillometry and max load in exercise tests were lower and IT higher in patients with occlusion than in those without. PT did

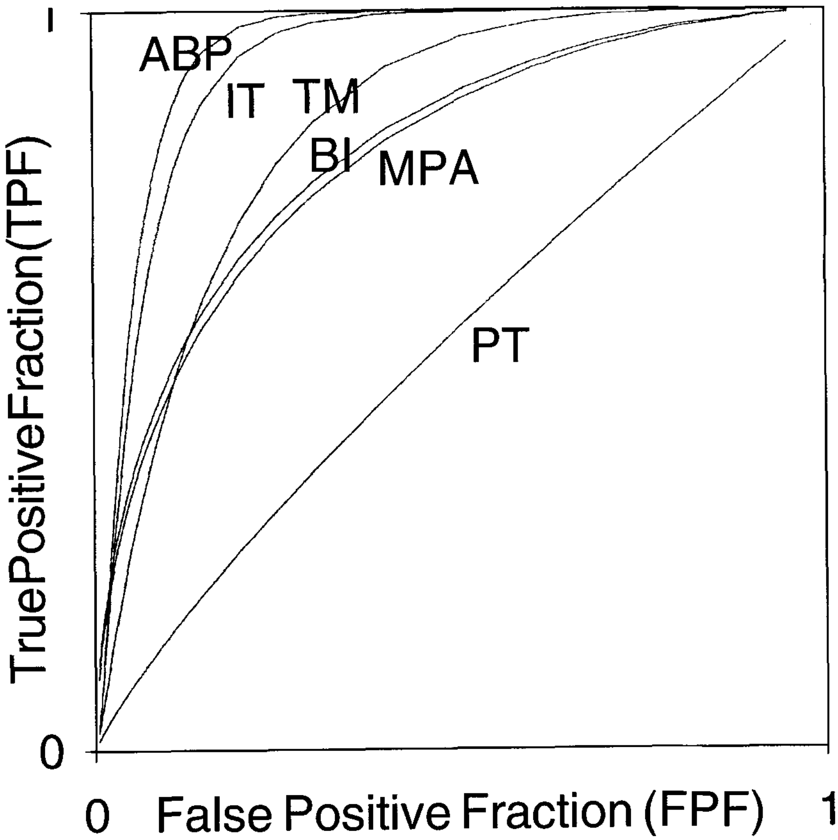


Fig. 1c (bilateral occlusion): The A_z-values for ABP, IT, TM, C, MPA and PT are 0.94, 0.93, 0.85, 0.81, 0.80 and 0.55 respectively. ABP and IT did not differ significantly, but both were significantly better than the other test methods.

not seem to correlate with occlusion.

In an earlier paper (10) we investigated the correlation between routine physiological tests and certain atherosclerosis-related variables, derived from digitized femoral angiograms. Close correlations were found between lumen volume and all tests except PT and between edge roughness and IT. In the present study, too, PT seemed to be of little value. IT and ankle-arm ratio of systolic blood pressure were the variables most capable of detecting occlusions. Patients with bilateral occlusion should, if possible, be spared invasive arteriography, as they will not be randomized into a

Table 2. Sensitivity (= 1 - false-positive fraction FPF) and critical test values at three levels of specificity (=true-positive fraction TPF) for certain diagnostic tests performed with use of ankle/arm ratio of systolic blood pressure (ABP ratio) and inclination time (IT).

Test variable	Occluded on	Spec.	Sens.	Critical value
ABP ratio	Right side	0.80	0.85	0.99
		0.90	0.38	0.86
		0.95	0.28	0.73
	Left side	0.80	0.73	1.01
		0.90	0.53	0.94
		0.95	0.34	0.84
	Bilateral	0.8C	0.92	1.04
		0.90	0.87	0.98
		0.95	0.83	0.91
IT (ms)	Right side	0.80	0.85	340
		0.90	0.76	310
		0.95	0.25	290
	Left side	0.80	0.82	340
		0.90	0.77	310
		0.95	0.72	290
	Bilateral	0.80	0.88	350
		0.90	0.83	320
		0.95	0.73	300

follow-up trial such as the PQRST. From this point of view, it is worth noting that both ABP and IT proved even more useful for detecting bilateral than unilateral occlusion, in the sense that for each fixed specificity value the corresponding sensitivity value was higher (see Table 2, Fig. 1 a-c). Both tests are directly related to aorto-femoral blood flow, while the exercise tests reflect it more indirectly. The results of the cycle test are usually linked more to the capacity of the central circulation than to the femorals; in groups with a high prevalence of ischaemic heart disease, this will be determined by the state of the coronary arteries. The oscillometric ratio distal/proximal thigh is the only one in the investigated set of variables that depends solely on the femoral artery, and does not represent occlusions situated more proximally.

With digital plethysmography alone as the discriminative test, excluding patients with an inclination time $\geq$320 ms, a specificity of 0.90 and a sensitivity of 0.83 were obtained. When using ABP measurement instead, excluding patients with an ankle/arm ratio $\leq$0.98, the corresponding figures would be specificity = 0.90 and sensitivity = 0.87. Both these designs seem to be acceptable and by combining the two, further improvement ought to be possible. The above results may also be compared with those of other diagnostic procedures. In a study concerning detection of microcalcifications in mammograms (1) a specificity of 0.92 was obtained at a sensitivity level of 0.90. The corresponding A_z-value was 0.94. In the detection of pneumothorax in chest x-rays (6) A_z-values $\geq$ 0.99 have been reported, while the corresponding values for detection of fibrosis were 0.82 to 0.95. Thus, the accuracy of ABP and IT in the detection of arterial occlusions is quite acceptable in a clinical setting.

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