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CLINICAL RESEARCH

Improving stress echocardiography accuracy for detecting left circumflex artery stenosis: A new echocardiographic sign?

Amélioration de la performance diagnostique de l'échographie de stress pour détecter une sténose circonflexe : un nouveau signe ?

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Summary
Background. — The accuracy and reproducibility of stress echocardiography (SE) for the detection of coronary artery lesions requires improvement, particularly in the left circumflex artery (LCx).
Aims. — To evaluate the feasibility and diagnostic value of a new sign: Rise of the Apical lateral wall and/or Horizontal displacement of the Apex toward the septum (''RA-HA'') in apical echocardiographic views.
Methods. — Consecutive patients with normal left ventricular function at rest, positive SE and an indication for coronary angiography were included. SEs were analysed blindly by three independent cardiologists: two seniors (S1 and S2) and one junior (J).
Results. — Of 81 patients, 58 had an exercise SE and 23 had a dobutamine SE. Significant coronary stenosis was found in 59 of 77 patients who underwent coronary angiography (76.6%). Interobserver reproducibility for the presence of RA-HA was very good between S1 and S2 (κ = 0.86), and good between S1 and J (0.67) and S2 and J (0.70). The sensitivity, specificity and positive and negative predictive values of RA-HA for the detection of significant coronary artery stenosis were, respectively, 39—41%, 83—89%, 88—92% and 29—31% for S1/S2; and 29%,

83%, 85% and 26% for J. To predict LCx stenosis (single or multivessel): 67—70%, 89%, 80—81% and 80—82% for S1/S2, respectively, and 50%, 89%, 75% and 74% for J.

Conclusion. — With a short learning curve, RA-HA is easily diagnosed with a very good inter-observer reproducibility. It has high specificity and PPV for the detection of a coronary artery stenosis, particularly in the LCx artery, during exercise or dobutamine SE.

Résumé

Objectif. — La performance diagnostique et la reproductibilité de l'échographie de stress (ES) pour détecter une lésion coronaire est imparfaite, notamment pour l'artère circonflexe. Nous avons évalué la faisabilité et la valeur diagnostique d'un nouveau signe échographique appelé « Aplha » pour ascension de la paroi latérale et/ou déplacement horizontal de l'apex vers le septum dans les incidences apicales.

Méthodes. — Quatre-vingt-un patients consécutifs avec une cinétique segmentaire VG normale au repos, une échographie de stress positive (58 en effort et 23 sous dobutamine) et une indication de coronarographie, ont été inclus. Les ES ont été relues en aveugle par trois lecteurs : deux cardiologues seniors (S1 et S2) et un junior (J). « Aplha » était défini comme une ascension du segment apico-latéral et/ou un déplacement horizontal de la pointe vers la droite en incidence apicale 3 ou 4 cavités au pic du stress. Une sténose coronaire significative a été observée chez 59 patients (81 %). La reproductibilité interobservateur pour « Aplha » était très bonne entre S1 et S2 (kappa = 0,86), et bonne entre S1 et J (kappa = 0,67) et S2 et J (kappa = 0,7). Pour la détection d'une lésion coronaire significative, les sensibilité (Se), spécificité (Sp), valeur prédictive positive (VPP) et négative (VPN) de « Aplha » étaient respectivement de 41 %, 89 %, 92 %, et 31 % pour les seniors et 29 %, 83 %, 85 % et 26 % pour J. La performance diagnostique de « Aplha » a été également évaluée pour détecter une sténose circonflexe significative (atteinte mono ou pluritronculaire). Pour S1 et S2 (pas de différence significative), Se = 70 %, Sp = 89 %, VPP = 81 %, VPN = 82 % ; pour J : Se = 50 %, Sp = 89 %, VPP = 75 %, VPN = 74 %.

Conclusion. — Après un court apprentissage, « Aplha » est facilement identifié avec une très bonne reproductibilité interobservateur. Il a une très bonne spécificité et VPP pour la détection d'une sténose coronaire, particulièrement la circonflexe, que ce soit pendant l'effort ou sous dobutamine.

Background

Stress echocardiography (SE) has become a reference method for the diagnostic and prognostic evaluation of coronary artery disease [1—3]. It has good accuracy for the detection of coronary artery stenosis (sensitivity 70—97%; specificity 64—93%), which is similar for exercise and dobutamine echocardiography [4], but varies according to the artery involved. The reported sensitivity for the identification of left anterior descending (LAD) or right coronary artery (RCA) stenosis is superior to that for left circumflex (LCx) artery stenosis (72% for LAD, 76% for RCA vs 55% for LCx in a meta-analysis [1]).

The reported reproducibility of interpretation is poor even in expert centres of SE [5]. This can be explained by the fact that diagnosis of ischaemia is based upon subjective criteria such as hypokinesia or a delayed motion of the myocardial wall. To overcome these limitations, quantitative techniques such as tissue Doppler imaging (TDI) or strain using two-dimensional speckle have been proposed [6—10]. Nevertheless, these are time consuming and not fully validated for clinical practice. In our experience, when the LCx artery is involved, one can often observe an asymmetry of contraction during stress in the four-chamber view, leading to torsion of the apex, which is very easy to recognize. This Rise of the Apical lateral wall and/or Horizontal displacement of the Apex ("RA-HA" sign) can be seen in Fig. 1. This wallmotion abnormality frequently occurs without a significant hypokinesia or a delayed motion of the endocardium. In the present study, we sought to evaluate the interobserver reproducibility and diagnostic value of this new sign.

Methods

Inclusion criteria

Patients referred to our laboratory for routine diagnostic SE were prospectively considered for inclusion. Consecutive patients were included provided they fulfilled the following criteria: SE considered positive by the cardiologist who performed the test; normal left ventricular function at rest; indication for coronary angiography. Significant valve disease was an exclusion criterion. The decision to perform the angiography was based on routine clinical practice (after discussion with the cardiologist who referred the patient, taking into account clinical symptoms and/or severity of ischaemia). Examinations were reanalysed without any impact on the patient's treatment.
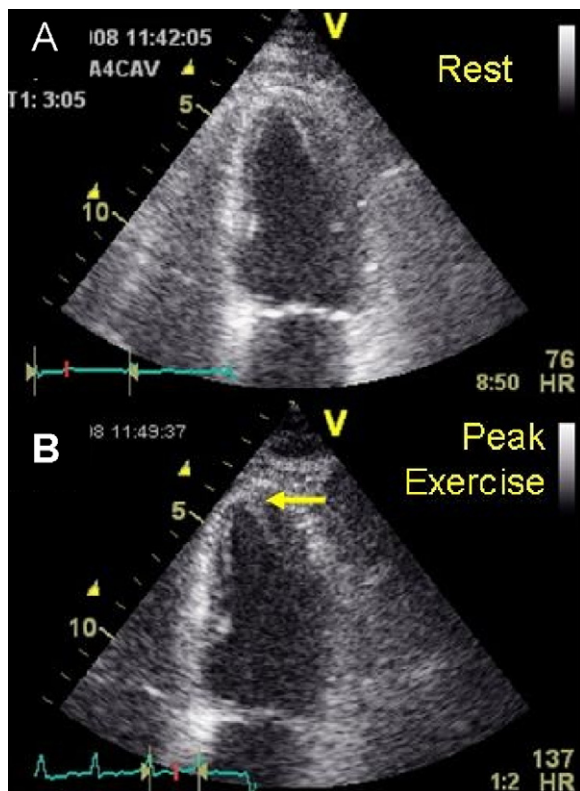
Figure 1. Exercise echocardiography: four-chamber view at rest (A) and at peak exercise (end-systole) (B). The characteristic RA-HA sign is observed at peak stress with lateral motion of the apex towards the right.

Stress echocardiography protocols

SE was performed by a senior cardiologist, using a VIVID 7 (General Electric Medical System, Horten, Norway). Basic acquisitions at rest were made to appreciate wall motion contraction. Ejection fraction was evaluated using eyeball estimation and/or using the modified biplane Simpson's rule.

Exercise echocardiography was performed using a bicycle protocol with the patient in a semisupine position. The patient was asked to pedal at a constant rate of 60—65 rpm, and the workload was increased in a stepwise fashion (increments of 10—40 W every 2 min). Imaging (parasternal long-axis and short-axis, apical long-axis, four-chamber and two-chamber views) was recorded at baseline, at each stage until peak stress, and during recovery (immediately after the end of exercise). A 12-lead electrocardiogram (ECG) was continuously displayed on a screen to provide the operator with a reference for ST-segment changes and arrhythmias. Cuff blood pressure was measured in a resting condition and at each stage thereafter.

The dobutamine stress protocol consisted of a continuous intravenous infusion of dobutamine, starting with 5 mg/kg/min and increasing every 2 minutes to 10, 20, 30 and 40 mg/kg/min. If there were no contraindications, atropine was injected during the 20-mg/kg/min stage of dobutamine (0.25 mg up to a maximum of 1.5 mg). After peak stress images, a beta-blocker (atenolol) was administrated intravenously.

Diagnostic endpoints were: achievement of target heart rate (defined as 85% of the age-predicted maximum heart rate), new or worsening wall-motion abnormalities of moderate degree, maximal dose for dobutamine stress, significant arrhythmias, hypotension (> 40 mmHg drop in blood pressure), severe hypertension (systolic blood pressure > 220 mmHg or diastolic blood pressure > 120 mmHg, and intolerable symptoms (severe chest pain, dyspnea or exhaustion).

Stress echocardiography analysis

The examinations were analysed blindly by three independent readers: two seniors (E.A. and C.C.) and one junior (L.R.), based on a 16-segment model of the myocardium. ECG and clinical status were unknown. Analysis was performed using a quad-screen format (baseline, low stress, peak stress and recovery) for each of the five views. The two seniors readers had to answer the following questions:
- what was the informative stage during which the diagnosis made: peak stress or recovery?
- how many segments were considered as ischaemic?
- was there any wall-motion abnormality, namely akinesia, hypokinesia and/or induced delayed contraction (in at least two segments)?

The new sign was a Rise of the Apical lateral wall and/or a Horizontal displacement (pulling) of the Apex towards the septum (RA-HA), in a four-chamber view or in an apical long-axis view, at peak stress or during recovery (Video S1). To evaluate the feasibility of this new sign, we trained a junior cardiologist. This training was very simple and took less than 30 minutes, explaining the RA-HA sign with five video clips of stress echo with typical involvement. The three readers (two seniors and one junior) were then asked to decide whether there was a RA-HA sign.

For each examination, the quality was noted, as well as the systolic blood pressure at peak level, and the percentage of the age-predicted maximum heart rate achieved.

Coronary angiography

All patients underwent coronary angiography within 1 week of SE. Significant coronary artery stenosis was defined as greater or equal to 50% luminal diameter narrowing (visual assessment). Lesions were classified as follow: LAD, LCx, RCA, two-vessel disease (LAD-LCx, LAD-RCA or RCA-LCx) or three-vessel disease.

Statistical analysis

The Cohen κ coefficient for interobserver concordance and for agreement between echographic and angiographic territories was calculated to test the hypothesis that concordance was greater than chance alone. The coefficient of agreement, κ, was graded as poor (0—0.20), fair (0.21—0.40), moderate (0.41—0.60), good (0.61—0.80) or very good (0.81—1.00). The diagnostic value of the RA-HA sign to detect coronary stenosis and to localize the lesion at coronary angiography was also calculated in terms of sensitivity, specificity and positive and negative predictive values (PPV and NPV). Accuracy was calculated as the total number

Table 1 Patient and SE characteristics.

	All patients ($n = 81$)
Men	52 (64.2)
Age (years)	65 ± 10
Type of SE	
Exercise	58 (71.6)
Dobutamine	23 (28.4)
SE image quality	
Good	35 (43.2)
Medium	42 (51.9)
Poor	4 (4.9)
ECG at rest	
Normal	76 (93.8)
Left bundle branch block	3 (3.7)
Atrial fibrillation	2 (2.5)
Percentage of maximum age-predicted heart rate	89 ± 12
Systolic blood pressure, mmHg	197 ± 35

Data are mean $\pm$ standard deviation or count (%). ECG: electrocardiography; SE: stress echocardiography.

Table 2 Diagnostic criteria for ischaemia during SE.

	Senior 1 ($n = 81$)	Senior 2 ($n = 81$)
Best stage for diagnosis		
Peak	67 (82.7)	73 (90.1)
Recovery	14 (17.3)	8 (9.9)
Number of segments	3.7 ± 2.0	3.8 ± 2.3
Akinesia	39 (48.1)	37 (45.7)
Hypokinesia	15 (18.5)	17 (21.0)
Tardokinesia	44 (54.3)	23 (28.4)
RA-HA sign	27 (33.3)	26 (32.1)

Data are mean $\pm$ standard deviation or count (%). SE: stress echocardiography. Each patient may have more than one criterion, e.g. RA-HA and akinesia.

of true positive and true negative tests divided by the total number of patients. A true positive test was defined when a RA-HA sign was present along with a significant lesion on coronary angiography.

Results

Characteristics of the 81 patients are shown in Table 1, along with information on the type and quality of SE, percentage of age-predicted heart rate achieved and systolic blood pressure.

Stress echocardiography analysis

Diagnostic criteria for ischaemia during SE are presented in Table 2. Diagnosis was performed using recovery data in 14/81 patients (six exercise and eight dobutamine SE) for senior 1 and 8/81 patients (eight dobutamine) for senior 2. Hypokinesia was described in only around 20% of cases, whereas tardokinesia was often observed (54.3% for senior 1 and 28.4% for senior 2). SE was considered strictly normal in the same four patients for senior 1 and senior 2. A RA-HA sign was identified in 27 patients by S1 and in 26 patients by S2. Concordance between the senior readers was poor for the usual signs of ischaemia ($\kappa = 0.07$, 95% confidence interval [CI] -0.12 to 0.26] for tardokinesia), but good for the RA-HA sign ($\kappa = 0.86$, 95% CI 0.64—1.08). For S1, among the 27 patients with a RA-HA sign, eight had no other sign of positivity, i.e. no wall motion abnormality.

RA-HA sign to diagnose significant coronary artery stenosis

Among 77 patients who underwent angiography, the RA-HA sign was observed in 24 patients (by S1) and 23 patients (by S2) with significant coronary artery stenosis; but only two or three patients, respectively, without significant coronary artery stenosis (Table 3). Sensitivity, specificity, PPV and NPV

Table 3 Presence of the RA-HA sign according to the result of coronary angiography.

	CA result ($n = 77$)	RA-HA sign Senior 1 ($n = 77$)	RA-HA sign Senior 2 ($n = 77$)
No significant coronary artery stenosis	18	2	3
Significant coronary artery stenosis	59	24	23
LAD alone	16	0	0
LCx alone	4	4	4
RCA alone	5	1	1
LAD and LCx	12	7	7
LAD and RCA	8	2	1
LCx and RCA	5	4	4
Three vessels	9	6	6

Data are numbers of patients. CA: coronary angiography; LAD: left anterior descending coronary artery; LCx: left circumflex artery; RA-HA: Rise of the Apical lateral wall and/or Horizontal displacement of the Apex towards the septum; RCA: right coronary artery.

Table 4 Diagnostic performance of the RA-HA sign.

Coronary artery	Reader	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (%)	NPV (%)
LAD	Senior 1	33.3 (20.4—49.1)	65.6 (46.8—80.8)	57.7	41.1
	Senior 2	31.1 (18.6—46.8)	65.6 (46.8—80.8)	56.0	40.4
LCx	Senior 1	70.0 (50.4—84.6)	89.4 (76.1—96.0)	80.8	82.4
	Senior 2	66.7 (47.1—82.1)	89.4 (76.1—96.0)	80.0	80.8
RCA	Senior 1	48.1 (29.2—67.6)	74.0 (59.4—84.9)	50.0	72.6
	Senior 2	44.4 (26.0—64.4)	74.0 (59.4—84.9)	48.0	71.2

Diagnostic performance of RA-HA sign (for the two senior readers) to detect significant stenosis of the LAD, LCx or RCA, irrespective of whether the patient had single, double or triple vessel disease. CI: confidence interval; LAD: left anterior descending coronary artery; LCx: left circumflex artery; NPV: negative predictive value; PPV: positive predictive value; RA-HA: Rise of the Apical lateral wall and/or Horizontal displacement of the Apex towards the septum; RCA: right coronary artery.

for the RA-HA sign to detect any significant lesion at coronary angiography were, respectively, 41%, 89%, 92% and 31% for S1; 39%, 83%, 88% and 29% for S2; and 29%, 83%, 85% and 26% for the junior reader.

RA-HA sign to localize significant coronary artery stenosis

Results of RA-HA presence according to which artery was affected are shown in Table 3. Sensitivity, specificity, PPV and NPV for the RA-HA sign to detect LAD, RCA or LCx lesions are shown in Table 4 for both senior readers. For senior 1, the diagnostic accuracy of the RA-HA sign to detect LCx lesions was 81%, while it was 46.7% for LAD and 64.9% for RCA. Among patients with only a LAD lesion, the RA-HA sign was never found; but among those with LCx alone, the RA-HA sign was always present (Table 3).

Reproducibility of the RA-HA sign

As already mentioned, the κ coefficient of agreement for the presence or absence of RA-HA sign was very good between S1 and S2 (0.86, 95% CI 0.64—1.08). κ was good between S1 and J (0.67, 95% CI 0.46—0.88) and between S2 and J (0.70, 95% CI 0.48—0.91).

Discussion

In the present study, we evaluated the accuracy of a new sign — ''RA-HA'' — for the detection of coronary lesions during SE. We found that the RA-HA sign is easy to learn, is highly reproducible and has a high specificity for the detection of coronary lesions, particularly when LCx is involved.

Diagnosis of ischaemia using stress echocardiography

The decision to perform coronary angiography is of critical importance for patient care and cost-effectiveness. Such a decision is based on detection of myocardial ischaemia, and SE is one of the first-line methods for this purpose. Routine criteria for the diagnosis of myocardial ischaemia during SE are subjective, mainly worsening of regional wall thickening in at least one [5] or two [2] adjacent segments. Published

sensitivities and specificities for the detection of coronary artery lesions during SE are usually high (from 70% to 95% for both) [1,4]. However, recent data from a US patient registry (n = 398.978) have demonstrated that ''real-life'' results may be different: among patients referred for coronary angiography after a non-invasive test, only 41.0% had significant coronary artery lesions [11].

To improve the diagnostic performance of SE, additional subjective criteria have been proposed, e.g. delayed contraction (''tardokinesia''). In the present study, this criterion has a poor reproducibility among senior readers and, to the best of our knowledge, there is no evaluation of its diagnostic performance in the literature. Quantitative criteria are mandatory. Preliminary results using left ventricular TDI or 2D strain at peak stress are encouraging, with an improvement of accuracy to detect coronary lesion from 75% (conventional approach) to 87% [6]. However, these techniques need sophisticated material and are time consuming (up to 30 minutes to analyse velocities in eight segments) [10]. Moreover, they require high image quality [6], and diagnostic value is generally higher for anterior circulation as compared to posterior circulation [6,10].

In addition to usual criteria (hypokinesia, akinesia and tardokinesia), we observed that, in patients with LCx stenosis, a wall motion abnormality of the apex (sometimes without reduction of the endocardial excursion or wall thickening) was frequently present at peak stress. This ''pulling of the apex'', which we called RA-HA, is easily visible when the reader is aware of its implication for diagnosis. This new sign is of interest for several reasons:

- it is applicable with any commercially available system;
- it can be detected even when image quality is not optimal, since it involves the apex (which is easier to analyse than basal segments);
- it is highly reproducible, regardless of the experience of the reader;
- its presence has a high PPV for the diagnosis of coronary stenosis, particularly when posterior circulation is involved.

Topographic diagnosis of ischaemia

Different studies have demonstrated that detection of LCx lesions remains a challenge when using SE. Sensitivity as low as 36% during exercise echocardiography has been reported

[12], while a mean sensitivity of 55% has been published in a meta-analysis of dobutamine echocardiography accuracy [1]. This lower sensitivity for LCx, compared to the sensitivity for LAD or RCA ischaemia detection, can be explained by a small amount of myocardium supplied by this artery. In fact, Elhendy et al. have demonstrated, in a series of 290 patients referred for dobutamine SE, that sensitivity for the detection of LCx involvement decreased from 55% (using one ischaemic segment as a criteria for positivity) to 36% (using at least two ischaemic segments) [13].

Another explanation may be a poorer endocardial border detection of the lateral wall, related to the parallel orientation of the ultrasound beam. Improvement obtained with quantitative analysis is still questionable. Using automated strain rate imaging, performance was poor in the posterior circulation as compared to LAD territory [6]. Using pulsed TDI, accuracy for the detection of LCx disease was 78.3%, while there were no applicable criteria for the detection of RCA lesion [10]. In the MYDISE study, using tissue tracking, the best results for the detection of LCx lesions were obtained for the inferior wall, with a sensitivity and specificity of 77% [7].

In our population, the sensitivity of the RA-HA sign to detect LCx significant lesions was around 70%, with a high specificity of 89% and an accuracy of 81%. The fact that there is no need to analyse the endocardial lateral wall to detect the RA-HA sign contributes to this high diagnostic value. In all four patients with a single-vessel LCx disease, the RA-HA sign was present, confirming our preliminary observation. For one of the senior readers, eight patients had an isolated RA-HA sign (i.e. no other signs of ischaemia, such as hypokinesia or akinesia), and six of these had LCx stenosis (single or multivessel disease) (Video S2). Although lower than for LCx, we also observed good accuracy of the RA-HA sign for the detection of significant RCA lesions. This may be explained by coronary anatomy, since the inferolateral wall may be irrigated by the RCA or LCx.

Our results were obtained from a population with a high prevalence of coronary disease (patients referred with a suspicion of coronary artery disease), but with normal left ventricular function at rest. Most published studies on SE (45/62 studies in a recent report [14]) have included a significant proportion of patients with resting wall motion abnormalities. It has been demonstrated that the sensitivity of dobutamine SE for the detection of coronary artery stenosis is lower among patients without previous myocardial infarction [14]. Hence, the results of this study, and the RA-HA sign, are of further importance in the detection of ischaemia.

Reproducibility of criteria for ischaemia during stress echocardiography

The high diagnostic value of SE contrasts with a non-optimal reproducibility. Indeed, inter-institutional agreement in the interpretation of dobutamine SE is poor, with a mean κ-value of 0.37 [5]. Although agreement was 100% for patients with the highest image quality, it was only 43% when the image quality was low [5]. With improvements in image quality and standardized reading guidelines, κ has improved to 0.55, but this is still disappointing [15—17]. Moreover, in order

to obtain such a performance, the technique requires an important learning curve, with lower accuracy of beginners compared to experienced readers (61% vs 85%) [18]. Indeed, current guidelines for SE practice suggest that ≥ 100 examinations must be performed before a physician is capable of performing routine diagnosis [2,3]. Our results suggest that the RA-HA sign is highly reproducible among experienced readers (κ = 0.86), but also when comparing beginners to experienced readers (mean κ = 0.68).

Limitations of the study

In the present study, only patients with positive SE were included. Thus, sensitivity and specificity must be interpreted according to the high prevalence of coronary artery disease in our population. However, our results are clinically relevant in the real-life scenario of an SE laboratory where a patient is referred for a diagnostic test, and if SE is considered positive, coronary angiography can be discussed.

The present study demonstrates that the RA-HA sign is easy to detect and highly reproducible, even for a junior reader. However, it remains a subjective tool of wall motion during stress. Quantitative criteria are desirable for SE analysis, but at the time of the study, remain a research tool.

Ideally, to test precisely the value of the RA-HA sign to detect LCx lesions, we have to consider only patients with one vessel stenosis. Indeed, a patient with a RA-HA sign and both LAD and LCx lesions at coronary angiography will increase the value of the sign equally for both lesions.

Angiography as a reference is problematic, as we know from animal studies that ischaemia can occur in patients with stenosis less than 50%, and sometimes may be absent in those with stenosis greater than 70%. Moreover, a significant proportion of patients with markedly abnormal stress did not have significant stenosis at coronary angiography. It has been demonstrated that the outcomes of patients with false-positive results are similar to those of patients with true-positive results [19]. In our population, five patients with markedly positive stress (≥ 4 segments involved) had normal coronary angiography.

Conclusions

The '''RA-HA'' sign — a Rise of the Apical lateral wall and/or a Horizontal displacement of the Apex toward the septum — is a potential new SE diagnostic criterion. It is highly reproducible and easy to detect at peak stress or during recovery. It has a high diagnostic value to consider the test as positive as regard to the presence of a significant coronary lesion. Moreover, it has good accuracy for predicting an LCx lesion, which is considered as the most difficult lesion to identify with SE.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.acvd.2012.02.008.

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