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Results of dipyridamole plus atropine echo stress test for the diagnosis of coronary artery disease

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Abstract

Sensitivity of dipyridamole stress echocardiography (DIP-E) has been reported to be less than ideal in particular subsets of patients such as those with less severe extent of coronary artery disease (CAD). To verify if sensitivity could be improved, ATRO (1 mg in 2 minutes) was added at the end of a negative high-dose (0.84 mg/kg over 10 minutes) DIP-E in 61 consecutive patients (58 men, aged 53 ± 7 years) evaluated for chest pain (33%) or for detection of residual ischemia after acute myocardial infarction (AMI) or previous MI (67%). DIP-E was positive in 28/61 (46%) and negative in 33/61 (54%) patients. Additional echo positivity was obtained in 18/33 (54%) patients after ATRO. Coronary arteriography was normal in 6 patients (10%); 1-vessel CAD was diagnosed in 28 (46%), 2-vessel CAD in 16 (26%) and 3-vessel CAD in 11 (18%) cases. The sensitivity for CAD diagnosis was 49% (27/55) for DIP-E and 84% (46/55) for DIP-E + ATRO ($p < 0.001$). Specificity was 83% and 80%, respectively. Diagnostic accuracy increased from 52% to 83% ($p < 0.001$). The better diagnostic accuracy of DIP-E was mainly related to the significant increase in sensitivity of the combined test in patients with 1-vessel CAD (from 46% to 75%) ($p < 0.005$). At quantitative coronary evaluation, compared to patients with positive DIP-E + ATRO or negative DIP-E + ATRO test, patients with positive DIP-E had a higher mean % diameter stenosis: 80 ± 13% vs 72 ± 24% and 65 ± 36%, respectively. Peak heart rate was significantly higher after the addition of ATRO vs basal and DIP alone in patients with a positive DIP-E + ATRO test. The addition of ATRO to DIP increases diagnostic accuracy of DIP-E particularly in patients with less severe extent of CAD; ATRO may be considered as a useful routine procedure for increasing diagnostic value of DIP-E test.

Introduction

Dipyridamole echo stress test (DIP-E) has gained a wide clinical acceptance for the diagnosis of coronary artery disease (CAD) and for risk stratification in patients after myocardial infarction (MI). Specificity for CAD diagnosis varied a little from 90% to 100% in different clinical settings [1–7]. Sensitivity has been usually reported over 80% in patients with diffuse CAD [3, 5, 7] but may be very low, sometimes less than 50% [6–8], in patients with single vessel disease. Similarly to what has been done with dobutamine [9], recently atropine (ATRO) has been proposed as an adjunctive pharmocological stressor to DIP for increasing sensitivity of the test [10]. Accordingly we altered the protocol of DIP-E to incorporate the addition of ATRO at the end of a negative DIP-E to assess if the combination of the 2 drugs could improve the sensitivity of DIP-E for detecting the presence of myocardial ischemia and the presence and severity of CAD.

Methods

Patient population

Sixty-one consecutive patients (58 men, aged 53 ± 7 years) were enrolled in the study. Fourty-three patients

Table 1. Patient population (n = 61).

Mean age (yrs) and sex (m/f)	53 ± 7; 58/3
Chest pain	20/61 (33%)
Previous MI	13/61 (21%)
Recent MI	28/61 (46%)
Normal coronary arteries	6/61 (10%)
1-vessel CAD	28/61 (46%)
2-vessel CAD	16/61 (26%)
3-vessel CAD	11/61 (18%)

(54%) performed DIP-E test for the evaluation of chest pain of suspected coronary origin; a previous myocardial infarction (MI) was present in 13/43 (30%) of these patients. The remaining 28/61 patients (46%) were evaluated after a recent (less than 6 weeks) acute MI for the detection of residual myocardial ischemia (Table 1). Patients with unstable angina, cardiac failure, valvular heart disease or cardiomyopathy were excluded from the study. Patients were also excluded in the presence of glaucoma and severe prostatic hypertrophy, well established contraindications to the administration of ATRO. All patients were evaluated while not taking antianginal therapy: betablockers were discontinuated at least 48 hours and nitrates and calcium antagonists 24 hours before the test. An informed consent was obtained by all patients before performing echo stress test.

Study protocol

DIP was given under two-dimensional echocardiographic and 12-lead electrocardiographic monitoring following the high-dose infusion protocol previously proposed by Picano [1]. A first dose of 0.56 mg/kg over 4 minutes was infused followed by 4 minutes of control and, if the test was considered negative, by a second dose of 0.28 mg/kg over 2 minutes with a total dose of DIP equal to 0.84 mg/kg over 10 minutes.

At the 4th minute after the end of DIP infusion, ATRO was given intravenously in 2 separate doses of 0.5 mg at 1-minute interval in those patients who did not develop a new or worsening dyssynergy of contraction. The administration of ATRO was timed at the 4th minute after the high dose of DIP because it is known from large clinical trials that at this time wall motion abnormalities induced by DIP infusion have been already demonstrated in most cases [3]. The test was considered positive when a transient asynergy of contraction, which was absent or of lesser degree in the baseline echo developed; in patients with previous MI akinesia becoming dyskinesia in the infarcted region was not considered as a positivity criterion.

In the absence of a positive echo response end points of the test were:

- severe chest pain;
- major supraventricular or ventricular arrhythmias;
- symptomatic hypotension; or
- other untolerable side effects.

Aminophylline (120–240 mg) was given intravenously after DIP or DIP + ATRO in positive and negative tests; propranolol (2–5 mg i.v.) was given after 5 minutes from the last ATRO dose to counterbalance the effects of ATRO.

Two-dimensional echocardiography was performed utilizing a commercially available imaging system (Hewlett-Packard Sonos 1000, 2.5 MHz transducer). All standard transthoracic views were recorded in the baseline study and during stress testing on a videotape.

All the tests have been evaluated blinded to the clinical data of the patients. During the test the same operator (L.L.) had the responsability of judging the DIP-E test as positive or negative and adding ATRO at the end of DIP infusion in case of negativity. All the exams were subsequently reviewed off line by the same operator and a second independent observer. In case of disagreement a consensus was reached. Inter- and intra-observer concordance for positive or negative test was 100% and 95%, respectively. The very good inter- and intra-observer reproducibility of echo stress readings in our experience has been previously published elsewhere [11]. Wall motion analysis was performed on a 11-segment left ventricular model [12]. An asynergy score was calculated in each patient at baseline, at peak DIP and after the addition of ATRO. The score was derived by the sum of individual segment scores; a value equal to 0 was assigned to segments with normal kinesis, 1 to hypokinetic, 2 to akinetic and 3 to dyskinetic segments.

A 3-region scheme of coronary perfusion was utilized to define the territory perfused by the 3 major coronary arteries and to correlate the wall motion abnormalities during the test with the site of coronary lesions. Apex, proximal and distal anterior septum, proximal and distal anterior wall were considered to be region of the left ventricle perfused by the left anterior descending coronary artery; proximal and distal inferior septum, proximal and distal inferior wall as perfusion territories of the right coronary artery; proximal

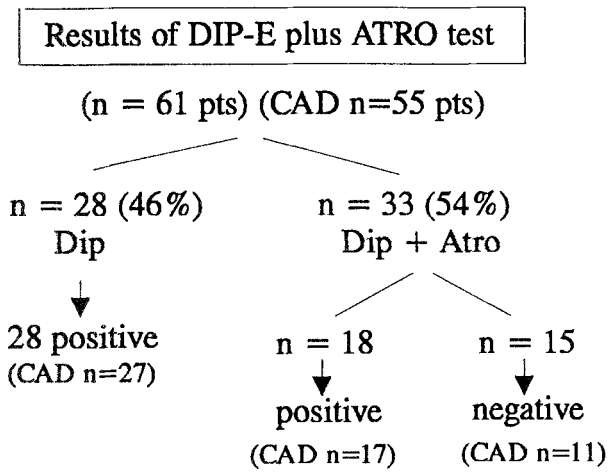

Fig. 1. Results of dipyridamole plus atropine echo stress test (DIP-E plus ATRO). Sixty-one consecutive patients were studied. Fifty-five were found to have significant coronary artery disease (CAD) at angiography. A positive DIP-E response was present in 28/61 patients (46%) with 1 false positive result. The remaining 33 patients (54%) with a negative response to high-dose DIP-E received ATRO after DIP infusion. A positive response was judged to be present in 18 additional patients of whom 1 was found to be a false positive response. Fifteen patients were considered to have a negative test also after the addition of ATRO. Four out of these 15 patients were found to be true negative patients.

and distal lateral wall as territories of the circumflex coronary branch. The occurrence of angina and significant ST-segment depression (=/> 1 mm shift compared to basal in 2 adjacent leads measured 80 msec after the J point) was also recorded.

Coronary arteriography

All patients underwent selective right and left coronary arteriography using the Judkins' technique within 15 days from stress test independently from the results of the test. Coronary lesions were evaluated in a qualitative manner by an experienced examiner blinded to the results of the tests and, once the projection that best showed a stenosis was identified, images were loaded on an automatic digital angiographic computer system for quantitative evaluation of the stenosis (Imagecom system) that utilizes an automatic edge detection system that has been previously described elsewhere [13]. Intra- and inter-observer variability in the quantitative assessment of coronary stenoses with this method has been reported in a previous experience of our group [14]. At quantitative analysis a vessel was considered to have a significant obstruction if its diameter was narrowed by 50% or more in respect to the pre-stenotic tract. A correlation between the left ventricular region rendered ischemic by the drugs and the affected vessel was then made according to the distribution of coronary perfusion previously described.

Table 2. Clinical and angiographic characteristics of group A and group B patients.

	Group A	Group B
Mean age (yrs)	52 ± 7	50 ± 8
Angina	7/28 (26%)	13/33 (40%)
Previous/recent MI	21/28 (74%)	20/33 (60%)
No CAD	1/28 (3%)	5/33 (15%)*
1-vessel CAD	14/28 (50%)	14/33 (43%)*
2-vessel CAD	6/28 (22%)	10/33 (30%)*
3-vessel CAD	7/28 (25%)	4/33 (12%)*
Angina during test	10/28 (36%)	10/33 (30%)
ST-segment depression during test	15/28 (53%)	11/33 (33%)
Asynergy score: Basal	3.1 ± 2.5	4 ± 0
Peak	7.3 ± 2.5**	7.2 ± 3.8**

Group A: n = 28 DIP-E test; group B: n = 33 DIP/ATRO test.
* = $p < 0.05$ for CAD distribution between groups.
** = $p < 0.001$ vs basal.

Statistical analysis

Values are reported as mean ± 1 standard deviation. Differences between the results of DIP-E and DIP-E + ATRO were compared using the Chi-square test. Clinical and angiographic characteristics of patients who received DIP or DIP + ATRO were compared using Chi-square test or unpaired Student t test when appropriate. Differences in haemodynamic variables during the test were compared using Student t test for paired samples or 1-way analysis of variance followed by Scheffè test. A p value equal or less than 0.05 was considered the level of significance.

Sensitivity, specificity and diagnostic accuracy for detection of CAD were calculated according to standard definitions.

Results

Among the 61 patients studied, 28 (46%) achieved echocardiographic positivity after the first (8/28) (29%) or the second (20/28) (71%) dose of DIP alone (group A), whereas the remaining 33 patients (54%) received

ATRO according to the protocol of the study (group B). After the addition of ATRO the test was considered positive in 18 additional patients (30%) and remained negative in 15 (24%) patients (Fig. 1). A minority (10%) of the 33 group B patients developed ischemic electrocardiographic changes or angina at the end of DIP infusion; however, because the test was considered positive only at the occurrence of echocardiographic signs of ischemia, ATRO was added also in these patients resulting in echo positivity in all of them. Coronary arteriography revealed no significant coronary lesions in 6/61 (10%), 1-vessel CAD in 28/61 (46%), 2-vessel CAD in 16/61 (26%) and 3-vessel CAD in 11/61 (18%) patients. A false positive result was observed in 1 of the 28 group A and in 1 of the 33 group B patients. Both patients showed during the test an extension of a baseline asynergy of contraction in the area of a previous MI.

Clinical and angiographic characteristics of group A and group B patients are illustrated in Table 2. A significant difference between group A and B was present only for coronary artery disease distribution; in patients with a positive test after DIP alone a higher proportion of multivessel coronary disease was present whereas no significant coronary lesions and 1-vessel CAD were more frequently present in patients in whom positivity of the test was achieved after the addition of ATRO.

Haemodynamic changes

Changes in heart rate, systolic blood pressure, diastolic blood pressure and rate-pressure product in group A and B patients are illustrated in Table 3 and 4, respectively. Compared to basal, DIP induced a little but significant increase in heart rate with no change in diastolic and systolic blood pressure. A significant increase of rate-pressure product was observed. In the 33 patients in whom ATRO was added after DIP, a further increase in heart rate was obtained in respect to DIP alone; in this group of patients systolic and diastolic blood pressure slightly decreased after DIP with no significant changes after the addition of ATRO. Due to a 54% increase in heart rate after ATRO compared to basal and a 18% increase compared to peak DIP, rate-pressure product significantly increased after ATRO in respect to basal and peak DIP. The value of rate-pressure product of patients with DIP + ATRO positive test and DIP + ATRO negative test did not differ significantly.

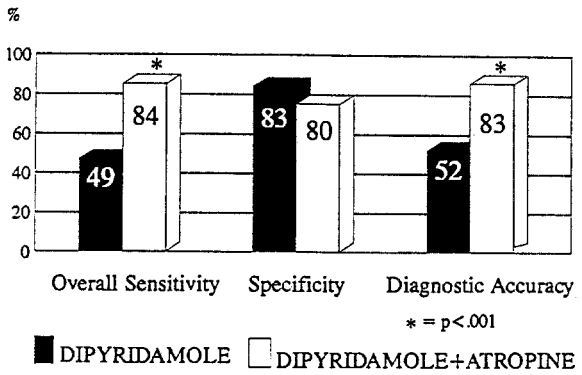

Fig. 2. Sensitivity, specificity and diagnostic accuracy of dipyridamole echo stress test (black bars) and dipyridamole plus atropine echo stress test (white bars). * $p < 0.001$ vs dipyridamole alone.

Diagnostic accuracy of DIP-E and DIP-E + ATRO stress test

Overall sensitivity, specificity and diagnostic accuracy of DIP-E and DIP-E + ATRO are shown in Fig. 2. Sensitivity of DIP-E for CAD detection was 49% (27/55), specificity 83% (5/6) and diagnostic accuracy 52% (32/61); ATRO significantly increased overall sensitivity of the test to 82% (45/55) ($p < 0.001$ vs DIP-E). Specificity did not change significantly (80%), thus a significant increase of diagnostic accuracy to 82% (49/60) was observed after ATRO ($p < 0.001$ vs DIP-E). Compared to DIP, DIP + ATRO showed a higher sensitivity in patients with less severe extent of CAD: sensitivity demonstrated a non significant increase from 80% to 100% in patients with 3-vessel CAD, whereas a higher increase was obtained in patients with 2-vessel CAD (from 38% to 75%) and 1-vessel CAD (from 46% to 75%) ($p < 0.005$ vs DIP-E) (Fig. 3).

The increase in sensitivity was similar in patients with or without previous MI: from 49% (20/41) to 78% (32/41) ($p < 0.005$) and from 35% (7/20) to 60% (12/20) ($p < 0.01$), respectively.

During DIP infusion 11 patients developed angina and 15 patients ST-segment shift; ATRO induced the occurrence of angina and ST-segment shift in 10 and 11 additional patients, respectively.

Low-dose DIP positivity occurred in 8 patients, half of whom had multivessel CAD. In patients with 1-vessel coronary artery disease and a true prositive test, a transient asynergy was induced in all cases in the territory perfused by the diseased vessel. Multiregional asynergy developed in 7/27 (26%) patients with multivessel CAD (5 after DIP alone and 2 after the addition

Table 3. Haemodynamic parameters in group A pts (n = 28).

	Basal	Peak DIP
HR (beats/min)	66 ± 14	88 ± 15*
SBP (mmHg)	135 ± 23	138 ± 23
DBP (mmHg)	82 ± 10	83 ± 10
RPP (mmHg·beats/min)	9135 ± 3000	12300 ± 3300*

DIP: dipyridamole; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate-pressure product. * = p < 0.001 vs basal.

Table 4. Haemodynamic parameters in group B pts (n = 33).

	Basal	Peak DIP	Peak ATRO
HR (beats/min)	64 ± 13	83 ± 13*	100 ± 18*,**
SBP (mmHg)	132 ± 21	126 ± 19	131 ± 20
DBP (mmHg)	81 ± 10	76 ± 9*	78 ± 12
RPP (mmHg·beats/min)	8240 ± 1695	10300 ± 2270*	13160 ± 3250*,**

DIP: dipyridamole; ATRO: atropine; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RPP: rate-pressure product.
* = p < 0.05 vs basal; ** = p <0.05 vs peak DIP.

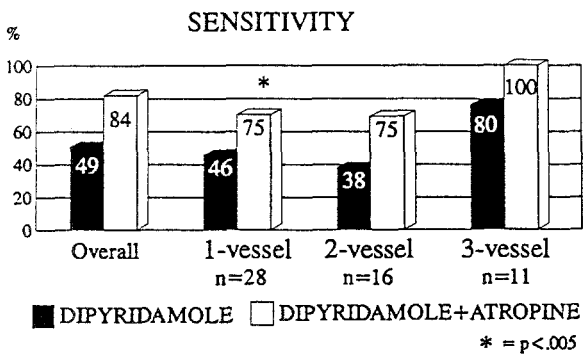

Fig. 3. Comparison of sensitivity of dipyridamole (black bars) and dipyridamole plus atropine (white bars) echo stress test for the diagnosis of coronary artery disease according to the extension of coronary artery lesions. * p < 0.005 vs dipyridamole alone.

of ATRO). In these 27 patients left main coronary artery was involved 1 times, left anterior descending coronary artery 19 times, right coronary artery 23 times and left circumflex artery 20 times; an antero-apical transient asynergy was induced in the patient with left main coronary artery disease; an asynergy in the territory of perfusion of all the 3 affected vessel was detected in 3 cases; 2 areas were involved in the other 3 patients (right and circumflex, left anterior descending and right territories in 2 and 1 case, respectively).

Asynergy score increased from a basal value of 3 ± 2.5 to a peak value of 7 ± 2.4 in patients with positivity after DIP alone; a similar increase in asynergy score was observed after the addition of ATRO (from 4 ± 3.8 to 7 ± 3.8).

In patients with previous MI a new asynergy in an area within the infarcted region that was normal at baseline developed in 53% of cases (including 3 patients with multiregional asynergies), whereas in the remaining 47% a further deterioration from hypokinesia to akynesia was observed.

In Fig. 4 the severity of coronary lesions by quantitative analysis in patients with a positive DIP-E, a positive DIP-E + ATRO and a negative response to the test is compared. For positive test the lesion of the ischemia-related artery was quantitated, while for negative test the most severe coronary lesion was analyzed.

Patients with a positive response to DIP-E test showed a greater reduction in mean % diameter (80 ± 13%) and in mean % cross sectional area (94 ± 5%) of the ischemia-related vessel in comparison with patients with a positive response after ATRO (72 ± 23% and 87 ± 23%, respectively) or with a negative DIP-E + ATRO test (65 ± 36% and 75 ± 40%, respectively).

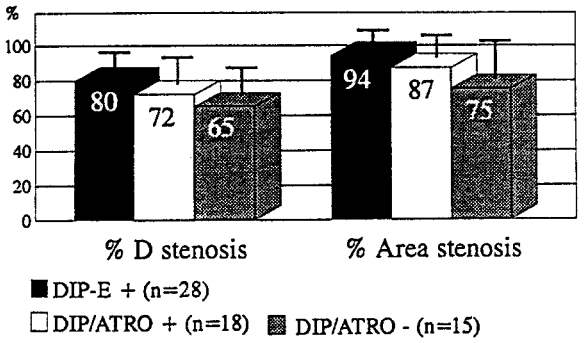

Fig. 4. Quantitative evaluation of coronary stenoses in patients with positive dipyridamole echo stress test (DIP-E) (black bars), positive dipyridamole plus atropine echo stress test (DIP/ATRO +) (white bars) and negative dipyridamole plus atropine echo stress test (DIP/ATRO -) (grey bars). On the left part of the figure are illustrated the values of percent diameter stenosis (% D stenosis) in the 3 groups of patients; on the right are reported the results of percent area stenosis (% Area stenosis).

However, these differences did not reach statistical significance.

Side effects

Mild and not significant side effects (headache, flushing, paresthaesia and palpitations) were induced by DIP in 45% of our population. ATRO did not induce any additional side effect and was well tolerated by all patients.

Discussion

Atropine is a novel method in conjunction with DIP for assessing myocardial ischemia and the presence of CAD [10]. The combination of DIP with another stressor for eliciting myocardial ischemia is warranted by the less than ideal sensitivity demonstrated by DIP in particular subsets of patients such as those with 1-vessel CAD [6–8], with coronary stenoses of mild degree [15] or under the effects of antianginal therapy [16]. For the same purpose, DIP has been already combined with stressor that increase myocardial oxygen consumption such as exercise [17] or handgrip [18]. The improvement in sensitivity was significant only with exercise; however, during an exercise plus DIP stress test, patient is required to perform a physical stress, while the addition of ATRO does not modify the general strategy of a pharmacological echo stress test. Moreover, the two ATRO doses are infused at a time at which a DIP positivity is usually evident and patients with left main coronary artery disease or patients with severe 3-vessel CAD are already recognized [12, 19]. ATRO may act as a synergistic stress with DIP by increasing myocardial oxygen demand throughout an increase in heart rate and by reducing myocardial oxygen supply to the sub-endocardial layers. In the presence of DIP-induced coronary vasodilation flow maldistribution may be present distal to a critical coronary stenosis [20]. Sub-endocardial flow depends principally on diastolic perfusion time [21] and ATRO, by increasing heart rate, reduces diastolic time, thus permitting a further decrease of perfusion. The hypothesis that combining DIP-induced flow maldistribution and ATRO-induced increase in oxygen consumption may be of clinical value [10] is confirmed in our study: the addition of ATRO to DIP increased the overall sensitivity of the test from 49% to 82% ($p < 0.001$) with no significant loss in specificity (from 83% to 80%) thus increasing diagnostic accuracy of DIP-E from 52% to 82% ($p < 0.001$). Picano [10] has recently demonstrated that ATRO increased sensitivity of DIP from 72% to 87%. The high sensitivity reported by Picano [1–3, 15] with DIP alone is not confirmed by our and other studies [6–8]. This discrepancy may be related to the influence of the anti-ischemic therapy [16], subjective evaluation of echo results [22, 23] and different patients population with variable proportion of patients with single and multiple vessel CAD. It is well known that sensitivity of DIP-E may be lower than 50% [6–8] in patients with 1-vessel CAD who represent 46% of patients of our population compared to only 31% of patients studied by Picano [10]. Moreover, in the patients with 1-vessel CAD studied by Picano [10] the severity of coronary stenoses by quantitative coronary angiography was greater than that of patients studied in our work (% diameter stenosis: 94 ± 3% vs 80 ± 13%).

In our experience the higher overall sensitivity of DIP + ATRO stress test is mainly related to the increased sensitivity in patients with 1- and 2-vessel CAD (from 49% to 75% and from 38% to 75%, respectively). Patients showing a positive response to DIP + ATRO test had a less severe coronary stenosis in the ischemia-related vessel than patients with positivity after DIP alone.

On the other hand the diagnostic value of adding ATRO to DIP seems to be not influenced by the presence or absence of baseline wall motion abnormalities.

A significant increase of myocardial oxygen demand was obtained adding ATRO to DIP due to the positive chronotrophic effect of ATRO. The value of rate-pressure product at peak ATRO in positive tests was the highest reached in our population. It is not well known if a higher ATRO dosage could induce a positive echo response in those patients with CAD and a negative DIP + ATRO test. The total dose of ATRO utilized in our study has been chosen on the basis of the wider experience of dobutamine echo stress test [24] and is probably a clinical useful compromise between safety of the test and power of the stressor. In fact we did not observe any significant additional side effect adding ATRO to DIP both in patients with and without a previous MI.

Clinical implications

Our experience indicates that the addition of ATRO to a negative DIP-E increases the overall sensitivity and diagnostic accuracy of the test mainly by increasing sensitivity in patients with 1-vessel CAD. Patients with a positive response after ATRO showed a less severe degree of coronary stenoses compared to patients with positivity after DIP alone. We did not find any significant additional side effect with ATRO during DIP-E so that DIP-E + ATRO test may be considered a safe and useful tool to increase the diagnostic accuracy of DIP-E.

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