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Echocardiography

ORIGINAL INVESTIGATION

Transient Ischemic Dilatation during Stress Echocardiography: An Additional Marker of Significant Myocardial Ischemia

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Aim: Left ventricular (LV) transient ischemic dilatation (TID) is not clear how it relates to inducible myocardial ischemia during stress echocardiography (SE). Methods and Results: Eighty-eight SEs were examined from the site certification phase of the ISCHEMIA Trial. LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured at rest and peak stages and the percent change calculated. Moderate or greater ischemia was defined as ≥3 segments with stress-induced severe hypokinesis or akinesis. Optimum cut points in stress-induced percent EDV and ESV change that identified moderate or greater myocardial ischemia were analyzed. Analysis from percentage distribution identified a > 13% LV volume increase in EDV or a > 9% LV volume increase in ESV as the optimum cutoff points for moderate or greater ischemia. Using these definitions for TID, there were 27 (31%) with TID_{ESV} and 12 (14%) with TID_{EDV}. By logistic regression analysis and receiver operating characteristic curves, the percent change in ESV had a stronger association with moderate or greater myocardial ischemia than that of EDV change. Compared to those without TID_{ESV}, cases with TID_{ESV} had larger extent of inducible wall-motion abnormalities, lower peak stress LVEF, and higher likelihood of moderate or grater ischemia. For moderate or greater myocardial ischemia detection, TID_{ESV} had a sensitivity of 46%, specificity of 83%, positive predictive value of 70%, and negative predictive value of 64%. Conclusion: Transient ischemic dilatation by SE is a marker of extensive myocardial ischemia and can be used as an additional marker of higher risk. (Echocardiography 2016;00:1–7)

Key words: stress echocardiography, myocardial ischemia, coronary artery disease

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Stress echocardiography (SE) is widely used in clinical settings and plays an important role in defining the diagnosis, risk stratification, and prognosis for patients with known or suspected

severe coronary artery disease.[1,2] Left ventricular (LV) transient ischemic dilatation (TID) during nuclear myocardial perfusion imaging (MPI) is considered a marker of extensive coronary artery disease and a predictor of future cardiac events.[3–5] TID has been noted on SE as a marker of extensive angiographic coronary artery disease (CAD) and worse prognosis.[6,7] However, TID has not been as well characterized on SE as for MPI. For example, it is not clear which phase of TID, end diastolic or end systolic, should be used for quantification of TID. While TID during SE has been associated with extensive angiographic CAD, it is not clear how it relates to inducible myocardial ischemia on SE.[6] Thus, the purpose of this study was to characterize TID in SE and identify whether it can serve as an indicator of a greater degree of inducible myocardial ischemia.

Methods:

Subject Population:

Stress echocardiography examinations submitted in the preenrollment site certification phase of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial were studied. The ISCHEMIA Trial is a randomized study comparing an initial invasive strategy of cardiac catheterization, revascularization, and optimal medical therapy with a conservative strategy of optimal medical therapy alone among stable patients with at least moderate myocardial ischemia.[8] As a prelude to this trial, participating sites were encouraged to submit stress imaging studies to the core laboratories. These SE could be any mode of stress (exercise or pharmacologic) and could demonstrate any degree of ischemia from none to severe as the goals of this phase were to determine whether the digital submissions could be viewed on the core laboratory workstations and also if the site could differentiate varying degrees of ischemia. One hundred eighteen SEs were submitted to the echocardiography core laboratory at the Massachusetts General Hospital from April 2012 to April 2013. Of these 118 cases, 30 were excluded for technical reasons (poor image quality, noncompatible format), leaving 88 cases submitted from 43 sites from 13 countries. Demographic and clinical data were not provided to the core laboratory.

Core Laboratory Assessments:

Two experienced cardiologists in the echocardiography core laboratory who were blinded to the site interpretations interpreted the SE. Specifically, rest and peak stress segmental LV function was evaluated using a modified 17 segment model (apical cap excluded).[9] Moderate or greater LV myocardial ischemia was defined as associated with an approximately 5% per year rate of MI or death. Based on literature review and expert consensus, this was determined as occurring when at least 3 segments developed significant wall-motion abnormality (WMA) during SE.[10] Significant WMA was defined as stress-induced severe hypokinesis or akinesis which means at least 1 grade worsened change at baseline to peak stage was needed, for example, normal to hypokinesis or hypokinesis to akinesis. In addition, the LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured by the biplane method of disks at both baseline and peak stages. Rest and peak LV ejection fraction (LVEF) was calculated from these volumes. All measurements were made on a digital image management system (Xcelera version R3.2, Philips Healthcare, Andover, MA, USA).

Statistical Analysis:

Variables are presented as mean $\pm$ standard deviation (SD). The LV EDV and ESV at peak stage were compared to baseline in each case to determine the percent change in volume. The percent change in LV EDV and ESV and the presence or absence of moderate or greater myocardial ischemia for each patient were then examined by the analysis of percentage distribution around 10% LV volume change according to the former evidences of myocardial perfusion image to determine the optimum cut point in volume change that was associated with moderate or greater myocardial ischemia.[5,11] Cut points for EDV and ESV change were selected that favored sensitivity rather than a balance of sensitivity and specificity. These values served as the definitions for TID in both diastole (TID_{EDV}) and systole (TID_{ESV}). Groups with (+) and without (−) TID were compared using nonpaired *t*-tests and chi-square test for dependent and categorical variables, respectively. Logistic regression model examining both changes in EDV and ESV and a comparison of receiver operating characteristic (ROC) curves were used to determine whether TID_{EDV} or TID_{ESV} was best for identifying moderate or greater LV myocardial ischemia.[12] To confirm the value of the thresholds for TID derived from this population, we then tested them in another cohort of 145 patients submitted from same institutions. Intra-observer and inter-observer variabilities were assessed for EDV, ESV, and LVEF values in 10 randomly selected cases and expressed as a percent difference. A P-value <0.05 was considered statistically significant.

Results:

Of the 88 SEs evaluated, 39 were exercise SEs (treadmill, upright bike or supine bike), 47 were pharmacologic (dobutamine or vasodilator

agent), and 2 were unknown stress type. In 13 of the cases, an echocardiographic contrast agent was utilized for LV opacification. Table I shows the echocardiographic and stress test variables. SE was positive on 83 (94.3%). 42 (47.7%) had mild myocardial ischemia (defined as 1–2 segments with stress-induced WMA), and 41 (46.6%) had moderate or greater LV myocardial ischemia (≥3 segments). The average number of segments with stress-induced WMA was 2.7 ± 1.8.

Intra- and inter-observer variabilities for LV volume measurement are shown in Table II. The absolute mean % intra-observer variability when all the measurements of volume are combined (diastolic, systolic, rest, stress) was 11.0 ± 8.9% (2.7 ± 30.1 by Bland–Altman plots meaning mean % ± 1.96SD) and the absolute mean inter-observer variability was 8.9 ± 12.7% (4.7 ± 26.4 by Bland–Altman plots).

Figure 1 is an example of TID_{ESV}. In this example, the biplane end-systolic volume increased by 63%. Based on the analysis of percentage distribution, the optimum cut point for EDV change to discriminate moderate or greater ischemia during SE was an increase >13%. For ESV change, it was an increase >9%.

The stress echocardiographic variables for those with and without TID based on the diastolic and systolic volume change cut points are shown in Tables III and IV, respectively. Using the

TABLE I

Echocardiographic Data

	N = 88
EDV baseline, mL	86.4 ± 28.4
EDV peak, mL	79.5 ± 30.8
%Δ EDV, %	−7.4 ± 19.2
ESV baseline, mL	36.7 ± 19.0
ESV peak, mL	34.5 ± 20.0
%Δ ESV, %	−4.3 ± 31.4
LVEF baseline, %	58.9 ± 8.9
LVEF peak, %	58.5 ± 10.0
%Δ LVEF, %	0.2 ± 15.5
HR baseline, bpm	67.2 ± 11.3
HR peak, bpm	124.3 ± 23.5
%Δ HR, bpm	89.0 ± 46.5
+ SE (%)	83 (94.3)
Total # + ischemic segments	2.7 ± 1.8
0 + segments (%)	5 (5.7)
1–2 + segments (%)	42 (47.7)
≥3 + segments (%)	41 (46.6)
WMA with LAD region (%)	51 (57.9)

EDV = end-diastolic volume; %Δ = percent change; ESV = end-systolic volume; LVEF = left ventricular ejection fraction; HR = heart rate; SE = stress echocardiography; WMA = wall-motion abnormality; LAD = left anterior descending artery.

TABLE II

Intra-Observer and Inter-Observer Variability

	Baseline				Peak			
	Correlation Coefficient	Pearson's R	Mean Difference	Mean % Difference	Correlation Coefficient	Pearson's R	Mean Differences	Mean % Difference
Intra								
EDV, mL	0.83, P < 0.01	0.83, P < 0.01	8.8	11.1	0.98, P < 0.0001	0.98, P < 0.0001	4.9	6.0
ESV, mL	0.98, P < 0.0001	0.99, P < 0.0001	2.8	7.5	0.96, P < 0.0001	0.96, P < 0.0001	4.5	12.1
LVEF, %	0.83, P < 0.01	0.83, P < 0.01	3.3	6.0	0.89, P < 0.001	0.89, P < 0.001	3.7	6.6
Inter								
EDV, mL	0.96, P < 0.0001	0.96, P < 0.0001	8.8	11.1	0.94, P < 0.001	0.94, P < 0.001	9.2	11.2
ESV, mL	0.98, P < 0.0001	0.98, P < 0.0001	3.2	8.6	0.94, P < 0.0001	0.94, P < 0.0001	4.8	12.9
LVEF, %	0.89, P < 0.001	0.89, P < 0.001	3.8	7.0	0.89, P < 0.001	0.89, P < 0.001	3.2	5.8

EDV = end-diastolic volume; ESV = end-systolic volume; LVEF = left ventricular ejection fraction.

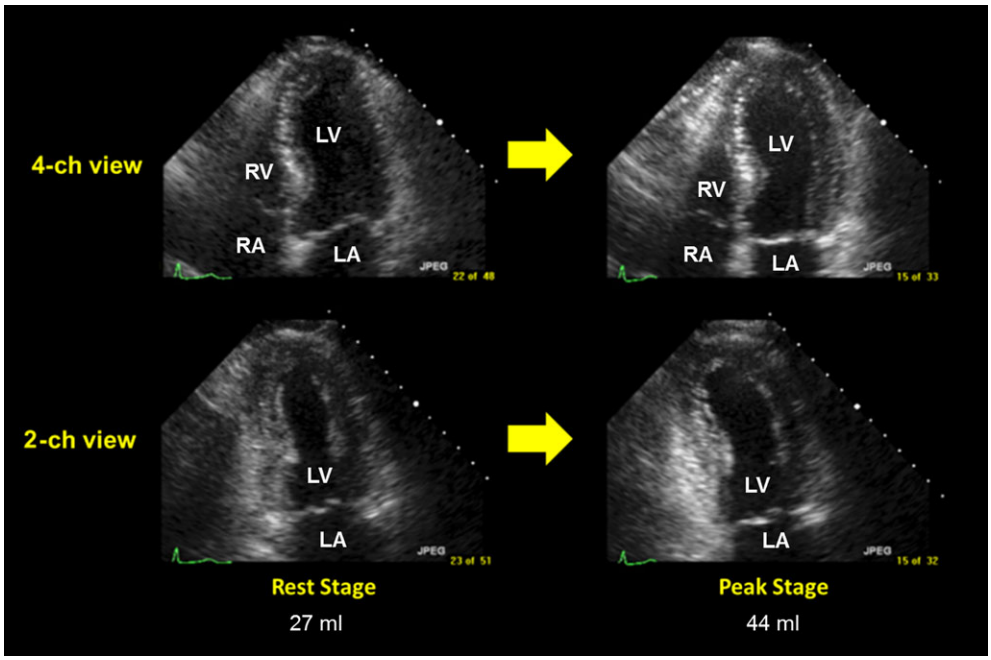

Figure 1. Example of systolic transient ischemic dilatation (TID_{ESV}). End-systolic frames of the LV apical four-chamber views (top) and apical two-chamber views (bottom) at baseline (left) and peak stress (right). LV end-systolic volume increased by 63% at peak stress compared with baseline in this case. 4-ch = apical four-chamber; 2-ch = apical two-chamber; RV = right ventricle; RA = right atrium; LV = left ventricle, LA = left atrium.

EDV increase of >13% to define TID, 12 (14%) cases had TID_{EDV} ($TID_{EDV}+$). The extent of ischemia based on number of stress-induced ischemic segments was greater in those with TID (3.8 ± 2.8 vs. 2.6 ± 1.7, $P < 0.05$). The mean peak stress LVEF was lower in the TID_{EDV+} group (53 ± 10% vs. 59 ± 10%; versus < 0.05). Patients with $TID_{EDV}+$ as defined by a > 13% increase in volume had a positive predictive value of 67% to detect moderate or greater LV myocardial ischemia with a sensitivity of 20%, specificity of 92%, and a negative predictive value of 57%.

Using the ESV increase of >9% to define TID, 27 (31%) cases had TID_{ESV} ($TID_{ESV}+$). In comparison with those without TID ($TID_{ESV}-$), $TID_{ESV}+$ was associated with a larger extent of ischemia as measured by the number of segments with inducible wall-motion abnormality (4.0 ± 2.3 segments vs. 2.2 ± 1.4 segments, $P < 0.0001$). Also for $TID_{ESV}+$ subjects, the peak stress LVEF was lower (53 ± 8% vs. 61 ± 10%, $P < 0.001$) due to stress-induced decreases in LVEF in the $TID_{ESV}+$ group (mean LVEF change −13 ± 9% vs. 6 ± 14%, $P < 0.0001$). Those in the $TID_{ESV}+$ group had a higher likelihood of moderate or greater LV myocardial ischemia (70% vs. 36%, $P < 0.01$). The majority of cases in the $TID_{ESV}+$ group had stress-induced WMA in at least 3 segments typically perfused by the left anterior descending (LAD) coronary artery. Patients with $TID_{ESV}+$ as defined by a > 9% increase in volume had a positive predictive value of 70% to detect moderate or greater LV myocardial ischemia with a sensitivity of 46%, specificity of 83%, and a negative predictive value of 64%.

In the verification group of 145 patients, an increase of >13% in LV end-diastolic volume had a good positive predictive value of 84.0% to detect moderate or greater LV myocardial ischemia with a sensitivity of 22.3%, specificity of 92.2%, and a negative predictive value of 39.2%. The patients with $TID_{ESV}+$ as defined by an increase of >9 in LV end-systolic volume had a positive predictive value of 92.9% to detect moderate or greater LV myocardial ischemia with a sensitivity of 55.3%, specificity of 92.2%, and a negative predictive value of 52.8%.

Logistic regression analysis revealed that TID_{ESV} was a stronger predictor of moderate or greater myocardial ischemia than TID_{EDV} (Table V). Assessment of the ROC curves of %ΔEDV and %ΔESV for identification of moderate or greater LV myocardial ischemia also showed that %ΔESV had a significantly stronger association with extensive ischemia than that of %ΔEDV (area under curve 0.70 vs. 0.61, $P < 0.05$) (Fig. 2).

Discussion:

This study demonstrates that dilation of end-systolic LV volume during SE is an ancillary marker of significant myocardial ischemia. In our patient cohort submitted from echocardiography

TABLE III

Echocardiographic Data for TID_{EDV}

	$TID_{EDV}-$ (N = 76)	$TID_{EDV}+$ (N = 12)	P-Value
EDV baseline, mL	89 ± 28	73 ± 28	NS
EDV peak, mL	78 ± 31	88 ± 32	NS
%Δ EDV, %	−12 ± 17	21 ± 9	<0.0001
LVEF baseline, %	59 ± 9	57 ± 11	NS
LVEF peak, %	59 ± 10	53 ± 10	<0.05
%Δ LVEF, %	1 ± 16	−5 ± 15	NS
+ SE (%)	72 (94.7)	11 (91.7)	NS
Total # + ischemic segments	2.6 ± 1.7	3.8 ± 2.8	<0.05
0 ischemic segments (%)	4 (5.3)	1 (8.3)	NS
1–2 ischemic segments (%)	39 (51.3)	3 (25.0)	NS
>3 ischemic segments (%)	33 (43.4)	8 (66.7)	NS
WMA includes LAD region (%)	43 (56.6)	8 (66.7)	NS

EDV = end-diastolic volume; %Δ = percent change; ESV = end-systolic volume; LVEF = left ventricular ejection fraction; HR = heart rate; SE = stress echocardiography; WMA = wall-motion abnormality; LAD = left anterior descending artery.

TABLE IV

Echocardiographic Data for TID_{ESV}

	$TID_{ESV}-$ (N = 61)	$TID_{ESV}+$ (N = 27)	P-Value
ESV baseline, mL	38 ± 19	34 ± 18	NS
ESV peak, mL	30 ± 18	45 ± 22	<0.01
%Δ ESV, %	−21 ± 19	33 ± 20	<0.0001
LVEF baseline, %	58 ± 10	61 ± 7	NS
LVEF peak, %	61 ± 10	53 ± 8	<0.001
%Δ LVEF, %	6 ± 14	−13 ± 9	<0.0001
+ SE (%)	56 (91.9)	27 (100)	NS
Total # + ischemic segments	2.2 ± 1.4	4.0 ± 2.3	<0.0001
0 includes segments (%)	5 (8.2)	0 (0)	NS
1–2 includes segments (%)	34 (55.7)	8 (29.6)	<0.05
>3 includes segments (%)	22 (36.1)	19 (70.4)	<0.01
WMA includes LAD region (%)	27 (44.3)	24 (88.9)	<0.001

EDV = end-diastolic volume; %Δ = percent change; ESV = end-systolic volume; LVEF = left ventricular ejection fraction; HR = heart rate; SE = stress echocardiography; WMA = wall-motion abnormality; LAD = left anterior descending artery.

TABLE V

Logistic Regression Analysis

	Odds Ratio	95% CI	P-Value
%ΔEDV	0.97	0.93–1.01	NS
%ΔESV	1.04	1.02–1.07	<0.01

%ΔEDV = percent change in end-diastolic volume; %ΔESV = percent change in end-systolic volume.

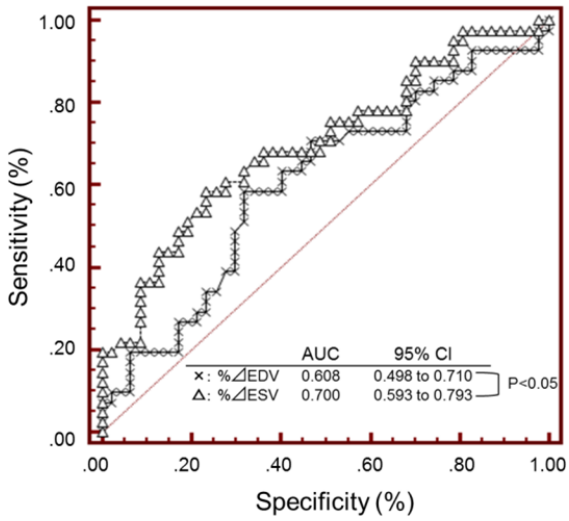

Figure 2. Receiver operating characteristic (ROC) curves of percent change in end-diastolic volume (%ΔEDV) and percent change in end-systolic volume (%ΔESV) to identify moderate or greater myocardial ischemia. AUC = area under curve; %ΔEDV = percent change in end-diastolic volume; %ΔESV = percent change in end-systolic volume.

laboratories around the world, when a >9% increase in LV end-systolic volume during stress was observed, it was associated with moderate or greater ischemia 70% of the time. This finding was present in 46% of those with moderate or greater myocardial ischemia as defined by 3 or greater segments with stress-induced WMAs. Thus, when present, TID, as defined by a >9% increase in LV end-systolic volume, should raise suspicion for more significant myocardial ischemia.

During both exercise and pharmacologic stress, the normal response of the LV is a reduction in both diastolic and systolic volumes. This response is due to many factors including enhanced contractility and stroke volume,

reduced preload either due to direct drug effect (for pharmacologic stress) or reduced filling time with increasing heart rate and altered afterload with dobutamine.[13] With experimentally induced acute ischemia due to coronary ligation, an increase in LV volume can be observed at rest.[14] However, with stress-induced ischemia, the enhanced contractility of nonischemic segments and reduced diastolic filling time may counteract the regional dilation. When the extent of ischemia reaches a certain threshold, however, the resultant systolic dysfunction and the regional geometric distortion induced by regional ischemia result in cavity enlargement. While our results suggest this ischemic dilatation occurs in both diastole and systole, the results demonstrate that systolic enlargement is a stronger marker of greater degrees of stress-induced ischemia.

Myocardial perfusion imaging defects occupying 10% of the LV myocardium are associated with an approximate 5% annual cardiac event rate and are defined as moderate ischemia. SE studies have described a similar event rate with inducible WMA of 3 or more myocardial segments.[10] Thus, we defined moderate ischemia by SE as such. While we recognize that not all subjects with moderate ischemia would exhibit a 9% degree of volume enlargement, our goal was to identify a degree of enlargement that could be used as an additional feature to discriminate mild from more moderate ischemia and thus discriminate lower from higher risk.

The finding of TID during nuclear MPI has long been considered a marker of extensive coronary artery disease and a predictor of future cardiac events.[3–5] In the MPI studies, TID is typically defined as an increase in LV area. When a 12% area change was used with stress thallium-201 scintigraphy, this finding had a 60% sensitivity and 95% specificity for severe coronary artery disease.[5] A 12% area change would translate into a larger volume change than the one we defined for SE. Thus, since the cut point for TID was larger, it is not surprising that specificity would be higher and sensitivity lower for MPI than SE.

Previous SE studies have described this phenomenon of TID but defined it as occurring when volumes increased by 12 or 17%.[6,15,16] The threshold of 12% was identified as the best cut point for identifying 3 vessel coronary artery disease and the 17% cut point was selected to identify with 100% sensitivity those with severe and extensive angiographic CAD.[6,15]

Thus, while the concept of TID has been studied in stress echo in the past, our work provides further detail to the knowledge base. Specifically, we focused on using TID to identify high-risk myocardial ischemia rather than a certain degree of anatomic CAD as in prior studies. By providing a detailed analysis of the relationship between the percent change in LV volume and the presence of moderate myocardial ischemia, we were able to determine an optimum cut point for both LV end-diastolic and end-systolic volume change. We have demonstrated that the cut points differ for each and showed that end-systolic volume TID change was better than end-diastolic volume change for identifying moderate or greater myocardial ischemia. Using data from the Heart and Soul Trial, Turakhia and colleagues showed that a failure of LV end-systolic volume to decrease during exercise stress echo was associated with a higher risk of subsequent mortality. Our results suggest that the degree of myocardial ischemia is the major explanation for this adverse outcome in these patients.[17]

Our results indicated that TID_{ESV} in SE was a better marker than TID_{EDV} to identify moderate or greater stress-induced LV myocardial ischemia. This is similar to that observed in post-MI remodeling where systolic changes are a stronger prediction of outcome.[18] Recent observations with reverse remodeling after successful cardiac resynchronization therapy also suggest that systolic volume changes are the preferred parameter rather than diastolic volume improvements.[19, 20] We observed that a majority of the patients with TID have ischemia that involves the anterior territory and this is similar to that observed with post-MI remodeling where the majority of adverse volume changes occurs with anterior myocardial infarctions.[21] Studies with radionuclide myocardial perfusion imaging suggest that significant dilation during exercise or pharmacologic stress can be due to extensive subendocardial hypoperfusion and systolic LV dysfunction. This also supports a stronger role for ESV changes.[3]

Study Limitations:

The number of patients in our study with TID was small but reflects the real-world experience of unselected patients undergoing stress echocardiography for evaluation of chest pain at our enrolling sites. Due to the lack of availability of demographic, clinical variables, angiographic data, and outcomes at the echocardiography core laboratory in this site certification phase of this actively enrolling multicenter randomized trial, we were unable to determine whether such variables are associated with TID. Echocardiographic contrast agents were used in 13 of the cases and this will result in larger LV volumes in these cases.[22] However, since the change within patients was the variable of interest and such changes in volume would occur at both rest and stress, this variable use of contrast should not impact the results. The type of exercise stress (treadmill, upright bike, or supine bike) or

pharmacologic agent (dobutamine or vasodilator agent) may influence LV volume differently because of their different effects on loading conditions. There are little data on the effect of position during stress echocardiography. Of most importance for this study, the TID occurred in both upright exercise and supine dobutamine studies. Whether position influenced the extent of volume change is unknown and our sample size for each stress type is not sufficient to assess this possibility.

Conclusions:

As with MPI, in patients with stable ischemic heart disease, TID of the LV during SE is an ancillary marker of more extensive myocardial ischemia especially when calculated from end-systolic volumes. This finding can be integrated with the interpretation of stress-induced segmental LV function to assist in the identification of higher risk patients.

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Disclosures:

Dr. Senior is a member of the speaker's bureau for and has received honoraria from Bracco Diagnostics (Milan, Italy) and Philips Healthcare (Eindhoven, Netherlands) and is a member of an advisory board for GE Healthcare (Milwaukee, WI).

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