Examining a novel threshold for defining electrocardiographic ischemia with vasodilator stress

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Based on their 8615-patient study in which 133 patients had ≥ 0.5 mm of ST depression during regadenoson stress, Doukky and colleagues propose the use of a new threshold to define electrocardiographic ischemia during vasodilator stress.¹ Previous investigators evaluated the diagnostic and prognostic significance of ST depression during vasodilator stress using the same thresholds as those used for exercise-induced ischemia—either (1) 1 mm of horizontal or downsloping ST depression, as recommended in the 2002 ACC/AHA guidelines,^{2–5} or (2) 1 mm of horizontal or downsloping ST depression or 1.5 mm of upsloping ST depression,^{6–10} the latter as defined by Ellestad.^{11,12}

The concept of using different thresholds for exercise and vasodilator induced ischemia has merit as the causes of ST depression are thought to be different, demand ischemia during exercise testing compared to myocardial steal or differential coronary flow reserve in different coronary territories during vasodilator stress.^{9,13}

ST depression during vasodilator stress with normal SPECT perfusion images is unusual, typically occurring in 1% to 2% of studies. Table 1 summarizes the findings of many of the key studies that have examined this

scenario. As would be expected, ST depression is more common in patients in whom perfusion is abnormal than in whom perfusion is normal. Investigators who examined ST depression in the setting of abnormal perfusion have found such patients to have more extensive CAD and a worse prognosis than those without ST depression.^{1,5,6,14–16}

Intuitively, ST depression in patients undergoing vasodilator stress with normal perfusion would also be predictive. This is unless the perfusion images trump ECG response. A review of the studies summarized in the table demonstrate that cardiac death, non-fatal myocardial infarction (MI), and revascularization are higher than would be expected in all comers with ST depression and normal perfusion.

The 2003 seminal studies of Klodas,³ Abbott,⁶ and colleagues found a substantial event rate in their studies of 49 and 66 patients, respectively. Subsequent studies observed a lower frequency of events, but still more than would be expected among patients with normal perfusion. Studies which included patients with known CAD and/or abnormal baseline ECGs observed higher event rates than those in which such patients were excluded from the sample that was studied.^{16,17}

Apparently only two studies have examined whether ST depression during vasodilator PET adds incremental information to normal ⁸²Rb PET perfusion. While Chow and co-workers did not find that it added incremental information,⁷ Aljizeeri observed a hazard ratio of 2.2 for cardiac events in this population.¹⁸

In 2015, Doukky and colleagues reported a study of 629 patients who underwent both regadenoson MPI and clinically indicated coronary angiography within 6 months.¹⁵ In this study they evaluated the a priori hypothesis that a lower threshold, ≥ 0.5 mm of ST depression, may optimize diagnostic and predictive

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Table 1. Summary of studies evaluating outcomes in patients with ECG changes and a normal MPI

Year	Study author	Number of patients	% Cohort	Pharmacologic stress agent	Women (%)	Mean follow-up (months)	Endpoint (number of events/revascularizations)
2003	Klondas et al ³	49	1	D/A	88	28	2 cardiac deaths 4 non-fatal MI 5 coronary revascularization
2003	Abbott et al ⁶	66	7	A	82	29	2 cardiac deaths 5 non-fatal myocardial infarction 9 coronary revascularization
2006	Hage et al ⁸	65	1	A	80	24	0 cardiac deaths 0 non-fatal MI 6 coronary revascularization
2009	Hage et al ⁹	73		A	81	21	0 cardiac deaths 0 non-fatal MI 7 coronary revascularization
2010	Sharma et al ¹⁰	76	2	A	87	24	0 cardiac deaths 0 non-fatal MI 10 coronary revascularization
2012	Azemi et al ⁵	130	5	D/A		29	Prognostic cohort Approximately 3% cardiac death/non-fatal MI per year (Figure 3 of Azemi, et. al.)
2013	Uthamalingam et al ⁴	43	2	R	77	14	1 cardiac death 0 non-fatal MI 5 coronary revascularization
2018	Doukky et al ¹	91	1-1.5	R		30	ST depression of ≥ 0.5 mm predicted a composite of cardiac death/non-fatal MI and coronary revascularization
PET							
2005	Chow et al ⁷	72	4	D	83	27	⁸² Rb PET MPI 0 cardiac deaths 1 non-fatal MI 2 coronary revascularization

Table 1 continued

Year	Study author	Number of patients	% Cohort	Pharmacologic stress agent	Women (%)	Mean follow-up (months)	Endpoint (number of events/revascularizations)
2018	Aljizeeri et al ¹⁸	114	4	D/R	82	24	⁸² Rb PET MPI Hazard ratio of 2.24 for composite endpoint of cardiac death, non-fatal MI, admission for ACS, late coronary revascularization

R, regadenoson; A, adenosine; D, dipyridamole; MI, myocardial infarction; ACS, acute coronary syndrome

information. This degree of ST depression was observed in 117 of the 629 patients. Among these, CAD was more severe in patients with abnormal and normal SPECT MPI compared to those without ST depression. More cardiac events were also seen in those with ≥ 0.5 mm of ST depression whose MPI was normal. There was also a trend in those with ≥ 0.5 mm of ST depression and an abnormal MPI to have more events.

Doukky and colleagues further examined this hypothesis in the current 2.5-year prognostic study. They found ≥ 0.5 mm of ST depression to predict cardiac death, non-fatal MI, and coronary revascularization in patients with abnormal or normal MPI, if adjusted for clinical and other imaging factors.¹ Among those in the subgroup of patients with greater ST depression, ≥ 1.0 mm, ST depression was not predictive. Fewer patients were in the latter group, 133 vs 89 with ≥ 0.5 mm, making this latter finding likely secondary to the smaller sample size. Doukky and colleagues concur.¹⁵ Based on their 2015 and current studies, the investigators propose that ≥ 0.5 mm ST depression be reported if observed during vasodilator stress and is predictive of ischemia and cardiac outcomes.

The study does have limitations that limit the generalizability of their recommendations. The investigators used 1:3 rest:stress ^{99m}Tc radioisotope dosing.^{1,15} The recently published 2017 EXERRT trial found that “shine through” using 1:3 dosing without a prolonged delay between rest and stress decreased the ability to assess ischemia by MPI compared to multi-day MPI in which “shine through” would not occur.^{19–21} In retrospect, the use of 1:3 dosing could have resulted in less ischemia on MPI, thus decreasing the predictive power of perfusion and overestimating the predictive impact of ECG changes relative to an optimal perfusion protocol.

Another study limitation is its retrospective design and hence the use of the clinician’s interpretation of the ECG.¹ While practical, a blinded independent review of ECG changes would provide more confidence that ST depression of 0.5 to 0.9 mm was indeed the maximum observed rather than simply the most apparent to the testing clinician. The authors also cite this as a limitation.

CONCLUSIONS

How shall we incorporate the important contributions of Doukky and colleagues? As we await further studies, ideally prospective and from multiple sites, we recommend that ST depression of 0.5 to 0.9 mm occurring during vasodilator stress not be dismissed but be reported and considered as an equivocal finding. As seen in exercise testing, increasing ST depression predicts more severe CAD and worse prognosis.^{12,22} The

astute nuclear practitioner will incorporate 0.5 to 0.9 mm of ST depression into their clinical judgment/ Bayesian analysis as they integrate the perfusion results with ECG results and clinical information about the patient.

If pretest likelihood of CAD is *very low*, normal perfusion with ST depression of 0.5 to 0.9 mm likely represents a false positive ECG response. If pretest likelihood is *low*, coronary calcium testing or closer monitoring and potentially repeat testing at a later time will often be of benefit. If the pretest likelihood is *intermediate* or *high*, coronary calcium testing or CT coronary angiography would often be helpful to determine if invasive coronary angiography or guideline based medical therapy for CAD is indicated.

Disclosure

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