The Long-Term Prognostic Value of Negative Contrast Stress Echocardiography

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Abstract

Stress echocardiography is a sensitive and specific non-invasive technique for evaluation of my-ocardial ischemia. Stress echocardiography is portable and does not involve ionizing radiation. A known limitation of stress echocardiography is inadequate definition of the endocardial border, especially in patients with suboptimal imaging windows. Contrast echocardiography is indicated for detection or definition in these patients or in cases where more than two cardiac segments are not adequately visualized. To date, few studies have evaluated the long-term prognostic value of contrast stress echocardiography. This study sought to determine the prognostic value of contrast stress echocardiography in patients at low to intermediate risk of coronary atherosclerotic disease.

Methods: Patients referred to the Emory University Hospital echocardiography lab for stress echocardiography and received Optison (R) contrast for left ventricular (LV) endocardial enhancement were included in this study. Patients received contrast when two or more cardiac segments were not adequately visualized. Demographic data and indication for examination was collected for each patient. Each study was classified as either negative for ischemia or positive if there was a new wall motion abnormality or worsening of a baseline abnormality. The comprehensive electronic medical record was subsequently reviewed for major adverse cardiovascular events including death from any cause, death from a cardiovascular cause, myocardial infarction, congestive heart failure exacerbation, need for hospitalization for anginal chest pain, need for revascularization. This study was approved by the Emory University Hospital institutional review board.

Results: Fifty-one patients met the inclusion criteria for this study. Three patients had a positive stress echocardiogram. Of these three patients, one was treated with optimal medical therapy and the other two underwent angiography with percutaneous coronary intervention. During the mean follow-up period of 2.2 +/- 1.02 years (median 1.95 years) there was one death attributed to a patient discharge to Hospice, and there were no deaths attributable to a cardiac etiology. There was one hospitalization for unstable angina and one hospitalization for a congestive heart failure exacerbation in the same patient. No patients underwent revascularization or had a myocardial infarction. Three cardiac catheterizations were performed during the follow-up period with no significant coronary artery disease.

Conclusions: Contrast stress echocardiography is useful for the noninvasive assessment of myocardial is-chemia. A negative contrast stress echocardiogram conveys a favorable prognosis over a two year period with a 98.0% negative predictive value.

Keywords: Stress echocardiography, Demographic data, Ischemia, Myocardial infarction, Coronary intervention

Introduction

Coronary artery disease is the leading cause of morbidity and mortality in the US [1]. While invasive coronary angiography is the gold standard for evaluation of coronary stenosis, the invasive nature of the test, radiation dose, and contrast load limit its routine use in low and intermediate risk patients.

For patients at intermediate risk of coronary artery disease, current guidelines recommend the use of non-invasive testing as the first line diagnostic modality [2]. In the US the most common non-invasive tests are nuclear myocardial perfusion imaging (MPI) and stress echocar-diography. Stress echocardiography and MPI have comparable sensitivities and specificities [3]. Compared to nuclear imaging, stress-echocardiography does not require any degree of ionizing radiation, is portable, and relatively less expensive.

An inherent limitation of stress echocardiography is the ability to define the endocardial borders in approximately 20% of the patient population. Contrast echocardiography is commonly per-formed to better delineate the left ventricular endocardium, which allows for better evaluation of wall motion. Current American Society of Echocardiography guidelines recommend contrast echocardiography to assess segmental wall motion abnormalities, increase the proportion

of di-agnostic studies, and increase reader confidence in interpretation [4]. Optison (Perflutren Protein-Type A Microspheres, injectable suspension, GE Healthcare) is indicated for enhancement of the left ventricle endocardium in patients with suboptimal echocardiograms. The agent is stable at room temperature for 24 hours, does not require a vial mixture, and can be injected at any stage of the echo procedure.

While multiple studies have assessed the diagnostic utility and safety of Optison for contrast stress echocardiography [5], to date few studies have evaluated the long-term prognostic value of contrast stress echocardiography. The reported negative predictive value of stress echocardiography is greater than 95% [6]. This study sought to determine the prognostic value of contrast stress echocardiography in patients at low to intermediate risk of coronary atherosclerotic disease.

Methods

This study was approved by the Emory University institutional review board. This is a single-center study based on review of the Emory University Hospital echocardiography database. Patients included in the study were referred to the Emory University Hospital echocardiography lab for stress echocardiography and received Optison (R) contrast for LV endocardial enhancement. Contrast was used when 2 or more segments could not be adequately visualized. Study enrollment began in 2012. Sample size was determined using a one group *Chi-Squared* test. Approximating that the echo contrast would improve the technically inadequate stress echo to only 5% compared to 15-20%, a one group *Chi-Squared* test with a 0.050 one-sided significance level would have 80% power to detect the difference between the null hypothesis proportion and the alternative proportion at a sample size between 42-79 patients. The echocardiographic images were acquired on either Phillips or GE scanners and analyzed with either Phillips and GE software. Data was collected and analyzed using SPSS 22.0.0 for Macintosh.

Patient's demographic data was collected including-age, sex, history of-congestive heart failure, hypertension, diabetes mellitus, hyperlipidemia, tobacco use, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. The indication for each study was collected using ICD codes. Each study was classified as either negative for ischemia or positive if there was either a new wall motion abnormality or worsening of a baseline abnormality. The comprehensive electronic medical record was subsequently reviewed for major adverse cardiovascular events including death from any cause, death from a cardiovascular cause, myocardial infarction, congestive heart failure exacerbation, need for hospitalization for anginal chest pain, need for revascularization.

Results

Fifty-one patients met the inclusion criteria for this study (21 female; 30 male). Stress was induced with Dobutamine in 41 patients and exercise in 10 patients. Baseline patient

demographics are shown in **Table 1** and indications for examination are outlined in **Table 2**. **Table 3** summarizes the cardiovascular medications prescribed to patients. Mean follow-up time for all patients was 2.2 +/- 1.02 years (median 1.95 years).

The patient outcomes are summarized in **Figure 1**. Specifically, three patients had a positive stress echocardiogram. Of these three patients, one had known coronary artery disease and was treated with optimal medical therapy without a cardiac catheterization performed, and the other two underwent angiography that revealed obstructive coronary artery disease requiring percutaneous coronary intervention. During the follow-up period there was one non-cardiac death attributed to a patient discharge to Hospice, and there were no deaths attributable to a cardiac etiology.
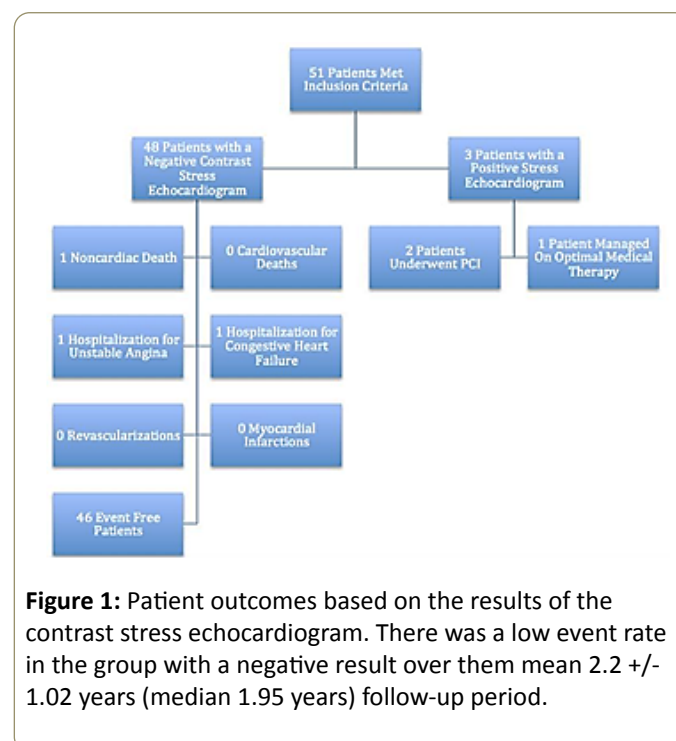
Figure 1: Patient outcomes based on the results of the contrast stress echocardiogram. There was a low event rate in the group with a negative result over them mean 2.2 +/- 1.02 years (median 1.95 years) follow-up period.

There was one hospitalization for unstable angina and one hospitalization for a congestive heart failure exacerbation in the same patient. No patients underwent revascularization or had a myocardial infarction. Three cardiac catheterizations were performed during the follow-up period with no significant coronary artery disease. Furthermore, in the negative stress group 3 patients underwent cardiac catheterization during the follow up period with no significant coronary artery disease.

Discussion

This small study summarizes the Emory University Hospital experience with Optison contrast stress echocardiography from 2012 onward. The majority of patients in this study had a normal Optison stress echo, paralleling the trend in decreasing

stress induced ischemia during SPECT-MPI studies, previously published by Rozanski [7].

Table 1: Baseline study population characteristics.

Age	59.6 years
Sex	41.1% Female
History of CHF	2
History of HTN	33
History of Diabetes Mellitus	17
History of Tobacco Use	23
History of Dysplipidemia	16
History of MI	2
History of PCI	2
History of CABG	2
Describes the baseline characteristics of patients included in the study. The risk factors in this population place those who underwent contrast stress echocardiography at intermediate risk for coronary artery disease	

Table 2: Indications for contrast stress echocardiogram.

Indication for Exam	Number of Exams
Cardiomyopathy	1
Chest Pain	16
Dyspnea	1
Evaluate Cardiac Function	1
Family History of Ischemic Heart Disease	1
Palpitations	1
Pre-Operative Evaluation	28
Screening for Cardiovascular Conditions	2
Details the indication for each contrast stress echocardiogram by ICD code.	

Table 3: Cardiovascular medications during follow-up period.

Medication/Medication Class	Negative Stress Cohort	Positive Stress Cohort
Aspirin	16	3
Statin	8	2
ACE/ARB	17	2
Clopidogrel	1	1
Beta-Blocker	13	2
Calcium Channel Blocker	15	2
Diuretic	9	1
Details cardiovascular medications taken by patients in the follow-up period		

The study was conducted at a tertiary referral center; however the baseline demographics approximate the severity and prevalence of illness seen across practice settings. While multiple studies have evaluated the prognostic role of stress echocardiography [8,9] there are limited studies in patients exclusively undergoing contrast stress echocardiograms [10].

This study further delineated the value of contrast stress echocardiography in patients at intermediate risk for coronary artery disease. Notably, in this study cohort, patients without evidence of inducible ischemia had a favorable prognosis during the follow-up period. This can be at least partially explained by the enhanced delineation of the endocardial border using Optison. The negative predictive value of 98.0% over approximately a two year period emphasizes the utility of contrast stress echocardiography. Following a negative study, patients can be reassured of the low-likelihood of a major adverse cardiovascular event. Additionally, the addition of Optison contrast led to 100% interpretability of stress echocardiograms, eliminating the need for repeat or invasive studies.

Contrast stress echocardiography is a portable and radiation free non-invasive evaluation of cardiac structure, function, and assessment for ischemia. It conveys meaningful diagnostic and prognostic information in patients at intermediate risk of coronary artery disease. The low event rate following a negative study underscores the value of a negative contrast stress echocardiogram.

Limitations

This was a single center study with a relatively small number of patients. Despite being performed at one center, multiple cardiologists were involved in the interpretation of the studies. Additionally, as the study was performed in a tertiary setting there is a diverse case mix to avoid bias in an overly low risk population. Further studies are warranted with a larger sample population.

Acknowledgements

References

1. Alan SG, Dariush M, Véronique LR, Emelia JB, Jarett DB, et al. (2014) Heart disease and stroke statistics--2014 update: a report from the Ameri-can Heart Association. Circulation. 129: e28-e292.

2. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, et al. (2012) 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology 60: e44-e164.

3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European So-ciety of Cardiology. Eur Heart J 34: 2949-3003.

4. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, et al. (2008) American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr 21: 1179-1201.

5. Wei K, Mulvagh SL, Carson L, Davidoff R, Gabriel R, et al. (2008) The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 21: 1202-1206.

6. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, et al. (2007) The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 49: 227-237.

7. Rozanski A1, Gransar H, Hayes SW, Min J, Friedman JD, et al. (2013) Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. J Am Coll Cardiol 61: 1054-1065.

8. Yao SS, Wever-Pinzon O, Zhang X, Bangalore S, Chaudhry FA (2012) Prognostic value of stress echocardiogram in patients with angiographi-cally significant coronary artery disease. Am J Cardiol 109: 53-58.

9. Supariwala A, Makani H, Kahan J, Pierce M, Bajwa F, et al. (2014) Feasibility and prognostic value of stress echocardiography in obese, morbidly obese, and super obese patients referred for bariatric surgery. Echocardiography 31: 879-885.

10. Yokoyama N, Schwarz KQ, Steinmetz SD, Li X, Chen X (2004) Prognostic value of contrast stress echocardiography in patients with image quality too limited for traditional noncontrast harmonic echocardiography J Am Soc Echocardiogr 17: 15-20.