The combined pharmacological stress echocardiography protocol for predicting viability in territories supplied by coronary arteries at varying degrees of obstruction

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Abstract

Background: Pharmacological stress echocardiography has gained wide acceptance for identification of myocardial viability.

Aim: We sought to explore the diagnostic accuracy of the combined pharmacological stress echocardiography protocol to predict viability of myocardial segments supplied by arteries at varying degrees of stenosis/occlusion.

Methods: We enrolled 100 consecutive patients with significant coronary stenosis/occlusion, prior myocardial infarction, and regional wall motion abnormality in the distribution of the affected artery. All patients underwent assessment of global and regional left ventricular systolic function. Patients underwent 3 pharmacological stress echocardiography protocols: low dose dobutamine, infra-low dose dipyridamole, and combined protocols. They underwent thereafter successful coronary revascularisation either by percutaneous coronary angioplasty, or by surgical bypass grafting. Follow-up echocardiography was performed 8 weeks later. Segments were subdivided according to the severity of stenosis/occlusion of the supplying artery into 3 subgroups, namely: those supplied by totally occluded, critically stenosed, or subcritically stenosed arteries. Predicted recovery by any of the 3 protocols for each category of segments was compared with real contractility improvement after revascularisation.

Results: The combined protocol had a significantly higher sensitivity for predicting contractile recovery in all segment categories compared with the other 2 protocols. In addition, it had a similar specificity in segments supplied by subcritically stenosed arteries, though with a lower specificity in segments supplied by totally occluded and critically stenosed arteries when compared with the other two protocols.

Conclusion: The combined pharmacological stress protocol would better predict viability, as compared to the low dose dobutamine and the infra-low dose dipyridamole protocols, particularly in segments supplied by subcritically stenosed arteries.

Key words: stress echocardiography, viability, percutaneous coronary intervention

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Introduction

With the recent advances in myocardial revascularisation over the past two decades, identification of myocardial viability has gained special attention, particularly in patients triaged for interventional therapy [1]. Myocardial viability represents a state of impaired contractility as a result of reduced blood supply, which is probably reversible with restoration of blood flow [2]. Apparently, improving blood flow to dysfunctional but viable regions results in improvement of regional and global left ventricular (LV) function, NYHA class, functional capacity, and long-term survival. Therefore, a chief concern is whether 'weakly contracting' segments represent viable myocardium with seriously compromised blood flow, or scar tissue with irreversible damage [3]. This theme was sustained by the previous findings that only patients with severe LV dysfunction who had viable myocardial segments improved after revascularisation [4].

Pharmacological stress echocardiography is widely approved for identification of viable myocardium, chiefly because it is feasible, safe, with a high diagnostic and prognostic accuracy [5]. Low dose dobutamine echocardiography is widely used now for detecting viable myocardium, being able to induce an increase in myocardial contractility. Positive dobutamine response has a high specificity for predicting viability; however, its sensitivity is still limited [6]. Several studies have found that coronary vasodilator stress can recruit an inotropic reserve in viable segments [7-11]. The recently described infra-low dose

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dipyridamole regimen successfully predicts viable myocardium, with almost no ischaemic hazard. Despite its high specificity, its sensitivity is again unsatisfactory [7, 8].

The combination of low dose dobutamine and infra-low dose dipyridamole would therefore be an appealing means of increasing the sensitivity of pharmacological stress echocardiography. It has gained wider acceptance because it is widely available, well-tolerable, inexpensive, has no radiation exposure, and moreover, has better diagnostic accuracy when compared to either agent used separately [12, 13]. In a prospective study design, we tried to explore the diagnostic accuracy of the combined pharmacological stress echocardiography protocol for predicting viability of myocardial segments supplied by arteries at varying degrees of stenosis/occlusion.

Methods

Patients

We included 100 consecutive patients referred from our catheterisation labs with significant coronary stenosis/occlusion, during the period from January 2004 to December 2007. Patients were considered eligible for inclusion if they had regional wall motion abnormality in the territory of the affected artery as explained later, an affected artery amenable for revascularisation, and evidence of prior myocardial infarction (MI) at least 3 months before study enrolment. Significant coronary stenosis was defined as at least 70% luminal obstruction of at least one sizable coronary artery (measuring 2.5 mm or more in diameter) estimated by quantitative coronary angiography, seen in 2 different projections. Total coronary occlusion was defined as 100% luminal obstruction with Thrombolysis In Myocardial Infarction (TIMI) grade 0 forward flow distal to the site of obstruction. Prior MI was defined based on 12--lead ECG showing abnormal Q waves (≥ 1 mm in width) in at least two contiguous leads or previous lab evidence of elevated cardiac biomarkers at the time of the index infarction: CK MB isoenzyme and/or troponin more than twice the upper limit of normal lab reference. We excluded patients with post-infarction unstable angina or severe haemodynamic instability, protruding fresh LV thrombus, significant valvular or congenital heart disease, any myocardial disease apart from ischaemia, LV ejection fraction (EF) > 45%, contraindication to dobutamine (for example: history of complex ventricular arrhythmias, uncontrolled hypertension with blood pressure > 180/110), contraindication to dipyridamole (for example: bronchial asthma, second or third degree heart block), and patients with limited life expectancy due to coexistent disease (for example: malignancy). Before inclusion, informed consent was obtained from each patient and the study protocol was reviewed and approved by our local institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Resting echocardiographic assessment

Assessment of regional and global LV systolic function was performed in all patients by trans-thoracic echocardiography within 48 h of coronary angiography. Doppler echocardiography was performed using a Hewlett Packard Sonos 5500 cardiac ultrasound machine (Hewlett Packard, Andover, Massachusetts, USA) equipped with harmonic imaging capabilities. A 2.5 MHz phased array probe was used to obtain standard 2D, M-mode and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Images were digitised in cine-loop format and saved for subsequent playback and analysis. Views were analysed by a single echocardiographer employing the software program of the echocardiography machine. Biplane global LV systolic function was assessed in apical 4-chamber and 2-chamber views using the modified Simpson's rule. Regional wall motion was assessed according to the standard 16-segment model recommended by the American Society of Echocardiography [14]. Individual segments were then subgrouped based on the known vascular distribution into left anterior descending territory, left circumflex territory, right coronary artery territory, and overlap segments [14]. Regional wall motion was visually assessed for each segment individually, considering both endocardial excursion and systolic thickening, and each segment was graded according to the semi-quantitative scoring system described by Knudsen et al. [15]. Segments with poorly defined endocardial borders for 50% or more of their length were considered non-visualised and assigned a score of 0 [16]. Wall thickening was assessed at a distance of at least 1 cm from the adjacent segment to minimise the effect of tethering [17]. Wall motion in a vascular territory was considered abnormal if wall thickening was abnormal in at least two contiguous non-overlap segments [14]. Wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments.

Stress echocardiographic protocols

Once patients were identified as eligible, they underwent the following stress echocardiography protocols in separate sessions shortly after the performance of resting echocardiography. The 3 stress protocols were performed to all patients on 3 successive days (each test on a separate day).

1. Low dose dobutamine: Dobutamine was infused starting at 5 µ/kg/min, increased by 5 µ/kg/min every 3 min (that is at 5, 10, 15 and 20 µ/kg/min) up to 20 µ/kg/min.
2. Infra-low dose dipyridamole: Dipyridamole was given intravenously in a dose of 280 µ/kg over 4 min.
3. Combined protocol: Infra-low dose dipyridamole was given, immediately followed by low dose dobutamine infusion as before.

Standard views were recorded at baseline, during each stage of the infusion protocol, as well as during recovery. Visual assessment of wall motion and thickening was

performed by the same echocardiographer as before. Global LV systolic function and wall motion score index were evaluated at the end of each stage. The presence of viability was defined by improvement of regional wall motion score by at least one grade (dyskinesis changing to akinesis was not considered viability) in at least two contiguous non-overlap segments in the territory of the index artery, as compared to baseline evaluation [17].

Our stress test protocols were performed with the patients on their full anti-ischaemic and anti-heart failure medications, and before infra-low dose dipyridamole, all caffeine beverages and theophylline-containing preparations were stopped for at least 24 h. The other recommendations of the European Association of Echocardiography were followed [18].

Coronary revascularisation

All patients underwent successful complete coronary revascularisation within one week after stress echocardiography, either by percutaneous coronary angioplasty, or by surgical bypass grafting, according to the decision of the attending physician. The decision was based on coronary anatomy and clinical characteristics, but not on the presence or absence of contractile reserve by any of the stress test protocols. Complete revascularisation was defined as revascularisation of all sizable coronary arteries affected by significant stenosis/occlusion, according to the above-mentioned definitions.

Echocardiographic follow-up

Follow-up echocardiographic re-assessment was performed 8 weeks after revascularisation to evaluate regional and global LV systolic function as described before. Evaluations were performed offline by the same echocardiographer, who was blinded to both clinical and angiographic data. The presence of viability was defined by improvement of regional wall motion score by at least one grade (dyskinesia changing to akinesia was not considered viability) in at least two contiguous non-overlap segments in the territory of the index artery, as compared to pre-revascularisation resting assessment. During follow-up, patients were interrogated for the occurrence of new MI or congestive heart failure by clinical visits, telephone calls, hospital chart reviews, or personal communication with the referring physician.

Statistical analysis

All continuous variables are presented as mean ± SD, if they were normally distributed. Differences in the normally distributed variables were assessed using the t-test and the paired t-test for dependent variables. Categorical variables were described with absolute and relative (percentage) frequencies. The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated according to the standard definitions for each of the 3 stress echocardiography protocols to predict viability (contractility improvement after revascularisation). Segments were subdivided according to the severity of stenosis/occlusion of the supplying artery into 3 subgroups: group with totally occluded supplying artery, group with critical stenosis of the supplying artery (defined as luminal obstruction ≥ 90% but < 100%), and group with subcritical stenosis of the supplying artery (defined as luminal obstruction ≥ 70% but < 90%). The above statistical values were then calculated individually for each of the 3 stress echocardiographic protocols in each subgroup of segments. Twenty cases were randomly selected for analysis of intra-observer variability. Assessment of variability was performed using linear regression analysis. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

A total of 100 consecutive patients with evidence of prior MI who underwent coronary revascularisation for significant coronary stenosis/occlusion were included in the current study. The baseline characteristics of the whole series are shown in Table I. Of all myocardial segments studied 564 segments were hypokinetic, 502 akinetic, and 23 dyskinetic. Moreover, 57 segments were poorly defined and assigned a score of 0. Revascularisation was performed by surgical bypass grafting in 40 (40%) patients, and by percutaneous coronary angioplasty in 60 (60%) patients. All patients revascularised surgically received a left internal mammary artery graft to the left anterior descending coronary artery, of whom 35 patients received 69 saphenous vein grafts to other coronary arteries, as well. Of the patients revascularised percutaneously, 54 patients underwent balloon angioplasty and stenting, 3 underwent direct stenting, and 3 underwent balloon angioplasty only.

At 8 weeks of follow-up, wall motion score index was 1.8 ± 0.26, and LVEF was 39.3 ± 7.1, neither of which was significantly different from the baseline values (data not shown).

Table II shows the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of the 3 stress echocardiographic protocols to predict viability (contractility improvement after revascularisation). The sensitivity of the combined protocol was considerably higher, yet its specificity was slightly lower when compared to either of the other 2 protocols.

Table III shows the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of the 3 stress echocardiographic protocols to predict viability individually for each segment group. For segments with totally occluded supplying artery, the sensitivity of the combined protocol was markedly higher; yet, its specificity was somewhat lower when compared to either of the other 2 protocols. For segments with critically stenosed

Table I. Baseline clinical, echocardiographic and angiographic characteristics of the whole series

	Study cohort (n = 100)
Age [years]	52.6 ± 8.8
Males	85 (85)
Smoking	77 (77)
Diabetes	33 (33)
Hypertension	50 (50)
Dyslipidaemia	75 (75)
FH of IHD	23 (23)
Infarction site	
anterior	52 (52)
inferior	40 (40)
lateral	8 (8)
Echo data	
LVEF	38.5 ± 8.1
WMSI	2.04 ± 0.38
mitral regurgitation	33 (33)
Angiographic data	
SVD	37 (37)
DVD	28 (28)
MVD	35 (35)

All continuous variables are presented as mean ± SD, while categorical variables are presented as numbers (percentage)
Abbreviations: FH – family history, IHD – ischaemic heart disease, LVEF – left ventricular ejection fraction, WMSI – wall motion score index, SVD – single vessel disease, DVD – double vessel disease, MVD – multi-vessel disease

supplying artery, the sensitivity of the combined protocol was appreciably higher; yet, its specificity was rather lower when compared to either of the other 2 protocols. For segments with sub-critically stenosed supplying artery, the sensitivity of the combined protocol was fairly higher when compared to either of the other 2 protocols; yet, the specificity was quite similar between the 3 protocols.

All 3 stress echocardiography protocols were well tolerated by all patients, with no major side effects during or after the test. Moreover, no patient reported any clinical events during the period from revascularisation to follow-up echocardiographic evaluation.

Analysis of intra-observer variability revealed a close correlation between repeated measurements of regional wall motion by the single operator, with a correlation coefficient r = 0.92.

Discussion

Our data showed that the combined protocol had a remarkably higher sensitivity for predicting functional recovery in all segment categories as compared to either of the other 2 protocols, in addition to a similar specificity in segments supplied by subcritically stenosed arteries, though with a slightly lower specificity in segments supplied by totally occluded and critically stenosed arteries. The diagnostic accuracy of the combined protocol was consistently higher than the other 2 protocols in all segment categories.

Table II. Sensitivity, specificity, positive and negative predictive values of the 3 pharmacological stress echocardiography protocols for predicting recovery of all basally dyssynergic segments (1089 segments)

Stress protocol	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Accuracy [%]
Low dose dobutamine	76	94	96	67	82
Infra-low dose dipyridamole	72	97	98	64	80
Combined protocol	95	87	94	90	92

Table III. Sensitivity, specificity, positive and negative predictive values of the 3 pharmacological stress echocardiography protocols for predicting viability in individual groups of segments

Stress protocol	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Accuracy [%]
Group with totally occluded supplying artery (314 segments)					
Low dose dobutamine	56	97	95	68	76
Infra-low dose dipyridamole	61	98	97	71	79
Combined protocol	92	88	89	91	90
Group with critical stenosis of supplying artery (379 segments)					
Low dose dobutamine	77	90	93	69	81
Infra-low dose dipyridamole	73	96	97	67	81
Combined protocol	93	83	91	87	89
Group with subcritical stenosis of supplying artery (396 segments)					
Low dose dobutamine	86	97	99	61	88
Infra-low dose dipyridamole	77	97	99	49	81
Combined protocol	98	95	99	91	97

The ability of low dose dobutamine to elicit a contractile response in dysfunctional but viable myocardial segments supplied by occluded/critically stenosed arteries has been a controversial issue. Some previous studies reported the limited ability of even very low doses of dobutamine to unmask the presence of viable myocardium in the setting of severe coronary stenosis or total occlusion, where coronary flow reserve is exhausted and resting myocardial perfusion is severely reduced [19].

In contrast, others demonstrated that low dose dobutamine can ameliorate contractile dysfunction in viable segments supplied by occluded/critically stenosed arteries despite a reduced resting perfusion, and therefore is capable of predicting functional recovery in these segments after revascularisation [20]. Proposed mechanisms include increasing maximal work of the hypoperfused myocardium even in the presence of reduced subendocardial blood flow, improving myocardial blood flow through preserved coronary reserve distal to a critical stenosis, peripheral vasodilator effect of dobutamine causing reduction in LV size and wall stress thus increasing systolic wall thickening for the same myocardial blood flow, flow redistribution from the subendocardium to the subepicardium, and finally, some unknown myocellular adaptive responses [21-24]. As it recruits contractile improvement through a haemodynamic mechanism that is linked to increased coronary flow, the response to infra-low dose dipyridamole is significantly conditioned by the severity of existing coronary stenosis [25]. Consequently, the limitations of separately administered infusion of either agent were accentuated in segments supplied by occluded/critically stenosed arteries.

A few previous studies have segregated myocardial segments according to the obstruction severity of their supplying arteries (subcritical, critical or total occlusion) when reporting functional recovery after revascularisation. However, all of them addressed the predictive accuracy of dobutamine stress echocardiography. To our knowledge, no studies to date have reported similar data for the infra-low dose dipyridamole or the combined protocols. Previously, one study reported similar sensitivity, but lower specificity for viability prediction by low dose dobutamine echocardiography in case of an occluded infarct-related artery as compared to a patent one [26]. Conversely, in contrast to our results, two studies observed that low dose dobutamine echocardiography can identify viability regardless of the angiographic extent and severity of coronary stenosis [27, 28].

Our results showed a modest sensitivity of dobutamine stress echocardiography to predict viability in dyssynergic segments (76%), though with a high specificity (94%). Previously, two reports observed a somewhat similar sensitivity (range from 71 to 83%) and a slightly lower specificity (range from 82 to 90%) for predicting functional recovery by dobutamine stress echocardiography [26, 27]. The divergent results might be explained by the heterogeneous nature of the underlying disease, variable prevalence of collaterals, variable selection criteria and sample sizes, different timing of revascularisation, and echocardiographic reassessment following revascularisation.

Clinical implications

Our results suggest that contractile improvement in response to the combined protocol in segments supplied by subcritically stenosed arteries is both highly sensitive and specific to predict functional recovery after revascularisation. Adopting the combined protocol for viability assessment in this setting would overcome the limited sensitivity of the 'single agent protocol', yet without loss of specificity. Evaluation of myocardial viability is frequently needed before the decision of percutaneous or surgical revascularisation is taken. Therefore, it would be attractive to choose the 'more appropriate' protocol of viability assessment, based on the severity of coronary occlusion seen in the cath lab.

Conclusion

The combined pharmacological stress echocardiography protocol would offer better diagnostic accuracy for predicting viability, as compared to the low dose dobutamine and the infra-low dose dipyridamole protocols, particularly in myocardial segments supplied by subcritically stenosed coronary arteries.

Limitations of the study

Our findings are based on a single centre study with a relatively small sample size of the cohort, a fact that makes it difficult to generalise our results to all patients undergoing risk stratification for predicting functional recovery after revascularisation. Multicentre studies using the same protocol and examining a larger number of patients are needed. Moreover, the follow-up period of 8 weeks might have been inadequate to allow recovery of some dyssynergic but viable segments, thereby underestimating the specificity of the observed functional recovery. Delayed recovery can further occur in a substantial number of segments up to a median of 14 months following revascularisation, a fact that warrants repeated assessment after longer periods of follow-up. Additionally, we did not assess viability by radionuclide scintigraphy or magnetic resonance imaging for comparison. Finally, follow-up coronary angiography was not done; therefore, restenosis or reocclusion cannot be definitely excluded, something that would hazard the achieved functional improvement and again underestimate specificity. However, no patient reported any clinical events during the period from revascularisation to follow-up echocardiographic evaluation. Furthermore, specificity was already relatively high for all the 3 protocols in all segment categories.

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Zastosowanie kombinowanej farmakologicznej echokardiografii obciążeniowej w celu przewidywania żywotności mięśnia sercowego w obszarach zaopatrywanych przez tętnice wieńcowe o różnych stopniach zwężenia

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Streszczenie

Wstęp: Farmakologiczna echokardiografia obciążeniowa stała się powszechnie akceptowaną metodą oceny żywotności mięśnia sercowego.

Cel: Zbadanie dokładności diagnostycznej kombinowanej farmakologicznej echokardiografii obciążeniowej w przewidywaniu żywotności mięśnia sercowego w obszarach zaopatrywanych przez tętnice wieńcowe o różnych stopniach zwężenia (okluzji).

Metody: Włączono 100 kolejnych pacjentów z istotnym zwężeniem (okluzją) naczyń wieńcowych, przed wystąpieniem zawału mięśnia sercowego, z odcinkowymi zaburzeniami kurczliwości w obszarze zaopatrywanym przez zmienioną tętnicę. U wszystkich pacjentów dokonano globalnej i odcinkowej oceny czynności skurczowej mięśnia lewej komory serca. W badaniach wykorzystano 3 protokoły farmakologicznej echokardiografii obciążeniowej: z niską dawką dobutaminy, z infraniską dawką dipirydamolu oraz protokół kombinowany. Następnie pacjenci przeszli pomyślnie zabieg rewaskularyzacji wieńcowej metodą przezskórnej angioplastyki wieńcowej lub operacji pomostowania aortalno-wieńcowego. Po 8 tygodniach wykonano kontrolne badanie echokardiograficzne. Odcinki mięśnia sercowego podzielono na podstawie stopnia zwężenia (okluzji) zaopatrujących je tętnic na 3 podgrupy: z tętnicą całkowicie zamkniętą, ze zwężeniem krytycznym oraz ze zwężeniem subkrytycznym tętnicy. Przewidywany stopień poprawy wg każdego z trzech zastosowanych protokołów porównano z rzeczywistą poprawą kurczliwości po rewaskularyzacji.

Wyniki: Protokół kombinowany wykazał istotnie wyższą czułość w przewidywaniu poprawy kurczliwości dla wszystkich podgrup niedokrwienia w porównaniu z pozostałymi dwoma protokołami. Ponadto jego swoistość dla odcinków zaopatrywanych przez tętnicę ze zwężeniem subkrytycznym była podobna jak w pozostałych protokołach, przy niższej swoistości dla odcinków z tętnicą całkowicie zamkniętą lub krytycznie zwężoną.

Wnioski: Na podstawie kombinowanej farmakologicznej echokardiografii obciążeniowej można lepiej przewidywać żywotność mięśnia sercowego w porównaniu z protokołami z niską dawką dobutaminy i infraniską dawką dipirydamolu, szczególnie dla odcinków zaopatrywanych przez tętnicę ze zwężeniem subkrytycznym.

Słowa kluczowe: echokardiografia obciążeniowa, żywotność, przezskórna plastyka naczyń wieńcowych

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