

Combined low-dose dobutamine and exercise stress echocardiography: a new hybrid protocol to detect inducible ischaemia

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Received 6 February 2024; accepted after revision 3 April 2024; online publish-ahead-of-print 7 May 2024

Abstract

Aims

Myocardial response to stress echocardiography may be elicited physiologically, through exercise, or pharmacologically, often with dobutamine. Both have advantages but also limitations due to reduced exercise capacity or side-effects to stressor agent/lack of closeness to true pathophysiology of ischaemic cascade. We have combined low-dose dobutamine and exercise, creating a 'hybrid' protocol to utilize the advantages of both techniques and limit the drawbacks. The aim of the study was to evaluate its safety and feasibility.

Methods and results

In the hybrid protocol, low-dose dobutamine infusion (up to 10 µg/kg/min) is enhanced by supine bicycle exercise at 3-min increments of workload of 25 W to achieve target heart rate (THR). We analysed safety and outcome data for all the patients who underwent this protocol from 2017 to 2022. Out of 835, 727 (87.1%) patients referred for evaluation of ischaemia underwent the hybrid protocol. The median age was 61 years old and 61% (442/727) were men. The median exercise time was 11 (9–13.5) min with a median maximum workload of 100 W (75–125). Out of 727, 670 (92.2%) achieved THR. Atropine was not used. Out of 727, 192 (26.4%) of studies were positive for ischaemia. Out of 122, 102 (83.6%) with positive stress who underwent invasive angiography had significant coronary disease. The incidence of complications was low: 1/727—severe arrhythmia, 5/727 (0.7%) developed a vasovagal episode, and 14/727 (1.9%) had a hypertensive response to exercise.

Conclusion

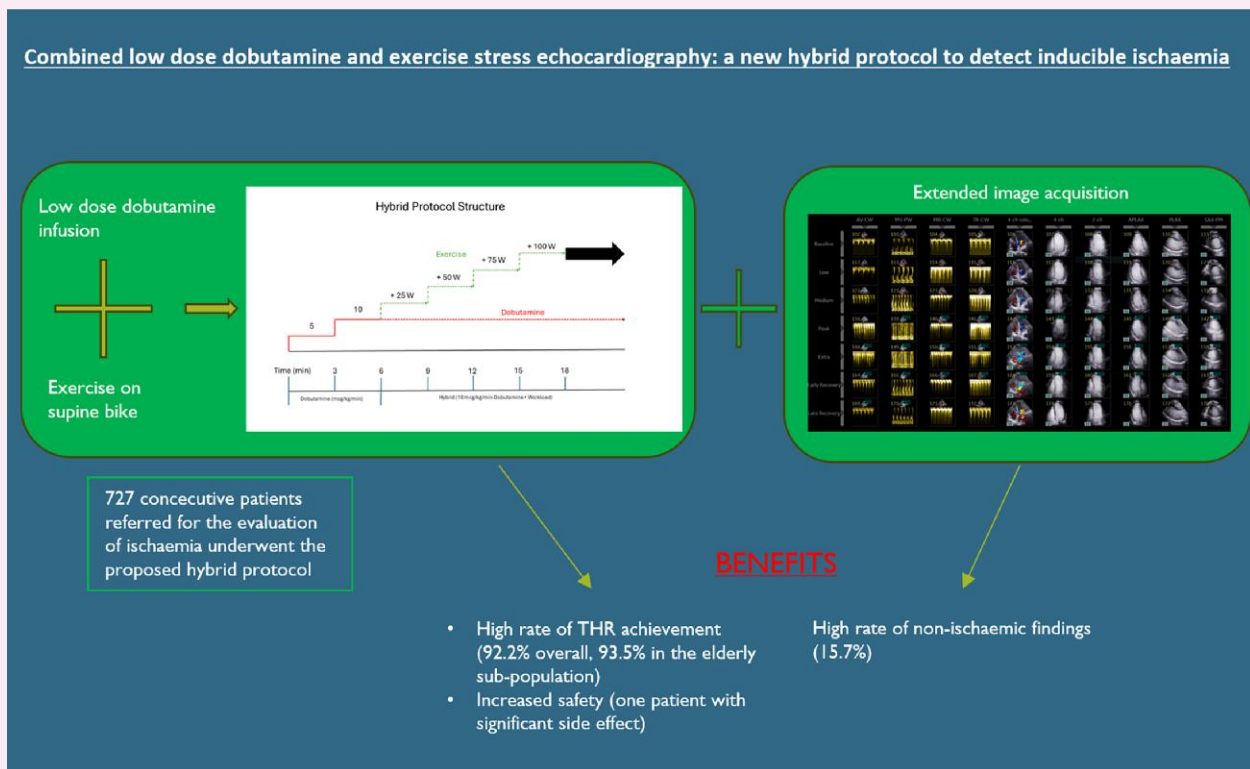
Our findings suggest that this protocol is safe, feasible, and has a high success rate in achieving THR.

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Graphical Abstract



Keywords

stress echocardiography • hybrid protocol • coronary artery disease • non-invasive tests • dobutamine stress echocardiography • exercise stress echocardiography

Aims

Stress echocardiography (SE) is an established imaging modality for the detection of inducible cardiac ischaemia.¹⁻³ Current practice is to elicit myocardial response to stress either pharmacologically or physiologically with exercise.⁴

Exercise is the preferred mechanism of stress because it induces the ischaemic cascade physiologically and offers the ancillary benefit of assessing an individual's exercise capacity and symptomatic burden.⁵ However, it is limited by mobility and level of fitness: two in five patients are unable to achieve the required heart rate.⁴

Among those deemed incapable to exercise to required heart rate, dobutamine stress echocardiography (DSE) protocol is used to pharmacologically increase myocardial oxygen demand and induce regional ischaemia in flow-limiting coronary lesions. Recruitment of regional contractility is easy to appreciate even at the low infusion rates and images do not have interference from respiration. In contrast to exercise, it gives no assessment of exercise capacity and might not provoke daily symptoms. Moreover, at high dose, dobutamine causes vasovagal response and tachyarrhythmias, which are stressful for patients and disturb the efficient running of stress echo lists.^{6,7} Atropine which is used to counteract vasovagal episodes is often used as an adjunct to dobutamine to bolster the heart rate response. The use of atropine causes inconvenience for patients due to antimuscarinic effects and they are not allowed to drive home.⁸

We developed a hybrid stress echocardiography protocol (HPSE) combining low-dose dobutamine infusion (maximum 10 µg/kg/min) with supine bike exercise for assessment of myocardial ischaemia. The purpose was to maximize the proportion of individuals able to achieve a target heart rate (THR) through exercise while minimizing expected complications of higher dose dobutamine and avoid the use of atropine.

The aim of the current study was to evaluate the feasibility and safety of this protocol among the consecutive patients referred to our department for ischaemic assessment between 2017 and 2022 and to compare this with the data obtained from DSE studies performed in the department prior to 2017.

Methods

Study design

Among those deemed likely to achieve the THR, we used exercise-only stress echocardiography (ESE) protocol as a first choice. In all other patients the HPSE became the standard SE format. We reserved standard DSE for patients with severe mobility issues that are totally unable to pedal on a supine bike.

We received ethical approval for prospective and retrospective data collection following the initiation of the hybrid protocol as a quality control assessment from relevant oversight bodies at Harefield site of Guys and St Thomas's NHS Foundation Trust (Rec Reference 20/EM/0112).

Echocardiography

Echocardiography was performed using smart stress protocol on GE Vivid E95 machine. Post-processing analysis was performed offline on TomTec software (TTA 2.50).

In our protocol, 10-echo views are acquired for each stage (Figure 1): four Doppler (Aortic Valve Continuous Wave—AV CW, Mitral Valve Pulse Wave—MV PW, Mitral Valve Continuous Wave—MV CW, Tricuspid Valve Continuous Wave—TR CW) and six colour and 2D left ventricular (LV) images including apical 4-chamber with and without colour Doppler (A4C), apical 2 chamber (A2C), apical 3 chamber (A3C), parasternal long-axis (PLAX), and mid-segment short-axis LV (mid SAX). Endocardial visualization is optimized with Sonovue™ contrast. We visualize five stages: Baseline, low-dose dobutamine, early exercise (HR~100 BPM), peak exercise (THR), and recovery (with an option to add extra peak and early recovery in cases of abnormal exercise findings).

Dobutamine stress protocol

Dobutamine was infused according to standard guideline-directed fashion (Figure 2).⁴

Hybrid stress protocol

The hybrid protocol combines the pharmacological effects of low-dose dobutamine with the physiological effect of supine bike exercise (Figure 3). While the patient is at rest, dobutamine is infused intravenously starting at 5 µg/kg/min, for 3 min. This is then titrated up to 10 µg/kg/min (the maximum dose) and is maintained until the recovery phase.

During the initial low-dose dobutamine infusion (3 min of 5 µg/kg/min and 3 min of 10 µg/kg/min), the second set of images is acquired. After 6 min of dobutamine-only infusion, the THR is achieved by addition of supine bicycle exercise at 3-min increments of workload of 25 Watts (W) until test termination criteria are met. Exercise capacity is assessed as ability to perform

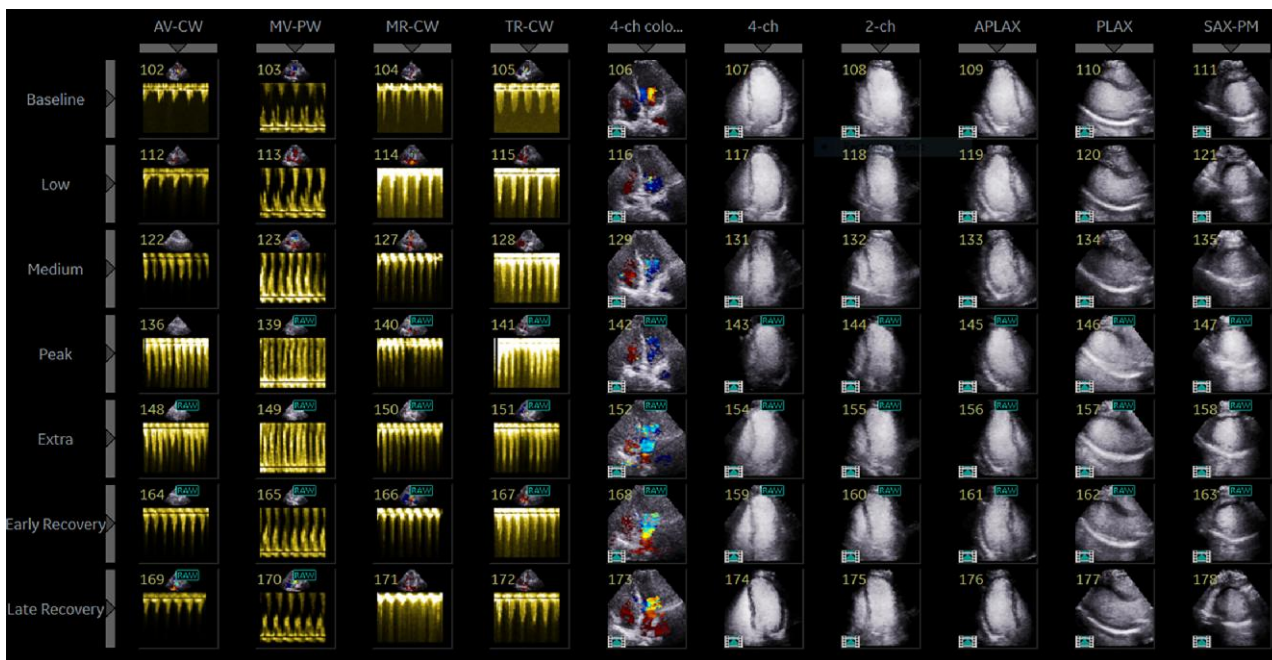


Figure 1 Protocol screen.

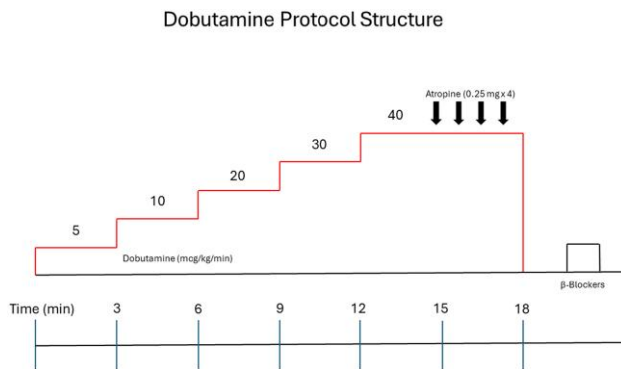


Figure 2 DSE protocol structure.

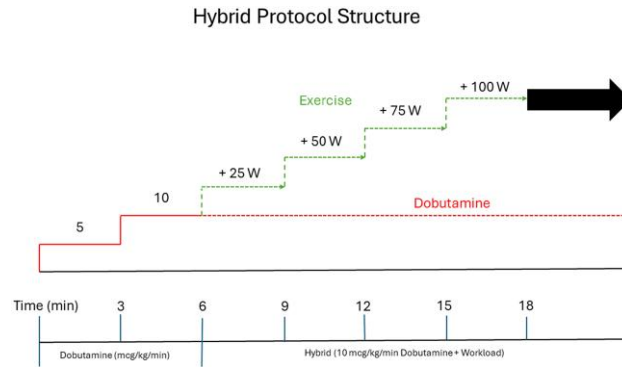


Figure 3 HSE protocol structure.



Figure 4 Hybrid stress echocardiography laboratory.

on-protocol incremental exercise time, which excludes the dobutamine-only initial phase. Sublingual glycerine trinitrate and metoprolol are the protocol's approved medication for the relief of symptoms of ischaemia.

Supine exercise

We use a supine exercise bike that can be tilted in the left lateral decubitus position (Figure 4). We find this substantially improves image acquisition during exercise compared with an inability to tilt the bike. Pedal resistance is manually adjusted in increments of 25 W every 3 min.

Safety, contraindications, and termination criteria

All procedures are preceded by a standardized checklist (Figure 5). Standard dobutamine and exercise echocardiography contraindications are used as exclusion criteria: unstable angina within last 24 h of scheduled test, MI in the last 4 weeks, poorly controlled hypertension, recent ventricular tachycardia (VT), persistent LV thrombus, and recent pulmonary embolism.⁴

Standard termination criteria for dobutamine and exercise echocardiography were used.⁴ These are achieving THR, sustained systolic blood

Checklist

Please Affix Patient Details
Name
DOB
Hospital No.

**Stress Echocardiography
Integrated Care Pathway (2023)**

Date:	___/___/2023	Staff (Echo)		Referring Consultant	
NHS PP	<input type="checkbox"/>	Staff (Infusion)		Referring Hospital	

Referral Source:	OP Clinic / RACPC / Inpatient / MDT / DVLA / Other: _____	CVS Risk Factors <input checked="" type="checkbox"/>
Referral Reason:		Heart Disease: _____
Symptom Hx:		HTN _____
Cardiac Hx: <i>Recent LHC Prev PCI/CABG Valve Pathology Cardiomyopathy Arrhythmia</i>		Diabetes _____
		Hypercholesterolemia _____
		Current Smoker _____
		Ex-Smoker _____
		FHx Premature IHD _____
		BMI > 30 kg/m2 _____
		PVD _____
		Previous CVA/ TIA _____
		Prothrombotic Dx: _____

PMH (other relevant):	Allergies:	Personal Details:
	Medication:	Gender: M / F
		Height: _____ cm
		Weight: _____ kg
		Ethnicity: _____

Pre-Procedure Checklist:

Exclude Contraindications <input checked="" type="checkbox"/>	Action <input checked="" type="checkbox"/>
No Resting typical chest pain within 24hrs	1. Safety equipment checked
No MI within the last 4 weeks	2. Brief history taken
Resting BP is not >200/110mmHg	3. NBM for 3hrs (if applicable)
No Recent VT	4. Contraindications excluded
No LV Thrombus	5. Procedure explained
No Recent PE	6. Written consent obtained
For low-dose Dobutamine study only if:	7. Prescription completed
1. Severe LVSD	8. Gown offered
2. Severe AS with LVSD	9. Need to report symptoms explained
Please seek Consultant advice if:	10. ECG and BP recorded
3. Complex PMH	11. Time-out completed with Sonographer
4. TTE suggestive of cardiomyopathy	

Signature: _____ Print Name: _____ 1

Figure 5 Pre-procedural notes.

pressure >220 mmHg or diastolic blood pressure >120 mmHg, sustained significant tachyarrhythmia, leg exhaustion, and irretractable symptoms. THR was calculated as 85% of maximum predicted heart rate (MHR)

for age. In our safety monitoring we define significant arrhythmias as ventricular fibrillation, VT, or others, if they led to haemodynamic instability. Blood pressure was measured on the right arm every 3 min. The 12-Lead

Periprocedural notes

Please Affix Patient Details
 Name
 DOB
 Hospital No.

Prescription Chart

Medication	Dose	Route	Signature	Print Name
Dobutamine Infusion (50mg Dobutamine made up to 50mls with Sodium Chloride 0.9%)	As Per Protocol	IV		
Sodium Chloride 0.9%	500ml	IV		
SonoVue Contrast (Sulphur Hexafluoride)	5 -10ml	IV		
Other:				

Stress Test Observations

Protocol	Time	HR	BP	SpO ₂	ECG: Arrhythmia/ Ischaemia	Symptoms/ Comments
Baseline						
Dobutamine Dose (micrograms/kg/min)	5					
	10					

Semi-Supine Exercise Bike (Watts, RR 50-55 rpm)	+25					
	+50					
	+75					
	+100					
	+125					
	+150					
	+175					
	+200					
	+225					
	+250					
	+275					
Recovery (mins)	1					
	5					
Total Exercise Time (mins and secs)				Reason of test termination		

Additional Comments

Post-Procedure Checklist:

Action	
1. Patient recovered prior to discharge	<input checked="" type="checkbox"/>
2. Advice regarding restarting B-Blockers if appropriate	<input type="checkbox"/>
3. Advice regarding driving home	<input type="checkbox"/>

Signature: _____

Print Name: _____

2

Figure 6 Periprocedural notes.

ECG was monitored throughout the test and paper prints were done for each stage. Detailed recording of all haemodynamic parameters and symptoms was made during the test using periprocedural notes (Figure 6).

Tests are considered positive for inducible regional dysfunction if more than one LV segments have an abnormal response at peak stress.

Statistics

All continuous variables were assessed for normality *via* Shapiro–Wilk testing. Parametric data are presented as mean \pm standard deviation and non-parametric data presented as median (interquartile range). Categorical data are presented as percentages (*n* value). Descriptive statistics were analysed using SPSS Statistics v28.0 (IBM Corp, Armonk, NY, USA).

Table 1 Baseline population characteristics

Baseline characteristics	Hybrid population (n = 727)
Demographics	
Age (years)	61 (52–70)
Age ≥ 80 years % (n)	6.4 (46)
Age 70–80 years % (n)	19.4 (141)
Male gender % (n)	60.8 (442)
BMI (kg/m ²)	27.5 (24.6–31.3)
Comorbidities	
CAD % (n)	54.3 (395)
Other heart disease % (n)	9.8 (71)
Hypertension % (n)	50.9 (370)
Diabetes % (n)	19.5 (142)
Hypercholesterolemia % (n)	60.9 (443)
Smoking % (n)	9.8 (71)
Ex-smoker % (n)	31 (208)
Family history of premature IHD % (n)	26.5 (193)
BMI > 30% (n)	33 (240)
Peripheral vascular disease (PVD) % (n)	2.6 (17)
Cerebral vascular accident (CVA) / transient ischaemic attack (TIA) % (n)	3.4 (22)
Prothrombotic risk factors % (n)	8.5 (62)
Previous coronary interventions	
PCI % (n)	29.3 (213)
CABG % (n)	8.9 (64)

IHD, ischaemic heart disease.

Table 2 Referral characteristics

Referring indication	
Referral source (n = 654)	
OP clinic % (n)	66.1 (432)
RACPC % (n)	28.9 (189)
Other % (n)	5 (33)
Referral symptom (n = 642)	
Chest pain % (n)	69.3 (445)
Shortness of breath % (n)	22.5 (144)
Asymptomatic % (n)	5.1 (33)
Other % (n)	3.1 (20)

Table 3 Baseline—peak exercise stress parameters

	Baseline	Peak Stress
Haemodynamics		
Heart rate (bpm)	70 (63–79)	152 (141–156)
Systolic blood pressure (BP) (mmHg)	138.9 (±19.1)	163 (±23.8)
Diastolic BP (mmHg)	80 (72–87)	82 (71–93)
Echo characteristics		
LV ejection fraction (%)	65 (62–69)	79 (71–83)
LV end-diastolic volume (LVEDV) ml	96 (79–117)	78 (64–96)
LV end-systolic volume (LVESV) ml	33 (26–43)	16 (11–25)
Tricuspid annular plane systolic excursion (TAPSE) mm	22 (20–25)	27 (±3.6)
Fractional area change (FAC) %	48.5 (43.75–52.25)	60 (±6.5)
TR gradient mmHg	21 (17–45)	44 (36–50)

Results

Study population

Among all patients referred from September 2017 to January 2022, 88/835 (10.5%) underwent ESE, 20/835 (2.4%) DSE, and 727/835 (87.1%) HPSE. The completeness of studies of HPSE was compared with the data from 105 consecutive patients who underwent DSE in our department prior to 2017 (median age 63 year old, 70% males).

Baseline characteristics of study population are summarized in [Table 1](#). The median age of the population was 61 year old, 187/727 (25.7%) were older than 70 years. Out of 727, 442 (61%) were males. There was a high prevalence of cardiovascular risk factors: 395/727 (54.3%) had a previous history of coronary artery disease (CAD), 370/727 (50.9%) hypertension, 142/727 (19.5%) diabetes, and 443/727 (60.9%) hypercholesterolaemia. Out of 727, 213 (29.3%) had a prior history of percutaneous coronary intervention (PCI) and 64/727 (9%) a previous history of coronary artery bypass grafting (CABG). One-third of patients (240/727) were overweight (BMI > 30 kg/m²) and 10% (71/727) were current smokers.

The cardiology department, outpatient (OP) and rapid access chest pain (RACPC) clinics, was the main referring source (621/727, 85%). Out of 727, 85 (11.7%) did not have symptomatic status reflected in the referral form. The most common symptoms were chest pain in 445/727 (61.2%) patients and shortness of breath in 144/727 (19.8%) ([Table 2](#)).

Study results

Atropine was available but was not required in any study using HP. Isometric hand-grip exercises were encouraged in addition to supine bicycle exercise for the achievement of THR in 6/727 (0.8%) cases. Contrast agent was used in 692/727 (95.2%) of tests.

Haemodynamic parameters and echocardiographic characteristics at baseline and peak exercise are presented in [Table 3](#). The use of the hybrid protocol led to high percentage of complete studies: 670/727 (92.2%) of all patients achieved the THR compared with 83/105 (79%) in DSE group ($P < 0.0001$). Amongst those who achieved THR, 181/670 (27%) in HPSE group were able to exercise at the MHR; whereas in DSE group, there were 6/83 (7%) patients ($P < 0.0001$). The median HP exercise time was 11 (9–13.5) minutes, and the median maximum workload was 100 W (75–125) ([Table 4](#)).

The elder patients did not differ from the main HP cohort. Hybrid protocol resulted in high rates of THR achievement among patients between those 70 and 80 y old (131/141, 95%) and older than 80 years (43/46, 93.5%).

Ischaemia assessment

Out of 727, 192 (26.4%) of studies were positive for inducible regional dysfunction, the distribution of the number of segments involved is displayed in [Supplementary data online, Table S1](#). Out of 727, 527 (72.5%) of the

Table 4 Procedure results

Procedure details—Results	HPSE population (n = 727)	DSE population (n = 105)	P
THR achieved % (n)	92.2% (670)	79% (83)	<0.0001
MHR achieved % (n)	24.9% (181)	5.7% (6)	<0.0001
MHR achieved among patients reaching THR % (n)	27% (181/670)	7% (6/83)	<0.0001
Exercise time (min)	11 (9–13.5)		
Maximum workload (watts)	100 (75–125)		
Elderly population			
Age ≥ 80			
THR achieved % (n)	93.5% (43/46)		
MHR achieved % (n)	52.2% (24/46)		
Age < 80 ≥ 70			
THR achieved % (n)	95% (134/141)		
MHR achieved % (n)	50.4% (71/141)		

Table 5 Non-ischaeamic assessment

Concomitant findings	
Total % (n)	15.7 (114)
Dynamic LVOT gradient % (n)	1.1 (8)
LV intraventricular gradient % (n)	7.7 (56)
Change in LV filling pressures % (n)	6.9 (50)

Table 6 Complications

Periprocedural complications	
Significant arrhythmia % (n)	0.14 (1)
Vasovagal episode % (n)	0.7 (5)
Hypertensive response % (n)	1.9 (14)

studies were negative and 6 (0.8%) were inconclusive. The reasons for inconclusive studies are displayed in [Supplementary data online, Table S2](#).

Concomitant findings

The extension of the image acquisition to 10 images per stage allowed the identification of concomitant cardiac pathology. Significant non-ischaeamic findings during hybrid protocol were identified in 114/727 (15.7%) of studies ([Table 5](#)). Out of 727, 64 (8.8%) of patients developed left ventricular outflow tract (LVOT) or intraventricular gradients on CW Doppler assessment and 50/727 (6.9%) developed changes in diastolic function.

Complications

There was 1/727 (0.14%) case of severe arrhythmia (idioventricular rhythm), 5/727 (0.7%) patients developed vasovagal episodes, and 14/727 (1.9%) had a hypertensive response to exercise ([Table 6](#)).

Conclusion

In this prospective analysis of consecutive 727 patients who underwent the novel HPSE 92% achieved THR with a low complications rate. 0.7% of patients experienced a vasovagal episode and 0.14% a severe tachyarrhythmia. Our findings suggest that this protocol is safe, feasible and has a high success rate in achieving THR.

Exercise is a preferred stressor in patients with suspected coronary artery disease as it is likely to reproduce daily symptoms and trigger ischaemic cascade in presence of obstructive coronary lesions.⁹ But it is perceived as a challenging and demanding technique,¹⁰ hence many laboratories use pharmacological SE even in patients who can exercise. Also, many patients, especially the elderly and those with complex comorbid profile are often limited in their mobility.¹¹ Treadmill stress protocol requires certain agility from patients to get on and off the treadmill for swift image acquisition and supine bicycle stress protocol is reported to be terminated early due to muscular soreness caused by pedalling.¹² These limitations were attenuated with the hybrid protocol. Unlike the majority of reported SE with relatively young male patients with normal body habitus^{13,14} our cohort included large proportion of elderly (26%) and those with obesity (33%) who managed to achieve THR. The exercise element of HPSE offers valuable insight into other factors such as lung function, the general health, nutritional status, and orthopaedic restrictions which is pivotal in risk stratification, particularly if patients are undergoing cardiac and non-cardiac interventions.¹⁵ The presence of intravenous cannula allowed to use contrast to enhance the endocardial border definition.¹⁶

Pharmacological stress is an established alternative, but complications are not infrequent, many of which lead to early termination without achieving the THR.⁶ The inconclusive results usually lead to further testing and delay in defining management plan. In the 105 consecutive patients at our centre who underwent DSE prior to our hybrid protocol only 79% achieved a THR which was significantly less than in HPSE group. The management of side effects is often prolonged and distresses patients on both ends—experiencing side effects and waiting longer for their diagnostic tests due to disruption of the stress lists. By avoiding these side effects while maintaining a high success rate we benefited our patients and the management of our stress echo laboratory. Another advantage of this protocol is that none of our patients were administered atropine to facilitate the achievement of THR. The use of atropine is related to a longer recovery time, can elevate the incidence of side effects due to paralysis of vagal control and is often associated with adverse sensations experienced by patients.⁶ Furthermore, it can restrict their ability to drive following the test.

With more subtle breathing effort, less respiratory related artefacts and less dobutamine associated side-effects, there is sufficient time during each stage for extended image acquisition. In our protocol, we included 2D images of the right ventricle and Doppler data for diastolic function and pulmonary pressures. Hence, we identified significant non-ischaeamic findings in 15.7% of our patients.

The limitation of our study is the pragmatic design, which is based on clinical needs, hence it is not possible to fully establish the sensitivity of our protocol in the detection of flow-limiting coronary artery disease given that coronary angiography cannot be performed for the entire study population. In general, given the established accuracy of both dobutamine and exercise SE we did not seek ethical approval to conduct invasive coronary angiography.¹⁷ Nevertheless, among the 122 patients with positive studies who underwent angiography 102/122 (83.6%) had significant coronary disease. This is significantly higher than the data from the UK-wide EVAREST study involving 31 participating hospitals which demonstrated that only 55% of the positive studies (208/378) were found to have obstructive coronary artery disease on invasive angiography. The predominant protocol was DSE (73%) involving 5131 patients.¹⁸ In the future, non-invasive coronary imaging may be an avenue to investigate this, at least it is worth performing sub-group analysis.

In summary, our hybrid stress protocol for the evaluation of ischaemia is a safe and a feasible alternative to existing stress echo protocols. It allows acquisition of wider image data to assess for non-ischaemic cause of chest pain and shortness of breath. We have grown in our experience and confidence in HPSE and would advocate strongly for its use outside of our centre to benefit both patients and those involved in the management of stress echo laboratories.

Supplementary data

Supplementary data is available at *European Heart Journal - Imaging Methods and Practice* online.

Consent

Written informed consent was obtained for the patient whose echocardiographic images and videos are included in the manuscript.

Funding

None declared.

Conflict of interest: none declared.

Data availability

Anonymized clinical metadata, source code used for analysis, and supplemental figures and tables are available at contacting with the first author. Guys and St Thomas' Electronic Research Records Interface (GERRI) is governed by the overarching Clinical Research Analytics Governance Group (CRAG). The CRAG welcomes specific and detailed proposals under the ethical clearance of GERRI. Initial enquiries should be directed to Finola Higgins (CRAG Manager) Finola.higgins@kcl.ac.uk.

Lead author biography



Dr Konstantinos Vakalis is a consultant cardiologist in London, UK at Queen Elizabeth Hospital (Lewisham and Greenwich NHS trust) and at Harefield Hospital (Guy's and St Thomas' NHS Trust). He was trained in cardiology in Greece and in the UK. He has been awarded the honorary title of Fellow of the European Cardiology Society (FESC) and Fellow of the European Society of Cardiovascular Imaging (FEACVI). His main interests in cardiology include imaging and heart failure.

His clinical expertise is stress echocardiography. He is the heart failure lead at Queen Elizabeth Hospital.

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