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Occurrence of Atrial Fibrillation

During Dobutamine Stress Echocardiography

Running head: Atrial Fibrillation and Dobutamine Stress Echocardiography

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Abstract

Dobutamine stress echocardiography (DSE) is a widely used examination for assessment of coronary ischemia, but several complications have been reported. The aim of this study was to assess the incidence of atrial fibrillation (AF) during DSE and a systematic review and metaanalysis were also performed to determine an accurate estimate of the AF incidence. Over a 16year period, we reviewed all patients referred for DSE. We systematically analyzed all ECG performed during DSE to detect AF during the examination. DSE was completely performed in 4818 patients (mean age: 62.1 ± 11.7 years). AF was observed in 40 patients (31 men, mean age: 79.7 ± 8.9 years). Incidence of AF during DSE was 0.83%. Regarding the meta-analysis, the combined AF incidence was 0.86%. In our study, patients with AF occurrence had more frequent previous history of paroxysmal AF (p = 0.02), were also older (p < 0.0001) and incidence of AF during DSE increased with age: 0% below 60 years, 0.45% in patients 60-69 years, 1.3% in patients 70-79 years and 4% in patients >80 years (p <0.0001). In multivariate analysis, the factors significantly associated with an increased risk of AF were age (aOR = 2.4, 95% CI: 1.5 -3.3, p = 0.003) and previous history of paroxysmal AF (aOR = 1.5, 95% CI: 1.1 - 1.9; p = 0.04). In conclusion, AF is uncommon during DSE, and elderly patients and patients with previous history of paroxysmal AF are at risk of AF during DSE.

Keywords: atrial fibrillation; dobutamine stress echocardiography; complications; side effect, meta-analysis.

Dobutamine stress echocardiography (DSE) is routinely performed for the assessment of coronary ischemia, with an excellent diagnostic and prognostic value. Despite its wide use, several complications or side effects of DSE have been reported: myocardial infarction, supraventricular or ventricular arrhythmias, hypotension, coronary spasm and death.^{1,2} Thus, atrial fibrillation (AF) may occur during DSE, but studies for the incidence of this specific side effect of DSE remain rare.³⁻³⁰ The aim of this study was to assess the incidence of AF during DSE and to pool it with the AF incidence during DSE of all other published studies, in order to determine an accurate estimate with an aggregated incidence.

Methods

Over a 16-year period (from November 2001 to October 2017), we reviewed all consecutive patients (n = 4917) referred for DSE. Entry criteria included age > 18 years and all patients who underwent DSE. Patients presenting with permanent or persistent AF were not included in this study. All DSE were performed by a medical doctor. We distinguished patients presenting with normal DSE (no significant symptoms, no ECG modifications nor wall motion abnormalities during examination) from patients presenting with positive DSE, according to guidelines. All patients had an ECG monitoring during DSE and we systematically analyzed all ECGs performed during the echocardiographic examination, thus identifying occurrence of atrial fibrillation (> 5 seconds). All echocardiographic examinations were performed using a Siemens/Sequoia Acuson C512 system (Acuson, Mountain View, CA, USA) or a Vivid 7 or 9 system (GE Medical Systems, Horten, Norway), equipped with multifrequency transducers and capable of low energy (0.2 to 0.3 mechanical index). In the case of suboptimal acoustic windows, left ventricular cavity opacification was performed by peripheral venous injection of Sonovue® contrast agent (Bracco

Altana Inc, Milan, Italy). Dobutamine was administered intravenously in an incremental regimen of 10, 20, 30 and 40 μ g/kg/min every 3 minutes for each dose (from 2001 to 2004) and every 2 minutes after this first period. Atropine (0.25-1 mg) was administered at the beginning of 20, 30 and 40 μ g/kg/min of dobutamine (in case of non-contraindication) and DSE was stopped when the target heart rate [85% of the predicted maximal heart rate (220- age (years)] was achieved. Without contraindication, intravenous beta-blockers were performed at the end of DSE. Dobutamine stress echocardiography was interpreted according to guidelines.

Continuous variables were compared using Student's test. Categorical data are compared using the chi-square test, Fisher's exact test or Wilcoxon test as appropriate. We performed a multivariate logistic regression analysis to identify sets of factors that together are significantly associated with the occurrence of AF. All the tests were two-sided and the results were considered significant at p < 0.05. Statistical analysis was performed with STATA 12.0 (Stata-Corp, College Station, TX). To further determine an accurate estimate of the AF incidence during DSE, we performed a meta-analysis. A previous literature review was published in 2010, but the combined incidence of AF during DSE was not calculated.¹ Moreover, this review was not exhaustive and since 2010 other studies have been published. Our meta-analysis complies with the preferred reporting items of PRISMA for systematic reviews and meta-analyses. A comprehensive search of several electronic databases (between 1948 and August 26, 2018) was conducted in EMBASE between 1988 and August 26, 2018; Ovid MEDLINE in-process and other non-indexed citations and Ovid MEDLINE between 1948 and August 26, 2018; and EBM Reviews-Cochrane Central Register of Controlled Trials and EBM Reviews-Cochrane Database of Systematic Reviews between 2005 and August 26, 2018. In addition, we searched the reference lists of relevant studies and reviews for additional published and unpublished data and used the web search engine "Google" for abstracts, conference proceedings, and unpublished

studies. We used a combination of keywords related to the type of exposure ("dobutamine stress echocardiography") and to the type of outcome ("atrial fibrillation"). The studies involved adults and could be of any design and any language. We excluded animal studies, ex vivo and toxicological studies, duplicates, summaries, commentaries, editorials, case reports, studies that did not evaluate AF incidence during DSE and studies without original data. Two independent reviewers (N.M. and H.M.) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then screened to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus. Data extraction using a standardized form included a full description of the study characteristics. Incidences were reported in percentage with 95% confidence interval (CI) and the combined incidence was estimated using a random-effects model. This model was chosen because of anticipated significant heterogeneity between studies in terms of population and methods. The random-effects model is the most conservative approach in this setting because it incorporates within and between-study heterogeneity in the CI. Statistical heterogeneity across the studies was calculated by the I² statistics to quantify inconsistencies between studies. I² values <25%, 25%-50%, 50%-75% and >75%, respectively represent low, moderate, high and very high inconsistency. To assess the potential for publication bias, we added the Egger's regression test P-value for funnel symmetry, a p-value <0.05 is an argument for a potential publication bias. All analyses were performed with Comprehensive Meta-analysis software, version 2.0 (Biostat, USA).

Results

Among 4917 patients referred for DSE in our institution, 4818 patients (3592 [76%] men) underwent complete DSE (Figure 1). Mean age was 62.1 ± 11.7 years. Dobutamine stress echocardiography was considered as positive in 1535 patients and negative in 3283 patients. Atrial fibrillation occurred in 40 patients (31 men, mean age: 79.7 ± 8.9 years). Incidence of AF during DSE was 0.83% (95% CI: 0.57-1.09) and was similar whatever the result of DSE (0.85% in case of positive DSE versus 0.82% in case of negative DSE, p = 0.93). Atrial fibrillation occurred with 40y/kg/min of dobutamine in 29 patients (72.5%) versus with 30y/kg/min of dobutamine in 6 patients (15%), with $20\gamma/kg/min$ of dobutamine in 2 patients (5%) and in early recovery in 3 patients (7.5%). The use of atropine was similar in the 2 groups of patients (Table 1). Several patient characteristics were univariately associated with the occurrence of AF (Table 1). Atrial fibrillation during DSE was significantly more frequent in patients with previous history of paroxysmal AF (p = 0.02). Patients with AF occurrence were also significantly older (p<0.0001) and incidence of AF during DSE increased with age: 0% below 60 years, 0.45% in patients 60 to 69 years, 1.3% in patients 70 to 79 years and 4% in patients >80 years (p <0.0001). In multivariate analysis, the factors significantly associated with an increased risk of AF during DSE were age (aOR = 2.4, 95% CI: 1.5 - 3.3, p = 0.003) and previous history of paroxysmal AF (aOR = 1.5, 95% CI: 1.1 - 1.9; p = 0.04).

Dobutamine infusion was immediately discontinued in case of AF. Duration of AF was less than one hour in most of patients (67.5%) with spontaneous termination of AF (Table 2). For the 13 patients with duration of AF higher than one hour and after anticoagulation, pharmacological cardioversion (amiodarone or flecainide) was systematically attempted and only 7.5% had persistent AF. For those patients, an electrical cardioversion was performed at distance and all patients had a recovery of sinus rhythm. Regarding the meta-analysis, the search strategy on the mentioned electronic databases, identified 199 citations to which we added 3 citations from reference lists of relevant studies and reviews. After screening titles, abstracts, 35 citations were considered potentially eligible and the full-text article was retrieved. Of those, 7 citations were excluded, resulting in 28 selected studies to which we added our present study (Figure 2).³⁻³⁰ Thus, we calculated a combined incidence of AF during DSE from a total of 29 studies. Interrater agreement for study selection was very high between the two reviewers. The number of DSE performed per study ranged between 63 and 11806, the number of AF incident cases ranged between 1 and 122. AF incidence during DSE ranged from 0.29% to 2% and this incidence was investigated in several sites on every continent from 1990 to 2017. The combined incidence of AF during DSE was 0.86% (95% CI: 0.70-1.02), the statistical heterogeneity across the studies was high (I²=71.5%) but expected and there was no statistical argument for any publication bias (Egger's regression test p = 0.15) (Figure 3).

Discussion

The main results of the present study were: 1) atrial fibrillation during DSE is uncommon (our study incidence was 0.83% and of the same magnitude order as the combined incidence of the meta-analysis); 2) age and previous history of paroxysmal AF are predictive factors of AF occurrence; 3) most of AF are paroxysmal and cardioversion is rarely performed.

DSE is a routine test performed for the diagnosis of coronary artery disease because of its accuracy. Its indications have increased notably these last years, leading to more DSE tests and consequently more side effects. Several complications or side effects of DSE may occur.¹ The most frequent complications are hypertension, hypotension and induced arrhythmias. However, other less frequent complications may occur, such as myocardial infarction, coronary artery

spasm, and death. Occurrence of AF is a potential side effect of DSE. Dobutamine acts directly through β -adrenergic receptor activation, leading to increase the risk of AF through enhancement of intracellular 3'-5'-cyclic adenosine monophosphate. In the present study, we found an incidence of 0.83% and very close to the aggregated incidence of AF in our meta-analysis, confirming that AF during DSE remains uncommon. The heterogeneity between the studies was very high but expected because of the different methodologies used, the analyzed populations also were different in terms of age, sex, history of AF, high blood pressure. There was no statistical argument for a publication bias and therefore the estimate by the aggregated incidence must be pretty close to the real incidence.

We found that the main factor associated with AF occurrence during DSE is age. The incidence of AF significantly increased with age (0% in patients < 60 years versus 4% in patients \geq 80 years). Previous history of paroxysmal AF is also a predictive factor of AF during DSE. Physicians should be aware of these interactions between AF and elderly patients and previous history of AF, should discuss the utility of this specific examination and could eventually propose another ischemic test with less risk of AF.

The occurrence of AF during DSE is usually associated to a prompt and fast recovery of sinus rhythm in most of patients (< 1 hour), with discontinuation of dobutamine infusion and intravenous betablockers. For the remaining patients with AF > 1 hour (32.5%), an attempt to restore sinus rhythm with antiarrhythmic agents was performed and finally only 7.5% of our patients had AF > 1 day. These remaining patients had persistent AF and we performed electrical cardioversion, allowing to restore sinus rhythm. Thus, at distance, with adequate and conventional management, no patient had persistent AF secondary to DSE.

The limits of our study are that only 40 patients presented with AF during 4818 complete DSE. However, this population was in sinus rhythm and no patient was in atrial fibrillation at the

beginning of DSE. Thus, we were able to clearly identify AF occurrence during DSE. This sideeffect of high-level of dobutamine infusion remains uncommon and we demonstrate that elderly patients and patients with previous history of paroxysmal AF are at risk of AF during DSE.

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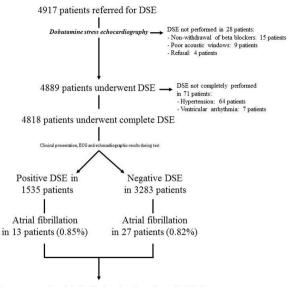
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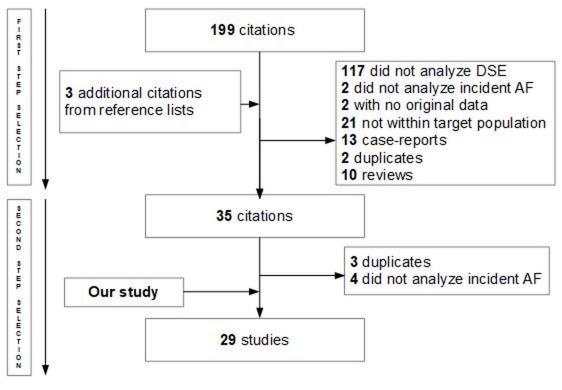
Figure legends

Figure 1. Flowchart of patients in the study. DSE = dobutamine stress echocardiography.

Figure 2. A. Search strategy and study selection flowchart for the meta-analysis. **B.** Incidence of atrial fibrillation during dobutamine stress echocardiography -meta-analysis forest plot. AF = atrial fibrillation; CI = confidence interval; DSE = dobutamine stress echocardiography.



Occurrence of atrial fibrillation in 40 patients (0.83%)



Study name	AF inc	idence (%	6) and 95%	% CI	
Mansencal 2018	0,83	0,57	1,09		1
Acharya 2017	1,04	0,80	1,28		
Sheldon 2010	1,03	0,85	1,21		
Abdel-Salam 2010	2,00	-0,34	4,34		
Aggeli 2008	0,48	0,30	0,66		
Mikheev 2008	1,30	-0,07	2,67		- C
San Roman 2008	0,62	0,13	1,11		-
Wejner-Mik 2006	0,29	-0,05	0,63		
Carasso 2006	1,95	1,51	2,39		
Tsutsui 2004	1,20	0,82	1,58		
Cortigiani 2002	1,25	0,55	1,95	- I -	
Coisnes 2001	1,59	-0,70	3,88		
Chenzbraun 1999	0,50	-0,09	1,09		
Mathias 1999	0,79	0,52	1,06		
Plonska 1999	0,52	-0,03	1,07	-	
Elhendy 1999	0,35	-0,16	0,86	-	
Takeuchi 1999	0,64	0,17	1,11	-	
Bremer 1998	1,96	1,13	2,79	-	
Pezzano 1998	0,49	0,24	0,74		
Hennessy 1997	1,05	0,14	1,96		
Lamisse 1997	1,17	0,32	2,02		6
Pinton 1997	0,27	-0,05	0,59		
Secknus 1997	1,06	0,70	1,42		
Yeo 1997	1,33	-0,60	3,26		
Zahn 1996	1,00	0,39	1,61		
Cornel 1996	1,26	0,04	2,48		
Fetiveau 1995	1,17	-0,07	2,41		
Poldermans 1994	1,23	0,39	2,07		
Mertes 1993	0,63	0,17	1,09	-	
Combined	0,86	0,70	1,02	•	1
(l² = 71,5%, Egger's re	gression to	est, P = 0,15)		0%	2,5%

Relative weight 5,40 5,52 5,82 0,43 5,82 1,11 3,93 4,87 4,26 4,65 2,85 0,45 3,37 5,31 3,61 3,82 4,05 2,31 5,46 2,06 2,25 5,00 4,74 0,61 3,26 1,34 1,31 2,28 4,11

5%

Variable	AF occurrence during DSE		P value
	No	Yes	
	(n = 4778)	(n = 40)	
Age (years)	62.0 ± 11.6	79.7 ± 8.9	< 0.0001
Men	3588 (75%)	31 (78%)	0.73
Previous history of paroxysmal AF	573 (1%)	10 (25%)	0.02
Cardiovascular risk factors			
Smoker	1615 (34%)	13 (32.5%)	0.86
Hypertension	2435 (51%)	30 (75%)	0.17
Diabetes mellitus	514 (11%)	5 (13%)	0.72
Dyslipidemia*	1720 (36%)	15 (38%)	0.84
Echocardiographic measurements			
Left ventricular enddiastolic diameter (mm)	51 ± 6	49 ± 7	0.64
Left ventricular ejection fraction (%)	60 ± 7	61 ± 5	0.92
Left atrial volume (ml/m ²)	32 ± 4	35 ± 7	0.41
Dobutamine stress echocardiography			
Mean dosing of dobutamine (y/kg/min)	37 ± 3	38 ± 2	0.73
Mean duration of examination (min)	12 ± 2	11 ± 3	0.86
Use of atropine during examination	4252 (89%)	35 (88%)	0.96
Use of intravenous betablockers at the end of examination	4526 (95%)	39 (98%)	0.72

Table 1. Characteristics of patients with complete DSE (n = 4818)

AF: atrial fibrillation; DSE: dobutamine stress echocardiography

*Defined as high low-density lipoprotein cholesterol \geq 4.14 mmol/L or patients treated with statin

Table 2. Characteristics and bacebile of DBE in 40 patients with	atriar normation
Heart rate according to dobutamine dose	
At baseline	67 ± 12
At 10γ/kg/min	70 ± 13
At 20γ/kg/min	77 ± 17
At 30γ/kg/min	109 ± 21
At 40γ/kg/min	147 ± 27
Systolic blood pressure according to dobutamine dose	
At baseline	149 ± 18
At 10γ/kg/min	158 ± 17
At 20γ/kg/min	159 ± 25
At 30γ/kg/min	167 ± 31
At 40γ/kg/min	170 ± 26
Diastolic blood pressure according to dobutamine dose	
At baseline	75 ± 11
At 10γ/kg/min	80 ± 10
At 20γ/kg/min	76 ± 11
At 30γ/kg/min	80 ± 14
At 40γ/kg/min	78 ± 13
Ischemia documented during DSE	13 (32.5%)
Inferior or lateral wall ischemia	9 (69%)
Septoapical or anterior wall ischemia	4 (31%)
Duration of AF	
< 1 hour	27 (67.5%)
< 24 hours	10 (25%)
Persistent (> 7 days, < 1 month)	3 (7.5%)

Table 2. Characteristics and outcome of DSE in 40 patients with atrial fibrillation

AF: atrial fibrillation; DSE: dobutamine stress echocardiography