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ORIGINAL ARTICLE

Gender-related differences in side-effects and hemodynamic response to regadenoson in patients undergoing SPECT myocardial perfusion imaging

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Abstract

Purpose To evaluate differences in side-effects and hemodynamic response between men and women undergoing regadenoson-stress SPECT myocardial perfusion imaging (MPI).

Methods The initial population of the study included 858 consecutive patients who underwent regadenoson-stress MPI at our institution. These patients underwent prospective assessment and classification of regadenoson-induced side-effects in six categories and recording of heart rate (HR) and blood pressure (BP) before and after regadenoson administration. From this initial population, after adjustment with 1:1 propensity matching using gender as the dependent variable and age, BMI, diabetes mellitus, hypertension, smoking, presence of coronary artery disease, LVEF, baseline systolic and diastolic blood pressure (BP) and HR, on-going use of cardio-active medications during test, and abnormal MPI scan as independent variables, a population of 279 pairs of opposite gender was formed and studied.

Results Compared with men, women had a significantly higher rate of any side-effect (71% vs. 58%, $p = 0.002$), chest pain (23% vs. 12%, $p < 0.001$), gastrointestinal discomfort (20% vs. 12%, $p = 0.01$), dizziness (12% vs. 5%, $p = 0.002$), and headache (20% vs. 13%, $p = 0.03$) and similar rates of dyspnea and other side-effects. Women demonstrated a higher median HR-response compared with men (41% (− 8, 127) vs. 34% (− 5, 106), $p = 0.001$) while men demonstrated a lower median systolic BP response (− 3% (− 27, 48) vs. 0% (− 36, 68), $p = 0.02$) compared with women.

Conclusions Gender is independently associated with a differential response to regadenoson with regard to overall side-effects and HR-response. These observations have the potential of important management and prognostic implications respectively.

Keywords Regadenoson · Gender · Heart rate response · Side-effects

Introduction

Regadenoson is a selective antagonist of A_2A receptors which was approved for clinical use by the FDA in 2008 and by the European Medicines Agency in 2010. Since its marketing, the simple usage protocol and the good tolerability and safety profile have resulted in an exponential growth in its use. Hence, regadenoson has now become the most commonly used vasodilator in the USA—where, based on 2013 data, holds an 84% of the vasodilator market share [1]—while its use is continuously expanding also in Europe. With dipyridamole and dobutamine being only infrequently used for pharmacologic stress testing, the main rival of regadenoson in the arena of pharmacologic stress testing is adenosine, which is easier to manage, more available, and has more predictable results during stress compared with

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dipyridamole and dobutamine. With regard to adenosine, regadenoson has been proven equally effective regarding diagnostic and prognostic information and better tolerated in head to head comparisons in the general population [2–7]. Also, regadenoson has been tested regarding safety and tolerability in a number of special populations with favorable results [8–11]. However, the gender preponderance in clinical effects of regadenoson has not been adequately studied yet. Bearing this in mind and on the occasion of the recent introduction of regadenoson in our institution, we designed and performed a study to evaluate differences in side-effects and hemodynamic response between men and women undergoing regadenoson stress.

Methods

Regadenoson was introduced in the Nuclear Medicine Department of our hospital in September 2016. In the context of an audit to evaluate its safety, we designed in parallel a 1:1 propensity-matched, prospective, observational study to evaluate differences in side-effects and hemodynamic response to regadenoson between men and women. The study complied with the Declaration of Helsinki and its protocol was approved by the local ethics committee.

We included consecutive patients with suspected or confirmed coronary artery disease (CAD) and clinically indicated pharmacologic stress myocardial perfusion imaging (MPI) who underwent regadenoson-stress SPECT-MPI at our institution without the adjunctive use of exercise. Exclusion criteria were systolic blood pressure (BP) < 95 or > 200 mmHg, heart rate (HR) < 50 bpm, obstructive pulmonary disease of any type and severity, acute coronary syndrome within 3 months, glomerular filtration rate < 30 ml/min/1.73 m^2, left ventricular ejection fraction (LVEF) < 30%, second or third degree atrioventricular block or sinus node dysfunction in the absence of a pacemaker, severe aortic stenosis, pregnancy or breastfeeding, active use of dipyridamole or methyl-xanthines (including caffeine), hypersensitivity to adenosine or regadenoson, history of seizures, long QT syndrome, and any contraindication to aminophylline.

The sample size for the study was calculated on the basis of the expected rate of any side-effect, as there were no previous data available regarding gender-related differences in hemodynamic parameters. First, we assumed an overall side-effects rate of 70% for women and 60% for men based on the 10% difference between men and women observed in the pooled population of ADVANCE-MPI 1 and 2 trials [4] and the 63% overall rate of side-effects in the largest available tolerability study in a European population [12]. Then, we calculated that a population of 279 pairs of opposite gender would be sufficient to detect the above difference, with an 80% power and a 90% confidence interval and set this number as the sample size target. After the enrollment of the 558th patient, periodic application of propensity score matching was initiated to check when the degree of successful matching would exceed the sample size set for the study. On December 10, 2017, with 858 consecutive patients being already enrolled in the study, the application of propensity scores returned 279 matched pairs, recruitment of additional patients was terminated, and these 558 patients were used as the study's population.

Imaging protocol

A one-day, stress-rest, Tc-99m sestamibi protocol was used in all patients. A Millennium VG dual-head gamma camera (GE Medical Systems, Milwaukee, USA) was used for image acquisition, which was performed with the step and shoot method and a 180° arc rotation. Instrumentation, radiopharmaceutical dosing, image acquisition protocols, and processing were in accordance with the Guidelines established by the EANM [13]. For stress imaging, regadenoson (Rapiscan, GE Healthcare) was administered as a 10-s injection of 400 μg into a peripheral vein using a 22-gauge catheter followed by a 5-ml saline flush. The stress dose of Tc-99m sestamibi (10 mCi) was administered intravenously 10–20 s after regadenoson administration into the same catheter, followed again by a normal saline flush. Thirty to 60 min post injection of the tracer, the stress imaging was performed. Rest-imaging was performed 2 h after stress imaging and 30–60 min post injection of the resting dose of Tc-99m sestamibi (25–30 mCi). Both stress and rest studies were acquired in an ECG-triggered, "gated" mode.

Continuous ECG monitoring was performed throughout the test while hemodynamic measurements were performed at baseline and repeated every 2 min—or more frequently if necessary—until HR and BP returned to pre-regadenoson administration levels. The most extreme of the BP and HR values recorded after regadenoson injection were registered as the peak values for hemodynamic parameters. The use of cardio-active medications was allowed or discontinued for at least 24 h before the test as per the referring physician's instructions. Cardio-active medications were considered beta blockers; calcium channel blockers; antiarrhythmics class I, III, and V; nitrates; ranolazine; nicorandil; angiotensin-converting enzyme or angiotensin receptor inhibitors; and ivabradine.

All images were interpreted during routine daily clinical practice by two experienced nuclear medicine physicians (MK, AT) in a semi-quantitative fashion using a 17-segment left ventricular model and a 5-point scale (0, normal uptake to 4, no uptake) according to EANM guidelines [13]. For the purpose of the present study, the results of perfusion analysis were used in a binary fashion (normal vs. abnormal) using as a cut-off for an abnormal scan a summed stress score of 2.

Before stress, all patients gave informed consent for their inclusion in the study and were instructed to note any new symptom that would appear starting from the injection of regadenoson until the time of their discharge from the laboratory.

Side-effects recording

For the purpose of unbiased side-effects reporting, no information about the nature of the potential side-effects of regadenoson was given to the patients, beyond the standard safety-related information of the test that is given to every patient in our laboratory before consenting them to undergo the stress MPI. The cardiologist supervising the test interviewed the patients at the end of the stress phase and again before their discharge for potential side-effects and recorded these symptoms in detail. After completion of patients' enrollment, a member of the authors (AK) processed these recordings, being blinded to the patient to which the symptoms belonged to, and assigned them to one of 6 predefined categories: dyspnea, chest pain, dizziness, flushing, headache, and unspecified (other). These categories were formed in accordance with the ADVANCE-MPI trials for the sake of comparisons with preexisting literature. No monitoring of delayed-onset symptoms was performed after patients' discharge.

Statistics

The normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. All continuous variables studied had an asymmetric distribution and are presented as median with range values. Categorical data are presented as counts and percentages. Baseline characteristics of men vs. women before and after matching were compared with the Pearson chi-square and Mood's median test (or the Mann-Whitney test where stated) for independent samples, as appropriate. Given the significant differences in baseline characteristics between males and females, we used a propensity score analysis to assemble a cohort in which the two gender-based groups were balanced on all baseline characteristics that could act as confounding variables in the manifestation of side-effects and hemodynamic changes. The propensity score was obtained by logistic regression analysis with gender as the dependent variable and the following parameters as independent variables: age, body mass index (BMI), diabetes mellitus, hypertension, active smoking status, presence of CAD, baseline LVEF, baseline systolic and diastolic BP and HR, on-going use of cardio-active medications during the test, and abnormal MPI scan. Nearest neighbor matching without replacement was implemented by applying a "greedy" algorithm on the logit of the propensity score within a caliper equal to 0.12 times the pooled standard deviation of the logit. The effectiveness of matching to alleviate covariate imbalance was evaluated by the standardized difference "*d*" of the covariates between treatment groups, with a $d \leq 10\%$ being considered as an indication of negligible differences in the mean or prevalence of covariates between groups. Matching was performed using the Matching package (Sekhon, 2011) and covariate balance was assessed using the Cobalt package (Greifer, 2018) of R software version 3.5.1 while all statistical analyses were carried out with PASW version 22 (SPSS, Inc., Chicago, Illinois). All tests were 2-tailed, and a p value < 0.05 was considered statistically significant.

Results

The characteristics of both the initial pool's (unadjusted sample) and the study's population (adjusted sample) are presented in Table 1. The groups in the adjusted sample were well matched in all baseline characteristics (i.e., standardized mean differences < 10%), except for history of myocardial infarction, prevalence of irreversible ischemia on MPI scan, pre-test symptoms, and use of statins and antiplatelet agents. The performance of the model in terms of propensity scores and covariates balance is demonstrated graphically in Fig. 1. On direct comparisons in the adjusted sample, the male population included more asymptomatic patients before testing and more patients on antiplatelet agents and with irreversible ischemia—but with similar rates of overall abnormal scans and reversible ischemia—compared with the female population. All other baseline characteristics demonstrated no statistically significant differences.

Side-effects and safety

For the total cohort of patients, the overall rate of side-effects was 64%. The observed rates of any side-effect were 71% for women and 58% for men, satisfying the assumptions on which sample size determination was performed. This difference was statistically significant in favor of men ($p = 0.002$). The rates of the pre-specified individual components of the side-effects profile of regadenoson according to gender are presented in Table 2. Women had significantly higher rates of chest pain, gastrointestinal discomfort, dizziness, and headache and non-significantly higher rates of dyspnea and other side-effects. Men had slightly higher rates of flushing, but this difference was not statistically significant. There were no deaths, myocardial infarctions, sustained or non-sustained ventricular arrhythmias, or episodes of advanced atrioventricular block during regadenoson stress in the population studied and this was the case also for the initial pool of 858 patients. Details of the ECG-related changes observed in the study's population during regadenoson stress are also presented in Table 2.

Table 1 Baseline characteristics of the initial population and the matched cohort

Characteristics	Unadjusted sample (before matching)				Adjusted sample (after matching)			
	Male	Female	*p*	*SMD*	Male	Female	*p*	*SMD*
Number of patients (*n*)	548	310	NA	*NA*	279	279	NA	*NA*
Age (years)	69 (36–87)	69 (43–90)	0.9	0.005	67 (36–86)	69 (43–90)	0.3	− 0.05
Risk factors for CAD (%, *n*)	–	–	–	–	–	–	–	–
Diabetes	35 (191)	36 (111)	0.7	− 0.02	34 (94)	34 (94)	1	< 0.001
Hypertension	73 (401)	68 (211)	0.1	0.11	68 (189)	68 (189)	1	< 0.001
Dyslipidemia	65 (355)	55 (172)	0.007	0.2	63 (175)	58 (162)	0.3	0.01
Smoking	45 (245)	30 (92)	< 0.001	0.3	37 (103)	33 (92)	0.3	0.08
Family history	24 (134)	23 (70)	0.5	0.04	24 (68)	22 (62)	0.5	0.05
Atrial fibrillation (%, *n*)	3 (16)	2 (5)	0.2	0.07	2 (6)	2 (5)	0.7	0.02
Pacemaker (%, *n*)	1 (7)	1 (4)	0.9	0.001	2 (5)	1 (4)	1	0.03
Pre-test symptoms (%, *n*)	–	–	–	–	–	–	–	–
Asymptomatic	38 (209)	26 (82)	0.001	− 0.25	40 (111)	27 (76)	0.002	− 0.33
Dyspnea	19 (103)	21 (66)	0.3		23 (39)	21 (59)	0.06	
Chest pain	34 (187)	38 (118)			64 (107)	37 (105)		
Other*	9 (49)	14 (44)			13 (22)	14 (39)		
Test indication (%, *n*)	–	–	–	–	–	–	–	–
Inability to exercise	86 (471)	87 (269)	0.3	0.05	85 (237)	87 (242)	0.5	0.07
Pacemaker or LBBB	8 (42)	9 (28)			8 (23)	9 (24)		
Other**	6 (35)	4 (13)			7 (19)	5 (13)		
BMI	29 (17–50)	29 (17–50)	0.2	− 0.07	29 (17–50)	30 (17–50)	0.2	− 0.02
CAD history (%, *n*)	15 (82)	9 (27)	0.008	0.17	11 (32)	9 (24)	0.3	0.08
Myocardial infarction	9 (49)	4 (13)	0.01	0.16	7 (21)	4 (11)	0.07	0.12
Revascularization	12 (68)	7 (21)	0.009	0.17	9 (25)	7 (19)	0.3	0.06
Baseline hemodynamics	–	–	–	–	–	–	–	–
Systolic BP	130 (100–180)	130 (95–182)	0.9	0.005	130 (100–180)	125 (95–182)	0.8	0.01
Diastolic BP	80 (55–100)	80 (60–100)	0.7	0.04	80 (55–100)	80 (60–100)	0.1	0.04
HR	68 (50–116)	71 (50–111)	0.001	− 0.31	71 (50–116)	70 (50–111)	0.6	0.003
MPS result (%, *n*)	–	–	–	–	–	–	–	–
Abnormal	69 (378)	38 (117)	< 0.001	0.67	44 (124)	42 (117)	0.5	0.05
Scar	37 (201)	10 (31)	< 0.001	0.55	23 (64)	11 (31)	< 0.001	0.24
Ischemia	49 (268)	30 (94)	< 0.001	0.37	32 (90)	34 (94)	0.7	− 0.03
Medications (%, *n*)	–	–	–	–	–	–	–	–
On cardio-active medications	77 (424)	68 (212)	0.004	− 0.21	68 (190)	68 (191)	0.9	− 0.01
Beta blockers	56 (306)	44 (136)	< 0.001	0.2	48 (133)	45 (125)	0.5	0.06
Calcium channel blockers	20 (111)	18 (57)	0.5	0.04	18 (51)	18 (50)	0.9	0.01
Nitrates	9 (51)	4 (12)	0.003	0.18	5 (14)	4 (12)	0.7	0.02
Digoxin	1 (3)	0 (0)	0.2	0.07	0.4 (1)	0 (0)	1	0.05
Ranolazine	2 (11)	2 (6)	0.9	0.005	2 (6)	2 (6)	1	< 0.001
Antiarrhythmics class I, III	5 (25)	5 (15)	0.8	− 0.01	4 (12)	5 (14)	0.7	− 0.03
Statins	51 (280)	44 (136)	0.04	0.14	51 (142)	44 (124)	0.1	0.13
ACEIs or AT II	51 (280)	45 (138)	0.06	0.13	43 (120)	44 (124)	0.7	− 0.03
Antiplatelets	57 (313)	35 (109)	< 0.001	0.44	52 (144)	36 (100)	< 0.001	0.32
LVEF < 50% (%, *n*)	8 (45)	3 (8)	0.001	0.2	4 (11)	3 (8)	0.5	0.04

Abbreviations: *SMD*, standardized mean difference; *ACEI*, angiotensin-converting enzyme; *ATII*, angiotensin receptor blockers; *MPS*, MPI scan

*Including palpitations and syncope

**Including hypertensive response to exercise and exercise-induced arrhythmias

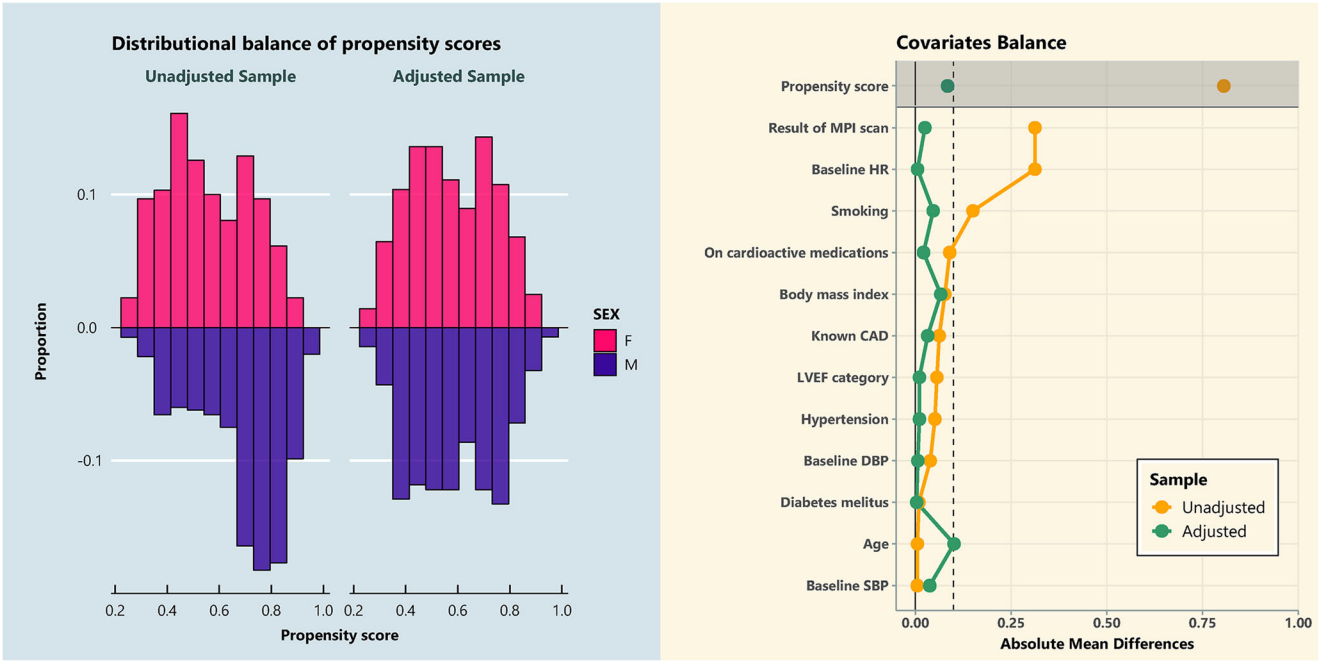

Fig. 1 Performance characteristics of the propensity matching model. In the left panel, a mirror image of the distribution of propensity scores before and after matching is shown while in the right panel, a Love diagram of the model is demonstrated. F females, M males

Table 2 Clinical, hemodynamic, and ECG-related effects of regadenoson

Characteristic		All ($n = 558$)	Male ($n = 279$)	Female ($n = 279$)	p
Side-effects (%, n)	Any	64 (359)	58 (162)	71 (197)	0.002
	Dyspnea	19 (106)	17 (48)	21 (58)	0.3
	Chest pain	18 (98)	12 (33)	23 (65)	< 0.001
	Gastrointestinal	16 (88)	12 (33)	20 (55)	0.01
	Flushing	21 (116)	23 (63)	19 (53)	0.3
	Headache	17 (93)	13 (37)	20 (56)	0.03
	Dizziness	9 (49)	5 (14)	12 (35)	0.002
	Other	7 (41)	6 (18)	8 (23)	0.4
Hemodynamic changes	ΔHR (bpm)	26 (− 7,97)	24 (− 4, 60)	29 (− 7, 97)	< 0.001
	%HRR	37 (− 8, 127)	34 (− 5, 106)	41 (− 8, 127)	0.001
	ΔSBP (mmHg)	0 (− 50, 65)	− 4 (− 35, 49)	0 (− 50, 65)	0.02
	%SBPR	0 (− 36, 68)	− 3 (− 27, 48)	0 (− 36, 68)	0.02
	ΔDBP (mmHg)	0 (− 35, 30)	0 (− 20, 30)	0 (− 35, 30)	0.004*
	%DBPR	0 (− 35, 50)	0 (− 25, 50)	0 (− 35, 50)	0.004*
Arrhythmias (%, n)	Extra-systoles	17 (96)	20 (55)	15 (41)	0.2
	AF	0.7 (4)	0.7 (2)	0.7 (2)	
	AVB	0.2 (1)	0.4 (1)	0 (0)	
	IVCD	0.5 (3)	0.7 (2)	0.4 (1)	
ECG changes (%, n)	ST depression ≥ 1 mm	3 (14)	1 (4)	4 (10)	0.1

*p values correspond to Mann-Whitney test

Abbreviations: *Δ*, change in parameter; *AVB*, 1st or 2nd type I degree atrioventricular block; *IVCD*, intraventricular conduction delay

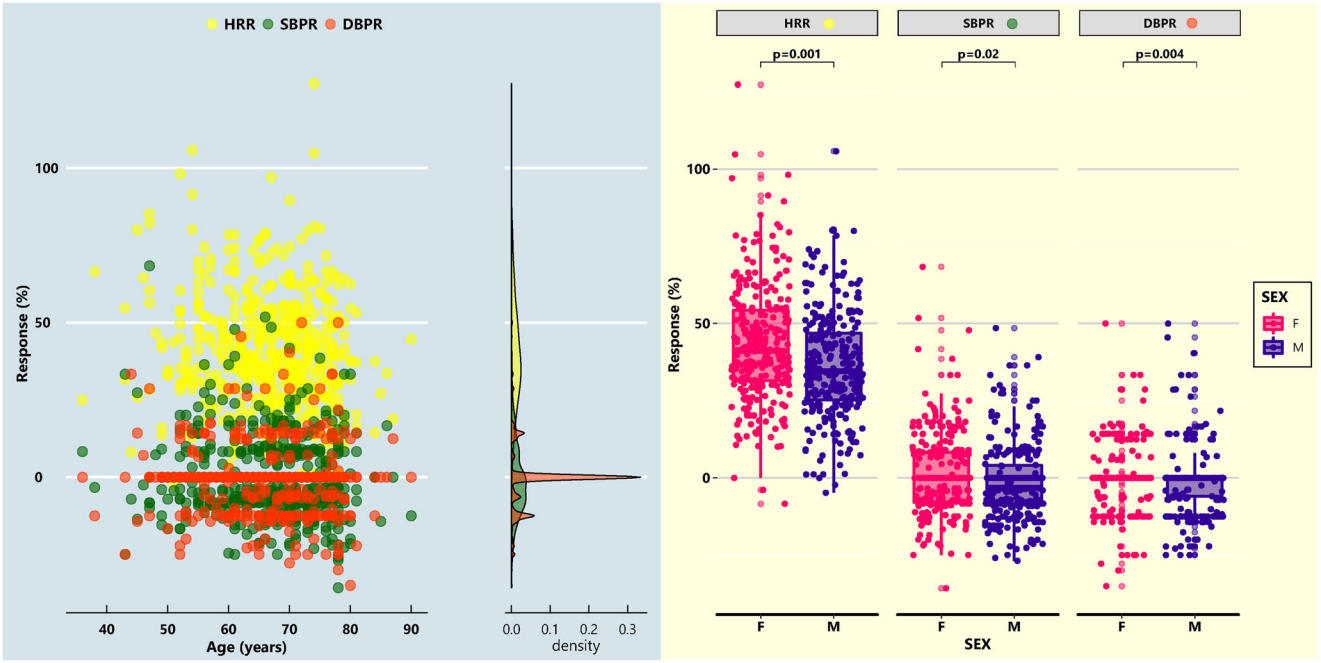

Fig. 2 Response of hemodynamic variables to regadenoson. In the left panel, the response of all hemodynamic variables for the total cohort stratified by age is demonstrated in overlap. In the right panel, the response of each hemodynamic variable according to gender is demonstrated in the form of jittered box-plots where horizontal lines indicate the medians and boxes the interquartile range

Hemodynamic response

Regarding hemodynamic changes, the overall pattern was that of clinically negligible differences in BP and a median increase of 26 bpm in HR after regadenoson administration. Table 2 presents in detail the absolute and relative changes in hemodynamic variables observed during regadenoson stress for both the total cohort and the two gender-based groups. The relative changes are given in the form of response of the variable, defined as the value at the end of the test minus

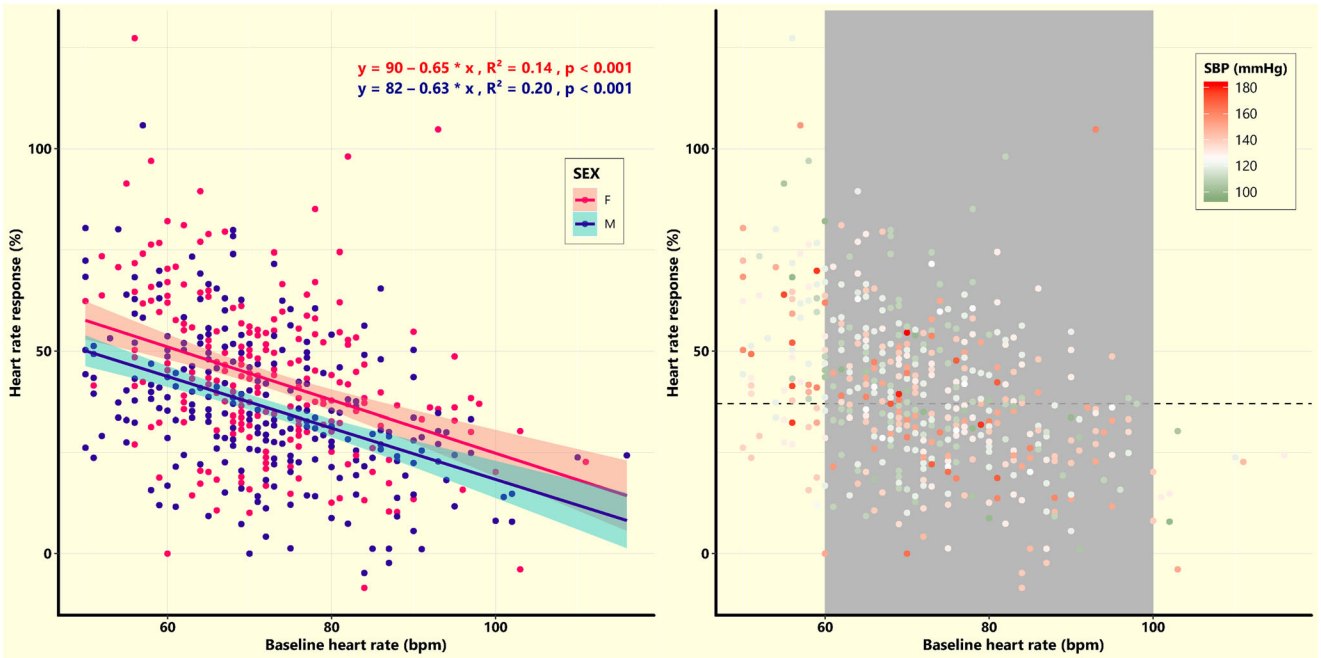

Fig. 3 Relationship between baseline HR and HRR. In the left panel, the relationship is stratified according to gender, while in the right panel according to baseline systolic BP. In the latter, the dotted, horizontal, black line corresponds to the median HRR and the white area in the range indicator to the median SBP

the value at baseline divided by the value at baseline, for systolic BP (SBPR), diastolic BP (DBPR), and HR (HRR). The response of these variables is also presented graphically for both the total cohort and the two gender-based groups in Fig. 2. Women demonstrated a significantly higher median HRR compared with men (41 (−8, 127) vs. 34 (−5, 106), $p = 0.001$), while for both males and females, a strong, inversely proportional, linear relationship between baseline HR and HRR was observed, as seen in Fig. 3. Men demonstrated a significantly lower median SBPR (−3 (−27, 48) vs. 0 (−36, 68), $p = 0.02$) compared with women, while the median DBPR was 0 for both males and females, but the distribution of DBPR values was significantly different between the two gender-based groups (Mann-Whitney $U = 34$, $p = 0.004$).

Left ventricular ejection fraction reserve

The median LVEF at rest was 57% (30–81) for men and 60% (30–83) for women. At peak stress, the median EF increased to 61% (20–89) for men and 69% (24–92) for women. Median LVEF was significantly higher in women at both rest ($p = 0.004$) and peak stress ($p < 0.001$). The ejection fraction reserve % (%EFR), defined as [(LVEF at peak stress − LVEF at rest)/LVEF at rest]%, was also higher in women compared with men (8% (−38, 60) vs. 7% (−51, 43), $p = 0.002$). However, the ratio of %EFR to %HRR was not significantly different between men and women (0.17 (−3.6, 5.5) vs. 0.19 (−1.5, 7), $p = 0.4$). As shown in Fig. 4, there was no correlation between %EFR and %HRR and this was the case for both men (Pearson's $r = 0.02$) and women (Pearson's $r = 0.03$).

Subgroup analysis

In a subgroup analysis according to diabetes status (presence vs. absence of either type I or medically treated type II diabetes mellitus), BMI (obese vs. non-obese, using a cut-off value of 30), age (young vs. elderly, using a cut-off value of 65 years), and pattern of perfusion (normal vs. abnormal MPI scan, using a summed stress score cut-off value of 2), women demonstrated a significantly higher HRR to regadenoson in all subgroups, except for diabetic and young patients, which were the only subgroups that included less than 100 patients. The results regarding HRR in subgroups are presented in detail in Table 3. Regarding the rates of any side-effect, the results observed in subgroups matched the results observed in the overall population in elderly, obese, non-obese, diabetics, and non-diabetics. The higher rate of overall side-effects in women was not statistically significant only in the younger patients' subgroup. Figure 5 demonstrates in detail the differences in overall rates of side-effects observed between men and women.

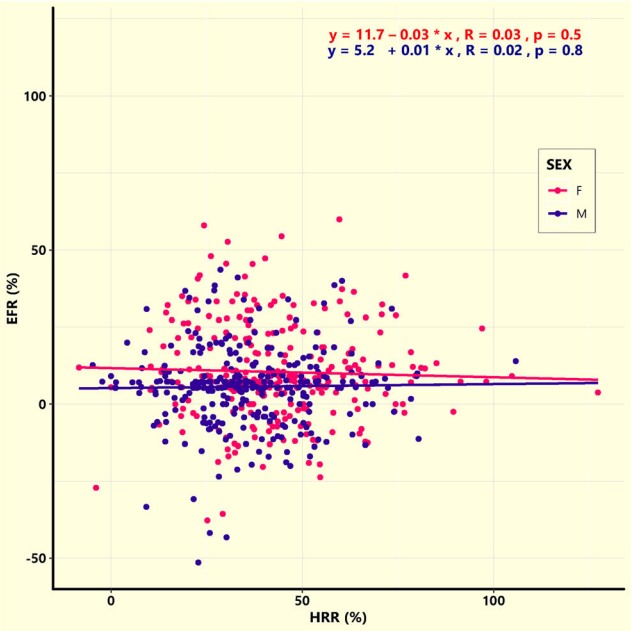

Fig. 4 Scatter plot diagram of %EFR vs. %HRR. There was no correlation between the values of %EFR and %HRR, either linear (results of linear regression analysis presented in the top right part of the figure) or non-linear (all non-linear models tested demonstrated *p*-values > 0.05). This was the case for both genders

Discussion

To the best of our knowledge, this is the first study to specifically address the issue of gender-related differences in tolerability and hemodynamic response to regadenoson. Its key points are that women exhibit a higher rate of any side-effect and an increased HRR after regadenoson administration compared with their male counterparts. These findings hold true after adjustment for all the factors described in the literature [14, 15] as having a potential impact on the results observed.

A number of studies have reported on the frequency of regadenoson-related side-effects in populations from both the USA and various different European countries. At present, the two largest studies on this topic include the pooled population of the ADVANCE-MPI 1 and 2 randomized trials ($n = 1240$) [4] and a cohort of 1581 patients evaluated in an observational European study by Brinkert et al. [12]. In the latter, patients underwent regadenoson stress combined with submaximal exercise while in the former, patients underwent pure regadenoson stress and the overall rates of any side-effect were 63% and 73% respectively. In our study, 64% of the patients experienced at least one side-effect following regadenoson injection. This relatively low figure could be partially explained by the low-risk features of the population studied. However, it is conceivable that given the differences in population origin and characteristics, the protocols of regadenoson stress used, and the methods for collecting the

Table 3 HRR in subgroups

Subgroup		Male		Female		*p*
Criterion	Category	Value	Number	Value	Number	
Diabetes	Diabetics	33 (−5, 106)	94	39 (0, 105)	94	0.19
	Non-diabetics	35 (−2, 80)	185	41 (−8, 127)	185	0.005
BMI	Obese	31 (−2, 80)	121	38 (10, 127)	131	0.006
	Non-obese	37 (−5, 106)	158	42 (−8, 91)	148	0.016
Age	Elderly	33 (−5, 80)	181	41 (0, 127)	192	< 0.001
	Young	38 (−2, 106)	98	41 (−8, 98)	87	0.212
MPS result	Abnormal	33 (−2, 106)	124	40 (−8, 127)	117	0.034
	Normal	35 (−5, 78)	155	42 (0, 105)	162	0.037

side-effects, some variance in the reported rates of regadenoson-related side-effects is to be expected.

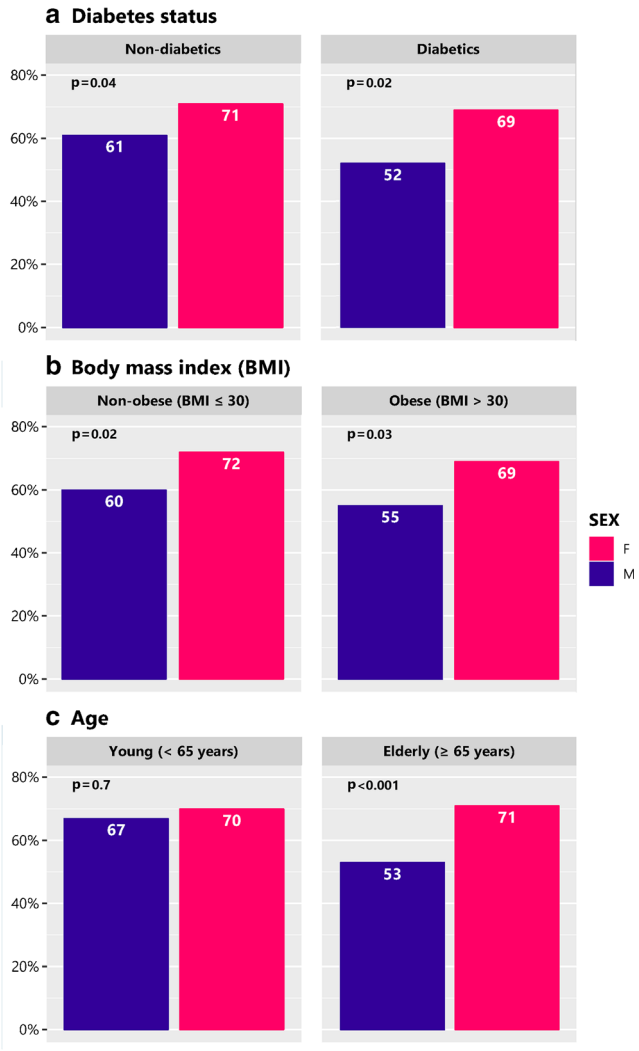

Fig. 5 Differences in overall side-effects between males and females in subgroups according to diabetes (**a**), BMI (**b**) and age (**c**). The bars denote the percentage (%) of the overall side-effects observed between men and women in various subgroups

Regarding gender differences in tolerability of regadenoson, a 10% difference in the rate of all side-effects (80% for women vs. 70% for men) was reported in the pooled population of the regadenoson arms of the ADVANCE-MPI 1 and 2 trials. The latter were methodologically identical, multicenter trials in which all patients underwent an initial adenosine study and were then randomized in a 2:1 fashion to a second study using regadenoson or adenosine. These trials, however, were designed to demonstrate non-inferiority of regadenoson compared with adenosine; hence, the randomization corresponded to the stress agent and not the gender. Subsequently, the gender differences observed in the regadenoson arm did not take into account the multiple confounders in baseline characteristics that were adjusted for in our study. Our results reproduce but most importantly establish the above observations by adjusting for confounders. Regarding the individual components of the side-effects profile of regadenoson, our results were in general accordance with the ADVANCE-MPI trials, but differences were observed regarding flushing and dizziness.

We are not aware of any previous studies reporting on gender-related differences in hemodynamic response to regadenoson, although numerous studies have reported on the regadenoson-induced hemodynamic changes. In the ADVANCE-MPI trials, a modest decrease in systolic and diastolic BP (average of 13 and 8 mmHg, respectively) and an average increase of 25 ± 11 bpm in HR were observed. In our study, the observed differences in BP were negligible, while the median HR increase was 26 bpm. The overall pattern of hemodynamic changes observed, which was similar for both men and women, was in accordance with the currently prevailing pathophysiologic mechanism of the HRR to regadenoson which suggests that it does not represent a baroreflex-mediated epiphenomenon secondary to peripheral vasodilation, but a regadenoson-related transient modulation of the autonomous nervous system function [16].

The mechanisms of the results observed cannot be fully elucidated by the present study and should be considered

multifactorial. Although the exact causes have not been identified, animal studies have provided some evidence supporting sex-related differences in adenosine A2A receptor sensitivity [17], with ovarian hormones being reported to increase the sensitivity of the D2/A2A receptor system in females [18]. Furthermore, there is substantial clinical evidence of gender-related differences in the function of the autonomic nervous system, which plays a major role in the regulation of the cardiovascular system under both physiological and pathophysiological conditions [19]. Hence, it is logical to assume that these differences might have played a role in the differential hemodynamic response to regadenoson observed in our study. Another potential explanation for the differential response to regadenoson observed in women compared with men could be the impact of microvascular dysfunction. It has been suggested that abnormal vascular response is more common in women, especially after menopause, and this hypothesis has been proposed to explain a number of clinically relevant differences observed after vasodilator stress between men and women [20]. Could the residual imbalances observed in some baseline characteristics of the matched population also play some role? As mentioned in the results, the male population included more asymptomatic patients before testing and more patients with irreversible ischemia and on antiplatelet agents. Someone could argue that the female population was primed to demonstrate more symptoms after regadenoson administration, as it included less asymptomatic patients at baseline compared with the male population. This argument, however, has no pathophysiologic basis as regadenoson-induced dyspnea and chest pain have a different mechanism compared with similar symptoms induced during exercise. Furthermore, we are not aware of any literature describing interactions between antiplatelets and regadenoson-induced symptoms.

Our results have multi-level clinical relevance. Firstly, they could serve to tailor the application of the various approaches used to reduce regadenoson side-effects, like preemptive aminophylline use [21] and concomitant low-level exercise [22, 23], in order to maximize their efficiency. Indeed, now an evidence-based background exists to test the hypothesis that women exhibit not only more side-effects but also a larger benefit from these maneuvers than men in terms of side-effects reduction. In our study, no specific subgroup was identified in which the overall rate of side-effects in women was substantially larger than the rate observed in the total cohort, but the higher rate of side-effects in women was a consistent finding across most subgroups. In a sub-study of the ASSUAGE trial, Rangel et al. compared the absolute and relative benefits of aminophylline administration vs. placebo in men and women and reported that men received a greater absolute risk reduction in gastrointestinal adverse effects than women [24]. However, the ASSUAGE trial [21] was not powered to detect differences between any subgroups and was randomized based on aminophylline use and not gender. Hence, these results should be considered only as hypothesis generating.

Secondly, although the effects of regadenoson on BP have no prognostic significance, strong evidence suggests that the opposite is true for the effects on HR [14], regardless of whether the baseline rhythm is sinus or atrial fibrillation (AF) [25]. Indeed, HRR cut-offs linked with all-cause mortality prediction and incremental prognostic value over MPI findings and resting LVEF have been proposed [26]. Values greater than 30% are thought normal, whereas less than 15% abnormal or blunted [14], but these cut-offs are not gender specific. The present study provides a background to explore the prognostic utility of gender-specific HRR cut-offs.

Finally, it is conceivable that the application of this study's results extends to all imaging modalities and interventional procedures using regadenoson as a stressor, like cardiac MRI perfusion scans and invasive fractional flow reserve measurements.

Limitations

The main limitation of the study relates to its non-randomized nature. Propensity score–based observational studies are generally considered as the second best quality evidence after randomized trials, but well-described limitations apply. In our study, all literature described potential confounding variables were measured and included, the ratio of any side-effect per confounding variable was well above 10, which is commonly used as a crude rule of thumb, while some residual imbalances observed in the baseline characteristics of the matched cohort could not affect the results observed, as discussed in detail earlier. Still however, the definitive answer to the study's question must be derived from a randomized trial. Furthermore, no sensitivity analyses were performed, as this approach has been proposed by some authorities to check the stability of the results observed in propensity score studies but no gold standard exists regarding these methods.

The conclusions reached here were arguably based on a low-risk population for regadenoson-related side-effects and did not account for delayed-onset side-effects. Although there is no basis to expect different results with regard to the overall rate of side-effects between men and women in a higher risk population, we cannot exclude a magnification of the differences observed in the individual components of the side-effects profile of regadenoson. In addition, the results of the subgroups analysis should be considered as hypothesis generating due to the small sample size and the fact that matching was confined to gender.

Finally, although no serious safety issues were raised, the frequency of serious adverse events, including but not limited to death, myocardial infarction, and life-threatening arrhythmias with regadenoson, is extremely small [27] and the study

was underpowered to detect such serious side-effects. The latter holds true also for the differences observed in the ECG-related parameters.

Conclusions

In conclusion, the present study demonstrated that gender is independently associated with a differential response to regadenoson with regard to overall side-effects and HR-response. These observations have the potential of important management and prognostic implications respectively.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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