Regadenoson for Pharmacological Stress Tests: Blood Pressure, Heart Rate and Major Side Effects in 5780 Patients referred for Myocardial Scintigraphy. A High-Volume Single-Center Experience.

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Background:

Regadenoson is a highly selective A2A receptor agonist and approved in many countries for myocardial perfusion pharmacological SPECT stress imaging. As a vasoactive drug, Regadenoson does have side effects, but there is only data regarding this issue available from some smaller studies, no prospectively collected data from real world application in high-volume centers.

Methods:

A standard dose of 400 µg i.v. was injected. Soon after the injection of Regadenoson, usually at a clearly visible increase of the heart rate, 99m Tc-Tetrofosmin was injected. Heart rate, blood pressure and ECG were continuously monitored before injection (rest), and up to 10 minutes. 395 patients (7%) had a history of COPD, 113 patients (2%) had a history of bronchial asthma. 1051 patients (18.2%) had a pre-existing 1st degree AV-block (PQ time > 200 ms).

Demographic Data and Stress Tests

Due to inability of physical exercise, Regadenoson was needed in 5780/28351 cases (20.4 %). The mean age was 71.9 ± 9.7 (33 – 95) years. 2576 cases were male (44.6%) and 3204 cases were female (55.4%).

The vast majority of the cases (n=5011) didn't show any relevant/diagnostic ST-segment changes during the observation period of 10 minutes.

Results: ALL PATIENTS Heart Rate

	Mean ± SD
Rest (baseline)	70.2 ± 12.3 bpm
Maximum	94.6 ± 17.3 bpm* (vs. Rest)
After 10 minutes	79.4 ± 13.2 bpm* (vs. Rest)

* p < 0.001 according to Student's t-Test

Results: ALL PATIENTS Blood Pressure

	Mean ± SD
Systolic Blood Pressure	
Rest (baseline)	128.9 ± 16.2 mmHg
Minimum	123.3 ± 20.3 mmHg* (vs. Rest)
After 10 minutes	123.9 ± 15.5 mmHg* (vs. Rest)
Diastolic Blood Pressure	
Rest (baseline)	73.7 ± 8.1 mmHg
Minimum	69.3 ± 9.0 mmHg* (vs. Rest)
After 10 minutes	70.8 ± 8.0 mmHg* (vs. Rest)

Results: COPD / BRONCHIAL ASTHMA Heart Rate

	Mean ± SD
Rest (baseline)	67.2 ± 8.7 bpm
Maximum	97.0 ± 18.3 bpm* (vs. Rest)
After 10 minutes	77.9 ± 7.6 bpm* (vs. Rest)

* p < 0.001 according to Student's t-Test

Results: COPD / BRONCHIAL ASTHMA Blood Pressure

	Mean ± SD
Systolic Blood Pressure	
Rest (baseline)	125.6 ± 13.3 mmHg
Minimum	116.7 ± 28.6 mmHg* (vs. Rest)
After 10 minutes	125.0 ± 24.8 mmHg
Diastolic Blood Pressure	
Rest (baseline)	72.2 ± 9.7 mmHg
Minimum	68.9 ± 10.5 mmHg* (vs. Rest)
After 10 minutes	71.1 ± 10.5 mmHg

Heart Rate according to Systolic Blood Pressure Response:

	Blood Pressure *Drop* > 5 mmHg	Blood Pressure *No Change* ± 5 mmHg	Blood Pressure *Increase* > 5 mmHg
Percentage of Patients	55.6 %	30.5 %	13.9 %
Systolic Blood Pressure	- 19.1 mmHg	- 0.2 mmHg	+ 16.7 mmHg
Diastolic Blood Pressure	- 7.6 mmHg	- 1.2 mmHg	- 0.3 mmHg
Heart Rate	+ 23.9 bpm	+ 23.3 bpm	+ 25.5 bpm

The increase of heart rate following the injection of Regadenoson is independent of the systolic blood pressure response.

Frequent Side Effects:

	Nr. of Cases	Percentage
Shortness of Breath "Feeling of Increased Breathing"	3709	64.2 %
Headache	1199	20.7 %
Feeling of Warmth	1168	20.2 %
Pressure in the Chest	971	16.8 %
Pressure in the Stomach	935	16.2 %
Dizziness	519	9.0 %
Nausea	342	5.9 %
Sensation in the Legs	266	4.6 %

Rare Side Effects:

	Nr. of Cases	Percentage
Tightness in the Throat	200	3.5 %
Feeling of Weakness	176	3.0 %
Tussive Irritation	173	3.0 %
Feeling of Dry Throat and/or Mouth	116	2.0 %
Sensations in the Hands	99	1.7 %
Palpitations	102	1.7 %
Vomiting	39	0.7 %
Sweating	43	0.7 %

Severe Complications:

	Nr. of Patients	Percentage
Asystole (≥ 6 seconds) (both patients had 1st degree AV-Block at baseline)	2	0.03 %
Intermittent 2nd or 3d degree AV-Block (with a relevant pause)	2	0.03 %
Symptomatic Bradycardia (< 40 bpm)	2	0.03 %
Symptomatic Drop in Blood Pressure	2	0.03 %
Epilepsy	2	0.03 %

These severe and potentially life threatening complications could be immediately interrupted with i.v. Theophyllin and Atropine. No patient died. There was neither a history of bronchial asthma nor of COPD in the group of cases showing severe complications. There was neither any case of Regadenoson-induced bronchospasm nor any stroke. All severe complications were observed within 10 minutes after the injection of Regadenoson, none was observed afterwards.

Safety Recommendations for Regadenoson:

1. **Continuous monitoring of blood pressure and ECG for 10 minutes. To be on the safe side, don't remove the injection needle for at least 20 minutes.**
2. **Be aware of the contraindications (2nd degree AV-block).**
3. **According to our experience, increased alert for patients with preexisting 1st degree AV-Block is advisable.**
4. **Keep the antidotes ready and available for immediate use:**
   - **Theophylline, 10ml = 200 mg, slowly i.v.**
   - **Atropine, 1 ml = 0.5 mg, 1 - 2 vials i.v.**

Summary and Conclusions:

1. **After the injection of Regadenoson, there was a significant mean heart rate increase of 25 bpm. The mean decrease of the systolic blood pressure was also significant with approx. 6 mmHg and so was the decrease of diastolic blood pressure with approx. 5 mmHg.**
2. **The increase of heart rate was independent of the systolic blood pressure response.**
3. **Generally, Regadenoson is well tolerated.**
4. **The most frequent side effect was a feeling of increased breathing / shortness of breath in appr. 2/3 of all cases.**
5. **There are various different unspecific and transient rare side effects.**
6. **Severe / life-threatening side effects are very rare (0.17%) and easy to treat with Atropine and – as officially recommended - with Aminophylline (if regionally available) or – like in Germany - with Theophylline.**
7. **In patients with COPD or bronchial asthma, no severe side effects were observed.**

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