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CLINICAL STUDY

Midazolam and dexmedetomidine sedation impair systolic heart function

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ABSTRACT

BACKGROUND: Sedation is an essential part of clinical practice. Despite this fact, we still lack data describing the exact impact of sedation on heart function.

PURPOSE: To compare the changes in heart function, induced after sedation with either midazolam or dexmedetomidine, using cardiac magnetic resonance imaging (MRI).

METHODS: A total number of 30 volunteers were randomized into two groups: 15 participants in the midazolam group (MID) and 15 participants in the dexmedetomidine group (DEX). Every participant underwent a one-session cardiac MRI before and after sedation onset. The following parameters were recorded: left and right ventricle stroke volume (Ao-vol and Pul-vol resp.) and maximum flow velocity through the mitral valve during early (E-diast) and late diastole (L-diast). A monitor recorded values of mean blood pressure (MAP), pulse (P) and blood oxygen saturation (SpO_2) in 5-minute intervals.

RESULTS: Dexmedetomidine led to a statistically significant decrease in Ao-vol ($p = 0.006$) and Pul-vol ($p = 0.003$), while midazolam decreased E-diast ($p = 0.019$) Ao-vol ($p = 0.001$) and Pul-vol ($p = 0.01$). The late diastolic filling was not influenced by the sedation technique.

CONCLUSION: Both sedation regimens worsened the systolic function of both ventricles. Midazolam moreover attenuated early diastolic filling of the left ventricle *(Tab. 3, Fig. 4, Ref. 19)*. Text in PDF *www.elis.sk*

KEY WORDS: cardiac magnetic resonance imaging, cardiac function, midazolam, dexmedetomidine, sedation, critical care.

Introduction

In the 21-century, sedation has become a cornerstone and an essential part of modern critical care practice. The main goals of sedation are to ensure the patient's comfort and to prevent anxiety, thus ensuring an overall state of calmness and well-being during the intensive care unit stay. Using sedation, alone or in combination with analgesics, increases tolerance to mechanical ventilation and the daily provided invasive procedures, by avoiding the stress and adverse hemodynamic response that accompanies these procedures (1, 2).

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Numerous papers have already been published comparing different sedation techniques and their effect on hemodynamic parameters (3–9). However, no study has yet examined the impact of sedation on cardiac function using cardiac MRIs in a clinical setting.

The study tested the hypothesis that the use of dexmedetomidine leads to a less negative impact on heart function compared to midazolam.

Materials and methods

The study protocol was approved by the Ethics Committee of University Hospital in Hradec Kralove, Czech Republic. Reference Number: 201612S15P. All the participants signed an informed consent.

Study characteristics

This is a randomized study, which included volunteer patients, who were admitted to our department due to chest pain, in whom an acute coronary syndrome was ruled out. Participants had normal systolic function of both ventricles, had sinus rhythm, had no heart valve disease, had no history of heart failure, had no liver, kidney no lung disease, had no contraindication to perform a cardiac MRI or to receive sedation (Tab. 1).

A total number of 56 participants were evaluated for the initial screening phase, of whom 26 were excluded: 6 for atrial

Tab. 1. Study population characteristics.

	MID group (n=15)	DEX group (n=15)	p
Sex (M/F)	8/7	10/5	N/A
Age	48.4±11.7	53.4±16.2	N/A
BMI	27.2±5.6	29.4±6	N/A
Hypertension	9	10	N/A
CAD	5	5	N/A
Diabetes mellitus	2	1	N/A
Nephropathy	0	0	N/A

BMI: body mass index, CAD: coronary artery disease, MID: midazolam, DEX: dexmedetomidine

fibrillation, 6 refused to participate, 11 had structural heart disease and 3 participants were excluded due to claustrophobia. Then, 30 participants were randomized by the envelope method into two groups: 15 participants in the midazolam group (MID) and the same number in the dexmedetomidine group (DEX).

Each study participant underwent a baseline cardiac MRI. Then the participants received sedation – either by midazolam or dexmedetomidine. Five minutes after the onset of sedation, a control cardiac MRI was performed during the same session (see MRI scans) to detect sedation-induced changes in heart function.

Sedation technique

The participants were fasting for 6 hours before the study initiation. Initially, a baseline cardiac MRI was performed prior to sedation administration. Then sedation was administered according to each participant's group. The MID group received 2 mg of midazolam intravenously as a single dose, since it's the most common way of its administration in outpatient procedures. As for the DEX group, dexmedetomidine was given as an infusion at the rate of 0.7 ug.kg^{-1}.hr^{-1}, which continued till the end of the study. Dexmedetomidine was administered without a loading dose and in a relatively low dose for several reasons: risk of hypertension and tachycardia during dexmedetomidine bolus administration (10); risk of severe hypotension and bradycardia at higher dexmedetomidine infusion rates (10); furthermore, influencing the afterload during dexmedetomidine bolus administration could influence the monitored parameters of cardiac function monitored by MRI.

An infusion pump (Compactplus, B. Braun, Melsungen AG, Germany) with a long infusion set was used to deliver dexmedetomidine during the investigation from out of the magnetic field. Following 5 minutes of sedation administration, a control cardiac MRI was performed (Fig. 1).

MRI scans

Cardiac MRI was performed on a 3Tesla MR scanner (Philips Ingenia, Philips, Best, The Netherlands) using a 32-channel body surface coil. Retrospectively ECG-triggered, balanced turbo-field echo sequences (BTFE) were obtained in 4-chamber, 3-chamber, 2-chamber and short-axis planes during multiple breath holds.

Subsequently, we set appropriate planes perpendicularly to blood flow through the aortic, pulmonary and mitral valves in the BTFE sequences for flow velocity and maximum flow measurements.

Initially, a baseline cardiac MRI was acquired then, after the patients had been sedated with either midazolam or dexmedetomidine, a repeated cardiac MRI was obtained.

Data were transferred to an offline workstation for postprocessing and quantification.

The quantitative flow measurement was performed using a phase contrast quantification flow mapping.

The anatomical positions of the 2-dimensional flow MRI slices were automatically extracted from the BTFE sequences. On each sequence, the contour of the valves was segmented with a B-spline interpolation algorithm. The segmentation was then carefully adapted manually to each time point through the cardiac cycle accounting for pulsation and heart motion. Extracted hemodynamic parameters were: E-diast, L-diast, Ao-vol and Pul-vol before and after sedation.

Hemodynamic monitoring

The participants were monitored to avoid complications associated with a sedation administration such as: hypotension defined by a decrease in the MAP below 65 mmHg, hypertension defined by a rise in MAP above 100 mmHg, bradycardia defined by a decrease in P below 50 min^{-1}, tachycardia defined an increase in P above 90 min^{-1} and hypo saturation defined by a decrease SpO_2 below 93 %.

The hemodynamic parameters were monitored using an MRI-compatible monitor (Philips Expression MR 200, Philips, Best, The Netherlands). The following parameters were recorded: MAP, P, SpO_2. Five measures were taken before and after sedation administration in 5-minute intervals. During MRI scans, the participants had to be cooperative and repeatedly were asked to hold their breath

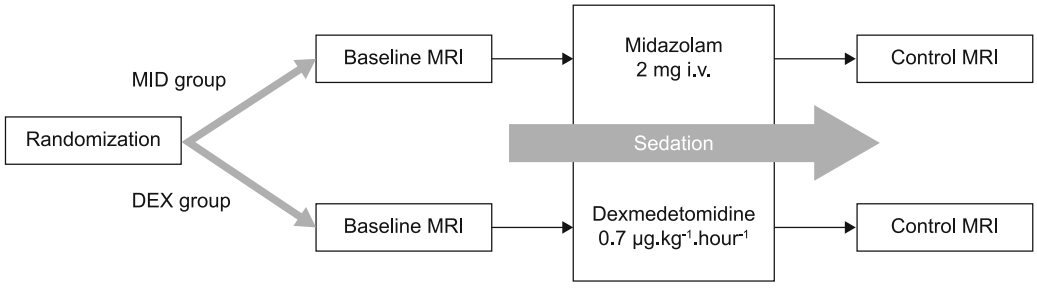

Fig. 1. Study design.

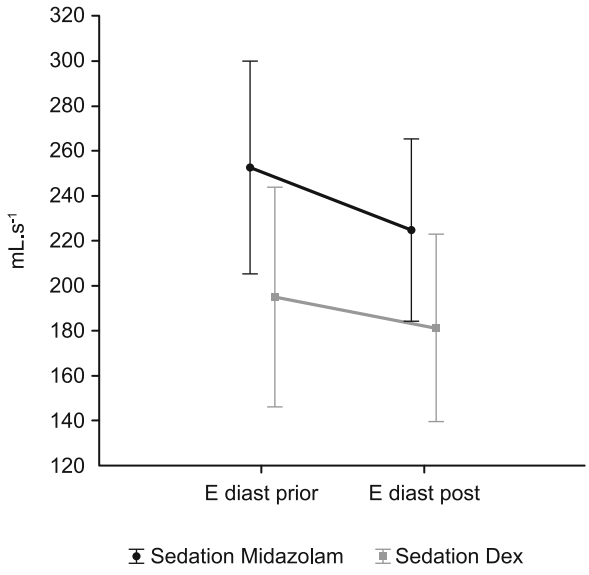

Fig. 2. A. The effect of sedation on early diastolic filling (E-diast) of the left ventricle. Midazolam impaired significantly E-diast of the left ventricle (p = 0.019), while dexmedetomidine sedation did not (p = 0.2).

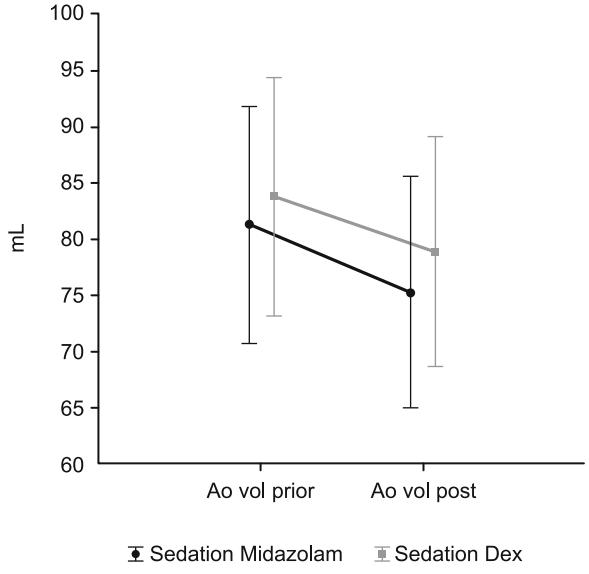

Fig. 3. The impact of sedation on left ventricular output (Ao-vol). Both sedation regimens impaired output of the left ventricle (MID: p = 0.001, DEX: p = 0.006).

during MRI sequences acquiring, therefore the target sedation level, according to the RASS scale, did not exceed –1. After the end of the study, the participants were monitored for 4 more hours.

Statistical analysis

The primary outcome measure was the systolic function of both left and right ventricle assessed by Ao-vol and Pul-vol, respectively. The secondary outcome measure was the early diastolic filling of the left ventricle assessed by E-diast. According to data

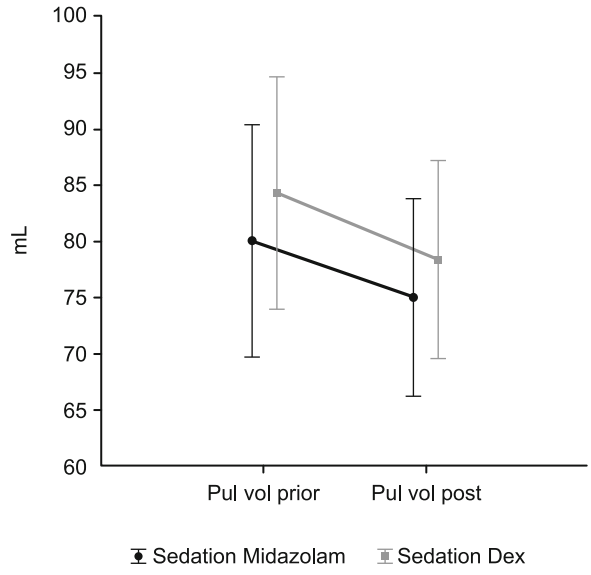

Fig. 4. The impact of sedation on right ventricular output (Pul-vol). Both sedation regimens impaired output of the right ventricle (MID: p = 0.01, DEX: p = 0.003).

processed from the first 8 participants, a 10 % difference of these parameters, following sedation administration, was accepted to be of clinical significance. Our previous pilot study established standard deviation (SD) for the following parameters in the DEX group: Ao-vol = 9.0, Pul-vol = 8.9, E-diast = 20.5. In the MID group, the standard deviation was as follows: Ao-vol = 5.5, Pul-vol = 5.7, E-diast = 12.2.

To achieve a statistically significant data at $p < 0.05$ and power of 80 %, a total number of 5 participants in the MID group and 9 participants in the DEX group was sufficient to prove the primary outcome measure. As for the secondary outcome measure, a total number of 14 participants was required in the MID group while 35 participants were needed to achieve a reliable power for the secondary outcome measure in the DEX group.

The statistical analyses were performed using STATISTICA software (data analysis software system, version 13 TIBCO Software Inc).

All values are presented as the average ± standard deviation. After a normal distribution was confirmed, the analysis of variance for repeated measures with post hoc Fisher's Least Significant Difference test was used for statistical testing of significant differences in each group and between the groups before and after sedation. Sample size calculation was performed using the PASS 2019 Power Analysis and Sample Size Software (NCSS, LLC. Kaysville, Utah, USA) using one-Sample T-Tests (paired t-test).

Results

Cardiac MRI was performed in all the participants without adverse events. Sedation was well tolerated; no events associated with its administration were recorded. During monitoring of hemodynamic parameters, neither heart rhythm disturbance,

Tab. 2. Acquired hemodynamic parameters.

	MID group			DEX group		
	prior sedation	during sedation	p	prior sedation	during sedation	p
P (min^{-1})	66±10	72±9	0.0003	63±7	59±6	0.007
MAP (mmHg)	85.7±8.8	83.4±7.5	0.18	87.4±9.1	80.1±8.7	0.0001
SpO_2 (%)	97.3±1.3	95.8±1.4	0.002	95.4±2.2	95.4±2	0.8

P: pulse, MAP mean blood pressure, SpO_2: blood oxygen saturation, MID: midazolam, DEX: dexmedetomidine

Tab. 3. Acquired parameters of cardiac function by MRI.

	MID group			DEX group		
	prior sedation	during sedation	p	prior sedation	during sedation	p
E-diast ($mL.s^{-1}$)	252.4±100.3	225±87.2	0.019	195±76.3	181.5±62.8	0.2
L-diast ($mL.s^{-1}$)	151.2±61.6	141.1±58.2	0.2	146.8±85.9	138.5±75.9	0.3
Ao-vol (mL)	81.2±19.8	75.2±17.1	0.001	83.7±20.2	78.8±21.5	0.006
Pul-vol (mL)	80±22.9	75±18.5	0.01	84.1±15.5	78.2±14.6	0.003

E-diast: maximal blood flow velocity through the mitral valve during early diastole, L-diast: maximal blood flow velocity through the mitral valve during late diastole, Ao-vol: left ventricular stroke volume, Pul-vol: right ventricular stroke volume, MID: midazolam, DEX: dexmedetomidine

hypotension, hypertension nor blood oxygen desaturation was registered.

Midazolam had a negative impact on early diastolic filling (252.4 $mL.s^{-1}$ ± 100.3 vs 225 $mL.s^{-1}$ ± 87.2, p = 0.019) (Fig. 2).

When following left and right ventricle output midazolam sedation decreased the left ventricle (Ao-vol: 81.2 mL ± 19.8 vs 75.2 mL ± 17.1, p = 0.001) (Fig. 3) and right ventricle output (Pul-vol: 80 mL ± 22.9 vs 75 mL ± 18.5, p = 0.01) (Fig. 4). Accordingly, these changes were noticed in the DEX group (Ao-vol: 83.7 mL ± 20.2 vs 78.8 mL ± 21.5, p = 0.006, Pul-vol: 84.1 mL ± 15.5 vs 78.2 mL ± 14.6, p = 0.003).

The values of hemodynamic parameters acquired by the monitor are shown in Table 2.

The parameters of the cardiac function obtained by cardiac MRI are presented in Table 3.

Discussion

To our best knowledge and after a thorough research in the Pubmed database, no study investigated the impact of sedation on heart function using a cardiac MRI in a clinical setting. Another reason for the uniqueness of our work is the fact that it is dealing with spontaneously ventilating patients, which eliminates the influence and interference of artificial lung ventilation and other co-administrated sedatives with cardiac function.

While monitoring E-diast in the MID group, a statistically significant decline (by 11 %) from baseline values was recorded following a sedation administration. Midazolam also worsened L-diast (by 7 %), however, this change did not gain a statistically important value. Our results are consistent with the conclusion of Gare et al. According to their report, midazolam in a dose of 0.05 $mg.kg^{-1}$ in patients without pre-existing diastolic dysfunction caused a notable reduction in early left ventricular filling (by 13 %) and a negligible reduction in late left ventricular filling (by 7 %), evaluated by the mean of transthoracic echocardiography (3). The potential explanation for this finding is either in a delayed release of Ca^{+2} from the contractile microfilament of the left ventricle during diastole or worsening of venous return due to sedation-induced venodilation. These mechanisms could be responsible for worsening of left ventricle relaxation and reducing flow velocity through the mitral valve during an early diastole (4, 5). As for the late diastolic filling, a direct negative inotropic effect of midazolam on atrial mechanical properties could be encountered (5).

Dexmedetomidine in our cohort led to an insignificant reduction in E-diast by 7 %. A similar trend, although with a statistically significant result, as observed by Lee et al., where according to their report administration of dexmedetomidine as an adjuvant to general intravenous anaesthesia significantly worsened (by 23 %) early diastolic filling of the left ventricle (6).

On contrary, according to literature, administration of dexmedetomidine in healthy volunteers (7) or patients as an adjuvant to total intravenous anaesthesia (8) had no considerable effect on myocardial diastolic function (7, 8).

As for systolic biventricular performance of midazolam, sedation decreased both left (by 8 %, p = 0.001) and right (by 7 %, p = 0.01) ventricle output evaluated by a direct measuring of left and right ventricles stroke volume in the aortic and pulmonary valve, respectively. Our finding is in line with several studies supporting a decline in systolic cardiac function following midazolam administration (11–13). Other studies, however, concluded that the decrease in cardiac contractility is compensated by the reduction in afterload render cardiac output unchanged (14–16).

Dexmedetomidine sedation had also a slight negative impact on both left (by 6 %, p = 0.006) and right (by 7 %, p = 0.01) systolic function. Our study is in concordance with other reports from literature, suggesting a decrease in cardiac inotropy due to beta-blocker like effect of dexmedetomidine leading to a decrease in cardiac output (7, 8). Another potential explanation for this finding is worsening of venous return due to sympatholysis-induced venodilation leading to decrease in preload and a decrease in cardiac stroke volume (9). An increase in pulmonary vascular resistance following dexmedetomidine administration could play a role in decreasing right ventricular output (17).

The current results should be interpreted considering several potential limitations: 1) Our study isn't a placebo-controlled study. 2) Innumerable measurements of cardiac function parameters using cardiac MRI; doing so could extend the examination time beyond the ability of participants to tolerate the investigation. 3) The absence of a comparison of cardiac function parameters obtained by the mean of cardiac MRI with the gold standard, which is echocardiography. The absolute values of early and late left ventricular filling velocity obtained by phase-contrast differ from

the absolute values obtained by the mean of echocardiography. This difference is given by the method of measurement and the method of obtaining individual data, however, it should not lead to a misinterpretation of myocardial diastolic function (18, 19). 4) A sample size of 35 participants was required to achieve a sufficient statistical power (≥ 80 %) for E-diast in the DEX group. Because dexmedetomidine in our cohort didn't influence early diastolic filling of the left ventricle ($p = 0.2$), further enrolling of participants in this arm could only more likely empower this statistically unimportant finding.

The results herein presented showing that the study protocol is safe and feasible and may represent a core for further clinical studies assessing the effect of sedation/analgosedation on cardiac function using cardiac MRI with a larger number of patients.

Conclusion

Both sedation techniques impair cardiac output of both left and right ventricle. Midazolam moreover worsens diastolic heart function by altering an early diastolic filling of the left ventricle.

References

1. Durbin CG Jr. Sedation in the critically ill patient. New Horiz 1994; 2 (1): 64–74.

2. Jacobi J, Fraser GL, Coursin DB et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002; 30 (1): 119–141.

3. Gare M, Parail A, Milosavljevic D, Kersten JR, Warltier DC, Pagel PS. Conscious sedation with midazolam or propofol does not alter left ventricular diastolic performance in patients with preexisting diastolic dysfunction: a transmitral and tissue Doppler transthoracic echocardiography study. Anesth Analg 2001; 93 (4): 865–871.

4. Pagel PS, Grossman W, Haering JM, Warltier DC. Left Ventricular Diastolic Function in the Normal and Diseased Heart. Anesthesiology 1993; 79 (4): 836–854.

5. Couture P, Denault AY, Shi Y et al. Effects of anesthetic induction in patients with diastolic dysfunction. Can J Anaesth 2009; 56 (5): 357–365.

6. Lee SH, Na S, Kim N, Ban MG, Shin SE, Oh YJ. The Effects of Dexmedetomidine on Myocardial Function Assessed by Tissue Doppler Echocardiography during General Anesthesia in Patients With Diastolic Dysfunction. Medicine (Baltimore) 2016; 95 (6): e2805.

7. Snapir A, Posti J, Kentala E et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. Anesthesiology 2006; 105 (5): 902–910.

8. Lee SH, Choi YS, Hong GR, Oh YJ. Echocardiographic evaluation of the effects of dexmedetomidine on cardiac function during total intravenous anaesthesia. Anaesthesia 2015; 70 (9): 1052–1059.

9. Yu T, Pan C, Liu S et al. Different effects of propofol and dexmedetomidine on preload dependency in endotoxemic shock with norepinephrine infusion: a randomized case-control study. Crit Care 2014; 18: 417.

10. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets 2009; 10 (8): 687–695.

11. Kawar P, Carson IW, Clarke RS, Dundee JW, Lyons SM. Haemodynamic changes during induction of anaesthesia with midazolam and diazepam (Valium) in patients undergoing coronary artery bypass surgery. Anaesthesia 1985; 40 (8): 767–771.

12. Samuelson PN, Reves JG, Kouchoukos NT, Smith LR, Dole KM. Hemodynamic Responses to Anesthetic Induction with Midazolam or Diazepam in Patients With Ischemic Heart Disease. Anesth Analg 1981; 60 (11): 802–809.

13. Singh R, Choudhury M, Kapoor PM, Kiran U. A randomized trial of anesthetic induction agents in patients with coronary artery disease and left ventricular dysfunction. Ann Card Anaesth 2010; 13 (3): 217–223.

14. Magunia H, Jordanow A, Keller M, Rosenberger P, Nowak-Machen M. The effects of anesthesia induction and positive pressure ventilation on right-ventricular function: an echocardiography-based prospective observational study. BMC Anesthesiol 2019; 19 (1): 199.

15. Dahlgren G, Settergren G, Ribeiro A, Brodin LA. Changes in left ventricular diameter during intravenous induction of anesthesia. J Cardiothorac Vasc Anesth 1993; 7 (4): 399–401.

16. Messina AG, Paranicas M, Yao FS et al. The effect of midazolam on left ventricular pump performance and contractility in anesthetized patients with coronary artery disease: effect of preoperative ejection fraction. Anesth Analg 1995; 81 (4): 793–799.

17. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93 (2): 382–894.

18. Webb J, Fovargue L, Tøndel K et al. The Emerging Role of Cardiac Magnetic Resonance Imaging in the Evaluation of Patients with HFpEF. Curr Heart Fail Rep 2018; 15 (1): 1–9.

19. Rathi VK, Doyle M, Yamrozik J et al. Routine evaluation of left ventricular diastolic function by cardiovascular magnetic resonance: a practical approach. J Cardiovasc Magn Reson 2008; 10 (1): 36.

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