

Response of myocardial oxygenation to breathing manoeuvres and adenosine infusion

Kady Fischer¹, Dominik P. Guensch^{1,2}, and Matthias G. Friedrich^{1,3*}

¹Philippa and Marvin Carsley CMR Centre at the Montreal Heart Institute, 5000 Belanger Street, Montreal, QC, Canada H1T 1C8; ²Department Anesthesiology and Pain Therapy, Bern University Hospital, Bern, Switzerland; and ³Departments of Cardiology and Radiology, Université de Montréal, Montreal, QC, Canada

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Aims

Testing for inducible myocardial ischaemia is one of the most important diagnostic procedures and has a strong impact on clinical decision-making. Current standard protocols are typically limited by the required infusion of vasodilatory substances. Recent data indicate that changes of myocardial oxygenation induced by hyperventilation and breath-holds can be monitored by oxygenation-sensitive (OS) cardiovascular magnetic resonance (CMR) and may be useful for assessing coronary vascular function. As tests using breathing manoeuvres may be safer, easier, and more comfortable than vasodilator stress agent infusion, we compared its impact on myocardial oxygenation with that of a standard adenosine infusion protocol.

Methods and results

In 20 healthy volunteers, we assessed changes of myocardial oxygenation using OS-CMR at 3 T during adenosine infusion (140 µg/kg/min, i.v.) and during voluntary breathing manoeuvres: a maximal breath-hold following normal breathing and a maximal breath-hold following 60 s of hyperventilation. The study was successfully completed in 19 subjects. There was a significantly stronger myocardial response for hyperventilation (decrease of $-10.6 \pm 7.8\%$) and the following breath-hold (increase of $14.8 \pm 6.6\%$) than adenosine ($3.9 \pm 6.5\%$), whereas a simple maximal voluntary breath-hold yielded a similar signal intensity increase ($3.1 \pm 3.9\%$). Subjective side effects occurred significantly more often with adenosine, especially in females.

Conclusions

Hyperventilation combined with a subsequent long breath-hold and hyperventilation alone both have a greater impact on myocardial oxygenation changes than an intravenous administration of a standard dose of adenosine, as assessed by OS-CMR. Breathing manoeuvres may be more efficient, safer, and more comfortable than adenosine for the assessment of the coronary vasomotor response.

Keywords

Oxygenation-sensitive • CMR • Blood oxygen level-dependent • Adenosine • Vasodilation • Vasoconstriction

Introduction

Ischaemic heart disease is the most frequent cause of death in developed countries, and imaging for inducible myocardial perfusion defects is one of the most frequent diagnostic procedures performed. Typically, a vasodilator agent is injected to trigger a response in the coronary perfusion beds, which, when compared with a baseline scan, may identify areas of impaired perfusion. Vasodilator agents commonly used in clinical settings include non-selective (adenosine and dipyridamole) and selective adenosine agonists (regadenoson and others).¹ With respect to their clinical utility for diagnostic purposes, however, adenosine and its agonists have limitations: while generally considered safe, >90% of patients report side effects,²

including chest pain, palpitations, dyspnoea, light-headedness, flushing, sweating, nausea, headache, and anxiety, and recently the US food and drug administration released a warning due to adenosine as a rare, but serious risk of heart attack and death.³ Adenosine infusion can cause arrhythmia, especially sinuatrial- and atrioventricular (AV) block, and thus the presence of a trained health professional during infusion is required. It is contraindicated in patients with a second- or third-degree AV block and sinus node disease, and should also be avoided in patients with known bronchoconstrictive disease. Furthermore, the short half-life and variable response to adenosine may make it difficult to verify that an adequate level of adenosine is reached in the coronary vasculature, especially in patients with low cardiac output where the long transit time between the

* Corresponding author. Tel: +1 514 376 3330; Fax: +1 514 376 1355, Email: mgwfriedrich@gmail.com

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peripheral injection site and the myocardium may lead to its inactivation. Importantly, adenosine and regadenoson also add significant costs to the diagnostic procedure.

It is known that breathing manoeuvres, i.e. hyperventilation and long breath-holds, elicit significant changes of cerebral and coronary perfusion,^{4–6} largely induced by the vasodilatory effects of blood carbon dioxide, which increases with apnoea and decreases with hyperventilation. While most imaging methods do not have sufficient temporal or spatial resolution to monitor these changes, oxygenation-sensitive cardiovascular magnetic resonance (OS-CMR) allows for monitoring changes of myocardial oxygenation, including those induced by adenosine infusion.^{7–14} In both an animal model and healthy volunteers, it has recently been shown that OS-CMR can also track changes of myocardial oxygenation during breathing manoeuvres,^{15,16} which could be very well induced by long breath-holds and hyperventilation. It is however unknown how the response to these breathing manoeuvres on myocardial perfusion/oxygenation compares with that of standard adenosine infusion. If such impact would be similar or even stronger, breathing manoeuvres may be considered an alternative to vasodilator infusion in patients with suspected inducible myocardial ischaemia.

We hypothesized that breathing manoeuvres, specifically long breath-holds and hyperventilation as well as a combination thereof, lead to myocardial oxygenation changes at least as significant as those induced by intravenous adenosine.

Methods

Subjects

We studied 20 healthy subjects without a history of smoking, cardiovascular, or respiratory disease, and aged 18 years or older. All subjects were newly recruited for this study through public advertisements. Subjects were required to provide informed written consent and were interviewed to rule out general MRI contraindications. Furthermore, they were asked to refrain from the consumption of adenosine antagonizing agents such as caffeine for at least 12 h prior to the MRI examination.

Protocol

Before image acquisition, resting non-invasive blood pressure and heart rate were obtained in a supine position. An alarm ball was provided; heart rate, peripheral haemoglobin saturation (SpO₂), respiratory rate, and blood pressure were monitored during the scan.

Cardiovascular magnetic resonance

Imaging was performed in a clinical 3-T scanner (MAGNETOM Skyra 3T; Siemens, Erlangen, Germany) using an 18-channel cardiac coil. Images were obtained during breath-holds at comfortable end-expiration. Left ventricular (LV) function was assessed using an ECG-gated balanced steady-state free precession (bSSFP) sequence [echo time (TE)/repetition time (TR) 1.43/3.3 ms, flip angle 65°, voxel size 1.6 × 1.6 × 6.0 mm, matrix 192 × 120, and bandwidth 962 Hz/Px] in six long-axis slices with LV-centred radial positioning and three short-axis views. OS-CMR images were acquired in one mid-ventricular short-axis slice using an ECG-triggered bSSFP sequence (TE/TR 1.70/3.4 ms, flip angle 35°, voxel size 2.0 × 2.0 × 10.0 mm, matrix 192 × 120, bandwidth 1302 Hz/Px, and acquisition time/measurement 4 heartbeats). Shimming was always performed along with frequency scouts if required

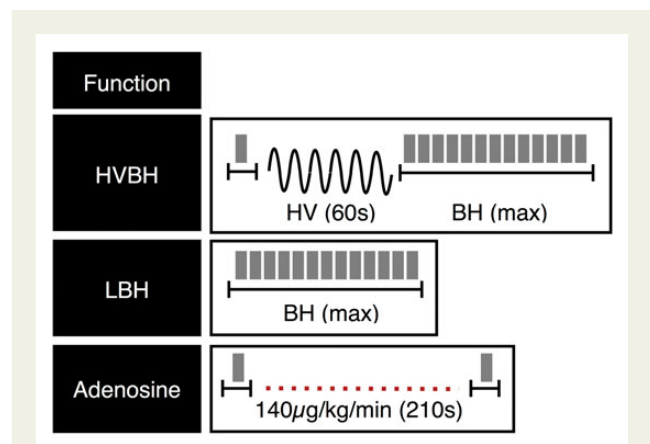


Figure 1 Representation of the scanning protocol. OS images (grey-shaded box) are obtained during a breath-hold. Extended breath-holds are imaged continuously with repeating measurements, while baseline and adenosine images with a single measurement. HVBH: hyperventilation (HV) followed by a maximal breath-hold (BH); LBH: long breath-hold from normal respiration.

OS-CMR protocol

- (i) Combined hyperventilation/breath-hold (HVBH): hyperventilation for 60 s aiming for a rate of 35–40 breaths per minute, followed by a maximal voluntary breath-hold with a single measurement acquired prior to hyperventilation and continuously during the entire breath-hold after hyperventilation. When subjects announced their need for inspiration by using the alarm ball, scanning was stopped (Figure 1).
- (ii) Long breath-hold from normal respiration (LBH) with continuous imaging; as for the previous maximal breath-hold, subjects were asked to indicate their need for inspiration.
- (iii) Adenosine infusion (140 µg/kg/min) with image acquisition before and 3.5 min into the drug infusion.

Imaging during adenosine infusion was randomly performed either before or after imaging during breathing manoeuvres. There was a break of at least 3 min between each series to allow for the patient to recover. After the MRI examination, the subjects completed a questionnaire on the difficulty of each manoeuvre, using a scale of increasing difficulty of 1–5, and were also asked to identify the incidence of any adverse effects for each manoeuvre.

Image analysis

Analysis of LV function was performed from epi- and endocardial contours in diastolic and systolic images of the six long-axis views using the certified software (cvi⁴², Circle Cardiovascular Imaging, Calgary, AB, Canada). For OS-CMR images, the end-systolic image from each measurement was chosen for analysis. Images were first visually graded on image quality scale from 1 to 4 with decreasing image quality.⁶ Individual segments were entirely excluded from analysis if >33% of the segment area was removed due to artefact. The mean myocardial signal intensity (SI) in the OS-CMR images was automatically calculated after manual tracing of endo- and epicardial contours and further segmented based on current recommendations.¹⁷ A blood pool contour was drawn in the middle of the LV cavity (SI_{BP}[%]). SI was expressed as the % change (ΔSI[%]) between two images. Both hyperventilation and adenosine were compared with their respective baseline images obtained prior to

the manoeuvre, while for the HVBH and LBH the first measurement of the breath-hold was used as the reference. SI changes were specifically assessed for: (i) SI at 15 s into the breath-hold; (ii) SI at 30 s into the breath-hold; (iii) the maximum SI reached during the breath-hold; and (iv) SI at the end of the breath-hold. Color maps were calculated using open source imaging postprocessing tool NeuroLens (www.neurolens.org, last accessed May 20, 2014).

Statistical analysis

Data are expressed as mean \pm SD. Continuous variables were assessed for normal distribution with the D'Agostino–Pearson test. A paired Student's *t*-test was used to compare signal intensities within a subject, and comparisons of variation between groups were assessed with an *F*-test. Associations among groups were assessed with analysis of variance and multiple comparison tests. To account for excluded segments, a linear mixed-effects analysis was performed to assess the within-subjects relationship between the change in SI and the myocardial segment using a compound symmetry covariance structure and segment identification as a fixed factor. The breath-holds were further analysed by plotting the SI over time fitted by non-linear regression. The questionnaire and image quality results were analysed with the Friedman's non-parametric test. For assessing interobserver reliability, 66 randomly selected images were read by an independent second reader and assessed with a one-way mixed intraclass correlation test. Tests were performed with GraphPad Prism version 6.0 for mac (GraphPad Software, La Jolla, CA, USA) and SPSS version 21 (SPSS IBM, New York, NY, USA). Results were considered statistically significant if the *P*-value was <0.05 .

The local scientific and ethics committees at the Montreal Heart Institute approved the study.

Results

Participant characteristics

Nineteen subjects completed all manoeuvres of the protocol. One participant withdrew from the study due to claustrophobia. Data from the LV function analysis are shown in Table 1.

Image quality

Overall, image quality was good (1.8 ± 0.6) and did not differ between the manoeuvres. No complete image set was excluded due to poor image quality. In the segment-based analysis, 38/684

(5.8%) data points were excluded, primarily in the anterior wall, based on predefined criteria for severe artefacts. There was an excellent interobserver reliability between the two readers with an intraclass correlation of 0.94 (CI: 0.90–0.96; $*P < 0.01$).

Myocardial SI changes in OS-CMR images

Compared with the baseline, all manoeuvres induced a significant SI change (Figure 2B and Table 2). Of note, this was the case even only 15 s into the breath-hold following hyperventilation (HVBH; SI increase $7.6 \pm 5.7\%$; $P < 0.05$), which was statistically not different from the response to adenosine ($3.9 \pm 6.5\%$; $P = 0.07$). An even stronger effect was observed by 30 s (11.7 ± 6.4) with the maximal effect of 14.8 ± 6.6 observed at an average time of 40 s, all greater than the adenosine change ($*P < 0.05$). On the other hand, during the LBH, only the maximum peak differed significantly from the baseline, while other time points did not. The maximal

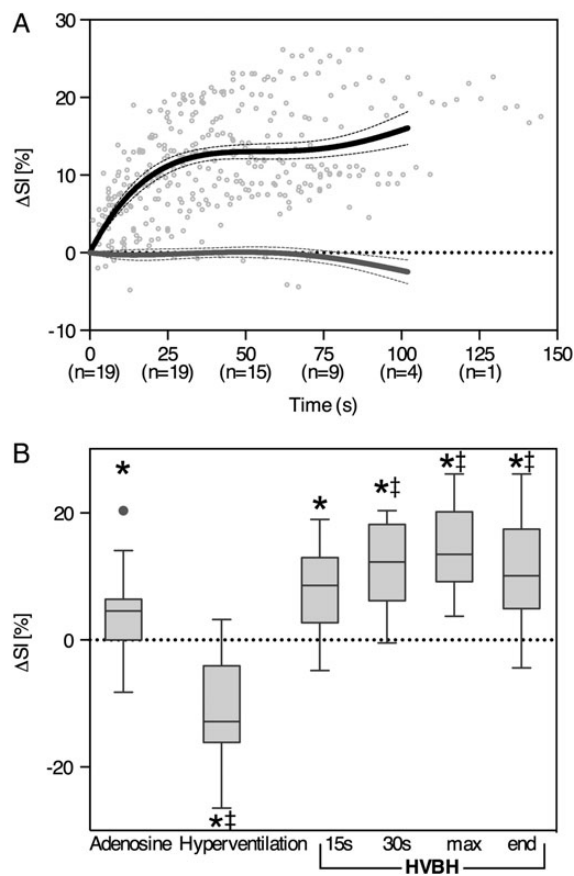


Figure 2 Oxygenation SI. (A) The fitted curve demonstrates the increase in myocardial (black) SI (Δ SI[%]), while blood pool Δ SI[%] simultaneously decreased (dashed grey). (B) OS-SI global myocardial results. All manoeuvres (mean \pm SD) significantly changed SI from baseline ($*P < 0.05$), including just 15 s into the HVBH. Additionally, the oxygenation responses from hyperventilation and time points from 30 s and later in the HVBH were significantly different than that of adenosine ($^\ddagger P < 0.05$, $n = 19$).

Table 1 Volunteer characteristics and function analysis

Age (years)	43 \pm 14
Gender	8F/11M
BMI (kg/m ²)	24.0 \pm 3.0
Resting BP (mmHg)	128 \pm 17/81 \pm 13
Resting HR (bpm)	62 \pm 6
EF (%)	67 \pm 6
CO (L/min/m ²)	3.4 \pm 1.0
LV mass index (g/m ²)	69 \pm 20

Mean \pm SD age, gender, body mass index (BMI), resting systolic/diastolic blood pressure (BP, mmHg), resting heart rate (HR, bpm), ejection fraction (EF, %), Cardiac output index (CO, L/min/m²), and myocardial mass (g/m²) indexed to body surface area.

Table 2 Manoeuvres and related changes of heart rate and myocardial oxygenation

	<i>n</i>	Δ SI (%)	Time (s)	Δ HR
Adenosine	19	3.9 ± 6.5^a		17.8 ± 14.4^a
Hyperventilation	19	$-10.6 \pm 7.8^{a,b}$	60	$25.2 \pm 14.0^{a,b}$
HVBH				
15 s	18	7.6 ± 5.7^a	15.1 ± 1.2	
30 s	18	$11.7 \pm 6.4^{a,b}$	29.7 ± 1.1	
Maximum	19	$14.8 \pm 6.6^{a,b}$	40.3 ± 16.1	
End	19	$10.3 \pm 7.7^{a,b}$	73.6 ± 28.6	$-15.0 \pm 18.7^{a,b}$
LBH				
15 s	19	$-0.6 \pm 2.9^\ddagger$	15.0 ± 1.0	
30 s	16	-1.3 ± 4.8	30.0 ± 1.6	
Maximum	19	3.1 ± 3.9^a	25.9 ± 19.5	
End	19	1.4 ± 5.5^b	45.3 ± 20.9	2.8 ± 10.4^b

Mean \pm SD values from each manoeuvre including the actual time points of data acquisition (s) and change in heart rate (HR, bpm). Both the Δ SI[%] at the maximum and the end of the breath-hold are shown for the LBH and HVBH.

SI: signal intensity; HVBH: hyperventilation breath-hold; LBH: long breath-hold from normal breathing.

^aSignificantly different from the baseline ($P < 0.05$).

^bSignificantly different from the adenosine manoeuvre ($P < 0.05$).

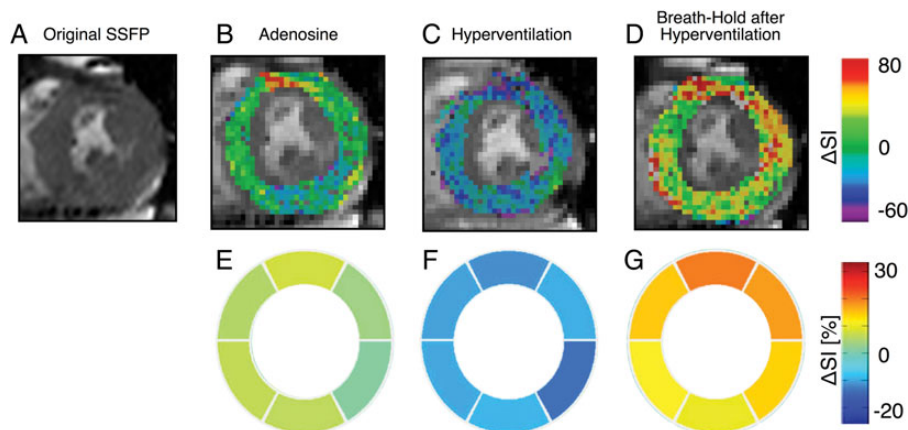


Figure 3 Images showing oxygenation of SI changes. OS image at end-systole (A). A subtraction image displays the absolute difference in SI from baseline for adenosine (B), hyperventilation (C), and the maximum point of SI in the breath-hold following hyperventilation (D) from one participant. The bottom row (E–G) displays the Δ SI[%] averaged from all subjects, per segment of the mid-ventricular slice.

signal intensities in both, HVBH and LBH, were significantly greater than at the end of the breath-hold and were the values used for subsequent calculations. There was a significant change in the Δ SI_{BP}[%] at the end of the maximal breath-holds ($-2.6 \pm 4.9\%$; $P < 0.05$) for the HVBH as well as for the LBH ($-3.2 \pm 5.4\%$; $P < 0.05$), but not at the maximal myocardial Δ SI[%].

After hyperventilation, subjects were able to hold their breath for 28 ± 23 s longer than after regular ventilation ($P < 0.05$). In addition, the maximum SI occurred 14 ± 19 s later with HVBH than with LBH ($P < 0.05$). In HVBH experiments, the variation in the time-to-maximal SI time was significantly less than that in

the time-to-the end of the breath-hold, which was not the case in LBH.

Segmental analysis

There were no differences in SI changes between segments with hyperventilation (Figure 3B). Yet, with HVBH, the anterior and anterolateral segments had significantly higher Δ SI[%] than the inferior and inferoseptal segments, while similarly with adenosine, the anterior segment also had the greatest increase of Δ SI[%], above changes in lateral segments ($P < 0.05$).

Relationship between gender and heart rate

Only gender was a factor for the adenosine protocol, in which the females had a larger $\Delta SI[\%]$. There was an increase in heart rate of 25.2 ± 14.0 bpm after hyperventilation (Table 2), and yet the increase in heart rate was not significantly correlated with $\Delta SI[\%]$ ($r = -0.41, P = 0.10, n = 18$). Heart rate was not a statistically relevant factor for the other manoeuvres.

Subjective difficulty and side effects

The difficulty score was the same for all manoeuvres ($1.8 \pm 1.0, P = \text{n.s.}$). Side effects were not noted with the LBH test. The HVBH led to mild side effects in 5 (26%) of the subjects, most notably tingling in the fingers during hyperventilation ($n = 3$), dizziness ($n = 1$), and dry mouth ($n = 1$), which disappeared after the manoeuvre and normal breathing recommenced in all cases. With adenosine, 13 (68%) of the subjects noted side effects, most commonly chest tightness ($n = 6$), flushing ($n = 4$), breathing difficulties ($n = 4$), and dizziness ($n = 3$). When asked about the duration of side effects from adenosine, two of these subjects responded that they still felt the adverse effects more than 60 s after the drug infusion had stopped. Of note, all females experienced side effects during adenosine.

Discussion

Our head-to-head comparison data provide evidence that, in healthy subjects, breathing manoeuvres, specifically hyperventilation alone and in combination with a maximal voluntary breath-hold, have an impact on myocardial oxygenation at least as strong as an intravenous administration of a standard dose of adenosine. This has potentially strong clinical implications, as the combination of breathing manoeuvres with OS-CMR would allow for assessing coronary vascular function without the need for contrast agents or vasodilating drugs. Moreover, the test directly reflects tissue oxygenation in contrast to currently used surrogate markers such as tracer accumulation, first-pass perfusion inflow characteristics, or fractional flow reserve.

The concept combines the validated technique of OS-CMR with relatively simple physiological manoeuvres. Multiple studies have used OS-CMR to assess this response in cardiac disease using adenosine or dipyridamole and validated this technique against quantitative coronary angiography,¹⁰ first-pass perfusion,¹² positron emission tomography,¹¹ and fractional flow reserve.¹⁴ Breathing manoeuvres can significantly alter systemic O_2 and CO_2 tensions within a relatively short time.^{18,19} Both, adenosine and the primary metabolites, O_2 and CO_2 , have a direct impact on the arterioles,^{20,21} which keep $\sim 40\%$ of the coronary resistance at rest. When dilated, these vessels are responsible for the large decrease in vascular resistance and the strong increase in coronary blood flow.^{22,23} The arteriolar response is blunted in diseases related to atherosclerosis such as hypercholesterolaemia, diabetes, and hypertension, as well as in coronary artery disease.²⁴ In the presence of significant coronary artery stenosis, these arterioles are already dilated at rest in order to maintain adequate myocardial perfusion and thus show a blunted response to a vasodilator stimulus.

As with previous studies,²⁵ we found that hyperventilation is associated with minor side effects. Our data, however, indicate that breathing manoeuvres may be better tolerated than adenosine infusion, especially by women. The interesting observation that female subjects are more prone to discomfort during adenosine infusion is in agreement with previous reports.²⁶ Even if side effects occurred during breathing manoeuvres, they appear to be of shorter duration. Another advantage of breathing manoeuvres is that patients have full control over their breathing and thus can resume normal breathing if they feel uncomfortable, without requiring immediate action by a medical staff. This on the other hand requires compliance to yield meaningful results, similar to physical stress tests. We did not assess patients and thus cannot infer that long breath-holds with or without hyperventilation are as easily tolerated by subjects with heart disease. Thus, results may be different in patients. Yet, the fact that none of the subjects reported the test to be difficult or inconvenient indicates that also patients would likely tolerate breathing manoeuvres better than vasodilator infusions.

The duration of a voluntary breath-hold may be influenced by many factors such as initial gas content, lung volume, chemoreceptor sensitivity, secondary diseases, tolerance, and patient compliance.²⁷

Interestingly, we observed that the maximal change, independent from the duration of the breath-hold, was rather consistent among individuals, suggesting that this parameter may be less reliant on patient compliance than the overall change and could more accurately distinguish the vascular response with minimal influence of breath-holding ability. As we could show, preceding hyperventilation facilitates long breath-holds and subjects were able to hold their breath on average for >60 s, while the maximum SI was reached after about 40 s. Yet, even as early as 15 s into the breath-hold after hyperventilation, we observed significant changes. In addition to its apparently better feasibility, the HVBH protocol demonstrated stronger and more consistent results than the LBH. With CO_2 being the strongest breathing stimulus, previous hyperventilation extends the breath-hold duration by reducing the CO_2 content and thus shifting the starting level farther from the threshold at which the breakpoint of a breath-hold occurs.^{19,27} With the extended breath-hold, the participant undergoes a greater range in CO_2 and coronary vasomotion. On the other hand, hyperventilation has a vasoconstrictive effect, which may not be tolerated as well in patients, and the relationship between hyperventilation-induced vasoconstriction and the severity of coronary artery stenosis deserves more research. Furthermore, the significant increase in heart rate we have observed may increase oxygen demand and thus hyperventilation-related changes may be more pronounced in patients.

The evaluation and interpretation of OS-CMR images during voluntary breathing manoeuvres in patients' needs to be further elucidated. Although this study demonstrates that changes of myocardial oxygenation can be induced with breathing manoeuvres, we are unable to assess the ability of the technique to detect myocardial ischaemia until a patient population is investigated. While SI changes may be simple, this approach can be compared with parameters such as area under the curve, maximal slope, or specific time points. Furthermore, several potential confounders for the SI in OS-CMR images have to be considered, such as the total amount of dHb as well as the ratio of dHb to free tissue water.^{28–30}

Of note, our observation that breathing manoeuvres have a strong effect on the myocardial oxygenation also indicates that breathing patterns during standard imaging protocols with pharmacological agents may be important confounders.

Limitations

As discussed before, the utility of breathing manoeuvres may be subject to participant compliance. Hyperventilation may induce coronary vasospasms, yet such reports however related to hyperventilation periods longer than 5 min^{5,25} and thus, the risk of a 60-s period likely is smaller. We only acquired data on a single slice in order to achieve the temporal resolution for monitoring oxygenation changes. In clinical settings, the experiment may have to be repeated for more coverage. Yet as the entire data acquisition time per slice mounts to <5 min, this may not be a truly limiting factor.

As the expected risk is very small, our sample size did not allow us to assess safety.

Conclusion

Our data provide evidence that breathing manoeuvres, specifically hyperventilation with or without a subsequent long breath-hold, may have a stronger impact on myocardial oxygenation than intravenous administration of a standard dose of adenosine. Both the vasoconstrictive and vasodilative response of the coronary vasculature can be observed by OS-CMR during the same manoeuvre. Breathing manoeuvres may serve as a safer, more comfortable, and more efficient alternative to intravenous vasodilators for diagnostic procedures and future development for this technique would be to assess if breathing manoeuvres can detect inducible myocardial ischaemia in clinical settings.

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Conflict of interest: K.F., D.P.G., and M.G.F. hold a pending patent for inducing and measuring myocardial oxygenation changes as a marker for heart disease (patent pending, serial no. PCT/CA2013/050608). M.G.F. is also a board member and consultant of Circle Cardiovascular Imaging, Inc.

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IMAGE FOCUS

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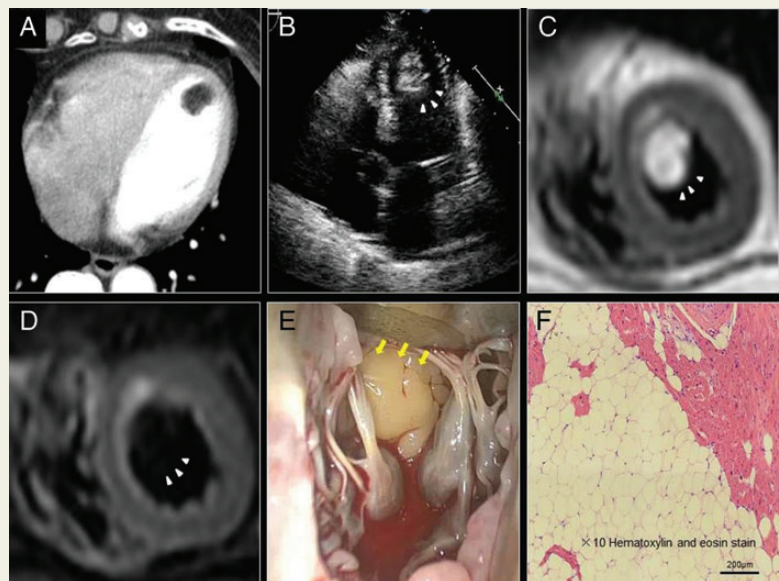
Video-assisted transmitral resection of primary cardiac lipoma originated from the left ventricular apex

Yoshihiro Tanaka, Tsuyoshi Yoshimuta, Masakazu Yamagishi, and Kenji Sakata*

Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

* Corresponding author. Tel: +81 76 265 2259; Fax: +81 76 234 4210, E-mail: kenjis@yu.incl.ne.jp

A 77-year-old woman who suffered from weight loss was referred to our hospital. She lost 8 kg of weight a year, and whole-body computed tomography (CT) scan was performed for the evaluation of malignancies. Contrast enhanced CT demonstrated a low-intensity (–100 to –120 Hounsfield) mass without contrast opacification (Panel A). Echocardiography revealed a high echogenic and well-demarcated movable mass (25 × 28 mm) located in the left ventricular apex (Panel B, arrow; see Supplementary data online, Video S1). T2 and fat suppression T2 magnetic resonance imaging suggested that the tumour was a lipoma (Panels C and D, arrow). Transmitral endoscopy via the left atrium demonstrated the yellowish and well-demarcated mass originating from the left ventricular wall (Panel E, arrow; see Supplementary data online, Video S2). Intraoperative consultation revealed that the tumour was a lipoma without malignancy (Panel F), which was completely resected by transmitral approach without ventriculotomy. The patient was event free with no relapse for at least a year.



Cardiac lipomas are rare and often asymptomatic. Benign lipomas are sometimes difficult to diagnose; therefore, surgical resection of the tumour may be warranted for the precise diagnosis. Recently, video-assisted removal of cardiac tumours, which can avoid a left ventriculotomy, has been reported to be a useful method of resecting cardiac tumours. In this case, transmitral endoscopy via the left atrium clearly showed the appearance of the tumour and the intra-cardiac anatomy, which enabled us to avoid an unnecessary ventriculotomy.

Conflict of interest: None declared.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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