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Non-invasive measurement of hemodynamic response to postural stress using inert gas rebreathing

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Abstract. In postural stress, an increased preload volume leads to higher stroke volume (SV) according to the Frank-Starling law of the heart. The present study aimed to evaluate the hemodynamic response to postural stress using non-invasive inert gas rebreathing (IGR) in patients with normal as well as impaired left ventricular function. Hemodynamic measurements were performed in 91 patients undergoing cardiac magnetic resonance imaging (CMR). Mean cardiac output and SV determined by IGR were 4.4±1.3 l/min and 60±19 ml in the upright position, which increased significantly to 5.0±1.2 l/min and 75±23 ml in the supine position (P<0.01). Left ventricular systolic function was normal [ejection fraction (EF) ≥55%] in 42 patients as determined by CMR. In 21 patients, EF was mildly abnormal (45-54%), in 16 patients moderately abnormal (30-44%) and in 12 patients severely abnormal (<30%). An overall trend for a lower percentage change in SV (%ΔSV) was indicated with increasing impairment of ejection fraction. In patients with abnormal EF in comparison to those with normal EF, the %ΔSV was significantly lower (13% vs. 22%; P=0.03). Non-invasive measurement of cardiac function using IGR during postural changes may be feasible and detected significant difference in %ΔSV in patients with normal and impaired EF according to the Frank-Starling law of the heart. Several clinical scenarios including cases of heart rhythm disturbances or pulmonary or congenital heart disease are worthy of further investigation.

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Introduction

When changing from the upright to the supine position, an increase in preload leads to a higher stroke volume (SV) according to the Frank-Starling law of the heart (1,2). For non-invasive determination of hemodynamic parameters, numerous techniques have been proposed including impedance cardiography (ICG) and inert gas rebreathing (IGR). ICG has been demonstrated to track changes in heart rate, diastolic blood pressure, total peripheral resistance, stroke volume and cardiac output during tilt table testing (3), while IGR is considered a viable option due to its relatively high accuracy and reproducibility (4-8). In patients with heart failure, a missing compensation of hemodynamic parameters may be expected. Ejection fraction (EF) is an established surrogate parameter for the estimation of systolic left ventricular function (LVF) in echocardiography. Echocardiography may support non-invasive diagnosis of left ventricular function by determining ventricle size, wall thickness and ejection fraction, as well as identifying pericardial effusion or a thrombus (9). Reduced systolic left ventricular function is established in patients following myocardial infarction, myocarditis or with congenital heart disease (9). However, it is not possible to adequately apply this method in patients with obesity or pronounced emphysema (10).

Hemodynamic data including SV and cardiac output (CO), however, may be more physiological measures. Furthermore, the posture dependent measurement of these data may provide additional information on LVF from pathophysiological considerations. The present study aimed to evaluate the hemodynamic response to postural stress using non-invasive IGR in patients with normal as well as impaired LFV.

Materials and methods

Subjects. The total numbers of patients and patients with normal EF enrolled was 91 patients undergoing IGR and CMR. Patients were enrolled at the First Department of Medicine, University Medical Center Mannheim (University of Heidelberg, Mannheim, Germany) from August, 2006 to January, 2007. Inclusion criteria were as follows: Arterial hypertension (36.3%), coronary heart disease (19.8%) and

cardiomyopathies (17.6%). The exclusion criteria were inability to perform rebreathing manoeuvre, claustrophobia and implanted foreign devices including a pacemaker or cardioverter defibrillator. The criteria for valid IGR data were complete mixing of the insoluble (indicated by a steady-state) and reduction of the soluble test gas, measurement of respiratory rate and absence of a relevant leak flow evaluated by oxygen consumption curves. The study protocol was approved by the Medical Ethics Commission II, Medical Faculty Mannheim of the University of Heidelberg and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study protocol. Non-invasive hemodynamic measurements using IGR were performed once, prior to or following cardiac magnetic resonance imaging (CMR), in upright and supine position. An interval of 5 min between the measurements was adhered to in order to guarantee complete elimination of test gases according to previous recommendations (11). Stabilization of circulation was awaited and controlled by measurement of blood pressure (BP) and heart rate (HR). Blood pressure and heart rate were measured directly prior to the rebreathing maneuver-and implemented in the IGR system.

IGR. IGR is based on the Fick principle and has been previously described in detail elsewhere (4). Nitrous oxide (N_2O; 0.5%) as a soluble gas and insoluble sulfur hexafluoride (SF_6; 0.1%) were used as test gases. Concentrations were measured by an online photo-magnetoacoustic gas analyzer (Innocor software version 5.01; Innovision ApS, Glamsbjerg, Denmark), and a valid shunt correction was applied using the patient's individually measured hemoglobin value; hemoglobin levels were measured during routine laboratory testing within one week of IGR measurements.

CMR. Electrocardiogram-gated cine images were acquired using a segmented steady-state free precession sequence (TrueFISP) during repeated end-expiratory breath-holds on a 1.5 Tesla whole-body imaging system (MAGNETOM Sonata; Siemens Healthineers, Erlangen, Germany). Three long-axis views and 7 to 12 short-axis views were obtained. Areas subtended by endocardial tracings were determined in each end-diastolic and end-systolic slice. Total end-diastolic and end-systolic cavity volumes (EDV and ESV, respectively) were calculated using a modified Simpson's rule equation (9) calculating EF as EF (%)=[(EDV-ESV)/EDV] x100. EF was defined as normal (≥55%), mildly abnormal (45-54%), moderately abnormal (30-44%) and severely abnormal (<30%) according to European Association of Echocardiography/American Society of Echocardiography recommendations (9).

Statistical analysis. Data were presented as the mean ± standard deviation. Statistical analyses were performed using MedCalc® for Microsoft Windows®, version 12.3.0 (MedCalc Software bvba, Ostend, Belgium). Statistical testing comprised Student's t-tests and one-way analysis of variance with the post-hoc Student-Newman-Keuls test, and Pearson's product-moment correlation coefficient, considering P<0.05 to indicate statistical significance. All data was used for the respective statistical tests.

Table I. Baseline characteristics (n=91).

Parameter	Unit	Value	Range
Age	Years	52±17	16-79
Male gender	n (%)	57 (62.6)	-
Weight	kg	79±15	47-118
Height	cm	173±8	155-190
c_{Hb}	g/dl	14.0±1.6	9.8-17.2

c_{Hb}, hemoglobin concentration.

Table II. Concomitant pathologies.

Pathology	Total cases, n (% total)
Arterial hypertension	33 (36.3)
Coronary heart disease	18 (19.8)
Cardiomyopathy, *thereof*	16 (17.6)
- Hypertrophic	9 (9.9)
- Dilated	6 (6.6)
- Restrictive	1 (1.1)
Myocardial hypertrophy	13 (14.3)
Atrial fibrillation	11 (12.1)
Myocardial infarction	8 (8.8)
Pleural effusion	8 (8.8)
Myocarditis	7 (7.7)
Pericardial effusion	7 (7.7)
Obstructive lung disease	5 (5.5)
Brugada's syndrome	4 (4.4)
Takotsubo	3 (3.3)

Results

A total of 91 patients undergoing CMR were analyzed. Information on their baseline characteristics is provided in Table I. The most frequent concomitant diseases were arterial hypertension (36.3%), coronary heart disease (19.8%) and cardiomyopathies (17.6%), as listed in Table II. All hemodynamic parameters measured by IGR and CMR in upright and supine position are listed in Table III.

IGR. Mean CO and SV measured by IGR were 4.4±1.3 l/min and 60±19 ml in the upright position, which both significantly increased to 5.0±1.2 l/min and 75±23 ml in the supine position, respectively (P<0.01). Conversely, HR decreased significantly from 74 to 69 bpm (P<0.01).

CMR. As determined by CMR, EF was normal (EF ≥55%) in 42 patients. In 21 patients it was mildly abnormal (45-54%), in 16 moderately abnormal (30-44%) and in 12 severely abnormal (<30%) according to European Association of Echocardiography/American Society of Echocardiography recommendations (9). An overall trend for a lower percentage change in SV (%ΔSV) was identified between the four EF

Table III. Hemodynamic parameters.

		EF										
		Overall (n=91)		Normal (n=42)		Mildly abnormal (n=21)		Moderate abnormal (n=16)		Severely abnormal (n=12)		
Parameter	Unit	Value	Range	Value	Range	Value	Range	Value	Range	Value	Range	P-value
CO_{CMR}	l/min	5.2±1.4	2.7-9.0	5.2±1.4	2.7-8.8	5.9±1.5	3.4-9.0	5.0±0.9	3.2-7.1	4.0±0.9	2.8-5.7	0.002
SV_{CMR}	ml	79±22	32-147	84±21	45-147	82±23	41-127	76±18	35-113	62±23	32-113	0.02
HR_{CMR}	bpm	67±13	36-109	63±9	36-76	75±16	42-109	68±12	52-91	69±16	45-96	0.004
EF	%	50±14	10-74	62±4	55-74	51±3	46-54	39±5	31-45	23±6	10-30	<0.01
$LVEDV_{CMR}$	ml	169±62	73-336	136±35	73-239	159±46	85-267	197±50	101-278	269±58	152-336	<0.01
Upright												
CO_{IGR}	l/min	4.4±1.3	1.2-8.8	4.3±1.3	1.4-6.6	4.9±1.3	3.1-8.0	4.1±1.3	1.2-7.2	3.9±1.0	2.5-5.7	0.09
SV_{IGR}	ml	60±19	18-122	60±17	18-97	63±17	36-101	57±18	25-85	59±29	33-122	0.84
HR_{IGR}	bpm	74±14	44-108	72±12	49-93	80±16	44-108	73±15	47-98	72±18	48-103	0.20
$BP_{systolic}$	mmHg	129±15	91-167	126±13	97-147	127±12	102-148	135±21	91-165	132±18	102-167	0.22
$BP_{diastolic}$	mmHg	78±11	52-111	76±10	52-96	78±8	58-91	81±12	56-101	82±14	58-111	0.44
Supine												
CO_{IGR}	l/min	5.0±1.2	2.2-7.6	5.1±1.3	2.8-7.6	5.5±1.0	3.8-7.3	4.5±1.0	2.2-6.1	4.4±1.3	2.7-6.1	0.04
SV_{IGR}	ml	75±23	25-148	79±22	50-148	74±18	45-112	66±18	25-101	70±36	36-134	0.21
HR_{IGR}	bpm	69±14	39-105	66±11	39-96	76±14	52-105	71±15	47-103	71±18	45-102	0.05
$BP_{systolic}$	mmHg	127±16	96-161	125±17	96-160	123±10	108-150	133±18	102-159	132±15	104-161	0.15
$BP_{diastolic}$	mmHg	75±11	41-111	72±11	42-100	74±8	54-86	78±10	49-96	80±15	54-111	0.08

EF was classified as normal (≥55%), mildly abnormal (45-54%), moderately abnormal (30-44%) and severely abnormal (<30%) according to European Association of Echocardiography/American Society of Echocardiography recommendations (9). P<0.05 was considered statistically significant in one-way analysis of variance with post-hoc Student-Newman-Keuls test. CO, cardiac output; SV, stroke volume; HR, heart rate; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; BP, blood pressure; CMR, cardiac magnetic resonance imaging; IGR, inert gas rebreathing.

classes in the order of normal to severely abnormal values, respectively, though this was deemed to be non-significant (P=0.17; Fig. 1A). When comparing patients with abnormal EF values to those with normal values, there was a mild yet significantly lower %ΔSV (P=0.03; Fig. 1B) and %ΔHR, of 13 and 4% vs. 22 and 11%, respectively (P=0.01; Fig. 1C). No significant difference was identified in CO between the four EF groups (P=0.69) nor between patients with normal and abnormal EF, respectively (P=0.20; data not shown). There was a significant negative pearson's product-moment correlation coefficient between %ΔSV and %ΔHR (r=-0.48, P<0.01). By contrast, no association between %ΔCO and %ΔHR was identified (r=-0.07, P=0.49; data not shown).

Discussion

Postural changes of cardiac function may be tracked non-invasively using IGR. The present study demonstrated an increase in both CO and SV when changing from upright to supine position as expected according to the Frank-Starling law of the heart (1,2). In accordance with the previous findings of Stefadouros *et al* (12), this study identified a reduced ability to adapt stroke volume in patients with systolic heart failure. This was indicated by a lower percentage change in SV between EF classes, and a significant difference between patients with abnormal and normal EF values. In heart failure with preserved left ventricular ejection fraction (HFpEF), a decrease in SV and CO has been previously reported, which was associated with a reduced left ventricular distensibility in response to postural change (13). Accordingly, growth differentiation factor 15, as a novel marker of HFpEF, was also associated with a reduced cardiac output response in an orthostatic test (14).

Apart from IGR, numerous non-invasive techniques for the determination of hemodynamic parameters including IGR have been proposed in previous years. Hamm *et al* (15) examined IGR in patients with aortic valve stenosis, and also Saur *et al* (16) in patients with lung diseases. While IGR has been demonstrated to be relatively accurate (4), techniques not requiring active collaboration including impedance cardiography (ICG), pulse contour analysis and continuous wave Doppler have exhibited greater reproducibility (17-19). This may be advantageous in serial measurements. Shortly following its introduction in 1966, ICG was used to track hemodynamic changes during tilt table testing (3). Uncalibrated non-invasive pulse-contour analyses were able to recognize CO changes induced by fluid challenge and passive leg raise test (20). However, changes in thoracic water content, arrhythmias and movement artifacts

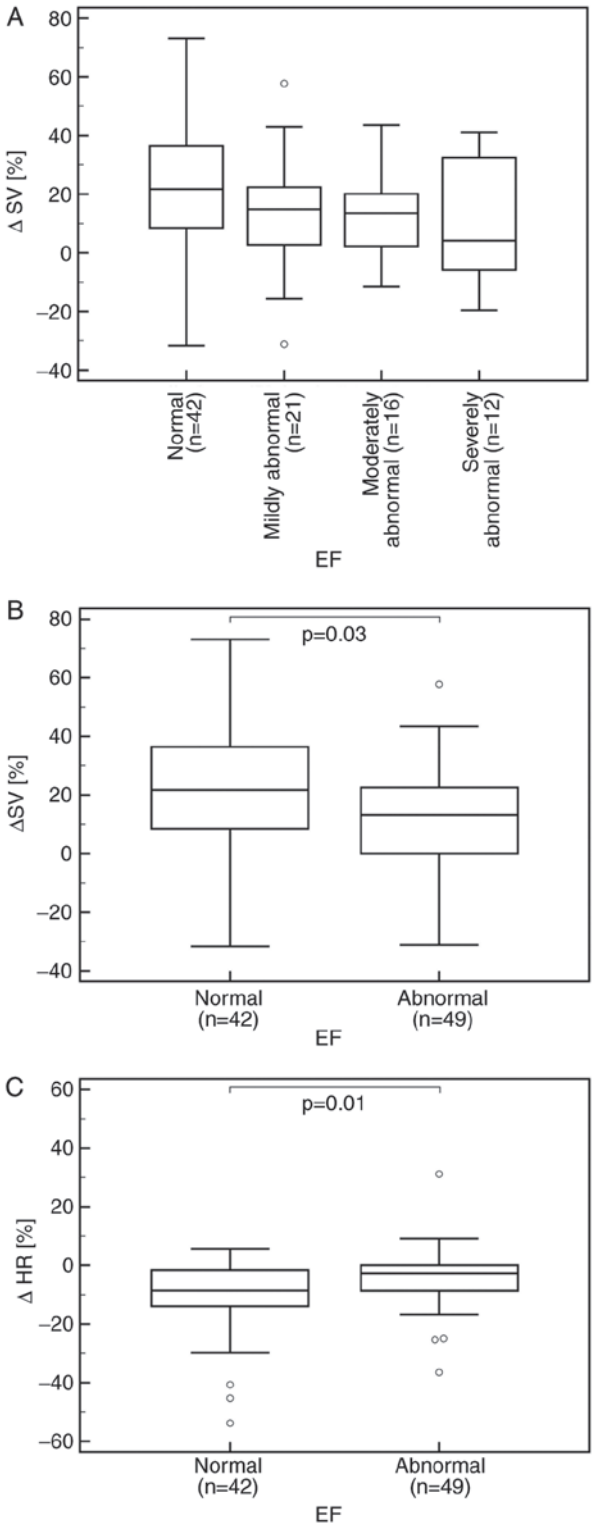

Figure 1. Box and whisker plots of the %ΔSV separated according to EF normality. (A) Trend toward a lower %ΔSV with reduced EF (P=0.17; one-way analysis of variance). (B) Significant difference between patients with normal vs. abnormal EF (P=0.03; t-test). (C) Significant difference between patients with normal vs. abnormal EF (P=0.01; t-test). %ΔSV, percentage change in stroke volume; EF, ejection fraction. %ΔHR, percentage change in heart ratio.

were demonstrated to alter the measurement accuracy of ICG (21-23), as was hemoglobin based pulmonary shunt flow correction (24). Further research is required to identity the optimal non-invasive technique; with IGR representing a promising technology.

Although the present cohort included a sufficient number of patients, there are limitations to be considered. First, there was no standardization of orthostatic testing of only single measurements. Second, the assertions are restricted to systolic heart failure while HFpEF may be of special interest due to a reduced ventricular distensibility, this should be studied further due to unique/different cardiac characteristics. Nevertheless, non-invasive measurement of cardiac function during postural changes using IGR is feasible, easy to perform and associated with low costs. The maneuver may also be performed by trained nursing staff and medical technical assistants. It therefore may be useful in the evaluation of patients presenting with syncope, and during the treatment of heart failure and arterial hypertension.

In conclusion, previous study our group demonstrated that IGR measurements were easy to perform and exhibited agreement with CMR (4). In the present study it was demonstrated that use of IGR to estimate hemodynamic response to postural changes may be feasible. Using IGR, a significant difference in the %ΔSV was detected between patients with normal and impaired EF. Several clinical scenarios affecting left ventricular function as well as an evaluation of the ideal non-invasive technique are worthy of further prospective investigations.

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Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

KS and FT were responsible for study design and writing the manuscript draft. TP and JDM were responsible for data collection. CD was conducted data analysis. FT and JB were responsible for the statistical analyses. JS, IA and MB critically revised the manuscript for important intellectual content.

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Commission II, Medical Faculty Mannheim of the University of Heidelberg (Mannheim, Germany) and conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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