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Dynamic left ventricular dyssynchrony contributes to B-type natriuretic peptide release during exercise in patients with systolic heart failure

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Aims Plasma B-type natriuretic peptide (BNP) is an emerging biomarker in heart failure. In this setting, the extent of left ventricular (LV) dyssynchrony contributes to exercise symptoms. Whether exercise-induced changes in LV dyssynchrony might be a trigger of BNP release has never been investigated.
Methods and results Fifty-seven patients with systolic LV dysfunction underwent quantitative analysis of BNP, mitral regurgitation (MR), and dyssynchrony at rest and during exercise. None had inducible ischaemia on perfusion imaging. By multiple regression analysis, end-systolic volume index ($P < 0.0001$), effective regurgitant orifice (ERO) ($P < 0.001$), and E/Ea ($P = 0.002$) emerged as independent determinants of BNP at baseline ($R^2 = 0.67$). Exercise induced a significant rise in BNP levels ($P < 0.0001$). In multivariate analysis, a smaller change in systolic blood pressure ($P = 0.04$), a larger increase in ERO ($P = 0.017$), and in systolic dyssynchrony index ($P = 0.006$) during exercise emerged as independent determinants of exercise-induced increases in BNP ($R^2 = 0.45$).
Conclusion MR severity, volume overload, and LV filling pressure are surrogates of BNP at rest. During exercise, changes in BNP reflect the presence of dynamic changes in both LV dyssynchrony and MR severity in the absence of inducible ischaemia.

Introduction

B-type natriuretic peptide (BNP) correlates with symptoms, exercise capacity, and prognosis in congestive heart failure (HF).[1] In patients with chronic HF, the BNP level increases in proportion to the degree of left ventricular (LV) dysfunction and the severity of mitral regurgitation (MR).[2–4] Several studies have shown that circulating BNP levels may rise acutely as an evolving response to clinical instability resulting from acute HF, acute pulmonary embolism, or acute coronary syndromes.[5–7] More recently, short-term changes in BNP levels have also been reported in patients with exercise-induced myocardial ischaemia. In this setting, the rise in BNP, although brief, could be reliably detected and the magnitude of increase correlated with the extent of inducible ischaemia.[8] Although symptoms mainly occur during exercise, there is little information on the potential usefulness of measuring the exercise-induced changes in BNP levels in chronic stable HF patients. Dynamic LV dyssynchrony—changes in the sequence of electromechanical coupling during exercise—has been shown to be associated with dynamic MR, exertional symptoms, and reduced exercise capacity and is correlated with the extent of MR improvement in resynchronized patients.[9–11] Whether exercise-induced changes in the sequence of activation of LV might be a trigger of BNP release has never been investigated. We tested the hypothesis that an acute increase in the extent of LV dyssynchrony during exercise may lead to transient elevation in plasma levels of BNP, which could serve as a biochemical marker of dynamic LV dyssynchrony.

Methods

Population

The present study concerned 57 consecutive patients (mean age, 66 ± 10 years; range 45–80 years) in sinus rhythm with chronic ischaemic LV dysfunction [mean ejection fraction (EF) $31 \pm 6\%$; range 18–44%] and at least mild functional MR who underwent quantitative exercise Doppler echocardiography. All of them were stable

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since at least 1 month and none had the following exclusion criteria: technically inadequate echocardiogram, more than trivial aortic regurgitation, history of myocardial infarction <6 months, atrial fibrillation or flutter, and evidence of inducible ischaemia. All patients were in New York Heart Association functional class II or III. All patients gave their informed consent and the protocol was approved by the Local Ethics Committee.

Exercise echocardiography

Beta-blockers were stopped 24 h before the test. A symptom-limited graded bicycle exercise test was performed in the semi-supine position on a tilting exercise table. After an initial workload of 25 W maintained for 3 min, the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were available throughout the test. The presence of inducible myocardial ischaemia was excluded by the use of technetium-99m sestamibi single photon emission computed tomography as previously described.[12]

Echocardiographic measurements

All echocardiographic parameters were obtained at rest and at peak exercise in the same cycling semi-supine position (Vivid 7 imaging device, GE Healthcare, UK). Quantitation of MR was performed by averaging both the quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area method as previously described.[13] From the mitral inflow, the E- and A-wave velocities, E-deceleration time, and E/A velocity ratio were measured. LV end-diastolic and end-systolic volumes and left atrial maximal volume were measured by the biapical Simpson disk method. Colour-tissue Doppler imaging was performed in the apical views (two, three, and four-chamber). Intra-LV dyssynchrony was referred to as LV dispersion and systolic dyssynchrony index. LV diastolic dispersion was determined as the difference between the longest and the shortest times to early diastolic velocities. The systolic dyssynchrony index was defined as the standard deviation of the time-to-peak systolic velocities of the 12 LV segments (six walls).[9,10] Interventricular dyssynchrony was determined as the difference between the time interval in the basal lateral segment of the right ventricle and of the LV. Peak velocities during early (Ea) and late (Aa) diastole obtained at the level of septal, lateral, inferior, and anterior mitral annulus were measured separately and averaged. The E/Ea ratio was then calculated.

Measurement of B-type natriuretic peptide levels

Two millilitres of venous blood were drawn at rest and at peak exercise and placed in a vacutainer tube containing potassium ethylenediaminotetraacetic acid. The samples were placed within 30 min on a Triage BNP test slide (Biosite Diagnostic, San Diego, CA, USA) and analysed in the Biosite MeterPlus machine, a point-of-care test based on fluorescence immunoassay.

Statistical analyses

Data are expressed as mean ± SD. Student's paired two-tailed *t*-test was used to compare measurements obtained at rest and during exercise. Categorical variables were compared with Fisher's exact test. A value of $P < 0.05$ was considered significant. Linear regression analysis was applied to study the correlation between BNP at rest and at exercise and different parameters. To determine independent predictors of BNP at rest and of exercise-induced changes in BNP during exercise, a stepwise multiple linear regression was performed (STATISTICA version 6). All variables with a $P < 0.10$ were included in the multivariate model. To determine independent determinants of a decrease in BNP during exercise, a logistic regression analysis was performed.

Results

Baseline and exercise characteristics

The QRS duration was 122 ± 30 ms (QRS ≥ 120 ms in 33). Of the 57 patients, 29 stopped exercise because of dyspnoea. The test duration was 9 ± 3.2 min for a maximum workload of 84 ± 22 W. During test, LV end-diastolic volume remained unchanged, whereas end-systolic volume decreased and EF increased (*Table 1*). During test, BNP increased from 375 ± 356 pg/mL (34–1480, median 217 pg/mL) to 435 ± 367 pg/mL (41–1622, median 292 pg/mL) ($P < 0.0001$). The median of BNP increment during exercise was 26 pg/mL (−50 to 613 pg/mL) (*Figure 1A*). At peak exercise, MR severity as quantitated by effective regurgitant orifice (ERO) increased from 13 ± 7 mm^2 to 22 ± 12 mm^2. Inter- and intra-ventricular dyssynchrony did not change significantly during test. However, LV synchronicity during exercise varied substantially from one patient to another; most patients experienced an increase in LV asynchrony, whereas others (~50%) experienced no change or a decrease in LV dyssynchrony (*Figure 1B*). Left atrial volume, mitral E-wave, mean peak Ea, and Aa velocities rose during exercise, whereas mitral E-wave deceleration time decreased. Contrary to E/A ratio, E/Ea ratio increased significantly.

Table 1 Patients characteristics at rest and at exercise

	Rest	Exercise	*P*
BNP (pg/mL)	375 ± 356	435 ± 367	<0.0001
Heart rate (bpm)	76 ± 13	114 ± 21	<0.0001
Systolic blood pressure (mmHg)	129 ± 18	161 ± 22	<0.0001
LV end-diastolic volume index (mL/m^2)	166 ± 39	164 ± 32	0.06
LV end-systolic volume index (mL/m^2)	116 ± 32	105 ± 33	<0.0001
LV ejection fraction (%)	31 ± 6	36 ± 8	<0.0001
Effective regurgitant orifice (mm^2)	13 ± 7	22 ± 12	<0.0001
Transtricuspid pressure gradient (mmHg)	31 ± 11	52 ± 18	<0.0001
LV d*P*/d*t* (mmHg/s)	737 ± 220	1013 ± 247	<0.0001
Left–right ventricular dyssynchrony (ms)	37 ± 31	39 ± 29	0.78
Systolic dyssynchrony index (ms)	32 ± 18	36 ± 19	0.11
LV diastolic dispersion (ms)	74 ± 46	54 ± 34	0.005
Left atrial volume (mL)	67 ± 24	74 ± 23	0.0002
Mitral E-wave (cm/s)	70 ± 26	107 ± 32	<0.0001
Mitral A-wave (cm/s)	61 ± 26	67 ± 27	0.03
Mitral E/A wave	1.5 ± 1.1	1.7 ± 0.69	0.5
Mitral E-wave deceleration time (ms)	169 ± 55	113 ± 34	<0.0001
Peak Ea velocity (cm/s)	3.9 ± 1.7	5.3 ± 2.9	<0.0001
Peak Aa velocity (cm/s)	4.2 ± 1.9	5.1 ± 2.2	0.0003
E/Ea (average annuli)	19 ± 8	23 ± 12	0.011

BNP, B-type natriuretic peptide; LV, left ventricular; A, late diastolic transmitral flow velocity; Aa, late diastolic mitral annular velocity; E, early diastolic transmitral flow velocity; Ea, early diastolic mitral annular velocity.

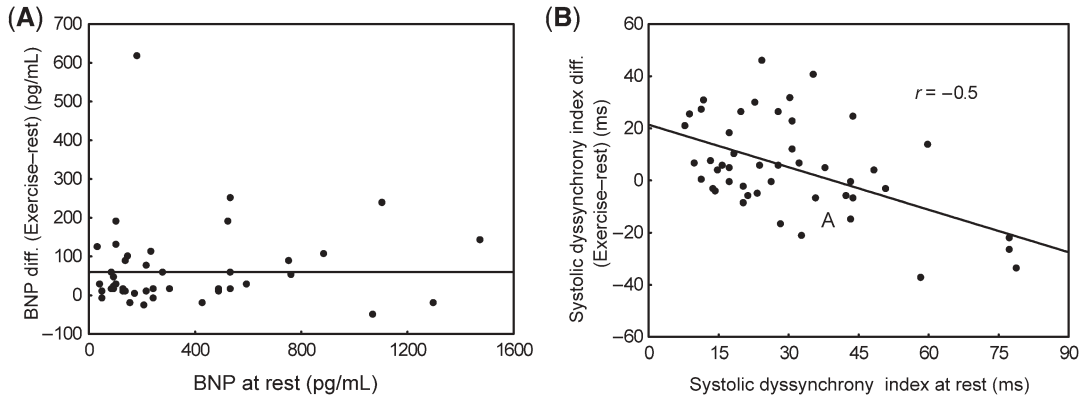

Figure 1 (*A*) Correlations between exercise-induced changes in B-type natriuretic peptide (BNP) and BNP at rest. (*B*) Correlations between exercise-induced changes in systolic dyssynchrony index and the degree of dyssynchrony at rest. Diff, difference.

Table 2 Determinants of B-type natriuretic peptide levels at rest

BNP at rest	*r*	*P*
LV end-diastolic volume index	0.68	<0.0001
LV end-systolic volume index	0.71	<0.0001
LV ejection fraction	−0.4	0.0018
Transtricuspid pressure gradient	0.31	0.017
Systolic dyssynchrony index	0.36	0.006
Effective regurgitant orifice	0.58	0.0002
Left atrial volume	0.56	<0.0001
Mitral A wave	0.38	0.004
Mitral E/A wave	0.29	0.033
E/Ea	0.61	<0.0001

LV, left ventricular; A, late diastolic transmitral flow velocity; E, early diastolic transmitral flow velocity; Ea, early diastolic mitral annular velocity.

Determinants of B-type natriuretic peptide at rest

Under resting conditions, BNP levels were not affected by age, sex, QRS width, NYHA class, medical history, and treatment. Correlation coefficients between BNP levels and echocardiographic parameters are presented in *Table 2*. Conversely to LVEF ($r = -0.41$), higher LV volumes were associated with higher BNP. The strongest correlation was observed with LV end-systolic volume. Greater left atrial volume, larger ERO of MR, higher E/A and E/Ea ratios were also associated with higher BNP (*Figure 2*). The correlations with transtricuspid pressure gradient and the systolic dyssynchrony index were significant but weak. By stepwise multiple regression analysis, the LV end-systolic volume index ($P < 0.0001$), the severity of MR as quantitated by ERO ($P < 0.001$), and the E/Ea ratio ($P = 0.002$) emerged as independent determinants of BNP levels at rest ($R^2 = 0.67$).

Determinants of exercise-induced changes in B-type natriuretic peptide levels

Determinants of exercise-induced changes in BNP levels during exercise are depicted in *Table 3*. The wide range of exercise-induced changes in BNP neither correlate with levels at rest nor with clinical parameters and treatment. At peak exercise, transtricuspid pressure gradient, LV systolic dispersion, systolic dyssynchrony index, and E/Ea ratio correlated with changes in BNP. The strongest correlations with BNP changes were observed with the differences in systolic dyssynchrony index and in ERO. Examples of dynamic changes in LV dyssynchrony are provided in *Figure 3*. In multivariate analysis, a smaller change in systolic blood pressure ($P = 0.04$), a larger increase in ERO ($P = 0.017$), and in systolic dyssynchrony index ($P = 0.006$) during exercise emerged as independent determinants of exercise-induced increases in BNP ($R^2 = 0.45$) (*Figure 4*).

Discussion

Cardiac BNP has emerged as a powerful diagnostic and prognostic biomarker in HF patients.[1–3] Under resting conditions, the BNP level represents an indirect marker of the severity of MR, LV remodelling, and the presence of increased LV filling pressure. In the absence of inducible myocardial ischaemia, exercise testing is accompanied by substantial changes in BNP levels in patients with chronic systolic LV dysfunction. To the best of our knowledge, this study is the first to show that the extent of dynamic LV dyssynchrony results in detectable increases in BNP levels during exercise. Besides, the magnitude of changes in BNP also reflects the dynamic behaviour of MR during test.

Plasma B-type natriuretic peptide levels at rest

BNP is mainly produced in response to myocardial stretching.[14] In the normal state, plasma concentration of BNP—resulting from both atrial and ventricular release—is very low and largely influenced by patient age, gender, and renal function.[15–17] In the failing heart, the ventricle becomes the dominant chamber for BNP production and BNP levels rise proportionally to the extent of LV dysfunction.[2] In severely depressed LV, BNP is notably increased in patients with a Doppler echocardiographic restrictive filling pattern, an enlarged LV, or a severe MR.[3,4,18] The present study confirms and extends these previous observations. Indeed, BNP exhibited direct relations with LV end-systolic volume—a witness of LV remodelling, E/Ea ratio—a non-invasive estimate of mean pulmonary wedge pressure,

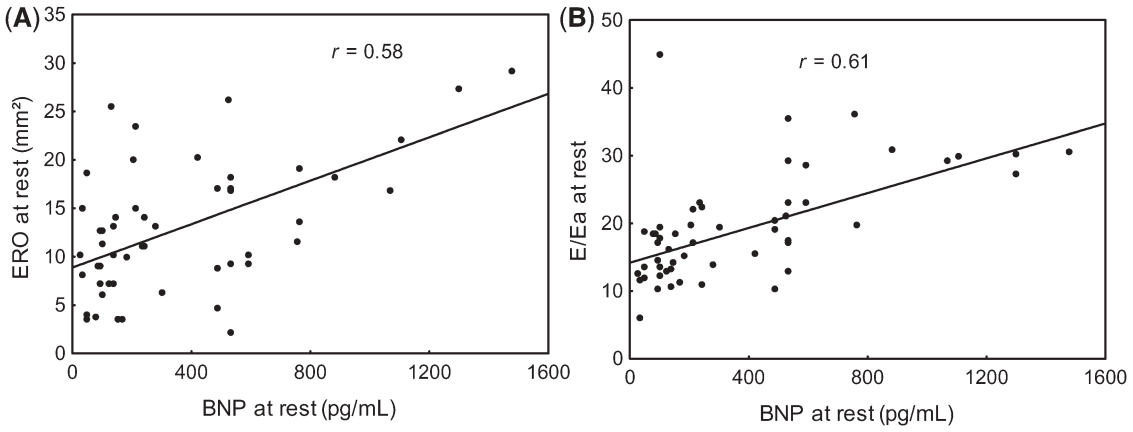

Figure 2 Correlations between B-type natriuretic peptide at rest and effective regurgitant orifice (*A*) and E/Ea ratio (*B*).

Table 3 Determinants of exercise-induced changes in B-type natriuretic peptide levels

BNP difference (exercise−rest)	*r*	*P*
Systolic blood pressure diff.	−0.35	0.008
LV end-diastolic volume index diff.	0.37	0.005
Effective regurgitant orifice at exercise	0.43	0.0007
Effective regurgitant orifice diff.	0.58	<0.0001
Transtricuspid pressure gradient at exercise	0.54	0.0001
Transtricuspid pressure gradient diff.	0.47	0.0003
Systolic dyssynchrony index at exercise	0.54	0.0001
Systolic dyssynchrony index diff.	0.56	<0.0001
E/Ea at exercise	0.45	0.0005

LV, left ventricular; E, early diastolic transmitral flow velocity; Ea, early diastolic mitral annular velocity; diff., difference from rest to exercise.

and the quantified degree of MR—a parameter associated with LV volume overload. Furthermore, all these factors influence symptoms and are predictive of an adverse outcome.[19]

Dynamic changes in B-type natriuretic peptide levels during exercise

Although modest, the dynamic nature of BNP release in response to exercise has been previously reported.[20–22] In coronary artery disease, the magnitude of rise in BNP is proportional to the degree of inducible ischaemia.[8] In patients with HF, plasma BNP levels at exercise are related to LV end-diastolic pressure and inversely correlated to cardiac index at peak test.[23,24] In the present study, exercise-induced changes in BNP were moderately related to the level of BNP in basal conditions. Most patients exhibited an increase in BNP at peak exercise. The rise in BNP was greater in patients with larger exercise-induced increases in MR severity and in LV dyssynchrony and blunted changes in systolic blood pressure. These dynamic changes are known to contribute to exertional symptoms through pulmonary congestion and a limitation of forward stroke volume adaptation during exercise.[9,25] Thus, the acute exacerbation in volume overload and in LV end-diastolic wall tension during exercise might acutely trigger BNP degranulation from cardiac myocytes.[26] Inadequate adaptation of peripheral circulation in these HF patients might also contribute to LV dyssynchrony by progressive modifications in ventricular shape, which becomes more spherical. Transient increases in BNP levels in relation to the asynchronous activation sequence of the LV have also been reported in patients submitted to different cardiac pacing modes.[27] The exercise-induced decrease in BNP was, in contrast, observed in patients with a larger increase in LV d*P*/d*t*—a marker of LV systolic performance—and smaller changes in LV systolic dyssynchrony during exercise. Reduction in BNP might be related to exhausted BNP production, higher BNP clearance, or diminished BNP release secondary to improved haemodynamic condition.[28] Animal studies have indeed suggested that production and/or release of BNP might be independently regulated.[29]

Limitations

N-terminal pro-BNP has not been evaluated. However, because N-terminal pro-BNP has a longer half-life than BNP, its plasma concentrations may be less responsive to exercise.[20] Serial measurements of BNP were not performed after the recovery period. Renal function that could affect BNP levels at rest but not during exercise was not available. Withdrawing of beta-blockers, although of short duration, might affect the level of BNP at rest. Patients in NYHA class IV were excluded. In these patients, both dynamic MR and LV dyssynchrony could be more severe. The analysis of tissue Doppler imaging parameters was performed off-line. As a result, E/Ea ratio appears to be higher than previously reported.[30] No evaluation of strain and strain rate parameters was performed to differentiate passive from active motion.

Conclusion

Dynamic increases in MR severity and in LV dyssynchrony during exercise are new findings contributing to exercise intolerance in patients with chronic systolic LV dysfunction. Both are associated with larger exercise-induced increases in BNP levels. Further studies are however required to determine the clinical utility of exercise BNP and its prognostic impact in patients with systolic HF.

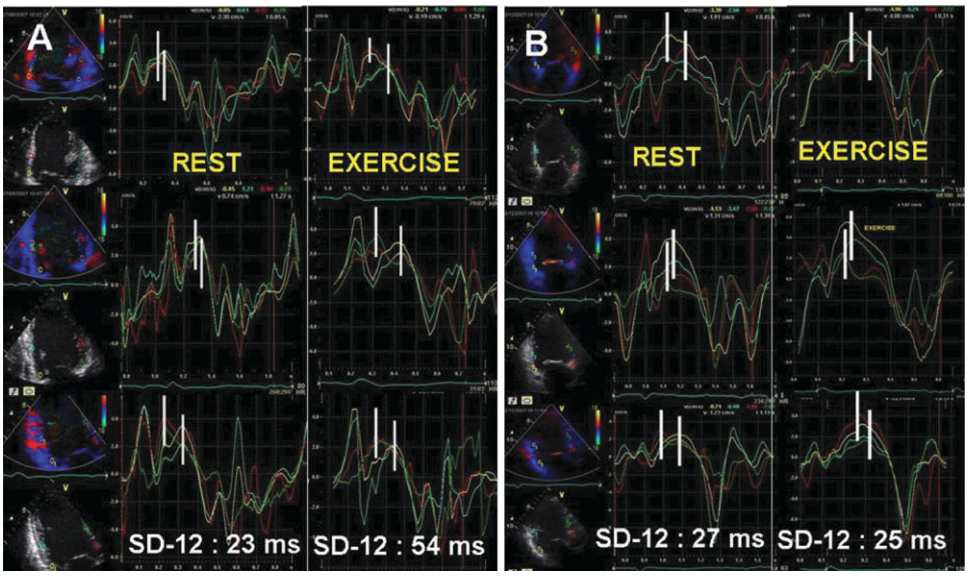

Figure 3 Tissue Doppler imaging echocardiograms depicting exercise-induced changes in systolic dyssynchrony index being estimated as the standard deviation of the time-to-peak systolic velocities of the 12 LV segments (SD-12). (*A*) A patient with an increase in dyssynchony index; (*B*) a patient without significant change in dyssynchrony index.

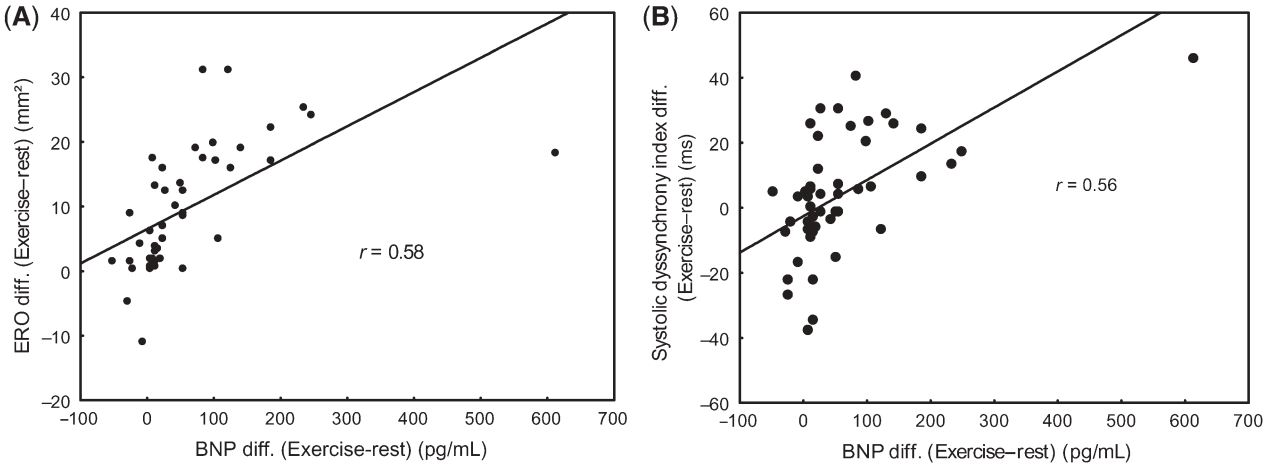

Figure 4 Correlations between changes in B-type natriuretic peptide and changes in effective regurgitant orifice (*A*) and changes in systolic dyssynchrony index; (*B*) during exercise. Diff, difference.

Conflict of interest: none declared.

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