Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis

Gudrun Dieberg, Hashbullah Ismail, Francesco Giallauria, and Neil A. Smart
School of Science and Technology, University of New England, Armidale, New South Wales, Australia

Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. J Appl Physiol 119: 726–733, 2015. First published March 6, 2015; doi:10.1152/japplphysiol.00904.2014.—Exercise training induces physical adaptations for heart failure patients with systolic dysfunction, but less is known about those patients with preserved ejection fraction. To establish whether exercise training produces changes in peak \(\dot{V}O_2\) and related measures, quality of life, general health, and diastolic function in heart failure patients with preserved ejection fraction. We conducted a MEDLINE search (1985 to October 10, 2014), for exercise-based rehabilitation trials in heart failure, using search terms "exercise training, heart failure with preserved ejection fraction, heart failure with normal ejection fraction, peak \(\dot{V}O_2\), and diastolic heart dysfunction". Seven intervention studies were included providing a total of 144 exercising subjects and 114 control subjects, a total of 258 participants. Peak \(\dot{V}O_2\) increased by a mean difference (MD) 2.13 ml·kg\(^{-1}\)·min\(^{-1}\) [95% confidence interval (CI) 1.54 to 2.71, \(P < 0.00001\)] in exercise training vs. sedentary control, equating to a 17% improvement from baseline. The corresponding data are provided for the following exercise test variables: \(\dot{V}E/\dot{V}CO_2\) slope, MD 0.85 ml·kg\(^{-1}\)·min\(^{-1}\) (95% CI 0.05 to 1.65, \(P = 0.04\)); maximum heart rate, MD 5.60 beats per minute (95% CI 3.95 to 7.25, \(P < 0.00001\)); Six-Minute Walk Test, MD 32.1 m (95% CI 17.2 to 47.1, \(P < 0.0001\)); and indices of diastolic function: E/A ratio, MD −2.31 (95% CI −3.44 to −1.19, \(P < 0.0001\)); deceleration time (DT), MD −13.2 ms (95% CI −19.8 to −6.5, \(P = 0.0001\)); and quality of life: Minnesota Living with Heart Failure Questionnaire, MD −6.50 (95% CI −9.47 to −3.53, \(P < 0.0001\)); and short form-36 health survey (physical dimension), MD 15.6 (95% CI 7.4 to 23.8, \(P = 0.0002\)). In 3,744 h patient-hours of training, not one death was directly attributable to exercise. Exercise training appears to effect several health-related improvements in people with heart failure and preserved ejection fraction.

exercise training; cardio-respiratory fitness; heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) is defined as an inability of the ventricles to optimally accept blood from the atria with blunted end-diastolic volume response by limiting the stroke volume and cardiac output. Exercise intolerance and reduced quality of life are known as the primary chronic symptoms in HFpEF patients. HFpEF prevalence is higher in elderly and women and may be linked to hypertension, diabetes mellitus, and atrial fibrillation (2, 18). Chronic heart failure (CHF) patients with either normal or abnormal systolic function have similar mortality rates (4). In the United States, CHF affects ~5 million individuals with heart failure, and more than 555,000 are newly diagnosed with CHF annually (22). Corresponding costs to the health care systems are enormous. A review by Smart (25) estimated the hospital-based exercise therapy treatment costs to prevent mortality in one CHF patient to be approximately (U.S.) $60,000/yr. Meta-analyses have shown exercise training to be beneficial in HFpEF patients in terms of improved cardiorespiratory fitness (12, 30).

In people with HFpEF, as well as systolic heart failure, cardiorespiratory fitness (peak \(\dot{V}O_2\)) is impaired. Impaired peak \(\dot{V}O_2\) has been associated with increased mortality risk (10) and

Address for reprint requests and other correspondence: N. A. Smart, School of Science and Technology, Univ. of New England, Armidale, NSW 2351, Australia (e-mail: nsmart2@une.edu.au).
decreased quality of life in heart failure patients. As measured by traditional indices such as ejection fraction, systolic function appears largely normal under resting baseline conditions in HFpEF. However, studies have shown through global assessment of systolic function by other techniques, such as strain rate imaging, systolic abnormalities do exist in HFpEF patients (17). Despite the preservation of systolic function at rest, mortality rates in HFpEF are similar to those observed in systolic failure (5), highlighting the clear need for effective treatment strategies for these patients.

Interestingly, conventional methods for treating heart failure have proven largely ineffective for HFpEF patients. Currently, effective therapeutic approaches for HFpEF are limited and focus primarily on managing cardiovascular risk factors, especially hypertension. Exercise therapy is a promising effective adjunct therapy that can delay disease progression, minimize pharmaceutical use, and improve functional limitations and quality of life. While, to date, ~100 randomized, controlled trials of exercise training have been published in systolic heart failure patients, strikingly, only 10 such trials exist examining HFpEF.

In this meta-analysis, our purpose was to assess the effects of exercise on a number of outcome measures that are commonly used to assess clinical status in HFpEF. First, we evaluated the impact of exercise training on changes to exercise capacity in HFpEF patients compared with sedentary controls through examination of peak $V\dot{O}_2$, $V\dot{E}/V\dot{CO}_2$, heart rate, and the Six-Minute Walk Test (6MWT). Second, we studied clinical measures of diastology, including early-to-late filling ratio (E/A), $E/E'$ (a widely accepted noninvasive surrogate of left ventricular filling pressure) and deceleration of early ventricular filling. Third, we examined whether exercise training produces better quality of life and/or general health through use of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (21) and the SF-36 (which has established norms) (3). Finally, we examined whether rates of serious events, mortality, and hospitalization were more frequent with exercise training in HFpEF patients.

**METHODS**

**Search Strategy**

Studies were identified through a MEDLINE search (1985 to October 10, 2014), Cochrane Controlled Trials Registry (1966 to October 10, 2014), CINAHL, SPORTDiscus, and the Science Citation Index. The search strategy included a mix of MeSH and free text terms for key concepts related to exercise training, heart failure with normal ejection fraction, and heart failure with preserved ejection fraction, peak $V\dot{O}_2$, and diastolic heart failure for clinical trials of exercise training in heart failure patients. Studies were included when patients exhibited baseline left ventricular ejection fraction above 45%. These searches were limited to prospective, randomized, or controlled trials and human studies, with no language restrictions on publications. Manuscript reference lists and latest journal editions were scrutinized for new references. Full journal articles were assessed by three reviewers (N. A. Smart, G. Dieberg, and H. Ismail) for relevance and eligibility. Methodological disagreements were resolved by reviewers through discussion. For two studies (9, 16), authors were contacted and requested to provide further data about the protocol for implementing desired exercise intensity.

---

Fig. 1. Consort statement.

**Study Selection**

Included were randomized controlled designs of exercise training in heart failure patients with normal or preserved ejection fraction. Studies of heart failure patients with abnormal systolic function were excluded. All included studies are comparisons between exercise training and sedentary control. Records identified 32 papers through database searching. Six additional records from reference lists were added. Only principal studies, with the most subjects, were included—studies for which multiple publications existed from the same dataset. After initial screening, 19 studies were removed, which included overlapping studies, duplicates, duplicate data, abstracts, irrelevant articles (e.g., editorials and discussion papers). We further excluded 12 studies in which the control group received additional intervention, nonrelevant studies, and acute exercise responses. Seven studies of exercise training intervention were included (see Consort Statement, Fig. 1).

**Outcome Measures**

We recorded the following: peak $V\dot{O}_2$ (baseline and postexercise), $V\dot{E}/V\dot{CO}_2$, maximum heart rate, 6MWT, diastolic function [$E/A$ and $E/E'$ ratios, deceleration time (DT)], MLHFQ, short form-36 health survey, participant completion rates, adverse medical events, hospitalization, and mortality.

**Data Synthesis**

We calculated patient-hours of exercise training and percentage change in peak $V\dot{O}_2$.

**Assessment of Study Quality**

We assessed study quality using the 15-point TESTEX scale (29), which is a validated study quality assessment tool specific to exercise training studies. Median TESTEX score was 10, with two studies scoring 8, three scoring 10, and two studies scoring 12.
### Table 1. Patient and training characteristics for randomized control trials included in the meta-analysis on exercise training studies with HFpEF patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sessions Attended, %</th>
<th>Participants Included in the Final Analysis</th>
<th>Training Characteristics</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves et al. (1)</td>
<td>Portugal</td>
<td>100</td>
<td>Total patients: $N = 98$</td>
<td>6 mo of interval exercise training. First month, 3 sessions per week, and 15 min at 70–75% of maximal heart rate. Following 5 mo, 3 sessions per week, and 35 min at 70–75% of maximal heart rate</td>
<td>LVEF Diastolic function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exercise (&gt;55% LVEF): $n = 20$, 22 m/9 f, mean age: 62.9. Control: $n = 11$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exercise (45–54% LVEF): $n = 23$, 24 m/9 f, mean age: 63.6. Control: $n = 10$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exercise (&lt;45% LVEF): $n = 22$, 27 m/7 f, mean age: 62.0. Control: $n = 12$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NYHA class I/II/III/IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edelmann et al. (6)</td>
<td>Germany</td>
<td>34 participated in &gt;90%, 52 in 70–90% and 14 in &lt;70% of the exercise sessions.</td>
<td>Total patients: $N = 64$ Exercise: $n = 44$, 24 m/20 f, mean age: 64 Control: $n = 20$, 12 m/8 f, mean age: 65 NYHA class II/III</td>
<td>32 sessions of continuous exercise training. Weeks 1–4, 2 sessions per week, 20–40 min at 50–60% of peak $V_{\text{O}2}$, Week 5 onward, 3 sessions per week at 70% of peak $V_{\text{O}2}$ and resistance training, 15 reps at 60–65% 1 RM</td>
<td>LVEF Peak $V_{\text{O}2}$ Heart rate 6MWT MLHF SF-36</td>
</tr>
<tr>
<td>Gary et al. (9)</td>
<td>USA</td>
<td>100</td>
<td>Total patients: $N = 28$ Exercise: $n = 15$, 15 f, mean age: 67 Control: $n = 13$, 13 f, mean age: 69 NYHA class II/III</td>
<td>12 wk of continuous exercise training (walking). 3 sessions per week, 20–40 min at 40% –60% of the maximal heart rate</td>
<td>6MWT MLHF</td>
</tr>
<tr>
<td>Karavidas et al. (15)</td>
<td>Greece</td>
<td>100</td>
<td>Total patients: $N = 30$ Exercise: $n = 15$, 6 m/9 f, mean age: 69.4 Control: $n = 15$, 6 m/9 f, mean age: 68.5 NYHA class II/III</td>
<td>6 wk of functional electrical stimulation (FES) training. 5 sessions per week, 30 min at 25 Hz for 5 s followed by 5-s rest</td>
<td>MLHF KCCQ BDI 6MWT Diastolic function BNP</td>
</tr>
<tr>
<td>Kitzmann et al. (16)</td>
<td>USA</td>
<td>86, final testing; 88, exercise training</td>
<td>Total patients: $N = 63$ Exercise: $n = 24$, 23 m/9 f, mean age: 70 Control: $n = 30$, 25 m/6 f, mean age: 70 NYHA class II/III</td>
<td>4 mo (~16 wk of continuous exercise training. 3 sessions per week, 60 min at 40–70% HRR</td>
<td>LVEF Peak $V_{\text{O}2}$ $V_{\text{O}2}$/ $V_{\text{CO}_2}$ Heart rate 6MWT Diastolic function EDV and ESV SBP and DDP MLHF SF-36</td>
</tr>
<tr>
<td>Palau et al. (20)</td>
<td>Australia</td>
<td>100</td>
<td>Total patients: $N = 26$ Exercise: $n = 14$, 7 m/7 f, mean age: 68 Control: $n = 12$, 6 m/6 f, mean age: 74 NYHA class II/III/IV</td>
<td>12 wk of interval exercise training. 2 sessions per week, 20 min. Subjects started breathing at a resistance equal to 25–30% MIP for 1 wk, and each subsequent session was adjusted to 25–30% MIP.</td>
<td>LVEF Peak $V_{\text{O}2}$ $V_{\text{O}2}$/ $V_{\text{CO}_2}$ Heart rate 6MWT Diastolic function NT-proBNP MLHF</td>
</tr>
<tr>
<td>Smart et al. (28)</td>
<td>Australia</td>
<td>87.6</td>
<td>Total patients: $N = 25$ Exercise: $n = 12$, 7 m/5 f, mean age: 67 Control: $n = 13$, 6 m/7 f, mean age: 61 NYHA class II/III</td>
<td>16 wk of interval exercise training. 3 sessions per week, 30 min at 60–70% peak $V_{\text{O}2}$</td>
<td>LVEF Peak $V_{\text{O}2}$ $V_{\text{O}2}$/ $V_{\text{CO}_2}$ Heart rate Diastolic function MLHF</td>
</tr>
</tbody>
</table>

Peak $V_{\text{O}2}$, maximal oxygen consumption; FES, functional electrical stimulation; peak HR, maximal heart rate; MHR, maximum heart rate; HRR, heart rate reserve; m/f, male/female; MIP, inspiratory muscle trainer; 1 RM = 1 repetitive maximum; 6MWT, Six-Minute Walk Test; LVEF, left ventricular ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; MLHF, Minnesota Living with Heart Failure Questionnaire; SF-36, short form-36 health survey; $V_{\text{O}2}$/ $V_{\text{CO}_2}$, ventilatory equivalent for carbon dioxide; KCCQ, Kansas City Cardiomyopathy Questionnaire; BDI, Beck depression inventory; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; and NT-proBNP, N-terminal prohormone of brain natriuretic peptide.
Statistical Analyses

Revman 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. Continuous data were reported as means and SD. Revman 5.1 enabled calculation of postintervention change from baseline for SD, using change in mean values, number of subjects, and P value or preferably 95% CIs. In many cases in which exact P values were not provided, we used default values e.g., P = 0.05 became P = 0.049. Mean difference (MD) in these data from baseline was analyzed. We used a 5% level of significance and a 95% CI to report change in outcome measures. Egger plots were produced to identify sources of publication bias (7).

RESULTS

Included Studies

Seven studies met selection criteria (1, 6, 9, 15, 16, 20, 28), providing a total of 144 exercising subjects and 114 control subjects, a total of 258 participants (Table 1). Total patient-hours of exercise training reported were 3,744 h.

Exercise Training Parameters

Program length for high-intensity training varied from 6 to 26 wk and frequency from two to five sessions weekly. Three studies used walking and cycle training, one used only walking, one used cycling only, one used functional electrical stimulation, and one inspiratory muscle training.

Outcome Measures

Change in peak VO₂. Data from four studies showed MD for peak VO₂ was 2.13 ml·kg⁻¹·min⁻¹ [95% confidence interval (CI) 1.54 to 2.71, P < 0.00001] in exercise vs. control (Fig. 2A).

Change in peak V̇E/V̇CO₂ slope. Data from three studies for V̇E/V̇CO₂ slope showed MD was 0.85 units higher (95% CI 0.05 to 1.65, P = 0.04) in exercise vs. control (see Fig. 2B).

Change in heart rate. Data from four studies showed MD for maximum heart rate was 5.60 bpm (95% CI 3.95 to...
A Change in E/A ratio for Exercise Training studies with HFpEF patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Control</td>
<td>Weight</td>
</tr>
<tr>
<td>Alves 2012</td>
<td>0.12</td>
<td>0.138</td>
</tr>
<tr>
<td>Kitzman 2013</td>
<td>-0.04</td>
<td>0.065</td>
</tr>
<tr>
<td>Smart 2012</td>
<td>-0.05</td>
<td>0.1627</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>56</td>
<td>52</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 8, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)

B Change in E'/E ratio for Exercise Training studies with HFpEF patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Control</td>
<td>Weight</td>
</tr>
<tr>
<td>Ekedahl 2011</td>
<td>-2.3</td>
<td>2.3024</td>
</tr>
<tr>
<td>Karadas 2013</td>
<td>-3.25</td>
<td>5.898</td>
</tr>
<tr>
<td>Patou 2013</td>
<td>-3.3</td>
<td>0.4503</td>
</tr>
<tr>
<td>Smart 2012</td>
<td>4.4</td>
<td>9.8491</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>85</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 8.18, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 4.02 (P < 0.0001)

C Change in Deceleration Time for Exercise Training studies with HFpEF patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Control</td>
<td>Weight</td>
</tr>
<tr>
<td>Alves 2012</td>
<td>-14</td>
<td>16.1562</td>
</tr>
<tr>
<td>Kitzman 2013</td>
<td>-4</td>
<td>14.2763</td>
</tr>
<tr>
<td>Smart 2012</td>
<td>5</td>
<td>6.5057</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>56</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 1.91, df = 3 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.89 (P < 0.0001)

The improvements in peak VO₂ observed with exercise training are complemented with changes in maximum heart rate, but not in VE/VCO₂ slope. This current analysis produced peak VO₂ changes of similar effect size seen previously (30). Although one trial has established a -4.4 unit improvement in VE/VCO₂ slope (28), our analysis does not identify an improvement with exercise training. A previous meta-analysis did not report significant changes in E/A ratio, E'/E ratio, and deceleration time with exercise training.
analyze change in \( \frac{\text{Ve}}{\text{VCO}_2} \) slope in HFpEF patients (30). A previous report established a strong prognostic relationship between peak \( \text{VO}_2 \), \( \frac{\text{Ve}}{\text{VCO}_2} \) slope, and mortality in heart failure patients with reduced systolic function (23). Our analysis showed maximum heart rate to be higher after exercise training; the resultant increase in maximal cardiac output would at least partially explain why peak \( \text{VO}_2 \) improved with training. Although \( \frac{\text{Ve}}{\text{VCO}_2} \) slope did not decrease in our analysis, a reduction would imply improved ventilatory efficiency and would likely contribute to improved cardiorespiratory fitness. A mean 10-12 bpm increase in maximum heart rate after training has been reported in systolic heart failure and HFpEF in previous trials (26, 28).

Diastolic Function

Our analysis of E/A ratio is the first to identify that exercise training may significantly improve this aspect of diastolic function. Neither individual studies, nor pooled analyses published previously, have shown a postexercise training benefit. Our analysis of E/E\(_i\) confirms the finding of Edelmann et al. (6), but not the findings of the pooled analysis of Taylor et al. (30). E/E\(_i\) is a surrogate for filling pressure, and our analysis suggests a small reduction (improvement) is elicited with exercise training in HFpEF patients. We suspect that these changes in E/E\(_i\) do not account for all of the improvement in peak \( \text{VO}_2 \). Therefore, we acknowledge that some changes may be due to improved endothelial function (11). Deceleration time (DT) was also significantly reduced in our analysis; this is the first analysis to demonstrate such a benefit. Together, these three measures of diastolic function have shown a trend toward normalization after exercise training. While improved diastolic function due to exercise training has been previously demonstrated in healthy people (19), previous work in HFpEF has failed to show a trend toward improved E/A and DT in people with HFpEF (20). Unfortunately, study-level (as opposed to patient-level) meta-analyses do not allow examination of the relationship between changes in noninvasive measures of cardiac function to other comprehensive measures of systole/diastole generated by catheterization, e.g., pressure-volume loops. Further well-designed and appropriately powered studies of HFpEF are required to provide clarification of how noninvasive and catheter-based techniques interrelate to avoid speculation regarding the probable long-term consequences of chronically increased left ventricular pressures (8).

Quality of Life and General Health

Our analysis showed HFpEF patients exhibited reductions (improvements) in MLHFQ scores of similar magnitude to those seen in patients with systolic heart failure (27). Our analyses also showed HFpEF patients exhibited increased (im-
proved) SF-36 scores. The effect size was of a similar magnitude to improvements seen previously in heart failure patients with normal (HFpEF) and abnormal systolic function (26).

Limitations

The major limitation of this analysis is that only seven datasets currently exist, and associated sample sizes were generally small. In terms of study quality, the median TESTEX score for the included studies indicated of good study quality and comprehensive reporting. There were insufficient data to warrant analysis of study withdrawal, adverse events, hospitalization, and mortality rates.

Heterogeneity scores indicated the majority of our analyses were justified, but those of V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} slope and 6MWT may exhibit heterogeneity at levels too high to justify these analyses.

Meta-analysis of continuous data is problematic; we adjusted for baseline difference in primary outcomes between allocation groups by measuring preintervention vs. postintervention change. Often, we were accurately able to calculate change in SD, but in cases in which exact P values were not provided by study reports, we used default values e.g., P < 0.05 or P < 0.001 in our calculations, which may introduce errors.

Our funnel plots appear to suggest negligible risk of publication bias. We suggest that unpublished datasets with perhaps negative results do not exist.

Finally, we acknowledge that factors related to volume of exercise may explain some of the outcomes reported; for example, intuitively one suspects longer study duration variations may yield better results, but the small number of included studies precluded subanalyses of exercise volume parameters.

Previous work by one of our authors shows that people with HFpEF typically tend to be five or more years older and more likely to be female than their systolic dysfunction counterparts (26). While the precise volume of screening to identify people with HFpEF for this work were not published, it can be revealed that screening of more than 4,000 echocardiograms yielded less than 20 exercise training participants. The explanation of this low yield is that for the purposes of scientific rigor, trials of HFpEF need to demonstrate participants do not have ischemic heart disease. Isolation from any hint of ischemic heart disease is rare in HFpEF and, therefore, makes suitable trial participants extremely difficult to find. This is possibly the primary explanation why over 100 randomized exercise training trials exist in systolic heart failure patients, while only 7 exist to date in HFpEF.

In terms of expected health benefits for people with HFpEF who undertake exercise, one may expect extended survival in one person for approximately every 17 people treated for one year with exercise (24). These data were generated from systolic heart failure studies, but as the expected, improvement in peak VO\textsubscript{2} from exercise training is similar in HFpEF, one would expect the survival benefit to be comparable.

Conclusions

Exercise training does yield improvements in cardiorespiratory fitness, diastolic function, quality of life, and general health in heart failure patients with preserved ejection fraction.

![Table 3. Study quality assessment of included studies using TESTEX scale](http://jap.physiology.org/doi/10.1152/japplphysiol.00904.2014)
GRANTS
This work received no financial support and has no relationship to industry.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

REFERENCES