Left atrial phasic function interacts to support left ventricular filling during exercise in healthy athletes

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Wright S, Sasson Z, Gray T, Chevanathan A, Esfandiari S, Dimitry J, Armstrong S, Mak S, Goodman JM. Left atrial phasic function interacts to support left ventricular filling during exercise in healthy athletes. J Appl Physiol 119: 328–333, 2015. First published July 2, 2015; doi:10.1152/japplphysiol.00307.2015.—We studied the contribution of phasic left atrial (LA) function to left ventricular (LV) filling during exercise. We hypothesized that reduced LV filling time at moderate-intensity exercise limits LA passive emptying and increases LA active emptying. Twenty endurance-trained males (55 ± 6 yr) were studied at rest and during light (-100 beats/min) and moderate-intensity (-130 beats/min) exercise. Two-dimensional and Doppler echocardiography were used to assess phasic volumes and diastolic function. LV end-diastolic volume increased from rest to light exercise (54 ± 6 to 58 ± 5 ml/m², P < 0.01) and from light to moderate exercise (58 ± 5 to 62 ± 6 ml/m², P < 0.01). LA maximal volume increased from rest to light exercise (26 ± 4 to 30 ± 5 ml/m², P < 0.01) related to atrioventricular plane displacement (r = 0.55, P < 0.005), without further change at moderate exercise. LA passive emptying increased at light exercise (9 ± 2 to 13 ± 3 ml/m², P < 0.01) and then returned to baseline at moderate exercise, whereas LA active emptying increased appreciably only at moderate exercise (6 ± 2 to 14 ± 3 ml/m², P < 0.01). Thus, the total atrial emptying volume did not increase beyond light exercise, and the increase in LV filling at moderate exercise could be attributed primarily to an increase in the conduit flow volume (19 ± 3 to 25 ± 5 ml/m², P < 0.01). LA filling increases during exercise in relation to augmented LV longitudinal contraction. Conduit flow increases progressively with exercise in athletes, although this is driven by LV properties rather than intrinsic LA function. The pump function of the LA augments only at moderate exercise due to a reduced diastolic filling time and the Frank-Starling mechanism.

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Less is understood about the functional response of the left atrium (LA) to both dynamic exercise and chronic endurance training and its contribution to LV stroke volume during exercise. The LA exhibits complex phasic function during the cardiac cycle that modulates LV filling. The LA offloads the pulmonary circulation while filling during the reservoir phase and is mechanically coupled to LV emptying via the atrioventricular plane. Early diastolic passive LA emptying (conduit phase) fills the LV from I) the atrial reservoir and 2) conduit flow volume drawn into the ventricle through the LA from the pulmonary veins (5), aided by LV untwist secondary to active relaxation and elastic recoil. This untwist contributes to the rapid decay of LV pressure, the augmentation of the transmitral pressure gradient, and the generation of LV suction (22), factors that allow for the augmentation of LV diastolic filling at lower pressures and can be affected both by acute exercise and chronic training (18, 24). During late ventricular diastole, the LA actively contracts (pump phase) to reestablish the transmitral pressure gradient and increase LV EDV.

Similar to the LV, the LA remodels in response to chronic endurance training (12). Although it has been traditionally believed that SV plateaus at ~40% of VO2max in healthy adults (28), a considerable body of literature has identified divergent SV responses to exercise in athletes, with the arguments for both cases having been detailed previously (29). Notwithstanding, it is now generally understood that endurance-trained athletes can progressively increase EDV and SV during exercise secondary to enhanced diastolic function (13) and training-related structural remodeling (11), yet the role of the LA in supporting this rise is not well characterized. During dynamic exercise, increases in HR and changes in LV function should have interactions with LA function due to the relative constancy of total heart volume, presumably affecting LA volumes and transmirtal flow. This is a growing area of investigation, as chronic training-induced LA and LV remodeling have been linked to elevated risk for atrial fibrillation (1), and athletes may serve as a model of coupled electromechanical derangement of the LA. Therefore, our objective was to examine both LA morphology and function during exercise in well-trained endurance athletes. We tested the hypothesis that reduced LV filling time at moderate-intensity exercise limits LA passive emptying and increases LA active emptying and that increasing exercise intensity is associated with progressive LA dilatation.

METHODS

Subjects. We recruited male runners, cyclists, and triathletes >45 yr old who participated in intensive year-round endurance training of

IT IS WELL UNDERSTOOD that left ventricular (LV) function responds to meet the elevated oxygen requirements of dynamic exercise, increasing cardiac output through increased heart rate (HR) and stroke volume (SV). The increase in SV is attained by a significant increase in LV end-diastolic volume (EDV) (14, 30), which is supported by increased diastolic filling rate and a modest rise in contractility that is more pronounced as exercise intensity increases. These responses are augmented further after chronic endurance exercise training through functional and morphological LV remodeling.
≥ 6 h or 35 km/wk (runners) for a minimum of 10 yr and participated in one or more marathons/road races/triathlons per year. These selection criteria were chosen to allow for the accrual of a sufficient stimulus for training-induced cardiac remodeling and functional adaptations. Exclusion criteria included smoking, diabetes mellitus, hypertension, use of cardiovascular drugs, and a history of cardiovascular, pulmonary, or any other chronic systemic disease. All participants provided informed written consent, and the study was approved by the local institutional research ethics boards in Toronto, ON, Canada.

Cardiac assessment. Subjects abstained from training for 48 h prior to the study and from caffeine for 12 h prior. Upon arrival, subjects underwent resting 12-lead ECG and had venous blood sampled for hemoglobin and hematocrit determination. A clinical baseline echocardiogram (Echo) was conducted at rest with the subject in a supine left lateral decubitus position. The subject was then transferred to an imaging cycle ergometer (Ergosprint 1200E; Ergoline), and elevated to a semi-upright (45°) position with slight leftward rotation. HR was monitored with three-lead ECG, and blood pressure was monitored using an automated system (Tango+; SunTech Medical).

Exercise protocol. Participants were instructed to pedal at a self-selected cadence between 60 and 80 rpm, and work rate was adjusted in the first 2 min of each exercise condition to elicit a target HR. The exercise protocol included three sequential conditions: rest, i.e., resting semi-upright for 3 min; light exercise at a target HR of 100 beats/min for 8–10 min; and moderate exercise at a target HR of 130 beats/min for 8–10 min. After 2 min from the start of each stage to allow the subject to reach a steady state, Echo images were acquired offline (EchoPAC 11; GE Healthcare) by a single trained observer blinded to study order and subject characteristics, in accordance with current guidelines (17, 21), averaged over three cardiac cycles whenever possible, with gain optimized for delineation of the endocardial border. LV EDV, end-systolic volume (ESV), and LA maximum, minimum, and precontraction volumes were measured in apical two- and four-chamber views using the modified biplane Simpson’s method (LV) and biplane area-length method (LA) (4, 17). LA maximal volume was measured at the end of systole immediately prior to mitral valve opening. LA minimal volume was measured at the end of diastole immediately following mitral valve closure. LA precontraction volume was measured at the onset of the ECG P-wave. Conduit volume represents the dynamic throughput volume driven from the pulmonary veins to the LV while the mitral valve is open, and it was determined by subtracting the LA reservoir volume (max − min) from LV SV. Atrioventricular plane displacement (AVPD) was quantified from the Doppler tissue velocity map using tissue tracking. Sample volumes were placed at the septal and lateral annular sites of four-chamber color tissue Doppler images and at the anterior and inferior annular sites of two-chamber images. AVPD was calculated as an average of the displacement in millimeters at each of the four sample sites.

Statistical analysis. Statistical analyses were performed using SPSS Statistics software version 20 (IBM). Normality was assessed using the Shapiro-Wilk test, and continuous variables were analyzed using repeated-measures analysis of variance. The three levels included were rest, light exercise, and moderate exercise. Significant effects were analyzed post hoc using Bonferroni-corrected t-tests. The relationship between AVPD and LA volumes was explored using Pearson correlations. An α-level of 0.05 was considered statistically significant. All data presented are reported as means ± SD unless otherwise noted.

RESULTS

Subjects. Twenty subjects were included in this analysis, and characteristics are reported in Table 1. The mean age was 55 ± 6 yr, with a body mass index of 23.9 ± 2.2 kg/m². Indices of LV size were within normal ranges (17).

Cardiac volumes. Cardiac volumes are presented in Table 2, and the phasic partitions of LV SV are illustrated in Fig. 1. LA maximal volume at rest was 26 ± 4 ml/m². LA maximal volume increased significantly at light exercise (P < 0.01), with no further increase at moderate exercise. LA precontraction volume remained stable at light exercise before increasing offline.

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55 ± 6</td>
<td>45–65</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177 ± 5</td>
<td>166–187</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>75 ± 8</td>
<td>63–92</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.9 ± 2.2</td>
<td>21–28</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>16 ± 3</td>
<td>10–22</td>
</tr>
<tr>
<td>V̇O₂max, ml·kg⁻¹·min⁻¹</td>
<td>46 ± 7</td>
<td>36–67</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>54 ± 6</td>
<td>45–69</td>
</tr>
<tr>
<td>LVIDd, cm</td>
<td>4.7 ± 0.3</td>
<td>4.0–5.3</td>
</tr>
<tr>
<td>LVIDs, cm</td>
<td>3.1 ± 0.3</td>
<td>2.7–3.5</td>
</tr>
<tr>
<td>IVSd, cm</td>
<td>1.1 ± 0.1</td>
<td>0.9–1.3</td>
</tr>
<tr>
<td>LVPWd, cm</td>
<td>0.8 ± 0.1</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>81 ± 11</td>
<td>61–102</td>
</tr>
<tr>
<td>LV mass index, cm²/m²</td>
<td>3.6 ± 0.4</td>
<td>3.0–4.2</td>
</tr>
<tr>
<td>RA area, cm²</td>
<td>23 ± 4</td>
<td>18–30</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI, body mass index; HR, heart rate; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; IVSd, interventricular septal wall thickness; LVPWd, left ventricular posterior wall thickness; LV mass index, left ventricular mass index; LVIDd, left ventricular internal diameter; RA area, right atrial area.

### Table 2. Cardiac volume indexes at rest and during exercise

<table>
<thead>
<tr>
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<th>Baseline (Range)</th>
<th>Light (Range)</th>
<th>Moderate (Range)</th>
</tr>
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<tbody>
<tr>
<td>LVEDV, ml/m²</td>
<td>62 ± 4 (54–68)</td>
<td>69 ± 4 (59–75)**</td>
<td>76 ± 4 (70–83)**</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>54 ± 6 (45–65)</td>
<td>58 ± 5 (49–67)**</td>
<td>62 ± 6 (54–75)**</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>41 ± 3 (37–45)</td>
<td>43 ± 3 (39–47)**</td>
<td>45 ± 3 (40–50)**</td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>33 ± 4 (26–42)</td>
<td>40 ± 4 (32–47)**</td>
<td>47 ± 4 (40–57)**</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>26 ± 4 (21–37)</td>
<td>30 ± 5 (23–40)**</td>
<td>30 ± 5 (21–43)**</td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>16 ± 4 (9–25)</td>
<td>17 ± 3 (12–26)**</td>
<td>22 ± 4 (15–33)**</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>9 ± 3 (5–15)</td>
<td>10 ± 2 (6–14)</td>
<td>8 ± 3 (5–16)</td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>15 ± 2 (11–20)</td>
<td>21 ± 4 (15–28)**</td>
<td>22 ± 3 (14–28)**</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>9 ± 2 (7–13)</td>
<td>13 ± 3 (9–19)**</td>
<td>8 ± 2 (5–13)</td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>6 ± 2 (4–10)</td>
<td>7 ± 2 (4–13)**</td>
<td>14 ± 3 (9–19)**</td>
</tr>
<tr>
<td>LVESV, ml/m²</td>
<td>18 ± 4 (10–24)</td>
<td>19 ± 3 (11–24)</td>
<td>25 ± 5 (19–34)**</td>
</tr>
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</table>

Values are means ± SD. LV, left ventricular; EF, ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; LA, left atrial; MIN, minimal volume; reservoir; MIN, minimal volume; conduit; conduit flow volume; passive, passive emptying volume; active, active emptying volume. *P < 0.05 vs. rest; **P < 0.01 vs. rest; ‡P < 0.01 vs. light exercise.
significantly during moderate exercise ($P < 0.01$ vs. light exercise). LA minimal volume was not changed by exercise ($P = 0.08$). LA reservoir volume increased significantly from rest to light exercise ($P < 0.01$) and remained steady during moderate exercise. The LA passive emptying volume increased ($P < 0.01$) during light exercise before returning to baseline values at moderate exercise. LA active emptying volume increased slightly during moderate exercise ($P < 0.05$) and then rose markedly during moderate exercise ($P < 0.01$ vs. rest, $P < 0.01$ vs. light exercise).

LV EDV increased from rest to light exercise ($P < 0.01$) and from light to moderate exercise ($P < 0.01$), whereas LV ESV and ejection fraction (EF) increased accordingly at each exercise stage ($P < 0.01$).

**Doppler imaging.** Doppler measures of diastolic function at rest and during light and moderate exercise, including transmitral flow and mitral annular motion velocities and AVPD, are presented in Table 3. Transmitral early and late flow velocities increased proportionately at each subsequent stage of exercise, with the E/A ratio remaining unchanged across the range of HR. Early and late diastolic mitral annular velocities also increased with HR at both septal and lateral sampling sites. The mean AVPD increased significantly at light exercise ($P < 0.01$), with no significant change at moderate exercise. The change in AVPD with increasing intensity was related to the change in LA maximal volume ($r = 0.55$, $P < 0.005$).

**DISCUSSION**

This study characterized the phasic role of the LA in the diastolic filling of the LV during light- and moderate-intensity exercise in healthy middle-aged endurance athletes. Our data indicate that the relative contributions of each phase of atrial function changes with increasing HR to optimize ventricular filling. A novel finding was a biphasic response where atrial filling increases acutely with performance of light exercise, without further dilatation at moderate-intensity exercise. Improved LV filling at moderate-intensity exercise is supported primarily by LV diastolic reserve and increased conduit flow concomitant with augmented LA pump function serving to maintain, rather than increase, the total LA contribution to LV filling. This pattern illustrates the phasic coupling of LA function to the LV via the atrioventricular plane within the construct of the constant volume heart and represents a key mechanism by which LV filling is regulated despite progressively less filling time.

The ability of athletes to progressively increase SV during exercise has been attributed to enhanced diastolic function (13), which is influenced by atrial but predominantly ventricular properties. In untrained males during cycle exercise, AVPD increases at light-intensity exercise without further change at moderate-intensity exercise (26), similarly, LV EDV and SV increase at light exercise without further change at moderate-intensity exercise. In endurance-trained males, despite a similar pattern of AVPD increase and plateau and no further increase in the LA contribution to LV filling at moderate-intensity exercise, we observed progressive increases in LV EDV and SV at moderate exercise. As such, the increase in LV EDV at moderate exercise must be attributed to intrinsic diastolic reserve of the LV, serving to augment the conduit inflow, which is enhanced with endurance training, and the pump function of the LA maintaining the total atrial contribution to EDV.

**Systolic atrioventricular interaction/left atrial filling.** Simultaneously with the reservoir phase of LA filling, LV systolic ejection occurs as the product of longitudinal, radial, and circumferential shortening. The longitudinal component of LV contraction draws the AV plane apically (7), inducing passive atrial expansion and aspirating volume from the pulmonary veins into the LA (27), similar to a piston in a syringe (5). This effect can be observed on the LA pressure waveform as the $x’x’$-descent, where atrial pressure drops despite initial filling through a combination of initial active relaxation and then AVPD (3) and as the S-waves of spectral Doppler interrogation.
of the pulmonary vein flow. Therefore, LA filling is mechanically coupled to LV emptying via the AV plane, and accordingly, we hypothesized that LA filling during exercise would increase related to enhanced LV systolic function mediated by AVPD. Indeed, at light exercise (100 beats/min), both LA maximal volume and AVPD increased significantly; however, at moderate exercise, neither AVPD nor LA filling increased further. Although E/E’, an index of LA pressure, followed a similar trend, it must be noted that the values remained in the range for “normal” rather than “elevated” filling pressure. Taken together, these observations support the prediction of the constant volume heart model such that LV longitudinal shortening is the primary determinant of LA filling (5). Since AVPD does not increase linearly with HR (26), exercise-induced LA dilatation is limited beyond light exercise in the healthy human. We speculate that this is an adaptive mechanism that protects the thin-walled LA from an exacerbated wall stress at moderate-to-high intensity exercise if LA maximal volume was to increase continually with exercise intensity.

**Diastolic atrioventricular interaction/left atrial emptying.** This study highlights the dynamic nature of diastolic atrioventricular coupling during exercise and, in particular, the specific role of the LA as a pump. At rest, 63% of atrial emptying occurred passively during early diastole, with the balance transferred during atrial contraction. From baseline to light exercise, LA maximal volume increased with no change in precontraction volume, reflecting a larger atrium with increased passive emptying, and no change in active emptying (“booster pump” function). External work applied to the LA by the LV via the AV plane during systole causes atrial myocardial stretch. With LV myocardial inactivation, stored elastic energy in the LA myocardium is released, drawing the AV plane back toward the atrial ceiling. Restitution of the AV plane contributes to the maintenance of LA pressure during early diastole (the y-descent), which in turn maintains the AV pressure gradient (15) even as the LV fills, and facilitates the transfer of volume into the LV (19). Thus, at light submaximal exercise, diastolic filling of the LV is autoregulated predominantly by augmented apical excursion of the AV plane during systole secondary to the enhanced longitudinal component of LV contraction and coupled to more rapid LV relaxation during early diastole.

The coupling of LV systolic contraction and diastolic recoil and relaxation has been described thoroughly (16). The observed decrease in LV ESV with exercise reflects an increase in LV inotropy occurring with a concomitant increase in Doppler indices of LV early diastolic relaxation. LV SV is a product of both longitudinal and radial contraction, and 60% of SV is attributable to LV longitudinal function at rest (8); however, the augmentation of longitudinal and radial function is neither equal nor linear in response to increasing HR. As discussed above, the greatest augmentation of LV longitudinal function occurs from rest to light exercise (HR = 100 beats/min) (10, 26). From light to moderate exercise (HR = 120–130 beats/min), the primary augmentation observed is in LV rotation (10), which is likely due its rapid effect in the face of less filling time.

In the present study, we found that the further increase in LV EDV and SV at moderate exercise (130 beats/min) is due primarily to a greater conduit flow volume. Conduit flow represents the dynamic throughput of the LA during the conduit phase/LV early diastole, which is appreciable as the D-wave of the pulmonary venous Doppler spectral occurring simultaneously with the transmitral E-wave. Although this study did not quantify strain indices of LV untwist, both the timing and velocity of LV diastolic recoil and relaxation are important factors in generating the transmitral pressure gradient and mitral inflow (19). Normal LV relaxation follows a temporal sequence consisting of untwist, long-axis relengthening, and finally, short-axis expansion, with the development of an apical-to-basal intraventricular pressure gradient closely following peak untwist (23), extending into the atrium following mitral valve opening. LV untwist and transmitral pressure gradient generation facilitates LV suction, augmenting LV diastolic filling during exercise (25), with the remaining untwist reserve recruitable at moderate exercise (10), a pattern that may be altered by age and exercise training (18). Since conduit flow is dependent on the transmitral pressure gradient, which is itself dependent primarily on LV recoil and relaxation, conduit function should be considered a property of the LV (5). As such, LV diastolic reserve, the extent to which the transmitral pressure gradient and mitral inflow may be augmented, likely dictates the ability to increase conduit flow volume and maintain LV EDV through progressive exercise, a capacity that may be enhanced in athletes.

During moderate exercise, the total LA contribution to LV filling (the reservoir volume) remained stable vs. light exercise, as discussed above. However, we observed a reversal in the relative contribution of LA passive and active emptying to LV filling, with the passive component decreasing to 42% of total emptying. As exercise intensity increases, diastasis is effectively eliminated and LA emptying transitions directly from passive to active partitions, as has been described previously (9). This results in atrial contraction beginning before the atrium can passively empty to equilibrium (31), as is apparent from the fusion of the E- and A-wave transmitral Doppler spectra at heart rates above ~100 beats/min. With a greater precontraction volume, the result is augmented output secondary, in part to the Frank-Starling mechanism that maintains the LA contribution to LV filling despite the reduced diastolic duration and time for passive LA emptying. We did not observe direct evidence of increased LA contractility (i.e., a decrease in LA minimal volume), although this mechanism may be recruited during vigorous exercise and may further explain the ability of endurance-trained athletes to recruit SV progressively with increasing HR. Conversely, exercise intolerance in patients with atrial fibrillation likely reflects relatively well-preserved LV diastolic augmentation that maintains EDV, but the loss of LA pump function results in a failure to augment LV end-diastolic pressure and volume during moderate-intensity exercise.

**Limitations.** Our study has certain limitations. We studied healthy, endurance-trained, middle-aged males that may not be generalized across sex differences or younger or less-trained males. However, the endurance-trained, middle-aged male cohort is increasingly recognized to be susceptible to training-induced atrial remodeling that in some cases may be proarrhythmic (20), and our data may provide insight into how exercise training induces this state. Future work should include female cohorts and be powered to examine sex-related differences. Our exercise protocol could alternatively have targeted relative intensities (%HR_{max}, %V_{O2max}, etc), which would
potentially provide superior individualized estimates of “light” and “moderate” intensity and be less susceptible to differences in fitness. However, given our focus on diastolic function and the influence of heart rate on indices of diastolic function, controlling for and setting targeted absolute HR was considered more important in controlling diastolic patterns. We also acknowledge that biplane 2D Echo is a widely accepted method to assess LA volume, but the unusual geometry of the atrium requires a number of geometric assumptions. Compared with MRI and 3D echo, 2D offers good correlation with modest volume underestimation across the cardiac cycle (6). As 3D Echo becomes more widely available, future studies should consider its use when quantifying LA volume.

Conclusions. During light exercise, LA reservoir phase filling is increased related to augmented atrioventricular plane displacement, secondary to enhanced longitudinal LV contraction within the constant volume heart. This mechanism does not increase further during moderate exercise. At light- and particularly moderate-intensity exercise, LA conduit phase flow is increased significantly, which is due presumably to enhanced LV relaxation and diastolic suction. Increased LA pump function is only appreciably augmented during moderate-intensity exercise via the atrial Frank-Starling mechanism. These data highlight the remarkable ability of the LV to regulate both filling and emptying during exercise in health. It also reiterates the important role that the LA plays in maintaining and increasing LV EDV when filling is compromised, such as tachycardia and diastolic dysfunction (2).

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GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

S.W., S.T.G., E.S., J.M.G., and J.M.G. conception and design of research; S.W., S.T.G., E.S., J.D., S.A., S.M., and J.M.G. performed experiments; S.W., S.T.G., and A.C. analyzed data; S.W., S.T.G., A.C., J.D., S.A., S.M., and J.M.G. interpreted results of experiments; S.W. prepared figures; S.W. drafted manuscript; S.W., S.T.G., A.C., E.S., S.M., and J.M.G. edited and revised manuscript; S.W., S.T.G., E.S., J.D., S.A., S.M., and J.M.G. approved final version of manuscript.

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