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Citation:

DOI: https://doi.org/10.1016/j.jsams.2017.06.017

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Exercise-intensity dependent alterations in plasma redox status do not reflect skeletal muscle redox-sensitive protein signaling

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\textbf{A B S T R A C T}

Objectives: Redox homeostasis and redox-sensitive protein signaling play a role in exercise-induced adaptation. The effects of sprint-interval exercise (SIE), high-intensity interval exercise (HIIE) and continuous moderate-intensity exercise (CMIE), on post-exercise plasma redox status are unclear. Furthermore, whether post-exercise plasma redox status reflects skeletal muscle redox-sensitive protein signaling is unknown.

\textbf{Design:} In a randomized crossover design, eight healthy adults performed a cycling session of HIIE (5 \times 4 \text{ min at } 75\% \text{ W}_{\text{max}}), SIE (4 \times 30 \text{ s Wingate's}), and CMIE work-matched to HIIE (30 \text{ min at } 50\% \text{ W}_{\text{max}}).

\textbf{Methods:} Plasma hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}), thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD) activity, and catalase activity were measured immediately post, 1 h, 2 h and 3 h post-exercise. Plasma redox status biomarkers were correlated with phosphorylation of skeletal muscle p38-MAPK, JNK, NF-\kappaB, and IкB\textalpha{} protein content immediately and 3 h post-exercise.

\textbf{Results:} Plasma catalase activity was greater with SIE (56.6 \pm 1.8 \text{ U ml}^{-1}) compared to CMIE (42.7 \pm 3.2, p < 0.01) and HIIE (49.0 \pm 5.5, p = 0.07). Peak plasma H\textsubscript{2}O\textsubscript{2} was significantly (p < 0.05) greater after SIE (4.6 \pm 0.6 \text{ mmol/l}) and HIIE (4.1 \pm 0.4) compared to CMIE (3.3 \pm 0.5). Post-exercise plasma TBARS and SOD activity significantly (p < 0.05) decreased irrespective of exercise protocol. A significant positive correlation was detected between plasma catalase activity and skeletal muscle p38-MAPK phosphorylation 3 h post-exercise (r = 0.40, p < 0.04). No other correlations were detected (all p > 0.05).

\textbf{Conclusions:} Low-volume SIE elicited greater post-exercise plasma catalase activity compared to HIIE and CMIE, and greater H\textsubscript{2}O\textsubscript{2} compared to CMIE. Plasma redox status did not, however, adequately reflect skeletal muscle redox-sensitive protein signaling.

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1. Introduction

Excess reactive oxygen species (ROS) can result in an oxidation-reduction (redox) imbalance, commonly referred to as oxidative stress, often leading to oxidative damage and/or modification to lipids, proteins, and DNA.\textsuperscript{1} Elevated systemic oxidative stress and/or attenuated antioxidant defense, as measured through biomarkers in whole blood, plasma or serum, are associated with physical inactivity, excess adipose tissue, and contributes to the development and progression of cardiometabolic disease.\textsuperscript{1,2}

Paradoxically, systemic oxidative stress and/or antioxidant activity also increase following a single session of aerobic exercise.\textsuperscript{3} Depending on the exercise-intensity, duration, volume, and type of exercise (e.g. extreme muscle damaging exercise), elevated systemic oxidative stress or antioxidant activity may be present and/or appear for up to several days after exercise.\textsuperscript{3} In contrast to the pathological effects of chronic systemic oxidative stress, exercise-induced oxidative stress is transient (i.e. returns to pre-exercise...
levels within hours/days following exercise) and is reported to be a beneficial and necessary requirement for optimal physiological functioning and cardiometabolic adaptation. 5,6,7,9,10,11,12 Likewise, high-intensity interval exercise (HIIE; repeated intervals at near-maximal intensity) and sprint interval exercise (SIE; repeated intervals at supramaximal intensity) also elicit elevated systemic oxidative stress and antioxidant activity.5,6,8 However, comparisons with continuous moderate-intensity exercise (CMIE) are less clear.9,10 Considering that SIE and HIIE may elicit many of their reported cardiometabolic health benefits through post-exercise alterations in plasma redox homeostasis,7,11,12 further research is warranted.

The systemic increase in oxidative stress following acute exercise is said to originate primarily from increased reactive oxygen species (ROS) in skeletal muscle.13 Exercise-induced ROS are also reported to contribute to the post-exercise adaptation via activation of skeletal muscle redox-sensitive protein signaling which include c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).14-16 Although systemic biomarkers of redox status (i.e. those measured in blood, serum or plasma) are reported to adequately reflect redox status of various tissues including skeletal muscle,17 their mechanistic value to reflect more complex compartmentalized redox-sensitive cellular signaling has been questioned.18 Exploring the association between plasma redox status and redox-sensitive protein signaling linked to exercise adaption is important, as many studies rely on simple measures of plasma redox homeostasis to infer a beneficial redox-sensitive signaling effect elicited by exercise.

The aims of this study were to first investigate the effects of a single session of HIIE, SIE, and CMIE work-matched to HIIE, on post-exercise plasma redox status. We then determined whether post-exercise plasma redox status was able to adequately reflect skeletal muscle redox-sensitive protein signaling pathways that are linked to exercise adaptation.

2. Methods

Plasma was analyzed from eight (6 male and 2 female) young, recreationally active, and healthy adults (age: 25 ± 2 years; BMI: 25 ± 1 kg m⁻²; VO₂max: 48.4 ± 4.0 ml kg⁻¹ min⁻¹; mean ± SEM), from a previous study.19 Exclusion criteria for participation included smoking, musculoskeletal or other conditions that prevent daily activity, symptomatic or uncontrolled metabolic or cardiovascular disease, prior (less than 3 months) or current supplementation (e.g. antioxidant supplements) or medications that may affect outcome measures, and females taking oral contraception. To minimize the effect of hormonal fluctuations on outcome measures, females were tested in the early follicular phase of the menstrual cycle (2–7 days after the onset of menses). Verbal and written explanations about the study were provided prior to obtaining written informed consent. The study was approved by, and conducted in accordance with, the Victoria University Human Research Ethics Committee.

Detailed methodology and participant demographics have previously been reported.19 In brief, following adequate screening eligible participants completed a graded exercise cycling test to measure peak aerobic capacity (VO₂peak), maximal power output (Wₘₐₓ), and to determine the subsequent workloads for the three exercise sessions (SIE, HIIE, and CMIE).

All exercise sessions were performed on a Velotron cycle ergometer. The SIE protocol consisted of 4 × 30 s all-out (Wingate) cycling sprints, interspersed with 4.5-min passive recovery periods. The HIIE protocol consisted of 5 × 4-min cycling bouts at 75% of Wₘₐₓ (~77% of VO₂peak), interspersed with 1-min passive recovery periods. The CMIE protocol was work-matched to the HIIE protocol and consisted of continuous cycling for 30 min at 50% of Wₘₐₓ (~54% of VO₂peak).

On three separate occasions, separated by a minimum of one week, participants arrived in the laboratory after an overnight fast and performed in a randomized crossover fashion either the SIE, HIIE, or CMIE protocol. Immediately after exercise, participants rested on a bed for 3 h. Muscle biopsies were taken from the vastus lateralis at rest, immediately after exercise, and 3 h after exercise, and were processed and analyzed for phosphorylated p38 MAPK, JNK, NF-κB, and total IκBα protein content as previously described.19 Venous blood samples were taken at rest, immediately after exercise, and 1, 2 and 3 h after exercise. Venous blood was collected in collection tubes containing ethylenediaminetetraacetic acid, separated into plasma by centrifugation (10 min at 3500 rpm, 4 °C), then aliquoted and stored at −80 °C until analyzed.

Plasma thiobarbituric acid reactive substances (TBARS; Cayman Chemical, Ann Arbor, MI, USA), Catalase activity (Cayman Chemical, Ann Arbor, MI, USA), Superoxide Dismutase (SOD) activity (Cayman Chemical, Ann Arbor, MI, USA) and hydrogen peroxide (H₂O₂; Amplex UltraRed assay, Molecular Probes, Eugene, Oregon, USA) were analyzed by a spectrophotometer (xMark microplate spectrophotometer, Bio-Rad Laboratories, Mississauga, ON, Canada) in duplicate as per the manufacturer’s instructions. Intra-assay coefficients of variation were determined and averaged from each duplicate for all participants and resulted in a coefficient of variation of 2%, 5%, 4% and 3% for TBARS, SOD, catalase and H₂O₂, respectively. Inter-assay coefficients of variation for assay standards between each 96 well plate were averaged and resulted in a coefficient of variation of 1%, 3%, 4%, 1%, for TBARS, SOD, catalase and H₂O₂, respectively. All redox biomarkers were normalized to shifts in plasma volume which were calculated from changes in hematocrit and hemoglobin using a formula previously described.20 Peak post-exercise plasma redox status is highly variable.21 As such, the peak concentration that was recorded for each participant throughout the post-exercise recovery period was used to calculate and compare peak post-exercise plasma redox status.

Data were checked for normality and analyzed using Predictive Analytics Software (PASW v20, SPSS Inc., Chicago, WI, USA). Comparisons of multiple means were examined using a repeated measures analysis of variance (exercise protocol × time point). Planned contrast analysis of the baseline sample to all post-exercise samples, and identical time-points between exercise protocols, were conducted using Fisher’s LSD pairwise comparison test for all significant main and interaction effects. Pearson’s correlation coefficient was determined for plasma redox status markers and skeletal muscle redox-sensitive protein signaling immediately after exercise and 3 h after exercise. All data are reported as mean ± standard error of mean (SEM) and statistical analysis conducted at the 95% level of significance (p ≤ 0.05). Trends were reported when p-values were greater than 0.05 and less than 0.1.

3. Results

A significant effect for exercise intensity (p = 0.02) was detected for plasma catalase activity with the greatest activity seen with SIE compared to CMIE (p < 0.01) and HIIE (p = 0.07; Fig. 1). A significant effect of time was detected for plasma H₂O₂ (p = 0.03), SOD activity (p < 0.01) and TBARS (p = 0.01). Greater plasma H₂O₂ was detected immediately and 1 h after exercise compared to baseline. All exercise sessions lowered TBARS immediately, 1 h, and 2 h after exercise (Fig. 1). Similarly, SOD activity was lower immediately, 1 h, 2 h and 3 h after exercise compared to baseline (Fig. 1).
A significant effect for exercise-intensity was detected for peak post-exercise H$_2$O$_2$ (p = 0.02) and catalase activity (p = 0.05). Specifically, there was greater peak H$_2$O$_2$ after both SIE (∼40%) and HIIE (∼24%) compared to CMIE; and greater peak catalase activity after SIE (∼52%) compared to CMIE (Fig. 2). No significant effects for exercise intensity were detected for peak TBARS or SOD activity (p = 0.41 and p = 0.26, respectively).

Pearson’s correlation coefficient indicated a significant positive correlation between plasma catalase activity and skeletal muscle p38 MAPK phosphorylation 3 h after exercise (Table 1). No other significant correlations were detected (all p > 0.05, Table 1).

4. Discussion

We report that a single session of SIE elicited greater post-exercise plasma catalase activity compared to HIIE and CMIE, and greater peak post-exercise H$_2$O$_2$ compared to CMIE. Furthermore, SIE elicited a similar decrease in plasma SOD activity and TBARS as CMIE and HIIE, despite consisting of significantly less total work. Importantly, apart from p38 MAPK and catalase activity at 3 h post-exercise, alterations in post-exercise plasma redox status did not adequately reflect post-exercise skeletal muscle redox-sensitive protein signaling.

The effects of acute continuous aerobic exercise on systemic redox status has received considerable attention over the past few decades. In contrast, despite increased popularity, the effects of SIE and HIIE on systemic redox status are less clear. Nevertheless, previous reports indicate that three weeks of SIE training in healthy humans upregulates systemic antioxidant defenses, including catalase activity, and attenuates markers of systemic oxidative stress. Even a single session of acute SIE is reported to elicit a transient increase in markers of systemic antioxidant activity and oxidative stress which can last for up to 48 h post-exercise. Few studies have directly compared the effects of SIE, HIIE, and CMIE, on post-exercise redox status. Previously reported that low-volume HIIE (10 × 1 min at 80% VO$_{2\text{max}}$) increases plasma lipid peroxidation and decreases protein carbonyls in untrained males to a similar extent as work-matched high-intensity (20 min @ 80% VO$_{2\text{max}}$) and moderate-intensity continuous cycling protocols (27 min @ 60% VO$_{2\text{max}}$). However, redox status was only measured up to 30 min post-exercise, a time-period which may not reflect peak plasma oxidative stress and antioxidant activity. We extend previous findings by demonstrating that in healthy
Despite factor (D) to H2O2 compared catalase activity, which finds Pearson’s total correlation coefficients and support homeostasis activity in CMIE. Table findings are p < 0.05). Exercise-induced oxidative stress and antioxidant activity. Plasma hydrogen peroxide (A), TBARS (B), catalase activity (C), and SOD activity (D), after high-intensity interval exercise (HIIE), sprint interval exercise (SIE), and continuous moderate-intensity exercise (CMIE). Significantly different (p < 0.05) compared to CMIE and HIIE. Symbols in parenthesis are p < 0.1. SOD: superoxide dismutase activity. TBARS: thiobarbituric acid reactive substances.

Fig. 2. Exercise-induced changes in peak plasma oxidative stress and antioxidant activity. Plasma hydrogen peroxide (A), TBARS (B), catalase activity (C), and SOD activity (D), after high-intensity interval exercise (HIIE), sprint interval exercise (SIE), and continuous moderate-intensity exercise (CMIE). Significantly different (p < 0.05) compared to #-CMIE and †-HIIE. Symbols in parenthesis are p < 0.1. SOD: superoxide dismutase activity. TBARS: thiobarbituric acid reactive substances.

Table 1
Pearson’s correlation coefficients analysis between post-exercise plasma redox status and skeletal muscle redox-sensitive protein signalling.

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Skeletal muscle</th>
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<tbody>
<tr>
<td></td>
<td>Hydrogen peroxide (nmol/ml)</td>
<td>p-p38 MAPK</td>
</tr>
<tr>
<td>Immediately post-exercise</td>
<td>R = 0.08</td>
<td>p-JNK</td>
</tr>
<tr>
<td></td>
<td>p = 0.73</td>
<td>p-NF-κB</td>
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<tr>
<td></td>
<td>TBARS (μM)</td>
<td>R = −0.23</td>
</tr>
<tr>
<td></td>
<td>p = −0.02</td>
<td>p = 0.14</td>
</tr>
<tr>
<td></td>
<td>SOD activity (U ml⁻¹)</td>
<td>R = 0.94</td>
</tr>
<tr>
<td></td>
<td>p = 0.45</td>
<td>p = 0.33</td>
</tr>
<tr>
<td></td>
<td>Catalase activity (U ml⁻¹)</td>
<td>R = 0.18</td>
</tr>
<tr>
<td></td>
<td>p = 0.50</td>
<td>R = 0.02</td>
</tr>
<tr>
<td></td>
<td>Catalase activity (U ml⁻¹)</td>
<td>R = 0.41</td>
</tr>
<tr>
<td></td>
<td>p = 0.50</td>
<td>p = 0.41</td>
</tr>
<tr>
<td>3 h post-exercise</td>
<td>Hydrogen peroxide (nmol/ml)</td>
<td>R = 0.16</td>
</tr>
<tr>
<td></td>
<td>p = 0.47</td>
<td>R = −0.32</td>
</tr>
<tr>
<td></td>
<td>TBARS (μM)</td>
<td>p = 0.23</td>
</tr>
<tr>
<td></td>
<td>R = −0.13</td>
<td>p = 0.38</td>
</tr>
<tr>
<td></td>
<td>SOD activity (U ml⁻¹)</td>
<td>R = 0.23</td>
</tr>
<tr>
<td></td>
<td>p = 0.30</td>
<td>R = −0.35</td>
</tr>
<tr>
<td></td>
<td>Catalase activity (U ml⁻¹)</td>
<td>R = 0.64</td>
</tr>
<tr>
<td></td>
<td>p = 0.10</td>
<td>R = 0.11</td>
</tr>
</tbody>
</table>

SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substance; p38 MAPK, p38 mitogen-activated protein kinases; JNK, c-Jun N-terminal kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; lBeRα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha. Bold values are significant (p < 0.05).

recreationally active individuals, SIE elicits greater post-exercise catalase activity compared to HIIE and CMIE, and greater peak H2O2 compared to CMIE. Low-volume SIE also elicits a similar decrease in post-exercise plasma TBARS and SOD activity. These findings support previous work that has reported exercise intensity to play a larger role in post-exercise plasma redox homeostasis than total work done. Despite consisting of considerably less total work than CMIE and HIIE, SIE effectively elicited alterations in redox homeostasis which have been linked to exercise-induced improvements in cardiometabolic health. However, the protocols in the current study were matched for total exercise session duration. Future research should therefore elucidate whether time-efficient SIE, consisting of much shorter rest periods, is able to elicit a similar post-exercise plasma redox status response compared to HIIE and CMIE.

In addition to the transient increase in allosterically mediated antioxidant activity, acute exercise also elicits increased gene expression, protein synthesis and subsequent upregulation
of endogenous antioxidant buffering systems. The increase in antioxidant activity and upregulation of systemic endogenous antioxidant defense through regular exercise plays an important role in attenuating chronic systemic oxidative stress and improving cardiometabolic health. For example, greater plasma total antioxidant capacity 16–18 h after acute HIIE is associated with greater improvements in postprandial endothelial function compared to CMIE. Similar findings have also been reported after 12 weeks of HIIE in heart failure patients. Furthermore, a single session of SIE also elicits greater protection against postprandial lipaemia and systemic oxidative stress 24 h later compared to CMIE. As such, alterations in post-exercise systemic redox status may contribute to the often-reported superior systemic cardiometabolic benefits of SIE and HIIE. The mechanisms for greater alterations with post-exercise plasma redox homeostasis following interval exercise are unclear, but may occur through increased mechanical stress in the skeletal muscle and/or increased intermittent cellular metabolic fluctuations. As such, in populations where chronic oxidative stress may persist, the type and/or intensity of exercise may be an important consideration for the prescription of exercise.

In addition to the effects of acute exercise on systemic redox homeostasis, exercise-induced oxidative stress can activate redox-sensitive protein signaling pathways that have previously been linked to exercise adaptation. These pathways include skeletal muscle JNK, p38 MAPK, NF-κB, and Klotho protein signaling, which we have previously reported to increase after acute SIE, HIIE, and CMIE. The systemic increase in exercise-induced oxidative stress is proposed to originate primarily from xanthine oxidase and NADPH oxidase ROS production in skeletal muscle tissue. However, despite reports that redox status biomarkers measured in blood often provide adequate surrogate indicators of tissue redox status including skeletal muscle, their ability to reflect redox-sensitive cellular signaling is unclear and often questioned. To explore this phenomenon we investigated if there were any associations between post-exercise plasma redox status and post-exercise skeletal phosphorylation of JNK, p38 MAPK, NF-κB, and total Klotho protein content (as previously published).

Despite an exercise protocol dependent effect, plasma redox status for the most part did not adequately reflect skeletal muscle phosphorylation of JNK, p38 MAPK, NF-κB, or protein content of Klotho. The only exception was a significant weak to moderate correlation between plasma catalase activity and p38 MAPK phosphorylation 3 h post-exercise. As previously reported, inhibition of p38 MAPK phosphorylation blocks the hydrogen peroxide mediated increase in catalase activity, gene expression and protein synthesis, in V79 fibroblasts. It is possible that plasma catalase activity 3 h post-exercise may reflect its upregulation via the p38 MAPK pathway. However, due to the week correlation, and the finding that catalase activity and p38 MAPK phosphorylation are greater immediately post-exercise compared to 3 h post-exercise, further research is required to confirm the physiological relevance of this finding.

The increase in protein signaling measured after acute exercise may occur through pathways independent of exercise-induced ROS. However, it is unlikely that plasma markers of redox homeostasis are able to predict specific cellular redox signaling as these networks are complex. Specifically, ROS can exert vastly different biological effects depending on the concentration, the type (e.g., hydrogen peroxide versus hydroxyl radical), the exposure time (e.g., acute versus chronic exposure), the cellular source (e.g., membrane bound NADPH oxidase versus mitochondrial electron leak), cell site specificity (e.g., mitochondrial inner membrane versus matrix), and the subcellular localization of redox-sensitive proteins within the cell (e.g., nuclear versus cytosolic).

Many studies rely heavily on the assumption that alterations in plasma redox homeostasis through exercise are reflective of, or are likely to lead to, alterations in redox-sensitive protein signaling. We provide novel evidence that support the hypothesis that common biomarkers of redox status provide little mechanistic value in predicting redox-sensitive protein signaling. In addition to directly measuring downstream redox-sensitive protein signaling pathways, future studies would benefit from adopting modern techniques, such as redox proteomics or fluorescent probing, to establish the “true” redox signaling role of exercise-induced oxidative stress.

5. Limitations

A potential limitation of the study is the combined analysis of both males and females. However, exercise-induced oxidative stress is reported to be similar between sexes. The potential effects of hormone fluctuations on study outcomes were minimized by testing all females in the early follicular phase of the menstrual cycle, and excluding females that were taking oral contraception. Future studies may be required to confirm these findings in both males and females separately. Plasma TBARS, H2O2, catalase and superoxide dismutase activity have been used extensively in previous research to explore plasma oxidative stress and antioxidant activity in humans. As such, the plasma redox status assays adopted provide an appropriate surrogate measure of gross systemic oxidative stress and antioxidant activity. However, redox status biomarkers such as TBARS are non-specific and the antioxidant activity of catalase and SOD primarily exert their antioxidant properties intracellularly. Future research would benefit from employing additional measures of oxidative stress in plasma such as the oxidized/reduced glutathione ratio, F2-isoprostanes, or the direct measurement of ROS through spin trapping and electron spin resonance spectroscopy. Finally, findings in this study are delimited to young recreationally active adults, the specific exercise-protocols, and a single session of exercise. Future research is required to confirm these findings with subsequent bouts of exercise over a longer period of time, in more diverse populations with different exercise protocols and a larger sample size.

6. Conclusion

Despite consisting of less total work, SIE elicited a similar and/or greater post-exercise systemic redox status response compared to HIIE and CMIE. Although systemic redox status is a useful biomarker for assessing overall cardiometabolic health, it does not adequately reflect skeletal muscle post-exercise redox-sensitive protein signaling linked to exercise adaptation.

Practical implications

- Post-exercise redox homeostasis is associated with exercise-induced cardiometabolic health adaptations.
- Low-volume sprint interval exercise elicits greater alterations in post-exercise systemic redox homeostasis compared to high-intensity interval or moderate-intensity continuous cycling exercise.
- Biomarkers of systemic redox homeostasis do not, however, adequately reflect skeletal muscle redox-sensitive protein signaling linked to exercise adaptation.
- Biomarkers of systemic redox homeostasis are a useful tool to assess overall cardiometabolic health, however their capacity to reflect redox-sensitive cellular signaling appears to be limited.
Authors’ contribution

LP, AT, IL, CSS and NS contributed to the study design and acquisition of ethical approval. LP, AT, IL, CSS and NS contributed to data collection. LP analyzed the data, interpreted the data, and drafted the initial manuscript. The remaining authors critically revised the manuscript. All authors approved the final version of the manuscript. NS and LP are guarantors of the manuscript and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. External funding agents did not have a role in in the collection of data, their analysis and interpretation, and in the right to approve or disapprove publication of the finished manuscript.

Acknowledgments

A/Prof Levinger was supported by Future Leader Fellowship (ID: 100040) from the National Heart Foundation of Australia. A/Prof Nigel Stepto is supported by the Australian Governments Collaborative Research Network. The project was part funded by a start-up grant (Nigel Stepto, Itamar Levinger, Chris Shaw and Lewan Parker) from the Australian Governments Collaborative Research Network.

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