Modelflow underestimates cardiac output in heat-stressed individuals

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1Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, Texas; 2Department of Environmental and Life Sciences, Nara Women’s University Graduate School of Humanities and Sciences, Nara, Japan; 3Departments of Biomedical Sciences and Specialty Medicine, Ohio University College of Osteopathic Medicine, Athens, Ohio; 4Department of Anesthesia, Rigshospitalet, University of Copenhagen, Denmark; and 5Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

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Shibasaki M, Wilson TE, Bundgaard-Nielsen M, Seifert T, Secher NH, Crandall CG. Modelflow underestimates cardiac output in heat-stressed individuals. Am J Physiol Regul Integr Comp Physiol 300: R486–R491, 2011. First published November 17, 2010; doi:10.1152/ajpregu.00505.2010.—An estimation of cardiac output can be obtained from arterial pressure waveforms using the Modelflow method. However, whether the assumptions associated with Modelflow calculations are accurate during whole body heating is unknown. This project tested the hypothesis that cardiac output obtained via Modelflow accurately tracks thermodilution-derived cardiac outputs during whole body heat stress. Acute changes of cardiac output were accomplished via lower-body negative pressure (LBNP) during normothermic and heat-stressed conditions. In nine healthy normotensive subjects, arterial pressure was measured via brachial artery cannulation and the volume-clamp method of the Finometer. Cardiac output was estimated from both pressure waveforms using the Modelflow method. In normothermic conditions, cardiac outputs estimated via Modelflow (arterial cannulation: 6.1 ± 1.0 l/min; Finometer 6.3 ± 1.3 l/min) were similar with cardiac outputs measured by thermodilution (6.4 ± 0.8 l/min). The subsequent reduction in cardiac output during LBNP was also similar among these methods. Whole body heat stress elevated internal temperature from 36.6 ± 0.3 to 37.8 ± 0.4°C and increased cardiac output from 6.4 ± 0.8 to 10.9 ± 2.0 l/min when evaluated with thermodilution (P < 0.001). However, the increase in cardiac output estimated from the Modelflow method for both arterial cannulation (2.3 ± 1.1 l/min) and Finometer (1.5 ± 1.2 l/min) was attenuated compared with thermodilution (4.5 ± 1.4 l/min, both P < 0.01). Finally, the reduction in cardiac output during LBNP while heat stressed was significantly attenuated for both Modelflow methods (cannulation: −1.8 ± 1.2 l/min, Finometer: −1.5 ± 0.9 l/min) compared with thermodilution (−3.8 ± 1.19 l/min). These results demonstrate that the Modelflow method, regardless of Finometer or direct arterial waveforms, underestimates cardiac output during heat stress and during subsequent reductions in cardiac output via LBNP.

hyperthermia; lower body negative pressure; blood pressure

AN INCREASING NUMBER OF STUDIES are using the waveform from the Finometer, and related volume-clamping devices, to estimate cardiac output via the Modelflow approach developed by Wesseling et al. (27). Modelflow estimates aortic flow, and thus stroke volume, via a three-element model using aortic characteristic impedance, arterial compliance, and systemic vascular resistance (27). The accuracy of this methodology has been compared with other cardiac output measurements such as echocardiography, pulse dye-densitometry, and thermodilution during a number of conditions such as orthostatic stress, exercise, and clinical evaluations (3–4, 6, 14, 18, 23, 25). These, and related studies, generally conclude that averaged Modelflow data provide a reliable estimation of the changes in cardiac output to various perturbations. However, each of these comparisons was performed on normothermic subjects.

Heat stress causes pronounced reductions in systemic vascular resistance, due primarily to increases in cutaneous vascular conductance (1). This response is accompanied by increases in vascular resistance in noncutaneous beds such as the renal and splanchnic circulations (15–16, 19–22). In order for arterial pressure to be reliably maintained in the face of large reductions in systemic vascular resistance, cardiac output increases upward to twice that of resting levels (21, 28). Given these pronounced changes, it is unknown whether the assumptions used by the Modelflow to estimate cardiac output are accurate in heat-stressed individuals.

This study tested the hypothesis that the Modelflow methodology accurately estimates cardiac output during heat stress, with thermodilution-derived cardiac outputs being the comparative standard. Because of the possible confounding effect of changes in finger skin blood flow and volume during heat stress in altering the Finometer waveform, Modelflow cardiac outputs were simultaneously obtained from both Finometer and brachial artery catheter waveforms. Finally, the effects of a moderate hypotensive challenge (i.e., lower-body negative pressure; LBNP) on measures of cardiac output were also evaluated while subjects were normothermic and heat stressed.

METHODS

Subjects. Nine healthy male subjects participated in this study; physical characteristics of the subjects were mean age of 29 ± 5 yr, height of 180 ± 5 cm, weight 75 ± 4 kg (mean ± SD). Subjects were not taking medications and were free of any known cardiovascular, metabolic, or neurological diseases and were nonsmokers. Written informed consent was obtained from all subjects before participating in this study. The study procedures and consent were approved by the local ethical Committee of the capital region of Denmark (H-KF-11–090/04).

Instrumentation. Electrocardiogram and skin temperature probes were attached to monitor heart rate and mean skin temperature, respectively. Mean skin temperature was indexed from the weighted average of the six thermocouples (26). Arterial pressure waveforms were obtained from a brachial artery catheter referenced to the midaxillary line, as well as by the volume-clamp method using the Finometer. Cardiac output was measured via the thermodilution technique from a pulmonary artery catheter (Baxter Healthcare, Irvine, CA). Pulmonary artery blood temperature was monitored via a ther-

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mister incorporated into this catheter. Thermodilution-derived cardiac outputs were obtained immediately following acquisition of Finometer and direct arterial pressure waveforms for Modelflow-based cardiac output measures.

Protocol. Upon entering the laboratory (room temperature: 22–23°C), each subject donned a water-perfused suit and was placed in the supine position in an LBNP device. The suit covered the entire body except for the head, one forearm (cannulation arm), hands, and feet. While in this position, a catheter (20 gauge) was inserted in the left brachial artery and was connected to a pressure transducer (Baxter, Uden, the Netherlands) positioned at the midaxillary level. The cuff from the Finometer was attached to a finger of the left hand, which was positioned at the same level as the pressure transducer. A catheter inserted through the basilic vein of the left arm was advanced which was positioned at the same level as the pressure transducer. A foot. While in this position, a catheter (20 gauge) was inserted in the left brachial artery and was connected to a pressure transducer (Baxter, Uden, the Netherlands) positioned at the midaxillary level. The cuff from the Finometer was attached to a finger of the left hand, which was positioned at the same level as the pressure transducer. A catheter inserted through the basilic vein of the left arm was advanced into the pulmonary artery for thermodilution-based cardiac outputs.

While subjects were normothermic, and following an equilibration period, Finometer- and arterial catheter-derived blood pressure waveforms were obtained. Immediately following this period, duplicate or triplicate thermodilution cardiac output measures were obtained via rapid injection of 10 ml iced saline through the pulmonary artery catheter, with these values averaged. The subjects were then exposed to 30 mmHg LBNP. When arterial pressure was stable, Modelflow and thermodilution cardiac output data were obtained again. After release of LBNP, subjects were exposed to whole body heating by increasing the temperature of the water perfusing the suit. Once internal temperature was elevated by at least 1°C, and after an equilibration period, cardiac outputs were obtained again. This was followed by subjects again being exposed to 30 mmHg LBNP, during which time the final set of cardiac outputs were measured.

For each condition, mean arterial pressure was obtained by integrating the waveform from the brachial artery catheter, whereas average Modelflow cardiac outputs were obtained during a 2-min period and compared with subsequent thermodilution-derived cardiac outputs. Modelflow-derived cardiac outputs from the Finometer were calculated online, whereas arterial catheter-derived cardiac outputs were calculated offline using the same technology as Modelflow (i.e., Beatscope software; Finapres Medical Systems, Arnhem, Netherlands).

Data analysis. Data were sampled at 100 Hz by a data acquisition system (MP150; Biopac). Student’s paired t-tests were used to identify the effect of heat stress on thermal and hemodynamic responses. Pre-LBNP cardiac outputs were statistically analyzed via two-way repeated-measures ANOVA with main factors of thermal condition (normothermia and heat stress) and device (thermodilution, Finometer Modelflow, and arterial cannulation Modelflow). The reduction in cardiac output to LBNP was also analyzed via two-way repeated-measures ANOVA also with main factors of thermal condition and device. Post hoc analyses were performed if a significant main effect or interaction was identified. The level of agreement and confidence intervals between cardiac outputs obtained via the respective Modelflow methods and thermodilution were also evaluated via Bland-Altman plots. In addition, a Pearson correlation analysis was performed between thermodilution and the respective Modelflow cardiac output techniques. The α-level for all statistical analyses was set at 0.05. Unless otherwise noted, results are reported as means ± SD.

RESULTS

Heat stress increased mean skin temperature from 34.9 ± 0.2 to 37.7 ± 0.4°C, resulting in an increase in pulmonary artery blood temperature from 36.6 ± 0.2 to 37.8 ± 0.3°C (P < 0.01 for both variables). This thermal stress increased heart rate (60 ± 11 to 89 ± 11 beats/min; P < 0.01) and decreased catheter-derived mean arterial pressure (90 ± 8 to 81 ± 7 mmHg; P < 0.01) before the onset of LBNP. While normothermic, application of LBNP did not change mean arterial pressure but increased heart rate by 7.9 ± 6.4 beats/min, whereas, while heat-stressed, LBNP reduced mean arterial pressure by 8.3 ± 5.7 mmHg and increased heart rate by 22.0 ± 13.9 beats/min (P < 0.05). Stroke volume was not different between methodologies while subjects were normothermic (P = 0.41). Likewise, the subsequent reduction in stroke volume to LBNP was not different between methodologies (P = 0.40). However, while heat-stressed, stroke volume was significantly greater when obtained by thermodilution (123 ± 28 ml) relative to Finometer (87 ± 14 ml) and arterial catheter

![Fig. 1. Bland-Altman plots comparing cardiac output measured by thermodilution and Modelflow from arterial cannulation (top) and Finometer (bottom) before and during lower-body negative pressure (LBNP) in normothermic subjects. The plots indicate relatively good agreement between the methods regardless of the perturbation (before and during LBNP) and the source of the arterial waveform (i.e., catheterization or Finometer). Black lines depict mean bias and ± 2 SD for the pre-LBNP period, whereas the gray lines depict these values during LBNP.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00602.2010)
Cardiac output. Similar to previous studies (3–4, 6, 14, 18, 23, 25), mean normothermic cardiac output values estimated via Modelflow from direct arterial catheterization (6.1 ± 1.0 l/min) and the Finometer (6.3 ± 1.3 l/min) were similar to cardiac outputs estimated via thermodilution (6.4 ± 0.8 l/min). The Bland-Altman plots (Fig. 1) reveal that, independent of the comparative devices and inclusive of LBNP, the mean difference between cardiac outputs was close to zero with a 95% confidence interval being <2 l/min around the mean difference. Application of LBNP significantly decreased cardiac output (Fig. 2), and the reduction to LBNP was similar among these three devices (thermodilution: 1.5 ± 0.5 l/min, Finometer: 1.3 ± 0.9 l/min, and catheterization: 1.2 ± 0.7 l/min). The correlation coefficients between thermodilution and Modelflow estimates of cardiac output during all perturbations while normothermic (i.e., inclusive of baseline and normothermic LBNP) were 0.79 (Finometer) and 0.65 (catheterization).

Whole body heating increased cardiac output regardless of methodology (thermodilution: 6.4 ± 0.8 to 10.9 ± 2.0 l/min, Finometer: 6.3 ± 1.3 to 7.8 ± 1.4 l/min, and catheterization: 6.1 ± 1.0 to 8.4 ± 1.0 l/min, all P < 0.01); however, the magnitude of increase in thermodilution cardiac output was at least twice the increase in Modelflow-derived cardiac outputs, regardless of the source of the pressure waveform (Fig. 3). The subsequent reduction in thermodilution cardiac output during LBNP was greater relative to that from either Modelflow method, although LBNP decreased cardiac output for all three methods (Fig. 4, both P < 0.01). The heat stress Bland-Altman plot (pre-LBNP) revealed a mean bias of 2 l/min regardless of the comparative methods (Fig. 5). During LBNP while heat stressed, that bias was reduced close to zero, but this smaller bias occurred due to larger decreases in thermodilution measures of cardiac output coupled with relatively smaller decreases in Modelflow measures (see Fig. 4). The 95% confidence intervals around the mean for the Bland-Altman plots for both heat stress with and without LBNP were approximately twice that observed when subjects were normothermic (see Fig. 1). The correlation coefficient between thermodilution and Modelflow estimates of cardiac output during all perturbations while heat stressed (i.e., inclusive of baseline heat stress and heat stress LBNP) were 0.64 (Finometer) and 0.77 (catheterization).

Tables 1 and 2 illustrate the percent of observations where differences in cardiac output between thermodilution and either Modelflow approaches were <0.5, 1, and 2 l/min for normothermia, normothermia + LBNP, heat stress, heat stress +
LBNP, and for all data combined within each thermal condition. Particularly noticeable is the large percentage of observations (i.e., >50%) where differences in cardiac output between Modelflow and thermodilution were >2 l/min while subjects were heat stressed.

**DISCUSSION**

When subjects were normothermic, Modelflow estimations of cardiac output, for both the Finometer and direct catheterization, were similar relative to thermodilution-derived cardiac outputs. In addition, normothermic LBNP decreased cardiac output similarly for all three measurement approaches (Figs. 1 and 2), which is consistent with previous studies (4, 14). As shown in the Bland-Altman plot (Fig. 1), there was a relatively good agreement between Modelflow estimation of cardiac output and thermodilution-derived cardiac output while subjects were normothermic, although the 95% confidence interval was upward to 2 l/min. During heat stress, Modelflow estimates of cardiac output, as well as the subsequent reduction in cardiac output with LBNP, were significantly attenuated when compared with thermodilution-derived cardiac outputs (Figs. 3 and 4). Equally poor responses, for both mean differences and 95% confidence intervals, were observed in the heat stress Bland-Altman plots (Fig. 5).

At the onset of the study, it was reasoned that digit cutaneous vasodilation, coupled with possible increases in cutaneous venous volume, during the heat stress may alter the arterial pressure waveform resulting in inaccuracies in Modelflow-derived cardiac outputs from the Finometer. In contrast to that hypothesis, cardiac output calculated from the brachial artery pressure waveforms also underestimated thermodilution cardiac output. This observation strongly indicates that the inaccuracies of Modelflow to estimate cardiac output in heat-stressed subjects are unrelated to cutaneous vasodilation of the digit. However, we cannot rule out a possible effect of heat stress on the Finometer-derived waveform given that cardiac output responses from the Finometer tended to be lower relative to thermodilution.

**Table 1.** Percentage of observations where differences in cardiac outputs between thermodilution and Modelflow (via Finometer) were >0.5, 1, and 2 l/min

<table>
<thead>
<tr>
<th>Thermodilution vs. Modelflow-Finometer</th>
<th>&gt;0.5 l/min</th>
<th>&gt;1 l/min</th>
<th>&gt;2 l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermia</td>
<td>78</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Normothermia LBNP</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heat stress</td>
<td>100</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>Heat stress LBNP</td>
<td>89</td>
<td>56</td>
<td>33</td>
</tr>
<tr>
<td>Normothermia (combined baseline and LBNP)</td>
<td>50</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Heat stress (combined baseline and LBNP)</td>
<td>94</td>
<td>78</td>
<td>44</td>
</tr>
</tbody>
</table>

**Table 2.** Percentage of observations where differences in cardiac outputs between thermodilution and Modelflow (via arterial cannulation) were >0.5, 1, and 2 l/min

<table>
<thead>
<tr>
<th>Thermodilution vs. Modelflow-Arterial Cannulation</th>
<th>&gt;0.5 l/min</th>
<th>&gt;1 l/min</th>
<th>&gt;2 l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermia</td>
<td>77</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Normothermia LBNP</td>
<td>56</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Heat stress</td>
<td>89</td>
<td>78</td>
<td>56</td>
</tr>
<tr>
<td>Heat stress LBNP</td>
<td>89</td>
<td>56</td>
<td>22</td>
</tr>
<tr>
<td>Normothermia (combined baseline and LBNP)</td>
<td>67</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Heat stress (combined baseline and LBNP)</td>
<td>89</td>
<td>67</td>
<td>39</td>
</tr>
</tbody>
</table>
tive to direct cannulation-derived cardiac outputs. Nevertheless, the primary source of the error resulting in inaccurate cardiac outputs by Modelflow in heat-stressed subjects is most likely inherent to assumptions associated with Modelflow algorithms that may be altered by heat stress.

Modelflow estimates of stroke volume are based upon a three-element model, corresponding to the characteristic impedance of the aorta, total arterial compliance, and systemic vascular resistance. Subjects’ age and sex, based upon the work of Langewouter et al. (12), are included in the calculation of aortic characteristic impedance. Furthermore, it is assumed that aortic impedance for a given subject is not changed by an applied perturbation. Thus, if heat stress alters aortic impedance and/or other related variables, it seems reasonable that the Modelflow would not accurately estimate cardiac output. Such possibility could be an effect of nitric oxide. Heat stress causes pronounced increases in cardiac output, which may increase shear stress resulting in increased nitric oxide formation from large conduit arteries (e.g., the aorta), as well as possibly from the skin (8–10, 24). Nitric oxide alters arterial elasticity in the human brachial artery (11) and thus has the potential to affect aortic impedance and compliance (5), both of which are critical in the Modelflow calculation of stroke volume and are assumed to not change by experimental conditions. Although speculative, it may therefore be that heat stress changes aortic characteristics resulting in change in impedance and compliance, perhaps through nitric oxide, resulting in underestimation of cardiac output via the Modelflow.

Similar to the present findings, Dyson et al. (3) recently showed that Modelflow underestimated stroke volume upon reductions in systemic vascular resistance via systemic infusions of isoproterenol. Likewise, Jellema et al. (7) reported elevated thermodilution cardiac outputs, relative to Modelflow-derived cardiac outputs (precalibration comparison), in septic shock patients that often have reduced systemic vascular resistance. Given that whole body heat stress likewise decreases systemic vascular resistance (1–2), perhaps it is not surprising that, while heat stressed, Modelflow-derived cardiac outputs underestimated thermodilution-derived cardiac outputs.

The assumption of this protocol is that thermodilution provides an accurate estimation of cardiac output under both normothermic and heat-stressed conditions. The difference between blood and injectate temperatures is an important determinant in the thermodilution calculation of cardiac output. With the system used in the present study, the temperature of the injectate is measured via a thermistor residing between a thermistor port associated with heat stress. Second, in clinical settings, thermodilution cardiac outputs are routinely obtained in febrile patients whose increases in internal temperatures are more than double what was imposed in the present protocol. Finally, it is important to emphasize that the observed increases in thermodilution-derived cardiac output in the present study are consistent with the findings of others using techniques such as dye dilution (21), soluble gas rebreathing (15), and magnetic resonance imaging (17) at comparable increases in body temperature. Together, these observations strongly suggest that thermodilution-derived cardiac outputs are an appropriate measure by which to compare Modelflow-derived cardiac outputs in heat-stressed individuals.

Only male subjects participated in this study. It remains unclear whether Modelflow similarly underestimates cardiac output in female subjects during heat stress, with and without LBNP. Because sex differences are critical factors in cardiovascular research, future studies are required to identify whether the observed responses are consistent in females.

In conclusion, the present data confirm prior findings that Modelflow, regardless of whether the source of the waveform is from the Finometer or direct arterial catheterization, appropriately tracks cardiac output in normothermic subjects and during moderate gravitational stress via 30 mmHg LBNP. However, in the heat-stressed condition, regardless of the source of the arterial waveform, Modelflow-derived cardiac output was significantly lower compared with thermodilution cardiac output. Moreover, the reduction in Modelflow-derived cardiac output during LBNP in heat-stressed subjects was ~50% less than the reduction in cardiac output identified via thermodilution. Based upon these findings, caution should be taken when evaluating Modelflow-derived cardiac outputs in heat-stressed individuals.

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GRANTS

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DISCLOSURES

No conflicts of interest are declared by the authors.

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