IS RESPIRATION-INDUCED VARIATION IN THE PHOTOPLETHYSMOSMGRAM ASSOCIATED WITH MAJOR HYPOVolemIA IN PATIENTS WITH ACUTE TRAUMATIC INJURIES?

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ABSTRACT—It has been widely accepted that metrics related to respiration-induced waveform variation (RIWV) of the photoplethysmogram (PPG) have been associated with hypovolemia in mechanically ventilated patients and in controlled laboratory environments. In this retrospective study, we investigated if PPG RIWV metrics have diagnostic value for patients with acute hemorrhagic hypovolemia in the prehospital environment. Photoplethysmogram waveforms and basic vital signs were recorded in trauma patients during prehospital transport. Retrospectively, we used automated algorithms to select patient records with all five basic vital signs and 45 s or longer continuous, clean PPG segments. From these segments, we identified the onset and peak of individual heartbeats and computed waveform variations in the beats’ peaks and amplitudes: (1) as the range between the maximum and the minimum (max-min) values and (2) as their interquartile range (IQR). We evaluated their receiver operating characteristic (ROC) curves for major hemorrhage. Separately, we tested whether RIWV metrics have potential independent information beyond basic vital signs by applying multivariate regression. In 344 patients, RIWV max-min yielded areas under the ROC curves (AUCs) not significantly better than a random AUC of 0.50. Respiration-induced waveform variation computed as IQR yielded ROC AUCs of 0.65 (95% confidence interval, 0.54–0.76) and of 0.64 (0.51–0.75), for peak and amplitude measures, respectively. The IQR metrics added independent information to basic vital signs (P < 0.05), but only moderately improved the overall AUC. Photoplethysmogram RIWV measured as IQR is preferable over max-min, and using PPG RIWV may enhance physiologic monitoring of spontaneously breathing patients outside strictly controlled laboratory environments.

KEYWORDS—PPG waveform variation, hemorrhage, trauma, prehospital care

INTRODUCTION

Exsanguination is the singularly treatable mechanism of mortality for trauma casualties (1–4), and the earlier hemorrhagic hypovolemia is detected, the greater the opportunity exists for caregivers to administer volume replacement and/or surgically intervene. Recently, it has been suggested that photoplethysmography (PPG), which is a component of routine pulse oximetry, may be useful for detecting hypovolemia and hypotension (5–13). In a set of reports, metrics related to respiration-induced waveform variation (RIWV) of the PPG were associated with hypovolemia and hypotension for mechanically ventilated patients (5–11) and also for spontaneously breathing volunteer subjects during controlled laboratory protocols (12, 13). In these reports, the subjects were either cooperative or sedated, and the environmental conditions were relatively well controlled.

In this study, we examined the relationship between PPG RIWV and hypovolemia in patients transported by air ambulance after major trauma. We had two goals: (1) evaluate the univariate discriminatory value of PPG RIWV metrics for diagnosing hemorrhagic hypovolemia and (2) investigate the potential of PPG RIWV metrics to provide independent information above and beyond basic vital signs. If PPG RIWV metrics can be shown useful for detecting hypovolemia in a prehospital context, these metrics might be applicable to a wide range of clinical arenas in which environmental and physiologic factors are minimally controlled.

MATERIALS AND METHODS

Clinical data collection

This study was based on physiologic data collected from 898 trauma patients during medical helicopter transport between August 2001 and April 2004, from the scene of injury to the level I unit at the Memorial Hermann Hospital in Houston, Tex (14). The data were measured by Propaq 206EL transport monitors (Protocol Systems, Beaverton, Ore), downloaded to an attached personal digital assistant, and ultimately stored in our database (15). The variables consisted of electrocardiogram, PPG, and respiratory waveform signals recorded at 182, 91, and 23 Hz, respectively, and their corresponding monitor-calculated vital signs, recorded at 1-s intervals (heart rate [HR], oxygen saturation of arterial hemoglobin [SpO2], and respiratory rate [RR]). In addition, systolic (SBP), mean, and diastolic (DBP) blood pressures were collected intermittently at multiminute intervals. Attribute data were collected retrospectively via chart review, including demographics, injury descriptions, prehospital interventions, and hospital treatments. There were 100 attribute parameters for each patient, and these data have undergone prior analysis (16–21). Investigational review board approval for the data collection was given by the Memorial Hermann Hospital and the US Army Medical Research and Materiel Command Office of Research Protection, Fort Detrick.
Is Respiration-Induced Variation in the Photoplethysmogram Associated with Major Hypovolemia in Patients with Acute Traumatic Injuries?

Photoplethysmogram waveforms and basic vital signs were recorded in trauma patients during prehospital transport. Retrospectively, we used automated algorithms to select patient records with all five basic vital signs and 45 s or longer continuous, clean PPG segments. From these segments, we identified the onset and peak of individual heartbeats and computed waveform variations in the beats' peaks and amplitudes: (1) as the range between the maximum and the minimum (max-min) values and (2) as their interquartile range (IQR). We evaluated their receiver operating characteristic (ROC) curves for major hemorrhage. Separately, we tested whether RIWV metrics have potential independent information beyond basic vital signs by applying multivariate regression. In 344 patients, RIWV max-min yielded areas under the ROC curves (AUCs) not significantly better than a random AUC of 0.50. Respiration-induced waveform variation computed as IQR yielded ROC AUCs of 0.65 (95% confidence interval, 0.54Y0.76) and of 0.64 (0.51Y0.75), for peak and amplitude measures, respectively. The IQR metrics added independent information to basic vital signs (P G 0.05), but only moderately improved the overall AUC. Photoplethysmogram RIWV measured as IQR is preferable over max-min, and using PPG RIWV may enhance physiologic monitoring of spontaneously breathing patients outside strictly controlled laboratory environments.
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Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18
Respiratory rate data determined to be reliable by the RR algorithm were
When the HR algorithm identified reliable data, in 97% of the cases,
We also computed the differences between the first quartile and the third
The max-min of the amplitudes was computed in an analogous fashion,
Continuous cleaning waveform segments of 45 s or longer, we then computed the
preceding onset (Fig. 1).
As a predictor of major hemorrhage and mortality, the Revised Trauma
Score (RTS) automatically computed from reliable RR and SBP data was
Reliable SBP, as determined by the blood pressure algorithm, was found
to be statistically superior to unreliable SBP, as a predictor of major
hemorrhage (20).

Inclusion criteria
Patients were selected for analysis based on the availability, within the first
25 min of transport, of (a) 45 s or longer continuous, clean PPG waveform data;
(b) 45 s or longer continuous, non-zero HR, RR, and SpO2 data; and (c) at least
one SBP and DBP measurement. Patients without clean PPG waveform data or
missing any one of the basic vital signs were excluded. Determination of clean
PPG data segments was accomplished using a computer algorithm, which, in
a prior report, yielded a high rate of agreement with human expert review about
whether PPG waveform segments were clean (specifically, whether beats were
deemed to be unambiguously identifiable by the reviewer), although the algo-
rithm’s performance was relatively more conservative, i.e., more specific, about
what data were clean, relative to the human evaluators (22).

PPG waveform processing and measurement of RIWV
For each patient, metrics of PPG RIWV were computed using all contin-
uous clean waveform segments of 45 s or longer that were identified in
the aforementioned analysis. In each clean PPG waveform segment, we identified
the onset and peak locations for each beat, using an automated computer
algorithm that has been previously reported (23). The algorithm identifies
PPG peaks as local maximal positions on the PPG waveform, and beat onsets
as the nearest minimal position preceding each corresponding peak. Each
beat’s amplitude is defined as the difference in heights between a peak and its
preceding onset (Fig. 1).
After identifying the peaks, onsets, and amplitudes of each beat in all
continuous clean waveform segments of 45 s or longer, we then computed the
investigative PPG metrics.

First, we computed the difference between the maximum and the minimum
(max-min) of the peak heights of all beats within a moving 45-s window
and advanced the time window 15 s at a time within the clean PPG seg-
ments. We then averaged the max-min values over all time windows in the
25-min data record that contained clean PPG waveform data.
The max-min of the amplitudes was computed in an analogous fashion,
using a moving 45-s window and then averaging the max-min results from
all eligible windows of each patient record.
We also computed the differences between the first quartile and the third
quartile values (the interquartile range [IQR]) for both the peak heights and
the amplitudes within a moving 45-s window and then averaged the results
from all eligible windows of each patient record.

Calculation of basic vital signs
For each of the five basic vital signs (HR, RR, SpO2, SBP, and DBP), we
computed the average parameter value within the initial 25 min of data
collection using the most reliable vital-sign measurements and excluding from
calculation the less reliable data. Reliability was determined by automated algo-
rithms that have been previously validated, which rate each vital-sign datum
as less reliable or reliable. If the ROC AUC was significantly greater than 0.50. As a basis for inter-
preting the results, we also computed the ROC AUC of HR and SBP.
We also tested if the PPG metrics were correlated with the number of
PRBC units transfused in the first 24 h.

Univariate analysis—The diagnostic performances of the investigational
PPG metrics were evaluated by constructing the receiver operating charac-
teristic (ROC) curves and calculating the area under the curve (AUC) for each
ROC curve. We used the ROCKIT freeware (University of Chicago, available at:
http://aybbsd.uchicago.edu/k/krl_roc/software/index.htm) for these
analyses (24). ROCKIT assumes a binormal ROC model, i.e., data for each
of the decision outcomes (hemorrhage versus control) are considered to be
normally distributed and the ROC parameters can be estimated based on the
model assumption. The ROC curves calculated by this method are smoother
than empirically evaluated ROC curves and can better represent the rela-
tionship between vital-sign variables and decision outcomes (24, 25).
Using ROCKIT, we tested if each ROC was significantly different from chance, i.e.,
if the ROC AUC was significantly greater than 0.50. As a basis for inter-
preting the results, we also computed the ROC AUC of HR and SBP.

Statistical methods
For each patient, metrics of PPG RIWV were computed using all contin-
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preting the results, we also computed the ROC AUC of HR and SBP.
We also tested if the PPG metrics were correlated with the number of
PRBC units transfused in the first 24 h.

Multivariate regression analysis—We used a linear multivariate regression
routine “stepwisefit” in MATLAB (version 7.0; The MathWorks, Natick,
Mass) to compare the discriminatory power of models with and without each
investigational PPG metric, in addition to the five basic vital signs (i.e.,
HR, RR, SpO2, SBP, and DBP). The routine uses an F statistic to evaluate
additional discriminatory power provided by the investigative PPG metric and
decides whether the PPG metric should be included based on a significance
threshold of P < 0.05.

In theory, prehospital fluids might obscure PPG RIWV in patients with
major hemorrhage. To study if prehospital fluid administration was a major
determinant of PPG metrics, we (a) computed the correlation between pre-
hospital fluid volume and PPG RIWV metrics and (b) tested if both PPG
metrics and fluid volume were independently correlated with major hemor-
hage, in a multivariate regression model.
RESULTS

The study population was similar to the total population in sex, age, injury type, and rates of major respiratory intervention and major hemorrhage, but with lower rates of mortality and prehospital intubation (Table 1). The investigative IQR PPG metrics generated ROC AUCs of 0.64 or greater, significantly greater than 0.50 (Table 2). The two max-min metrics generated nonsignificant discriminatory power, with ROC AUC 95% confidence intervals (CIs) for the AUCs spanning 0.50.

The PPG metrics were weakly correlated with the PRBC transfusion requirement. For instance, the correlation (r) between PPG peak height IQR versus the units of PRBCs transfused was 0.14 (P < 0.01) for all patients. Looking exclusively at the 26 patients with one or more unit of PRBC, there was a trend toward higher correlation, r = 0.39, but because there were fewer patients, this was not a significant finding (P = 0.06).

The two IQR PPG metrics were both significant independent correlates (P < 0.01) of major hemorrhage in a multivariate regression model that also included all five basic vital signs (Table 3). However, per ROCKIT, the resultant improvements in ROC AUC (by +0.02 and +0.03, when either one of the two metrics was separately added to a linear model that also included all five basic vital signs) were not significant. Moreover, adding them into the linear model did not further improve the ROC AUC. These two IQR PPG metrics correlated significantly with each other (correlation coefficient = 0.80, P < 0.0001).

Based on the Youden (26) criterion, the peak height IQR metric had an optimal univariate sensitivity of 0.54 and a specificity of 0.73 (Fig. 2, left and right panels, line a). The five

### Table 1. Demographics of the study and the overall population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall database</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size, n</td>
<td>898</td>
<td>344</td>
</tr>
<tr>
<td>Male</td>
<td>660* (73%)</td>
<td>266 (77%)</td>
</tr>
<tr>
<td>Female</td>
<td>234* (26%)</td>
<td>78 (23%)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>37 (16†)</td>
<td>37 (15†)</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>778 (87%)</td>
<td>308 (90%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>94 (10%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Prehospital intubated</td>
<td>201 (22%)</td>
<td>55 (16%)</td>
</tr>
<tr>
<td>Major respiratory intervention‡</td>
<td>102 (11%)</td>
<td>30 (9%)</td>
</tr>
<tr>
<td>Major hemorrhage§</td>
<td>94 (10%)</td>
<td>26 (8%)</td>
</tr>
</tbody>
</table>

We excluded 399 patients because they had no suitable PPG waveform data available, 121 because they received blood transfusion without an explicitly hemorrhagic injury, and 34 because they had one or more of the other basic vital signs unavailable; see text for further details of the exclusion criteria.

*Four patients had no assigned sex in the total population.
†SD.
‡Received major respiratory lifesaving interventions in the hospital, i.e., endotracheal intubation or chest tube insertion.
§Received blood transfusion in the hospital and also had documented injuries that were consistent with major hemorrhage.

### Table 2. Univariate analysis of the association between four PPG metrics (1–4), HR (5), and SBP (6) with major hemorrhage

<table>
<thead>
<tr>
<th>No.</th>
<th>PPG metric</th>
<th>Control, mean (SD)</th>
<th>Hemorrhage, mean (SD)</th>
<th>Student t test P</th>
<th>ROC AUC* (CI†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak height max-min</td>
<td>101 (42)</td>
<td>115 (38)</td>
<td>NS</td>
<td>0.60 (0.48–0.71)</td>
</tr>
<tr>
<td>2</td>
<td>Amplitude max-min</td>
<td>76 (40)</td>
<td>85 (40)</td>
<td>NS</td>
<td>0.57 (0.45–0.68)</td>
</tr>
<tr>
<td>3</td>
<td>Peak height IQR</td>
<td>24 (12)</td>
<td>31 (14)</td>
<td>0.01</td>
<td>0.65 (0.54–0.76)</td>
</tr>
<tr>
<td>4</td>
<td>Amplitude IQR</td>
<td>15 (7)</td>
<td>19 (8)</td>
<td>0.01</td>
<td>0.64 (0.51–0.75)</td>
</tr>
<tr>
<td>5</td>
<td>HR</td>
<td>92 (18) bpm</td>
<td>100 (19) bpm</td>
<td>0.048</td>
<td>0.62 (0.50–0.73)</td>
</tr>
<tr>
<td>6</td>
<td>SBP</td>
<td>134 (22) mmHg</td>
<td>115 (23) mmHg</td>
<td>&lt;0.001</td>
<td>0.75 (0.65–0.84)</td>
</tr>
</tbody>
</table>

*ROC AUC computed by the ROCKIT software (University of Chicago).
†95% confidence interval.
NS indicates not statistically significant.
basic vital signs had an optimal sensitivity of 0.77 and specificity of 0.76 (Fig. 2, right panel, line b). The optimal point for the multivariate model that included the peak height IQR metric and the basic vital signs yielded a sensitivity of 0.73 and a specificity of 0.82 (Fig. 2, right panel, line c). The amplitude IQR metric yielded similar results.

In our data set, patients with major hemorrhage received more total prehospital fluid than control patients (median, 850 [IQR, 500–1,200] mL and 250 [IQR 100–500] mL, respectively). However, total volume of prehospital fluid was not correlated with PPG metrics \((P > 0.05)\) for neither hemorrhage patients nor control patients. In multivariate regression, PPG metrics and prehospital fluid volume were both independently associated with major hemorrhage \((P < 0.01\) for both). Therefore, administration of prehospital fluids did not seem to alter the utility of PPG RIWV for identifying patients with major hemorrhage.

**Sensitivity analyses**

We verified that PPG RIWV metrics had relatively stable diagnostic performances even when we explored alternative analysis methodologies (Table 4). Exclusion of mechanically ventilated patients did not significantly change the ROC AUCs \((changing by +0.01 and −0.02)\). When we selected cases and controls with longer and cleaner PPG segments, fewer patients were available, whereas, conversely, selecting for shorter and less clean PPG segments increased the number of eligible patients. Overall, changing the length of the PPG waveform segments \(i.e., changing our inclusion/exclusion criteria\) did not improve the ROC AUCs. Photoplethysmogram RIWV

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**Table 4. Sensitivity analysis of PPG metrics**

<table>
<thead>
<tr>
<th>No.</th>
<th>Exclusion of ventilated patients</th>
<th>PPG length, s</th>
<th>PPG waveform, % clean</th>
<th>Hemorrhage criteria</th>
<th>Scaled to max amplitude</th>
<th>Population</th>
<th>ROC AUC*</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>No</td>
<td>45</td>
<td>100</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>318</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>45</td>
<td>100</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>270</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>30</td>
<td>100</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>382</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>60</td>
<td>100</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>270</td>
<td>21</td>
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<tr>
<td>4</td>
<td>No</td>
<td>45</td>
<td>90</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>359</td>
<td>28</td>
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<tr>
<td>5</td>
<td>No</td>
<td>45</td>
<td>80</td>
<td>Dx + PRBC</td>
<td>No</td>
<td>397</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>45</td>
<td>100</td>
<td>Dx + 5 PRBC</td>
<td>No</td>
<td>318</td>
<td>10</td>
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<tr>
<td>7</td>
<td>No</td>
<td>45</td>
<td>100</td>
<td>PRBC or 3 L§</td>
<td>No</td>
<td>284</td>
<td>90</td>
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<tr>
<td>8</td>
<td>No</td>
<td>45</td>
<td>100</td>
<td>PRBC</td>
<td>No</td>
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<td>56</td>
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<tr>
<td>9</td>
<td>No</td>
<td>45</td>
<td>100</td>
<td>Dx + PRBC</td>
<td>Yes</td>
<td>318</td>
<td>26</td>
</tr>
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</table>

*P restates the primary analysis and results \(from Table 2\). In analyses 1 to 5, we varied the inclusion criteria: whether ventilated patients were included, the minimal duration of PPG segments analyzed, and the minimal proportion of clean waveform of PPG segments analyzed. Note that when selecting for cases and for controls with longer and cleaner PPG segments, fewer patients are available. In analyses 6 to 8, we varied the definition of our outcome: major hemorrhage: receipt of five or more units of PRBCs and with documented injuries \(massive hemorrhage\), no requirement for explicit documentation of a hemorrhagic injury, and inclusion of patients with 3 L or more in hospital crystalloids. Bold font is used to highlight the different conditions within each group of analysis. In analysis 9, we rescaled the PPG waveform before computing the investigational RIWV metrics; see text for further details.

*ROC AUC computed by the ROCKIT software \(University of Chicago\).

"Documented anatomic injuries \(Dx\)."

*AUC significantly greater than 0.5 \(P < 0.05\).

"Inhospital crystalloid 3 L or more."
metrics were able to identify patients with massive hemorrhage (≥5 U of PRBCs transfused) at least as well as the primary definition. However, alternative definitions of major hemorrhage without requiring formal documentation of a hemorrhagic injury yielded a trend toward reduced ROC AUCs. Rescaling the PPG waveform did not improve the ROC AUCs.

**DISCUSSION**

This study demonstrates that PPG RIWV is associated with hemorrhagic hypovolemia in a minimally controlled clinical arena, i.e., immediately after major mechanism trauma in patients with varying degrees of pain, anxiety, head injury, chest injury, alcohol intoxication, confusion, and so on, although its discriminatory value is not great (ROC AUC generally <0.70). The methodology of using PPG RIWV is appealing because measurement of PPG RIWV is strictly noninvasive, and the necessary instrumentation (in the form of the familiar pulse oximeter) is essentially ubiquitous in most health care environments. Therefore, as an alternative approach for detecting hypovolemia, it would be relatively easy to disseminate. (Indeed, pulse oximeters that display metrics of waveform variation are already commercially available (27).)

Our multivariate analysis suggested that PPG RIWV metrics may be independent predictors of major hemorrhage (P < 0.01) above and beyond SBP, DBP, HR, RR, and SpO2, although the added benefit was incremental (raising the ROC AUC +0.03). Photoplethysmogram RIWV metrics could therefore be useful in conjunction with other vital signs for patient monitoring, perhaps as an input to computerized multiparameter alarm algorithms [such algorithms have been described by Imhoff and Kuhl (28), Chen et al. (17), and Tarassenko et al. (29)].

For our four investigative PPG metrics, we found that AUCs spanned from 0.57 to 0.65 (CIs from 0.45–0.76), which, considering the enormous variability of prehospital patients and their environments, was still somewhat less than what has been reported from an intensive care unit (ICU) setting during mechanical ventilation for the identification of volume-responsive patients (ROC AUC of 0.72) (13). We found that PPG peak height IQR yielded the highest AUC of our investigative metrics and was moderately sensitive (54%) at its optimal threshold, whereas its positive predictive value was less than 20%. These results do not support the use of PPG RIWV metrics for stand-alone hemodynamic monitoring. However, when PPG RIWV metrics are distinctly elevated, it would be prudent to carefully evaluate the patient, just as prudence is appropriate when HR is elevated.

Before this analysis, it was not obvious that PPG RIWV would be associated with hemorrhage in a spontaneously breathing prehospital population. The association between PPG RIWV and volume-responsive states has been mainly documented in mechanically ventilated patients (5–11), where it was found to be an analog of pulsus paradoxus, i.e., respiration-induced variability of arterial blood pressure (7, 30). Because the PPG signal is highly prone to motion artifacts caused by even minor movements of the pulse oximeter probe, an operating room (OR) or ICU is arguably the optimal clinical environment for making PPG measurements, because the patients, sedated or paralyzed, are stationary. Also, mechanical ventilation offers a controllable and consistent respiratory stimulus; in theory, monitoring PPG RIWV might be less effective in spontaneously breathing patients, given their wider range of breathing patterns [respiratory effort is another major determinant of PPG RIWV; e.g., see Rayner et al. (31)]. We are unaware of any prior reports of this association for clinical arenas as poorly controlled as the prehospital air ambulance.

We did find that a suitably clean PPG signal was often unavailable (44%) in our prehospital population, which would limit the clinical usefulness of these PPG metrics in this population. The patients with available PPG data tended to be less sick, versus the overall population (Table 1). For some of the higher-acuity patients, the medics may have fewer opportunities to tend to a noisy PPG signal, or the PPG signal (which is a function of skin perfusion) may have been fainter. Note that novel PPG probe designs, for different anatomic measurement locations, have been described to reliably measure the PPG signal in ambulatory patients (32) or after a mass casualty event (33). Ultimately, enhancement of pulse oximetry instrumentation, to obtain a reliable signal in most patients and to reduce motion artifacts, may be necessary for operational applications involving PPG RIWV metrics in minimally controlled settings.

In the multivariate analysis, PPG RIWV metrics were significant independent predictors of major hemorrhage, even though the increases in ROC AUC were nonsignificant. Nonsignificance can mean that there is no true effect, or it can mean that the effect is too small to be identified, given our sample size. Because the multivariate regression convincingly suggested an independent relationship between PPG RIWV and major hemorrhage (P < 0.01), we interpret our results to mean that there was, in fact, an independent association between PPG RIWV, but its discriminatory power was simply too weak to be identified in our study population.

**Limitations**

It is possible that our findings were dependent on our specific algorithm for measuring RIWV. However, in a prior brief report, we performed a human overread of 4,605 different PPG beats processed by this algorithm and identified only 15 points in which the algorithm incorrectly identified the takeoff or peak of any apparent PPG pulse (23). In this current report, our analysis was made more rigorous by analyzing a minimum of 45 s of data and computing their IQR for two of the investigative metrics. Both these steps made our final results less affected if any individual PPG beats were incorrectly analyzed, i.e., individual outlier beats whose peak or amplitude was incorrectly computed. Another advantage of this automated methodology is that it was entirely objective. Shamir et al. (5) relied on less objective hand measurements of paper recordings of the PPG waveform, whereas Golparvar et al. (6) videotaped the PPG waveform and then measured the investigational PPG metrics in units of pixels of a video display. We contend that, overall, our automated methodology is a strength of our study. Alternative computational methods would probably yield slightly different results, but we argue that it is unlikely that any other computational method would
substantially alter our findings. Our ROC AUCs were only moderately less than those previously reported for detecting hypovolemia in paralyzed, mechanically ventilated intraoperative patients (13).

The second question is if our ROC AUCs results are generalizable beyond the prehospital air ambulance, which may be unique in its incidence of motion, pain, hypothermia, and so on. Broadly speaking, different populations will have different incidences of confounding conditions. For example, a population with more respiratory pathology, e.g., asthma, would presumably have more cases of increased RIWV regardless of intravascular volume (31). Questions about how to best measure the PPG signal in uncontrolled clinical arenas, as well as the generalizability of our results, can be clearly answered only with future, broader clinical studies. We speculate that many clinical arenas (e.g., post–acute-care units, medical-surgical inpatient wards, etc.) will end up yielding ROC AUCs somewhere between our results, which may represent the lower end of clinical control, and AUCs from ICU trials with mechanically ventilated patients [e.g., see Natalini et al. (13)], which represent the highest levels of clinical control.

CONCLUSIONS

In prehospital trauma casualties, a significant univariate association between PPG RIWV and major hemorrhage was found. The ROC AUCs were comparable to that of HR, which suggests that they may have value for monitoring spontaneously breathing patients outside the OR, but not necessarily as a sole monitoring modality. In a multivariate analysis including basic vital signs, PPG RIWV metrics showed significant independent correlations with major hemorrhage. Photoplethysmogram RIWV metrics may enhance novel patient monitoring and automated multiparameter alarm algorithms outside the controlled environment of the OR and ICU.

REFERENCES