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Detection of Hemodynamic Status Using an Analytic Based on an Electrocardiogram Lead Waveform

OBJECTIVES: Delayed identification of hemodynamic deterioration remains a persistent issue for in-hospital patient care. Clinicians continue to rely on vital signs associated with tachycardia and hypotension to identify hemodynamically unstable patients. A novel, noninvasive technology, the Analytic for Hemodynamic Instability (AHI), uses only the continuous electrocardiogram (ECG) signal from a typical hospital multiparameter telemetry monitor to monitor hemodynamics. The intent of this study was to determine if AHI is able to predict hemodynamic instability without the need for continuous direct measurement of blood pressure.

DESIGN: Retrospective cohort study.

SETTING: Single quaternary care academic health system in Michigan.

PATIENTS: Hospitalized adult patients between November 2019 and February 2020 undergoing continuous ECG and intra-arterial blood pressure monitoring in an intensive care setting.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: One million two hundred fifty-two thousand seven hundred forty-two 5-minute windows of the analytic output were analyzed from 597 consecutive adult patients. AHI outputs were compared with vital sign indications of hemodynamic instability (heart rate > 100 beats/min, systolic blood pressure < 90 mm Hg, and shock index of > 1) in the same window. The observed sensitivity and specificity of AHI were 96.9% and 79.0%, respectively, with an area under the curve (AUC) of 0.90 for heart rate and systolic blood pressure. For the shock index analysis, AHI's sensitivity was 72.0% and specificity was 80.3% with an AUC of 0.81.

CONCLUSIONS: The AHI-derived hemodynamic status appropriately detected the various gold standard indications of hemodynamic instability (hypotension, tachycardia and hypotension, and shock index > 1). AHI may provide continuous dynamic hemodynamic monitoring capabilities in patients who traditionally have intermittent static vital sign measurements.

KEY WORDS: artificial intelligence; critical care; decision support systems; heart rate variability; hemodynamic monitoring; machine learning

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Delayed or missed recognition of patient deterioration remains a pervasive challenge for in-hospital care (1, 2). Subsequent failure to act early on patient deterioration and hemodynamic instability can result in care delays, adverse events, unanticipated transfers to higher levels of care, increased lengths of stay, and unexpected deaths (3). The current standard for identifying such instability is based mainly on abnormal vital signs, with several contemporary medical reviews using measures of hypotension (systolic arterial pressure < 90 mm Hg or mean arterial pressure [MAP] < 70 mm Hg) and tachycardia (> 100 beats/min) (4–8). However, monitoring of such vital signs

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DOI: 10.1097/CCE.0000000000000693

has limitations, including intermittent and irregular monitoring frequency, limited accuracy (specifically of noninvasive blood pressure monitoring), and accidental errors when validating vitals and entering data into the electronic medical record (9).

Clinical decision support systems with the ability to perform continuous hemodynamic monitoring to identify patients with abnormal hemodynamic vital signs may help mitigate these limitations. Loss of heart rate variability (HRV) reflects the declining health of the autonomic nervous system and has been used to reflect the state of the cardiovascular system in acute illness and injury (10–15). Changes in HRV have been reported to occur in the setting of sepsis, hemorrhage, respiratory failure, cardiogenic shock, and others, often preceding overt recognition of decompensation in these states (16). However, challenges in signal acquisition, sampling rates, signal noise, and processing of the electrocardiogram (ECG) signal have impeded the ability to leverage HRV for continuous hemodynamic monitoring.

In this study, we evaluated a newly developed HRV analytic specifically designed to address these challenges to determine if continuous HRV monitoring can accurately detect the combination of hypotension and tachycardia without the need for continuous direct measurement of intra-arterial blood pressure. The analytic leverages advanced signal processing and feature extraction of HRV and ECG morphologic features coupled with advanced machine learning that matches changes in HRV and ECG morphology to real-time changes in hemodynamic status (17).

METHODS

Study Setting

This was a pilot retrospective single-center observational cohort study conducted at Michigan Medicine, the University of Michigan's quaternary care academic health system. A waiver of patient consent was granted

by the University of Michigan institutional review board as the study analysis used retrospective de-identified data, approval number HUM00092309.

The HRV analytic is a Food and Drug Administration approved software as a medical device called the Analytic for Hemodynamic Instability (AHI; Fifth Eye, Ann Arbor, MI). The framework of AHI is a continuous analysis of ECG lead II that leverages the known physiologic relationship of HRV, the autonomic nervous system, and the cardiovascular system (17, 18). AHI performs a series of automated analytical steps to extract patterns from the continuous ECG data that reflect the compensatory burden of the autonomic nervous system, which includes signal quality assessment and processing the extracted patterns through a pretrained classification model. AHI embeds HRV complexity measures and ECG morphology analysis into a signal output displayed as a binary classification “Unstable” (tall red bars) or “Stable” (short green bars). Black and gray bars are presented as output below the axis indicating either missing or noisy input ECG data, respectively, which is automatically detected and flagged by the system during real-time processing. The system requires 120 heartbeats of data to generate an initial score that is then updated every 2 minutes (Fig. 1). The HRV complexity and ECG morphology measures captured by AHI have been previously reported (17, 18).

In order to compare AHI's performance to traditional continuous vital sign based measures of hemodynamic instability, we used two different definitions of hemodynamic instability: 1) a composite reference standard of hypotension (MAP < 70 mm Hg or systolic blood pressure [SBP] < 90 mm Hg) and tachycardia (heart rate [HR] > 100 beats/min) and 2) shock index (SI) (≥ 1.0). SI is a measure of hemodynamic instability (HR/SBP), SI with values of 1.0 and greater has been demonstrated to indicate potential hemodynamic instability in the critically ill (19–27). This combination of HR and blood pressure in the calculation of inpatient mortality and adverse outcomes

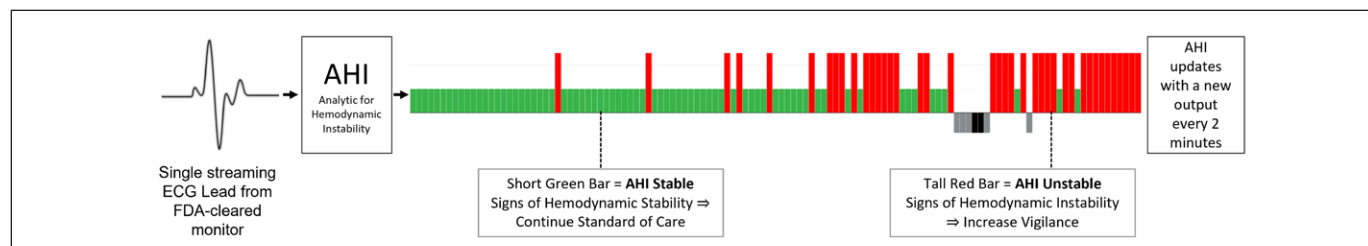


Figure 1. Overview of Analytic for Hemodynamic Instability's (AHI) principle of operation and visual output. ECG = electrocardiogram, FDA = Food and Drug Administration.

for critically ill patients is supported by several widely accepted critical care scoring and early warning systems (EWS) (Modified Early Warning Score [MEWS], National Early Warning Score [NEWS], electronic Cardiac Arrest Risk Triage [eCART]) (28–31). While hemodynamic instability characterized by only tachycardia or only hypotension is certainly possible, many other clinical conditions can cause this, which are unrelated to hemodynamic instability. Therefore, a more robust definition of hemodynamic instability includes the combination of tachycardia and hypotension. The combination indicates both an issue with circulation/perfusion (hypotension) and the burden on the autonomic nervous system through sympathetic activation (tachycardia), which left untreated can lead to compensatory failure and shock (32).

Data Description

The dataset included all consecutive hospitalized patients between November 26, 2019, and February 5, 2020, who had both continuous ECG and invasive arterial blood pressure monitoring in the adult emergency department's emergency critical care center and inpatient ICUs. The University of Michigan's Center for Integrative Research in Critical Care maintains a unique high-resolution physiologic signal collection system capable of storing all continuous physiologic waveform measures. For this study, the following signals were stored and analyzed: ECG lead-II (240 Hz), HR (0.5 Hz), MAP (0.5 Hz), and systolic arterial pressure (0.5 Hz). Demographic and medication information was also obtained from the electronic medical record.

Exclusion criteria were:

- 1) Less than 18 years old,
- 2) Cardiac transplant,
- 3) Ventricular assist device,
- 4) Sustained atrial or ventricular arrhythmia,
- 5) Pacemaker dependent during AHI data collection.

These contraindications were manually assessed through patient chart review by a team of clinical coordinators followed by review and adjudication by the lead physician. Criteria 2–5 are considered contraindications as they adversely impact HRV as a true measure of the autonomic nervous system as it relates to the cardiovascular system. Due to the retrospective nature of the study, 128 patients were excluded due to insufficient data in nursing flow sheets to determine contraindication applicability.

Sample Size Determination

This study was designed to evaluate AHI's classification model outputs based on 5-minute windows of ECG data against continuously monitored HR and blood pressure. The window level comparison uses a reference standard based on the annotation of median continuous vital signs (HR, intra-arterial blood pressure) across eligible (available and noise free) 5-minute windows of patient data versus the output of the AHI algorithm applied to ECG lead II from the same 5-minute window of patient data.

Given that no closed-form solutions are available to account for the within-subject correlation owing to the multiple windows sampled for AHI, simulation methods were used to investigate the sample size and power using the joint confidence region approach and bootstrap methods to calculate the confidence region (33). The simulation study determined that at least 200 subjects were required to achieve at least 90% power to assess whether AHI has acceptable performance relative to the vital signs-based reference standard. The estimates and data distribution characteristics for the simulation power analysis were determined from 3 weeks of preliminary data collected on a similar patient population from Michigan Medicine in order to reflect the intended use population. Note that this preliminary data are independent from the dataset used in the study. All eligible windows of data per patient were used in the study analysis. The distribution of windows across all patients in the analysis has been provided in **Appendix 2.0** (<http://links.lww.com/CCX/A988>).

A window was considered eligible if both AHI's binary classification ("AHI Stable" or "AHI Unstable") and a corresponding valid reference vital sign standard ("Normal" or "Out of Range") were available for that window. A total of 1.4% ($n = 51,482$) of all available windows ($n = 3,784,995$ million) across the eligible patient set ($n = 597$ patients) were flagged as noisy data in the ECG and unable to be interpreted by AHI as "Stable" or "Unstable."

Analysis

AHI is designed for application in real-time continuous monitoring settings and makes a new assessment every 2 minutes using the preceding 5-minute window of ECG data. Given its continuous monitoring nature, the window level analysis was conducted to estimate concordance between AHI's outputs against the above

hemodynamic reference standards and SI, produced using continuous hemodynamic vital signs for each 5-minute window of data (Fig. 2). To mitigate any possible inherent noise in the data used to compute the reference standard or SI for each window, the median values for each vital sign within each corresponding 5-minute window were used; a detailed description of this has been provided in Appendix 1.0 (<http://links.lww.com/CCX/A988>). Data analysis was performed using MATLAB 2019b (Natick, MA) to assess the test characteristics of AHI, in particular sensitivity, specificity, positive predictive value (PPV), negative predictive value, and resulting receiver operator area under the curve (AUC) performance as demonstrated in Figure 2. Additionally, AHI's performance was compared between subgroups of patients with or without vasopressors/inotropes and patients with or without beta-blockers using only the vital signs-based reference standard.

RESULTS

During the study period, data were collected from a total of 852 patients, of which 255 were excluded due to one or more contraindications for AHI use ($n = 142$) or due to certain key data elements not being available to determine contraindications ($n = 128$). In total, 597 patients were included for analysis (Fig. 3).

The mean subject age was 59.1 years with a range from 18 years old to 91 years old and 44.2% female. The racial distribution in the population reflected the distribution of patients generally seen in our health system: 80.1% White, 12.7% African American, 4.9% others, and 2.3% unknown or not reported (Table 1). Table 1 also provides information on the proportion of patients on vasopressors and inotropes as well as beta blockers.

Table 2 shows the window level sensitivity and specificity, relative to the predefined reference standards of hemodynamic instability and SI. For the reference standard analysis, AHI's observed sensitivity was 96.9% and the observed specificity was 79.0% with an AUC of 0.90. For the SI analysis, AHI's observed sensitivity was 72.0% and the observed specificity was 80.3% with an AUC of 0.81.

A subgroup analysis of the impact of cardiac and vasoactive medications on AHI's performance using only HR and SBP as definitions of instability was investigated for both vasopressors/inotropes and beta-blockers using only the reference standard. AHI's performance measures were compared between subgroups of patients with or without vasopressors/inotropes and patients with or without beta-blockers (Table 3).

Approximately 57% of the patients in the Analysis Set ($n = 597$) received vasopressor/inotrope medications while being monitored during their hospital stay and 41% of the patients received beta-blockers. When each of these subgroups were analyzed independently, AHI's performance of sensitivity, specificity, and other related measures for each of these subgroups were found to be consistent and very similar to those seen in the entire analysis (Table 2). Only the PPV shows variation between the subgroups, as this measure is impacted by the variation in the prevalence of windows with out-of-range vital signs within the subgroups (34).

DISCUSSION

Most hospitalized patients who are not at obvious risk of immediate hemodynamic deterioration will have intermittent vital signs monitored and recorded, often with hours between measurements

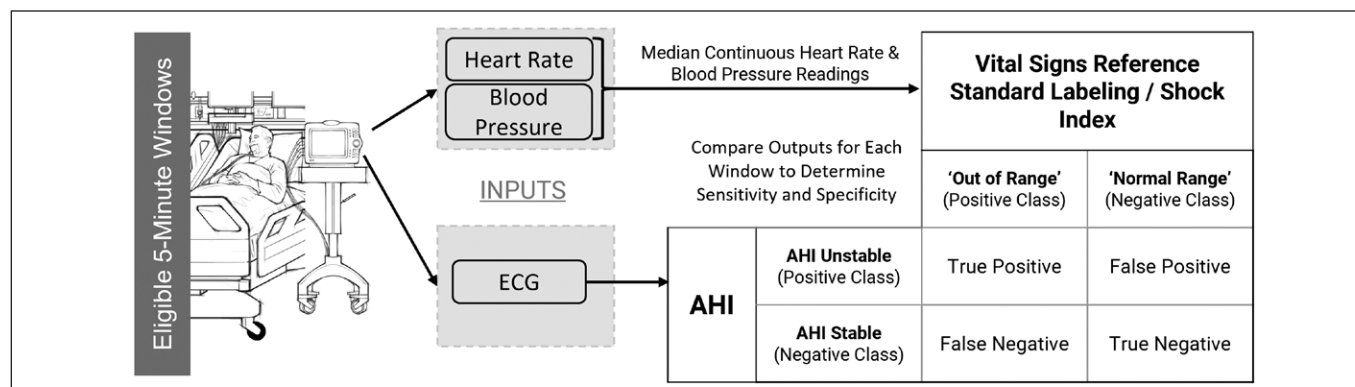


Figure 2. Performance analysis overview, determining sensitivity and specificity based on hemodynamic monitoring and Analytic for Hemodynamic Instability (AHI) output. ECG = electrocardiogram.

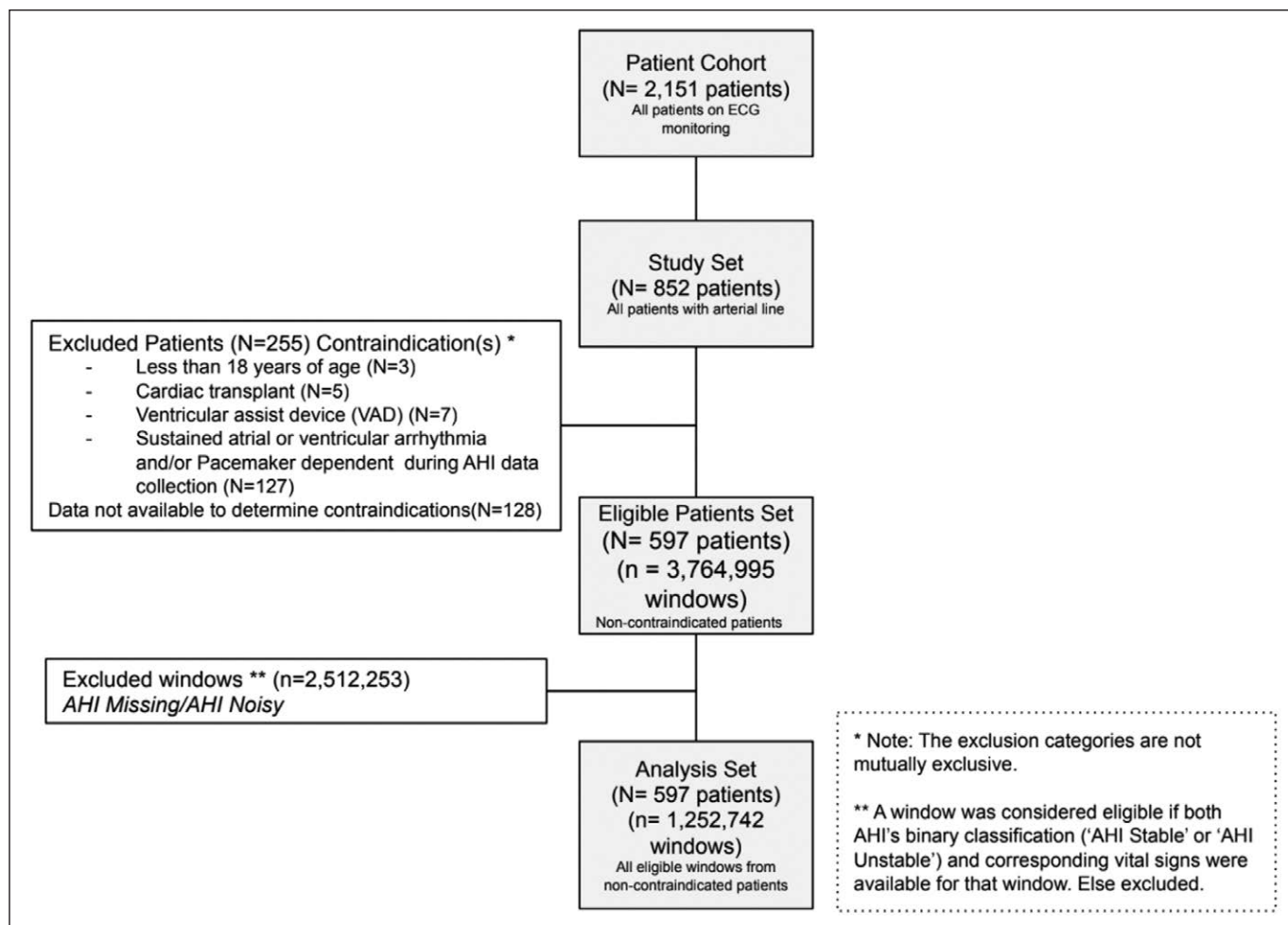


Figure 3. Consort diagram of analyzed dataset. AHI = Analytic for Hemodynamic Instability, ECG = electrocardiogram, VAD = ventricular assist device.

with standard clinical practice ranging from roughly 15 minutes to 4 hours (2). Even patients in step-down or telemetry units with continuous ECG monitoring will have blood pressure noninvasively monitored and intermittently recorded. Studies also indicate that the accuracy of noninvasive oscillometric blood pressure monitoring when compared with intra-arterial blood pressure monitoring in acute patients may be problematic for decision making (35–38). While the use of continuous noninvasive blood pressure (cNIBP) monitors may be helpful, cNIBP may be problematic from a scalability and workflow standpoint. In this regard, AHI may offer a bridge. We used ECG and invasive arterial blood pressure monitoring in an ICU setting to begin testing AHI's performance as a surrogate measure of hemodynamic instability based on predefined definitions measured with a gold standard of continuous intra-arterial blood pressure and ECG monitoring.

A multitude of clinical EWS have been developed and are variably used in less monitored inpatient settings to help identify or predict decompensation when less continuous data and vital signs are available. Examples include the MEWS, NEWS, eCART, and Predicting Intensive Care Transfers and Other Unforeseen Events and other scores that use intermittent vital signs and other data to assess risks for cardiac arrest, ICU transfer, or death (28, 39). These EWS products are limited in their outputs since they are restricted to the intermittent nature of the data imputation required for scoring.

Earlier recognition of clinical deterioration, which may be possible with AHI, may decrease the time to evaluation and intervention, which may translate to improved efficacy of interventions and decreases mortality. In addition, the early recognition of patient instability in real-time may allow for a more accurate disposition to a higher level of care in settings where

TABLE 1.
Demographic Characteristics of Total Analysis Set and Subgroups

Characteristic	Total Analysis Set (n = 597)	ON Vasopressors/ Inotropes (n = 338)	NOT ON Vasopressors/Inotropes (n = 259)	ON Beta Blockers (n = 247)	NOT ON Beta Blockers (n = 350)
Gender, n (%)					
Male	333 (55.8)	193 (57.1)	140 (54.1)	135 (54.7)	198 (56.6)
Female	264 (44.2)	145 (42.9)	119 (45.9)	112 (45.3)	152 (43.4)
Age (yr)					
Mean (sd)	59.1 (15.4)	60.1 (14.61)	57.8 (16.3)	61.5 (14.7)	57.5 (15.7)
Race, n (%)					
White	478 (80.1)	270 (79.9)	208 (80.3)	194 (78.6)	284 (81.1)
Black or African American	76 (12.7)	42 (12.4)	34 (13.1)	33 (13.4)	43 (12.3)
Unknown or not reported	14 (2.3)	8 (2.4)	6 (2.3)	5 (2.0)	9 (2.6)
Asian	15 (2.5)	10 (3.0)	5 (1.9)	8 (3.2)	7 (2.0)
Other	13 (2.2)	7 (2.1)	6 (2.3)	6 (2.4)	7 (2.00)
Native Hawaiian and other Pacific Islander	1 (0.2)	1 (0.3)	0 (0)	1 (0.4)	0 (0)
Ethnicity, n (%)					
Hispanic	12 (2.0)	4 (1.2)	8 (3.1)	5 (2.0)	7 (2.0)
Non-Hispanic	570 (95.5)	325 (96.1)	245 (94.6)	238 (96.4)	332 (94.9)
Unknown or not reported	15 (2.5)	9 (2.7)	6 (2.3)	4 (1.6)	11 (3.1)

frequent and high-resolution blood pressure monitoring is not possible. In the emergency department, for example, AHI may allow for a more rapid transition

of the patient to an area with improved nursing ratios and monitoring. Patients on a telemetry or intermediate care unit may benefit from earlier recognition so more

TABLE 2.
Primary Analysis of Window Level Performance Against Reference Standard and Shock Index

Analysis Set Characteristic	AHI vs Reference Standard (Tachycardia + Hypotension), n = 597 Patients, n = 1,252,742 Windows Observed (95% CI)	AHI vs Shock Index (> 1.0), n = 597 Patients, n = 1,252,742 Windows Observed (95% CI)
Prevalence	6.6% (5.2–7.6%)	12.1% (10.1–14.3%)
Sensitivity	96.9% (96.0–97.6%)	72.0% (66.8–78.0%)
Specificity	79.0% (74.7–82.1%)	80.3% (77.2–82.4%)
Positive predictive value	24.6% (19.7–28.2%)	33.4% (29.4–37.2%)
Negative predictive value	99.7% (99.6–99.8%)	95.4% (94.1–96.8%)
False positive rate	21.0% (17.9–25.3%),	19.7% (17.6–22.8%)
False negative rate	3.1% (2.4–4.0%)	28.0% (22.0–33.2%)
Area under the curve	0.90 (0.87–0.92)	0.81 (0.79–0.83)

AHI = Analytic for Hemodynamic Instability.

Bootstrap CIs are based on 100 samples with replacement from the Analysis Set with resampling done at the patient level.

TABLE 3.**Subgroup Analysis of Patients Receiving or Not Receiving Vasopressor/Inotrope Medications and Beta-Blockers on Analytic for Hemodynamic Instability Detected Instability Based on Heart Rate and Systolic Blood Pressure Parameters**

Analysis Set Characteristic	Subgroup ON, Vasopressors or Inotropes, AHI vs Reference Standard, <i>n</i> = 338, <i>n</i> = 922,623 Observed	Subgroup Not ON, Vasopressors and Inotropes, AHI vs Reference Standard, <i>n</i> = 259, <i>n</i> = 330,119 Observed	Subgroup ON Beta-Blockers, AHI vs Reference Standard, <i>n</i> = 247, <i>n</i> = 610,782 Observed	Subgroup Not ON Beta-Blockers, AHI vs Reference Standard, <i>n</i> = 350, <i>n</i> = 641,960 Observed
Prevalence	7.9%	2.9%	4.6%	8.5%
Sensitivity	96.9%	96.8%	96.7%	97.0%
Specificity	79.2%	78.5%	78.1%	79.9%
Positive predictive value	28.6%	11.8%	17.5%	30.9%
Negative predictive value	99.7%	99.9%	99.8%	99.7%
False positive rate	20.9%	21.5%	21.9%	20.2%
False negative rate	3.1%	3.2%	3.3%	3.0%
Area under the curve	0.90	0.91	0.89	0.90

AHI = Analytic for Hemodynamic Instability.

aggressive treatment or movement to an ICU can be performed. Last, AHI may be suitable as an adjunct analytic for newer ECG monitoring technologies such as wearable ECG patches, allowing more ubiquitous and scalable monitoring options for general ward patients where continuous monitoring is not traditionally available. While AHI will need prospective study in patients not undergoing continuous invasive blood pressure monitoring, we performed a separate analysis on the cohort of patients (2,151) undergoing both invasive and non-invasive blood pressure monitoring to examine AHI performance compared with the intermittent nurse validated vital signs placed in the patient's Electronic Health Record. When compared with the cohort undergoing only invasive arterial blood pressure monitoring, performance is nearly unchanged (**Appendix 4.0**, <http://links.lww.com/CCX/A988>).

Performance to detect clinical deterioration was based on predefined parameters. For all clinical decision systems including AHI, there are potentially significant implications for errors. A false negative implies that a clinician will see an "AHI Stable" output when the patient is actually unstable. If hemodynamic instability progresses unrecognized, there is a risk of failure to rescue a patient. A high sensitivity (95.6% in the study) helps minimize this scenario for missed hemodynamic instability. Conversely, a false positive means that a clinician will see an "AHI Unstable" output when the patient is stable.

The consequence of increasing vigilance on a stable patient (false positive) is the increase in resource allocation where it could be deemed excessive or deployed elsewhere. However, this may be viewed as minor in comparison to a false negative or when "traditional" infrequent vital sign monitoring and reporting is the norm. AHI is intended as adjunctive data that the clinician may consider when determining the clinical course of care. The observed specificity (84.9%) in the study indicates there are relatively few false positives (15.1%—type I error). However, these need to be accounted for when discussing items such as alarm fatigue and resource allocation. A detailed assessment of AHI's false positive rate has provided in **Appendix 3.0** (<http://links.lww.com/CCX/A988>).

The subgroup analysis results show comparable performance, suggesting that AHI performance remains clinically meaningful irrespective of the presence or absence of vasopressor/inotrope medications or the presence or absence of beta-blockers. The similarities between the primary endpoints of sensitivity and specificity for the subgroups with and without vasopressors/inotropes/beta-blockers suggest that AHI's performance is not only independent of cardiovascular medications but is also consistent across patients with differing prevalence of hemodynamic instability. While this may be counterintuitive, it may be that patients were not on significant enough doses of these medicines to impact HRV. Furthermore, some studies

have demonstrated that beta-blockers may not have a significant impact on HRV (40).

The difference in AHI's performance to detect instability using HR and SBP parameters compared with that of SI is not surprising since a SI of greater than or equal to 1 can occur with a SBP greater than 90 mm Hg (e.g., SBP 100 mm Hg and HR 110). Despite this, AHI's performance to indicate both SI greater than or equal to 1 and a combination of instability based on the combination of HR (> 100 beats/min) and SBP (< 90 mm Hg) were clinically acceptable.

LIMITATIONS

Certain limitations should be considered in the interpretation and application of this study. This was a retrospective analysis at a single academic healthcare center in the United States. Furthermore, to have well-defined definitions of stability versus instability, hard cutoffs for vital signs were used based on American Heart Association and Systemic Inflammatory Response Syndrome criteria (41). If these criteria are updated in the future, or if new criteria become the standard, then another analysis of AHI performance would be needed with the use of these new criteria. Interpretation of the analysis of false positives and false negatives provided in Appendix 3.0 (<http://links.lww.com/CCX/A988>) has its limitations, since different levels of care or units can have varying patient acuity and occupancy rates, thereby potentially providing differing levels of AHI unstable indications per hour. To accurately assess the rates of AHI unstable indications, false positives and false negatives for any given unit requires a prospective study of AHI that adjusts for and controls many factors that affect these rates. In addition, of all the AHI windows where ECG data was available from across the 597 patients for this study, only 1.7% of them were flagged as noisy by AHI indicating that the majority of continuous outputs (98.3%) AHI produces when ECG data are available is clinically usable.

Further studies are necessary to determine if AHI's dynamic continuous assessment of hemodynamic status provides clinical and resource allocation benefits in patients undergoing infrequent blood pressure monitoring. As AHI also provides feedback every 2 minutes, it may help clinicians gauge the therapeutic response to evolving patient conditions. Decreased failure to rescue, impact on length of stay, disposition planning, unanticipated escalations in care, and potential impact on patient morbidity and mortality are all potential topics of future work.

CONCLUSIONS

Early detection of hemodynamic instability has traditionally been difficult, even for experienced clinicians (physicians and nurses) observing a patient's intermittent vital signs. This pilot study has demonstrated the studied clinical support system's potential ability to indicate hemodynamic instability or stability based on a predefined vital signs criteria. As a noninvasive monitoring technology, the system may offer advantages in the continuous surveillance of patients and their hemodynamic status.

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Drs. Schmitzberger and Hall should be considered co-first authors.

This study was funded by Fifth Eye. The study was also supported by the Max Harry Weil Institute for Critical Care Research and Innovation.

Drs. Belle and Ward are inventors of the Analytic for Hemodynamic Instability technology, which is patented through the University of Michigan and licensed to Fifth Eye. Drs. Belle and Benson are employees of Fifth Eye. Drs. Belle, Benson, and Ward have equity in Fifth Eye. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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