**Supplementary Content**

**METHODS**

**Data conditioning: Signal Preprocessing, Heart Beat Detection, and Data Selection**

To make all the data consistent, all arterial pressure signal data from MIMICII, Edwards, and UCI databases were down-sampled to 100Hz. The arterial pressure waveforms of all the patients from all databases were then processed through the Edwards FloTrac algorithm (FloTrac, Edwards Lifesciences, Irvine , CA) to perform basic signal preprocessing and beat detection, as explained in details below. The FloTrac algorithm performed the arterial pressure waveform signal preprocessing, the heart-beat detection, the dicrotic notch detection, and removal of artifacts from the processed arterial pressure waveform data. All processing in the FloTrac algorithm is performed on a 20-second basis. This 20-second processing approach was adopted for the predictive algorithm as well. The FloTrac algorithm front-end stage includes a low pass filter to filter out noise and electrical interference and to compensate for the effect of the frequency response of the fluid filled catheter-tubing-transducer system. One of the goals of the arterial pressure waveform signal preprocessing stage is to minimize the effect of the frequency response of the fluid filled catheter-tubing-transducer system used to measure the arterial pressure signal through standard direct pressure transducers connected to arterial line catheters. Additional front-end signal processing features of the FloTrac algorithm eliminated signal drift and motion artifacts and rejected/removed all data segments with signal artifacts from the processed data. The FloTrac algorithm includes signal processing algorithms based pattern recognition to detect and remove artifacts. In the FloTrac algorithm artifacts are considered in the following situations:

* Signal artifacts resulting from patient’s movement, or surgical interventions and manipulations. These common types of artifacts cause large variations in the arterial pressure signal and therefore are easily detectable with simple signal processing algorithms.
* Signal artifacts resulting from disconnected arterial pressure line, or from flushing the arterial line. Also very common types of artifacts that cause flat lines in the signal and therefore are easily detectable with simple signal processing algorithms.
* Signal artifacts resulting from improperly zeroed and/or leveled pressure sensor. Also very common and easily detected by analyzing the change and magnitude of mean arterial pressure (MAP).
* Signal artifacts resulting from overdamping or underdamping of the arterial pressure line. Also very common artifacts that cause very distinct changes in the shape of the arterial pressure waveform. The overdamping usually results in appearance of reflected wavelets or oscillations in the signal and is therefore easily detectable by simple signal processing. Underdamping usually causes disappearance of the high harmonic components in the arterial pressure waveform, resulting in a smooth, almost sine wave-like arterial pressure waveforms. Those types of conditions are also easily detectable by simple signal processing techniques.

All types of artifacts listed above are detected by analyzing the shape of the arterial pressure waveform on a beat-to-beat basis. If the FloTrac algorithm detects any of the conditions above in the 20-second cycle, it flags the respective 20-second segment as artifacts and rejects the segment from further processing.

Then, the FloTrac algorithm heart-beat detection extracts the individual cardiac cycles and the features from the arterial pressure signal. The beat detection operates on the derivative of the filtered arterial pressure signal using an adaptive threshold, and decision logic. In addition to beat detection, the FloTrac algorithm performed dicrotic notch detection. The algorithm detects the inflection point that characterizes the arterial pressure waveform at the end of the systolic phase and the beginning of the diastolic phase. The dicrotic notch location (time) detection uses the 2nd derivative of the pressure signal, along with a decision logic.

**Featurization of the arterial pressure waveform (feature extraction)**

The purpose of feature extraction is to find waveform characteristics that are informative, thus facilitating the subsequent algorithm learning steps. In this section, we describe all the features extracted from the patients’ arterial pressure waveform time series.

As shown in Figure 1 - Full manuscript, there are two distinct phases in the arterial pressure waveform:

* Phase 1: corresponding to the systolic phase of the cardiac cycle (systolic phase), starting from the beginning of the beat (systole onset) and ending at the dicrotic notch.
* Phase 2: corresponding to the diastolic phase of the cardiac cycle (diastolic phase), starting from the dicrotic notch and ending at the end-diastole, the systole onset of the next cardiac cycle.

Although both the systolic phase and the diastolic phase of the arterial pressure waveform are part of the same signal, they correspond to independent cardiac phases and therefore contain different hemodynamic information. The systolic phase is where the heart contracts and blood is ejected from the heart into the aorta. The elasticity (compliance) of the aorta, which is a major determinant of the aortic characteristic impedance, is an important factor affecting cardiac output. During the diastolic phase, the aortic valve closes and the heart is not directly connected to the rest of the vascular system during this phase. The aortic compliance filled with blood discharges through the peripheral vessels. The major determinants of flow during this phase are the elasticity (compliance) of the proximal vasculature and the peripheral resistance of the small peripheral vessels1.

In addition to the two major phases (systolic and diastolic) of the arterial pressure waveform described above, the systolic phase is characterized by two additional distinct sub-phases:

- Phase 3: systolic rise: starting from the beginning of a beat and ending at the systolic pressure.

- Phase 4: systolic decay: starting from the systolic pressure and ending at the dicrotic notch.

These two systolic sub-phases have in common that they correspond to a phase of ejection where the aortic valve is open and therefore the left ventricle and the aorta are connected. However, about 70 percent of the emptying of the left ventricle occurs during the first third of the ejection period and the systolic rise is this period is more related to cardiac contractility than to aortic input impedance, while the remaining 30 percent is ejected during the next two thirds during the systolic decay, where the left ventricle is contracting less vigorously and represents more the effect of aortic input impedance than contractility1.

The arterial pressure waveform is characterized by one further phase of the overall pressure decay:

* Phase 5: overall decay: starting from the systolic pressure and ending at the beginning of the following cardiac cycle. The overall decay of the arterial pressure waveform represents the effect of the overall afterload, including aortic impedance and peripheral effects.

These five distinct phases in the arterial pressure waveform pave the way for calculating key hemodynamic parameters directly related to cardiovascular hemodynamics. Those extracted parameters are known as features in the machine learning jargon. The features are described in detail below. Each feature is calculated using the low pass filtered pressure signal from the preprocessing stage. Each of the features explained in this section is the median of corresponding features calculated over all individual heart beats over 20 second time intervals.

*Arterial pressure waveform time, amplitude, area and slope features*

Various time, amplitude, area, and slope features are calculated from the distinct phases of the cardiac cycle from the arterial pressure waveform signal (Table 1 – Supplementary Content). These features may provide subtle clinical signs of instability, especially when compared to the stable periods of a patient.

Time features include the durations of the five phases of the waveform, as well as the duration of the entire beat (related to heart rate). Amplitude features include the amplitudes of the five phases of the arterial pressure waveform, such as systolic pressure, pulse pressure, the pressure at the dicrotic notch (end-systolic pressure) and diastolic pressure. Other features classified under the amplitude features, include the standard deviation of the five phases of the waveform. The standard deviation is a measure of the pulsatility (or variability) of the arterial pressure signal during the respective phase. Area features include the areas of the five phases of the waveform (with and without the diastolic pressure, as well as normalized and non-normalized by the number of samples). The area features represent the energy of the arterial pressure signal during the respective phase of the arterial pressure waveform. Slope features include the slope of the systolic rise of the arterial pressure waveform (the maximum of dP/dt and dP2/dt2) and the slope of the diastolic discharge (diastolic time constant).

**Table 1 – Supplementary content. Arterial pressure waveform time, amplitude, area and slope features (The features are calculated for each beat, then averaged for all beats in a 20-second window. In addition, for each feature, a standard deviation for all beats in the 20-second window is calculated and they are hereafter called standard deviation features).**

|  |  |
| --- | --- |
| **Feature symbol** | **Description** |
| t\_sys\_rise | Duration of the systolic rise phase (Phase 3) |
| t\_sys\_dec | Duration of the systolic decay phase (Phase 4) |
| t\_dec | Duration of the overall decay phase (Phase 5) |
| ibi | Interbeat interval |
| t\_sys | The duration of the systolic phase (Phase 1) |
| t\_dia | The duration of the diastolic phase (Phase 2) |
| map\_dnloc\_time | Time from the first beat sample exceeding the beat mean to the dicrotic notch |
| dn\_sys | Difference between systolic pressure and pressure at dicrotic notch |
| dn\_dia | Difference between pressure at the dicrotic notch and diastolic pressure |
| avg\_sys | Average of the systolic portion of the waveform (Phase 1) |
| avg\_dia | Average of the of the diastolic portion of the waveform (Phase 2) |
| avg\_sys\_rise | Average of the systolic rise portion of the waveform (Phase 3) |
| avg\_sys\_dec | Average of the systolic rise portion of the waveform (Phase 4) |
| avg\_dec | Average of the overall decay portion of the waveform (Phase 5) |
| avg\_sys\_nodia | Average of the systolic portion of the waveform with diastolic pressure subtracted |
| avg\_dia\_nodia | Average of the of the diastolic portion of the waveform with diastolic pressure subtracted |
| avg\_sys\_rise\_nodia | Average of the systolic rise portion of the waveform with diastolic pressure subtracted |
| avg\_sys\_dec\_nodia | Average of the systolic decay portion of the waveform with diastolic pressure subtracted |
| avg\_dec\_nodia | Average of the overall decay portion of the waveform with diastolic subtracted |
| pulse\_pres | Pulse pressure = systolic pressure - diastolic pressure |
| sys\_area | Area under the systolic phase of the beat (from start to the dicrotic notch) |
| map\_dnloc\_area | Area under the pressure waveform greater than the beat mean pressure |
| pp\_area | Area under the entire beat waveform |
| pp\_area\_nor | Area under the beat normalized by the number of samples |
| sys\_area\_nor | Area under the systolic phase normalized by the number of samples |
| sys\_rise\_area | Area from the start of the beat to the systolic maximum |
| sys\_rise\_area\_nor | Area from the start of the beat to the systolic maximum normalized by the number of samples |
| sys\_dec\_area | Area from the systolic maximum to the dicrotic notch |
| sys\_dec\_area\_nor | Area from the systolic maximum to the dicrotic notch normalized by the number of samples |
| dec\_area | Area from the systolic maximum to the start of the next beat |
| dec\_area\_nor | Area from the systolic maximum to the start of the next beat normalized by the number of samples |
| dia\_area | Area under the diastolic portion of the waveform (from the dicrotic notch to the start of the next beat) |
| dia\_area\_nor | Area under the diastolic portion of the waveform normalized by the number of samples |
| pp\_area\_nodia | Area under the beat with subtracted diastolic pressure |
| pp\_area\_nor\_nodia | Area under the beat with subtracted diastolic pressure and normalized by the number of samples |
| sys\_area\_nodia | Area under the systolic portion of the waveform with subtracted diastolic pressure |
| sys\_area\_nor\_nodia | Area under the systolic portion of the waveform with subtracted diastolic pressure and normalized by the number of samples |
| sys\_rise\_area\_nodia | Area from the start of the beat to the systolic maximum with subtracted diastolic pressure |
| sys\_rise\_area\_nor\_nodia | Area from the start of the beat to the systolic maximum with subtracted diastolic pressure and normalized by the number of samples |
| dec\_area\_nodia | Area from the systolic maximum to the start of the next beat with subtracted diastolic pressure |
| dec\_area\_nor\_nodia | Area from the systolic maximum to the start of the next beat with subtracted diastolic pressure and normalized by the number of samples |
| dia\_area\_nodia | Area under the diastolic portion of the waveform with subtracted diastolic pressure |
| dia\_area\_nor\_nodia | Area under the diastolic portion of the waveform with subtracted diastolic pressure and normalized by the number of samples |
| dP/dt | Maximum of the first derivative of the arterial pressure signal |
| dP2/dt2 | Maximum of the second derivative of the arterial pressure signal |
| slope\_dia | slope of the diastole of a beat |
| slope\_sys | slope of the systole of a beat |

*FloTrac algorithm features*

The Edwards FloTrac algorithm computes key hemodynamic parameters, such as Cardiac Output (CO), Stroke Volume (SV), Vascular tone (the Kai-factor2), Windkessel Compliance (Cwk)3, Systemic Vascular Resistance (SVR), Stroke Volume Variations (SVV)4, as well as several measures of the morphology of the arterial pressure waveform2. All FloTrac features are summarized in Table 2 – Supplementary Content.

All features that were duplicate of the FloTrac algorithm features and the first set of time, amplitude, area and slope features, were removed.

**Table 2. FloTrac Algorithm features extracted from the arterial pressure waveform.**

|  |  |
| --- | --- |
| **Feature** | **Description** |
| *CO* | Cardiac Output |
| *SVV* | Stroke Volume Variation |
| *MAP* | Mean Arterial Pressure based on waveform average |
| *MAP\_empirical* |  |
| *SYS* | Systolic Pressure |
| *DIA* | Diastolic Pressure |
| *PR* | Pulse Rate |
| *Cwk* | Aortic windkessel compliance5,6 |
| *Std(BP)* | Standard deviation of the arterial pressure waveform |
| *Skewness* | Skewness (third statistical moment) of the arterial pressure waveform5,6 |
| *Kurtosis* | Kurtosis (forth statistical moment) of the arterial pressure waveform5,6 |
| *Mu* | Mean of the 20-second reconstructed arterial pressure waveform5,6 |
| *Sigma* | Standard deviation of the 20-second reconstructed arterial pressure waveform5,6 |
| *Skewness-2* | Skewness of the 20-second reconstructed arterial pressure waveform5,6 |
| *Kurtosis-2* | Kurtosis of the 20-second reconstructed arterial pressure waveform5,6 |
| *PPV* | Pulse Pressure Variation |

*COTrek features*

Similarly to the FloTrac algorithm features, we also considered the COtrek algorithm features. The Edwards COtrek algorithm is the pulse contour cardiac output algorithm obtained from the ClearSight system (Clearsight, Edwards Lifesciences, Irvine, CA formerly Nexfin, Bmeye BV, Amsterdam, the Netherlands). The COtrek algorithm is based on a 3-element Windkessel model that represents the effect of aortic input impedance and peripheral resistance and compliance7. The three COtrek algorithm features are COtrek (cardiac output from Windkessel Model based COtrek algorithm), SVtrek (stroke volume from Windkessel Model based COtrek algorithm), and the Pulsatile systolic area (PSA), computed as the area under the systolic portion of the arterial pressure waveform.

*Complexity features*

Hemodynamic complexity measures quantify the amount of regularity in cardiac measurements over time, as well as the entropy, i.e., the unpredictability of fluctuations in cardiac measurements.

Two types of entropy are calculated: Approximate Entropy (ApEn)5,6(see here: **https://www.physionet.org/physiotools/ApEn/)**, and Sample Entropy5,6 (SampEn) (see here: **https://www.physionet.org/physiotools/sampen/)**. The approximate entropy quantifies the amount of regularity and the unpredictability of fluctuations over time-series data, and the sample entropy is a modification of approximate entropy, which does not include self-matches while ApEn does. A low value of the entropy indicates that the time series is deterministic while a high value means that the time series is random. Sample and approximate entropy were calculated on a 20-second basis for all the features explained above. Additionally, sample and approximate entropy were also calculated directly for the arterial pressure signal (also on a 20-second basis).

*Baroreflex features*

Baroreflex sensitivity measures quantify the relationships between compensatory physiological processes (for example, a decrease in blood pressure in a healthy subject is typically compensated by an increase in heart rate and/or an increase in peripheral resistance). Several baroreflex sensitivity measures can be derived from arterial pressure waveform. The baroreflex sensitivities can be calculated in the time domain and in the frequency domain.

In the time domain, the baroreflex sensitivity is calculated with the cross-correlation method8 as explained in the following steps for the baroreflex sensitivity between MAP and inter-beat-interval (IBI). As an example:

* A 10-second window is made to progress in one-second steps over the beat to beat MAP and IBI
* Both MAP and IBI within the 10-second window are interpolated and resampled at every second
* MAP and IBI are then cross-correlated with 0, 1, 2, …, 5 seconds delay
* The delay with the highest cross-correlation is taken as best delay τ [s]
* If the highest cross-correlation is positive and significant at p = 0.05, the variance ratio of IBI against MAP is one determination of the baroreflex sensitivity (BRS) [ms/mmHg], that is,

where,

std(IBI) and std(MAP) are the standard deviation of beat-to-beat IBI and MAP values.

* The Variance ratio is taken only when a significant degree of coherence is present

In the calculation, there are two essential parameters, the 10-second window and the maximum delays of five seconds. Those determine what type of baroreflex sensitivity is calculated. For example, the 10-second window and the 5-second maximum delay are configured to calculate the sympathetic component of the baroreflex sensitivity on the heart rate; to calculate the vagal component of this baroreflex loop, the 5-second maximum delay should be changed to three seconds.

The following baroreflex sensitivities are calculated:

* Between pressures (SYS, DIA and MAP) and IBI,
* Between pressures (SYS, DIA and MAP) and vascular resistance (SVR),
* Between pressures (SYS, DIA and MAP) and dP/dt (as a peripheral measure of left-ventricle contractility), and
* Between pressures (SYS, DIA and MAP) and stroke volume (SV).

In the frequency domain, the baroreflex sensitivity is calculated with the cross-power spectral density method9, and with the spectral power method10, at the low frequency band from 0.03 to 0.15 Hz, and the high frequency band from 0.15 to 0.25 Hz.

The frequency-domain cross-power spectral method9 is calculated as follows,

* Calculate the cross-power-spectral density between systolic pressure and inter-beat interval (Sxy)
* Calculate power spectral density of systolic pressure (Sxx)
* Calculate the ratio: |Sxy|/Sxx, where “| |” is the absolute value
* Baroreflex sensitivity at low frequency: Average of the ratio from 0.05 to 0.15Hz, a range minimally impacted by respiration
* Baroreflex sensitivity at higher frequency: average of the ratio from 0.15 to 0.25Hz, a range driven by respiration

The frequency-domain spectral power method10 is calculated as follows,

* Calculate the spectral power of IBI, Px(f), where f is frequency
* Calculate the spectral power of systolic pressure, Py(f), where f is frequency
* Calculate the ratio, Px(f)/Py(f)
* Calculate the square root of the ratio,
* Baroreflex sensitivity at low frequency: from 0.05 to 0.15Hz
* Baroreflx sensitivity at higher frequency: from 0.15 to 0.25Hz

*Variability features*

The variability refers to the extent to which a feature changes with time. There are multiple ways to quantify variability 11.

In our algorithm the variability for each feature is computed in two ways:

* The first is the standard deviation of a feature for all its values in the 20 second window; that is,

where , x1, x2, …, xN are the beat to beat values of a feature in the 20-second window.

* The second is the same as the first, except it is normalized by the median value in that 20-second window.

Both calculations of variability were performed for all the features described above.

*Spectral features*

Frequency domain hemodynamic features quantify measures of cardiac performance as a function of frequency rather than time. For the power spectra calculation, a two 20-second pressure waveform is first linearly de-trended, by subtracting by a linear best-least-square fit of the waveform. The de-trended waveform is then normalized by subtracting by the mean value of the de-trended waveform. Then, in one calculation, the normalized waveform is tapered at two sides by a Tukey window of 2.5% taper section length; In another calculation, the normalized waveform is further normalized by the standard deviation of the normalized waveform. Then the resulted waveform is tapered at two sides by a Tukey window of 2.5% taper section length.

The two tapered waveforms are then Fourier transformed, respectively, and for each of them, amplitude spectra are calculated for multiple frequency bands, which include

• 0.03 to 0.15 Hz

• 0.15 to 0.25 Hz

• hr-0.2 to hr+0.2 Hz

• 2hr-0.1 to 8\*hr+0.1 Hz

where hr is the heart rate frequency.

These frequency bands are resulting from different physiological sources. Around 0.1 Hz is mainly ascribed to baroreflex blood pressure control12-15; around 0.2 Hz is the respiratory modulation of circulatory signals12-15; hr is the heart rate; and 2 to 8 times of hr frequency are the hr harmonics frequencies12-15.

*“Delta-change” features*

Delta-change” features result from subtracting a baseline from a feature. This is to detect how the feature changes with time relative to the baseline.

The baseline was calculated in three ways:

The first is an initial baseline, which is the average of the respective feature in the first 10 minutes, that is,

where N=30, as there are 10 minutes and each minute there is 3 data points, f(t) is the value of feature f at time t.

The second is a moving baseline, which is the average of the respective feature in a 10-minute period that spans from 15th minute to 5th minute prior to the current time, that is,

where N=30, i is the current time, and f(t) is the value of feature f at time t.

The third is also a moving baseline, which is the average of the respective feature from the beginning when the data is acquired to the current time, that is,

where i is the current time, M is the number of data points from the beginning of data is acquired to the current time, and f(t) is the value of feature f at time t.

The delta-change features are computed for all 20-second averaged features described above, that is:

*f(t) = f(t) - baseline*

where *f(t)* is the delta-change feature of feature f at time t, and baseline is calculated from one of the above two ways.

At this point, the total number of features extracted is 3,022 features (Figure 1 - Full manuscript).

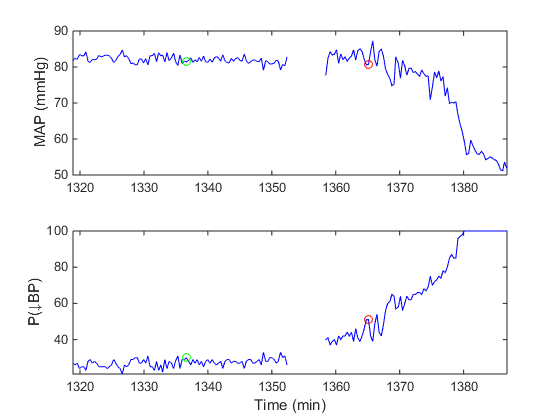
*Combinatorial features*

Combinatorial features are generated using power combinations of all features described in the sections above. Combinatorial features are calculated because they may provide extra information or better prediction than individual features. The individual features are mostly linear while the combinatorial features provide information about interaction effects and/or nonlinear effects. A simple example of a clinically adopted combinatorial feature is the shock index, which is the ratio of heart rate to systolic blood pressure16. The shock index is a better indicator of acute blood loss than heart rate or the systolic pressure alone because heart rate typically rises while systolic pressure typically drops17 as a way of compensation. When the blood loss is not significant, the change of heart rate and systolic pressure might be small, while their ratio might be high. Combinatorial features are calculated as shown in Figure 1 – Supplementary Content.

**Figure 1 Supplementary Content. Graphic Representation describing calculation of Combinatorial features**

*Analysis of hypotension prediction compared to actual occurrence of hypotensive events ( Hypotension Prediction Index (HPI) algorithm and Frequency of Hypotension Analysis)*

The algorithm output as a prediction should be close to the relative frequency of occurrence of hypotensive events, with a high degree of certainty for a sufficiently large data set. In this analysis, we plotted the frequency of occurrence of hypotensive events in the data samples at different ranges of the algorithm output. The analysis was performed as follow: 1) Hypotensive episodes were defined as MAP < 65mmHg for at least 1 minute , 2) Event samples were taken backwards exactly ‘t’ minutes prior to the start of a hypotensive episode (t = 5, 10, 15, 20) (Figure 2 – Supplementary Content), 3) Non-hypotensive episodes were at least 20 minutes away from any event and had a MAP > 75mmHg, 4) Non-event samples were taken as the midpoint of every 30 minute non-hypotensive episode (Figure 2 – Supplementary Content), 5) All algorithm output values for the above event and non-event samples, for a given data set, were accumulated and segmented into algorithm output bins, and 6) For each bin, the % of event samples in that bin was the rate of events, as the event samples have an event happening in ‘t’ minutes.



Start of Hypotension

Event Sample

Non-event Sample

**15 minutes**

ʃʃ

ʃʃ

**30 minutes**

HPI

**Figure 2. Backward Analysis Event and Non-Event Sampling Methodology for the analysis of hypotension prediction compared to actual occurrence of hypotensive events (Hypotension prediction Index (HPI) and Frequency of Hypotension Analysis).**

Algorithm development and comparison to previously published ML algorithms:

The development of our algorithm involved assessment of the compensatory mechanisms using analysis of physiological interactions between hemodynamic variables corresponding to cardiac preload, afterload and contractility. The algorithm development included the following steps:

1. Computation of basic hemodynamic variables corresponding to cardiac preload, afterload and contractility from the arterial pressure waveform:

The first step in the development of our algorithm was to extract the basic hemodynamic variables in the arterial pressure waveform corresponding to cardiac contractility, preload and afterload.

* 1. Computation of core hemodynamic variables:

To compute the core hemodynamic variables, the arterial pressure waveforms were all processed through the FloTracTM and COTrekTM hemodynamic algorithms. These algorithms computed the core hemodynamic variables out of the arterial pressure waveform, as follows:

CO, SV, SVR, PR, Arterial tone, Windkessel Compliance, Peripheral Resistance, SVV, PPV, MAP, SYS, DIA

Additionally, basic signal conditioning, noise filtering, artifact removals and beat detection were performed using the FloTracTM algorithm (see above in Methods section).

* 1. Computation of expanded set of hemodynamic variables:

The different phases of the arterial pressure waveform, such as the systolic rise, systolic decay and diastolic phase (see above in Methods section), were used to extract additional features corresponding to different measures of cardiac contractility, preload and afterload, such as: slopes, durations, amplitudes, pulsatilities and areas under the curve of the different phases of the arterial pressure waveform (see supplemental material)

There were a total of 166 basic hemodynamic variables extracted from the arterial pressure waveform.

1. Computation of variability, complexity and cross-correlation of the basic hemodynamic features

The 166 basic hemodynamic variables are not relevant to detection of the changes in the compensatory mechanisms that precede hypotensive events. Similarly to the standard clinical parameters (and many of them are), the 166 basic hemodynamic variables are static and do not undergo changes until late in the hypotension development process. What is relevant for the prediction are the complexity and variability and the interactions between all the basic hemodynamic variables, not their absolute values.

The complexity and variability of all the 166 features were therefore computed. Sample and approximate entropy and the standard deviation of each feature were used to compute the complexity and variability of all the basic features (see above in Methods section). Additionally, cross-correlational analyses of some of the 166 basic features were used to estimate compensatory mechanisms such as Baroreflex sensitivity (see above in Methods section).

By performing all these second level computations, a total of 3,022 features additional features were obtained.

1. Computation of physiological association of physiological variables

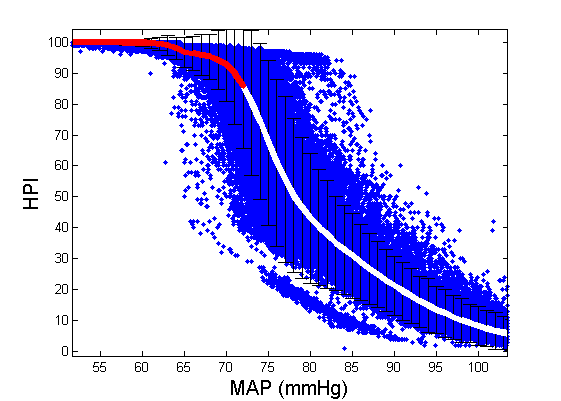
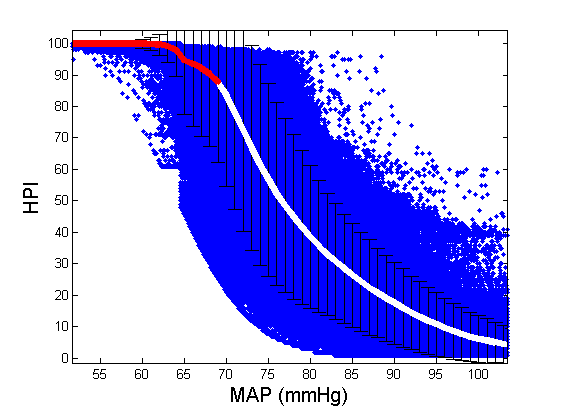
The assessment of the physiological associations is critical to our algorithm as it represents the effect of the dynamic links between hemodynamic variables resulting from compensatory mechanisms in the cardiovascular system. Alterations in the compensatory mechanisms are the first signs of the start of the development of hypotension. The assessment of the physiological associations included computations of linear/nonlinear combinations of all 3,022 variability/complexity features computed in the previous step. Combinatorial features are needed because they provide key information on the physiological interactions and dynamic links of all individual 3,022 variability/complexity variables. The individual variables are all linear while the combinatorial features provide information about interaction effects and nonlinear effects.

Since the number of individual variability/complexity variables was quite large, an interactive process based on ROC analysis of each variable out of the 3,022 variables was used to select the features with Area Under the Curve (AUC) higher than 0.85. The ROC analysis was performed on hypotension and non-hypotension classes explained in greater details below. The ROC analysis identified 51 variables out of the 3,022 variables with AUC>0.85. All permutations of the 51 features using 1, 2 and maximum of 3 at a time and at power levels [-2,-1,0,1,2] were then computed (see above in Methods section). The permutation process generated a total of 2.6 million features.

No algorithm previously published utilized such a large, comprehensive multivariate analysis of the interaction effects to assess compensatory mechanisms and capture multivariate cross-correlational changes in them that precede hypotension.

**RESULTS**

Figure 3 – Supplementary content plots Hypotension Prediction Index (HPI) and MAP for the internal validation cohort and for the UCI external validation cohort respectively. As shown in these figures, our algorithm output could vary within a wide range of values for any given MAP value.



**Figure 3 – Supplementary Content. Relationship between hypotension prediction index and mean arterial pressure for the internal validation cohort (left panel) and for the UCI external validation cohort (right panel).** HPI: Hypotension prediction index, MAP: Mean arterial pressure.

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