# MEASURING VENOUS OXYGENATION USING THE PHOTOPLETHYSMOGRAPH WAVEFORM

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**ABSTRACT. Objective.** We investigate the hypothesis that the photoplethysmograph (PPG) waveform can be analyzed to infer regional venous oxygen saturation. **Methods.** Fundamental to the successful isolation of the venous saturation is the identification of PPG characteristics that are unique to the peripheral venous system. Two such characteristics have been identified. First, the peripheral venous waveform tends to reflect atrial contraction. Second, ventilation tends to move venous blood preferentially due to the low pressure and high compliance of the venous system. Red (660 nm) and IR (940 nm) PPG waveforms were collected from 10 cardiac surgery patients using an esophageal PPG probe. These waveforms were analyzed using algorithms written in Mathematica. Four time-domain saturation algorithms (ArtSat, VenSat, ArtInstSat, VenInstSat) and four frequency-domain saturation algorithms (RespDC, RespAC, Cardiac, and Harmonic) were applied to the data set. **Results.** Three of the algorithms for calculating venous saturation (VenSat, VenInstSat, and RespDC) demonstrate significant difference from ArtSat (the conventional time-domain algorithm for measuring arterial saturation) using the Wilcoxon signed-rank test with Bonferroni correction ($p < 0.0071$). **Conclusions.** This work introduces new algorithms for PPG analysis. Three algorithms (VenSat, VenInstSat, and RespDC) succeed in detecting lower saturation blood. The next step is to confirm the accuracy of the measurement by comparing them to a gold standard (i.e., venous blood gas).

**KEY WORDS.** pulse oximeter, waveform analysis, plethysmograph, non-invasive monitoring, venous oxygen saturation.

## INTRODUCTION

The pulse oximeter is now a standard-of-care clinical monitor. In its most basic form, it measures the arterial oxygen saturation as well as the heart rate. It accomplishes this through the use of the photoplethysmograph waveform (PPG) at two or more wavelengths. Advances in digital signal processing are allowing for a re-examination of these waveforms. The movement of venous blood can be detected using the PPG. For the most part, this phenomenon has been seen as a source of artifact which interferes with the calculation of arterial saturation [1, 2]. If venous saturation can be reliably measured, interesting new possibilities are opened. Ideally, the degree of local oxygen extraction can be determined which in turn may

reflect adequacy of tissue perfusion in the area being measured. It is hoped that this would facilitate real-time, noninvasive monitoring of clinically important events such as early phases of shock.

The goal of this work is to investigate methods of using the PPG waveform to measure venous oxygen saturation. The necessary conditions for using spectroscopic measurements to infer the oxygen saturation in a given vascular compartment are: (1) pulsatile flow, and (2) differential spectral absorbance [3, 4]. The pulsatile flow allows the spectral absorbance to be measured at two different states of tissue perfusion (maximum perfusion and minimum perfusion). The change in the spectral absorbance profile of the tissue during this transition allows for the calculation of the spectral properties of the blood in motion, and hence its oxygen saturation.

The differential spectral absorbance of oxyhemoglobin and deoxyhemoglobin does not depend on the vascular compartment being studied. Thus, as we turn our attention to the venous compartment, condition (2) is trivially satisfied. However, regarding the pulsatility condition, there is an apparent impediment towards our goal of measuring venous oxygen saturation. Specifically, the peripheral venous compartments are conventionally thought of as lacking pulsatility. As the arteries progress to arterioles and capillaries, total cross section of the vasculature increases, resulting in a decreased resistance. Concomitant with this decrease in resistance is a transition from pulsatile flow to constant flow. Furthermore, the venous pathways connecting peripheral veins with the heart are typically interrupted by valves, which attenuate the retrograde pressure waves originating in the right heart. Nonetheless, the results described in this work suggest that it is possible to harness physiologic sources of periodic volume changes in the venous compartment. Before presenting these results, we summarize other approaches to measuring venous oxygen saturation. These approaches achieve the requisite pulsatility via mechanically-induced volume variations of the venous compartment.

## OTHER APPROACHES TO MEASURING VENOUS OXYGEN SATURATION

One way to increase the volume in the venous compartment in a given appendage is to occlude the venous outflow using a pressure cuff. When the pressure applied is greater than the venous pressure but smaller than the diastolic arterial pressure, blood will continue to perfuse the appendage and will pool in the venous compartment. By comparing the spectral absorbance at two or more wavelengths before and after the occlusion, it is possible to infer the oxygen saturation of the blood that collects in the venous compartment. This approach has been experimentally demonstrated [5, 6]. In Ref. [5], the investigators compared the venous oxygen saturation they measured via spectrophotometry with that obtained via co-oximetry (i.e., the gold standard in vitro method) on blood samples drawn from superficial veins. Comparing the saturations obtained by these two methods, they found a significant correlation ($n = 19$, $r = 0.7$, $p < 0.0001$). Interestingly, the systematic bias they observed was dependent on the lateral spacing between the light source and the light detector, which were positioned on the same side of the limb in a reflectance configuration. They inferred that as the distance between the source and detector increased, the light beam connecting them traveled deeper into the tissue, beyond superficial thermoregulatory arterio-venous shunts, leading to lower venous oxygen saturations.

There are two primary disadvantages with measuring venous oxygen saturation via venous occlusion. First, the method does not allow continuous measurement, since it relies on discrete interventions separated by enough time for the tissue to reach equilibrium. Second, it requires a substantial disturbance to the local physiology, leading to potential complications such as venous stasis, venous thrombosis, and interference with intravenous access. In Echiadis et al. [7], address these deficiencies by employing a more sophisticated method of externally modulating the volume in the venous compartment. Specifically, they use a finger pressure cuff that is driven by a pneumatic generator such that the finger experiences low pressure modulations at a frequency that does not overlap with the cardiac signal or its harmonics. A conventional PPG probe is placed on the same finger distal to the cuff. The resulting PPG waveform can then be decomposed into the relevant spectral components such that variation at the cardiac frequency (~1 Hz) can be isolated from variations at the pressure cuff frequency (~7.5 Hz). At that point, conventional frequency-domain algorithms are used to calculate oxygen saturation for the arteries (using the cardiac-frequency signal) and the veins (using the pressure cuff-frequency signal).

Echiadis et al. [7] reports the performance of this system in patients undergoing cardiopulmonary bypass (CPB). The venous saturation obtained via spectrophotometry is compared with the saturation measured by the CPB machine on the blood that is traveling from the patient to the machine. Since the spectrophotometric saturation is peripheral and the saturation measured by the CPB machine is central, the authors report that is not possible to infer the central venous saturation from the spectrophotometric saturation. However, the observed trends in

venous oxygen saturation during changes in temperature, $VO_2$, and cardiac index are similar for the two methods.

## MEASURING VENOUS OXYGEN SATURATION VIA PHYSIOLOGICAL SOURCES OF PULSATILITY

In the previous section, we described methods for measuring venous oxygen saturation in which an external pressure cuff achieves the requisite pulsation of the venous compartment. It is natural to ask whether the same information can be gathered without this artificial perturbation. Specifically, are there physiological sources of pulsation in the venous compartment that can be used to satisfy the pulsatility condition?

It is well known that the PPG waveform is influenced by both positive pressure ventilation [8] and the peripheral venous pulsations [1, 9]. In the case of positive pressure ventilation, we hypothesize that the effect on the PPG waveform is mediated by volume changes in the venous compartment. To test this hypothesis, we evaluate the performance of several novel PPG analysis algorithms which are designed to measure oxygen saturation using features of the PPG waveform associated with respiration. We label these algorithms VenSat, RespDC and RespAC, and describe them in detail below. In the case of peripheral venous pulsations, it has been found that during diastole, the natural venous pulsations can cause volume changes in the venous compartment to dominate those in the arterial compartment [2]. This should lead to lower overall oxygen saturation during this period between consecutive beats. To test this hypothesis, we evaluate the performance of the algorithms that we label ArtInstSat, VenInstSat, and Harmonic. These algorithms are also described in detail below. ArtInstSat and VenInstSat are derived from the concept of an ''instantaneous saturation,'' in which the overall oxygen saturation is tracked throughout the cardiac cycle. The Harmonic algorithm is a frequency-domain technique which targets blood moving at twice the frequency of the cardiac pulse, thus attempting to incorporate the influence of diastolic pulsations.

To summarize, the purpose of this work is to evaluate several new methods for extracting information regarding blood oxygen saturation from the PPG waveform. These new methods will be evaluated using data collected from 10 coronary bypass graft surgery patients, as described below. A preliminary goal is to verify that the methods proposed for measuring venous oxygen saturation yield lower saturations than the methods proposed for measuring arterial oxygen saturation. A further goal is to demonstrate that the values obtained for each method are within physiologic ranges.

## METHODS AND MATERIALS

The data analyzed in this work were collected by Panayiotis et al. at the City University, London, UK. They developed a special-purpose esophageal PPG probe [10] and used this probe to collect PPG waveforms on patients undergoing coronary artery bypass surgery and postoperative care in the intensive care unit [11, 12]. All patients were undergoing positive pressure ventilation. The experimental protocol received institutional approval, and each patient was consented before surgery. The purpose of these investigations was to evaluate the esophagus as an alternative site for measuring oxygen saturation. Their results show that while conventional finger pulse oximeters can fail during states of relative hypoperfusion, the esophageal PPG signal remained robust, providing a reliable indication of oxygen saturation (for a review of pulse oximetry in the esophagus, see 13]).

In this work, we analyzed the esophageal PPG waveforms for ten of the cardiac surgery patients described in Ref. [11], all of whom had coronary artery disease. While many comorbidities may have an impact on oxygen saturation (e.g., valvular disease, chronic obstructive pulmonary disease, congenital heart disease, ventilation/perfusion mismatch), none of these conditions were considered exclusionary. This liberal inclusion policy is in accordance with the exploratory nature of our investigation. For each patient, approximately 100 min of data were collected in blocks averaging 10 min. These data collections occurred in the operating room, the recovery suite, and the intensive care unit.

## COMPUTATIONAL TOOLS

Several software packages were used to analyze the data. The time-domain methods studied in this work required automated detection of the envelope of various waveforms. The envelope consists of a curve connecting the peaks of a periodic waveform and a curve connecting the troughs of the same waveform. This was accomplished using the ''Cyclic Measurements'' function of LabChart 7.0.3 (AdInstruments, adinstruments.com). The original waveforms along with the envelope waveforms were then analyzed in Mathematica 7.0 (Wolfram Research, wolfram.com), which was the environment in which all of the saturation calculations took place. Finally, the

resulting saturation data were analyzed for statistical significance using SPSS Statistics 17.0 (SPSS Inc., spss.com).

*Technical details of the experimental apparatus*

The PPG probe used by Kyriacou et al. consisted of a miniature circuit board containing a photodetector and two LEDs with center wavelengths 655 nm (Red) and 880 nm (IR) [11, 12]. This unit was placed in a sterile size-20 French gauge stomach tube and advanced down the esophagus of an anesthetized patient. Since the LEDs and the photodetector face the same direction, this is a reflectance-mode PPG probe. The two LEDs were time multiplexed by analog switches at 75 Hz. The signal from the photodetector was time demultiplexed such that each wavelength could be processed independently. The signals were then divided into a slowly changing signal (denoted "DC" to evoke quasi-static direct current electronic circuits), and a rapidly changing signal (denoted "AC" to evoke time-varying alternating current electronic circuits). The DC and AC signals were created with active filters designed to concentrate energy below 0.45 Hz in the DC signal, and energy above 0.45 Hz in the AC signal. These four analog waveforms were sampled by a 16-bit analog-to-digital converter at 100 Hz. The digital data streams were then stored on a personal computer for post-hoc analysis. Kyriacou et al. also recorded an EKG trace and data from an identical PPG probe placed on the finger; however, these additional waveforms will not be analyzed in the present work.

## ALGORITHMS FOR CALCULATING OXYGEN SATURATION

The algorithms examined in this work can be divided into time-domain algorithms and frequency-domain algorithms. The former are defined in terms of the time varying waveforms, while the latter are defined in terms of the Fourier transform of the time varying waveforms. For each algorithm, the PPG waveforms are used to calculate an equivalent of R, the "ratio of ratios." This quantity is then converted into an oxygen saturation using the relation $SO_2 = 110 - 25R$ (see [14] for a review of these basic pulse oximetry calculations).

*Time-domain algorithms*

*ArtSat: arterial oxygen saturation*

The ArtSat algorithm is the conventional time-domain algorithm for measuring the arterial oxygen saturation. Referring to Figure 1, the ArtSat algorithm is diagrammed on the far left. In this case, the numerator of R is the peak-to-trough amplitude of the AC waveform divided by the DC offset for the Red signals. The denomenator is the corresponding quantity defined in terms of the IR AC and IR DC signals. The modulations in the AC waveforms are dominated by the volume changes in the arteries, as evidenced by the fact that they are synchronous with the cardiac cycle.

*VenSat: venous oxygen saturation*

The VenSat algorithm is diagrammed in the middle of Figure 1. The numerator of R is the peak-to-trough amplitude of the DC waveform divided by the DC offset for the Red signals. The denomenator is the corresponding quantity defined in terms of the IR AC and IR DC signals. The modulations in the DC waveform are dominated by the influence of the positive pressure ventilation, as evidenced by the fact that they are synchronous with the 0.2 Hz respirator cycle. These modulations are thought to be due to volume changes in the venous compartment. Thus, we expect the oxygen saturations calculated by this algorithm to be lower than that calculated using the ArtSat algorithm.

*InstSat: instantaneous oxygen saturation*

The InstSat algorithm is diagrammed on the far right of Figure 1. Unlike the ArtSat and VenSat algorithms, the InstSat algorithm is not defined in terms of peak-to-trough amplitudes. Instead, the numerator of R is the value of the Red AC waveform minus the waveform minimum (defined as the waveform value at the preceding trough), divided by the Red DC offset. As with the previous two algorithms, the denomenator is the corresponding quantity defined in terms of the IR AC and IR DC signals. Unlike the ArtSat and VenSat algorithms, the InstSat algorithm does not attempt to measure the oxygen saturation in one vascular compartment. Rather, it aims to provide a moment-by-moment measurement of the average saturation of the blood in all the vascular compartments in the vicinity of the probe.

One complication of the InstSat algorithm is the inherent instability of the algorithm near the troughs in the AC waveform. Both the numerator and the denomenator of R are proportional to the change in the AC waveform relative to the value at the preceding trough. Therefore, in the vicinity of the troughs, the numerator and denomenator of R approach zero, and the overall fraction swings rapidly between the maximum and minimum allowable values. To address this instability, we modified the algorithm by adding a threshold feature. For each data point, the difference between the AC waveform and the preceding trough is compared to the DC offset. If the ratio of these two quantities is less than 0.03 (3%), the saturation calculated using these values is discarded. In that

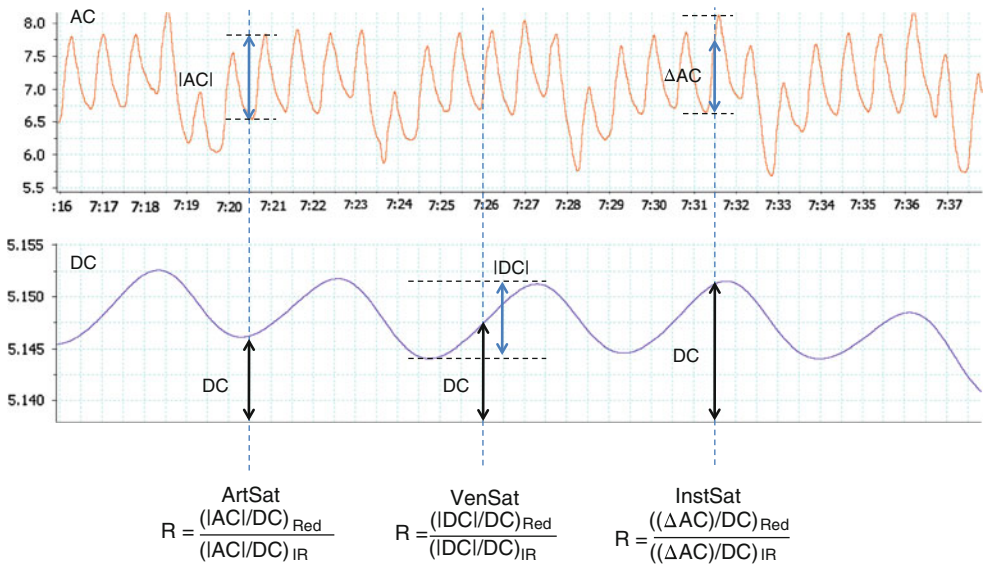


*Fig. 1. Time-domain algorithms defined in terms of the AC and DC photoplethysmograph (PPG) signals. These curves represent the AC and DC signals for one wavelength (either Red or IR). For each algorithm, the quantity R is defined in terms of the AC and DC waveforms at each wavelength. The oxygen saturation is calculated from R using the relation $SO_2 = 110 - 25R$. In the ArtSat algorithm the numerator of R is the peak-to-trough amplitude of the Red AC signal divided by the value of the Red DC signal at that moment (irrespective of where that DC value is in its oscillatory cycle). The denomenator of R is the same quantity defined using the IR AC and IR DC signals. In the VenSat algorithm the numerator of R is the peak-to-trough amplitude of the respiratory modulations in the Red DC signal divided by the value of the Red DC signal at that moment. As in the ArtSat algorithm, the denomenator of R is the same quantity defined using the IR signals. In the InstSat algorithm, the numerator of R is the height of the Red AC signal relative to the preceding trough divided by the value of the Red DC signal. As in the ArtSat and VenSat algorithms, the denomenator of R is the same quantity defined using the IR signals. The InstSat algorithm yields a time varying saturation waveform which has peaks that coincide with systole and troughs that coincide with diastole. The ArtInstSat waveform is constructed by connecting the peaks of these excursions. The VenInstSat waveform is constructed by connecting the troughs.*

case, the saturation from the previous time is carried forward until the change in the AC waveform exceeds 3% of the DC offset. We chose 3% for the threshold because this value prevented unphysiologic swings in saturation without over-smoothing the waveform.

This thresholding procedure can be thought of as a signal-to-noise cutoff. As the change in PPG waveform approaches zero, the corresponding volume of blood in motion also approaches zero. Since the overall algorithm for calculating saturation depends on blood in motion, the algorithm fails during the time periods when the blood is not moving. Fortunately, we may assume that the saturation of the blood in each compartment is approximately constant during these relatively short time periods. Therefore, it is reasonable to carry forward the saturation from the previous time instant.

This thresholding procedure introduces artifacts in the InstSat waveform near the points at which the change in the AC waveform crosses 3% of the DC offset. Therefore, we added a smoothing procedure which replaces the InstSat value with the mean of all of the InstSat values within 0.05s of the point in question.

The InstSat waveform is pulsatile, with peaks approximately coinciding with the peaks in the AC waveform. In order to obtain separate information about the arterial and the venous saturation, we used LabChart to take the envelope of the InstSat waveform, and associated the line connecting the peaks with the arterial saturation (ArtInstSat), and the line connecting the troughs with the venous saturation (VenInstSat).

### *Frequency-domain algorithms*

Both the time-domain and frequency-domain approaches to measuring oxygen saturation rely on the extraction of spectroscopic information about a region of tissue that is subject to time-varying engorgement with blood. In the time-domain algorithms, the motion of blood is quantified by subtracting the absorption at two moments in time (e.g., the peak and trough of the waveform). In the frequency-domain algorithms, the PPG waveform is decomposed into its spectral components. For any given frequency, the relative magnitude of the spectral amplitudes for the two wavelengths (Red and IR) gives an indication of the saturation of the blood which is moving with that frequency.

The general framework for these frequency-domain calculations is as follows. For each wavelength, the

relevant PPG signal (either the AC or the DC) is subject to a Fourier transform. Next, the frequency of interest is identified. This choice is typically made by associating a given peak in the spectrum with a physiological source of pulsatility at that frequency (e.g., the cardiac cycle, autonomic oscillations, the respiratory cycle, etc.). Once the frequency is chosen, a quantity analogous to R, the ''ratio of ratios,'' may be defined. Treating the Red signal first, the spectral amplitude at the frequency of interest is divided by the spectral amplitude at zero frequency to yield the numerator of R. The corresponding quantity is calculated using the IR signal, yielding the denomenator of R. Finally, as in the time-domain cases, R is converted into a saturation via the relation $SO_2 = 110 - 25R$.

*RespDC and RespAC: respiratory frequency algorithms*

The experimental apparatus divides the raw PPG signal for a given wavelength into ''AC'' and ''DC'' signals. The active filters which accomplish this signal processing are designed such that the ''DC'' signal contains spectral components below 0.45 Hz, while the ''AC'' signal contains spectral components above 0.45 Hz. It is well known that a real-time filtering circuit cannot achieve a transfer function which completely eliminates a specified range of frequencies. For example, we see that the envelope of the AC signal in Figure 1 oscillates with the same frequency as the DC signal, indicating that there is some leakage of spectral energy across the 0.45 Hz threshold. Thus, in targeting the respiratory frequency, we evaluated the same algorithm on both the DC and AC signals. We denote the results of this algorithm on the DC and AC signals RespDC and RespAC, respectively. The same reasoning that led us to expect that the time-domain algorithm VenSat would yield lower saturations suggests that RespDC and RespAC will also reflect the motion of venous blood.

The RespDC algorithm first finds frequency within the range [0.1, 0.3 Hz] at which the Fourier transform of the Red DC signal has the greatest amplitude. This peak-finding procedure is designed to identify the respiratory peak. Once this frequency is found, R is calculated as described above. Finally, the oxygen saturation is calculated using the relation $SO_2 = 110 - 25R$. The RespAC algorithm is identical to RespDC, except that the AC signals are used in place of the DC signals.

*Cardiac: oxygen saturation at the cardiac frequency*

The Cadiac algorithm first finds frequency within the range [0.75, 2 Hz] at which the Fourier transform of the Red AC signal has the greatest amplitude. This peak-finding procedure is designed to identify the cardiac peak. The saturation of the blood moving at this frequency is then calculated as in the previously described frequency algorithms. Since the cardiac frequency is associated with fluctuation in the arterial compartment, we expect the saturation obtained by this algorithm to reflect the motion of arterial blood.

*Harmonic: oxygen saturation at the cardiac harmonic frequency*

The Harmonic algorithm is identical to the Cardiac algorithm, except that the frequency used is twice the value of the cardiac peak, as determined by the Cardiac algorithm. The reasoning behind looking at this frequency is as follows. The central venous pulse waveform can be transmitted through the venous system, leading to peripheral venous pulsations and the appearance of a diastolic peak in the PPG signal [1]. When such a diastolic peak is superimposed on the systolic cardiac peak, the overall signal has peaks that occur at twice the cardiac frequency. Thus, we expect the saturation of blood moving at this frequency to reflect some combination of arterial and venous saturations.

## RESULTS

The eight saturation algorithms (ArtSat, VenSat, ArtInstSat, VenInstSat, RespDC, RespAC, Cardiac, and Harmonic) were applied to the esophageal PPG data recorded from ten patients undergoing cardiac surgery. Each patient record was divided into 1-min intervals. A given saturation algorithm applied to such a 1-min interval yields a time series of saturation values. The median of this set of saturation values was recorded as the value of that particular saturation algorithm applied to that particular patient. Quartile information characterizing this data is presented in Figure 2.

The primary goal of this work is to determine whether the proposed algorithms for measuring venous oxygen saturation yield lower saturations than the conventional algorithm used for calculating arterial saturation (ArtSat). The box-and-whisker plots presented in Figure 2 suggest that at least three of the proposed venous saturation algorithms (VenSat, VenInstSat, and RespDC) do indeed yield lower saturations. To show that these results are statistically significant, we compared the ArtSat algorithm with the seven other algorithms (VenSat, ArtInstSat, VenInstSat, RespDC, RespAC, Cardiac, and Harmonic), using seven separate applications of the Wilcoxon signed-rank test. Because we are making multiple comparisons, we use the Bonferroni correction to define the threshold for significance as $p = 0.05/n$, where n is the number of comparisons. In our case, $n = 7$, and the threshold for

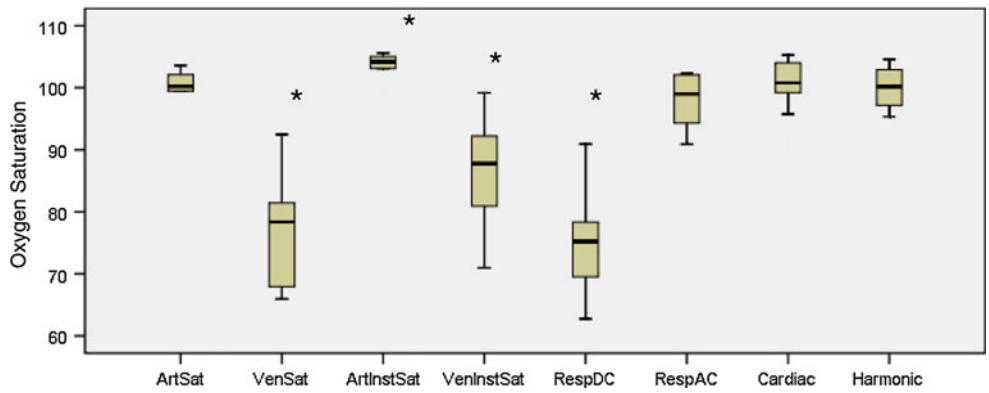


*Fig. 2. Saturation calculations using eight saturation algorithms applied to PPG waveforms collected from ten cadiac surgery patients. Quartiles and range are shown using box-and-whisker plots. The asterisks indicate statistical significance when compared to the standard algorithm for calculating arterial saturation (ArtSat) using a Wilcoxon signed-rank test with Bonferroni correction (statistical significance corresponds to $p < 0.0071$).*

significance is $p = 0.0071$. As indicated in Figure 2, four of the algorithms (VenSat, ArtInstSat, VenInstSat, and RespDC) show statistically significant differences from ArtSat. We examine the implications of these results in the following section.

## DISCUSSION

The purpose of this work is to evaluate several techniques for measuring venous oxygen saturation using the PPG signal. The general framework for these algorithms is based on the same principle that underlies conventional pulse oximetry. We first identify a vascular compartment that undergoes periodic volume changes. We then measure the change in optical absorbance that this motion produces at each of two wavelengths. This information is then combined with the known spectral properties of oxyhemoglobin and deoxyhemoglobin to infer the oxygen saturation of the blood in motion.

In conventional pulse oximetry, the detected volume change is due to the cardiac cycle. The dominant volumetric effect of the cardiac cycle on a given region of tissue is the periodic engorgement of the arterial compartment. Thus, this method is designed to measure the oxygen saturation of arterial blood. This approach can be implemented in the time-domain by calculating the change in absorbance between systole and diastole (ArtSat), or in the frequency-domain by comparing the strength of the cardiac peaks in the Fourier transforms of the PPG waveform at each wavelength (Cardiac).

In order to measure the oxygen saturation of venous blood, the methods that we investigate rely on two sources of volume change in the venous compartment: respiration and venous pulsations. In the case of respiration, we evaluate one time-domain algorithm (VenSat) and two frequency-domain algorithms (RespDC and RespAC). In the case of venous pulsations, we evaluate time-domain algorithms ArtInstSat and VenInstSat, which are derived from an ''instantaneous saturation.'' Unlike the other methods for calculating oxygen saturation, the instantaneous saturation algorithm yields a saturation waveform that reflects changes within a single cardiac cycle. We evaluate a frequency-domain algorithm (Harmonic) for detecting venous pulsations by comparing the energy in the PPG at twice the cardiac frequency for each wavelength.

The first step in evaluating a given method for measuring oxygen saturation is to determine if the differences between the new method and the conventional method are statistically significant. As reported in Figure 2, four of the algorithms (VenSat, ArtInstSat, VenInstSat, and RespDC) show statistically different saturation values when compared to the conventional algorithm (ArtSat). Contrariwise, the remaining three algorithms (RespAC, Cardiac, and Harmonic) do not show statistically significant difference from ArtSat. We next discuss the results for each algorithm individually.

As seen in Figure 2, the VenSat algorithm yields saturations that are clustered around 80%, which is within the physiologic range of venous saturations. The VenSat distribution is clearly distinct from the ArtSat distribution, which is tightly clustered around 100%. Thus, the VenSat algorithm satisfies both of the criteria we specified for a successful demonstration. First, the saturation values are statistically distinguishable from the conventional algorithm. Second, the saturation values are within a physiologic range for venous saturations.

RespDC and RespAC are the frequency-domain algorithms that correspond to the time-domain algorithm VenSat. RespDC involves comparing the respiratory peaks (~0.2 Hz) of the Fourier transforms of the "DC" signals, which are produced by a filter that passes frequencies less than ~0.45 Hz. RespAC is the same algorithm applied to the "AC" signals, which are produced by a filter that passes frequencies greater than ~0.45 Hz. Since RespDC is the frequency-domain equivalent of VenSat, we expect similar saturations, and Figure 2 confirms this. On the other hand, the majority of the respiratory modulation has been filtered out of the "AC" signals. One might therefore expect that the RespAC algorithm would yield saturations close to the isobestic point (85%). This is the saturation obtained when the signals at the two wavelengths are identically modulated, as in the case of pure noise [14]. If fact, Figure 2 shows that the saturations generated by RespAC are consistent with the arterial saturations generated by ArtSat. This suggests that the filter that creates the "AC" signals does not completely extinguish frequencies below ~0.45 Hz. Furthermore, it suggests that the pressure changes associated with respiration lead to volume changes in the arterial compartment as well as the venous compartment.

VenInstSat and ArtInstSat both yield saturations that differ from ArtSat such that the differences are statistically significant. Since the VenInstSat algorithm is designed to track the minimum excursions of the instantaneous saturation of the blood, we would expect these saturations to be in the venous range. Indeed, we see in Figure 2 that VenInstSat yields saturations that are clustered in the mid to upper 80s. The ArtInstSat algorithm is designed to track the maximum excursions of the instantaneous saturation. It is interesting to note that this algorithm yields saturations that are higher than those of the ArtSat algorithm. This may be due to the fact that the conventional ArtSat algorithm mixes some venous influence in the algorithm (venous blood is surely in motion to some degree during systole). In contrast, the ArtInstSat algorithm may provide a closer approximation to true arterial saturation because it is sensitive to the initial influx of arterial blood at the beginning of systole.

The Cardiac algorithm is the frequency-domain equivalent of ArtSat algorithm. Thus, is it not surprising that the difference between these two algorithms is not statistically significant. The Harmonic algorithm is a frequency-domain algorithm that is designed to detect venous pulsations by comparing the energy in the PPG at twice the cardiac frequency for each wavelength. As seen in Figure 2, this algorithm yields saturations that are consistent with Cardiac and ArtSat, indicating that Harmonic fails to detect venous blood. We may understand this failure in the following way. In analyzing the Fourier transforms of the PPG signals at twice the cardiac frequency, we are combining the effects of the systolic pulsation with whatever diastolic pulsations are present. Thus, even if the diastolic pulsations do represent the motion of venous blood, the contribution from the motion of the arterial blood during systole will dominate the overall saturation.

The approach we have followed in this work is subject to several limitations. First, as mentioned above, the equation we use for calculating saturation interprets random noise as blood with saturation 85%. Since this value is also in the physiologic range for the saturation of venous blood, it is possible that some of the low saturations that we measure are due to noise and not the motion of venous blood. However, we can be confident that the algorithms which yield saturations much lower than 85% (VenSat and RespDC) are less susceptible to this criticism. Second, as with all PPG analysis, our algorithms are subject to error due to the influence of artifacts in the raw signal. These artifacts may be due to a myriad of sources, such as optical noise, electrical noise, and motion artifacts. Third, the algorithms we investigate here rely on automated algorithms that are designed to detect the peaks and troughs of the PPG waveforms. When the PPG waveforms depart from sinusoidal behavior, these algorithms can provide spurious results. Fourth, the lack of a calibration step in the calculation of our saturations leads to values that range above the logical maximum (100%) and below the physiological reasonable minimum (50%).

Despite these limitations, it is still possible to make provisional conclusions in light of our results. Specifically, we have provided strong evidence that it is possible to gain information concerning the oxygen saturation of venous blood via analysis of the esophageal PPG waveform. The clearest demonstration of this effect is seen in the algorithms that target the respiratory cycle (VenSat and RespDC). The low saturations measured by these algorithms strongly support the hypothesis that the effect of positive pressure ventilation on the PPG waveform is mediated predominately by volume changes in the venous compartment.

It is premature to assess the clinical implications of the results presented here. In order to use these venous saturation algorithms to infer other physiological parameters, it will be necessary to compare these algorithms with a gold standard, such as blood gas analysis or co-oximetry. Nonetheless, given that we have strong evidence that we can detect the motion of venous blood, it is plausible that a calibration step similar to that used in conventional pulse oximetry would enable our algorithms to provide accurate, real-time, noninvasive measurement of regional venous oxygen saturation.

An important difference between the traditional methods for measuring arterial saturation and the methods we present here for measuring venous saturation is that the arterial saturations are presumed to be the same throughout the body, while the venous saturations depend on numerous local features of the tissue being studied. Instead of obtaining a surrogate for mixed venous saturation, these methods yield information about the venous blood in the particular region of the body that is illuminated by the PPG probe. The mixed venous saturation is known to provide valuable clinical information (for example in contributing to the early goal-directed therapy algorithm for treatment of sepsis [15]); thus, it may seem that regional venous saturation is less useful in a clinical setting. However, there are two factors that mitigate this criticism. First, by combining the regional venous saturation information from several PPG probes (finger, esophagus, earlobe, forehead), it may be possible to generate a surrogate for true mixed venous saturation. Second, there may be clinical settings in which regional venous saturation is preferable to mixed venous saturation. For example, given the predominate sympathetic innervation of the extremities, early signs of shock may be evident in the venous saturation of blood in the finger before other parts of the body are affected. In addition, regional venous saturation might facilitate better monitoring of the health of a surgical skin flap as reflected by its oxygen utilization.

Looking to the future, an important step in refining these algorithms is to obtain the raw PPG signal, before it is decomposed into the ''DC'' and ''AC'' waveforms. This will remove the ambiguity that arises due the relative proximity of important spectral features (i.e., the respiratory peak at 0.2 Hz) and the filter cutoff frequency 0.45 Hz. In addition, it will be necessary to evaluate these algorithms using PPG data collected from sites other than the esophagus. Furthermore, as mentioned above, it will be crucial to compare these algorithms for measuring venous saturation against a gold standard. This will also entail designing experimental methods for altering the venous oxygen saturation in the vicinity of the PPG probe. Such methods might include changing the inspired oxygen fraction or changing the elevation and/or temperature of the relevant limb.

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