



Estimation of the inferior caval vein saturation using high-fidelity non-invasive haemodynamic values and validation of modelled estimates

Original Article

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Abstract

Objectives: Monitoring venous saturation allows identification of inadequate systemic oxygen delivery. The aim was to develop a model using non-invasive haemodynamic variables to estimate the inferior caval vein saturation and to determine its prognostic utility. **Methods:** This is a single-centre, retrospective study. A Bayesian Pearson's correlation was conducted to model the inferior caval vein saturation. Next, a Bayesian linear regression was conducted for data from all the patients and from only those with parallel circulation. Venous saturation estimations were developed. The correlation of these estimates to the actual inferior caval vein saturation was assessed. The resulting models were then applied to two validation cohorts: biventricular circulation (arterial switch operation) and parallel circulation (Norwood operation). **Results:** One hundred and thirteen datasets were collected across 15 patients. Of which, 65% had parallel circulation. In all patients, the measured and estimated inferior caval vein saturations had a moderate and significant correlation with a coefficient of 0.64. In patients with parallel circulation, the measured and estimated inferior caval vein saturation had a moderate and significant correlation with a coefficient of 0.61. In the biventricular circulation cohort, the estimated inferior caval vein saturation had an area under the curve of 0.71 with an optimal cut-off of 49. In the parallel circulation cohort, the estimated inferior caval vein saturation had an area under the curve of 0.83 with an optimal cut-off of 24%. **Conclusion:** The inferior caval vein saturation can be estimated utilising non-invasive haemodynamic data. This estimate has correlation with measured inferior caval vein saturations and offers prognostic utility.

Monitoring of a venous saturation allows for the ability to identify inadequacy of systemic oxygen delivery and the increasing probability of morbidity and mortality in humans.¹⁻⁷ As venous saturation is one of the few components of the Fick equation for cardiac output, this should not be of surprise. However, monitoring a venous saturation can be invasive and costly and is thus not routinely done.

Anecdotally, many paediatric intensivists still routinely utilise indirect measures such as blood pressure to assess cardiac output which, combined with oxygen content, quantifies systemic oxygen delivery.⁸ However, pressure changes in any system are not always directly a result of changes in flow and may be a result of changes in resistance. In the clinical setting, direct, real-time monitoring of systemic vascular resistance is not particularly feasible. Previous studies have demonstrated that conventional haemodynamic variables, such as blood pressure, do not adequately reflect underlying adequacy of systemic oxygen delivery.^{9,10} Ongoing development in non-invasive estimation of the venous saturation utilising tools such as near-infrared spectroscopy has abated this, somewhat, allowing for more routine use of venous saturation monitoring. This has been particularly true in paediatric cardiac iCU.

The primary aim of this study was to develop a model using non-invasive haemodynamic variables to estimate the inferior caval vein saturation. A secondary aim of this study was to then apply the model to validation cohorts to determine its prognostic utility.

Methods

Study design

This was a single-centre, retrospective study aimed to try to estimate the inferior caval vein saturation using non-invasive monitoring data. The study was approved by the institutional review board and is in concordance with the Helsinki declaration.

Variables of interest

The variables of interest collected were as follows: venous saturation, heart rate, mean arterial blood pressure, arterial saturation by pulse oximetry, cerebral near-infrared spectroscopy, and renal near-infrared spectroscopy. The presence or absence of a functionally univentricular heart was also collected. Functionally, univentricular hearts were defined as those with parallel circulation, Glenn circulation, or Fontan circulation. Parallel circulation was defined as any circulation in which the saturation of blood going to the pulmonary and systemic circulations was equal.

Venous saturations were obtained by use of femoral lines terminating in the inferior caval vein. Line placement was confirmed by radiographs.

Two-site near-infrared spectroscopy values were collected. A cerebral and renal value were collected. Near-infrared spectroscopy values were obtained using the Casmed ForeSight Elite tissue oximeter. Cerebral near-infrared spectroscopy sensors were placed on midline in the forehead, while renal near-infrared spectroscopy sensors were placed on the back between the costal margin and the iliac crest with the sensor lateral to the spine and the remainder of the sensor wrapping around the flank. Only one renal near-infrared spectroscopy sensor was on the patient at a time. The sensors were replaced at 1-to-3-day intervals.

Heart rate, mean arterial blood pressure, arterial saturation by pulse oximetry, cerebral near-infrared spectroscopy, and renal near-infrared spectroscopy were collected as the mean of these values for the 20 minutes preceding when the venous saturation was obtained. Data were collected in this manner as to help lend insight into how the values correlate with the venous saturation prior to that data being available. This was done to help account for any outlying values. T3 captures these data in high fidelity in continuous fashion at user-defined intervals. For this study, T3 captured data every 5 seconds. T3 (Etiometry Inc., Boston, MA) is a software that captures physiologic streaming data from various clinical monitoring devices. The data are captured every 5 seconds. Selected variables can be displayed in a graphical interface, and captured data are stored for retrieval for future use.

The values of interest were all purposefully selected such that they may be obtained non-invasively.

Statistical analyses

Continuous variables were reported as mean and standard deviation, while categorical variables were reported as absolute frequency and percentage. A Bayesian Pearson's correlation was conducted to assess the correlation between the collected variables of interest, with a particular interest in trying to model the inferior caval vein saturation using heart rate, arterial saturation, mean arterial blood pressure, cerebral near-infrared spectroscopy, and renal near-infrared spectroscopy.

Next, a Bayesian linear regression was conducted with the inferior caval vein saturation as the dependent variable and the following independent variables: heart rate, arterial saturation, mean arterial blood pressure, cerebral near-infrared spectroscopy, and renal near-infrared spectroscopy. This was done utilising the Jeffreys–Zellner–Siow prior. This was repeated for data from all the patients and then for a subset of data from only those with parallel circulation. Parallel circulation was defined as those with the same saturation of blood entering the pulmonary and systemic circulations.

The resulting models were then used to develop a venous saturation estimation for all patients utilising the model developed from data from all the patients. Next, a second venous saturation estimate was developed using the model specific for those with parallel circulation.

The correlation of these estimates to the actual inferior caval vein saturation was then assessed with a Bayesian Pearson's correlation. Bland–Altman analysis was also conducted to determine the absolute relationship between the estimated and actual inferior caval vein saturation.

Clinical outcome validation

As the models developed utilised all the data collected, the resulting models were then applied to two separate validation cohorts. The first was a set of haemodynamic data collected immediately upon admission to the cardiac ICU in children who underwent an arterial switch operation, thus, representing a cohort of patients with biventricular circulation.

The second validation cohort was a set of haemodynamic data collected immediately upon admission to the cardiac ICU in children who underwent a Norwood operation, thus, representing a cohort of patients with parallel circulation.

Data for both these validation cohorts were historic and collected prior to the implementation of T3 at our institution. As venous saturations were not available for many of these patients, validation of the estimated venous saturation was done against clinical outcome. A composite outcome of cardiac arrest, need for extracorporeal membrane oxygenation, or inpatient mortality was created for both cohorts. An estimated venous saturation was then calculated for all patients. The estimated inferior caval vein saturation's ability to identify those who experienced this outcome was then identified and compared to the ability of the cerebral and renal near-infrared spectroscopy values in isolation. It should be noted that near-infrared spectroscopy data for the validation cohort came from a different oximetry system which was the Medtronic INVOS system.

Results

Model creation cohort

A total of 113 datasets were collected across 15 unique patients. Datasets, rather than patients, were treated as individual subjects. As such, the median age was 7 months. Of the 113 data points, 73 (65%) were from those with functionally univentricular hearts all of which had parallel circulation. Thus, there were none with Glenn or Fontan circulations. Of the 113 data points, 3 (3%) had transposition physiology.

Correlation of the inferior caval vein saturation and other haemodynamic variables

In all patients, there was a weak but significant correlation between the arterial saturation and the venous saturation, moderate and significant correlation between the cerebral near-infrared spectroscopy and the venous saturation, weak but strong correlation between the renal near-infrared spectroscopy and the venous saturation, and no correlation between the mean arterial blood pressure and the venous saturation (Table 1).

In those with parallel circulation, there was no correlation between arterial saturation and the venous saturation, there was a moderate and significant correlation between the cerebral

Table 1. Correlation of inferior caval vein saturation and collected variables.

| | Arterial saturation | Cerebral near-infrared spectroscopy | Renal near-infrared spectroscopy | Heart rate | Mean arterial blood pressure |
|---|---------------------|-------------------------------------|----------------------------------|------------|------------------------------|
| Venous saturation (all patients) | 0.440*** | 0.670*** | 0.375*** | -0.341** | 0.163 |
| Venous saturation (parallel circulation only) | 0.321 | 0.698*** | 0.18 | -0.242 | 0.036 |

*BF₁₀ > 10.**BF₁₀ > 100.***BF₁₀ > 1000.**Table 2.** Area under the curve of the estimated inferior caval vein saturation versus other admission haemodynamic variables in predicting a composite outcome.

| | Estimated inferior caval vein saturation | Cerebral near-infrared spectroscopy | Renal near-infrared spectroscopy | Heart rate | Mean arterial blood pressure | Arterial pH | Arterial lactate |
|----------------------|--|-------------------------------------|----------------------------------|------------|------------------------------|-------------|------------------|
| Norwood cohort | 0.83 | 0.75 | 0.73 | 0.33 | 0.73 | 0.41 | 0.43 |
| Transposition cohort | 0.71 | 0.55 | 0.67 | 0.32 | 0.72 | 0.64 | 0.52 |

Composite outcomes include cardiopulmonary arrest, need for extracorporeal membrane oxygenation, or mortality during the post-operative admission.

near-infrared spectroscopy and the venous saturation, there was no correlation between the renal near-infrared spectroscopy and the venous saturation, no correlation between the heart rate and the venous saturation, and no correlation between the mean arterial blood pressure and the venous saturation (Table 1).

Regression analyses, all patients

When data from all patients were entered into regression analyses, the resulting model had a Bayes Factor of 77.49 and an R-squared value of 0.70. The resulting equation was as follows:

$$-18 - (0.24 \times \text{age in months}) - (0.12 \times \text{arterial saturation}) + (0.45 \times \text{cerebral near-infrared spectroscopy}) + (0.86 \times \text{renal near-infrared spectroscopy}) - (0.13 \times \text{heart rate}) + (0.21 \times \text{mean arterial blood pressure})$$

When data from only those with parallel circulation were entered into the regression analyses, the resulting model had a Bayes Factor of 10.25 and an R-squared value of 0.73. The resulting equation was as follows: $46.74 + (2.0 \times \text{age in months}) - (0.66 \times \text{arterial saturation}) + (0.57 \times \text{cerebral near-infrared spectroscopy}) + (0.65 \times \text{renal near-infrared spectroscopy}) - (0.18 \times \text{heart rate}) + (0.05 \times \text{mean arterial blood pressure})$ (Figure 1).

Estimated and measured inferior caval vein saturation

When all data were considered, the average measured inferior caval vein saturation was 56, while the average estimated inferior caval vein saturation was 51. The measured and estimated inferior caval vein saturations had a moderate and significant correlation with a coefficient of 0.64. The mean between the estimated and measured inferior caval vein saturation was -5 (95% confidence interval -11-1).

When only data from those with parallel circulation were considered the median of measured inferior caval vein saturation was 54, while the average estimated inferior caval vein saturation was 53. The measured and estimated inferior caval vein saturation had a moderate and significant correlation with a coefficient of 0.61.

Clinical outcome validation

The arterial switch validation cohort consisted of 43 patients, 4 of whom experienced the composite outcome. In this cohort, the estimated inferior caval vein saturation had an area under the curve of

$$\begin{aligned} &\text{All patients} \\ &-18 - (0.24 \times \text{age in months}) - (0.12 \times \text{arterial saturation}) \\ &\quad + (0.45 \times \text{cerebral near infrared spectroscopy}) \\ &+ (0.86 \times \text{renal near infrared spectroscopy}) - (0.13 \times \text{heart rate}) \\ &\quad + (0.21 \times \text{mean arterial blood pressure}) \\ &\text{Parallel circulation only} \\ &46.74 + (2.0 \times \text{age in months}) - (0.66 \times \text{arterial saturation}) \\ &\quad + (0.57 \times \text{cerebral near infrared spectroscopy}) \\ &+ (0.65 \times \text{renal near infrared spectroscopy}) - (0.18 \times \text{heart rate}) \\ &\quad + (0.05 \times \text{mean arterial blood pressure}) \end{aligned}$$

Figure 1. Resulting equations after regression analyses for all patients and for those with parallel circulation only.

0.71 to identify patients with the composite outcome. The optimal cut-off was found to be 49. This had 100% sensitivity, 60% specificity, 16% positive predictive value, and 100% negative predictive value with respect to the composite outcome. Of these patients, 19 had an estimated inferior caval vein saturation of less than 49% on admission to the cardiac ICU immediately after the arterial switch, while the remaining 24 had an estimated inferior caval vein saturation of greater than 49%. The estimated inferior caval vein saturation had greater discriminative utility than cerebral near-infrared spectroscopy, renal near-infrared spectroscopy, heart rate, mean arterial blood pressure, arterial pH, and arterial lactate (Table 2).

The Norwood validation cohort consisted of 100 patients, 7 of whom experienced the composite outcome. In this cohort, the estimated inferior caval vein saturation had an area under the curve of 0.83 to identify patients with the composite outcome. The optimal cut-off was found to be 24%. The estimated inferior caval vein saturation had 100% sensitivity, 76% specificity, 24% positive predictive value, and 100% negative predictive value with respect to the composite outcome. Of these patients, 29 had an estimated inferior caval vein saturation of less than 24% on admission to the cardiac ICU immediately after the Norwood operation, while the remaining 71 had an estimated venous saturation that was greater than 24%. The estimated inferior caval vein saturation had greater discriminative utility than cerebral near-infrared spectroscopy, renal near-infrared spectroscopy, heart rate, mean arterial blood pressure, arterial pH, and arterial lactate (Table 2).

Discussion

These data demonstrate that the inferior caval vein saturation can be estimated using non-invasive values. The resulting estimates have moderate and significant correlation with the measured inferior caval vein saturation. More importantly, this estimate of the inferior caval vein saturation had strong discriminative value of a composite outcome of cardiopulmonary arrest, need for extracorporeal membrane oxygenation, or inpatient mortality, outperforming the other individual haemodynamic values. The 95% confidence interval of the mean difference does indicate that the estimate may not be the most precise, and it is still a helpful trending tool with good prognostic ability.

While such a tool can be helpful in clinical management, the underlying physiologic principles highlighted by an exercise in attempting to estimate a central venous saturation is equally important. The current data demonstrate the relative effects of various haemodynamic variables on the inferior caval vein saturation. Near-infrared spectroscopy seemed to contribute most to the underlying estimate and had greatest correlation with the actual inferior caval vein saturation. This should come as no surprise as near-infrared spectroscopy in the clinical setting was designed to help estimate the underlying venous saturation.

Arterial saturation had some significant correlation with the inferior caval vein saturation as well. Interestingly, heart rate and blood pressure had negligible correlation with the underlying inferior caval vein saturation. The lack of correlation between blood pressure and venous saturation should not be surprising as pressure is the product of flow and resistance. This means that systemic blood pressure is the product of systemic cardiac output and systemic vascular resistance.^{11,12} Of these two components, only systemic cardiac output contains oxygen and can directly augment systemic oxygen delivery. Systemic vascular resistance can directly modulate blood pressure but does not contribute to systemic oxygen delivery. In fact, blood pressure may increase due to an increase in systemic vascular resistance, while systemic cardiac output may actually decrease. This would lead to an overall decrease in systemic oxygen delivery. Thus, using blood pressure as a surrogate for cardiac output and systemic oxygen delivery is problematic if systemic vascular resistance cannot be monitored simultaneously. This has been previously demonstrated.^{13–15}

What is perhaps most telling is that when the estimated inferior caval vein saturation was applied to historic data in transposition and Norwood cohorts, the estimated inferior caval vein saturation had a strong ability to identify those who would experience post-operative, inpatient cardiopulmonary arrest, extracorporeal membrane oxygenation, or mortality. The estimated inferior caval vein saturation not only had strong discriminative value but outperformed the other haemodynamic variables when used in isolation, including the individual near-infrared spectroscopy values and the oft-used mean arterial blood pressure.

Previous data have demonstrated that the inferior caval vein saturation can be helpful in early detection of morbidity after paediatric cardiac surgery.^{7,16} Some of this data has even indicated that the inferior caval vein saturation may be more helpful than the superior caval vein in this regard.⁷ While both may be helpful, due to cerebral autoregulation, the inferior caval vein saturation may change first and more noticeably than the superior inferior caval vein saturation when global changes in systemic oxygen delivery are occurring. Anecdotally, mixed venous saturation tends to be credited with having the greatest prognostic utility, although there is no data that has compared the prognostic utility of superior caval

vein, inferior caval vein, and mixed venous saturations in the same patient cohort and demonstrated this. Many have also, anecdotally, then credited superior caval vein saturation to have more prognostic utility when compared to inferior caval vein saturation. This, however, has not been demonstrated to be the case.

The prognostic utility of central vein saturation should not be surprising. As bodily processes and organs require oxygen, monitoring systemic oxygen delivery seems to be, logically, an ideal metric to follow. Systemic oxygen delivery is the product of cardiac output and oxygen content. Oxygen content is the sum of the bound and dissolved amounts of oxygen in the blood. Cardiac output is described by the Fick principle and is the quotient of oxygen consumption and the arteriovenous oxygen content difference. The arteriovenous oxygen content difference then can be somewhat oversimplified into the arterial and venous saturations.¹¹ Thus, the venous saturation and its utility become apparent from the objective and quantitative breakdown of systemic oxygen delivery and its components. The association of low venous saturation or low near-infrared spectroscopy has been demonstrated to be associated with morbidity such as neurodevelopmental delay, acute kidney injury, necrotising enterocolitis, and hepatic insufficiency.^{17–27}

Monitoring the venous saturation can be done by sampling venous blood and running a blood gas. This, however, can be invasive and costly. Thus, non-invasive methods of estimating venous saturation may be helpful. Near-infrared spectroscopy has been one such tool, with regional near-infrared spectroscopy values being demonstrated to trend moderately well to the underlying regional venous saturation.²⁸ While the numbers provided by near-infrared spectroscopy may have significant absolute difference from the absolute underlying venous saturation, near-infrared spectroscopy still outperforms other indices in prognostic utility. The current study demonstrates that near-infrared spectroscopy may be utilised in modelling the underlying inferior caval vein saturation. When combined with other haemodynamic indices, the prognostic utility of the estimated inferior caval vein saturation demonstrates strong discriminative utility to detect adverse events.

There are many benefits in estimating the inferior caval vein saturation in the manner done by this study. First, it lends insight into what the relative contributions of the studies haemodynamic indices is to the underlying venous saturation. Second, it provides a value that can be calculated at the bedside and utilised. Third, it provides a tool with good prognostic ability, specifically sensitivity and negative predictive value. This makes this particularly valuable as a screening tool.

Previous studies have investigated prediction of cardiorespiratory deterioration such as a study by Rusin and colleagues. This study utilised high-fidelity physiologic data from three centres utilising Sickbay software to help develop a predictive model to predict a composite of cardiac arrest, extracorporeal membrane oxygenation, or unplanned intubation in patients with single-ventricle parallel circulation. The resulting algorithm could accurately predict approximately 53% of such events in the 2 hours preceding. The current study is additive to such studies as it provides a predictive model utilising different data inputs. The current study utilises data that is readily available such as age, heart rate, blood pressure, arterial saturation, and near-infrared spectroscopy values. Other algorithms, such as the one developed by Rusin and colleagues, utilised other metrics that are not as easily used by an individual at the bedside. These included heart rate variability, ST-segment variability, frequency of premature

ventricular contractions, and pleth variability index.²⁹ This is not a criticism by the efforts of the study by Rusin and colleagues as the aim for that study was to develop an automated means by which to predict an event. The current study aimed to develop a model which could be more easily applied by an individual in the clinical setting.

There are, however, limitations to this study as well. First, the estimate is based on 113 datasets which relative to other paediatric cardiology studies represents a large sample size. However, the estimate will improve with additional datasets. Venous saturations are not obtained routinely, and thus the number of venous saturations becomes a limiting factor. Second, the estimate was based on using the CasMed Foresight oximeter. While the validation cohorts utilised data from the Medtronic INVOS system, the lack of venous saturations in these cohorts only allowed for a validation of the prognostic ability of the tool and not its absolute correlation. Third, the estimated venous saturation does have a clinically large 95% confidence interval. Thus, it must be kept in mind that the absolute estimation may not be the most precise. However, the correlation coefficient implies that the estimate still offers insight into the underlying trend. Additionally, the prognostic utility is also high. Fourth, the model creation and validation cohorts all include patients from a single institution. This may not necessarily be a true limitation, but future validation cohorts from other centres would be insightful. Fifth, the estimated inferior caval vein saturation has low positive predictive value. This may not be a true limitation, either, but is worth mentioning. This is likely secondary to a relatively low number of composite events in the validation cohorts. Thus, future clinical outcome validation with larger cohorts may be additive. Sixth, the validation here is not actually validating the estimated inferior caval vein saturation. This was due to limitations in historic data for the inferior caval vein saturation. The clinical correlate validation was conducted, not in lieu of this, but to at least present some form of validation. Seventh, there is variability in where the femoral venous line may have terminated. There may be differences in the measured inferior caval vein saturation depending on where the tip of the catheter is. For example, those closer to the renal vein may provide a higher measured saturation compared to those that may be closer to the hepatic vein. This may impact the precision of the estimation and the results of the current study would represent this effect.

Application of the model to other validation cohorts for the assessment of absolute estimate difference, correlation, and clinical prognostic utility is required.

Conclusion

The inferior caval vein saturation can be estimated utilising non-invasive haemodynamic data. This estimate has correlation with measured inferior caval vein saturations and offers prognostic utility.

Availability of data and material. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests. The authors have no relevant financial or non-financial interests to disclose.

Ethical approval. The study have been approved by the appropriate institutional ethics committee and have been performed in accordance with

the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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