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Vector Autoregressive (VAR) Models and Granger Causality in Time Series Analysis in Nursing Research: Dynamic Changes Among Vital Signs Prior to Cardiorespiratory Instability Events as an Example

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Abstract

Background—Patients undergoing continuous vital sign monitoring (heart rate [HR], respiratory rate [RR], pulse oximetry [SpO₂]) in real time display inter-related vital sign changes during situations of physiologic stress. Patterns in this physiological cross-talk could portend impending cardiorespiratory instability (CRI). Vector autoregressive (VAR) modeling with Granger causality tests is one of the most flexible ways to elucidate underlying causal mechanisms in time series data.

Purpose—The purpose of this article is to illustrate development of patient-specific VAR models using vital sign time series (VSTS) data in a sample of acutely ill, monitored, step-down unit (SDU) patients, and determine their Granger causal dynamics prior to onset of an incident CRI.

Approach—CRI was defined as vital signs beyond stipulated normality thresholds (HR = 40–140/minute, RR = 8–36/minute, SpO₂ < 85%) and persisting for 3 minutes within a 5-minute moving window (60% of the duration of the window). A 6-hour time segment prior to onset of first CRI was chosen for time series modeling in 20 patients using a six-step procedure: (a) the uniform time series for each vital sign was assessed for stationarity; (b) appropriate lag was determined using a lag-length selection criteria; (c) the VAR model was constructed; (d) residual autocorrelation was assessed with the Lagrange Multiplier test; (e) stability of the VAR system was checked; and (f) Granger causality was evaluated in the final stable model.

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Results—The primary cause of incident CRI was low SpO₂ (60% of cases), followed by out-of-range RR (30%) and HR (10%). Granger causality testing revealed that change in RR caused change in HR (21%) (i.e., RR changed before HR changed) more often than change in HR causing change in RR (15%). Similarly, changes in RR caused changes in SpO₂ (15%) more often than changes in SpO₂ caused changes in RR (9%). For HR and SpO₂, changes in HR causing changes in SpO₂ and changes in SpO₂ causing changes in HR occurred with equal frequency (18%).

Discussion—Within this sample of acutely ill patients who experienced a CRI event, VAR modeling indicated that RR changes tend to occur before changes in HR and SpO₂. These findings suggest that contextual assessment of RR changes as the earliest sign of CRI is warranted. Use of VAR modeling may be helpful in other nursing research applications based on time series data.

Keywords

nursing care; nursing research; pathophysiology; physiologic monitoring; regression analysis; statistical models; time series analysis; vital signs

Many nursing phenomena are time-dependent. Beginning early in their training years and beyond, nurses are taught to measure changes in behavior, patient outcomes, and responses occurring along a delineated time interval. Ever since Nurse Linda Richard's invention of bedside records (Holder, 2004), flow sheet usage and time series data have been ubiquitous and important in nursing. More recently, real-time data capture of vital signs using telemetry and portable monitors has created the opportunity to time stamp longitudinal data. Such time series data have potential to reveal patterns in manifestations of the variables at specific time intervals (Chatterjee & Price, 2009). However, accurate and timely human-only interpretation of temporal patterns or trends in voluminous time series data is impossible. Finding patterns in time series data for nursing research purposes, particularly in identifying temporal pattern emergence prior to critical events, involves proper understanding and use of appropriate mathematical models to study changes across time at the level of the individual.

Models for time series analysis are idiographic in nature. This means that they are tools for analyzing unique and patient-specific fluctuations within a time series. As such, time series approaches provide a framework for analyzing future changes for an individual based on past trends and patterns. Predicting how a particular patient's time series data could behave based on past trends has numerous implications for bed-side nursing practice. It provides a framework allowing the uniqueness of each patient to exist as a basis for assessing change over time—not as a deviation from a predetermined pattern generalizable to all patients, but as an alteration in a personal pattern.

Time series data occur when sets of observations from an individual case are arranged in temporal order. The primary interest is the relationship of the values from one point in time to the next for individual cases. In order to develop reasonable models for illuminating interrelationships among the points in a time series, large datasets with observations distributed densely over time are needed. With real-time data acquisition systems now in place and “big data” ubiquitous, researchers can now define “sampling windows.” Sampling windows are shorter researcher-defined epochs within an overall time period—defined by a

duration of time (in minutes, hours, or days, as appropriate for the problem under study) and number of observations within the time period.

Time series models account for the fact that successive observations are correlated. The correlation among elements in a time series is called autocorrelation. Higher values signify greater association between an observation on a variable X (like heart rate) at some time t and at later times $t + k$, where k indicates the next 1, 2, up to N observations within the window, where $N \in \mathbf{Z}$ (the set of integers) is the maximum number of observations (Chatfield, 2003).

Multivariate time series analysis involves more than one variable (like heart rate, respiratory rate, blood pressure, and SpO₂). Strength of associations among different variables across time lags (shifts in time) are indexed with cross-correlations (Box, Jenkins, & Reinsel, 2008). Several possible lags can be used to examine cross-correlations. For instance, if X_t is the value of the variable in period t , $\text{lag}(X_t, 1)$ represents the value of the variable in period $t-1$ (lagged one period back in time).

The vector autoregression (VAR) model is one of the most commonly employed multivariate regression time series analytic techniques. The VAR model is advantageous because it can explain past and causal relationships among multiple variables over time, as well as predict future observations. Explanation and prediction of future observations in a time series is dependent upon correctly postulating a VAR model and estimating its parameters (Lütkepohl, 2005).

Physiologic nursing research often depends on the collection of multivariate time series data to be used in various statistical models. For instance, a multivariate time series model was used to forecast daily attendances at the hospital emergency department of an acute care hospital; autoregressive integrated moving average models were applied to three different acuity categories (most acute, acute and least acute) of patients seen in the emergency department, and used as tools for predicting emergency department workload both for staff roster as well as for resource planning (Sun, Heng, Seow, & Seow, 2009). In another study, a vector autoregressive time series model was used in a set of 450 intensive care unit patients to systematically learn and identify a collection of time series dynamics that were recurrent within each patient and that were shared across the entire cohort (Lehman et al., 2015). The time series dynamics in combination with baseline acuity measures were used to better characterize the physiological state of a patient and predict in-hospital mortality (Lehman et al., 2015).

Vital sign time series (VSTS) involves monitored physiologic vital signs (VS), such as heart rate (HR), respiratory rate (RR) or pulse oximetry (SpO₂). (See Figure 1.) Physiologically, dynamic interactions among the VS are indicative of a patient's efforts to compensate and attain homeostasis in response to values that exceed thresholds marking normal limits (Scharf, Pinsky, & Magder, 2001), where failure to compensate leads to cardiorespiratory instability (CRI). Patient-specific multivariate time series modeling approaches (Schulz et al., 2013) can be used to study the causal characteristics of the changes in physiological variables as they progress in time towards the development of CRI, which is a well-defined

event that occurs or does not occur within some period of time. The vector autoregressive (VAR) model is one of the most flexible models for the analysis of causality in multivariate time series.

Granger causality is a concept of causality derived from the notion that causes may not occur after effects and that if one variable is the cause of another, knowing the status on the cause at an earlier point in time can enhance prediction of the effect at a later point in time (Granger, 1969; Lütkepohl, 2005, p. 41). The VAR model has been widely employed in econometric analyses (Granger & Newbold, 1986) and in neurobiology (Tang, Bressler, Sylvester, Shulman, & Corbetta, 2012) to elucidate underlying mechanisms using Granger causality. To the best of our knowledge, VAR has never been implemented in studying causality in physiologic time series variables of HR, RR and SpO₂ as multivariate inputs to the development of CRI.

We therefore provide an example of using the VAR approach. The purpose of this study was to develop patient-specific multivariate time series VAR models using HR, RR and SpO₂ in a sample of acutely ill monitored step-down unit (SDU) patients. VAR model provided the framework in order to study the Granger casual dynamics among the VS leading up to CRI. Since CRI can occur multiple times during the hospitalization of unstable patients, we decided to consider the sampling window as only their first instance of CRI, which we called CRI₁.

Example

Design

The examples involve prospectively-collected physiologic data in patients who underwent continuous noninvasive VS monitoring. Heart rate (HR), respiratory rate (RR; bioimpedance), peripheral oximetry (SpO₂; plethysmography) were recorded once every 20 seconds ($t = 20$ seconds) for the entire monitoring period of their hospitalization on the SDU. Instability threshold limits for VS deviations outside of normal were set (HR: 40 or 140 beats per minute; RR: 8 or 36 breaths per minute; and SpO₂: 85%). Instability epochs were denoted by persistence of any deviation in VS for 3 minutes (60% duty cycle, which is the percentage of period the signal is active within a sampling window) of a 5 minute moving window. The instability epochs were then visually annotated by two expert critical care clinician reviewers. The instability epochs were coded as actual CRI or monitoring artifacts. The incident (first) CRI was denoted CRI₁. After rejecting artifact, we created a subset of data for CRI₁ instances and VSTS up to a maximum of 6 hours prior to the incident CRI and saved it in a flat file using comma-separated value (.csv) format. (Flat files using .csv formats enable compact storage of large amounts of data making it easy to store, retrieve and import across applications.)

Sample and Setting

Patients were recruited from a 24-bed step-down unit (SDU) located in a tertiary academic center. Those who had at least two hours of continuous noninvasive monitoring of HR, RR, and SpO₂ were eligible. Data were extracted from input obtained from noninvasive bedside

monitors (model M1204, Philips Medical, Bothell, WA) that included continuous HR (3-lead electrocardiogram), RR (bioimpedance signal), and plethysmographic peripheral blood oxygen saturation (SpO₂) signal (model M1191B, Philips Medical Systems). Additional inclusion criteria were admission to a monitored bed on the SDU and age ≥ 21 years. All patients were admitted to the study unit following the usual standard of care for monitored bed admission and utilization. A convenience sample of 20 patients took part; ages ranged from 35 to 92 years; men and women were equally represented; and most were White (80%). The study protocol was approved by the University Institutional Review Board (IRB).

Data Set and Data Preprocessing

The start of the CRI₁ epoch was indicated by the first point in the patient's streaming data at which any of a patient's VS first crossed an instability threshold. The end of the epoch was indicated by the point at which all VS returned to normal values. Using the beginning of the CRI₁ epoch, a 6-hour window period prior to that time was chosen for VAR analysis. This was because Hravnak et al. (2008), in the same patient population, determined that VS changes occur at least 6 hours prior to the onset of CRI.

In the current study, the first step was to preprocess the data to verify that a data value existed at every 20 seconds. Gaps were noticed within certain portions of the data stream (about 5–8% missingness). Missingness was likely due to poor signal capture. Gaps in the data stream were populated using linear interpolation between the points (Lehman, Nemati, Adams, & Mark, 2012) to make the data stream continuous for each of the three vital sign variables. We used this strategy since linear interpolation assumes that the unknown value of any given physiologic variable lies on the line between the two known values, similar to that of normal physiological mechanisms. Once missing values had been replaced with interpolated values, the data set was ready for VAR modeling.

Vector Autoregressive Modeling

A VAR(p) model for a multivariate time series is a regression model for outcomes at a specified time t and time lagged predictors, with p indicating the lag (e.g., $p = 1$ refers to the observation previous to t ; $p = 2$ refers to two observations prior to t , and so on). Key terms used in VAR modeling are defined in Table 1. The VAR model for vital sign time series data was developed using the following steps:

1. Stationarity of the individual VSTS (HR, RR, SpO₂) is tested.
2. Lag is determined using lag-length selection criteria.
3. A VAR model with appropriate lags is built.
4. Residual autocorrelation is assessed with the Lagrange Multiplier (LM) test.
5. Stability of the VAR system is assessed with the autoregressive (AR) roots graph.
6. The Granger causality test is performed.

Testing Stationarity

Stationary time series are detrended series, without periodic fluctuations. Stationarity is critical to development of a VAR model because in its absence, a model's statistics such as means and correlations will not accurately describe the time series signal. The augmented Dickey-Fuller test is used to test stationarity. The null hypothesis is that the time series is nonstationary and the alternative is that the series is stationary. Rejection of the null hypothesis indicates that the series does not need transformation to achieve stationarity and modeling can proceed to the lag length selection step.

Selecting Lag Length

Lag length selection refers to the number of previous observations in a time series that will be used as predictors in the VAR model. Typically, a large number of lags will be used to generate a model and then a restriction applied to select a more parsimonious model. Lütkepohl (2005) indicated that using too few lags can result in autocorrelated errors whereas using too many lags results in over-fitting, causing an increase in mean-square-forecast errors of the VAR model. Selection of an appropriate lag is critical to inference in VARs. The lag length for the VAR (p) model can be determined using model selection criteria. The most common approach is to fit VAR (p) models with orders $p = 0, 1, \dots, p_{\max}$ and choose the value of p which minimizes some model selection criteria. The three most commonly used criteria used are the Akaike Information Criterion (AIC), Schwarz Bayesian Information Criterion (BIC), and the Hannan-Quinn criterion (HQ) (Lütkepohl, Section 8.1; Vrieze, 2012). The lag associated with the minimum value of a criterion is selected (Lütkepohl, 2005).

Building the VAR Model

The general structure of the VAR model used in multivariate time series is that each variable, at a point in time, is a linear function of the most recent lag of both itself and the other variables. The general model is described in Supplemental Digital Content 1. To illustrate, a trivariate VAR(1) model for HR, RR and SpO₂ for one case has the usual matrix form for a regression equation with multivariate outcomes, such that

$$\begin{bmatrix} Y_{HR,t} \\ Y_{RR,t} \\ Y_{SpO_2,t} \end{bmatrix} = \begin{bmatrix} c_{HR} \\ c_{RR} \\ c_{SpO_2} \end{bmatrix} + \begin{bmatrix} A_{1,1} & A_{1,2} & A_{1,3} \\ A_{2,1} & A_{2,2} & A_{2,3} \\ A_{3,1} & A_{3,2} & A_{3,3} \end{bmatrix} \begin{bmatrix} Y_{HR,t-1} \\ Y_{RR,t-1} \\ Y_{SpO_2,t-1} \end{bmatrix} + \begin{bmatrix} e_{HR,t} \\ e_{RR,t} \\ e_{SpO_2,t} \end{bmatrix} \quad (1)$$

or, in scalar notation,

$$Y_{HR,t} = c_{HR} + A_{1,1}Y_{HR,t-1} + A_{1,2}Y_{RR,t-1} + A_{1,3}Y_{SpO_2,t-1} + e_{HR,t} \quad (2)$$

$$Y_{RR,t} = c_{RR} + A_{2,1}Y_{HR,t-1} + A_{2,2}Y_{RR,t-1} + A_{2,3}Y_{SpO_2,t-1} + e_{RR,t} \quad (3)$$

$$Y_{SpO_2,t} = c_{SpO_2} + A_{3,1}Y_{HR,t-1} + A_{3,2}Y_{RR,t-1} + A_{3,3}Y_{SpO_2,t-1} + e_{SpO_2,t} \quad (4)$$

As shown in Equations 1–4, the regressors (predictors) of each outcome are the same, which are the lagged values of HR, RR and SpO₂. Intercept terms are indicated by the c terms, regression coefficients are indicated by the subscripted A values, and error in prediction of each outcome at time t is indicated by the e terms. The equations can be solved using ordinary least squares (OLS) estimation. Since within the VAR (p), each equation has the same explanatory variables, each equation may be estimated separately. Recommended sources for information about estimation in VAR modeling are Lütkepohl (2005) and Hamilton (1994).

Testing for Residual Autocorrelation

Once a VAR model has been developed, the next step is to determine if the selected model provides an adequate description of the data. In familiar regression models, this is performed by examining the residuals, which are differences between the actual observations and model-fitted values. In time series models, autocorrelation of the residual values is used to determine the goodness of fit of the model. Autocorrelation of the residuals indicates that there is information that has not been accounted for in the model. The Lagrange Multiplier (LM) test is a standard tool for checking residual autocorrelation in VAR models. The null hypothesis is that there is no residual autocorrelation; the alternative is that residual autocorrelation exists (Lütkepohl, 2005, Section 4.4.4). Technical detail is provided in Supplemental Digital Content 1.

Assessing Stability of the VAR Model

Stability refers to checking whether the model is a good representation of how the time series evolved over the sampling window period. Technically, stability of a VAR system is evaluated using the roots of the characteristic polynomial of the coefficient matrix A , as in the example in Equation 1. Stability in a VAR model is indicated by roots that are all less than 0, and are typically shown in a graph. See Supplemental Digital Content 1 for more detail.

Evaluating Granger Causality

VAR models describe the joint generation process of a number of variables over time, so they can be used for investigating relationships between the variables. Granger causality is one type of relationship between time series (Granger, 1969). The basic idea of Granger causality (GC) can be stated as *if the prediction of one time series is improved by incorporating the knowledge of a second time series, then the latter is said to have a causal influence on the first*. Specifically, two autoregressive models are fitted to the first time series—with and without including the second time series—and the improvement of the

prediction is measured by the ratio of the variance of the error terms. The null hypothesis for GC is that no explanatory power is added by jointly considering the lagged values of y and x as predictors. The null hypothesis that x does not cause y is rejected if coefficients for the lagged values of x are significant; i.e., Granger called a variable x causal for a variable y if the lagged values of x are helpful for improving forecasts of y (y at future times). The VAR framework is flexible and provides an environment for implementing this type of analysis.

Software

In the current study, all data analysis was performed using EViews 8 Student version, a Windows-based econometric program commonly employed in the financial industry for econometric analysis, forecasting and simulation. Time series data for each of the individual variables of HR, RR and SpO₂ were provided as input after importing .csv files of time series data.

Application in Example Data

The time series data for each of the individual VS variables were first visualized using a graphical line plot of each of the variables over time (Figure 1). Graphs were assessed for trends and stationarity. From a visual perspective, the graphs verified that the series looked flat, without any upward or downward trend and with no periodic fluctuations over time.

Stationarity—The test for stationarity was performed individually for HR, RR, and SpO₂ for each patient. EViews 8 outputs an augmented Dickey Fuller (ADF) t -statistic value and its corresponding p -value for each variable. A p -value $<.05$ indicated that the time series was stationary for that particular variable. If the VS time series was not stationary, the series was differenced and the ADF test applied again on the differenced time series to check for stationarity. Among the 60 series (20 patients $\times$ 3 vital signs), 12 series were stationary when first tested and the rest were differenced once to achieve stationarity.

Lag length—Once stationarity of a series was determined, we proceeded with lag-length selection using AIC and HQ. Table 2 shows an example case, where the 12th lag was associated with the minimum AIC value. In selecting the 12th lag, all the lags from 1 to 12 are subsequently included in the models. Lags ranged from 8 to 20 among the 20 cases for the HR, RR, and SpO₂ time series.

VAR model with appropriate lags—VAR models were estimated to include the number of lags from 1 until the specified lag as described above. Table 2 shows the example of a VAR model with lags from 1 to 12 for HR for one patient. Models were also estimated for RR and SpO₂. Significance of the coefficients was assessed to decide whether another VAR model should be constructed so as to minimize the nonsignificant coefficients. In all, only 5 models were re-estimated because coefficients were nonsignificant.

Residual autocorrelation—We next applied the LM test to check for residual serial correlation for each patient. In general, after fitting a VAR model, the residuals should be white noise and should have no autocorrelation. If autocorrelation among the residuals is noticed, then it implies that there was some information which was not accounted for by the

model, such as insufficient lags. The null hypothesis of the LM test is that there is no serial correlation up to the specified lag order (past values of a variable do not affect the future value of the variable until the specified lag value). If a proper VAR system is obtained from the previous step, then the coefficients of the LM statistic are not significant, thus accepting the null hypothesis up to the specified lag. This is also illustrated in Table 2 for one patient.

Stability—Stability of the VAR system was evaluated using the roots of the characteristic polynomial with the variables of HR, RR and SpO₂ and the lag specification as per above criteria. Figure 2 shows stability evaluation using a graph of the characteristic roots for one patient. This evaluation was performed on a patient-by-patient basis. Of the 20 cases, models for 18 cases were stable (Table 3), based on inspection of the graphs.

Granger causality—Granger causality assessment for one patient is also shown in Table 2. In this case, all of the RR lags caused HR. This demonstrates that there was unidirectional causality running in one direction, from RR to HR, such that changes in RR causing changes in HR in the patient's time series prior to CRI₁.

Table 3 summarizes Granger causality assessment for all 20 cases. No causal structure was identified for three cases, and VAR models were unstable for two cases. The first VS over threshold to begin the CRI epoch was SpO₂ in 60% cases, followed by RR (30%) and HR (10%). Out of the 20 cases, assessment of Granger causality revealed that RR caused HR (i.e., RR changed before HR changed) more often than HR caused RR (21% vs 15%, respectively). Similarly, changes in RR causing changes in SpO₂ was more common than changes in SpO₂ causing RR (15% vs 9%, respectively). For HR and SpO₂, changes in HR causing changes in SpO₂ and changes in SpO₂ causing changes in HR occurred with equal frequency (18%). There were three cases with bidirectional causality (#8, #14 and #18).

Discussion

To demonstrate the utility of VAR modeling in nursing research, we carried out an analysis with the purpose of developing a stable patient-specific multivariate time series VAR model — using HR, RR and SpO₂ in a sample of SDU patients—in order to study the Granger casual dynamics among the monitored vital signs leading up to a first CRI. Our results suggest that using this information may be helpful to determine causality in VS threshold deviations, and determine a physiologic cause. For example in our 20 cases, SpO₂ falling below threshold was the first indicator of CRI. SpO₂ itself was generally not the cause for changed RR or HR, but rather RR and HR tended to be the cause for the fall in SpO₂. This suggests that SpO₂ is a later VS change, and is preceded by more subtle changes in other VS which in turn caused changes in SpO₂.

From an analysis standpoint, two cases had data only for 2 and 4 hours (cases #6 and #11, respectively) in the 6-hour window preceding CRI₁. Also, there were two cases with VSTS from only two variables prior to CRI₁—HR and RR—(# 3) and HR and SpO₂ (# 8). We also encountered two cases (#9 and #16) with intermittent monitoring (the reasons for the patients being off the monitor were not known) for an overall missing window period of at least 3 hours, within the 6-hour period prior to CRI₁. In these two cases, we used the Markov

Chain Monte Carlo (MCMC) approach to impute missing values to the dataset, since it was not possible to fill the data stream with linear interpolation. Briefly, for a continuous variable with missing values, MCMC uses the non-missing values to find the sample mean and standard deviation for the variable and then fills in the missing values with random draws from a normal distribution with mean and standard deviation equal to the sample values, limited within the range of the observed minimum and maximum values (Geyer, 2011; Young, Weckman, & Holland, 2011).

No smoothing or other filtering approaches were used to remove artifacts in our dataset—this was done by prior expert review before data preprocessing. Filtering approaches disturb the information content, leading to spurious and missed causalities (Florin, Gross, Pfeifer, Fink, & Timmermann, 2010). Hence, no filtering approaches were used, but the series was differenced to maintain stationarity, which is a prerequisite for inferring Granger causality. Finally, there were two cases (#12 and #20) where the VAR model could not be stabilized for reasons that were unclear. Interestingly, HR crossed the normality threshold first in both cases. It is possible that HR is less likely to induce compensatory changes than other VS, but this would require further exploration.

Limitations

A limitation to our study was the absence of continuous streaming data from all SDU patients for the entire 6-hour period. This is common in clinical care for a variety of reasons such as hallway ambulation, bathroom privileges, off-unit for testing or therapy, however. Linear interpolation or MCMC could have been avoided with totally uninterrupted data streams for all cases. We implemented these imputation procedures in order to maintain completeness of the VSTS for VAR modeling. Further, even though the VAR model is quite rich in capturing the temporal dynamics of highly complex hemodynamic responses, Granger causal relationships should not be over-interpreted as truly causal. An advanced discussion about Granger causality and causal inference with multiple time series is available in Eichler (2013).

Future Directions

Our study provides an example demonstrating that the VAR modeling approach is able to expose Granger causal dynamics involving vital signs in evolving CRI. Future studies with larger samples and longer periods of VSTS monitoring to study casual dynamics are warranted. Such information could enhance target surveillance monitoring, enabling nurses to better recognize impending CRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1. Illustration of time series plots for one patient

Time series plots for about 1 hour showing heart rate (HR), respiratory rate (RR) and pulse oximetry (SpO₂). The shaded portion represents incident cardiorespiratory instability (CRI) which this patient developed due to crossing of HR threshold limits, with changes in RR and SpO₂ occurring prior to CRI. Vector autoregressive (VAR) models are able to look at these evolving patterns over time for this specific patient to assess VS changes prior to incident CRI.

FIGURE 2. VAR System Stability Condition check for one patient

The stability of the VAR system is visually inspected by evaluating roots of the above VAR system. The dots represent the roots of characteristic polynomial. If no roots lie outside the unit circle, then the VAR system satisfies stability condition, indicating model stability.

TABLE 1

Glossary of Terms

Term	Definition
Differenced time series	A series constructed by computing the differences between consecutive observations. Differencing can help stabilize the mean of a series by removing changes in the level of a time series to eliminate trends.
Duty cycle	The percentage of period in which a signal is active; for example, 60% duty cycle means that within a sampling window (5 minutes), the signal was active or “on” for at least 3 minutes.
Granger causality (GC)	A statistical concept of causality involving improved prediction of one time series by incorporating knowledge of a second time series (with the latter said to have had a causal influence on the former).
Lag	A shift in the time base back by a given number of observations. For instance, if X_t is the value of the variable in period t , X_{t-1} is the value of the variable in previous period (lagged one period).
Linear interpolation	A method of estimating a value lying between two defined points using a linear (straight line) function.
Markov Chain Monte Carlo (MCMC)	A Bayesian-based algorithm that can be used to impute missing values of a particular variable within a time series.
Order of a lag	Refers to the number of lags (periods of observation) prior to the observation.
Serial correlation	Correlation between a given variable across various time periods.
Stationarity	A time series that has the property that the mean, variance and autocorrelation structure do not change over time. Upon visualization of the series in a time plot, a stationary series is one whose properties do not depend on the time at which the series is observed—the series looks flat without any trend, constant variance over time and no periodic fluctuations.
Trend	Trend is a time series component that is a long-term increase or decrease over time; i.e., an upward or downward movement of a series.
Vector autoregressive model (VAR)	Model that captures linear relationships among multiple time series.

TABLE 2

Lag Order Selection, Assessment of Residual Correlation, and Granger Causality for Heart Rate for One Patient

Step	Lag	AIC	HQ
Lag order selection	0	8.27	8.28
	1	7.63	7.65
	2	7.34	7.38
	3	7.27	7.32
	4	7.13	7.20
	5	7.08	7.17
	6	7.02	7.12
	7	6.99	7.10
	8	6.96	7.09*
	9	6.95	7.10
	10	6.94	7.11
	11	6.94	7.12
	12	6.91*	7.11
	13	6.91	7.13
	14	6.92	7.15
	15	6.93	7.18
Residual autocorrelation	Lag	LGM	<i>p</i>^a
	1	9.49	.39
	2	9.06	.43
	3	7.57	.57
	4	13.56	.13
	5	4.09	.90
	6	14.69	.09
	7	8.87	.44
	8	6.23	.71
	9	6.03	.73
	10	8.50	.48
	11	17.01	.05
	12	10.74	.29
Granger causality	χ^2	<i>df</i>	<i>p</i>
	Dependent/excluded		
	HR		
	RR	21.67	12 .04
	SpO ₂	17.56	12 .12
	RR		
	HR	16.74	12 .15

Step	Lag	AIC	HQ
SpO ₂	5.44	12	.94
SpO ₂			
HR	17.94	12	.11
RR	20.26	12	.06

Note. Lag order begins with an initial lag order set high (in this case, lags). The “best” lag is the lag with smallest AIC value, associated with a lag of 12. The LGM evaluates serial correlation (autocorrelation) for a single variables; in this case, none of the LGM tests were significant, indicating that past values of HR did not affect future values for this patient, up to the specified lag order. Granger causality treats each variable as dependent and other variables with all of their lags as independent; *p*-value <.05 is suggestive of causality between the dependent variable and independent variable. Using this criterion in this time series, only the effect of RR on HR was significant (*p* <.04). AIC = Akaike Information Criterion; *df* = degrees of freedom; HQ = Hannan-Quinn Information Criterion; HR = heart rate; LGM = Lagrange Multiplier; RR = respiratory rate; SpO₂ = peripheral capillary oxygen saturation.

^aFor χ^2 with *df* = 9.

TABLE 3

Granger Causality for Each Patient

ID	Data availability				Duration ^a	VS ^b	Granger causality
	RR	HR	SpO2	VS			
1	yes	yes	yes	6	SpO2	RR→HR	RR→HR
2	yes	yes	yes	6	SpO2	RR→HR RR→SpO2	RR→HR RR→SpO2
3	yes	yes	no	6	RR	RR→HR	RR→HR
4	yes	yes	yes	6	SpO2	HR←→SpO2 RR→HR RR→SpO2	HR←→SpO2 RR→HR RR→SpO2
5	yes	yes	yes	6	RR	No causal structure	No causal structure
6	yes	yes	yes	2	SpO2	HR→RR	HR→RR
7	yes	yes	yes	6	SpO2	RR→HR RR→SpO2 HR→SpO2	RR→HR RR→SpO2 HR→SpO2
8	no	yes	yes	6	SpO2	HR←→SpO2	HR←→SpO2
9	yes	yes	yes	6	RR	RR→SpO2	RR→SpO2
10	yes	yes	yes	6	SpO2	No causal structure	No causal structure
11	yes	yes	yes	4	SpO2	SpO2→RR HR→SpO2	SpO2→RR HR→SpO2
12	yes	yes	yes	6	HR	Unstable VAR model	Unstable VAR model
13	yes	yes	yes	6	SpO2	SpO2→HR	SpO2→HR
14	yes	yes	yes	6	RR	HR←→RR	HR←→RR
15	yes	yes	yes	6	RR	No causal structure	No causal structure
16	yes	yes	yes	6	SpO2	HR←→SpO2 HR→RR SpO2→RR	HR←→SpO2 HR→RR SpO2→RR
17	yes	yes	yes	6	SpO2	SpO2→HR	SpO2→HR
18	yes	yes	yes	6	RR	HR←→RR	HR←→RR
19	yes	yes	yes	6	SpO2	HR→RR SpO2←→RR SpO2←→HR	HR→RR SpO2←→RR SpO2←→HR
20	yes	yes	yes	6	HR	Unstable VAR model	Unstable VAR model

Note. Unidirectional relationships are indicated with (→) and bidirectional relationships are shown with (←→). CRI = incident cardiorespiratory instability; HR = heart rate; ID = patient identification code; RR = respiratory rate; SpO2 = peripheral capillary oxygen saturation; VS = vital sign.

$t_{p,1}$ Hours prior to start of CRI.
 q First vital sign threshold.

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