Modern Monitoring in Anesthesiology and Perioperative Care

Edited by

Andrew B. Leibowitz

Suzan Uysal

CAMBRIDGE Medicine

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Preface

Our current practice environment is daunting. Providing safe quality care using technology and receiving feedback that didn't even exist 15 years ago should be easy, but it isn't. The plethora of information and the number and variety of monitors available for use has increased in an almost exponential fashion. On October 27, 2019, a PubMed search of "noninvasive monitoring of cardiac output" yielded 809 references, a Google search for "anesthesiology guidelines" 25,700 references, and there are at least 9 different technologies for monitoring of cardiac output incorporated into commercially available products.

This book aims to be different than other monitoring books and focuses on the "practical." Chapters on statistics and electronic distraction are unique and provide a framework for evaluation of all monitors, and reveal the risk that too much information poses to the care that we provide. Other chapters focus on the "why" monitoring a certain variable may be advantageous, the basics of "how" the monitor works, and "what" is the evidence of the impact on patient outcome.

A basic theme of the chapters is that just because we can do something does not mean we should, and sometimes less may be more, but a working knowledge of the whys, hows, and whats of modern monitoring in anesthesiology and perioperative care will allow every provider to optimize their patient's safety and the quality of care they provide.

Andrew B. Leibowitz, MD

Chapter 1

Statistics Used to Assess Monitors and Monitoring Applications

Lester A. H. Critchley

Introduction

An evidence-based approach now prevails when recommending medical treatments. This applies as much to the latest therapies as to appropriate methods to monitor patients and their response to treatment. For an evidence-based approach to be successful, however, it must be based on good-quality clinical data from well-conducted research. The quality of clinical studies and their data is now graded according to the level of evidence they provide,[1] and guidelines exist on how to properly conduct clinical research. Cochrane reviews have set standards for best evidence. Working groups such as the National Institute for Clinical Excellence (NICE) and Resuscitation Council (UK) demonstrate how such an approach can be transformed into up-to-date guidelines and courses. When assessing the value of emerging clinical monitoring technologies for perioperative, emergency room, and critical care use, researchers should be aware that clinical validation studies must be of a sufficient standard to be of use in evidence-based reviews. This perspective drives the approach of this chapter, with a focus on cardiac output (CO) monitoring, since most of the literature on these statistical methods has arisen from analysis of this variable.

Cardiac Output Measurement

Cardiac output is the sum of stroke volumes expelled from the heart over one minute; it can be measured from either the pulmonary or the systemic circulations. As the arterial system leaving the heart branches, it is not possible to measure total CO at a distal point such as the arm or descending aorta, and corrections are needed (e.g., arterial pulse contour analysis and esophageal Doppler).[2,3] Measurement of CO at its source, the heart, is also difficult to achieve in the clinical setting because of restricted access, unless one is performing open-heart surgery. Instead, at-a-distance (e.g., transthoracic Doppler) or surrogate (e.g., bioimpedance) methods are utilized, which result in lack of precision.[4,5] Compared to measuring other more accessible hemodynamic variables such as blood pressure or heart rate, lack of accuracy and precision has hampered the development of routine CO monitoring in the clinical setting.[5]

Cardiac output can be measured accurately using techniques such as the Fick method and radionuclide imaging studies. These methods, however, have several limitations. They are only applicable in settings such as the physiology laboratory or radiology department; they are inapplicable at the point of care and therefore cannot be used in operating room, emergency medicine, or critical care settings. Furthermore, Fick and radionuclide studies only provide single readings, and there is need for technologies that measure CO on a frequent or continuous basis. The clinical significance of being able to assess changes or trends in CO is only now being recognized, and this is highlighted by the designs of recently marketed CO devices and the statistical approaches to their validation.

All validation studies require a reliable reference method against which comparisons are made. For CO monitoring, the accepted reference method has been and remains single bolus thermodilution using a pulmonary artery Swan–Ganz catheter. The pulmonary artery catheter, however, is now seldom used in clinical practice, and its use is associated with significant risk to patients.[6,7] Clinical validation studies incorporating pulmonary artery catheter measurements are mostly restricted to cardiac surgery and liver transplant. Some recent research studies have used the less invasive transpulmonary thermodilution method, which is employed in the PiCCO (Pulsion, Munich, Germany) and VolumeView (Edwards Lifesciences, Irvine, CA, USA) systems. Errors arise in thermodilution measurement because of injectate

and dead space issues,[8] and the degree of inaccuracy varies between clinical settings and different manufactured devices.[9] The precision of the thermodilution method is generally accepted to be ± 20%,[10,11] and this margin of error has played a significant role in the ongoing development of validation statistics.

Cardiac output is not a static variable; its value constantly changes. Achieving a steady state in which simultaneous comparative readings can be taken often proves difficult, and this hampers the collection of good-quality validation data.

Protocol Design and Data Collection

The need for ethical approval and patient consent is an obvious prerequisite for publication. Poorly planned data collection and inadequate sample size will limit the usefulness of collected data and thus the ability to publish the study findings. Common mistakes are (i) failure to blind investigators to comparative readings, (ii) failure to achieve simultaneous readings during steady-state hemodynamics, (iii) failure to have sufficient range of readings, (iv) failure to collect sufficient data resulting in inconclusive results, (v) inconsistent number and timing of repeated measurements from individuals (i.e., irregular data collection), and (vi) failure to collect serial data pairs that show adequate changes and hence fail to facilitate trend analysis. A well-designed study has clearly defined times of data collection, which are of sufficient number to allow comprehensive analysis.[12]

Sample size is difficult to calculate in this type of research, even if a pilot study is performed, because of the range of different variables and outcomes involved. A more pragmatic approach may be based on reviewing the sample sizes used in previous studies that were successful in detecting effects. Comparative studies with cohorts of over 30 patients and 6 or more serial data pairs are recommended.[12]

Background to Validation

Thirty years ago scatter plots and regression and correlation analyses were the principal analytical methods used to show how reliably a new measurement method compared to a reference standard.[13] Regression and correlation, however, only evaluate the degree of association between two measurement methods; they do not quantify accuracy. Quoting correlation coefficients and p values confirms little.

The whole approach to validation statistics changed in the 1980s when J. M. Bland and D. G. Altman introduced a new method of comparing measurements based on bias, the difference between pairs of comparative readings.[14] Bias was plotted against the average of each pair, and the standard deviation of the bias provided a statistic called *limits of agreement* (i.e., 95% confidence intervals for the bias). Bland and Altman, however, never provided guidance as to how the limits of agreement should be used to confirm clinical utility, leaving this to the discretion of the user. This was particularly unsatisfactory when Bland–Altman analysis was applied to CO studies where the reference method, usually thermodilution, was imprecise. Limits of agreement of less than 1 liter/min were considered to be acceptable,[15,16] but no provision for (i) variations in baseline CO or (ii) imprecision of the reference method was made.

To enable outcomes from Bland–Altman style CO studies to be compared in 1999, Critchley proposed the use of percentage error (PE), a statistic calculated from the limits of agreement (i.e., 95% confidence interval of the bias) divided by the baseline CO for the study.[10] A benchmark for acceptance of a new technique of less than 28.4% was set, which was rounded up to less than 30%. This benchmark was based on a reference method's precision of 20% and acceptance of the test method also being set at 20%. Although PE has been criticized over the years for being too strict,[11,17,18] its simplicity and robustness as an analytical tool have withstood the test of time.

In more recent decades, following advances in clinical medicine and monitoring technology, it has become increasingly important to have bedside monitors that accurately follow the vital signs of hospitalized patients. Unfortunately, Bland–Altman analysis does not assess the ability of devices to detect changes; it is limited to assessing accuracy of readings and agreement between methods.[19,20] Thus, new statistical approaches were developed, referred to as *trend analysis*.[21] Many researchers new to clinical monitoring, however, fail to recognize the need to show trending and restrict data collection to that suitable for Bland–Altman analysis.

How to effectively address the issue of trending capability has not been fully resolved in the literature. In a recent review of CO studies, Critchley and colleagues reported that only 20% of the studies performed some form of trend analysis; the analytical methods employed were (i) Bland–Altman analysis

of tables and histograms, (ii) regression analysis of scatter plots, and (iii) analysis of direction of change.[21]

When analyzing CO data from hospital patients, commonly used trend analysis methods are (i) concordance on a four-quadrant plot and (ii) polar plot analysis.[22,23] Both these analyses rely on comparing serial data from reference and test methods, calculating the serial change in consecutive readings (ΔCO), and excluding data where the change is small (i.e., < 10–15% change). The polar method involves transforming the data from a simple (x, y) Cartesian format to a radial format (radius, angle). Polar plots provide greater information about the agreement between two methods that is lost when just direction of change is used. Criteria for acceptable trending have been proposed for CO monitoring.[21,23] A more detailed description of these methods follows.

Bland–Altman Analysis

Practically all CO validation studies published today use Bland–Altman analysis and provide a Bland–Altman plot (Figure 1.1). The plot shows bias collected from the whole or subgroups of the study. Each plot should display horizontal lines indicating mean bias and the 95% confidence intervals or limits of agreement. Inspection of the plot allows one to assess (i) the distribution or spread of data, (ii) the degree of agreement between methods (i.e., size of the limits of agreement), and (iii) any systematic changes in bias as CO increases (i.e., offsets in calibration). One common problem with presenting Bland–Altman plots is using inappropriate scales, especially when more than one plot is shown. Rather than choosing scales that fill the page with data points, the axis of each plot should have similar scales and ranges. Otherwise visual comparisons between plots are difficult to perform. Very often the Bland–Altman plot is accompanied by an (x, y) scatter plot that shows the raw data (Figure 1.1), but regression lines and correlation coefficients are often omitted.

Bland–Altman analysis requires each data pair to be independent of all other pairs and ideally from separate subjects.[14] If data pairs are related (i.e., they come from the same subject), the size of 95% confidence intervals and limits of agreement for the analysis will be reduced. Use of repeated measures (i.e., data pairs from the same subject) is common in CO studies; thus, the data analysis should correct for

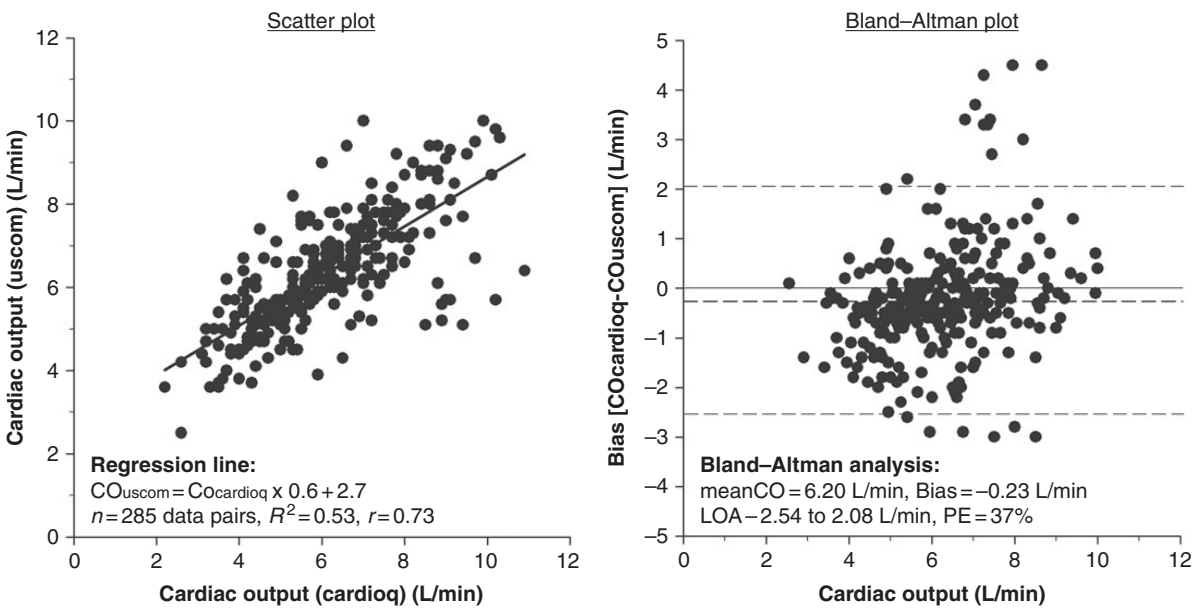

Figure 1.1 Scatter plot with regression line and accompanying Bland–Altman plot. Statistical analysis data are added to each plot. The Bland–Altman plot also displays the mean bias and limits of agreement of the analysis (dashed horizontal lines). Data are from a study that compared two Doppler CO measurement methods, transthoracic (USCOM) and esophageal (CardioQ).

Source: Huang L, Critchley LA. An assessment of two Doppler-based monitors to track cardiac output changes in anaesthetized patients undergoing major surgery. *Anaesth Intens Care* 2014;42:631–9. LOA: limits of agreement, PE: percentage error.

repeated measures by either (i) Bland and Altman or (ii) Myles and Cui methods, which differ slightly in complexity.[24,25] Statistical software programs that perform Bland–Altman analysis should also adjust for repeated measures; journal editors and reviewers expect that authors will employ such corrections and describe them in their manuscripts.

Percentage error is a key outcome statistic arising from CO studies that perform a Bland–Altman analysis.[10] It is used to compare findings of CO studies with findings of other published studies. It also allows criteria to be set for acceptance of a new CO monitor prior to starting a study. Most authors will use the less than 30% benchmark, from Critchley's 1999 paper that based the criteria on a 20% precision for thermodilution CO measurement and the need for less than 20% measurement error (i.e., 95% confidence intervals or precision).[11] A 20% error represented up to a 1 liter/min variation in CO if the mean CO was 5 liter/min.

Cecconi and colleagues have questioned the logic of assuming a 20% error in the reference method.[26] They recommended measuring its precision and using the error to set new acceptance criteria a priori. Their rational was that (i) the error in thermodilution or other reference method is very variable and 20% is just an approximation, and (ii) any significant variation from 20% would result in lesser or greater errors in the test method to be accepted, if the acceptance criteria are set at the standard 30%. Their approach to measuring the reference method's precision was to perform serial steady-state measurements from which the coefficient of variation was calculated and precision derived.[26]

Trend Analysis

Trending capability, the ability to follow changes in CO, can be assessed either by (i) multiple paired comparisons in a small number of subjects (i.e., $n = 6–10$ laboratory animals) or (ii) as part of a larger scale clinical trial with up to 8–10 comparative measurements in 20 or more patients. Statistical approaches are different for the two settings. Small cohort studies are dealt with later in the section Time Plots and Regression Analysis.

Concordance Analysis

For larger cohort clinical trials the current approach is concordance analysis using direction of change.[21,22] This analysis is based on serial data, and ΔCO is the study variable calculated from the difference between consecutive readings. Direction of change in CO can either be increased (i.e., positive direction change) or decreased (i.e., negative direction change); the magnitude of change is not included in the analysis. In the trial a test method is compared to a reference method, which provides pairs of directions of change of readings that can either agree (i.e., concord) or disagree. Concordance is measured as the proportion of readings that agree.

To make concordance analysis easier to visualize, a four-quadrant plot is drawn of ΔCO reference against ΔCO test (Figure 1.2). Data where directions of change agree fall into the right upper and left lower quadrants. The ratio of the number of data pairs where directions of change agree over the total number of data pairs for the study provides the concordance presented as a percentage.

Data pairs where the serial change in CO is small, however, can often have directions of change that disagree due to random errors in measurement; this is referred to as *statistical noise*. To eliminate statistical noise from the concordance analysis an exclusion zone is used that removes data where the change in CO is less than 10–15% of the mean CO for the study. The setting of limits for the exclusion zones is based on a receiver operator characteristic (ROC) curve analysis.[22]

Current advice for acceptable trending ability in CO studies is greater than 92%.[21] Ideally, confidence limits should be calculated for the concordance, which is based on sample size. The ΔCO data is treated as a binomial (i.e., direction of change either agrees or disagrees), and the standard deviation of the concordance ratio (p) is $\sqrt{[np(1-p)]}$, where n is the number of data points. A good example of how this statistic is generated and used is found in Axiak-Flammer and colleagues.[27]

Polar Plots

The introduction of polar plots (Figure 1.2) was to address the problems that (i) the four-quadrant plot method did not include magnitude of change and (ii) all data pairs were treated equally despite size.[14,21,23] By converting the data to (i) a radial distance that represented the size of the combined changes in CO from the two paired readings (i.e., average absolute change in ΔCO) and (ii) an angle that represented the degree of agreement (i.e., the greater the degree of disagreement the larger the angle), more information about the comparison between the two measurement