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The qualitative detection of decreases in cardiac output

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ABSTRACT

Background: Cardiac output is a major factor in the maintenance of physiological homeostasis and is difficult to measure with accuracy. This study describes an evidence-based technique, based on physiological changes, which may indicate small changes in cardiac output that cannot be measured by current techniques.
Method: Synchronous changes in blood pressure, heart rate, pulse amplitude and end-tidal carbon dioxide are analysed using runs analysis and a normalisation technique. An evidence-based algorithm was used to detect possible changes in cardiac output and data extracts from 31 consenting patients are presented as examples.
Results: The decrease in end-tidal carbon dioxide, during steady state ventilation, was greater in those events notified as hypovolaemia associated with a fall in cardiac output than those events notified as hypovolaemia alone. The difference in end-tidal carbon dioxide between the two groups was −0.25 kPa (CI −0.42 to −0.09) $p < 0.003$.
Discussion: Runs analysis can detect trends in $EtCO_2$ that during steady state ventilation may indicate a decrease in cardiac output. It is a safe technique; no additional hardware is required and the generated alerts only notify the clinician of the possibility of an adverse change. Determination of the rate of clinically significant false positives and negatives requires further work.

1. Introduction

Cardiac output (CO), the most fundamental of circulatory parameters, is difficult to measure. When comparing new devices for cardiac output measurement Cecconi et al. [1] stress the importance of knowing the precision and accuracy of the 'gold standard' reference technique; the most common referenced 'gold standard' technique being intermittent thermodilution (ITD) using an averaged set of measurements.

Critchley and Critchley [2] suggest that ITD measurements have a precision of 10–20% and the view of Cecconi et al. [1] is that the error associated with a measuring technique is related to the size of the smallest change, that can be measured by the device, that can be recognised as a real change. The usually accepted 10% CE [coefficient of error] for ITD means that a change can only be trusted as real only if it is greater than 28.3%. However, a study by Nilsson et al. [3] showed that to be 95% confident of accuracy within 5% an average of four measurements are required and two sets of such measurements need to differ by at least 7% before a change in cardiac output can be accepted.

Using ITD, Weil et al. [4] studied post cardiac arrest cardiopulmonary resuscitation (CPR) in pigs and reported that, in the presence of constant ventilation, the mean end-tidal CO_2 ($EtCO_2$) and cardiac output (CO) decreased to 21% and 33% respectively during CPR, and they showed a correlation of 0.79 ($p < 0.001$) between CO and $EtCO_2$. Omato et al. measured cardiac output (ITD) and $EtCO_2$ during controlled arterial haemorrhage [5]. They suggested a logarithmic relationship between CO and $EtCO_2$ ($r = 0.91$, $p < 0.001$). Idris et al. in 1994 [6] confirmed a close relationship between CO and $EtCO_2$ in a well-controlled study of ventilation and cardiac output. The cardiac index (CI) ranged from 0 to 5.37 mL/min/m^2 and correlated significantly ($p < 0.0001$) with $PETCO_2$.

If physiological changes in blood pressure, heart rate and pulse amplitude suggest hypovolaemia and there is a concurrent decrease in $EtCO_2$ then it is possible to deduce that the cardiac output has possibly decreased secondary to the hypovolaemia (this is exemplified by a study by Jones et al. [7]); assuming no change in ventilation or metabolic rate.

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The purpose of this study was to demonstrate how routinely monitored physiological variables may detect changes that are indicative of a fall in cardiac output associated with hypovolaemia.

2. Methods

With ethical committee permission (F13/003, University of Otago Human Ethics Committee) and patient consent, physiological data were collected from patients during surgery for hepatic resection and colonic surgery, anaesthesia being a combination of epidural blockade, remifentanil infusion and inhalational general anaesthesia.

The physiological variables (including intra-arterial pressure measurements) were downloaded from GE AS5 monitors with updates of values at 10 s intervals. Intra-operative notes were kept of significant events and the trend analysis was completed in real-time using Evidence-Based Monitoring (interactive) (EBMi, www.custos.co.nz) software.

The trends of changes in systolic blood pressure (SBP), heart rate (HR), pulse amplitude (PA) and $EtCO_2$ were determined by runs analysis, using a 'length of run' of at least four (Appendix A). A decrease in blood pressure was also considered significant if blood pressure fell at least 2SD (SBP–SD) using the normalisation technique as described by Harrison and Connor [8]. If four parameters (HR, SBP, PA and SBP–SD) changed appropriately hypovolaemia was notified ('HYPO'), if five parameters (HR, SBP, PA, $EtCO_2$ and SBP–SD) changed appropriately hypovolaemia with a possible fall in cardiac output was notified ('HYPO+CO').

The statistical analysis was performed using SAS version 9.3. A mixed linear model with a simple random effect for individual patients and the Satterthwaite approximation for the degrees of freedom was used. Two other random effect specifications; a compound symmetry model and an autoregressive model, did not have a markedly improved measure of model fit (Akaike's information criterion) and the simplest random effects specification was used.

3. Results

Thirty-one data sets were complete and from those sets 22 patients had 11 different combinations of events. There were a total of 23 HYPO events in 13 patients, 34 HYPO+CO events in 18 patients and nine patients had both sorts of events.

Examples can be seen in Fig. 1. Patient 2 and patient 9's events were associated with a decreased central venous pressure and an increase in the rate of infusion of metaraminol. Patient 15's event was associated with a decreased central venous pressure and total inflow occlusion of the portal vein and hepatic artery (this is the Pringle manoeuvre used during hepatic resection which is associated with a decrease in cardiac output). Patient 25's event was associated with increased doses of vasopressor.

The maximum SBP in the 5-min period before the notification of hypovolaemia (HYPO) was 106.6 mmHg ($\pm$23.8 SD), for the HYPO+CO group it was 103.7 mmHg ($\pm$17.3 SD).

Changes for each variable for each notification are tabulated in Tables 1 and 2. Plots of changes in $EtCO_2$, SBP, change in SBP and lowest SBP post event are shown in Fig. 2.

The results of the mixed linear model are presented in Table 3. Only the difference in the changes in $EtCO_2$ reaches a level of significance.

4. Discussion

There are many devices that attempt to measure cardiac output, some invasive, some non-invasive. Their accuracy and precision is widely discussed but the consensus is that they are inaccurate [9–13]. The gold-standard technique for measuring cardiac output has a precision that depends on multiple measurements (4×2 Nilsson et al. [3]) and requires a change of $\pm$7–28%, depending on which published source is considered correct, to be considered reliable. These measurements take time and are by definition intermittent. Because of the complex nature of ITD with its associated potential for patient harm its use is restricted to those patients who have some form of cardiovascular compromise or having major surgery. Non-invasive techniques have been developed for use in less risky situations but their accuracy and precision is less than ITD.

Because of inter-patient variability, absolute accuracy is not clinically necessary but precision is; that is the ability to repeat a measurement and get a closely similar result. Repeatability allows the following of trends and could answer the question 'Is the cardiac output changing?' The method described, using the evidence of changes in physiological parameters, can indicate that hypovolaemia is possible and, that if this is accompanied by appropriate changes in $EtCO_2$, that a decrease in cardiac output has also occurred. Those events where a decrease in cardiac output was suggested had a decrease in $EtCO_2$ that was significantly different to those where the diagnosis was not suggested. The assessment is continuously updated every 10 s with a moving window of 40 s.

The requirement of an early warning system is that the alert should be activated before a significant change has taken place. This means that current gold standard methodology is an inappropriate comparison as the cardiac output has to fall significantly before it can be assumed a real change has taken place.

With steady state ventilation $EtCO_2$ is closely related to cardiac output and could be used as an indicator of change in cardiac output. Body temperature could also change the metabolic rate, and hence $EtCO_2$, but the changes over the short periods, in this case 40 s, are very small. Core body temperature normally falls over the first hour of anaesthesia – a 1 °C fall over an hour, equivalent to an 8% reduction in metabolism and CO_2 production, would result in a miniscule change in $EtCO_2$.

The $EtCO_2$ of anaesthetised patients will depend on the ventilatory strategy of the anaesthetist. However, the average (SD) $EtCO_2$ of a set of 30 patients over a total of 50 h was 4.34(0.51) kPa, the average of changes over 10 s was 0 ± 0.15 kPa, over 30 s was 0 ± 0.18 kPa, over 60 s was 0 ± 0.21 kPa, over five minutes was 0 ± 0.26 kPa (unpublished data from study U1111-1139-2577, ANZCTR 363646). These are small values and would be difficult to detect by eye.

These data could be used to indicate a change in cardiac output. A decrease of 0.3 kPa (–2SD) over 10 s could be clinically significant. However, a single lower value is not a trend and the next value for $EtCO_2$ could be higher. Changing values over a longer time-frame is required.

To avoid the problem of different ventilation strategies, a trend can be detected by runs analysis using an historical median value as the baseline. This is independent of absolute values and units of measurement. In a completely random system the 'next' value (of $EtCO_2$) has a 1 in 2 chance of being below the recently historic median, a second value below the median 1 in 4, a third value 1 in 8. How many consecutive values below the median are required to denote a trend depends on the sensitivity required by the clinician. Physiological values are not completely random but the autocorrelation is low enough to allow the use of this technique [14]. Using this method, if the $EtCO_2$ has fallen below the median value in four consecutive measurements (that is over a period of forty seconds in this study) the likelihood of this happening by chance is 1:16. This is not a strong indication that cardiac output has decreased but if it is combined with other supportive evidence then the argument becomes much more compelling.

Progressive hypovolaemia eventually leads to a fall in cardiac output and so if signs of hypovolaemia co-exist with a downward trend in $EtCO_2$ then the case for a decrease in cardiac output is

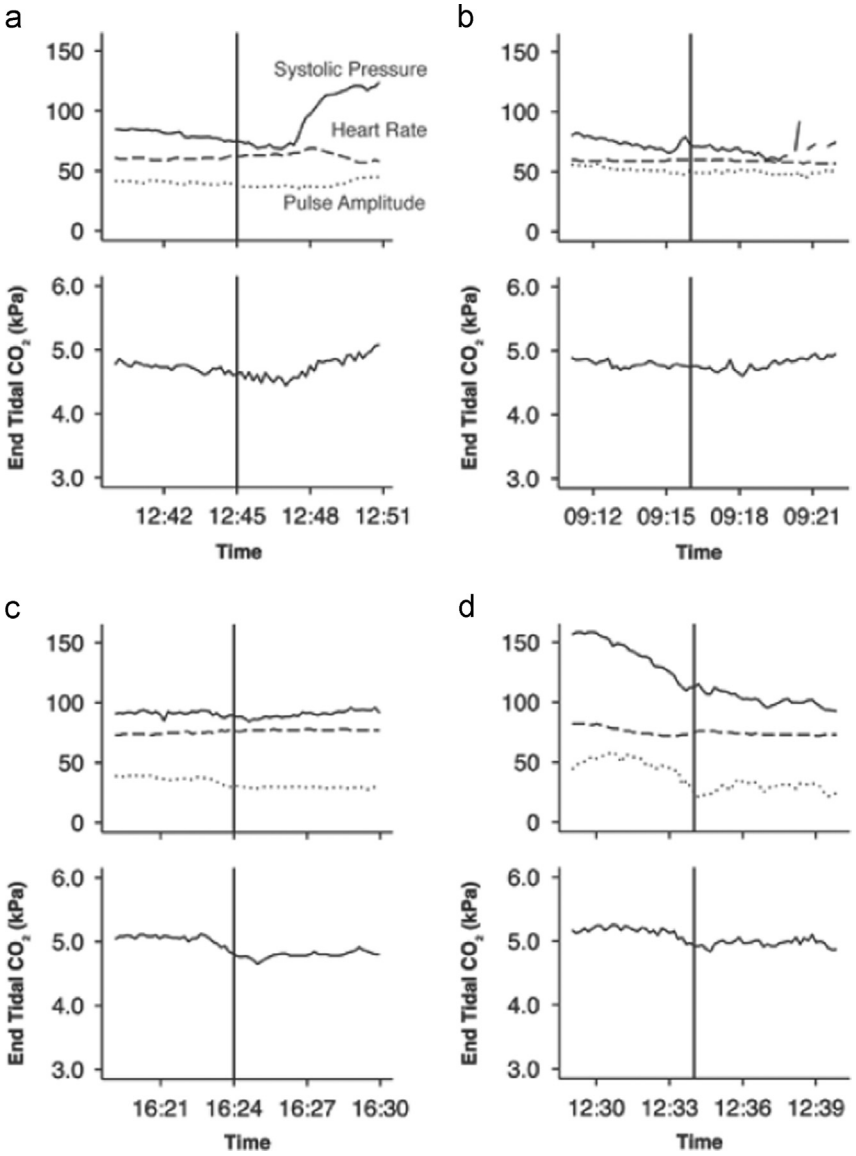

Fig. 1. Examples of changes in BP, HR, Pulse amplitude and $EtCO_2$ before and after notification of possible decrease in cardiac output. (a) Patient 2 – event notification at 12:45, (b) patient 9 – event notification at 9:16, (c) patient 15 – event notification at 16:24, and (d) patient 25 – event notification at 12:34. SBP ——, HR - - - - - -, pulse amplitude ....., $EtCO_2$ ——.

strengthened. A synchronous downward trend in blood pressure and pulse volume (amplitude) and an upward trend in heart rate suggests hypovolaemia, together with a downward trend in $EtCO_2$ is strong evidence of a decrease in cardiac output; a decrease that may not be measurable with current mechanical/electronic devices.

It can be seen from the data collected that some changes, particularly in heart rate, are small and would not be considered clinically significant. This is typical of patients receiving high dose opiates or beta-blockers, or in the extreme situation, a patient with a fixed rate pacemaker. However, using runs analysis these small trends can be detected and may reflect physiological homeostatic mechanisms that are trying to compensate for loss of blood volume. In the presence of a fixed rate pacemaker, the EBMi software omits the evidence of heart rate. This does lessen the strength of the evidence. In a situation where all four variables are considered independent then the trend of four consecutive measurements moving about the median in the appropriate direction (each variable has a likelihood of this happening of 1:16 individually) has a total likelihood of $(1:16)^4$, 1:65,536. The actual likelihood will be less than this because the variables are not in fact completely independent. However, the principle of detecting signals of change by using multiple variables still applies. In addition to these odds the change in the SBP is also analysed using a normalisation technique.

The notifications produced by this software indicate 'A fall in cardiac output is possible' and as such leaves the clinician to review the status of the patient and to consider whether intervention is required. It is unlikely that a device will be designed in the near future that can detect the early changes in cardiac output that precede those changes in cardiac output that may be harmful. The downside is that the ability to detect early changes in cardiac output may not be amenable to objective measurement. Although the changes in SBP in both groups are similar, the decrease in $EtCO_2$ in the HYPO+CO group suggests that these patients have passed the point where compensatory mechanisms can maintain normal homeostasis.

Accuracy describes how close a measurement is to the real value; for this qualitative technique, which generates an alert indicating change following a 40 s trend, this is difficult to gauge; only a technique that can show a change over 40 s could be used for

Table 1
Changes in $EtCO_2$ (kPa) and SBP (mmHg) over 5 min before and after notification of possible hypovolaemia.

Hypovolaemia				
Patient/time	**−5 min change dCO_2 (kPa)**	**−5 min change dSBP (mmHg)**	**Value at notification SBP (mmHg)**	**+5 min post event low BP**
3/12:47:00	1.63	27	89	
6/09:22:49	0.17	11	88	84
8/13:21:45	0.05	13	77	76
9/08:48:37	−1.29	9	90	59
9/08:54:37	0.06	31	66	60
9/09:35:57	0	38	106	72
9/11:49:16	0.17	11	88	89
12/11:00:55	0.09	4	84	83
13/08:47:58	0	7	155	107
14/09:53:13	0.03	6	89	80
14/09:59:53	0.14	9	82	77
14/11:14:33	0.16	10	89	85
14/11:31:33	0.08	8	77	78
14/11:41:23	0.06	8	83	75
16/08:50:18	0.04	19	89	83
18a/09:12:54	0.05	10	81	74
18b/16:05:04	0.09	37	80	76
20/09:03:14	0.02	9	91	80
20/09:12:24	0.1	5	76	76
24/09:14:39	0.02	21	131	128
26/09:32:22	0.01	19	75	67
26/09:42:22	0	58	98	88
26/11:46:32	0.11	9	86	73

Table 2
Changes in $EtCO_2$ (kPa) and SBP (mmHg) over 5 min before and after notification of possible hypovolaemia with a decrease in cardiac output.

Hypovolaemia + fall in cardiac output				
Patient/time	**−5 min change dCO_2 (kPa)**	**−5 min change dSBP (mmHg)**	**Value at notification SBP (mmHg)**	**+5 min post event low BP**
2/12:45:00	0.24	10	75	68
5/09:24:00	0.78	23	77	59
6/12:02:28	0.3	23	78	81
6/13:06:58	0.19	15	94	93
8/11:37:36	0.23	18	84	77
8/12:33:46	0.22	20	90	76
8/12:38:00	0.21	21	84	75
9/09:16:00	0.13	9	73	59
9/0 9:57:37	0.57	37	48	48
9/11:19:26	0.05	15	76	59
9/11:30:26	0.13	12	85	83
9/12:02:36	0.25	9	84	77
10/11:46:04	0.19	17	109	103
12/09:23:25	0.45	18	90	77
13/09:12:18	0.09	21	99	85
14/11:21:43	0.32	27	74	66
14/11:42:03	0.16	12	78	75
14/12:19:23	0.14	15	84	79
15/15:01:19	0.24	19	84	75
15/15:26:19	0.47	11	70	74
15/16:24:18	0.36	5	89	84
17/09:45:00	0.52	14	75	68
18b/12:28:34	0.35	42	80	79
18b/13:26:34	0.48	26	58	55
20/09:53:07	0.42	14	91	86
20/14:19:07	0.37	24	88	89
23/10:10:08	0.28	25	79	73
25/12:34:41	0.42	52	107	93
26/08:50:32	0.07	11	88	76
26/0 9:54:22	0.45	29	85	61
26/12:05:12	0.39	26	108	60
30/10:27:30	0.25	11	79	72
30/18:34:29	0.96	27	113	103
31/12:22:46	0.39	14	79	78

comparison; some ultrasound cardiac output monitors claim beat-to-beat measurements. Precision describes the closeness of repeated measurements; given the same, or very similar, circumstances, i.e. changes in all four variables, this technique would produce the same outcome. However, it is an assessment of change rather than providing an absolute value for cardiac output and so repeat measurements would only be valid if the same *change* took place. It is a very safe technique, involving no additional monitoring than

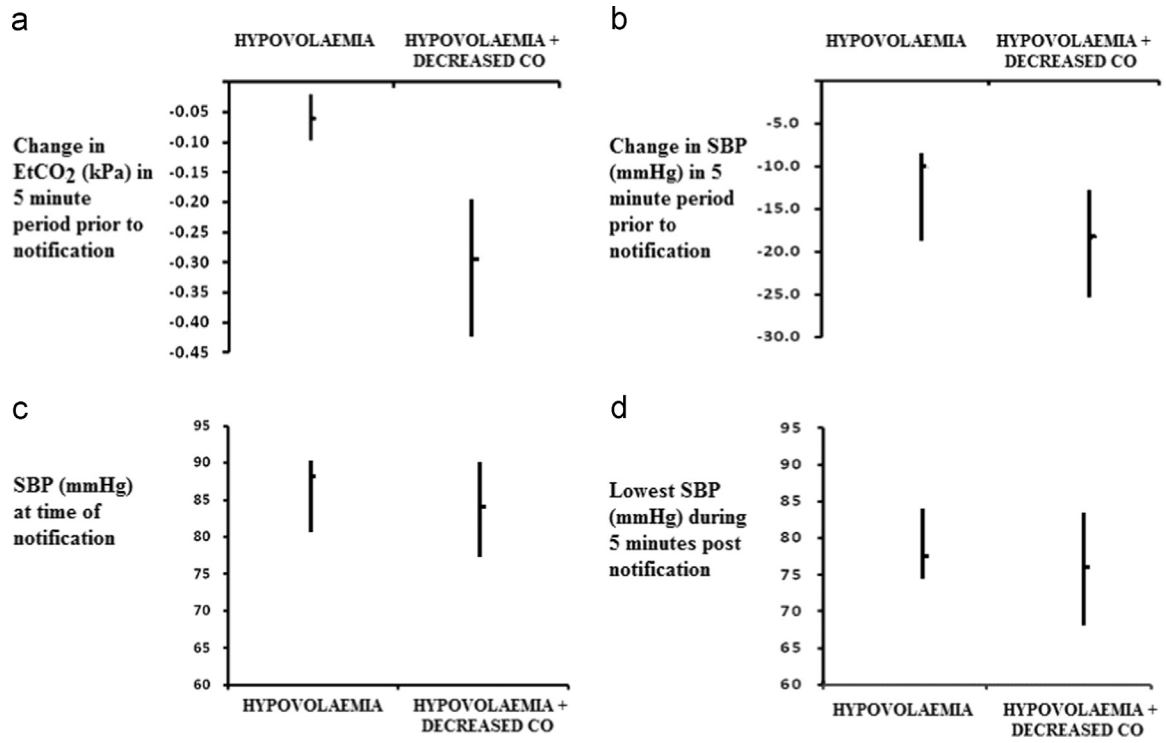

Fig. 2. Median and interquartile ranges for changes in $EtCO_2$ and SBP during the five minutes prior to notification of a possible event (a and b) and the SBP at notification and the lowest SBP in the 5 min post event notification (c and d).

Table 3
Statistical analysis of differences in $EtCO_2$ and SBP between possible hypovolaemia and possible hypovolaemia with a decrease in cardiac output notifications.

Variable	Difference (95% CI)	*p*
dCO_2 (kPa)	−0.25 (−0.42 to −0.09)	0.003
dSBP (mmHg)	−3.1 (−9.1 to 2.9)	0.31
SBP (mmHg) at notification	6.3 (−1.6 to 14.1)	0.12
SBP (mmHg) post-event low	5.5 (−0.7 to 11.8)	0.08

that used during many moderate to major procedures. The danger associated with a rare false positive is minimal as the generated alert just notifies the clinician of the possibility of an adverse change; it is up to the clinician to then assess the situation. False negatives (the failure of detection of change in one or more variables) are likely to be due to artefacts; sampling from the arterial cannula, repositioning of the pulse-oximeter probe or disconnection of the respiratory hose. Heart rate/pulse rate artefacts are minimised as there are three sources – electrocardiograph, arterial line and pulse-oximeter. Determination of the rate of clinically significant false positives and negatives requires further work.

One limitation of the method is, at present, related to the necessity for an intra-arterial cannula for pressure measurement; a non-invasive blood pressure based algorithm is an easy modification but using the trending methodology used here the time lapse for alerts would be extended to at least four times the time gap between measurements. Because of the importance of the $EtCO_2$ in the assessment of a change in cardiac output, it is also necessary for constant pulmonary ventilation; spontaneous ventilation and changes in intermittent positive pressure ventilation are detected and any alerts generated are suppressed.

Rules of evidence can be fine-tuned to give certain variables more power, this may be a way forward to refine this technique but at present it is probably the only way of continuously detecting early changes in cardiac output in a non-invasive manner.

Conflicts of interest statement

Michael Harrison owns the intellectual property of the software used in the study and is involved in a company involved with its development. Mathew Zacharias and Ross Scott-weekly have no conflicts of interest.

Summary

Cardiac output (CO), the most fundamental of circulatory parameters, is difficult to measure accurately and with precision. Intermittent thermodilution is the gold standard but requires multiple measurements over time and is associated with potential harm to the patient.

End-tidal carbon dioxide ($EtCO_2$) is physiologically linked to pulmonary blood flow and therefore to cardiac output. If physiological changes in blood pressure, heart rate and pulse amplitude suggest hypovolaemia and there is a concurrent decrease in $EtCO_2$ then it is possible to deduce that the cardiac output has possibly decreased secondary to the hypovolaemia assuming no change in ventilation or metabolic rate.

The purpose of this study was to demonstrate how routinely monitored physiological variables may detect changes that are indicative of a fall in cardiac output associated with hypovolaemia.

Physiological data were collected from patients during surgery for hepatic resection and colonic surgery. The trends of changes in systolic blood pressure (SBP), heart rate (HR), pulse amplitude (PA) and $EtCO_2$ were determined by runs analysis (using a 'length of run' of at least four) and a decrease in blood pressure was also considered significant if blood pressure fell at least 2SD (SBP–SD) using a normalisation technique. If HR, SBP, PA and SBP–SD changed appropriately hypovolaemia was notified ('HYPO'), if $EtCO_2$ also changed appropriately hypovolaemia with a possible fall in cardiac output was notified ('HYPO+CO').

In thirty-one data sets there were a total of 23 HYPO and 34 HYPO+CO. The only significant difference between the two types of notification was the change in $EtCO_2$.

The requirement of an early warning system is that the alert should be activated before a significant change has taken place. This means that current gold standard methodology is an inappropriate comparison as the cardiac output has to fall significantly before it can be assumed a real change has taken place. This novel assessment is virtually continuous being up-dated every 10 s with a moving window of 40 s. The methodology allows a calculation of the probability that the change is due to chance.

The notifications produced by this software indicates 'A fall in cardiac output is possible' and as such leaves the clinician to review the status of the patient and to consider whether intervention is required.

Although the changes in SBP in both groups are similar, the decrease in $EtCO_2$ in the HYPO+CO group suggests that these patients have passed the point where compensatory mechanisms can maintain normal homeostasis.

Rules of evidence can be fine-tuned to give certain variables more power and this may be a way forward to refine this technique but, at present, it is probably the only way of continuously detecting early changes in cardiac output in a non-invasive qualitative manner.

Acknowledgements

Our thanks go to Dr M Weatherall for help with the statistical analysis.

Appendix A

Classical runs analysis involves the use of time series data where the data points are not correlated. However, physiological data is autocorrelated but not to a significant degree. Wieringa J. Statistical Process Control for Serially Correlated Data. http://irs.ub.rug.nl/ppn/180435140.

No knowledge of measurement units is required, no upper or lower limits and the probability of event occurring is known. The number of times a value is above (or below) the median is counted and the detection of an event (a trend) is set by the length of the run, see below. Sensitivity of the system can be adjusted by altering the length of run that acts as the trigger.

In a time-series of data a moving window of recent values is used to determine a median value. The 'next' value is compared with this median value and it is determined whether it is above or below the median. The moving window is advanced one increment and again the 'next' value is again assessed against this median (above or below). The number of consecutive 'aboves' or 'belows' is counted. The 'length of run' (LOR) is the number of 'aboves' or 'belows' and if the LOR exceeds a set number a notification is generated. In a completely random set of data a LOR of 4 has a probability of 1:16; the simultaneous change of four random sets has a probability of $(1:16)^4$, which is 1:65536.

Computing combinations of variables (HR, BP, PA, and $EtCO_2$) may detect compensatory responses before they are clinically obvious. This is because the magnitude of change does not have to be large; it is the pattern of the combinations that reflect physiological responses.

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