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MONITORING CHRONIC RESPIRATORY PATIENTS BY CONTROL CHARTS WITH VARIABLE LIMITS

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ABSTRACT

Respiratory diseases constitute a serious public health problem due to their social and professional impacts, which result in a diminished working capacity and the corresponding treatment costs. Given the importance of this problem, we have applied Statistical Process Control techniques to a group of patients from an Hospital in Northwest Portugal. Aiming at an individualized follow-up of the patients, control charts were built for the variables oxygen partial pressure (PaO2) and carbon dioxide partial pressure (PaCO2).
However, because the patient´s health indicators are dynamic over time, the limits used in the control charts must suffer a constant actualization, based on the recent past of the patient himself. So, in accordance to a positive or negative evolution of the disease, we have built, for each patient, the control charts with varying limits, which permit the follow up of the patient while identifying, simultaneously, large changes relatively to the patient recent evolution.
Thus, the control chart with varying limits seems to be well adapted to the control and follow-up of chronic respiratory patients, since it provides an easy and adequate interpretation, by the health professionals, over the evolution of the patient´s health status, as well as the detection of acute situations. Therefore, the control charts with varying limits can be perceived as a tool for decision making, by medical doctors, in the follow-up of chronic respiratory patients.

INTRODUCTION

Statistical Process Control (SPC) dates back from the mid forties in the 20th century. It has been applied mostly in industry but, according to some authors (Woodal 2006), control charts and Statistical Process Control (SPC) theory can be alternative methods for the analysis and presentation of data, also in health related problems. In particular, its application to the control of the health status of patients has been a recent research topic. This research aims to use the patient as its own control.
Motivated by this possibility, a data set of chronic respiratory patients from an Hospital in Northwest Portugal (Centro Hospitalar do Alto Minho) has been studied with the techniques provided by SPC. Respiratory diseases constitute a serious public health problem due to their social and professional impacts, which result in a diminished working capacity and the corresponding treatment costs (Circular Normativa n.º 4). Moreover, they are still largely under diagnosed (Circular Normativa n.º 4). Using Control Charts, we aim to individually control these respiratory patients.
As main alternative charts presented in the literature (Montgomery 1991), the EWMA (Exponentially Weighted Moving Average) charts, the CUSUM (CUmulative SUM charts) charts and, more recently, the Q charts (Quesenberry 1997) must be referred. However, it should be noted that the Shewhart charts for variables are the simplest and easiest method to control the series under study (individual uncorrelated data). On the other hand, all the works (Montgomery 1991, Quesenberry 1997, Lucas and Saccucci 1990, Eljach et al. 2006) present the Shewhart charts as those that exhibit the best performance on the detection of large perturbations on the mean, which in the case of the present medical data, becomes more relevant than to signal small variations.
In the study of chronic respiratory patients the most relevant variables are oxygen partial pressure (PaO2) and carbon dioxide partial pressure (PaCO2) because Respiratory Diseases affect the gaseous transfers between lungs and blood, originating Respiratory Insufficiency (RI).
Respiratory Insufficiency (RI) can be defined as the incapacity of the respiratory system to maintain the gaseous exchanges at adequate levels. Thus, RI results in a deficient intake and deficient peripherical transport of oxygen (O2) and/or a deficient elimination of carbon dioxide (CO2).
On the other hand, excess weight is indicated, by medical doctors, as one possible factor disturbing the well being of chronic respiratory patients, by the difficulty that it might add on air flow. Thus, it is necessary to control the value of Body Mass Index (BMI) presented by the patients.

In a recent work (Correia et al. 2010), the authors have built univariate and multivariate, one and two-sided control charts, for each of the variables under study. This work has led to the identification, along the patient´s medical records, of previous out of control situations.

SHEWHART CHARTS

In the previous referred study (Correia et al. 2010), two chronic respiratory patients (Patient A and Patient B) have been monitored, by building, for each variable PaO2, PaCO2 and BMI, the corresponding Shewhart charts. The traditional Shewhart charts for controlling means of individual observations graphically show the evolution, throughout the time (t), of the values of a given variable X that represents a given quality characteristic that one aims to control. It is assumed that the observations of the variable under study are normal, independent and identical, with mean μ and standard deviation σ. In the graphic, a Central Line (CL) is drawn representing the known (or estimated) mean around which the represented values are going to be randomly distributed, if the process is controlled. On the graphic, two more lines are added, representing the Upper Control Limit (UCL) and the Lower Control Limit (LCL). These lines are located at distance from CL equal to 3 times the standard deviation σ. An out-of-control event requiring corrective measures is signaled, whenever an observed value is beyond the control limits. The analysis of the univariate Shewhart charts, for the patients under study, revealed the existence of out of control events for the variable PaCO2 (see Figure 1-b).

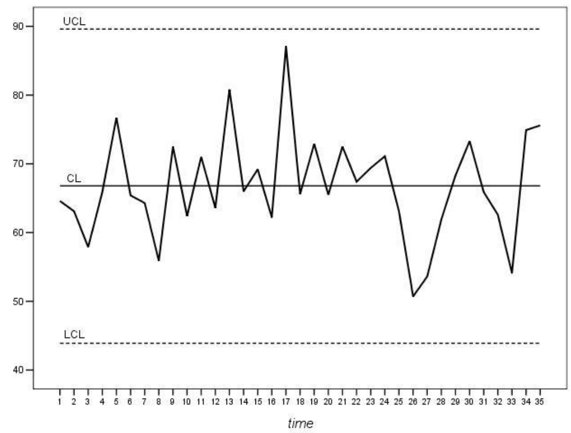

Figure 1a: Shewhart chart for variable PaO2 (mmHg) – Patient B

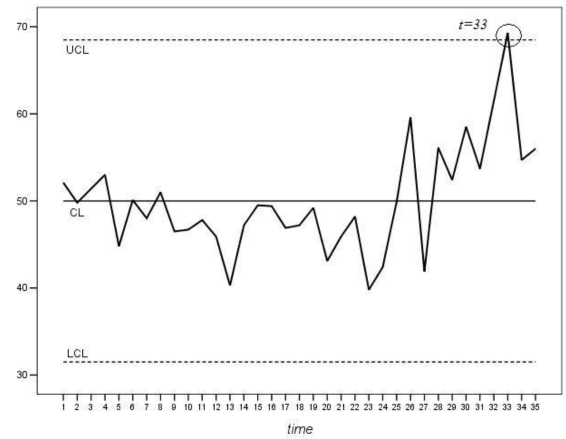

Figure 1b: Shewhart chart for variable PaCO2 (mmHg) – Patient B

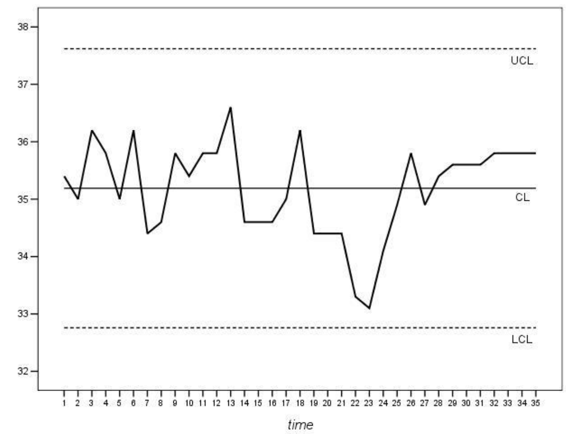

Figure 1c: Shewhart chart for variable BMI (Kg/m2) – Patient B

However, the simultaneous control of the several variables using univariate charts can be misleading, much more so in the case of correlated variables. Because the control variables tend to be correlated, in particular the variables PaO2 and PaCO2, multivariate control charts with variables PaO2 and PaCO2, as well as with variables PaO2, PaCO2 and BMI, were constructed with the aim of verifying if differences are detected by the influence of the variable BMI.

MULTIVARIATE CONTROL CHARTS

The first known work on multivariate statistical control was presented in 1947 (Hotelling 1947). Since then, similarly to the univariate case, many authors (Hawkins 1991, Tracy et al. 1992, Lowry and Montgomery 1995, Mason et al. 1995 and 1997, Jiang 2004, Testik and Runger 2006, Champ and Jones-Farmer 2007) have dealt with this approach and several works, with different applications, have been realized. Considering its scope and posterior references, the work of Alt (Alt 1985) is tantamount to the field.

The T^2 multivariate chart, proposed by Hotelling, in 1947, for the control of the mean of several variables, is based on the assumption that the joint distribution of the p variables follows a multivariate Normal $N_p(\mu,\Sigma)$, with mean vector $\mu' = (\mu_1, \mu_2, ..., \mu_p)$ and covariance matrix Σ. An out of control exists if $T^2 > UCL$ (Upper Control Limit).

However, the interpretation of multivariate charts is more complex than in the case of univariate charts. More details on methods for the interpretation of multivariate charts can be found in several articles (Correia et al. 2010, Mason et al. 1995 and 1997, Alt 1985, Hayter and Tsui 1994, Jackson 1980, 1981a, 1981b, and 1985, Runger et al. 1996, Nedumaran and Pignatiello 1998, Aparisi et al. 2006).

Thus, T^2 charts for Patient A and Patient B have been built, initially only for the variables PaO2 and PaCO2 and, next, for the variables PaO2, PaCO2 and BMI. The construction of the T^2 charts has led us to observe that the out of control events previously detected by the Shewhart chart were, again, clearly signaled (see Figure 2-a). However, a new problem arises with the use of these charts. These charts present similar numerical values, in spite of representing completely distinct situations with regard to good and bad indicators of patient well being (please refer to the observations at time instants t=17 and t=27, in Figure 2-a).

These findings have led to the conclusion that the two sided T^2 charts do not distinguish out of control events by noticeable degradation of the health status of the patient, from situations where an improvement has been observed. In the follow-up of patients, it is of capital importance to be able to distinguish between these two situations, since both imply quite different therapies. Therefore, for the same data, the one-sided charts (univariate and multivariate) will be studied.

One-sided control charts have deserved less attention, but some works should be mentioned (Robinson and Ho 1978, Dou and Sa 2002, Shu et al. 2007). The two-sided charts previously referred (univariate Shewhart and multivariate T^2) are used when one wants to detect a perturbation in the process, regardless if the perturbation corresponds to an increase or a decrease on the value of the mean. But, in the case of the medical data under study, an increase or decrease, for instance, in the value of PaO2 represents two completely different situations. In the first case, there has been an improvement and, therefore, the actual therapy should be maintained. In the second case, on the contrary, there is a worsening of the patient´s health, requiring corrective measures with respect to the therapy that has been followed. Thus, by using two-sided charts in the situations where one is just interested in detecting perturbations in one direction (increase or decrease of the mean), a delay may be introduced in the detection of the perturbation or result in the identification of an observation out of the control limits that is not due to the situation of interest to report. Nevertheless, to use one-sided charts, one has to assume that the direction of the perturbation that is to be signaled is known, i.e., it is mandatory to know previously if one is aiming at detecting an out of control situation when an increase on the mean occurs, or vice-versa, when a decrease occurs.

Considering the advantages of the one-sided charts on the detection of changes in a single direction, together with the increase sensitivity of multivariate charts in dealing with several related variables, the use of one-sided multivariate charts to the medical data will be studied.

The construction of the one-sided multivariate charts clarifies the observed peaks in the T^2 chart for time instants t=17 and t= 27, in Figure 2-a.

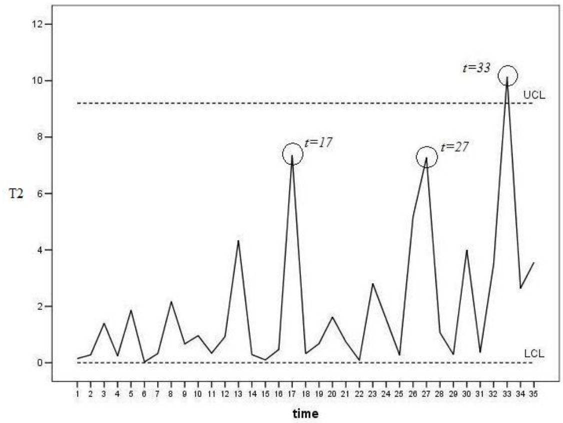

Figure 2a: Two-sided T^2 chart for Patient B, with variables PaO_2 and $PaCO_2$

In Figure 2-b, besides the out of control event at time instant t=33, already signaled in the previous charts, it is now registered a value superior to the control limit at time instant t=27.

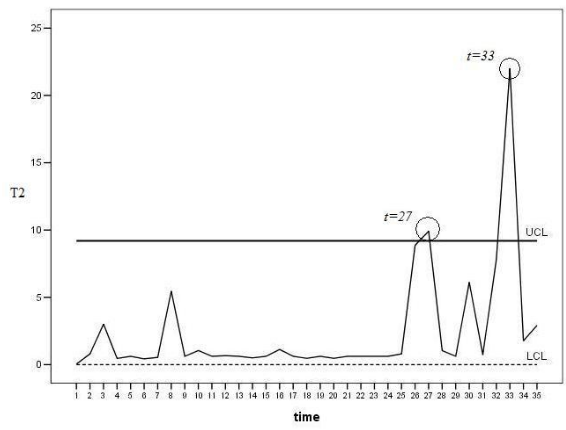

Figure 2b: One-sided T^2 chart for Patient B, with variables PaO_2 and $PaCO_2$

So, the one-sided multivariate control charts (Figure 2-

b) identified the out of control events that previously have not been pointed out by two sided Shewhart charts (observation t=27), as well as the recognition of potential false alarms signaled by the T^2 multivariate charts (observation t=17).
However, much more important than this retrospective analysis is the future follow up of individual patients. On the other hand, the control charts used in the referred work (Correia et al. 2010), the conclusions of which will be presented briefly, have the disadvantage that, after the control limits have been set, the limits stay unchanged throughout the time, regardless the positive or negative evolution that the patient might exhibit. The positive or negative evolution of the patient, which requires to be signaled, is an important indicator for medical action.
Thus, for each patient we have built the control charts with varying limits which permit the follow up of the patient while identifying, simultaneously, large changes relatively to the patient recent evolution.

CONTROL CHARTS WITH VARIABLE LIMITS

For each patient, the control charts with varying limits will be presented. In order to calculate the variable control limits, we have used past data from the patient, instead of fixed values, previously calculated, based on population data or in a long historical record of the same patient.
In a first approach, we represent, in the control charts with varying limits, the observed value of the variable at time instant t, with the respective control limits and central line calculated from the previous 10 observations. It should be noted that the variable control limits are represented starting from the 11th observation. The limits previous to this 11th observation are fixed and calculated from the mean and standard deviation of the first 10 observations. Thus:
- The central line (LC) at time instant t is calculated as follow Equation (1)

$$\begin{cases} \mathrm{CL}_t = \dfrac{\sum_{i=1}^{10} x_{t-i}}{10} & \text{if} \quad t > 10 \\ \mathrm{CL}_t = \dfrac{x_1 + x_2 + x_3 + \ldots + x_{10}}{10} & \text{if} \quad t \le 10 \end{cases} \tag{1}$$

-The control limits are at 3σ distance from the central line, being σ the standard deviation from the 10 observations used in the definition of the central line [Equation (2)].

$$\begin{cases} UCL_t = CL_t + 3\sigma_t \\ LCL_t = CL_t - 3\sigma_t \end{cases} \tag{2}$$

However, this chart does not provide the needed information. In fact, the observation at time instant t=33 is not signaled as out of control, as it has happened in all the control charts presented before. This results from the increasing values of the patient´s variable under study. As the patient exhibits this growing pattern, the variability of the observations increases and its consequence is an increase in the range of the control limits.
Therefore, aiming to overcome this difficulty and in order to define the control limits, the average of the last 10 standard deviations has been used. Thus, in equation (2) we have substituted σ_t by $\overline{\sigma}_t$, obtained from Equation (3).

$$\overline{\sigma}_t = \frac{\sum_{i=1}^{10} \sigma_{t-i}}{10} \quad \text{if} \quad t > 10 \tag{3}$$

The new control limits are smoother and detected the out of control situation at instant t=33.
Summarizing, in the control chart with variable control limits we represent the observed values at each time instant t, with the central line based on the average of the last ten observations of the variable. The upper and lower limits are at a distance equal to three times the average of the last ten standard deviations.
In Figure 3 we present the control charts with variable limits for the variables PaO2 (Figure 3-a) e PaCO2 (Figure 3-b) of patient B. This chart, for the patient under consideration, has clearly identified the out of control events previously referred. In order to best analyze the improvement or worsening of the patient´s health, we have also represented the reference value used by the medical community.

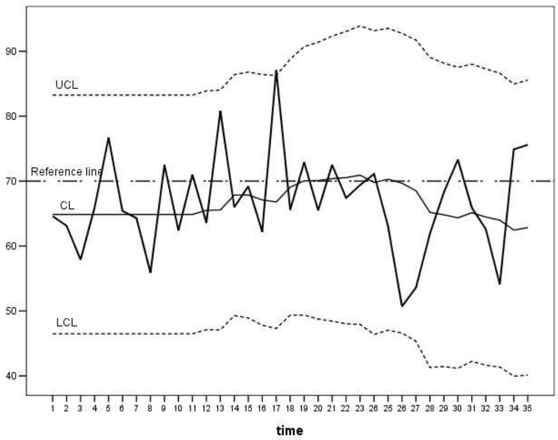

Figure 3a: Control chart for PaO_2 (mm Hg) with variable control limits, for Patient B

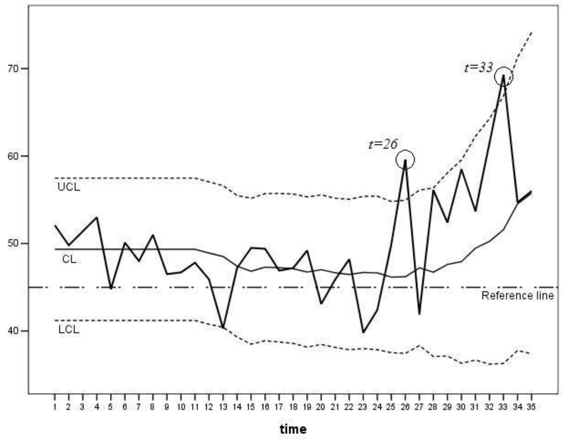

Figure 3b: Control chart for $PaCO_2$ (mm Hg) with variable control limits, for Patient B

Thus, the horizontal line, in Figure 3-a, represents the reference value for the concentration of PaO2, below which respiratory insufficiency exists. On the other hand, in Figure 3-b, whenever the value of PaCO2 is above the reference line, a pathological event is considered present.

As we can see, there is an increasing tendency on the last observed values of PaCO2, with greater variability in variable PaO2, which indicates a worsening of the patient´s health. On the other hand, the chart with varying limits registers also an out of control event for the variable PaCO2 at time instant t=26, a situation that, previously on the other control charts, was never reported. Furthermore, it can be noticed that it is from this very time instant that the worsening of the patient status is observed.

Similarly, Figure 4 represents the control charts with variable control limits and reference lines for variable PaO2 (Figure 4-a) and PaCO2 (Figure 4-b) for another patient, patient A.

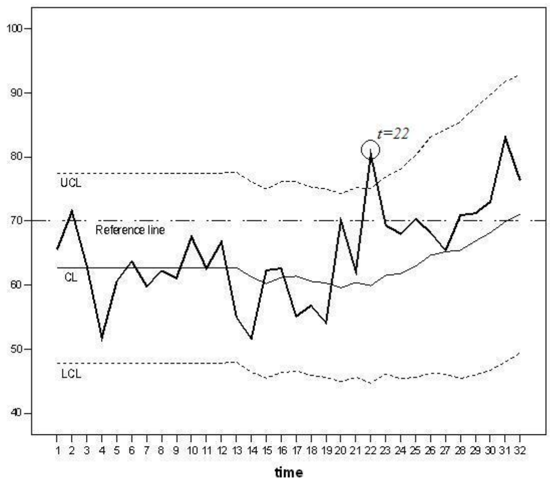

Figure 4a: Control chart for PaO_2 (mm Hg) with variable control limits, for Patient A

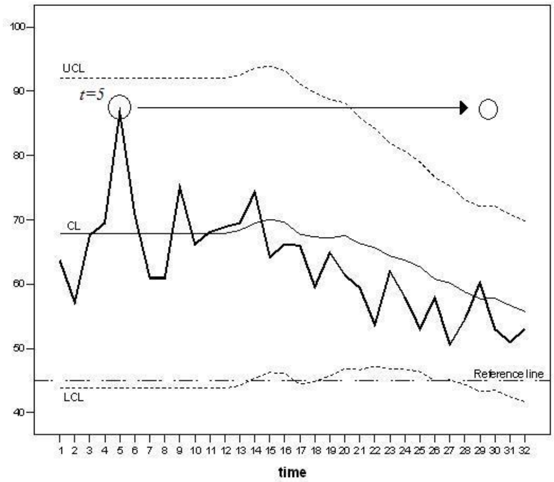

Figure 4b: Control chart for $PaCO_2$ (mm Hg) with variable control limits, for Patient A

Considering the positive evolution of the patient, new limits are calculated, adjusted to the new health status of this patient. We can observe that the patient presents a favorable peak for the variable PaO2, relatively to the past, at time instant t=22, as well as a constant tendency for improvement from that time moment.

Consequently, for instance, if a value of PaCO2 equal to the one observed at time instant t=5 was observed at time instant t=30 (Figure 4-b), this would be considered now an out of control event, requiring the analysis of the causes that originated this event. It should be noted that this change would not be detected with fixed control limits, which do not take into account the evolution of the disease.

BOOTSTRAP LIMITS

The reason behind using 10 observations for the construction of the control limits lies in the fact that this set of observations corresponds, approximately, to two and half years of patient follow-up. This situation is considered, in medical data, a long period. However, this approach might be questioned on the basis that, statistically, this is a small sample. Thus, parameter estimation might be arguable. In order to overcome some of the problems mentioned previously we have used bootstrap resampling.

The Bootstrap method, first presented by Efron (Efron 1979), is a resampling technique that, starting from a single sample, uses simulation to generate the sampling distribution.

The bootstrap technique is based on the following principle: through random sampling (with replacement) of the observations of the original sample, several samples are created (the so called bootstrap samples) of the same dimension. For each bootstrap sample the respective statistics are calculated. For a large number of

samples, it can be shown (Caparini 2009) that the statistics distribution obtained from the bootstrap samples converges to the real sampling distribution. Thus, for each set of ten observations used in each time instant t, 1000 bootstrap samples have been generated, for the definition of the confidence interval limits.
The normality of the bootstrap distribution is verified and, based on the bootstrap samples, we have built, for each variable, the 95% limits, assuming that the data are normally distributed.
These intervals were compared with the previous varying limits defined before. As can be seen in Figure 5, for Patient B, the bootstrap limits (dotted lines), generated by the bootstrap method, are very close to the variable limits (continuous lines) based on the moving average of the standard deviations, for k equal to 2. This validates the adopted methodology for the construction of the control charts with varying limits.

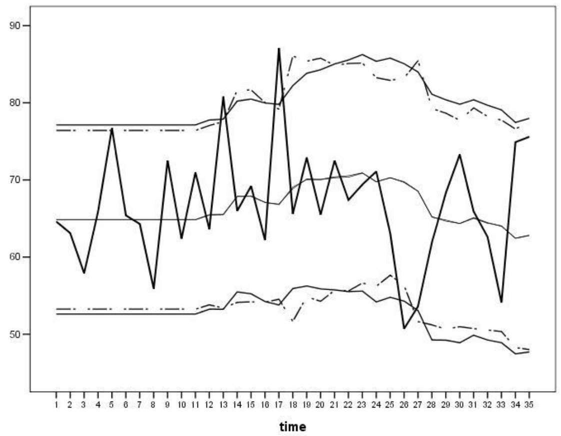

Figure 5a: Control chart for PaO_2 (mm Hg) with bootstrap and variable control limits, for Patient B

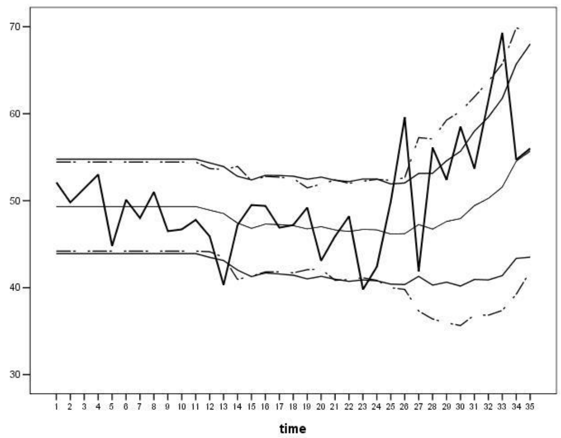

Figure 5a: Control chart for $PaCO_2$ (mm Hg) with bootstrap and variable control limits, for Patient B

DISCUSSION

According to some authors (Woodal 2006), control charts and Statistical Process Control (SPC) theory can be alternative methods for the analysis and presentation of data, also in health related problems. So, in a recent work (Correia et al. 2010), with the aim of monitoring chronic respiratory patients, the authors have built univariate and multivariate, one and two-sided control charts, in order to study the variation of variables PaO2, PaCO2 and BMI, since these variables are those that, according to medical doctors, best characterize the wellbeing of a patient. It was concluded that the control charts, particularly one-sided, are a powerful tool in the retrospective follow up and control of respiratory chronic patients, when the aim is to detect changes on the mean solely in one direction, as might be the case of the patient´s data.
However, because the patient´s health indicators are dynamic over time, the limits used in the control charts must suffer a constant actualization, based on the recent past of the patient himself. So, in accordance to a positive or negative evolution of the disease, we have built, for each patient, the control charts with varying limits.
We have observed that the control charts with varying limits explicitly show the tendency for worsening or improving of the patient´s health status, throughout the time. Furthermore, these charts permit the identification of abnormal values for the corresponding phase in the patient´s status, at each time instant.
Thus, the control chart with varying limits seems to be well adapted to the control and follow-up of chronic respiratory patients, since it provides an easy and adequate interpretation, by the health professionals, over the evolution of the patient´s health status, as well as the detection of acute situations.
Thus, we conclude that the control chart with varying limits is easy to implement and intuitive, allowing the health professionals an immediate reading of all the historical data of the patient, as well as the evolution throughout the time. The presented examples show the capacity of this chart in detecting abnormal events, often not detected by the control charts with fixed limits previously studied. Therefore, the control charts with varying limits can be perceived as a tool for decision making, by medical doctors, in the follow-up of chronic respiratory patients.

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