A functional test for the detection of infusion lines extravasation

Arnaldo Mayer, Adi Zholkover, Ilan Keidan

Abstract— **Extravasation during intravenous (IV) infusion is a common secondary effect with potentially serious clinical consequences. The correct positioning of the needle in the vein may be difficult to confirm when no blood return is observed. In this paper, a novel method is proposed for the detection of extravasation during infusion therapy. A small volume of a sodium bicarbonate solution is administrated IV and, following its consecutive dissociation, an excess of carbon dioxide (CO2) is rapidly exhaled by the lungs. The analysis of the exhaled CO2 signal by a pattern recognition algorithm enables the robust detection of the CO2 excess release, thereby confirming the absence of extravasation. Initial results are presented for the application of the method on a group of 89 oncology patients.**

I. Introduction

Over 100,000 doses of chemotherapy and in excess of 1,000,000 intravenous (IV) infusions are given every day around the world [1]. Minimizing adverse events and complications of these procedures is important both for the patients receiving them and the healthcare systems in which they take place. Extravasation and infiltration are common complications of intravenous (I.V.) infusion therapy. Extravasation can cause accidental administration of intravenously infused medicinal drugs into the surrounding tissue, either by leakage (e.g., because of brittle veins in very elderly patients), or direct exposure (e.g. because the needle has punctured the vein and the infusion goes directly into the arm tissue). In particular, solutions containing calcium, potassium, contrast media, some antibiotics, vasopressors, or chemotherapeutic agents may be very irritating and harmful. In mild cases, extravasation can cause pain, reddening, or irritation to the infused arm. Severe damage may include tissue necrosis and, in extreme cases, even the loss of an arm. It is critical that an extravasation is recognized and diagnosed early. The tools available today to recognize and detect extravasation in its early stages are mainly subjective and rely on the awareness to all relevant signs and symptoms. Analysis of the American Society of Anesthesiologists Closed Claims database revealed 2% of all claims were related to peripheral IV catheterization and over half of these were due to extravasation. Even higher rates could be expected with other health care providers given the presumed expertise of anesthesiologists in IV cannulation [2]. The best "treatment" of extravasation is certainly prevention [3]. To date, no objective test is available to confirm the intravascular placement of catheters. In this paper, we present a novel method that enables to assess functionally the presence of extravasation during IV infusions. The proposed method is validated on a group of 89 patients.

Research supported by Kamin grant of the Israeli Ministry of trade and industry.

Arnaldo Mayer is with the Diagnostic imaging department, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel (phone: 972544 811613; e-mail: arnmayer@gmail.com).

Adi Zholkover is with the Diagnostic imaging department, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel (e-mail: azholkover@gmail.com).

Ilan Keidan is with the anesthesiology department, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel (e-mail: ilan.keidan@sheba.health.gov.il).

II. Methods

A. The bicarbonate test

In a water solution, sodium bicarbonate ($NaHCO_3$) dissociates and exists mainly in the form of bicarbonate ions ($HCO3^-$). When injected into the blood, bicarbonate ions will further transform into water and CO_2 (equation 1):

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow CO_2 \uparrow + H_2O \quad (1)$$

The resulting CO_2 excess is rapidly exhaled by the lungs [4]. In fig. 1, the temporal plot of the CO_2 partial pressure (Pco_2) obtained by capnography is shown after IV injection of a diluted bicarbonate solution. Each wave corresponds to a breathing cycle, the peak of the wave being the end tidal value, denoted $Petco_2$.

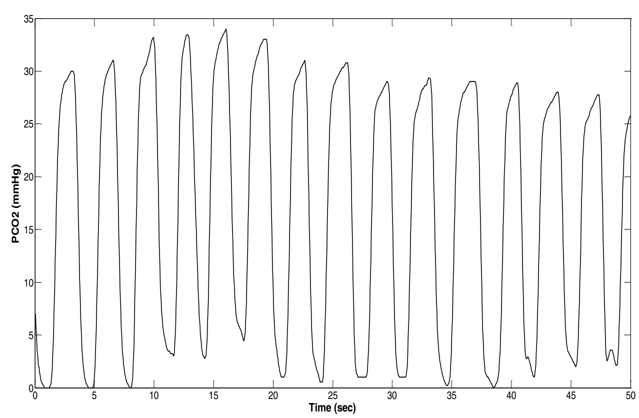

Figure 1. Temporal plot of the CO_2 partial pressure (Pco_2) obtained by capnography after IV injection of a diluted sodium bicarbonate solution.

Injection is performed at time = 0 seconds. It can be seen that a peak in Pco_2 at exhalation is reached at time =16 seconds, that is 4 breathing cycles after injection. Note that the peak is reached at the end of an exhalation cycle, where Pco_2 is equal to $Petco_2$.

The successful observation of a response wave consecutive to the bicarbonate injection is a strong evidence that the injection was effectively performed intravenously, without extravasation, since the CO_2 excess made it all the way out through the lungs. In the following section, an algorithm is presented for the automatic detection of the bicarbonate response wave using a machine learning approach. When extravasation occurs, the injected bicarbonate does not reach the lungs as it disperses in nearby tissues. Since real extravasation cannot be intentionally performed for ethical reasons, it is simulated in this work by an IV injection of a harmless saline solution that has no incidence on the amount of exhaled *CO2*.

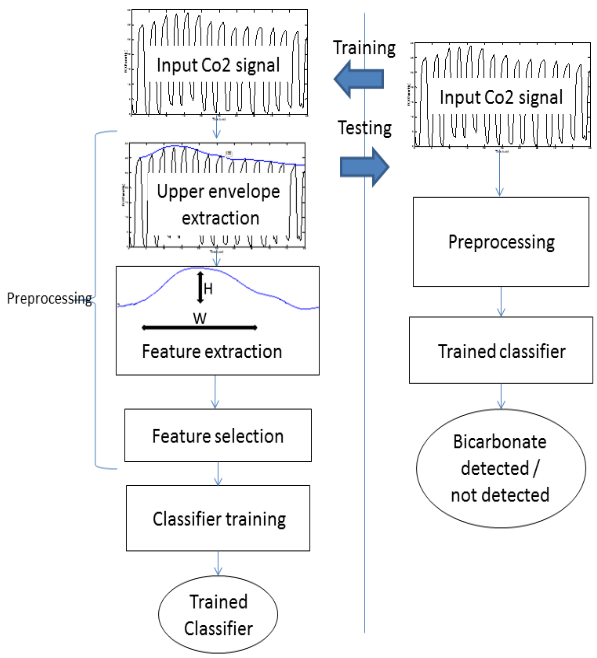

Figure 2. Main steps of the proposed method.

B. The detection algorithm

The main steps of the proposed method are given in the block diagram of fig. 2. In the training phase (left), a supervised classifier learns to recognize bicarbonate response waves in the Pco_2 signal generated by a capnograph.

For this purpose, the input signal is first processed to extract its upper envelope (blue curve). In fact, $Petco_2$ reflects most of the signal increase caused by the bicarbonate injection. However, since $Petco_2$ is measured only once per breath, the upper envelope is used to smoothly interpolate $Petco_2$. The resulting signal is better suited for the consecutive feature extraction step.

In order to obtain the envelope, the end tidal peaks need to be extracted for each breath. This is performed by thresholding the CO_2 signal at a constant value, empirically set to 20 mmHg, and extracting the maximal value in each resulting segment. The envelope is then obtained by fitting linear segments between the peaks and smoothing by a moving window averaging filter (width = 10 samples).

The next step is the computation of descriptors providing good discrimination power between the bicarbonate response wave and natural fluctuations of $Petco_2$. The discrimination power is quantified by the signal to noise ratio (SNR) of the descriptor define by [5]:

$$SNR = \frac{|\mu(bic) - \mu(sal)|}{\sqrt{(\sigma^2(bic) + \sigma^2(sal))}} \quad (2)$$

Where $\mu(bic)$, $\sigma(bic)$ and $\mu(sal)$, $\sigma(sal)$ are the average and standard deviation values of the given descriptor computed over a training set of $Petco_2$ envelope signals acquired following the injection of bicarbonate and saline solutions, respectively.

A set of descriptors were initially considered to describe the envelope signal and defined as follows:

- The Maximal peak amplitude (PA): amplitude of the highest peak observed in the envelope signal following injection and measured above the baseline value. The baseline being defined as the average signal value computed during the 10 seconds that preceded injection.
- The wave duration (WD): lapse of time between the first instant where a signal increase of 0.15xPA is observed above the baseline, to the first instant where the signal has decreased by 0.85xPA, after reaching the maximal peak value (defining PA) .
- The temporal location (PL) of the maximal peak after injection.
- The mean (MN) and standard deviation (SD).
- The skewness (SK), expressing the degree of asymmetry of the values around the mean [6].
- The kurtosis (KT), reflecting the relative *peakedness* or flatness in comparison to a normal distribution [6].
- Shanon entropy (SE), providing an indication of the signal randomness [7].

The features selected from the initial set are generally required to have high SNR while presenting a low mutual correlation. SNR and correlations for the features above will be computed on real data in the experiments section (section 3).

Eventually, a supervised classifier is trained on the training set [8]. Considering the limited size of the overall dataset, the support vector machines (SVM) are an attractive choice as they provide strong generalization properties with a good immunity to the curse of dimensionality [8].

In the testing phase (fig.2 , right), the input Pco_2 signal undergoes the same pre-processing as in the training phase, although only the feature selected during the training phase are actually computed to produce a feature vector x. Consecutively, the trained SVM classifier assigns a classification score *C(x)* according to [9]:

$$C(x) = \sum_i \alpha_i k(s_i, x) + b \qquad (3)$$

where s_i are the support vectors, α_i are the weights, b is the bias, and k is a kernel function. In the case of a linear kernel, k is the dot product between the input vector x and support vector s_i. The score indicates (in absolute value) the distance between the considered feature vector and an optimal decision hyper-plane. Therefore, large scores generally correspond to a confident classification, whereas small scores may lead to ambiguity. Non-linear kernel such as the radial basis functions are also popular choices for the kernel functions, defined by [9]:

$$k(s_i, x) = \exp - \left(\frac{\| s_i - x \|^2}{2\sigma^2}\right) \qquad (4)$$

where σ defines the Gaussian shaped window size around the support vector. Rbf kernels transfer the classification problem into a higher dimensional space where linear separation by hyper-plane may be better achieved for the data at hand.

Eventually, a threshold is applied to the score in order to obtain the desired working point on the receiver operator characteristic (ROC).

III. EXPERIMENTS

Following authorization by the hospital IRB, the test was validated on a dataset of signals acquired from of 89 oncology patients that provided their prior written consent. Oncological patients are particularly concerned by extravasation risks. The chemotherapy substances they regularly receive by IV infusion are particularly harmful if injected outside the vein. Each recruited patient was IV injected in the forearm 20 mLs of 4.2% sodium bicarbonate. 59 out the 84 patients were also administrated 20mLs of normal saline, at least 5 minutes before the bicarbonate solution was injected. The saline solution, injected to simulate the extravasation, was administrated before the bicarbonate to avoid any residual influence of the bicarbonate on the recorded saline signal. The CO_2 signals where acquired using a Capnostream 20, capnograph (Oridion, Israel) at 20 samples/s, for a time period of 90 seconds after injection. The signals were transferred via an RS232/USB converter to a laptop computer for processing.

In total, a dataset of 143 (=84+59) CO_2 signals was created.

The GUI and the processing algorithm were both implemented in Matlab (Mathworks, USA). The experimental setting is shown in fig. 3. When the nurse initiates a new test from the GUI, the algorithm starts to analyze the input signal. After 20 contiguous seconds of *flat* signal, the GUI vocally prompts the nurse to perform the injection. The flat signal is defined by a maximal excursion of the CO_2 envelope of less than 1 mmHg.

The *device triggered* injection has the advantage of giving a reliable baseline for the CO_2 signal before injection. Moreover, the variability of the actual injection starting time is minimized as the nurse waits for the vocal trigger to start the injection.

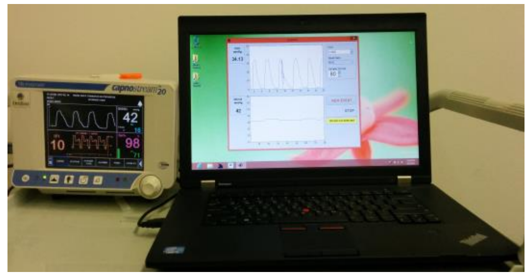

Figure 3. Experimental setting.

The acquired dataset was then transformed into feature vectors according to the method described in section 2. For the purpose of feature selection, 50 signals were selected randomly out of the 143. The remaining 93 were kept for testing and training the classifier. The SNR (table 1) was then computed for each feature in the original set (section 2): peak amplitude (PA), wave duration (WD), maximal peak location (PL), mean (MN), standard deviation (SD), skewness (SK), kurtosis (KT), and Shanon entropy (SE).

Table 1 : SNR values for the original set of features

PA	PL	WD	MN	SD	KT	SK	SE
0.62	0.01	0.53	0.17	0.55	0.20	0.44	0.06

The Correlation coefficient was also computed between the features and shown in fig. 4. For PA, WD, SD and SK, the SNR is in the 0.44-0.62 range, which is notably higher than for the remaining features. The correlation coefficient between these 4 features is below 0.65, which is reasonable (fig.4). In practice, these 4 features are selected together with the mean value (MN). Although MN gave a poor SNR, it may prove very useful for the identification of signals corresponding to non-physiological situations, where the baseline signal is out of range. This can happen, for instance, if the flexible *CO2* sampling tube connecting the patient to the capnograph has a leakage or is pinched.

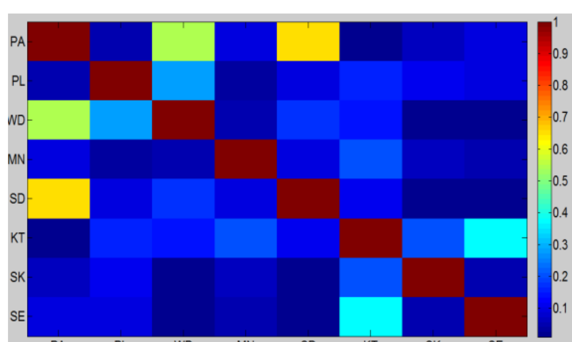

Figure 4. The Correlation coefficient computed between the features.

Next, a 10-folds cross validation framework was applied to evaluate the performance of the classification algorithm [10]. For this purpose the 93 signals not used for features selection (54 bicarbonate and 39 saline) were randomly divided into 10 disjoints sets containing approximately the same number of signals (that is 9-10), the complement (83-84 signals) being kept for training the classifier in the considered fold. SVM training and classification were performed using Matlab statistical toolbox SVM implementation. The SVM classification function provided by Matlab was modified to provide the classification score (equation 3) as output instead of a crisp label corresponding to the score sign.

Two kernel types were compared: linear and radial basis function. Matlab default value $\sigma=1$ was used for the rbf window size parameter. ROC curves were generated by applying a range of threshold values to the classification score in order to obtain crisp labels. The curves are shown in fig. 5 for both kernel types. Sensitivity is plotted against the false positive (FP) rate (=1-Specificity). The resulting area under the curve (AUC) for the ROC curves is 0.892 for the rbf kernel and 0.903 for the linear kernel, respectively. The superiority of the linear kernel over the rbf is best seen in the 0.1-0.3 range of the FP rate.

The choice of the optimal working point is usually application dependent. In real life scenario, only bicarbonate will be injected and if the classifier detects bicarbonate, the IV line is considered as correctly working and the therapeutic infusions will be injected to the patient through the line. Therefore, in order to stay on the safe side, FP rate should be minimized while keeping sensitivity at an acceptable rate. The working point at Sensitivity=0.844 and FP rate= 0.128 may give such a tradeoff.

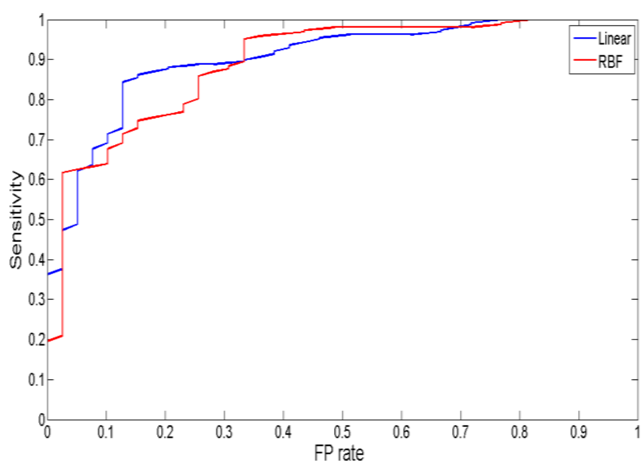

Figure 5. ROC curves for the linear (blue) and rbf (red) kernels. Sensitivity is plotted against the false positive (FP) rate.

IV. Conclusion

A new functional test was presented for the detection of infusion lines extravasation. The test relies on the detection of an exhaled *CO2* excess response wave induced by the injection of a diluted sodium bicarbonate solution. A supervised learning algorithm was developed for the automation of the test. The algorithm was successfully validated on a group of 89 patients, demonstrating the feasibility of the method. In future work, the signal dataset will be extended to larger populations with different backgrounds (not only oncology patients). Additional features will be investigated for the learning algorithm with more kernel types, as well as alternative classifiers. Another important aspect is the robustness of the test. For example, the current version requires from the patient to refrain from speaking during the test, in order to give accurate results. Similarly, biased results may be obtained if the *CO2* sampling line is pinched, by mistake, during the test. An algorithm will be developed for the detection of a *perturbed* test in order to invalidate its results automatically.

In that case, the test may be repeated after a few minutes, since the dose of bicarbonate is sufficiently small to allow for a second injection without any harm.

References

[1] Extravasation guidelines, European Oncology Nursing Society (EONS), 2007.

[2] C. Sauerland, C. Engelking, R. Wickham, R. Corbi. Vesicant extravasation part I: Mechanisms, pathogenesis, and nursing care to reduce risk. Oncol Nurs Forum .33:1134, 2006.

[3] S.M. Bhananker et al. Liability related to peripheral venous and arterial catheterization: a closed claims analysis. Anesthesia & Analgesia 109(1): 124-129, 2009.

[4] H. Okamoto et al. Changes in end-tidal carbon dioxide tension following sodium bicarbonate administration: Correlation with cardiac output and haemoglobin concentration. Acta anaesthesiologica scandinavica 39(1): 79-84, 1995.

[5] L. Goh et al. A Novel Feature Selection Method to Improve Classification of Gene Expression Data. 2nd Asia-Pacific Bioinformatics Conference (APBC2004), Conferences in Research and Practice in Information Technology, Dunedin, New Zealand, 2004.

[6] A. Nanopoulos, R. Alcock, and Y. Manolopoulos. Feature-based classification of time-series data. International Journal of Computer Research 10(3) ,2001.

[7] J. Bruhn et al. Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. Anesthesiology, 95(1): 30-35, 2001.

[8] C. Cortes, and V. Vapnik. Support-vector networks. Machine learning, 20(3):273-297, 1995.

[9] N. Cristianini,and J. Shawe-Taylor. An Introduction to Support Vector Machines, Cambridge University Press, Cambridge, UK. 2000.

[10] A. Moore. Cross-validation for detecting and preventing over-fitting. School of Computer Science Carneigie Mellon University, 2001.