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Developing Customized Evaluation Software for Clinical Trials: An Example with Obstructive Lung Diseases

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ABSTRACT

Corresponding customized software tool is usually unavailable, which increases the time and workload for evaluating the results of a clinical trial. In the present paper, we demonstrate the development process of a customized software for one clinical trial on patients with obstructive lung disease. Over hundred patients and volunteers as controlled were included in the clinical trial. They were examined by spirometry and EIT in a seated position during spontaneous tidal breathing. Subsequently, standard vital capacity maneuver and forced full expiration maneuver were performed. In order to evaluate the offline data, a customized software was developed. The requirements of the software were defined by investigators. The software was then tested on patients' data and refined based on feedbacks of the investigators. We finalized the customized software with analysis of various disease-specific parameters and indices. Compared to the data process with device specific programs and other commercial software, the customized software is more flexible, user-friendly and extendable. As conclusion, customized software simplifies the evaluation process distinctly and helps physicians to focus on study design and result interpretation.

1. Introduction

One effective way to validate a health intervention is clinical trial. It is usually prospective, has no well established protocol, and generates huge amount of data in order to reach sufficient statistical power. The data often need to be manually evaluated with commercial spreadsheet or statistical software (e.g. Microsoft Excel, IBM SPSS) according to our experiences. These softwares are unspecific and not extendable for novel algorithms. Therefore, the evaluation processes are time-consuming and tedious for the physicians on one hand, and on the other hand, limited to conventional analysis, which is unwanted especially for pilot studies.

Customized evaluation software for clinical trials does warrant under these circumstances. Such software need to be study specific, user-friendly and extendable for further studies. Close collaboration between physicians and engineers is the prerequisite of the customized software development. Recently in a series of clinical trials, the feasibility of electrical impedance tomography (EIT) on identifying inhomogeneous regional lung ventilation was examined in patients with obstructive lung disease (e.g. [1,2]). In the present paper, we report an example of

customized software for one of these clinical trials and demonstrate the development of the software for batching EIT data.

2. Materials and Methods

2.1. Electrical Impedance Tomography for Thorax

Thorax EIT is a noninvasive imaging technique used for monitoring the regional lung ventilation and tidal volume distribution [3]. The rationale of EIT measurement is that changes in regional air content and regional blood flow alter the electrical impedance of lung tissue [4]. The injected alternating current (typically chosen between 10 kHz - 100 kHz) through the thorax result in non-uniform distribution of electrical potentials at the chest wall surface. Thorax EIT systems with 16 electrodes are widely used, where 208 voltages are measured in each frame. EIT images showing time-difference impedance distribution within measuring layer are reconstructed based on the voltage measurement. Applications of EIT have been proposed to assess the ventilation distribution or guiding respiratory therapies in subjects without lung disease [5,

6] and in patients with mild, moderate, and severe lung diseases [7-9]. However, evaluation of EIT measurement is not easy for doctors since 1) there is no established guideline for measurement; 2) commercially available software is device specific and rarely extensible for various clinical trials; 3) open source software is comprehensive but not disease specific.

We recently developed a customized EIT evaluation software for a clinical study in university hospital Schleswig-Holstein. The examination protocol of the clinical trial is briefly described, followed by the development process of the software.

2.2. Examination Protocol

At the time point of writing the manuscript, over one hundred patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), or asthma were included in the clinical trial. All subjects were examined by spirometry (Jaeger pneumotachograph, CareFusion, Höchberg, Germany) and EIT (Goe-MF II EIT system, CareFusion, Höchberg, Germany) in a seated position during spontaneous tidal breathing. They were asked to perform full inspiration from functional residual capacity to total lung capacity, followed by standard forced full expiration maneuver and at the end back to spontaneous tidal breathing (**Figure 1**) [2]. For the EIT measurement, 16 ECG electrodes were placed on the chest circumference in the 5 - 6th intercostal space (parasternal line) and one reference electrode on the abdomen in each subject. Data acquisition lasted about 60 - 100 s.

2.3. Development of the Evaluation Software

Software requirements and design: The engineers from Furtwangen University and the clinicians from University Medical Center Schleswig-Holstein have held a series of meetings to discuss the settings of the clinical trial; to elicit, analyze, specify and validate the requirements of the evaluation software. Illustrations of various disease-specific parameters and indices were graphically summarized by the clinicians (e.g. **Figure 2(A)**). Evaluation requirements were described in functional flow block diagram (**Figure 2(B)**).

Software construction: Considering that a very useful EIT open source tool EIDORS [10] is programmed with MATLAB (The MathWorks, Natick, MA, USA), the evaluation software is written with MATLAB (Ver. 7.2) and built with MATLAB Deploy tool and C++ Compiler.

Software testing and refinement: The behavior and performance of the evaluation software was dynamically verified on a set of test cases before delivered to the physicians. Feedback was given by the physicians after testing the software on patient data. Unexpected behaviors of the software due to misunderstanding or bugs were cor-
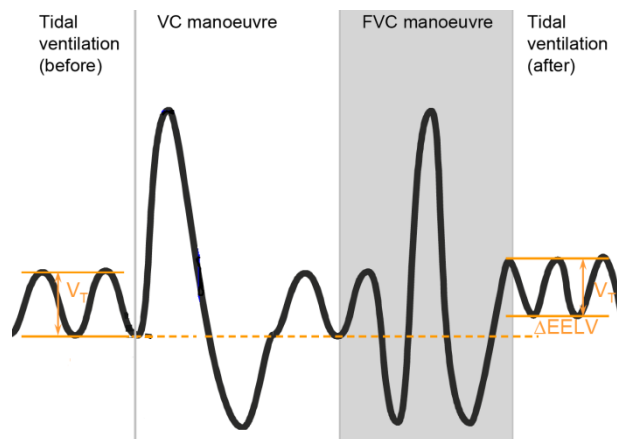

Figure 1. Spirogram of lung volume changes during the examination. Four phases are recognized: spontaneous tidal breathing, vital capacity maneuver, forced expiration maneuver and again spontaneous tidal breathing. V_T: tidal volume; $\Delta EELV$: change of end-expiratory lung volume.

rected. This testing-improving process was repeated several times to improve the software.

3. Results

The software consists of two parts: The physicians use the first part to process the raw measurement data (**Figure 3(A)**). Five different EIT raw and image data formats can be recognized. EIT images are reconstructed with either back projection or GREIT method and can be extended easily. Fifty frequently used clinical parameters such as forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) and their quotients can be quickly calculated by clicking the corresponding buttons. EIT data and results are graphically displayed and as different formats exported or printed (e.g. JPEG, TXT, XLS, PDF; **Figure 3(B)**). Simple filters such as moving average and butterworth are implemented to suppress signals other than respiration.

In the second part of the software, various disease-specific parameters and indices can be displayed as functional images or histogram in different scales and combinations (**Figure 4**). Comparison of the parameters between measurements, among different maneuvers or among different patients can be easily conducted via choosing the corresponding options. Several validity checks (e.g. the study group, the input ranges) are performed to prevent mistakes of data evaluation.

4. Discussion and Conclusions

In the present study, we demonstrated the development process of a customized evaluation software for a clinical trial of pulmonary function test with EIT. The customized software has the following advantages compared to the data process with device specific program and other
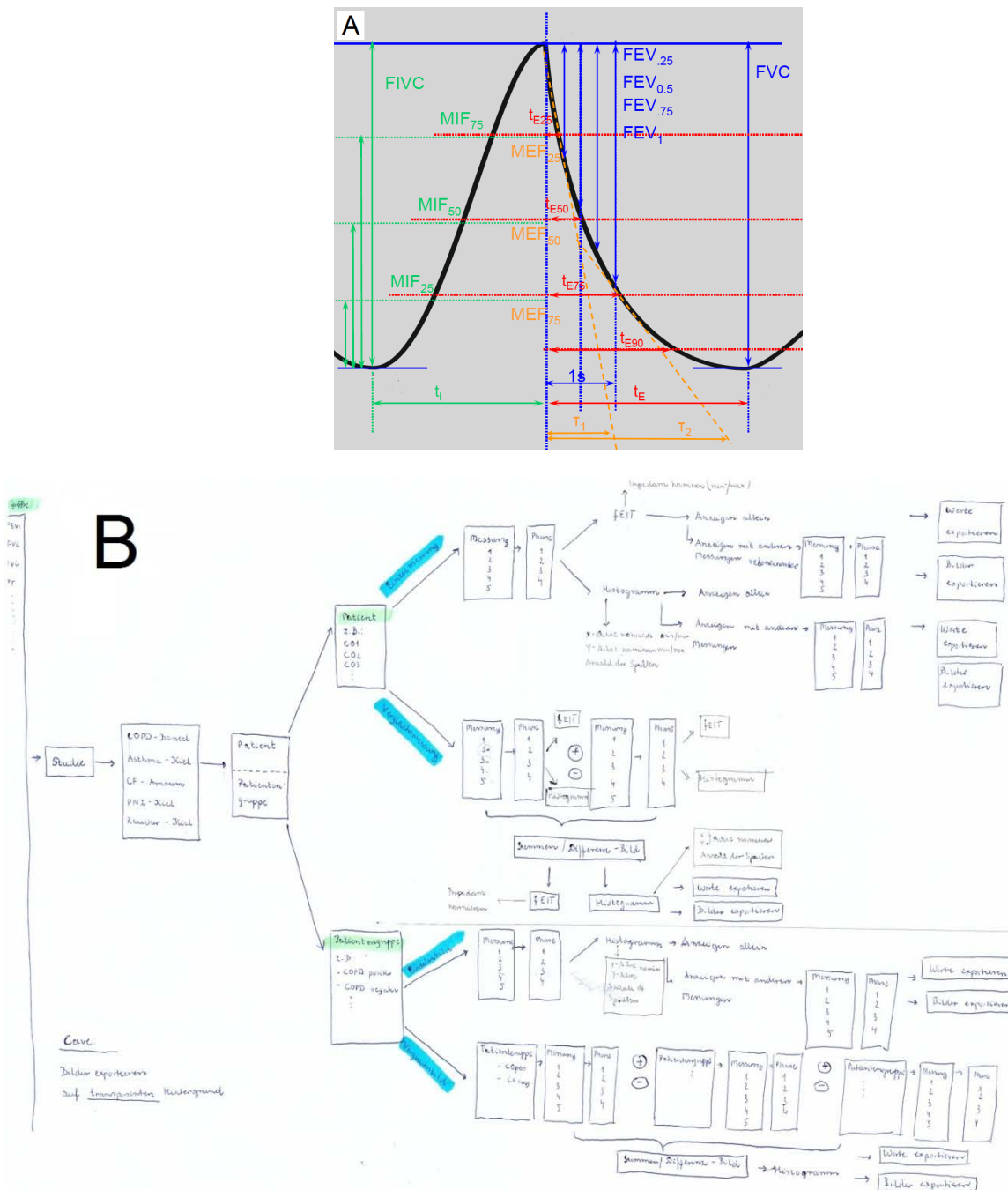
Figure 2. Requirements of the evaluation software. (A) illustration of parameters in pulmonary function test. Corresponding parameters in EIT data should be analyzed; (B) block diagram of the work flow.

commercial spreadsheet software: it is able to read different data formats and generate EIT images with different reconstruction methods; it analyzes and displays various disease-specific parameters and indices in functional images and histograms; it is user-friendly and extendable.

Up to now, most of the EIT analyses were made by comparison between simple geometric region of interests [11,12]. Lack of analysis tools limited the process of the data and restricted new finding in the results. With the disease-specific EIT evaluation software, the clinicians are able to assess EIT images pixel-by-pixel and implement new analysis ideas. Besides, the presented software simplifies the evaluation process distinctly and helps physicians to focus on study design and result interpretation. The software can be easily modified and extended to apply on patients with other lung diseases.

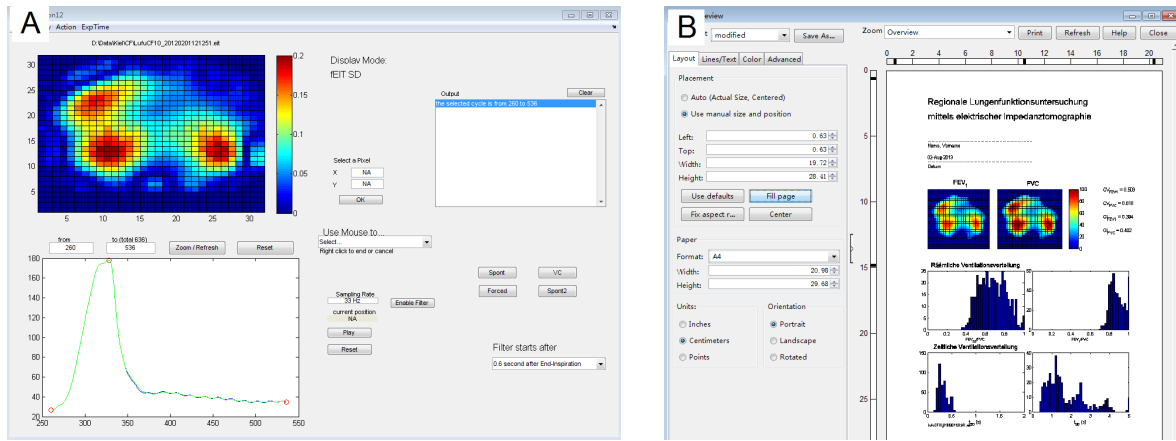The experiences collected in developing the present

Figure 3. The first part of evaluation software for processing raw measurement data. (A) interface. (B) as document for both investigator and subject, the measurement results consisting of important findings are ready for print.
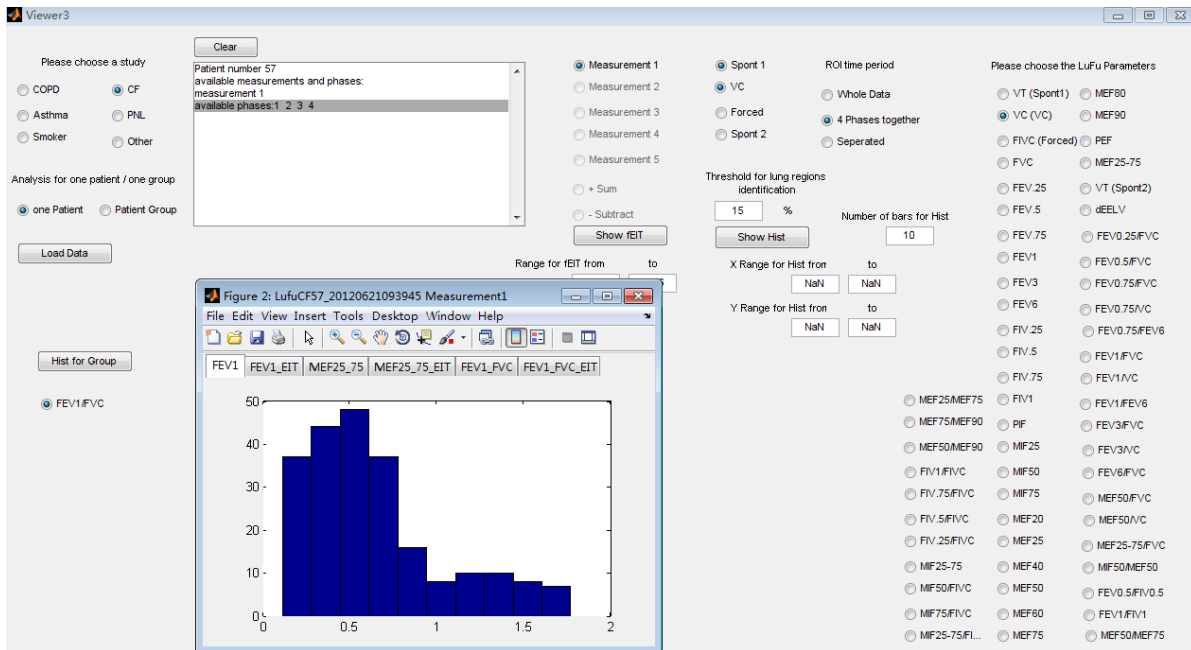

Figure 4. The second part of the evaluation software for processing various disease-specific parameters and indices. The selected parameters are graphically displayed as histograms and functional images.

software are transferable and applicable for other clinical trials. In the early stage of the development, it is very important for the engineers to understand the problem and background of the clinical trials. The physicians, on the other hand, have to define the tasks and specify the requirements in a way that the engineers can understand. Communication and discussion between the physicians and engineers are crucial in the stage of software requirement and design. Once the developer version of the software is ready, the engineers should test the software function together with the physicians and finalize the software accordingly.

A limitation of the paper is that we demonstrated the development process only on an observational study. In an interventional study, the need of evaluation software may be different. In order to develop customized software more efficiently, more experiences are needed.

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