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USING NEONATAL DATA: SIGNAL PROCESSING AND STATISTICAL MODELS

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INTRODUCTION

A great many potentially useful data are available in the newborn intensive care unit (NICU) in analog form, that is, time-varying signals from pressure transducers, impedance sensors, or bioelectric potentials. Although the instruments commonly used to process these signals are becoming more sophisticated, most commercially available monitors extract only simple parameters, such as heart rate or blood pressure, and sound an alarm if preset limits are violated.

We at Vanderbilt University are attempting to use computers, on a research basis, to extract more useful information about the patient by processing the signals from relatively noninvasive physiologic sensors. We are also involved in using statistical models to characterize a given patient population as to probable course and outcome on the basis of linear discriminant function analysis of a few variables observed at specific times.

Only patients selected for a given research protocol are included in the appropriate data collection and analysis schemes. Thus, we are not faced with the problems of managing data from all the 24 high-risk beds in our NICU or from all the 900-950 admissions per year to our

unit. This reduces our task from the realm of the impossible to that of the merely difficult.

HARDWARE

The hardware used in these studies includes a Digital Equipment Corporation (DEC) PDP-11/34 minicomputer with 12.5 megabytes (MB) of disk storage, 56 kilobytes (KB) of memory, a 16-channel analog-to-digital converter, a graphics display, and a printer/plotter. A serial link to the Vanderbilt University campus DEC PDP-10 system allows for the running of statistical analyses using the Biomathematics Data Programs (BMDP) package. The operating system for the PDP-11/34 is currently the single-user version of RT-11 V3B. This computer is interfaced to the baby via an instrumentation cart that can be moved to the bedside and connected to the computer's analog inputs via a multiconductor cable and one of a dozen jacks located strategically throughout the NICU. The cart contains modular amplifiers and preamplifiers, a pneumotachograph, a transthoracic impedance bridge, and a four-channel polygraph. A four-channel FM tape recorder is also included for off-line data processing. With today's technologic advances, a computer could probably be located on the cart for little more than the cost of the cabling required for our present system.

SIGNAL PROCESSING STUDIES

Transthoracic Impedance

It has long been recognized that the electrical impedance measured across the chest varies with the distribution of air and fluid within that volume. Transthoracic impedance (TTI) has been used in adults as a noninvasive means of estimating cardiac output.[1-3] Our own initial work with TTI was done in collaboration with investigators from the University of Gothenburg and Chalmers University of Technology in Sweden.[4-7] We participated in studies of breath-to-breath intervals in newborn infants, using TTI as the respiration signal. Histograms of the distribution of these intervals showed a periodic artifact reflecting impedance excursions correlating with the cardiac cycle.

A computer program was written to compute the average TTI during a 1-second time period surrounding the QRS complex and thus to extract the impedance cardiogram waveform from the thoracic impedance signal. The electrocardiogram (ECG) is used as a trigger, and 50-150 heartbeats are required to average out the respiratory component of the TTI. The method fails in those cases wherein respiration and heartbeat are locked in phase.

A four-electrode impedance bridge that minimizes skin resistance artifacts is used for all our studies. Small disk electrodes are employed rather than the circumferential bands often used by investigators dealing with adults. The choice of electrode positioning or configuration depends on the model being used to interpret the signals. The ECG signal is derived from the same set of electrodes. Continuous monitoring of the computer-derived impedance cardiogram is possible, with storage on disk for subsequent plotting or further analysis.

An example of a more or less typical impedance cardiogram is shown in Figure 18.1. The vertical line in the center corresponds in time to the point of maximum slope of the ECG R wave. Note the marked negative deflection in the TTI cardiogram during cardiac systole. According to the Olsson model,[4] the systolic deflection (ΔZc) is caused by an increase in the lung fluid/gas ratio as a result of the pulmonary vascular bed accepting a stroke volume of blood. This change in impedance is on the order of 0.05 and 0.5 ohms in small infants.

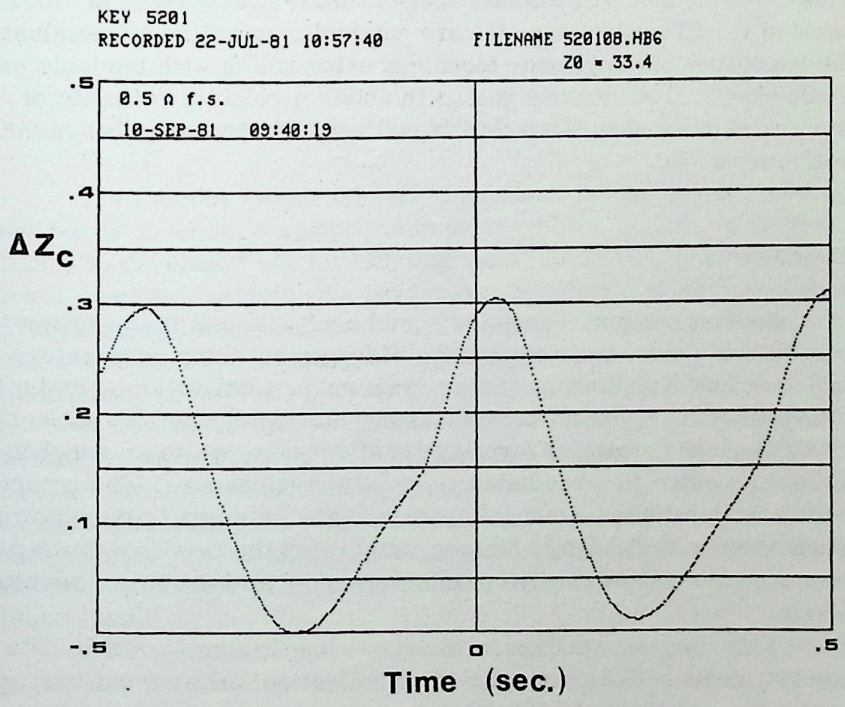

FIGURE 18.1. Typical example of an impedance cardiogram waveform averaged out by the computer from the transthoracic impedance respiration signal. The duration of the tracing is approximately 1 second and is centered about the R wave of the ECG, indicated by the central vertical line.

The ΔZc signal is superimposed on a respiratory impedance variation of 0.5-2.0 ohms. The baseline impedance, which is in the range of 25-50 ohms, is a function of the average thoracic fluid/gas ratio. It cannot be distinguished whether a gradual drop in baseline impedance, for example, is caused by a decrease in functional residual capacity (FRC), an increase in lung fluid such as one sees in pulmonary edema, or an increase in pulmonary blood volume.

We have observed larger than normal systolic cardiac impedance deflections in babies with symptomatic patent ductus arteriosus.[8-10] Since the infants studied are subjected only to the attachment of two double electrodes to the thorax, continuous assessment of ductal shunting is accomplished noninvasively and without disturbing routine patient care. We have used these observations to monitor the timing and degree of ductal closure following institution of therapeutic modalities such as administration of the drug indomethacin.[11]

In some patients the magnitude of ΔZc has not correlated well with other clinical evidence of a patent ductus arteriosus, however. This indicates that we still have much to learn about the physiologic basis of the TTI variations. We are continuing to refine and evaluate the impedance cardiographic technique using lambs with variable prosthetic shunts. The ultimate goal is to obtain a reliable estimate of changes in pulmonary blood flow in newborn infants using this noninvasive technique.

Lung Mechanics

Another computer-assisted signal analysis task in operation in our NICU is the on-line computation of lung mechanics parameters including lung compliance, airway resistance, tidal volume, and minute ventilation. A pneumotachometer connected between the patient's airway and the respirator furnishes gasflow data, while an esophageal balloon or water-filled catheter yields airway pressure. The computer software, developed by our collaborators at Chalmers University of Technology in Gothenburg, Sweden, integrates the flow to volume and computes the lung mechanics parameters over an interval of several breaths.[12, 13]

This program can also be run continuously; questionable data can be rejected either during or after collection. After a calibration period during which both transthoracic impedance and airway flow are sampled, the program can use the TTI signal instead of the integrated gas flow as a measure of volume variation.

The value of this system is diminished when used with respirator babies who make efforts to breathe spontaneously, but in those who do not or who have been paralyzed intentionally, it is still a useful technique.

STATISTICAL MODELING

Mathematical or statistical models have many potential applications in perinatal medicine. As clinical tools, models can help identify patients at risk for developing specific diseases, so that increased surveillance or actual preventive measures can be instituted. Models can also be used as educational tools to demonstrate the relative importance of various risk factors. In clinical research, models can be used to identify, in a consistent fashion, prospective patients for a clinical trial. Even those cases in which the model fails to predict the actual outcome are of special interest, since they can be scrutinized to find hidden risk factors that were not included in the original model.

We have developed a number of models in neonatal medicine that use the computer for statistical analyses. These statistical models rely on pattern recognition techniques to identify features that characterize a given clinical condition or disease course. Knowledge of the underlying pathophysiology involved is used during the process of selecting appropriate measurable variables to be included in the analysis.

The Symptomatic Patent Ductus Arteriosus Model

This model was developed in an effort to predict early those newborns in whom a symptomatic patent ductus arteriosus (sPDA) is likely to develop.[14] In formulating the sPDA model, a linear discriminant function analysis was performed on a "training set" population, evaluating the weighting factors of a number of possible predictors, and subsequently validating or rejecting these by computing the discriminant score prospectively for a new group of infants.

It was found that the probability of sPDA developing in an infant related to only a few factors, which included low birth weight, evidence of fetal growth retardation or small-for-gestational age, presence of hyaline membrane disease, need for positive-pressure ventilation, and a history of "acute perinatal stress." The latter includes one or more of a number of possible events, such as asphyxia or intrapartum blood loss.

On the basis of these easily observable variables, we were able to predict the development of sPDA with about 80 percent accuracy—both for the training set and prospectively for the test population.

An important application of this very simple model is to allow for institution of early preventive steps in cases predicted to be at high risk for developing the condition. Furthermore, if the patient population is stable, one can assess the efficacy of a preventive treatment by comparing the incidence of sPDA in the treated group with

that predicted by the model. Thus, if sufficient data are available to construct such a predictive model, a clinical trail can be validated without the ethical problems of a randomized treatment study.

The Hyaline Membrane Disease Outcome Model

This model for hyaline membrane disease (HMD) has proved remarkably successful in predicting the course of uncomplicated HMD.[15, 16] It is a dynamic or time-dependent model, in contrast to the static model used for sPDA.

There appears to be no generally accepted mathematical procedure for constructing time-dependent models. We have tried to incorporate a "severity" parameter and a "treatment" parameter into this model that attempts to predict the time-course of uncomplicated HMD from data obtained during the first 12 hours after birth. After trying several combinations of parameters, we used venous admixture computed from blood gases and F_IO_2, and the mean applied proximal airway pressure as the "severity" and "treatment" variables, respectively. The cumulative sum of the product of these two variables was then used as a function to describe the course of HMD. We found that the trajectory of this function over a 72-hour time course can be predicted from the slope of the function over the first 12 hours after birth.

Since this model predicts a quantitative course of HMD as influenced by therapy (i.e., application of distending airway pressure and enriched oxygen concentrations), its use should improve the design and execution of clinical trials of new modes of treatment, such as high-frequency ventilation or use of artificial surfactants. In addition, the model already serves as a reference or guide for front-line personnel, such as house staff, nurses, and respiratory therapists, who often have to make moment-to-moment decisions regarding things like changes in ventilator settings.

The collection and use of data for this HMD course and management model is now carried out using an Apple computer that is kept in the NICU. Blood gas and ventilator settings data are entered manually via the keyboard by respiratory therapists and occasionally by house staff. Raw and derived data can be listed and displayed in various formats with hard copies if desired.

FUTURE DEVELOPMENTS AND USE OF ARTIFICIAL INTELLIGENCE

One problem with trying to use dynamic models such as the HMD outcome model is that there is a random time lag between the collection

of important data points (e.g., blood gas values) and the reporting of results and subsequent adjustment of therapeutic modalities (e.g., after changes in the oxygen concentration or in the ventilator pressure settings. We recently acquired a number of transcutaneous PO_2 monitors, and we plan to set up another Apple system to monitor $TcPO_2$ continuously as well as proximal airway pressure for a single baby. In this fashion we will be able to derive parameters for this and perhaps other dynamic models on a continuous basis (e.g., a model to early predict the occurrence of pneumothorax). This will be our first halting step toward using continuously changing data in the NICU.

The mathematics involved in statistical models often obscure the logical relationships that help characterize the disease state. New techniques being developed in the field of artificial intelligence are able to incorporate expert medical knowledge and logical structures into computer-based systems, which in some ways can mimic the human reasoning process. If expert knowledge and the ability to learn from previous data could be incorporated into a computer-based data management system, expert neonatology consultation could be made more widely available.

We have no in-house expertise in this area, but we do have excellent opportunity for collaboration with several biomedical engineering groups that are, or soon will be, deeply involved in artificial intelligence techniques. At this stage we are not sure as to which hardware or software configurations would be required for such an undertaking. Artificial intelligence systems typically rely on very large systems running resource-hungry software written in languages such as LISP. Our campus DEC PDP-10 mainframe would probably be used for such applications, at least during the early stages.

Some medical applications of artificial intelligence in diagnosis have already had limited success, and such approaches could prove extremely important in the future. For us, the use of such knowledge-based systems as an aid to the interpretation of neonatal clinical data and to the administration of appropriate therapy represents an exciting field for future research.

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