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Symptom Index p-Value and Symptom Sensitivity Index p-Value (SIP and SSIP) to Determine Symptom Association between Apnea and Reflux in Premature Infants at Term

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Abstract

Background—The current method to determine temporal association (TA) between reflux and symptoms is the SAP (symptom association probability), but this method has limitations due to the constraints of binning and the violation of statistical principles of the Fisher exact test that lead to an invalid estimation of TA. The aim of this study is to develop improved methods of computing the TA between apneic and reflux events using simulation and permutation methods and to compare these to the SAP.

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Disclosures

Daniel Glen is affiliated to the National Institute of Mental Health, National Institute of Health but has contributed to this article in a private capacity and the views expressed in the article do not necessarily represent the views of NIH or the United States.

Peter Murakami and Jeanne Nunez, MD do not have any conflicts of interest.

Author Contributions

- Daniel Glen, a Computer Engineer from the Scientific and Statistical Computing Core of NIMH/NIH conceptualized the method and participated in the design of the methods used in this study. Daniel Glen also was the main author writing the manuscript.

Daniel Glen has approved the final draft submitted.

- Peter Murakami, a statistician from the Johns Hopkins University Biostatistics Center, participated in the design of the methods and wrote the statistical program. Peter Murakami provided statistical support and reference for this study.

Peter Murakami has approved the final draft submitted.

- Jeanne Nunez, MD is a clinician neonatologist, assistant professor at the Johns Hopkins University with a special interest on the role of gastro-esophageal reflux in neonates. Jeanne Nunez participated in the design of the study and methods, and is in charge of the clinical aspects of the study, grant support, and IRB approval. Jeanne Nunez has a significant role in the writing of the manuscript.

Jeanne Nunez has approved the final draft submitted.

Design—TA was analyzed between polysomnographic obstructive apneas and Multi-channel Intraluminal Impedance (MII) reflux events. Three new numerical methods were compared to the SAP in four former premature infants with persistent apneas at term. The experimentally found association was compared to the association observed in simulated or permuted data consistent with the lack of association beyond what is expected by chance alone. Temporal association was computed based on symptom and symptom sensitivity indices, SI and SSI, with varying window of association (WA) times from 15 to 300s.

Results—The three new methods estimated p -values at varying WA that generally followed the same pattern of the SAP which had a more erratic pattern. The WA that gave the lowest p -value was approximately 120s.

Conclusion—Each of the novel methods produced p -value results consistent with each other and the SAP yet not subject to its limitations. The variation of WA gave a temporal profile of TA providing clues to its etiology. These new metrics are called SIP and SSIP, Symptom Index and Symptom Sensitivity Index p -values.

Keywords

Obstructive Apnea; Gastro-esophageal Reflux; Multichannel Intraluminal Impedance- pH Probe; Premature Infants; Temporal Association; Permutation; Simulation

BACKGROUND

Gastro-esophageal reflux is often considered as a cause for a variety of non-specific symptoms, most commonly chest pain and heartburn. Association between reflux with other symptoms such as cough and apnea in infants has been more controversial despite the widespread use of anti-reflux medications and reflux surgery,[1]. GERD and its symptoms constitute an important problem that affect an estimated 5–40% of the adult population,[2–3]. Establishing a temporal association between these symptoms and reflux may suggest a cause-effect relationship and guide medical and surgical management. The typical statistical methods to analyze temporal association between gastro-esophageal reflux and symptoms include the SI (Symptom Index), SSI (Symptom Sensitivity Index), and SAP (Symptom Association Probability). These methods are included in commercial products such as the Sandhill Scientific MII software for analysis of reflux using multichannel intraluminal impedance (MII),[4–7]. Using these statistical methods, we have shown in a previous study, [8], that temporal association between polysomnographic obstructive apneas and reflux events in former premature infants at term, could be demonstrated at a single-subject level analysis and was consistent with both clinical history and outcome.

The SI measures the percentage of symptoms associated with reflux events out of the total number of symptoms,[4]. SI, a measure of sensitivity, is usually considered significant if >50%, [4–5]. SSI measures the percentage of reflux events associated with symptoms out of the total number of reflux episodes,[6], and may be interpreted as the positive predictive value of reflux for a symptom. SSI is arbitrarily considered significant if more than 10%, [6]. Rather than the commonly used fractional metrics SI and SSI, a statistical assessment of the significance of the association is required.

The Fisher exact test, used in the Sandhill SAP, was first devised by R.A.Fisher, and inspired by the well-known problem of “the lady drinking tea”, [9]. In order to fit the framework of a contingency table, the length of the study is discretized into time bins that are then classified as positive or negative for reflux or symptom events, [7]. The Fisher exact test computes the probability of observing this number of pairs of positive reflux-symptom events under the null hypothesis that pairs of symptom-reflux events may occur by chance.

Unfortunately, binning limits what can be considered associated or not. In the Sandhill “algorithm 1” of the SAP, a symptom is surprisingly not counted as associated with a reflux event if both occur in the same time bin even if they both occur within the same association window. In “algorithm 2” (Weusten method),[7], this issue is resolved but at the cost of violating the rule of independence of the Fisher exact test. If two symptoms occur within the same window of association with the same reflux event but in two successive bins, they are both counted as associated; however, the Fisher exact test is valid only for independent paired reflux-symptom events; neither multiple refluxes per symptoms nor multiple symptoms per reflux are allowed.

Another metric, the Ghillebert Probability Estimate or GPE (10), has also been used occasionally to analyze temporal association between reflux and symptoms and found to provide results comparable to the SAP (11). As opposed to the SAP which uses a two-by-two contingency table, the GPE separates the study into at risk and low risk periods. The high risk period is defined as the sum of the total time pH is less than 4 and the total of the 2 minute intervals for each reflux event. Unfortunately, this method has been tested only with pH monitoring and not with MII reflux. Furthermore, it has been shown that the GPE may overestimate the “at risk period” if reflux events are spaced less than 2 minutes apart (11–12). In this study, we examine the limitations of the SAP and compare it to three simulation and permutation methods for evaluating the statistical significance of the temporal association between apneic and reflux events. The null hypothesis of all the simulation and permutation methods is the lack of any association between apnea and reflux beyond what is expected by chance alone. While traditionally a two-minute window has been assumed between the onset of reflux event and a following symptom, the new methods introduced here are expanded to vary the size of the window of association. We use these new methods to re-examine the temporal association between apnea and reflux in our previously reported patients.

METHODS

The subject data used in this study were derived from the previously reported study of former premature infants with persistent clinical cardio-respiratory events at term,[8]. Informed consent was obtained from the parents. The Johns Hopkins IRB approved the protocol.

The infants recruited were born at 23 to 29 weeks gestation with persistent clinical cardio-respiratory events (CR events) at 39 to 48 weeks post-menstrual age (PMA). Clinical CR events, prompting inclusion in the study, were defined for any of the following conditions: a heart rate less than 80/min, oxygen saturations less than 90% or cardio-respiratory monitor-defined apnea > 20 seconds.

A standard polysomnography was performed with a 6.4 Fr trans-nasal MII-pH probe (Comfortec MII-pH probe, ZIN-BS-51, Sandhill Scientific, Highland Ranch, Colorado).

The polysomnography and MII-pH probe analysis systems were synchronized by digitally marking each tracing at the beginning of the study. The impedance data was analyzed using the Sandhill analysis software and validated manually. All signals were acquired digitally (Alice 4; Respiration/ Philip Andover, Massachusetts or Somnologica /Embla, Broomfield, Colorado). Polysomnography CR events were scored according to the standards of the American Academy of Sleep Medicine,[13].

Temporal association was analyzed between polysomnographic discrete obstructive apneas and all reflux events, detected by MII. For this study, the SAP (Weusten) method was

modified to include only the right-tailed test (only the positive association between reflux and apnea) expressed as a p -value.

We chose this subset of patients because they represent some interesting extremes. Three subjects showed some level of temporal association between reflux and apnea (subject 1, 2, and 3). Two of the infants were recommended for fundoplication reflux surgery based on clinical observation, (subjects 1 and 3); one infant continued to have symptomatic reflux at follow-up two years later (subject 2). Subject 4 was chosen to test the method on a “negative” subject. Subject 4 had numerous apneas and reflux events but no evidence of association with any method chosen.

In this study, three novel methods have been developed that will be denoted as “Simulation”, “Permutation Shuffling” and “Permutation Sliding”. All three methods represent some method of comparing the experimentally found occurrence of association to the null distribution of the association statistics obtained by independently simulating the two random series of events (reflux and symptom). For all three methods, the SI and SSI were computed for each simulated iteration, and compared to the observed value. A p -value for the test of no association is estimated as the fraction of iterations in which the association statistics (SI and SSI) obtained from the observed data were equaled or exceeded. For example, if 100 iterations of the 10,000 iterations gave at least the same SI value as the observed data, then a p -value = $100/10,000 = 0.01$ may be estimated as the probability of finding at least the same SI value by chance.

For each simulation method, the process is repeated while varying the temporal association window size from 15 to 300 seconds at 15 second intervals (for a total of 20 different windows of association sizes).

The software developed here written in “R” is available to the public at <http://www.biostat.jhsph.edu/~pmurakam/research.html>.

The diagram in Figure 1 shows a graphical comparison of the methods.

Simulation Method

If there are m episodes of reflux, n episodes of apneas, and h is the length of the sleep study, a random sample of m reflux events and a separate sample of n apnea events are generated 10,000 times from a uniform distribution on time interval $(0, h)$ for that subject. The SI and SSI for 20 association windows are then calculated, generating a null distribution of association.

In order to address the possibility of temporal clustering of unobservable events, reflux and apneic events are required to have a minimum gap between events. A gap of 30 seconds between reflux events was chosen according to the design of Sandhill Scientific software which merges multiple reflux episodes if they occur within 30 seconds of each other. A gap between apneas was estimated at 6 seconds based on an average respiratory rate of 40 breaths per minute with the minimal apnea time lasting at least 2 breaths + one breath before and after the apneic event.

Permutation Shuffling Method

In this method, we calculate the time intervals between events (including start and end times), and randomly re-order them, separately for apneas and refluxes. This is done 10,000 times, each time calculating the SI and SSI observed in the resulting sample. For example, given a group of reflux events and a group of apneic events, a calculation to get the time difference between events of each type is computed ($D1...Dn$). The time differences are

permuted (D1, D2, D3,...) $\rightarrow$ (D2, D1, D3,...). Then a new event time is computed by the cumulative sums of those time differences, e.g. (D2,D1,D3,...) $\rightarrow$ (D2, D2+D1, D2+D1+D3,...). In this way, all time-wise structure has been nullified, while (unlike in the Simulation method) any subject-wise structure of event intervals has been maintained. Rather than assuming event times to be uniformly distributed, we estimate their distribution from the observed data.

Permutation Sliding Method

This method independently shifts the subject's apnea and reflux times by random amounts, with wrap-around for the times that extend past the end time (Figure 1). This process is repeated 10,000 times, and each time SI and SSI are calculated as with the other two methods.

RESULTS

In Figures 2 and 3, the results of p -values for all methods are compared for the four subjects.

For all subjects, all methods give overall similar results of p -values. However, for all subjects, the SAP has a more erratic pattern of p -values depending on the temporal association window size while the Simulation, Shuffling and Sliding Permutation methods all have smoother temporal profiles.

In Subject 1 and 3, the distributions of the p -values for the Simulation method diverged from the other methods for both SI and SSI with longer association windows.

For the fourth subject, the three methods confirmed the results of the SAP reporting weak SI and SSI estimates with non-significant p -values (figures 2, 3 and 4).

Figure 4 shows the effect of the window association size on the SI and SSI values using the Permutation Sliding method. SI reaches the 50% threshold at 105 sec, 300 sec and 240 sec for subjects 1, 2 and 3 respectively. SSI reaches the 10% threshold at 45 sec, 30 sec, 15 sec and 90 sec for subject 1, 2, 3 and 4 respectively.

Figure 4 also shows that SI and SSI estimates even above the commonly used threshold values of 50% and 10% respectively may be associated with p -values at more than 0.05; and, conversely, SI and SSI estimates below threshold values may be associated with p -values at less than 0.05.

As in our previous study using only the SAP, a minimum p -value is seen at approximately 120 second temporal offset.

Obtaining p -values for the SSI for subject 1 for all 20 association window sizes, using 10,000 iterations, took between 15 minutes and 20 minutes for each of the methods used. These calculations were performed with R, version 2.12.1 under Mac OS 10.6.6, 2.4GHz Intel Core 2 Duo processor, 2GB of memory.

DISCUSSION

The application of the Fisher exact test to the analysis of the temporal association has serious limitations due to binning. This problem becomes apparent with the discontinuities we observed when varying the temporal window size demonstrating that the SAP underestimates or overestimates the probability of association at any specific temporal window size.

Effectively, the question under consideration when looking for an alternative method to replace the SAP, in a general sense, is the causal relation between two series of discrete events.

The most practical perspective here is to extend the Fisher exact test by simulation to another type of permutation test in the form of a Monte Carlo simulation. A similar null hypothesis as the Fisher exact test is used; namely, one series of events can produce matches with another series of events simply by chance but without the limitations imposed by binning. As with the Fisher exact test, permutations by Monte Carlo simulations are used in other fields in similar ways. For example, in fMRI analysis of the brain, clusters of activation may be found by spatially simulating the incidence of activation at multiple locations with the presumption that larger clusters are less likely to occur by chance,[14–16].

The variation of a temporal window size used in this study, is similar to the scan statistic used by others,[17]. The scan statistic has had varied use in spatial or geographic associations such as in epidemic detection or astronomical assessments of clusters of stars. While these methods look at the probabilities of finding associations in spatial clusters of varying sizes for a spatial or geographical association, our methods apply a similar technique to determine temporal association.

In order to fully evaluate the three methods introduced here, it is important to understand the subtle differences in what each of these methods is testing. The null hypothesis of all the methods described is the lack of any association between apnea and reflux beyond what is expected by chance alone. The null hypothesis for the Permutation Shuffling Method is similar but assumes a set of events that shares the same temporal frequency as the original observed data. The null hypothesis for the Permutation Sliding method goes further by restricting the events to the same order as the original events and can be summarized as: given two observed sets of events, a random association of events is seen by simply moving the temporal origin. This method is similar to previous methods described as cyclic permutation methods,[18]. Both the Shuffling and Sliding Permutation methods assume that the time-wise structure in the data for a given subject is representative of the underlying reflux- and apnea-generating mechanism for that subject; whereas, the Simulation method simply assumes that there is no underlying structure.

The Simulation method is conceptually simplest. However, it carries assumptions like that of a discrete uniform distribution and constraints imposed by unobservable events. Those constraints require specific knowledge of how the original events are determined in polysomnography and impedance analysis software packages, e.g. 30 seconds between reflux events. Furthermore, we observed a divergence of the p -values at longer duration of association windows for the Simulation method when compared to the two other methods of permutation. The divergence of the Simulation method may be explained by the fact that the assumption of uniformly distributed event times is not true because of the tendency of events to cluster together in time. The Shuffling and Sliding Permutation methods, on the other hand, do not assume a uniform distribution but rather estimate that distribution from the observed data. Both Shuffling and Sliding Permutation methods remove the constraint of the need for requiring a gap between events and the need for a uniform distribution. The Permutation Shuffling method removes these constraints by using the temporal frequency as it was observed. Still this method becomes less reliable when there are extremely few events. However, given only four refluxes and four apnea events, which is easily attainable for most clinically relevant studies, this method can generate >10,000 different random data sets. The final method, the Sliding method, gives a result that removes many of the disadvantages of the Permutation Shuffling method yet requires no further constraints as imposed in the Simulation method. However this method has a more specific null hypothesis

than the Simulation method in that the evaluation is based not on two series of random events but on the specific series of events acquired in the experiment. Despite their methodological differences, the temporal profile between the two permutation methods showed a similar pattern of p -values, suggesting that these methods are similar and correctly assess the temporal association. All methods, including the SAP, the simulation and permutation methods, give an overall similar pattern of p -values. However, the use of a temporal profile illustrates the limitations of the SAP by showing an erratic pattern relating to binning, and the limitation of the simulation method which assumes a uniform distribution not met in our patients.

These methods were tested on only four exemplar patients. While a larger population would have allowed us to extend the analysis to a group level and present inference on some population, the extension of the analysis to a group level would answer a completely different problem than a method directed at the single subject level and, consequently, a potentially useful clinical diagnostic measure. Furthermore, a group level inference was clearly not possible given the lack of any uniform group in our data. The population studied is not homogeneous for our case of infants with persistent apnea at term. For this population, there can be multiple causes for apnea besides reflux. The temporal profile showing a similar pattern of p -values for each subject among all the methods of analysis used; including the SAP; suggests that a sample of 4 patients was enough to test our new methods.

If both types of events were truly randomly distributed, one would expect the temporal profiles to show fairly flat profiles. Consequently, the minimum p -value and the timing of that minimum value in the temporal profile are useful measures. Further studies are needed to better explore and determine the optimal window of association for specified groups of subjects. In the cases examined here, the temporal window offset minimum value occurred at around 120 seconds which could provide a clue to the etiology of the association between apnea and reflux.

Any discussion of a physiological mechanism of reflux-induced apnea is very speculative, especially given our limited number of subjects and secondary to the main focus of this study. We can speculate that the apnea may be simultaneous or delayed as liquid accumulates in the oropharynx and eventually overwhelms the capacity of airway protection,[19–21].

In another recent study, the effect of varying window sizes was examined for regurgitation, cough and crying,[22]. Their method relied on the SAP but evaluated the window size by its agreement in longitudinal studies. Although, they did not examine the relationship to apnea, they found for cough, the same 120 second relationship.

Subjects 1 and 2 had p -values below 0.05 for SI and SSI for the majority of association windows suggesting that in these subjects the apneas were often associated with a preceding reflux (SI) but also that a reflux event was predictive of apnea (SSI). For subject 3, the reflux events were not as clearly predictive of apnea. These data suggest a stronger association between apnea and reflux in subject 1 and 2 than in subject 3. The absence of association seen in subject 4 was also consistent among all the methods. Further studies are needed to correlate the meaning of the different levels of temporal association with clinical outcome.

These simulation, permutation methods have been used here for the specific problem of temporal association between apnea and reflux in premature infants at term. Because the methods themselves are independent of these requirements, we believe the same methods can be easily extended to other types of symptom (pain, cough,...) and to other populations

(infants and adults), but this will need to be tested in further studies. The day to day variability will also need to be tested. Even more generally, these methods developed here may be used for the temporal analysis between any two series of events

The results presented here show both SI and SSI increase with the association window size, so a fixed cutoff such as 50% and 10% as a rule-of-thumb should be accompanied with the window size(s) on which they were evaluated and their associated p -value. Supplementing these measures of SI and SSI, we propose these new methods presented here as the measures of these p -values with the suggested nomenclature of SIP and SSIP (Symptom Index p -value and Symptom Sensitivity Index p -value, respectively).

CONCLUSION

In this study, three readily understandable methods have been developed and evaluated in comparison with the SAP. These methods provide important improvements over the binning limitations of the SAP and provide an accompanying p -value for the widely used SI and SSI. The use of a temporal profile highlights deficiencies in the SAP which underestimates or overestimates the probability of association. With further studies, these new methods may be used as more robust diagnostic tools to analyze temporal association between reflux and diverse types of symptoms

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Abbreviations

CR events	Cardiorespiratory events
GER	gastro-esophageal reflux
GPE	Guillebert Probability Estimate
MII	Multi-channel Intraluminal Impedance
SAP	Symptom association probability
SI	symptom index
SSI	Symptom sensitivity index
TA	temporal association
WA	window of association

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Figure 1.**Temporal Association Simulation and Permutation Methods**

For each iteration, the Simulation method shows the random distribution of the same numbers of events and the recounting of the association between reflux and apnea events; The Permutation Shuffling method shows the shuffling of the time differences, the original horizontal bars between events; the Permutation Sliding method also uses the time difference but maintains the same order as the original order, but wraps around past the end of the study. The relative position of the temporal origin, time zero shown with a star, is shifted with the relative times of the original observed events.

SI Method MII

Figure 2.

Temporal association using SI for MII reflux for Subjects 1, 2, 3, and 4.

Comparison of p -values of temporal association with varying windows of association as computed by three new methods and the SAP.

SSI Method MII

Figure 3. Temporal association using SSI for MII reflux for Subject 1, 2, 3, and 4. Comparison of p -values of temporal association with varying windows of association as computed by three new methods and the SAP

Effect of Window of Association Duration on SI and SSI

Figure 4. Effect of Window of Association Size on SI and SSI for MII reflux. Markers with dark outlines have p -values < 0.05 . Results are displayed using the Permutation Sliding Method.