Effects of Dialysate Glucose Concentration on Heart Rate Variability in Chronic Hemodialysis Patients: Results of a Prospective Randomized Trial

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Abstract

Background: Chronic hemodialysis (HD) patients suffer from an appallingly high cardiovascular mortality. During HD, patients are exposed to dialysate glucose, which may alter blood glucose levels and thus exert effects on the autonomic nervous system. Heart rate variability (HRV) is an established indicator of autonomic nervous system activity and a predictor of cardiovascular outcomes. This study investigated the effects of two commonly used dialysate glucose concentrations [100 mg/dl (HD100), and 200 mg/dl (HD200)] on HRV in chronic HD patients. Methods: In this prospective, randomized, controlled, single-masked, cross-over trial, subjects were randomized to receive HD100 or HD200 for a period of 3 weeks followed by a cross-over to the respective other dialysate (www.clinicaltrials.gov #NCT00618033). Blood glucose and insulin levels were measured before and after HD. Intradialytic Holter electrocardiograms were recorded and HRV time domain, frequency domain and complexity parameters analyzed. Results: Twenty-three HD patients (age 56 ± 12 years, 11 male, 14 black, 11 with diabetes) were studied. Diabetic subjects showed significantly higher serum glucose levels with HD200 as compared to HD100 (HD100: 146 ± 48 mg/dl; HD200: 192 ± 57 mg/dl; p < 0.01); this hyperglycemia was accompanied by an increase of the high-frequency band of HRV (p = 0.019), a reflection of increased parasympathetic activity. HRV did not change in nondiabetic subjects. Conclusion: In diabetic subjects, the use of HD200 increased vagal tone. Given the importance of sympathetic activation to counteract intradialytic hypotension, our findings support the use of HD100 in diabetic HD patients.

Key Words
Hemodialysis · Diabetes mellitus · Dialysate glucose concentration · Heart rate variability

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Introduction

Hemodialysate glucose concentrations differ widely between units and countries, 100 mg/dl (5.55 mmol/l; HD100) and 200 mg/dl (11.11 mmol/l; HD200) being used most frequently; nevertheless, glucose-free dialysate is used in some countries. Dialysate glucose exceeding serum concentrations results in a diffusive glucose flux into the patient and a rise of blood glucose levels with consecutive insulin secretion. In turn, insulin affects the cardiovascular system by reducing the vagal and increasing the sympathetic tone [1, 2]. Data on the direct effects of blood glucose on the autonomic nervous system (ANS) are scarce. Kanaley et al. [3] recently reported increased parasympathetic activation following an oral glucose load.

ANS activity can be studied noninvasively by heart rate variability (HRV) analysis. HRV refers to the variability of the length of R-R intervals in electrocardiograms. HRV is determined by the interactions of hemodynamic, electrophysiological and humoral factors and modulating ANS inputs [4, 5].

HRV can be quantified by descriptive statistics of R-R interval duration and its variation over time, i.e. range, mean and standard deviation. This analysis is called time domain analysis, and decreased HRV as determined by time domain analysis has been linked to poor prognosis [6]. In frequency domain analysis, R-R time series data are considered to be composed of individual sinus oscillations with different frequencies. The time series data are mathematically broken down into a spectrum of sinus waves, and it becomes possible to analyze the contribution of the amplitude of each frequency to the original time series data (power spectral analysis). In power spectral analysis, by convention, frequencies are grouped together and categorized as very low frequency (VLF, 0.003–0.04 Hz), low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) [7]. The LF and HF bands indicate sympathetic (LF) and parasympathetic (HF) activities. Accordingly, sympathetic activation increases the LF power whereas parasympathetic activation (and to some extent respiration) increases the HF power. The VLF band reflects slow regulatory mechanisms such as humoral, endocrine factors (e.g., endothelial factors or renin-angiotensin system) and the circadian rhythm [5].

Cardiovascular autonomic neuropathy is highly prevalent in patients with diabetes mellitus (DM) and results in a general reduction in HRV. Autonomic tests have demonstrated significantly reduced sympathetic responses, as reflected by the LF band, to orthostatic challenges in patients with DM. This finding was also present in diabetic patients who had not yet been diagnosed clinically with autonomic neuropathy [8, 9]. It is noteworthy that patients suffering from renal failure had markedly reduced total spectral power as well as reduced power in the LF and HF band [10, 11].

Congestive heart failure and myocardial infarction are also associated with alterations of HRV. An inverse relationship between HRV and cardiovascular mortality in patients with cardiovascular disease was reported previously [12–14]. Chan et al. [15] reported an association between left ventricular mass, HRV and physical performance in a large cohort of HD patients. The prognostic value of HRV analysis to predict cardiovascular events has recently been extended to HD patients [16, 17].

Since heart rate is determined by a complex interaction of networks of control mechanisms which quickly adapt the cardiac output to changing needs, nonlinear control characteristics arise. Goldberger et al. [18] recognized the presence of the long-term correlations in R-R intervals and its relationship to the concept of ‘dynamical disease’ [19]. To quantitatively describe these nonlinear characteristics, new measures of HRV were developed. Approximate entropy, ApEn(m,r), quantifies the unpredictability of fluctuations in a time series, measuring the logarithmic probability that patterns of m observations will repeat themselves within predetermined tolerance thresholds r on the next incremental comparisons (m + 1). A time series containing many repetitive patterns has smaller entropy values than a time series which does not present such patterns. Sample entropy, SampEn(m,r), is a measure closely related to approximate entropy [20]. For details, see appendix 1.

Another measure of complexity was developed by Lempel and Ziv [21] and is used for the assessment of algorithmic complexity, which is defined as the minimum quantity of information needed to define a binary string. In case of random strings, the algorithmic complexity is the length of the string itself. Lempel-Ziv complexity (LZC) reflects the rate of new pattern occurrences with time.

Compared to linear approaches, nonlinear statistics are more powerful in predicting mortality. In addition, nonlinear methods showed superiority in stratification of populations according to different physiological and pathological states [22].

Given the abysmal cardiovascular mortality in chronic HD patients, all aspects of dialysis therapy related to

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their cardiovascular system call for rigorous scientific inquiry. The present study aimed to test the hypothesis that HRV of chronic HD patients is affected by dialysate glucose concentration.

Methods

Study Design and Procedures

This study was a two-center, prospective, randomized, controlled, single-masked, cross-over clinical trial of HD100 versus HD200 (www.clinicaltrials.gov #NCT00618033). After enrollment, subjects were randomized to receive HD100 and HD200, respectively, for a period of 3 weeks (9 HD treatments). Thereafter, subjects were switched for 3 weeks to the respective other dialysate glucose concentration. Subjects were blinded to the dialysate glucose concentration. In adherence to the ceteris paribus principle, neither dialysis prescription (including temperature, electrolyte composition and flow rates of the dialysate) nor medications were changed in the course of the study.

Holter recordings were performed after the long interdialytic interval, once each with HD100 and HD200, commencing about 10 min before HD. ECGs were continuously recorded at a sampling rate of 250 Hz with a three-lead Holter device (clickholter; Cardioline, HealthFrontier Inc., N.J., USA) for 24 h. Holter recordings of subjects receiving HD100 and HD200 recordings were analyzed.

Patient Population

Subjects were recruited from two urban dialysis facilities of the Renal Research Institute in New York, N.Y., USA. Inclusion criteria were age above 18 years and HD vintage of at least 30 days. Exclusion criteria were dialysis frequency other than thrice weekly, hospitalization or antibiotic treatments in the preceding 8 weeks, or persistent intradialytic arrhythmia. The study was approved by the Institutional Review Board of Beth Israel Medical Center, New York, N.Y., USA, and written informed consent was obtained from each subject before enrollment into the study. The enrollment target was 30 subjects, and recruitment was aimed to sample a 1:1 ratio between subjects with and without DM at each center. DM was defined as either requiring oral antidiabetic medication or insulin or having random blood glucose levels over 200 mg/dl at routine clinical measurements in the preceding 12 months. Both type I and type II DM patients were eligible for the study.

Biochemical Analysis

Blood draws for pre-HD potassium, glucose and insulin (before and after HD) were collected at the beginning and end of four HD100 and during two HD200 treatments, respectively. Serum concentrations were averaged for each time point (beginning and end of dialysis) and for each regimen. The Olympus AU5400 (Olympus Diagnostic Systems, Center Valley, Pa., USA) was used for the measurement of glucose with a colorimetric assay and an ion-selective electrode for potassium. Insulin was measured with a chemiluminescent immunoassay using the Advia Centaur (Siemens Healthcare Diagnostic, Deerlied, Ill., USA).

Blood Pressure Measurements

Systolic and diastolic blood pressures were measured using an oscillometric method every 30 min during those treatments where Holter electrocardiograms were recorded.

HRV Analysis

HRV was analyzed by an observer masked to dialysate glucose concentration. Beat-by-beat series of R-R intervals and their annotations were obtained from the Holter recording with the software provided by the manufacturer. The entire recording was subdivided into 5-min epochs and only subsequences with at least 85% of qualified sinus beats (NN intervals, NNI) were included in the analyses. The subsequences were corrected by means of an adaptive filtering procedure to remove artifacts or ventricular premature complexes [23]. After filtering, the series were resampled at 2 Hz [7].

In recognition of changing pathophysiological circumstances in the course of an HD session [24], HRV was analyzed during three distinct time periods, two during HD (the first 30 min, the protodialytic period, HD proto and the last 30 min, telo-dialytic period, HD_telo), and one in the 60 min after the end of HD, HD_post.

Time Domain Analysis

The following indices were computed every 5-min epoch: (1) the mean NNI; (2) the standard deviation of the NNIs; (3) the square root of the sum of the squares of differences between adjacent NNIs, and (4) the percentage of pairs of adjacent NNIs differing by more than 50 ms in the sequence.

Frequency Domain Analysis

Autoregressive spectral analysis was performed and power in (1) the VLF (0.003 < f ≤ 0.04 Hz), (2) the LF (0.04 < f ≤ 0.15 Hz), and (3) the HF (0.15 < f ≤ 0.4 Hz) bands was computed, as well as (4) the total power and (5) the LF/HF ratio, in accordance with recommendations of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [7].

Entropy and Complexity Analysis

For each 5-min epoch, the regularity of the signals was estimated by computing ApEn and SampEn. The parameters adopted for the computation of ApEn and SampEn were: m = 2 and r = 15.

For the estimation of LZC, the R-R time series was encoded into a string. Given a signal \( x[n] \), the encoding rule adopted for the binary alphabet was the following: assign 0 if \( x[n+1] \leq x[n] + p \cdot x_n \), and 1 if \( x[n+1] > x[n] + p \cdot x_n \). The rule for the ternary alphabet was: assign 2 if \( x[n] - p \cdot x_n < x[n+1] \leq x[n] + p \cdot x_n \), 0 if \( x[n+1] < x[n] - p \cdot x_n \) and 1 if \( x[n+1] > x[n] + p \cdot x_n \). The factor \( p \) is a fixed parameter; in these analyses, \( p = 0.001 \).

Statistical Analysis

Treatment parameters were compared between HD100 and HD200 using the paired Student’s t test. Fisher’s exact test was used for categorical data. Patients were stratified by diabetes status. HRV indices were compared between HD100 and HD200 in a paired fashion. Glucose and insulin concentrations were compared using a paired Student’s t test. A p value <0.05 (2-tailed) was considered statistically significant.

Signal processing and statistical analyses were performed with MATLAB (The MathWorks Inc., Natick, Mass., USA).
Results

A total of 30 patients were enrolled between April and June 2008. Seven subjects were excluded from HRV analysis because of hospitalization, intradialytic arrhythmia, technical reasons and missing matched pairs (fig. 1). Table 1 reports the demographic data of the included subjects. All subjects underwent HD using Optiflux F180NR Polysulphone dialyzer (Fresenius Medical Care North America). Table 2 shows the HD treatment parameters on the days of the Holter recordings.

Comparisons between HD100 and HD200
Glucose and Insulin Levels
Significantly higher glucose concentrations were observed in diabetic subjects at the end of HD200 compared to HD100; insulin levels showed no difference (table 3). In contrast, nondiabetic subjects at the end of HD200 showed only marginally higher glucose concentrations. In nondiabetic subjects, post-HD insulin concentrations were significantly higher compared to HD100. Interestingly, during HD200, only 3 diabetic subjects (27%) had higher insulin levels at the end of dialysis as compared to 6 subjects (50%) in the nondiabetic group.

Blood Pressure
Figure 2a, b shows blood pressures during the 46 dialysis treatments with valid Holter recordings. Blood pressure declined significantly during all HD treatments, without significant differences between HD100 and HD200.

HRV Analysis
As outlined in detail below and in table 4, dialysate glucose significantly affected HRV.

Time Domain Parameters. In diabetic subjects, mean NNI was higher at HD200_telo (p = 0.024) and HD200_post (p value = 0.054) as compared to HD100 (fig. 3). In addition, in these subjects, the standard deviation of the NNIs was significantly higher at HD200_post compared to HD100_post. No significant differences were found in nondiabetic subjects.

Frequency Domain Parameters. In diabetic subjects, VLF, HF and total power were higher during HD200_post compared to HD100_post. VLF was significantly higher in HD200_telo as well (fig. 4, 5). Subjects without DM did not show any significant differences.

Complexity Parameters. Significant differences were found in the complexity indices. Diabetic subjects showed significantly higher values of SampEn(2,0.15) during HD200_telo compared to HD100_telo. On the contrary, ApEn(2,0.15) was significantly lower during HD200_post when compared to HD100_post (table 4).

In nondiabetic subjects, significantly higher values of ApEn(2,0.15) and LZC(3,0.001) were found at HD200_proto and HD200_telo respectively, in comparison to the same periods during HD100 (table 4).
When comparing HRV indices between the first and the last 30 min of dialysis, no significant differences were found in nondiabetic subjects, irrespective of dialysate glucose level. In contrast, in diabetic subjects, mean NNI, VLF power, total power and LZC(3, 0.001) differed significantly with HD100 (p < 0.05) (table 4).

**Discussion**

The key finding of the present study is that HD using HD200 resulted in a significantly increased vagal activation in diabetic subjects. This predominantly vagal activation may adversely affect the hemodynamic response to ultrafiltration and thus facilitate intradialytic morbid events, such as hypotension.

Cardiovascular disease is the leading cause of death in dialysis patients, and disturbances of the ANS, as analyzed by means of HRV analysis, have been shown to correlate with cardiovascular pathology and mortality risk in the general population [13, 14] and in HD patients [15–17, 25].

The present study in HD patients is the first randomized, controlled study to investigate the short-term effects of two commonly used dialysate glucose concentrations on autonomic function. To eliminate potential

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**Table 2. HD treatment parameters**

<table>
<thead>
<tr>
<th></th>
<th>Diabetic subjects (n = 11)</th>
<th>Nondiabetic subjects (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD100</td>
<td>HD200</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment time, min</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Dialysate K+ concentration (2/3 mmol/l)</td>
<td>206 ± 28</td>
<td>213 ± 30</td>
</tr>
<tr>
<td>Dialysate Ca&lt;sup&gt;2+&lt;/sup&gt; concentration (1.125/1.5 mmol/l)</td>
<td>10/1</td>
<td>10/1</td>
</tr>
<tr>
<td>Interdialytic weight gain, kg</td>
<td>2.8 ± 1.6</td>
<td>2.7 ± 1.1</td>
</tr>
<tr>
<td>Ultrafiltration volume, ml</td>
<td>2,677 ± 1,109</td>
<td>2,901 ± 869</td>
</tr>
<tr>
<td>Pre-HD serum potassium, mEq/l</td>
<td>4.8 ± 0.5</td>
<td>5.1 ± 0.9</td>
</tr>
<tr>
<td>Pre-HD systolic blood pressure, mm Hg</td>
<td>146.6 ± 27.8</td>
<td>146.5 ± 24.5</td>
</tr>
<tr>
<td>Intradialytic saline administration, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Reasons for saline administration</td>
<td>Cramps/hypotension/reason not available</td>
<td>1/0/1</td>
</tr>
</tbody>
</table>

Data reported as means ± standard deviation. n.s. = Not significant.

**Table 3. Glucose and insulin concentration at the beginning and the end of dialysis using HD100 and HD200, respectively**

<table>
<thead>
<tr>
<th>Dialysate</th>
<th>Time point</th>
<th>Diabetic subjects (n = 11)</th>
<th>Nondiabetic subjects (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>glucose, mg/dl</td>
<td>insulin, μU/l</td>
<td>glucose, mg/dl</td>
</tr>
<tr>
<td>HD100</td>
<td>HD start</td>
<td>176 ± 111</td>
<td>44 ± 48</td>
</tr>
<tr>
<td></td>
<td>HD end</td>
<td>146 ± 48**</td>
<td>23 ± 16</td>
</tr>
<tr>
<td></td>
<td>HD end – HD start (95% CI)</td>
<td>−30 (−84 to 24)</td>
<td>−21 (−47 to 7)</td>
</tr>
<tr>
<td>HD200</td>
<td>HD start</td>
<td>194 ± 142</td>
<td>38 ± 28</td>
</tr>
<tr>
<td></td>
<td>HD end</td>
<td>192 ± 57**</td>
<td>24 ± 23</td>
</tr>
<tr>
<td></td>
<td>HD end – HD start (95% CI)</td>
<td>−2 (−70 to 67)</td>
<td>−14 (−35 to 8)</td>
</tr>
</tbody>
</table>

Data reported as means ± standard deviation, or mean (95% CI in parentheses) and represent averaged values collected before and after treatments using HD100 (n = 4 per subjects) and HD200 (n = 2 per subject). Significant differences between HD100 and HD200 are indicated in bold.

* p = 0.05; ** p < 0.01, HD100 vs. HD200; a p < 0.05, HD start vs. HD end.
Fig. 2. Systolic blood pressure during HD using HD100 and HD200 in nondiabetic (a; n = 12) and diabetic (b; n = 11) subjects.

Fig. 3. Differences in mean NNI in diabetic subjects during the HD_{proto}, HD_{telo} and HD_{post} periods using HD200 and HD100, respectively. The difference, Δ, was calculated as: Δ mean NNI = mean NNI (HD200) – mean NNI (HD100). The box and whisker plots show median, 10, 25, 75 and 90% percentiles; values outside the 10 and 90% percentiles are marked as +. Individual data are shown as circles. * p value <0.05 indicates significance.

Fig. 4. Differences in spectral total power (ms²) in diabetic subjects during the HD_{proto}, HD_{telo} and HD_{post} periods using HD200 and 100 HD100, respectively. The difference, Δ, was calculated as: Δ total power = total power (HD200) – total power (HD100). The box and whisker plots show median, 10, 25, 75 and 90% percentiles; values outside the 10 and 90% percentiles are marked as +. Individual data are shown as circles. * p value <0.05 indicates significance.
confounding factors, dialysis prescriptions and drugs remained unchanged throughout the study. The only intervention was a change in dialysate glucose concentration. As subjects were analyzed in a paired fashion, drugs which potentially influence HRV (e.g. β-blockers) are unlikely to bias the results. Intradialytic positive sodium balance and body temperature have the potential to affect HRV although temperature has been previously shown not to influence HRV [26]. Except for a slightly higher ultrafiltration volume in nondiabetic subjects treated with HD200 (table 2), no significant differences of treatment time and rate of fluid removal were seen.

As mentioned earlier, the main finding of this study is a significant increase of the parasympathetic response (which is predominantly reflected by the power of the HF spectral component) in diabetic subjects using HD200. This is reflected by an increase in mean NNI [27] and VLF. Taylor et al. [28] demonstrated that the VLF component estimated on epochs of 20 min is highly dependent on parasympathetic tone, mainly because efferent vagal nerve traffic to the human heart can fluctuate over VLFs to HFs.

As expected, diabetic subjects showed a reduced sympathetic tone during and after dialysis. Diabetic subjects showed lower HRV in all indices, in particular a reduced power of their LF band (table 4), a reflection of their inability to mount a sympathetic response to HD and fluid removal [8]. Although not specifically addressed in our study, this lack of adequate sympathetic response may contribute to the increased incidence of intradialytic hypotensive episodes in diabetic HD patients [29]. In view of the association between intradialytic hypotension and mortality [30], we suspect that an increase in parasympathetic tone, as shown with HD200, is particularly adverse in this patient population.

To our knowledge, there are no data relating blood glucose level to changes in HRV following intravenous administration of glucose. Kanaley et al. [3] reported vagal stimulation (as determined by the power of the HF band) and increased total power in patients undergoing oral glucose tolerance testing; interestingly, the vagal activation was apparent in the supine but not in the upright position.

The observation that a rise in blood glucose induces a parasympathetic response may be related to direct or indirect effects of glucose both on peripheral vagal sensory fibers and on central components of vagovagal reflexes. The physiological insulin response to elevated blood glucose levels was seen in nondiabetic subjects only (table 3). Interestingly, nondiabetic subjects did not show any differences in HRV (time and frequency domain parameters) between HD100 and HD200. We propose that this is related to an adequate insulin response to the dialysate glucose load, resulting in a blunted blood glucose rise and mitigated parasympathetic activation. Under most circumstances, HD activates the sympathetic system in response to ultrafiltration [31, 32]. In addition to this ‘classical’ stimulus, a rise in insulin levels may stimulate the sympathetic nervous system [1]. In order to dissect and quantify the relative effects of glucose and insulin on HRV, euglycemic and hyperinsulinemic clamp studies may be helpful. Given a larger number of patients, stratification by types of diabetes (insulin dependent; non-insulin dependent) and therapy (e.g. diet, insulin and oral antidiabetic agents) may provide additional insights. Studies of HRV in a normoglycemic state would further help to better understand the relationship between metabolic changes and HRV, in particular in diabetic subjects, who presented in a state of hyperglycemia already prior to dialysis (table 3). Notwithstanding, the strength of the
current study is that patients were investigated under clinical ‘real life’ circumstances, reflecting treatment conditions they are exposed to 3 times a week.

The complexity measures of HRV displayed a heterogeneous pattern. In nondiabetic subjects, there were generally no differences between HD100 and HD200. In diabetic subjects, SampEn was significantly higher during HD200_telo compared to HD100_telo, whereas ApEn was significantly lower on HD200. These novel findings await physiological interpretation.

In conclusion, in maintenance HD patients with DM, HD200 results in pronounced hyperglycemia and parasympathetic activation without showing hemodynamic advantages compared to HD100. In light of these findings and given the importance of sympathetic activation to counteract intradialytic hypotension, the use of HD100 appears preferable, particularly in diabetic patients.

### Appendix

Pincus [33] proposed a family of statistics, called ‘approximate entropy’ (ApEn), which measures the occurrences of similar patterns in a time series. The computation of ApEn is based on the construction and comparisons of patterns of length $m$.

Given $N$ data points $[u(i)]$ with $i = 1, ..., N$, the algorithm constructs sequences $x_m(i)$ obtained by taking $x_m(i) = [u(i), ..., u(i + m - 1)]$ and it computes, for each $i \leq N - m + 1$, the quantity

$$C_m^r(r) = N - 1 \text{ [number of } x_m(j) \text{ such that } d[x_m(i), x_m(j)] \leq r],}$$

where $d[x_m(i), x_m(j)]$ is the distance between the vectors, defined as $\max(|x(i) - x(j)|, ..., |x(i + m - 1) - x(j + m - 1)|)$, $C_m^r(r)$ measures, with a tolerance $r$, the regularity of patterns by comparing them to a given pattern of length $m$ ($m$ and $r$ are fixed values: $m$ is the detail level at which the signal is analyzed, $r$ is a threshold which filters out irregularities).

The regularity parameter is defined as $\text{ApEn}(m,r) = \lim_{N \to \infty} \frac{\Phi^m(r) - \Phi^{m+1}(r)}{\Phi^m(r)}$, where $\Phi^m(r) = (N - m + 1)^{-1} \sum_{1 \leq i \leq N-m+1} \ln C_i^r(r)$.

$\text{ApEn}(m,r,N) = [\Phi^m(r) - \Phi^{m+1}(r)]$ is the estimator of this parameter for an experimental time series of fixed length $N$.
Richman and Moorman [20] developed a modification of this algorithm in order to improve ApEn; the name of this new statistic is ‘sample entropy’ (SampEn).

The differences with respect to ApEn are: (1) self-matches are not counted; (2) only the first \( N - m \) vectors of length \( m \) are considered, and (3) the conditional probabilities are not estimated in a template manner: they do not adopt as probability measure the ratio of the logarithmic sums, but they compute directly the logarithm of conditional probability.

Once defined, the following quantities for \( i, j \leq N - m \)

\[
A_{i,m}(r) = (N - m - 1)^{-1} \{ \text{number of } x_{m+1}(j) \text{ such that } d[x_{m+1}(j), x_{m+1}(i)] \leq r, i \neq j \} 
\]

\[
B_{i,m}(r) = (N - m - 1)^{-1} \{ \text{number of } x_m(j) \text{ such that } d[x_m(j), x_m(i)] \leq r, i \neq j \} 
\]

\[
A_{m}(r) = (N - m)^{-1} \sum_{i=1}^{N-m} A_{i,m}(r) 
\]

\[
B_{m}(r) = (N - m)^{-1} \sum_{i=1}^{N-m} B_{i,m}(r) 
\]

the parameter SampEn\((m,r)\) is given then by \(\lim_{N \to \infty} [-\ln(A_{m}(r)/B_{m}(r))]\) and the associated statistics SampEn\((m,r,N)\) = \(-\ln(A_{m}(r)/B_{m}(r))\).

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Disclosure Statement

J.A.D.-B. is an employee of Fresenius Medical Care North America. P.K. holds stocks of Fresenius Medical Care North America. All other authors do not have any potential financial interests in the results of the study.

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