Use of Anion Gap for the Quality Control of Electrolyte Analyzers

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A simple model for the simulation of patient Na, CO_2, Cl, and anion gap was formulated from patient electrolyte data. Analytical error, either random or systematic, was incorporated into the simulation of the electrolyte data and allowed study of the response of anion gap to error. Power functions, plots of probability of error detection *vs.* size of analytical error, were constructed and indicated a low probability of error detection when single patient specimens with abnormal anion gaps were reanalyzed. These power functions showed that pooling of the anion gap data by averaging consecutive anion gaps resulted in a high probability for detecting systematic error. We recommend, as a useful quality control procedure, averaging at least eight consecutive anion gaps and testing for a significant difference between the average and the established mean gap. (Key words: Quality control; Anion gap; Electrolyte measurements) Am J Clin Pathol 1983; 79: 688–696

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THE AVERAGE ANION GAP (AG = Na − Cl − CO_2) has been shown to be remarkably constant for groups of normal and hospitalized individuals. The average gaps (±SD) of apparently healthy individuals have been reported as 11.0 ± 2.5,[9] 13 ± 2.4,[23] and 11.0 ± 2.8 mEq/L.[23] The average gaps (±SD) of hospitalized patients have been reported as 12.2 ± 4.0,[15] 11.0 ± 2.5,[9] 12.0 ± 4.0,[23] and 11.5 ± 2.5 mEq/L.[16] (When potassium is incorporated into the anion gap formula, AG = Na + K − Cl − CO_2, the average anion gap will be approximately 4 mEq/L higher.) Because of this constancy, wide deviations may be indicative of disease states or of errors in the test results.

The causes of significantly elevated and decreased anion gaps recently have been reviewed.[7] Gabow and co-workers in a prospective study showed that most patients with gaps greater than 19 mEq/L had confirmed organic acidosis.[11] Only a few of the patients with slightly increased gaps (17–19 mEq/L) had organic acidosis. Goldstein showed, by retrospective review of patients with at least two consecutive low anion gaps, that low anion gap was secondary to hyponatremia, hypoalbuminemia, or attributed to laboratory error.[12]

Abnormal anion gaps also may be caused by errors associated with the aquisition, processing, and analysis of the patient specimens. Application of the anion gap calculation to monitor the quality of electrolyte analyis has been advanced by Witte and colleagues.[23] Buckley-Sharp and Miller[4] have cautioned that the anion gap's coefficient of variation greatly exceeded the coefficient of variation of individual analyses. Thomas and associates[19] stated that small systematic and indeterminate electrolyte analytical errors would not be detected by anion gap calculations.

For many years, the anion gap has been calculated in our laboratory whenever the electrolytes Na, Cl, and CO_2 have been ordered together. When the anion gap has been sufficiently abnormal (outside control limits of 5 and 19 mEq/L) the analyses have been repeated, usually after re-calibration, except if the patient had a previously abnormal anion gap or if there was evidence of disease that might result in an abnormally high anion gap. The repeated electrolytes have been reported if the new anion gap fell within the control limits, or if the results confirmed the previous measurements. Otherwise, the analytical methods have been inspected and appropriate troubleshooting procedures have been initiated.

Our experience with the anion gap as a control procedure mirrors the diverse opinions in the literature.[4,19,23] There have been occasions when analytical errors have been detected, and also many occasions when the additional investigative efforts have not been productive. In order to more objectively evaluate the capabilities of anion gap control procedures, it would be useful to determine the performance characteristics in terms of the expected probabilities for rejecting analytical runs having differing amounts of analytical error. This approach has been applied to the evaluation of other quality control procedures[22] and should also be applicable to anion gap algorithms.

In this paper we describe the development and validation of a simple model for the simulation of patient electrolyte data and the use of this model to determine the error detection capabilities of the anion gap control

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procedure. The error detection capabilities are expressed as power functions, graphs of probability of rejection *vs.* the size of error (either systematic or random) as used by Westgard and co-workers for comparing the performance characteristics of various control procedures.[22]

Materials and Methods

Model Development and Validation

The relationships between Na, Cl, and CO_2 were determined from the analysis of consecutive sets of patient electrolyte data, as measured during a one-day period (Period 1) by the ASTRA 4® analyzer (Automated Stat/Routine Analyzer, Beckman Instruments, Inc., Fullerton, CA). Regression analysis of these data indicated that there was little correlation between CO_2 and Na ($R^2 = 0.033$); therefore, anion gap could be modelled rather simply. Patient Na and CO_2 were generated independently with a random normal number generator that used the within day means and standard deviations determined from the patient data. The Cl value then was calculated from Na and CO_2 using the equation determined from the regression analysis ($Cl = -17 + 1.03\ Na - 0.91\ CO_2$).

The validity of the model for the simulation of patient electrolyte data was tested in three ways. First the frequency histograms of the simulated anion gaps were compared with that of the original anion gaps. Second, data from the medical literature were used to assess if the equation for the calculation of Cl adequately predicted Cl values for various acid-base and electrolyte abnormalities. Third, the sensitivity of the simulations to small changes in the regression equation was investigated by generating a second set of power functions using a regression equation determined from the analysis of a second group of consecutive patient data gathered approximately six months later (Period 2).

Simulation of Analytical Error

Random analytical error, or the inherent measurement error, was added to each of the simulated Na, CO_2, and Cl values using a random normal number generator having its mean set as the previously determined value for Na, CO_2, or Cl, and the standard deviation representing the long-term analytical variation. Estimates of the long-term standard deviations (Na: 1.2 mmol/L; Cl: 1.4 mmol/L; CO_2: 0.5 mmol/L) were obtained by assaying Moni-Trol I.X Chemistry Control® (American Dade, Miami, FL) three to four times daily for approximately 4 months.

To evaluate the response of anion gap to additional analytical errors, systematic error (SE) was simulated by adding (or subtracting) multiples of the long-term standard deviation to (or from) the previously simulated patient values. Increases in random error (RE) were simulated by using increasing multiples of s in the random normal number generator (mean = previously simulated patient value, s = multiples of the long term standard deviation). The multiples of standard deviation for simulating random and systematic error ranged from 0.5 to 5 and increased in increments of 0.5.

To study the response of *single* anion gap control procedures (i.e., control procedures that employ control limits for the AG determined on an individual patient specimen), groups of 500 sets of electrolyte results were simulated at each error level with the mean anion gap equal to 10.5 and the standard deviation (s_{AG}) equal to 1.95 mEq/L, representing patient specimens having no anion gap abnormalities. Anion gap was calculated as $Na - Cl - CO_2$. The proportions of gaps exceeding certain limits were tabulated and were used to estimate the probability of anion gaps exceeding a particular limit for various error levels. These probabilities were plotted *vs.* the size of error to provide graphical summaries, or power functions for the single anion gap procedure.

To study the response of the *mean* anion gap to systematic error only, the means of groups of consecutive patient anion gaps (N = 4, 8, 12, 20, 40) were compared with the accepted patient anion gap mean.[21] The proportion of statistically different means (compared with the stable mean by a Z-test having a 1% level of significance or false rejection) was plotted against systematic error. Power functions were determined for two different patient populations by employing different standard deviations for the patient anion gap, s_{AG} = 1.95 mEq/L representing patients with no anion gap abnormalities and s_{AG} = 3.4 mEq/L for patients with serious anion gap abnormalities such as those seen at our institution. The standard deviation of the patient anion gaps was increased from 1.95 to 3.4 mEq/L by increasing the analytical standard deviation in each of the methods. For each N and error level, 500 groups of patients were simulated.

Results

Model Validation

Frequency histograms for real and simulated anion gaps are shown in Figure 1. The first (top) histogram is that of the anion gaps from the first set of patient data (Period 1), the second is the histogram of simulated anion gaps without random analytical error, the third shows simulated anion gaps corresponding to a normal population, and the fourth shows simulated anion gaps corresponding to a hospital population.

For the third histogram, the mean of the simulated

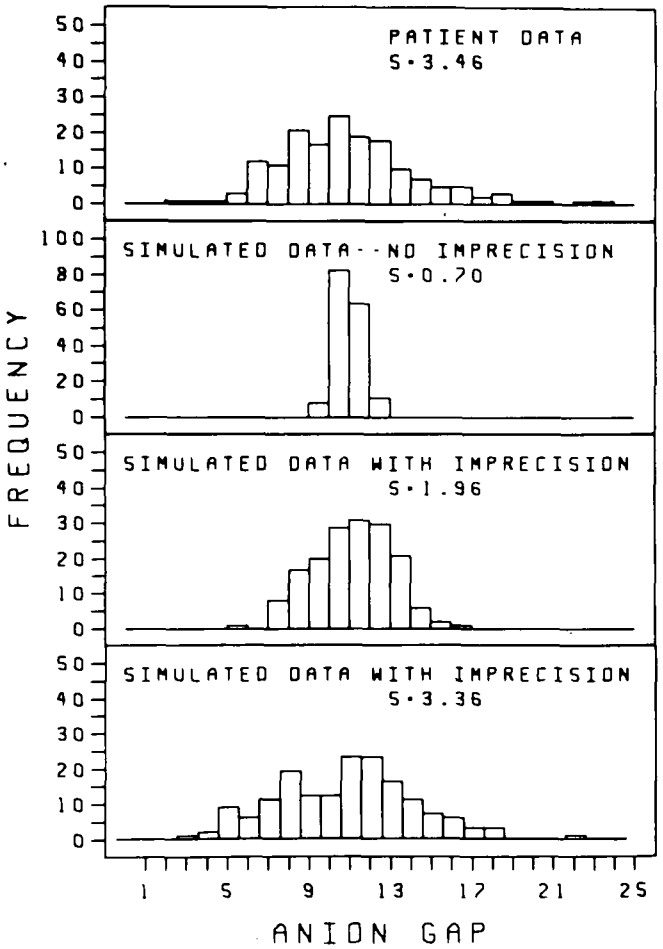

FIG. 1. Frequency histograms of consecutive anion gap data (*top*); simulated anion gaps without inherent random error (*second*); simulated anion gaps with random error, s = 1.96 (*third*); simulated anion gaps with random error, s = 3.36 mEq/L (*bottom*).

anion gaps is approximately equal to the mean of the real anion gaps, but the distribution is less skewed than the original patient population. This is because it lacks the abnormally high and low gaps attributed to disease processes. Most of the very abnormal anion gaps of the real data may be explained by concomitant hypoproteinemia and hypoalbuminemia (low gaps) and renal failure or lactic acidosis (high gaps). The distribution of the simulated anion gaps in the third histogram, therefore, corresponds to that of a healthy population, in the sense that there are no anion gap abnormalities caused by disease processes.

The fourth (bottom) histogram is an example of the simulated anion gaps of a hospital population having anion gap abnormalities resulting from disease processes. This population was simulated to further evaluate the performance of control procedures using the mean gap of groups of patients. It is apparent that this last distribution of simulated anion gaps more closely represents the distribution observed for our hospital patients.

Table 1 compares observed and calculated Cl values for extremely abnormal electrolyte data selected from the medical literature. All sets of electrolyte results had normal anion gaps and there was excellent correlation between the calculated Cl and actual Cl, as shown by the small differences in column 5.

Table 2 shows the summary statistics for the two groups of consecutive patient electrolytes measured on the ASTRA. Periods 1 and 2 were 1 to 2-day periods separated by approximately six months. Also shown are all the serum and plasma electrolytes in the laboratory computer files at those times. The means and standard deviations of the different groups and periods are very similar.

Table 3 shows the coefficients of the linear regression ($Cl = a + b\ Na + c\ CO_2$) determined from the ASTRA electrolyte data for the two periods. There is no significant difference between the regression coefficients of Period 1 and Period 2 ($P < 0.05$). Power functions gen-

Table 1. Electrolyte Data for Patients with Certain Acid-base and Electrolyte Disorders

Na (mmol/L)	CO_2 (mmol/L)	Cl (mmol/L)	Calculated* Cl (mmol/L)	Δ Cl (mmol/L)	Acid-Base/ Electrolyte Abnormalitity, Reference
105	35	60	59.3	−0.7	Diuretic-associated hyponatremia,[8] Case 14
122	17	94	93.2	−0.8	Syndrome of inappropriate ADH[20]
110	17	83	80.8	−2.2	Syndrome of inappropriate ADH[6]
157	33	109	114.7	5.7	Hypernatremia due to hypodipsia, elevated ADH threshold[13]
157	27	116	120.1	4.1	Hypernatremia due to ineffective regulation of ADH[5]
164	21	134	132.8	−1.2	Hyperosmolar dehydration,[18] Case 1
115	49	56	56.9	0.9	Metabolic alkalosis due to vomiting, diuretics[10]
142	38	90	94.7	4.7	Chronic respiratory acidosis[3]
135	3	121	119.3	−1.7	Renal tubular acidosis[14]
138	12	114	114.2	0.2	Heat stroke-induced metabolic acidosis,[17] Case 6

* $Cl = -17 + 1.03\ Na - 0.91\ CO_2$.

Table 2. Summary Statistics of Consecutive Patient Specimens Analyzed by the ASTRA 4 during Periods 1 and 2 and Summary of Electrolyte Data Resident in Laboratory Computer during Periods 1 and 2

	Period 1		Period 2	
	ASTRA Patients (N = 166)	Total Patients (N = 1350)	ASTRA Patients (N = 202)	Total Patients (N = 2050)
$\overline{Na}$ ± SD (mmol/L)	137.8 ± 5.77	137.5 ± 5.96	137.8 ± 4.97	137.5 ± 5.11
$\overline{Cl}$ ± SD (mmol/L)	100.1 ± 7.36	100.9 ± 7.47	100.3 ± 6.49	100.9 ± 6.46
$\overline{CO_2}$ ± SD (mmol/L)	27.3 ± 4.32	27.3 ± 5.13	27.9 ± 4.61	26.9 ± 5.27
$\overline{AG}$ ± SD (mEq/L)*	10.4 ± 3.46	9.3 ± —†	9.6 ± 4.06	9.7 ± —†

* Concentrations of monovalent electrolytes may be expressed in mmol/L or mEq/L.
† Not available.

erated with the Period 1 coefficients did not differ appreciably from those using the Period 2 coefficients; thus, the simulation results were not critically dependent on small changes in the regression equation.

Response to Analytical Error

Power functions for quality control procedures using single anion gaps are shown in Figures 2 and 3. These are plots of probability for rejection *vs.* random and systematic error, respectively. The probability represents the proportion of anion gaps observed to be outside the control limit. The size of random error (Fig. 2) is given relative to the standard deviations of the analytical methods, such that a value of 2.0 represents an increase in random error equivalent to a doubling of the long-term stable analytical standard deviation. The size of systematic error also is given as multiples of the standard deviation; thus, a value of 2.0 represents a systematic shift equivalent to twice the size of the long-term stable standard deviation. Each plot contains a family of curves, with each curve representing a different anion gap limit. For example, Figure 2A shows the probability of detecting errors with anion gaps greater than 14, 15, 16, 17, 18, 19, and 20 mEq/L. In these curves, the probability of detecting the various anion gaps is plotted against size of random error. Notice that for a given random error, the probability of detecting errors with small anion gaps tends to be greater than with larger anion gaps.

The following example illustrates the use of these power functions. If a laboratory retests patient specimens with anion gaps >19 mEq/L, the performance characteristics of the "retesting rule" can be found in Figures 2*A–C* and 3*A–C*. The capability for detecting random error in Cl is seen in Figure 2*A*. The line between those labeled 18 and 20 gives the probability for rejection with an anion gap limit of 19 mEq/L. By convention, the usual or inherent random error of a method corresponds to a value of 1.0s on the abscissa. If the random error is tripled (a value of 3.0 on the abscissa), then the probability of detecting this random error is very small, approximately 0.02, or 2%. If the random error is quintupled, the probability of observing an anion gap >19 mEq/L is 0.12. Figure 3*A* shows the probability of observing an anion gap >19 mEq/L if there is a negative systematic error in Cl. Normally there is no systematic error in a method, corresponding to a value of 0.0s on the abscissa. A systematic shift equivalent to −3.0s causes only 1% of the gaps to exceed 19 mEq/L. Review of Figures 2*A–C* and 3*A–C* demonstrates a low probability of finding anion gaps >19 mEq/L with even large analytical errors.

Figures 2 and 3 show that the probability of an anion gap exceeding a limit for any sized error is greatest for Cl, slightly smaller for Na, and greatly decreased for CO_2. This is due to the units of the abscissa being expressed in multiples of the long-term standard deviation ($s_{CL} > s_{Na} \gg s_{CO_2}$). The probability of detecting a systematic error is somewhat higher than for detecting random error. Comparison of these power functions to those of standard quality control rules[10] demonstrates that follow-up of single anion gaps has lower error detection capabilities.

Figure 4 shows power functions for mean anion gaps having N patients included in the average (N = 4, 8, 12, 20, 40). The vertical axis represents the probability of obtaining an average gap which differs from the stable patient average at $P = 0.01$. This is in effect a mean

Table 3. Coefficients of Regression (±SEM) for $Cl = a + bNa + cCO_2$

	Period 1 (N = 166)	Period 2 (N = 202)
a	−17.0 ± 6.47	−26.7 ± 7.63
b	1.03 ± 0.048	1.07 ± 0.059
c	−0.91 ± 0.063	−0.75 ± 0.063
R^2	0.778	0.647
$S_{Cl/Na,CO_2}$	3.46	3.86

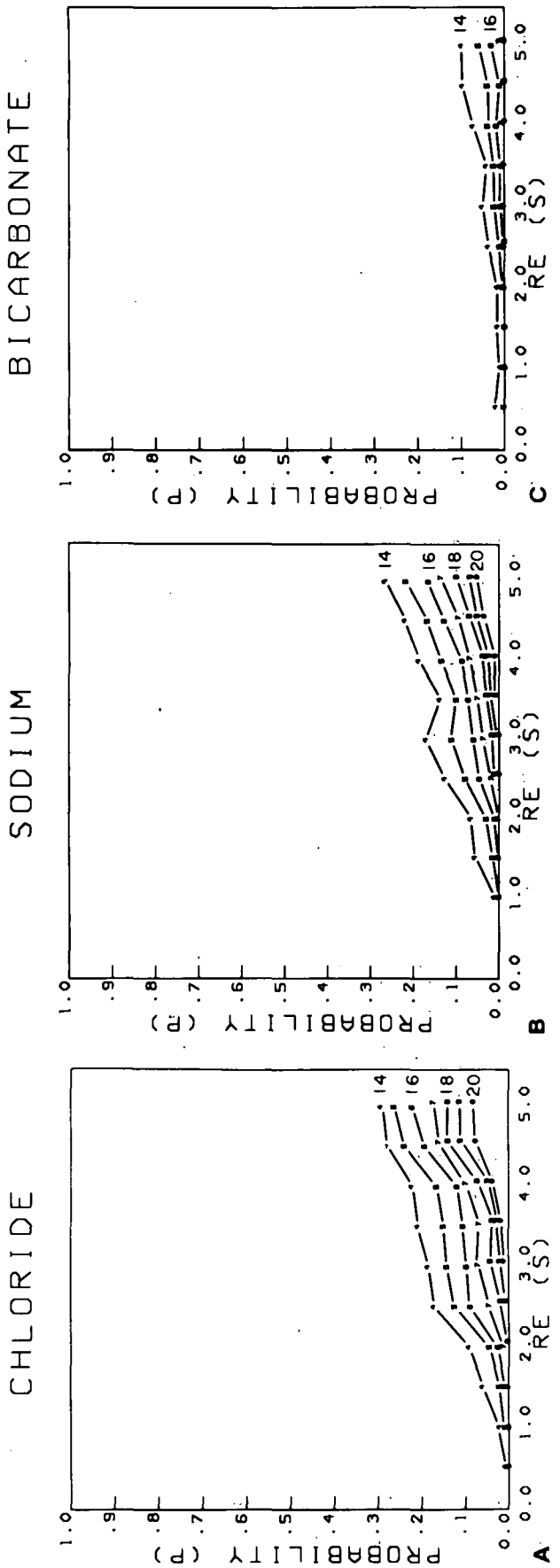

FIG. 2. Power functions for the detection of random error by *single* anion gaps for different anion gap limits. The probability of obtaining an anion gap outside these limits is plotted against size of random error. A healthy population was simulated with $\overline{AG}$ = 10.5 mEq/L, s = 1.95 mEq/L. Figures 2*A*–2*C* show the probability of detecting anion gaps >14, 15, 16···20. Figures 2*D*–2*F* show the probability of detecting anion gaps <7, 6, 5···1.

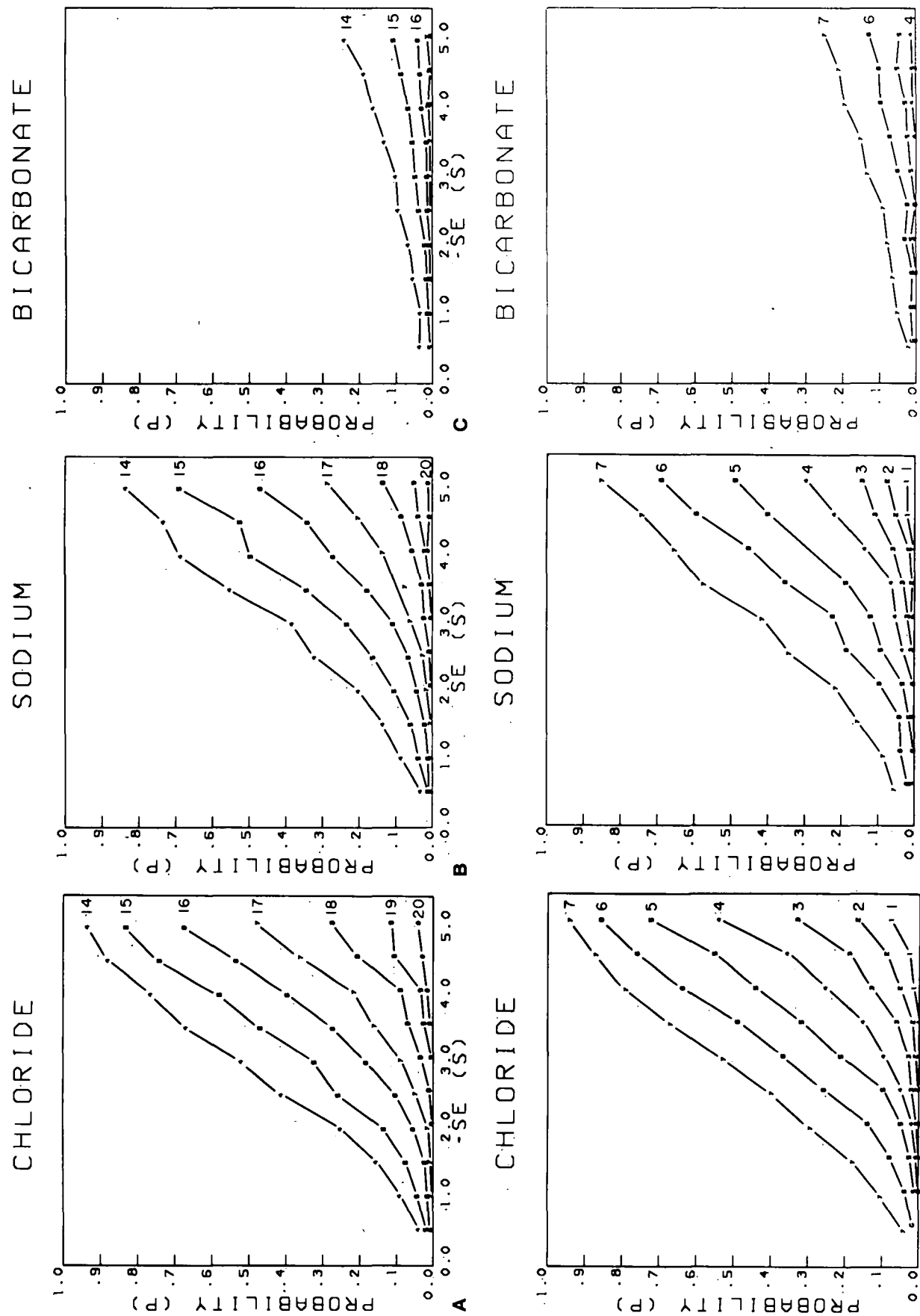

FIG. 3. Power functions for the detection of systematic error by *single* anion gaps for different anion gap limits. The probability of obtaining an anion gap outside these limits is plotted against size of systematic error. A healthy population was simulated with $\overline{AG}$ = 10.5 mEq/L, s = 1.95 mEq/L. Figures 3*A*-3*C* show probability of detecting anion gaps >14, 15, 16 · · · 20. Figures 3*D*-3*F* show probability of detecting anion gaps <7, 6, 5 · · · 1.

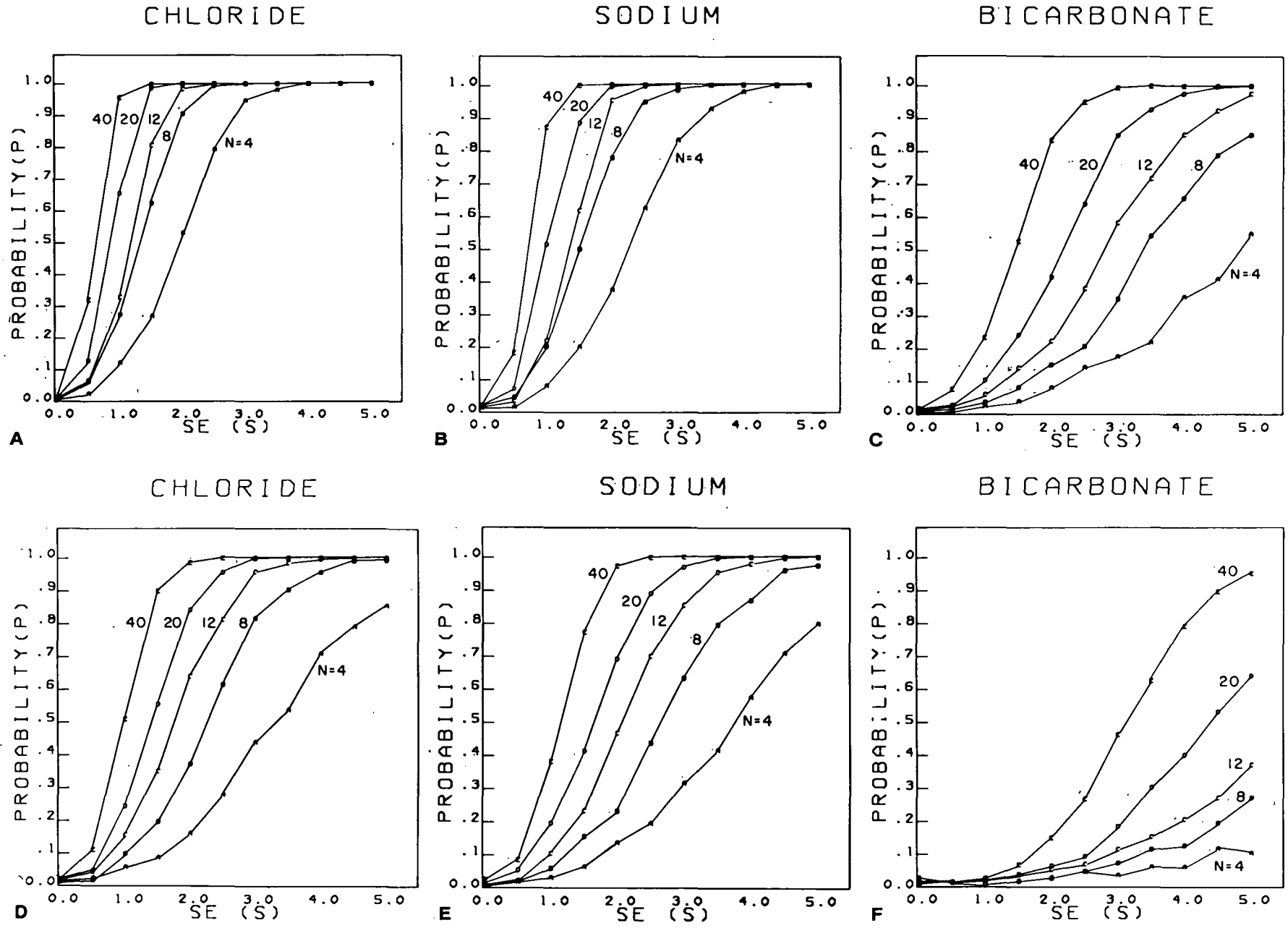

FIG. 4. Power functions for the detection of systematic error by the *averaging* of groups of N anion gaps, N = 4, 8, 12, 20, 40 (P_{fr} = 0.01). The probability of obtaining an anion gap average outside the P_{fr} = 0.01 limits is plotted against size of systematic error. Figures 4*A*–4*C*, simulation of a healthy population with s = 1.95 mEq/L. Figures 4*D*–4*F*, simulation of a hospital population with s = 3.40 mEq/L.

control rule having the probability of false rejections set at 1%. There are two sets of power functions, Figures 4*A*–4*C* with s_{AG} = 1.95 mEq/L simulating a population without serious anion gap abnormalities, and Figures 4*D*–4*F* with s_{AG} = 3.4 mEq/L simulating the population of a critical care hospital. Examination of the graphs shows a moderately high error detection capability with an N as small as 8.

Discussion

These studies indicate that procedures which monitor anion gaps of single patient specimens are not expected to be very sensitive to analytical errors. Retesting specimens whose individual anion gaps exceed limits such as <5 or >19 mEq/L is not likely to provide much improvement in analytical quality. However, the use of the mean anion gap of a group of consecutive specimens appears to offer much better detection of analytical errors. Retesting when the mean gap of a group exceeds control limits should improve analytical quality.

These conclusions are based on simulation studies employing a relatively simple model that includes only three analytes. This model was chosen after assessing the importance of a larger group of analytes that also included potassium, total protein, and albumin. The correlation between chloride *vs.* sodium and bicarbonate was only slightly less than the correlation *vs.* all five tests. Far more complicated models are required to realistically simulate patient abnormalities but are not necessary to evaluate the utility of anion gap for quality control purposes.

The power functions for control procedures utilizing individual anion gaps are more valid, and hence, more useful for a healthy population than for a severely ill hospital population. When control procedures for individual anion gaps are applied to a hospital population, there will be a higher probability for false rejections because some anion gaps will be abnormal and will result from underlying medical problems, rather than laboratory errors. In this regard, the power functions for the individual anion gap procedure show somewhat lower probabilities for rejection than might actually be observed, but any increase in rejections would be due primarily to an increase in false rejections.

The power functions for the mean anion gaps of groups of specimens have taken into account the differences between healthy and hospitalized populations. The power functions in Figures 4*A*–4*C* were generated for an anion gap having a standard deviation of 1.95 mEq/L, corresponding to a more normal population. The power functions in Figures 4*D*–4*F* are for anion gaps having a standard deviation of 3.4 mEq/L, corresponding to hospital population. Comparison of the two groups of power functions in Figure 4 shows loss of error detection due to a wider distribution of values in the patient population. Figures 4*A*–4*C* with S_{AG} = 1.95 mEq/L show good error detection capabilities for even N = 4. However, in the patient population, an average of at least eight anion gaps is recommended (Fig. 4*D*–*F*).

It seems clear that for purposes of quality control, the use of mean anion gaps should be encouraged, rather than the use of individual anion gaps. A laboratory that primarily tests normal individuals may expect a high probability of error detection using the mean anion gap of four consecutive specimens. Because very few laboratories test only normal individuals, laboratories would be better served by using the mean anion gap of at least eight consecutive specimens. When there are patients known to have low or high gaps because of medical problems, *e.g.*, renal disease, organic acidosis, severe hypoalbuminemia, *etc.*, it would be useful to exclude these specimens from the calculations. This may be difficult to do in practice, but would be desirable when possible.

Although this study is concerned primarily with determining performance characteristics based on theoretical grounds, we also are studying the use of the mean anion gap procedure prospectively in a real laboratory situation. The analytical system is one that has been reported to have some inaccuracies in the chloride channel.[1,2] Series of patient specimens with low anion gap averages are being reanalyzed after instrument maintenance and recalibration. This should allow verification of the performance of the mean anion gap procedure, and permit comparison with more commonly used control procedures employing stable materials.

The following example illustrates how averaging of consecutive gaps can signal the need for system maintenance. One recent series of eight consecutive patient specimens had the following anion gaps: 10, 7, 5, 6, 7, 4, 6, and 5 mEq/L. The average, 6.25 mEq/L, was outside the 1% limits, 7.5–13.5 mEq/L, for the usual patient mean. Controls run before and after this series were within two standard deviations of the control mean. After the chloride anode was cleaned and the system recalibrated, reanalysis of the same eight specimens resulted in individual Cl values falling by 1–3 mmol/L with the average Cl decreasing by 2.1 mmol/L. The Na values did not change significantly.

The anion gap is only one of many patient data algorithms that have been used for quality control purposes. Evaluation of patient data algorithms by application in a real laboratory situation is extremely difficult, and we think should be preceded by simulation studies that can aid in the optimization of the algorithms and in determining which algorithms should be applied and tested in real-time use.

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