vasodilator administration, acute dehydration, and/or intravenous diuresis. In addition, age- and sex-specific reference cutoffs were not used. A variety of in- and outpatient services now use BNP to assist in decision-making (Table 1). When the diagnostic accuracy of BNP testing in a large prospective trial was first reported in 2002, the overall test sensitivity and specificity were 90% and 76%, respectively (1). Similarly, we reported an apparent sensitivity and specificity of 94.8% and 77.1%, respectively. In the present report, BNP was increased in 92.8% of patients with a diagnosis of heart failure, suggesting that the sensitivity of the test remains high, but BNP was also high in >28% of patients who did not carry a heart failure diagnosis, suggesting that test specificity was much lower than 76%–77%. Although BNP was ≥100 ng/L in most patients with heart failure regardless of ordering location, it was also ≥100 ng/L in many patients without diagnosed heart failure, and this rate varied among locations (Table 1). Most astounding was the noncardiac ICU, where the test was positive in >90% of patients without a discharge diagnosis of heart failure. Many of the patients in the ICU had acute and/or chronic renal failure, volume overload, and/or multisystem organ failure, which increased BNP test results in the absence of CHF. Many BNP tests were ordered on ICU patients whose admission notes indicated a history of renal failure.

Our previous study examined test utilization during a familiarization period, when a majority of physicians ordering tests likely had formal interactions with laboratory medicine and/or cardiology staff to guide appropriate use and interpretation of the newly implemented test (1). In the current study period, fewer physicians ordering tests had formal opportunities to review test utilization criteria. Thus, we suggest that physician education is an important component for maintaining test accuracy and appropriate use. Given that our hospital trains resident physicians, leading to a high annual provider turnover, we propose periodic utilization reviews and refresher training for BNP and other tests. These measures could serve to maximize test accuracy, mitigate test overuse, enhance physician education, and improve patient care.

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References


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cups (3); this process, however, is prone to errors and is time-consuming.

In our study, we assessed the ability of the Abbott Architect ci8200 (Abbott Laboratories) to handle and directly sample from different types of primary, barcode-labeled pediatric lithium heparin gel tubes and determined the sample dead volumes of these tubes and the standard Abbott sample cup.

Five types of tubes were tested: the Sarstedt Microvette® (Sarstedt B.V.), Terumo CapijectTM (Omnilabo International B.V.), BD Microtainers 365986 and 365953 (BD B.V.), and Greiner MiniCollect® (Greiner Bio-One B.V.). To evaluate the overall handling and ability to directly sample from the pediatric tubes, in total more than 17 500 chemistry and immunochemistry assays were performed from these tubes, consisting of repetitive individual tests and panels of tests. All tubes were placed in tube extenders to create uniformity in the outer dimensions of pediatric and adult tubes and were loaded on the analyzer in standard sample racks. Two tubes of each type were barcode-labeled to test the ability of the analyzer to read primary barcode-labeled pediatric tubes. Liquid levels are generally higher in pediatric tubes placed in tube extenders than in adult tubes, and to test the ability of the chemistry and immunochemistry probes to sample from different liquid heights, repetitive individual tests were performed from tubes containing an excess of sample as well as from tubes with minimal sample volume.

Problems with liquid sensing and sampling were not seen in minimally filled pediatric tubes or in tubes with an excess of sample. No probe crash errors attributable to incorrect centering were generated, showing that sampling from small–internal diameter tubes is not a problem. In addition, no errors of lost liquid contact were generated during sampling for the chemistry and immunochemistry assays with the largest possible sample volume (35 and 150 μL, respectively) from all tube types, showing that both sample probes can handle the more rapid lowering of the liquid layer during sampling attributable to the small internal diameters of the tubes.

In addition to small sample volumes for the different tests, a low sample dead volume is desirable in pediatric settings. We therefore determined the sample dead volumes for chemistry and immunochemistry assays with the different pediatric tubes and the sample cup by requesting replicates of either the chemistry or the immunochemistry assay with the smallest sample volume (glucose and carcinoembryonic antigen; 2 and 10 μL, respectively). Filling volumes were chosen so that an aspiration error attributable to shortage of sample would occur. The dead volume was calculated based on the number of tests performed before the short sample error occurred. For the chemistry as well as the immunochemistry module, 10 tubes per tube type and 20 sample cups were used. The mean calculated dead volumes for chemistry assays of the Sarstedt, Terumo, BD 365986, BD 365953, and Greiner tubes and of the sample cup were 64, 65, 81, 41, 64, and 18 μL, respectively (see Fig. 1; also see the Data Supplement that accompanies the online version of this Letter at http://www.clinchem.org/content/vol52/issue4). For immunochemistry assays, these dead volumes were 60, 45, 59, 33, 47, and 13 μL, respectively. Although the dead volumes of the pediatric tubes were slightly higher than the dead volumes of the sample cup, they were still low.

In conclusion, this study shows that the Architect ci8200 can handle and directly sample from different primary pediatric tubes placed in tube extenders and requires only a small sample dead volume. This direct sampling, which is less time-consuming, eliminates errors attributable to manual sample transfer and sample identification.

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Six Sigma and Calculated Laboratory Tests

To The Editor:

New quality assessment (QA) systems such as Six Sigma have become more popular because they offer a different approach to problems in the clinical laboratory. Laboratory QA programs, however, deal only with measured tests, and thus QA procedures are not applied for most calculated tests, such as measurement of LDL, total globulins, unconjugated bilirubin, creatinine clearance, urea reduction ratio, corrected total calcium, international normalized ratio, plasma osmolality, and anion gap, for which the test results are not measured directly but are calculated based on relationships between measured values (1). We check only the components of calculated tests, not the calculated tests themselves, a practice that may not be adequate for good laboratory management. We should apply QA procedures to all calculated tests and modify the software in clinical laboratories to check the reliability of calculated test results.

The Six Sigma strategy measures the degree to which any process deviates from its goal. Any process can be evaluated in terms of a sigma metric that describes how many sigma fit within the tolerance limits. In quality management, Six Sigma is accepted as “world class quality”. For laboratory measurements, the sigma performance of a method can be formulated as below (2):

$$\sigma = \frac{(TE_a - \text{bias})}{\text{CV}}$$  \hspace{1cm} (1)

where TEa is allowable total error.

Because the CVs of calculated tests differ from the CVs of their components (1), we must calculate the CVs of equations. Consider a calculated variable $g$ that is a function of the random variables $x$, $y$, and $z$, i.e., $g = f(x, y, z)$. Now Eq. 1 can be written as follows:

$$\sigma_g = \frac{(TE_a - \text{bias}_g)}{\text{CV}_g}$$  \hspace{1cm} (2)

If the variances ($SD^2$) of $x$, $y$, and $z$ are known, the variance of $g$ can be approximately obtained by use of the Taylor series expansion of the function (3). If $g = f(x, y, z)$ is approximately linear with respect to $x$, $y$, and $z$ in the region of interest, the approximate variance of $g$ is obtained as:

$$SD_g^2 \equiv (\frac{\delta g}{\delta i})^2SD_x^2 + (\frac{\delta g}{\delta j})^2SD_y^2 + (\frac{\delta g}{\delta k})^2SD_z^2$$  \hspace{1cm} (3)

where $x$, $y$, and $z$ are the individual means of each test.

If we divide both side of this equation by $g^2$ and cancel the common terms, we obtain the following equation:

$$\text{CV}_g^2 = \text{CV}_x^2 + \text{CV}_y^2 + \text{CV}_z^2$$  \hspace{1cm} (4)

This equation is valid only if the variables (measured components of equation) are independent.

Eq. 4 can be used to obtain the CVs of calculated tests. Alternatively, we may observe CV empirically from the results of measured control materials on control charts.

Combining Eqs. 2 and 4, we get a new equation:

$$\sigma_g = \frac{(TE_a - \text{bias}_g)}{(\text{CV}_x^2 + \text{CV}_y^2 + \text{CV}_z^2)^{1/2}}$$  \hspace{1cm} (5)

Under ideal conditions for a reference method, bias can be assumed to be zero if the method is properly calibrated. Otherwise, we must calculate total bias (bias of equation). In this situation, Eq. 5 can be further simplified:

$$\sigma_g = \frac{TE_a}{(\text{CV}_x^2 + \text{CV}_y^2 + \text{CV}_z^2)^{1/2}}$$  \hspace{1cm} (6)

From Eq. 4, it is obvious that the CV of the equation is higher than the CV of any component of the equation. Thus, if $TE_a \leq \text{Table } 1. \text{ TEa (recommended by CAP) and desirable CV to obtain } 6 \sigma$ for measured lipids (bias accepted as zero).

<table>
<thead>
<tr>
<th>Test</th>
<th>TEa (recommended by CAP), %</th>
<th>Desirable CV to obtain 6 $\sigma$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>10</td>
<td>1.7</td>
</tr>
<tr>
<td>HDL</td>
<td>30</td>
<td>5.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>25</td>
<td>4.2</td>
</tr>
<tr>
<td>LDL</td>
<td>20</td>
<td>3.3</td>
</tr>
</tbody>
</table>

With a given TEa, which is recommended by CLIA or the College of American Pathologists (CAP), the sigma of calculated LDL will be lower than the sigma of measured LDL. As shown in Table 1, the CV of calculated LDL (7.4%; obtained with Eq. 8) is higher than the CV of mea-