Measurements of Serum Colloid Osmotic Pressure Are of Limited Usefulness

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We examined the usefulness of serum colloid osmotic pressure measurement in patients with chronic rather than acutely occurring low serum protein concentrations. We used two oncometers, the IL 186 Well Oncometer and the Wescor Model 4100; results from the two instruments were interchangeable. Values for the colloid osmotic pressure were compared with those for serum total protein (r = 0.783) and albumin concentrations (r = 0.882), which were similar to previously published values. Our day-to-day CV was 2.8%. In studying over 100 patients we found that the previously reported occurrence of pulmonary edema in almost all patients whose colloid osmotic pressure was <12.5 mmHg was not seen in the chronic hypoproteinemic patients. We noted only one fatality in our patients whose colloid osmotic pressure was <10.5 mmHg, a value found to be associated with fatality in one previous study of acutely ill patients. Factors such as ambulation, fasting, dehydration, and the nature of the blood sample can markedly affect the value for colloid osmotic pressure value, and this, coupled with the good correlation with the serum albumin in several studies, leads us to question the usefulness of measuring colloid osmotic pressure in a non-specialist hospital environment, either as an adjunct to the measurement of serum protein or albumin, or as an independent test.

Pulmonary edema is a possible consequence of acute cardiopulmonary failure or any other condition that may affect the exchange of fluid across the capillary membranes in the lungs. While the same factors that influence the development of pulmonary edema may induce edema in other tissues, the consequences of edema elsewhere are usually less critical for a patient. Fluid transfer across membranes is governed not only by the capillary and interstitial hydrostatic pressures and the coefficients of filtration and reflection of the endothelial capillary membranes, but also by the colloid osmotic pressure of the capillary and interstitial fluids. These forces are interrelated as expressed in the classical Starling equation (1).

Pulmonary edema is likely to arise when there is a relative increase of capillary pressure compared with that of the interstitial tissue or a reduction of the colloid osmotic pressure of the capillary plasma compared with that of the interstitial fluid. Although it is impossible to measure either the pressure or colloid osmotic pressure of the interstitial fluid, it is possible to measure pulmonary wedge arterial pressure and the colloid osmotic pressure of either peripheral or pulmonary blood plasma or serum. Pulmonary arterial pressure is technically difficult to measure, but the advent of simple oncometers has made it possible to determine plasma colloid osmotic pressure quickly and accurately in the laboratory. Although it is desirable to measure both colloid osmotic pressure and pulmonary arterial pressure so that the colloid hydrostatic pressure gradient may be calculated (2), there is accumulating evidence that colloid osmotic pressure measurements alone yield enough information to forewarn of incipient pulmonary edema (3).

Most of the plasma colloid osmotic pressure is attributable to protein, especially albumin. Measurement of both total protein and albumin in serum is simple and precise, and the question arises whether there is a clinical need for the additional or alternative measurement of colloid osmotic pressure. The study reported here was addressed to this issue. We were particularly interested in determining the overall relationship between the total protein and albumin concentrations and the colloid osmotic pressure of the same specimens. We also wished to determine whether the previously established critical value of 12.5 mmHg (1 mmHg ≈ 133 Pa) below which pulmonary edema frequently occurs in surgical or trauma patients (3) also applied to other patients in whom a low serum albumin concentration might have developed over a long period of time. We therefore studied many patients, both medical and surgical, with abnormal concentrations of total protein in their serum.

Materials and Methods

Specimens for serum colloid osmotic pressure measurements were obtained from four populations:

- healthy individuals
- hospital or clinic patients with various diseases
- patients with a low serum total-protein concentration
- patients with an abnormally high total serum protein concentration

Measurements were made repeatedly on several patients in whom the serum total protein was low initially, during their period of hospitalization, so that the response of the colloid osmotic pressure to treatment of the underlying medical condition could be determined.

Peripheral venous serum was used for all measurements of colloid osmotic pressure, although the serum colloid osmotic pressure is less than that in plasma (4). The influence of fibrinogen is small, about 0.35 mmHg, and we consider it of no clinical significance. Except when blood was drawn from the healthy individuals, no precautions were taken to avoid venous stasis. It is known that stasis for as long as 1 min affects both colloid osmotic pressure (4) and protein concentration (5), but in none of our subjects was a tourniquet used for as long as this. We also made no attempt to standardize the interval for which the patients were recumbent before specimens were collected for analysis, although the colloid osmotic pressure of specimens obtained from individuals who have been supine for 30 min may be as much as 15% less than in ambulatory individuals (6), a change similar to that observed in protein concentration.

Colloid osmotic pressure was measured by oncometers manufactured either by Wescor, Inc., Logan, UT 84321 (Model 4100 colloid osmometer) or Instrumentation Laboratory, Inc., Lexington, MA 02173 (IL 186 Well oncometer). Results obtained with the two systems were interchangeable. Repeated measurements of the same specimen from day to day yielded a mean value of 22.6 mmHg with a standard de-
Fig. 1. Relationship between serum total protein concentration and colloid osmotic pressure.

○ indicates specimens from patients known to have multiple myeloma.

The mean serum colloid osmotic pressure of 43 healthy men and women was 23.8 mmHg (SD 1.36). No influence of age or sex was observed. All individuals had been sitting for as long as 30 min before blood was collected.

Hospital or Clinic Patients

One hundred specimens in which the serum total protein concentration was above or below our normal range of 66–79 g/L were obtained from hospitalized patients and analyzed for colloid osmotic pressure. Twenty specimens in which the protein concentration was normal were also obtained from the same hospital population. The patients had a variety of diseases. The results were compared with the total protein concentration and are illustrated in Figure 1. The correlation coefficient was 0.783. It is apparent that many specimens with a high protein concentration fall below the overall line of best agreement. When the colloid osmotic pressure was compared with the albumin concentration in the same specimens, the correlation coefficient was 0.882 (Figure 2). Serum osmolality was also measured in the same specimens. The lack of a clear relationship between the colloid osmotic pressure and serum osmolality is illustrated in Figure 3.

Patients with Low Serum Protein Concentration

Random measurements. Colloid osmotic pressure was measured in serum specimens from patients in whom the serum protein concentration was noted to be low. The diagnoses of eight such patients are listed in Table 1. In all of these patients the serum colloid osmotic pressure was <12.5 mmHg, a value below which the risk of pulmonary edema is considered great. Only in patient D.N. was any accumulation of fluid noted in the lungs on clinical and radiological examination. Although patient L.F. demonstrated peripheral edema, he did not have pulmonary edema.

Serial measurements. 1. Patient I.B., a 73-year-old woman with many medical problems, including chronic lymphocytic leukemia and insulin-dependent diabetes mellitus, was admitted to the hospital with a seven-day history of fever, anorexia, and fatigue. On examination, she was found to have ankle edema and lung crepitations. She was treated for congestive heart failure but suffered a cardiac arrest five days after admission. Subsequently, she developed an aspiration pneumonia and pulmonary edema. Because of her low serum protein concentration, albumin was infused, but she became comatose rapidly. She required a tracheotomy and assisted ventilation for 10 days because of her respiratory problems. She was eventually discharged, but with borderline cardiac failure. Figure 4 illustrates the serial serum protein and colloid osmotic pressure measurements.

2. Patient P.K. was an 18-year-old man who suffered a traumatic amputation of his left arm at the middle of the humerus. His arm was re-attached within 6 h. During surgery he required 13 units of whole blood. He developed massive hemoglobinuria and edema of the lower limbs, but no pulmonary edema. Despite some local sepsis, he made a good recovery and eventually achieved reasonable function of his left arm. Figure 5 shows the relationship between his serum...
protein concentration and colloid osmotic pressure measurements.

3. Patient R.B., a 52-year-old woman who 10 years previously had received a renal transplant from a relative, was admitted to hospital after two weeks of fever of unknown origin. Because of her poor nutritional status she was started on total parenteral nutrition. A cholecystectomy was performed for gallstones in her gallbladder. Postoperatively she demonstrated a high cytomegalovirus titer. Ten days postoperatively she had a cardiac arrest but was resuscitated. However, she required assisted ventilation because of this. She developed hypotension and hypoproteinemia and was transfused with albumin for several days. She developed a staphylococcal infection and began to retain fluid, with oliguria, while still being hypotensive. Her fever persisted and the woman remained hypotensive despite aggressive therapy; she died 15 days after surgery. The course of her response to surgery is illustrated in Figure 6.

Discussion

The total osmolality of plasma is about 319 mOsmol/kg water, but when corrected for inter-ionic and intermolecular attraction or repulsion is about 287 mOsmol/kg. The osmotic pressure attributable to this is about 5535 mmHg (11). The osmotic pressure ascribable to colloids represents <0.5% of the total. Because the osmotic pressure of the colloids is such a small part of the total osmotic pressure, it is possible for one to vary without affecting the other. The lack of relationship between the two measurements is readily apparent from Figure 3. Most of the colloid osmotic pressure is attributable to serum albumin. Indeed, each gram of albumin exerts about twice the osmotic pressure of a gram of globulin. The correlation between the serum albumin concentration and the colloid osmotic pressure is better than that between the total protein concentration and the colloid osmotic pressure. That the total protein and colloid osmotic pressure correlate so well is attributable to the large albumin component. It should be noted, however, that protein solutions do not exhibit ideality and that there is a nonlinear increase in the plasma colloid osmotic pressure with increasing albumin or total protein concentration (11). The close relation between albumin and colloid osmotic pressure is upset in those patients with a very high serum total-protein concentration due to a monoclonal gamopathy. The relationship is also affected when patients have received plasma-expanding compounds other than plasma or a blood product, e.g., dextran. Despite the reported occurrence of pulmonary edema in patients with a serum or plasma colloid osmotic pressure of less than 12.5 mmHg (12), several patients without pulmonary edema were observed in whom values were less than this. Morissette et al. (13) have reported that no

Fig. 4. Relationship between serum total protein and colloid osmotic pressure in patient I.B.

PCWP = pulmonary capillary wedge pressure

Fig. 5. Relationship between serum total protein and colloid osmotic pressure in patient P.K.
individuals suffering from acute blood loss, especially when non-blood products have been used as plasma expanders. When capillary pulmonary artery wedge pressure is performed in addition to a colloid osmotic pressure measurement, it is possible to determine the underlying physiological causes of the development of pulmonary edema, i.e., whether it is pressure or protein related. This allows appropriate therapy to be instituted.

While workers in acute care medicine have advocated the measurement of colloid osmotic pressure as an aid to predicting the likelihood of pulmonary edema developing (6) and as a predictor of survival of these patients, the critical value being 10.5 mmHg (13), few data are available to relate colloid osmotic pressure in the less acutely ill patient to abnormal total protein values.

In our study of over 100 patients with hypoproteinemia, several inferences could be drawn. Namely, there is a good correlation between serum colloid osmotic pressure and albumin concentration \((r = 0.882)\). In several of these patients the colloid osmotic pressure value was well below the reported critical value of 10.5 mmHg, yet the patients did not develop pulmonary edema. Only one of these eight patients did not survive.

Because there is generally a good correlation between the serum albumin concentration and the colloid osmotic pressure and because the oncometers used to measure serum osmotic pressure are not trouble-free, we question whether the measurement of colloid osmotic pressure has more to offer than does information on the albumin concentration, alone or coupled with measurement of pulmonary arterial wedge pressures, even in the acute-care situation. Obviously, whether or not a physician uses any of these measurements depends on the availability of the test in the laboratory. Most laboratories can now provide serum total protein and albumin measurements, and it is doubtful whether the additional cost of a colloid osmotic pressure measurement is justified. Other studies (16, 17) have shown an even closer correlation than in our study \((r = 0.913\) and 0.92, respectively) between serum colloid osmotic pressure and total protein concentration when the latter is measured by refractometry. This method for total protein measurement is very simple and could be done in even the least sophisticated clinical laboratory.

While the studies on critically ill patients have shown that colloid osmotic pressure measurements, particularly if coupled with pulmonary arterial wedge pressures, are an excellent predictor for the development of pulmonary edema and even patient survival, these studies have been carried out in centers caring for large numbers of critically ill patients. For the average hospital with a more general patient population, the measurement of serum colloid osmotic pressure would be of limited usefulness.

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References
Two Serum Pancreatic Isoamylase Determinations Compared
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Serum pancreatic isoamylase activity was measured by a method involving inhibition of salivary isoamylase and by a well-known agarose electrophoretic method, modified by us. We saw changes in electrophoretic patterns of pancreatic isoamylase fractions after storage of serum samples for three weeks at 4–8 °C, but with the inhibition method no alterations in activities were found. Within-assay and between-assay imprecisions of both methods were about the same. Serum pancreatic amylase activities as measured by the inhibition method exceeded by about 10% those obtained by the electrophoretic method. The inhibition method seems to be a reasonable candidate for routine application, whereas the electrophoretic method is still time-consuming and requires special skill to perform. Some suggestions are given for improving the calibration of the inhibition method recommended by the manufacturer.

Semi-quantitative determination of “diastase” (α-amylase; 1,4-α-D-glucan glucohydrolase, EC 3.2.1.1) in urine as described by Wohlgemuth (1) has served as a test for pancreatic disease during more than 50 years. At the end of the sixties an improved method for measuring amylase in urine and serum was developed, based on the use of a chromogenic substrate (2–4).

In the seventies, several electrophoretic techniques appeared for separating the isoenzymes of amylase (5–9). After electrophoresis, a chromogenic method was used to make visible and quantify the isoenzymes. In the serum of healthy persons two groups of isoenzymes were found: those of pancreatic and of salivary origin. Although these showed differences in relative molecular mass and carbohydrate content, their amino acid compositions (10) and antigenicities (11) were similar.

The diagnostic specificity of total amylase in serum is very low (for a review see 12). A specific quantitative determination of pancreatic amylase in serum would be of importance to the diagnosis and therapy of malfunctions of the exocrine pancreas, but at present there appears to be no reliable method that is suited for routine application in a clinical chemical laboratory. Electrophoretic methods are tedious and very time-consuming.

In 1977, a fast method for determining isoenzyme activity in serum was published (13). These workers isolated a protein from wheat (14) that had a 100-fold more inhibitory activity towards human salivary than towards human pancreatic amylase. A pancreatic amylase assay was developed, involving a chromogenic substrate, and this inhibition method recently became available in a commercial form.

Our objective here was to compare results obtained by the commercially available inhibition method with those by the electrophoretic technique as described by Skude (5), with some modifications.

Materials and Methods
Preparation of Pancreatic and Salivary Homogenate
We collected human saliva in a plastic container after vigorous chewing and centrifuged it (2000 × g, 15 min) promptly. After filtration through a 0.45-μm filter the filtrate was stored at −20 °C until used. Adequate dilutions were made with a 9 g/L sodium chloride solution before electrophoresis.

Non-pathologic human pancreatic tissue, obtained a few hours post mortem, was promptly frozen and stored at −70 °C. After defrosting, about 20 g of tissue was cut into small pieces, which were put into a small Teflon barrel, together with a small steel bullet. After cooling the barrel in liquid nitrogen

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