10.6: The Implications

Stewart has essentially produced a mathematical model of the acid-base balance of body fluids.

His analysis gives new insights into what is really happening at the chemical level and this is different from the conventional approach. The conventional understanding of acid-base balance is: cluttered with jargon, chemically meaningless derived quantities, a misunderstanding of what is happening and an artificial use of the Henderson-Hasselbalch equation as the single equation determining acid-base balance in any body fluid (Stewart).

The Henderson-Hasselbalch equation is just one of the 6 equations which must always be simultaneously satisfied.

All disturbances of acid-base balance MUST result from a changes in the independent variables (& only the independent variables).

Respiratory acid-base disorders are caused by changes in the independent variable pCO₂

Metabolic acid-base disorders are caused by changes in SID and/or [A_TOt]

Changes in pCO₂ can occur quickly as ventilation can be rapidly altered. Changes in SID are due to changes in the concentrations of strong ions. The basic system for strong ions is absorption from the gut and excretion via the kidneys. These are both much slower processes than pCO₂ changes. The main contributor to [A_TOt] in body fluids are the proteins. For the ECF, this is essentially [albumin] as discussed previously. Most plasma proteins are produced by the
liver. Changes in protein concentration occur even more slowly than strong ion changes so changes in SID account for most metabolic acid-base disturbances. If plasma protein levels are normal ([ATot] constant), then acid-base disturbances can be analysed in terms of changes in pCO₂ and SID.

10.6.1: Interactions across Membranes

The Stewart approach seeks to determine the factors that determine the acid-base state in a given body fluid compartment. The fluid compartments in the body are separated by cell membranes or by epithelial layers. In each compartment, the [H⁺] is determined by the values of the independent variables. An acid-base disturbance in a compartment is due to a change in one or more of the independent variables occurring in that compartment.

How do acid-base interactions occur across the membranes that separate the different compartments?

Consider the following:

- The 3 major fluid compartments in the body are the ICF, ISF and plasma.
- These compartments interact with each other across membranes (eg cell membrane, capillary membrane).
- Acid-base interactions occur across these membranes also.
- These interactions can produce changes in acid-base status only if the result of the interaction is to change the value of one or more of the independent variables.

Carbon dioxide diffuses across membranes rapidly and easily. Changes in pCO₂ can occur rapidly via ventilatory changes. This has 2 important consequences:

- [H⁺] in all fluid compartments can be altered rapidly, but equally.
- Changes in pCO₂ cannot be used to produce differences in [H⁺] in fluids on opposite sides of a membrane.

Proteins are present in significant concentrations in ICF and in plasma but the ISF level is low. Proteins such as albumin are large molecules which cannot cross membranes except in unusual circumstances. The effect of this is that [H⁺] changes across a membrane cannot be due to movement of protein between the fluids. The phosphate level in plasma is low and regulated by the calcium control system. Transfer of phosphates across membranes could produce acid-base changes but these movements do not contribute significantly to acid base interactions.

This leaves only SID to consider. Strong electrolytes can cross membranes but usually via specific mechanisms such as ion channels and transport pumps. Strong ions can move down or against a concentration gradient. The movement of strong ions can be varied (eg pumps can be activated, ion channels can be open or closed)

So of the 3 independent variables:

- pCO₂: CO₂ crosses membranes very easily and cannot contribute to causing acid-base differences across a membrane
- [ATot]: Proteins cannot cross membranes at all and so cannot contribute to causing acid-base differences
- SID: Strong ions (the determinants of SID) can cross membrane and this transport can be varied.
Conclusion: A change in [SID] alone is the major mechanism by which acid-base differences occur across a membrane as the other two independent variables cannot be responsible.

Important processes involved include Na\(^+\)-H\(^+\) exchange and K\(^+\)-H\(^+\) exchange across the cell membrane.

The kidney is usually said to excrete acid from the body (i.e., if urine has a lower pH than plasma, some net amount of H\(^+\) is being excreted). This is not correct. The kidney certainly has a role in decreasing the [H\(^+\)] of plasma but the real mechanism is different from the conventional explanation. As proteins cannot cross membranes, this decrease in plasma [H\(^+\)] must be due to the kidney causing changes in SID across the renal tubules. The change in [H\(^+\)] is due to differential movement of strong electrolytes (e.g., Na\(^+\), Cl\(^-\), K\(^+\)) across the tubules causing a change in the SID on each side of the membrane: it cannot be due directly to the secretion or absorption of H\(^+\) or HCO\(_3^-\) (or adjustment in any of the other dependent variables). For example in the distal tubule, it is not the secretion of H\(^+\) that causes the pH of the distal tubular fluid to fall but the movement of the strong ion (e.g., Na\(^+\)) associated with the process.

A further example of acid-base interactions across a membrane is that occurring in the stomach. Gastric juice is acidic not because of the transport of H\(^+\) into the stomach but because of the movement of Cl\(^-\) that occurs. Alternatively, if the H\(^+\) was exchanged for a positive ion like Na\(^+\) or K\(^+\) then the SID would be altered by the same amount and again gastric secretions would be acidic. The factor which determines the [H\(^+\)] is the change in SID due to movement of Cl\(^-\) into the gastric juice.

The intracellular pH is altered mostly by control of intracellular SID. The ion pumps regulate concentrations of the various ions and thereby indirectly control the intracellular SID and pH.

The control of [H\(^+\)] in all body fluids is due to changes in the 3 independent variables.

Proteins don't normally contribute much to acid-base interactions because they cannot cross membranes. Most plasma proteins are synthesised in the liver. If protein levels fall (e.g., due to hepatic dysfunction or excretion as in the nephrotic syndrome) this will have predictable effects on acid-base balance. Strong ions are normally absorbed in the gut and excreted by the kidney. What is important is not the absolute concentrations of the individual strong ions, but the total amount of charge which is present on them which is not balanced by other strong ions (i.e., SID). The pCO\(_2\) is under respiratory control. Changes in pCO\(_2\) can cause rapid changes in the [H\(^+\)] of all body fluids.

Changes in SID are very important in controlling transmembrane exchanges which affect the acid-base situation in adjacent fluid compartments.

10.6.2: Acid-Base Disorders

Respiratory acidosis and alkalosis are due to hypercapnia and hypocapnia respectively (i.e., the pCO\(_2\) is the important independent variable in these disorders).
Metabolic acidosis is mostly due to a decreased SID and metabolic alkalosis is mostly due to an increase in SID. However changes in $[A_{Tot}]$ can also cause metabolic acid-base disorders. Hypoalbuminaemia causes a metabolic alkalosis and hyperalbuminaemia causes a metabolic acidosis. An example is the contribution of low albumin levels to the alkalosis associated with cirrhosis or the nephrotic syndrome. An increase in phosphate in plasma occurs in renal failure and contributes to the metabolic acidosis of uraemia. The phosphate level is low in plasma so a drop in phosphate level in plasma cannot contribute to causing a detectable metabolic alkalosis.

10.6.3: Conclusion

The Stewart approach "shows the way to a complete quantitative treatment of body fluids as physico-chemical systems, through numerical solution of the sets of simultaneous equations that describe their acid-base behaviour." (Fencl & Leith, 1993).

This approach is slowly gaining acceptance in research papers and in modeling of the acid-base homeostasis of body fluids. It also provides an insight into the chemical processes that determine the pH of body fluids. The conclusions are often quite different to those of the traditional approach. For example, the traditional approach to metabolic acid-base disorders is concerned with bicarbonate but the Stewart approach emphasises that chloride is the most important anion when causative factors are considered.

So, should we be using this approach?

From anaesthetist.com

- **Quote:** "There is little doubt in my mind that the Stewart approach makes sense, and provides a slightly better model of how acid-base works than does the conventional approach. I believe that Stewart provides a refinement of the conventional approach. Under many, perhaps most circumstances, the 'old-fashioned' approach works fine, but we should be aware of the exceptions (gross volume dilution with fluids which have a low SID; hypoalbuminaemia in association with metabolic acidosis) and invoke the physicochemical approach in these circumstances. This new approach also helps us explain how our therapeutic interventions work."

Much still needs to be done. We need a viable model based on physicochemical principles that can be consistently shown to be as good as or better than the older models. Ideally this model should also extend to assessment of whole blood acid-base status, and even allow us to predict whole-body pH changes in response to therapeutic interventions."

From acid-base.com

- **Quote:** "For most acid-base disturbances, and for the foreseeable future, the traditional approach to acid-base balance seems certain to prevail. For the clinician, the three variables of greatest use are the pH, pCO$_2$, and standard base excess (SBE). What might change this? The answer would have to be published cases where clinical management has been critically improved by using Stewart's approach. Such cases would have to be accumulated, evaluated, and approved before any major switch to his approach seems warranted."

https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Book%3A_Acid-base_pHysiology_(Brandis)/Chapter_10%3A_
An editorial view

- **Quote**: "... it would be premature at present to propound the SID approach. Although it certainly will remain a powerful tool in acid-base research, for clinical management it is more cumbersome, possibly more expensive, and not sufficiently better than a critical assessment of the base excess, anion gap, or pH/pCO$_2$ maps to warrant its widespread adoption. Interpretation of acid-base disorders will always remain partly an art, one that combines an intelligent synthesis of the clinical history, physical examination, and other ancillary laboratory data taken together in the context of the individual patient and the nature and temporal course of his or her disease."