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Concerning Acidification and Calcification of Dialysis Fluid

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Calcification of coronary vessels and heart valves is a well-known serious factor of the high rate of morbidity and mortality of CKD-5 patients. Several important factors will contribute to this severe clinical problem. One of them, the calcification of dialysis fluid, had not really recognized until today.

Homer W. Smiths had recognized the working principle of the acidification in mammalians (1953: "From Fish to Philosopher"). CO_2, produced by the local cells, will transformed by carbo-anhydrase (locally) and transported as HCO_3^- (bicarbonate) by the circulation (heart and lungs) up to the lungs. In the lungs, carbo-anhydrase is working again in order to re-transform bicarbonate back into CO_2 for elimination by breathing. Whenever the pK (6,11) has a bigger difference to the actual blood pH, the high concentration of bicarbonate (24 mmol/l) and the *open system* of the two important organs (lungs and kidneys) will keep the *milieu interieur* (pH of the blood) constant as an *original internal sea*. In this set-up, there is a relation of 20:1 between the base bicarbonate and the acid carbon dioxide. With other words: 5 % of the bicarbonate concentration had shifted into carbon dioxide, *in order to prevent the calcification between bicarbonate, Calcium and magnesium*.

Dialysis fluid with bicarbonate always needed and needs acidification. Several different ways had used for this acidification. The medical precondition was *the elevated bicarbonate concentration* (32 mmol/l) in order to treat the metabolic acidosis (at first by elimination of the anions, at second by buffering), as the treatment-time of dialysis in hours per week was *short* in relation to the time of living one week (168 hours). Alwall had used carbogen gas (5 % CO_2) for the acidification, as this was available in large quantities and not so expensive. The problem: These 5 % CO_2 had fitted for bicarbonate 24 mmol/l. But the bicarbonate of dialysis fluid had 32 mmol/l and so the calcification had introduced.

In 1965, Shaldon and Mion had introduced the buffer precursor acetate into the dialysis set-up. Shaldon had constructed a new dialysis fluid generator with single-pass system and monitoring of conductivity and temperature (bypass valve). This equipment had enabled the dialysis therapy to a much bigger number of patients by the simplicity of this set-up. Shaldon had realized this as home-dialysis. All solutes of dialysis fluid had solved in one can. Because of the *solubility*, Shaldon had replaced bicarbonate by the buffer precursor acetate. He was able to do this, as he had been a qualified *hepatologist*. This acetate set-up has not calcification problem at all. This prescription had used for nearly 20 years in the majority of the dialysis centres. Acetate has transformed by the liver into bicarbonate and CO_2. In the first hour of the dialysis treatment, there was a loss of the patient's bicarbonate (> and by this the patient became more acidotic as at start of dialysis), as the liver needed *time* to transform acetate into bicarbonate and CO_2.

The centre of Tassin (South France, Charras and Laurent) had treated their patients very successful with acetate dialysis for many decades: A big number of 80 years patients for 30 years dialysis and a second group of patients (90 years) for 40 years dialysis. Tassin had used long treatment times (24 hours per week), Na^+ 135 of dialysis fluid and salt intake of 2,0 g per day by own fresh cooking.

Unfortunately, the shortage of dialysis treatment-time had started (Scribner at the first: square metre hours hypothesis). In order to reach a qualified efficacy of the dialysis treatment, the surfaces of the dialyzers and their clearances had strong enlarged. Whenever this shortage of dialysis treatment-time was very popular, this had introduced discomfort of dialysis with the acetate dialysis in the mode of high efficacy (vomiting and instability of the cardiovascular system). With the enlarged clearances, the metabolic capacity of the liver had overrun. That was the reason for the *cry* for bicarbonate dialysis, as it seems much more physiologic. The problem of *calcification* had totally neglected.

The first dialysis generator with bicarbonate dialysis had presented and used for patient's treatment in 1978 (with a second concentrate pump). This bicarbonate dialysis fluid needs immediately acidification. According to the medical pre-concept of 32 mmol/l bicarbonate, 3mmol/l acetate had used. As there was a real calcification of the machine, a descaling manoeuvre for the machine was necessary. Higher concentrations of acetate (4 and 5 mmol/l, in seldom cases 7 – 9 mmol/l) had also used, but patients with COLD (limited lung ventilation, e.g. even patients

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in state of weaning from respirator) developed bigger problems to eliminate these additional CO_2 amounts. The dialyzer is well working in gas exchange, so the additional CO_2 from the dialysis fluid will come into the blood compartment. COLD patients cannot eliminate this additional CO_2 amount, as they have problems to eliminate their own amount of CO_2 of their body. By this, the calcification of the patient had introduced and nearly nobody had noticed this.

There are two set-ups of bicarbonate dialysis with *no calcification at all*. The first is the AFB (Acetate free Biofiltration) by Bené, developed in 1990. - This is a NaCl-Dialysis (with no buffer), where the acidification will done by the elimination of the patient's own bicarbonate. And at the venous expansion chamber, a bicarbonate infusion (as low-volume HDF in the mode of post-dilution) will be given to the patient in a dosage a little higher in comparison to the loss of bicarbonate by the dialyzer. The AFB treatment needs a monitor with special pre-sets. – The second way of bicarbonate dialysis *without any calcification* is the way of acidification with citric acid (0,85mmol/l). This had presented in 2000 by Riley (ART group). This prescription had introduced to work antithrombotic in order to replace the RCA (Regional Citrate Anticoagulation). But this concept failed totally in the target, when used as the single principle of anticoagulation. Later on, the main effect of the citrate anticoagulation (prevention of the calcification of the dialysis fluid, done by the chelate binding of citrate to disguise the problematic cat ions of calcification, Ca^{++} and Mg^{++}) and the side effect co-working to anticoagulation (reduction of heparin dosage up to 50 %) had recognized. In 2012, a second prescription had developed with 1,0mmol/l (and *no* further mini acetate (0, 3 mmol/l) by Gambro). Both set-ups (0,85mmol/l citrate + 0, 3 mmol/l acetate (ART) and 0, 3 mmol/l citrate (Gambro)) will produce the same CO_2 amount as the classical bicarbonate acidification with 3, 0 mmol/l acetate. But with both, there is the second principle of working inside, the chelate binding of citrate (> disguising Ca^{++} and Mg^{++}) in order to prevent the calcification. The majority of papers dealing with citrate acidification had only investigated *the side effect* of anticoagulation, the reduction of heparin. The main effect of citrate acidification, the prevention of calcification, had often *not well understood.* - The one and only point to consider, when working with citrate acidification, is to elevate the Ca^{++} concentration a little, as a part of citrate will reach the patient's blood compartment and will bind a smaller amount of patient's Ca^{++}. This is the working of the side way (> reduction of the heparin dosage).

Dialysis concentrate is by law a *medical product*. This means in short, that it requires the CE mark of the producer and the approval. When this has fulfilled, there will *never* be vigilance or a follow-up in case of a medical problem! The Medical Authorities for medical products (e.g. FDA Dep. Medical Products (US) or BfArMInstitut (Germany)) has casted with medical doctors, who are unable to evaluate a problem of chemical solubility in this case. There are other well-known problems with medical products with no vigilance (e.g. silicon of roadworks for breast surgery, metallic hip replacements (either mechanical breaking or metallic ionic efflux) or haemolysis by kinking or thrombosis of dialysis systems). Clearly spoken: At first, a material specialist will be necessary in the state of the approval of a medical product. This specialist must advise the medical doctors. At second, vigilance will need for the medical products. At third, the ministry of health should conducted by a medical doctor with the discipline medical health of the people. The actual boards of the Medical Authorities for medical products should send into *happily retirement* - because of *medical problems* (of the concerned patients . . .)

In conclusion, time is up to stop the calcifying dialysis fluid by shifting to citrate acidification. As the Medical Authorities do not interfere, so the single medical doctor will kindly asked to do this. It seems to me, that in case of medical products *nearly everything will allow . . .*

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