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Plea for an Air-Microbubbles and Air-Blood Interface Free Hemodialysis

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1. Abstract

Air microbubbles are common in the haemodialysis venous return line, especially in the very first minutes of HD session and with high blood flows. They might be damaging for the lungs microcirculation and stimulate the inflammation system. The origin of air microbubbles is discussed here and practical solutions are proposed to minimize them. We also focus on the venous bubble trap design: turbulence in this chamber not only contributes to passing air microbubbles but the permanent air-blood interface also directly stimulates the coagulation cascade. To correct this, we propose a modified venous chamber, without direct air-blood interface; we witness a long very positive experience using this type of chamber, especially in ICU patients with anticoagulation contraindication. These combined improvements can reduce the dialysis associated complement and coagulation systems stimulation. They do not entail significant additional costs for the bloodline manufacturer and do not require additional efforts from the user.

Haemodialysis (HD) stimulates several complement and inflammation activating pathways. This originates from the dialysis membrane material, dialyser design, sterilizing method of disposables, dialysate composition [1] and dialysate bacterial and endotoxin contamination [2]. To this classical list, we want to add the air microbubbles and air-blood interface interactions, on which we focus here because this problem is largely ignored and can be solved.

2. Origin of Air Microbubbles

Air bubbles can be life threatening after scuba diving decompression [3] or during cardiopulmonary bypass for open heart surgery [4]. These are usually single time accidents.

By contrast HD sessions are periodic (usually thrice-weekly) and microbubbles in the HD circuit are common. They can be precisely measured by non-invasive pulsed ultrasonic Doppler bubble counter. So, it has been shown that a variable, low amount of air microbubbles passes, unalarmed by the air detector, through the venous return line [5-9]. This may, at first look, seem clinically innocent [10], as it was supposed that air microbubbles are quickly absorbed [11], by adhesion to the blood cells in an extremely thin layer and subsequently cleared by the lungs. However, the adsorption depends of their size: for a microbubble of 100 µm for example this requires 100-600 seconds, but the larger the microbubble size the longer the process [12]; thus, with conventional blood flows, adsorption is far too slow to be significant and nearly all microbubbles pass through into the HD patients body. Technically, dialysis machine air detectors alarm for air bubbles with a diameter >200 µm; detectors cannot be made more sensitive because they would then continuously alarm, making HD impossible [10].

Wagner et al. recently measured the number of microbubbles whose diameter range from 10 up to 500 µm. Measurements were performed in the venous return line, thus after passing through the venous bubble catcher [13].

The figures ranged from 17 to 117 microbubbles per minute [13]; they originate from different sources and are the highest at the beginning of HD session [6,13-15], when the negative arterial pressure is high or when blood flow is high (the last two being usually correlated) [5,13-17] and when the blood level in the venous bubble trap is low [14-18].

3. Biological Effect of Microbubbles

It has been demonstrated that air microbubbles activate the complement system: plasma of 34 healthy individuals was incubated with air bubbles and complement activation measured [19]: anaphylatoxins C3a and C5a were generated in each test but the levels varied substantially between individuals. This was confirmed in another study [20], showing in addition that complement activation was air bubble dose-dependent and variable over the duration of the test.

The effect of blood flow rate on complement activation and leucocyte activation in HD patients has also been measured [21]; anaphylatoxin level was higher with a high blood flow (400 ml/min) compared to a low blood flow (200 ml/min); the authors concluded that a higher blood flow could possibly reduce biocompatibility, perhaps due to more intensive blood-membrane contact. But, as previously mentioned, higher blood flows also entail greater microbubbles. We hypothesize this might be the reason for this association.

The importance of complement and leucocyte activation in HD has attracted attention for decades [22], as an important index of biocompatibility; indeed, the activation of leukocytes generates inflammation and stimulates C-reactive protein, a strong biomarker of cardiovascular disease, the first cause of patient mortality in HD. This is why the original cellulosic based membranes were improved, or replaced by synthetic membrane dialysers, with a better biocompatibility.

In HD, we also face another, more stringent problem with microbubbles: the Umea group (Sweden) reported that air microbubbles disturb blood circulation in the lung capillaries (and also in other organs) of HD patients; they found pulmonary micro-emboli in the organs of deceased HD patients, with coagulation around the air bubbles [23-25]; these air bubbles activate the complement, the coagulation and inflammation cascades, as explained by Barak et al. [11].

4. Effect of the Air-Blood Interface

The air-blood interface in the venous bubble catcher also stimulates coagulation; this is frequently overlooked. In 1995, at the Cliniques universitaires Saint-Luc (UCL) in Brussels, we modified the venous blood chamber used in ICU patients on Continuous Veno-Venous Hemofiltration (CVVH) at high bleeding risk: the blood inlet was brought 2 cm lower than usual, keeping the level 1 cm higher than the inlet (see illustration in Figure 1). Blood sedimentation is quite fast and results, after a couple of minutes, in the formation of a layer of plasma at the top; this acts as a barrier between air and blood. Because plasma is free of platelets, this helps preventing clotting. Our results were rewarding with prolonged treatments before coagulation of the venous chamber did occur; this is in agreement with the literature stating that the complement and the coagulation systems interact [26]. After this positive experience, this principle was extended to maintenance dialysis patients. This principle offers several advantages, cited at the left hand side of this modified chamber in Figure 1. The cost of these lines was identical to that of standard blood lines (gently manufactured by a small competing company!).

Similar positive results were reported with the NxStage Streamline air-blood interface free bubble catcher, allowing a 33% reduction in heparin need [27].

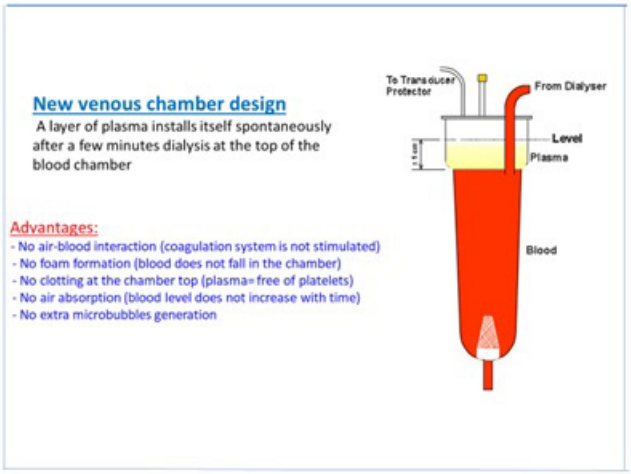

Figure 1: Alternative venous chamber without direct air-blood interface

5. Microbubbles Prevention

First, the microbubble air leakage at the arterial luer-lock connector should be tightened: Wagner et al. (13) detected in the arterial line 2 air microbubbles per min. upstream of the luer-lock connector compared to 46 downstream from it; the higher the negative arterial pressure, the more microbubbles are detected and vice versa (vide supra). How can this leakage be explained? In practice, when technicians connect two gas pipes they always use a seal, avoiding any leakages. However, in dialysis, the two connecting parts of the luer-lock connection are made of hard plastic without seal. Their air tightness relies on the contact surface smoothness and the strength with which the male part of the connector is pushed into the female one, and, in practice, the screwing force varies between nurses and also for the same nurse from day to day. We do not see any blood leakage at the venous luer-lock connector (positive pressure) whereas at the arterial luer-lock side, a variable amount of air microbubbles is sucked into the patients' bloodstream, due to the negative pressure. This is explained by the more than 200 times higher viscosity of blood compared to air: 4 versus 0.018 centipoise, respectively [28]. Even with a low haematocrit, this difference is high. Subsequently, within the blood stream, microbubbles get stuck in some of the dialyser fibres, contributing to clotting, but most of them pass through the whole dialysis circuit into patients.

Another point of concern is that the inspired microbubbles originate from the non-sterile environment air in the dialysis ward where air contaminants vary [29, 30]. Fortunately, the luer-lock

leakage opening is smaller than the mazes of a bacterial filter and air bacteria and fungi cannot pass through. But, after dialysis, they can remain accumulated at the entrance of the female part of the luer-lock, which could contribute to the infection threat associated with permanent catheters [31]. This is one more reason to develop an air-tight luer-lock connector! This can for example simply be obtained by moulding this connector with a little lower plastic hardness score. This would also avoid the luer-lock from being stuck upon disconnection. Solving this problem will ensure a better preservation of the dialyser clearance and less blood loss after disconnection.

Second, the air microbubble generation and blood-air interaction in the bubble catcher should be avoided: when the blood stream falls in the bubble catcher, it mixes with some air present in the chamber top: a very small fraction of it is conducted with the stream because the lifting force of micro bubbles is lower than the driving force of the blood stream. This problem is worst with a low blood level in the venous chamber (vide supra) or with a high blood flow, that increases turbulence (see above). The already discussed air-blood interface free venous chamber (Figure 1) also solves this problem and, in our hands, was associated with less clotting in CVVH patients in the ICU at high bleeding risk and with a 33% heparin reduction with the Streamline (NxStage) option [27]. This further results thus in some savings in heparin expenses. We have an experience of over 100,000 acute and chronic dialysis sessions using this improved venous chamber without any negative side effect.

Third, all air bubbles should be rinsed out of the dialyser capillaries during priming: the dialyser capillaries are in parallel position. In theory, all capillaries should be simultaneously and equally filled (principle of communicating vessels) during the slow priming with the venous outlet upside. But, in practice, this seems not to work perfectly, although it is not clear why. As soon as the capillaries are filled, saline takes the pathway with the lowest resistance, i.e. through the central fibers, while in some other fibers air bubbles remain. Using a higher priming saline volume is of little help. Blood, compared to saline, has a much higher viscosity with a much higher pressure drop over the dialyser, thus at the beginning of the dialysis session, residual air micro bubbles are rinsed out of the fibers. This explains why more micro bubbles were detected at the beginning of dialysis compared to later on and why wet stored dialysers entail less micro bubbles [17]. However, it is possible to solve this problem during priming: after the venous chamber is primed, a short phase of back filtration, with some 200-300 ml, is helpful: this entails positive dialysate pressure and the flux is identical for each capillary and, in this way, residual air is removed out of all capillaries. Perhaps the ultrafiltration controller could facilitate this. For this, it is recommended to dispose of ultra-pure dialysate, which is anyway the preferred option, as it has the potential to decrease inflammation [2].

It is obvious that any other air microbubble infusion in the negative pressure zone of the arterial line should also be prevented: the connector of the negative arterial pressure line to the dialysis machine should fit tightly, the blood line connection sites should be carefully closed and the heparin line, if not used, clamped and made airtight, using a plastic clamp [5].

6. Conclusion

Technical aspects of HD interfere with the complex medical care of HD patients. In this paper, we focused on the sources of air microbubbles and their health effects; we also discussed the air-blood interface and its clinical relevance: both activate the complement system. We propose practical solutions for a microbubbles and air-blood interface free dialysis, without increasing the nurses workload. Our proposals do not entail additional significant costs. Renal professionals could help convincing dialysis companies to offer this new progress in renal care.

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