The Sympathetic Nervous System in Chronic Renal Failure

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Diseases of the cardiovascular system contribute significantly to the morbidity and mortality in patients with chronic renal failure (CRF) on hemodialysis treatment. Hypertension is the basis of cardiovascular disease in the majority of dialysis patients. The etiology of high blood pressure in CRF patients is multifactorial. Hypervolemia and activation of the renin angiotensin system (RAS) are well-recognized important determinants of high blood pressure. It has been recognized over the last 30 years, that CRF represents a state of overactivity of the sympathetic nervous system and that hypertension in patients with end stage renal disease may be maintained by an inappropriately high level of sympathetic activation. The issue of sympathetic overactivity in CRF has been the topic of a recent excellent review by Koomans et al.

Physiology of the sympathetic nervous system

The autonomic nervous system occupies a central position in the normal regulation of the cardiovascular system. This is achieved principally through the effects of the sympathetic nervous system (SNS) on the function of the heart, large arteries, arterioles, veins, and the kidneys. The parasympathetic nervous system, through vago nerve regulation of the heart rate, plays a subsidiary role. The role played by circulating catecholamines secreted by the adrenal medulla in cardiovascular regulation in general, and blood pressure control in particular, is a contentious issue.

Norepinephrine (NE) is the main neurotransmitter of the SNS. NE binds to postsynaptic alpha- and beta-adrenergic receptors. Among other actions, alpha-adrenergic receptors mediate vasoconstriction and beta-adrenergic receptors mediated increases in heart rate, inotropy and peripheral vasodilatation. A feedback loop involves presynaptic adrenergic receptors. Genetic variants of the beta-2 adrenergic receptors have been linked to essential hypertension.

The influences of the SNS on normal cardiovascular control are both short- and long-term. Examples of the short-term sympathetic nervous circulatory control are the neural modification of venous capacitance, arteriolar resistance, and heart rate with upright posture and the regulation of regional blood flow. In healthy subjects, long-term circulatory control involves in particular the regulation of salt and water balance through the effects of the SNS on renin secretion and renal tubular reabsorption of sodium.

Schemes of the organization of circulatory control rightly emphasize the preeminence of reflex blood pressure homeostasis. This is achieved, on the afferent side, through arterial and low-pressure receptors, with reflex outputs to the heart, resistance vessels, capacitance vessels, and the kidneys. Afferent and efferent signals integrate the kidneys into sympathetic control. The central nervous system (CNS) integration of high-pressure baroreceptor influences involves, in particu...
lar, the nucleus tractus solitarius of the brainstem, while volume receptors project to the locus coeruleus. Efferent sympathetic activities in humans adjust accurately and appropriately with change in arterial pressure. There exists a precise relationship between sympathetic nervous response and the magnitude of pressure change. A fall in arterial blood pressure results in an activation of the sympathetic nervous system with a consecutive rise of heart rate and heart inotropic action of the sympathetic nervous system with a consecutive rise of arterial pressure. There exists a precise body chemoreflex, leading to sustained sympathet-

Methods for clinical testing of the SNS

Activity of the SNS can be studied by mainly three techniques: biochemical methods (static measurements of plasma norepinephrine NE concentration; measurements of NE spillover rates), microneurography in sympathetic muscle nerve fibres, and power spectral analysis of heart rate and blood pressure variability

a) Biochemical methods:

Static measurement of plasma NE concentra-
tion provides a useful global guide to SNS function, although limitations have to be kept in mind. One technical weakness is the dependence of the plasma concentration on the rate at which the transmitter is removed from plasma, after its overflow to the circulation, and not only on sympathetic nerve firing and NE release. Since plasma NE is a global index of SNS activity, it does not provide information on regional pattern of sympathetic activation. NE release can be studied using radiotracer-derived measurements of the appearance rates of NE in plasma, from individual organs or from the body as a whole. This method provides useful insights into the regional sympathetic innervation. Its major shortcoming is the complicated technical setup, which requires infusion of radiolabelled tracers.

b) Microneurography:

Microneurography was first developed in the 1960s and is a method for intraneural recording of sympathetic activity in conscious humans. The method requires the percutaneous insertion of tungsten microelectodes into a peripheral nerve (generally the peroneal or radial nerves are used) to record multi-unit sponta-
neous post-ganglionic sympathetic action potentials. This technique allows the measure-
ment of sympathetic nerve traffic targeted to the skeletal muscle circulation (muscle sympa-
thetic nerve activity, MSNA). The method is remarkably safe and well tolerated but it requires advanced technical expertise, there-
fore the availability of MSNA measurements is limited.

c) Power spectral analysis:

Power spectral analysis is a computer-based technique that quantifies the variability in hemodynamic parameters. Power spectral analyses of heart rate variability indicate that fluctuations are not random, but exhibit peri-
odicities of fairly constant frequency. The first component is synchronous with respira-
tion and occurs at relatively high frequency (0.15–0.4 Hz). The second component is identified as low frequency (0.1 Hz). The high-frequency variation in the R-R interval reflects vagal activity; the low-frequency component reflects predominantly sympathetic activity. By evalu-
ating the relative preponderance of these two components, it is possible to estimate the level of vagal and sympathetic activation in humans at rest of during activity. A rise of the low fre-
cuency/high-frequency ratio is consistent with greater sympathetic activation. The sympathet-
ic activity is perhaps better reflected in the beat-to-beat variability of diastolic blood pressure. This reflects the application of the method since continuous beat-to-beat blood pressure mea-
surements are necessary. A continuous beat-to-
beat hemodynamic monitoring including blood pressure can be done with the Task Force Monitor.

Evidence for increased SNA in CRF and hemodialysis patients

The first indications pointing towards an increased sympathetic nerve activity in CRF came from measurements of elevated plasma cate-
cholamine concentrations in the late 1970s. In 1992 Converse et al found by measurements of MSNA that the basal level of sympathetic firing was more than doubled in hypertensive hemodialysis patients compared with age-matched healthy normotensive volunteers with normal renal func-
tion. The individual firing rates were remarkably stable throughout the interdialytic period. Detailed studies of the baroreceptor function sur-
prisingly demonstrated a normal function in patients treated with hemodialysis. An increased MSNA has been found in many types of human hypertension (renovascular hypertension; malign-
ant hypertension; pre-eclampsia; hypertension associated with obesity and hypercapnia), renal disorders (human polycystic kidney disease, par-
tial renal ablation and other animal models of renal disease), smoking, obesity, and sleep apnea.

Origin of increased SNA in CRF

Signals arising in the failing kidneys seem to mediate sympathetic activation in CRF. Bilateral nephrectomy normalizes the increased SNA in dialysis patients and after renal transplantation. These observations point towards the kidneys as the origin of increased SNA, with renal ischemia being the main factor. The kidneys are normally richly innervated not only by sympathetic efferent fibers but also by sensory afferent fibers that signal the CNS of chemical and mechanical changes in the kidney and the renal pelvis. The local accumulation of adenosine in oxygen-depleted renal tissue may play a prominent role. These signals travel via renal nerves to the brainstem and increase the central sympathetic outflow. Consistent with this hypothesis is the observation that selective renal deafferentation ameliorates the increase of SNA in animal models of renal hypertension.

Angiotensin II (A II) can stimulate SNA by a direct effect of the vasomotor center in the brain stem. In addition, A II increases the NE release at the adrenergic nerve terminal and inhibits the presynaptic re-uptake of NE.

It is unclear whether a decrease in nitric oxide (NO) availability contributes to sympathetic hyperactivity in CRF. NO is known to normalize 
neurons after successful renal transplantation, making uremic toxins as triggers of sympathetic overactivity less likely. Stimulation of carotid chemoreceptors could increase SNA, because dialysis patients tend to be mildly acidotic and sleep apnea is highly prevalent in the dialysis population. It may sensitize the carotid body chemoreflex, leading to sustained sympathet-
ic overactivity and hypertension.

Detrimental effects of sympathetic overactivity

Cardiovascular disease is highly prevalent among patients with ESRD and is responsible for the increased mortality in that population. Hypertension plays a key role in the development of cardiovascular complications. Traditionally, hypertension in dialysis patients has been viewed as being largely volume-dependent. There is now mounting evidence that sympathetic hyperactivity contributes significantly to the generation and maintenance of hypertension in hemodialysis patients. In CRF an increased vascular resistance with an inappropriate normal cardiac output suggests that either impaired vasodilator mechanisms or augmented vasoconstrictor mecha-
isms play an important role in the pathogenesis of high blood pressure. Besides blood pressure ele-
vation, a tonic increase in sympathetic outflow causes functional and structural alterations at the myocardium, large arteries and the kidneys. Sympathetic overactivity may promote cardiac arythmias, increase myocardial oxygen demand, induce left ventricular hypertrophy and reduce the compliance of the large arteries. Interesting ob-
servations point towards relationships between the sympathetic nervous system, inflammatory and pro-coagulatory pathways.

The deleterious effects of sympathetic overac-
tivity have been convincingly demonstrated in a landmark study by Zoccali et al. in a cohort of 228 patients undergoing chronic hemodialysis. In these patients the plasma concentration of norepinephrine (NE) was used as a measure of sympa-
thetic activity. In a multivariate Cox regression model that included all univariate predictors of death as well as the use of beta-blockers: plasma NE proved to be an independent predictor of fatal and nonfatal cardiovascular events. The adjusted relative risk for cardiovascular complications in patients with plasma NE concentrations above the 75th percentile of the study population was 1.9 times higher than in those below this threshold.

How to fight sympathetic hyperactivity in CRF?

Sympathetic hyperactivity can be blocked at several levels: adrenergic receptor blockers bind to either alpha and/or beta adrenergic receptors. Alpha-blockers, such as prazosin and doxazosin can be used effectively in patients with CRF. Alpha-blockers may increase the rate of intradia-
lytic hypotension and their use has been associated with a higher risk of stroke and combined cardio-
vascular disease (Antihypertensive and Lipid-
Lowering Treatment to Prevent Heart Attack Trial; ALLHAT).

Beta-blockers have been shown to reduce mortality in patients with coronary artery disease or congestive heart failure. There have been no prospective randomized studies on beta-blockers in dialysis patients, though a prospective observa-
tional study did suggest a benefit of beta blockers in diabetic dialysis patients. Beta-blockers can be used safely in dialysis patients by applying a moderate dosage. In a prospective randomized trial examining the potential impact of beta-blockers on cardiovascular mortality in hemodialysis patients is very much needed.

Centrally acting sympatholytic drugs have been shown to reduce sympathetic overactivity. The older drugs of that group are clonidine and alpha-methyldopa. The newer selective I1 imidazo-
line receptor agonists (which may also have a central alpha-2 receptor agonistic mode of action) 

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Diffusion

It has been speculated that systemic anticoagulation is caused by diffusion of heparin from the catheter lumen. The author has pointed out that diffusion would take many days to clear a few mm of catheter length from heparin. The reply to this statement was “We are not dealing with a semipermeable membrane. We are dealing with a direct connection to the systemic circulation. Hence, diffusion distance is zero.” This discussion as well as a paper published recently shows that some information about the physical processes of diffusion and convection may be useful for the understanding of the processes leading to the spilling of lock solution from the catheter.

One hundred and fifty years ago Adolf Fick published the paper “Über Diffusion” (about diffusion) describing quantitatively the process of mass transport by diffusion. One hundred years ago Albert Einstein published the thermodynamic interpretation of diffusion (translated title: “On the Motion—Required by the Molecular Kinetic Theory of Heat—of Small Particles Suspended in a Stationary Liquid” ). Both papers are written in German and are theoretical papers. The paper published by Thomas Graham 1861, however, not only introduced the word “dialysis” for diffusion through a membrane but also described experiments about diffusion that are still enlightening today: He filled a cylindrical vessel (jar) with water and transferred the liquid to be diffused to the bottom of the jar. After four to fourteen days he removed and analysed layers (strata) consecutively from the top and analysed the content. Each sample contained 1/16 of the total volume. Figure 1 shows original data from Graham and an exponential fit to data. Hatched column = concentration at start. Each stratum ~8 mm.

As we can see, diffusion can be excluded as effect that causes significant mass transfer from the catheter lumen within the interdialytic interval.

The relevant effects that cause spillage of catheter locking solution are the Hagen-Poiseuille velocity distribution and gravity which causes convective exchange of fluids with different densities.

Diffusion can be excluded as effect that causes significant mass transfer from the catheter lumen within the interdialytic interval.

Velocity distribution during injection:
The catheter is basically a long, thin tube with a length to diameter ratio of > 80. Unlike flow in canulas used for blood access with fistulas or grafts flow in catheters is laminar. The flow velocity in cylindrical tubes under laminar flow conditions has been derived by Hagenbach. Integration leads to the well known Hagen-Poiseuille equation describing pressure drops as function of flow, diameter and length of the tube and, fluid viscosity. Hagenbach used Poiseuille’s data to corroborate his derivation which was based on reasoning. The flow velocity changes with the square of the radius:

\[ \frac{v}{v_0} = \frac{R_0^2 - r^2}{R^2} \]

Equation 1: Laminar flow velocity distribution

Equation 1 is the equation of a parabola with \( v = \text{velocity, } v_0 = \text{mean velocity, } R = \text{radius of the tube, } r = \text{distance from the tube axis.} \) This parabolic velocity distribution is shown in figure 2 together with a velocity profile for turbulent flow. Because the cross-section of the fluid path is small close to the center and maximal close to the wall the flow distribution maxima are not in the center of the tube but between the center and the wall which is shown by figure 3.

In Internet discussions it was speculated if injection time would change the amount of spillage (The fraction of the heparin that goes to the circulation will vary depending on the speed of injection of the heparin.). In patents, it was speculated that increasing viscosity would reduce spillage. As we see from equation 1, the velocity distribution is neither dependent on speed nor on viscosity as long as the flow is laminar.

Up to 25% of the catheter filling volume is spilled out at time of injection due to the laminar flow parabolic fluid velocity profile.

The flow velocity distribution changes from laminar to turbulent at Reynolds numbers (equation) of ~2200. With \( d = \text{tube diameter, } \nu = \text{fluid velocity, } \rho = \text{fluid density, } \eta = \text{fluid viscosity and } q = \text{flow speed.} \) We can calculate the injection time at which the flow profile would change. For low viscosity solutions as normal saline or heparin with a viscosity of 0.8 mPa.s the limit flow speed for 2 mm inner diameter catheters is ~165 mL/min equivalent to an injection time of less than 0.5 sec for 1.2 mL which is unrealistically short. Increasing the viscosity would require an even higher flow speed for creating turbulent flow.

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Figure 1: Diffusion of sodium chloride at 10°C. Concentration distribution after 4 days. Full circles = data from T. Graham, Table III. Line = exponential fit to data. Hatched column = concentration at start. Each stratum ~8 mm.

Figure 2: Velocity distribution for laminar flow (full line) and turbulent flow (dashed line).

Figure 3: Flow distribution for laminar flow (full line) and turbulent flow (dashed line) as function of the radius.
Neither injection speed nor fluid viscosity will change spillage during injection.

Spillage of catheter locking solution was tested in injection experiments published recently. The tests were done with catheters connected to an implantable blood access port. The results showed that ~16–20% of the locking solution was spilled when a solution volume equal to the filling volume was instilled. In these tests the concentration at the catheter tip was measured by squeezing the catheter and collecting the first drop coming out of the end. The concentration in this drop was ~90% of the nominal concentration. The results corroborate the finding that the theoretical results reported above represent an upper limit for locking solution spillage for catheters with constant inner diameters (e.g., simple tubes).

**Spillage caused by gravity**

Several years ago, I recognized spillage from side holes and the end of the catheter when this catheter was dipped into water. Further investigation led to the conclusion that this spillage was caused by density differences between the locking solution and water. In another work, finished recently spillage from the catheter was measured for different density differences and viscosities. Also, injection time was changed in one test from 2–3 sec to 23 sec. The results can be summarized briefly: Injection of a volume equal to the filling volume of a cylindrical catheter causes immediate spillage of 20%. Small density differences (0.1%) cause spilling by gravity. This spilling either follows spilling caused by injection or takes place passively when the pre-filled catheter is dipped into fluid. Spillage up to the highest point in the system is complete after a few minutes, with high viscous fluids (50–60 times the viscosity of water) complete loss takes 50–100 minutes. The photo series shows the events (1 to 7). The photos were taken with the test “catheter” and test fluid “water + red dye” described in. In brief: The test fluid consisted of 1 g/dL of a red dye (Basovit red) mixed with water. The glass vessel used for the photo series contained demineralized water. The tests were done at room temperature and the density of the red dye fluid was less than 0.1% higher than water. A PVC (Polyvinyl Chloride) tube with 2.2 mm inner diameter and 565 mm length (filling volume ≈ 2.2 mL) was used as catheter. This tube was guided by a vertical positioned brass tube.
One end of the tube was positioned ~1 cm below the water surface. The other end was fitted with a luer connector and a clamp. Water was aspirated with a syringe and the clamp closed. This syringe was replaced by a 2.5 mL syringe filled with red-dye fluid. The photo series was started (~2 pictures per second at VGA resolution), the clamp opened and the red-dye fluid injected within 2–3 seconds (photos 1–3). The second photo series was taken manually. The catheter was pre-filled with red-dye fluid, a photo was taken (photo 4) and the catheter was slowly lowered until the tip was below the surface (photo 5). Spillage was observed and photo were taken every few seconds. Photo 6 shows the accumulation of locking fluid at the bottom with spillage still going on.

**Locking solutions with densities higher than blood density will spill out under the influence of gravity.**

When locking solution flows out of the catheter, the lost fluid volume must be replaced by an equal volume of fluid from the vessel or beaker. This is shown by photo 7. A clear, highly viscous fluid in the tube is replaced by colored water from the beaker. This light colored fluid will eventually rise to the highest point of the catheter, usually a bend. The dense fluid will remain on the other side of the bend.

The effects shown by photos 4 to 7 are caused because the locking solution density is higher than water density. These effects can not be observed if the density of fluid in the tube is lower than the density of the fluid in the beaker.

The density of blood is ~1.05 g/mL and the density of 25000 IU/mL Na-heparin is 1.015 g/mL at room temperature which means that the heparin solution is lighter. Does this mean that heparin stays in the catheter? Patients usually lay down in the interdialytic interval and this will allow spillage of heparin by gravity. This has been demonstrated by another experiment and documented by a photo. By repeating the experiment of Moore and Twardowski18, I have observed that a dense fluid will immediately settle below a less dense fluid in a capillary. When the capillary is rotated into horizontal position, the dense fluid will again be at the bottom of the new horizontal capillary. If the capillary is slightly rotated an easily observable interface between dense and less dense fluid is established if one of the fluids is colored. In this experiment, PVP iodine (density =1.07 g/mL) was used. The high density colored fluid and heparin (5000 IU/mL), density ~1.007 g/mL was the low density clear fluid. The capillary was filled and kept closed on one end.

Photo 8 shows the interface between both fluids at a slightly tilted angle. Further tilting produces a horizontal fluid level and again further tilting results in exchange of the fluid position. The more dense fluid always flows to the lower position.

**Spillage of less dense locking solution will take place when the patient lays down.**

If gravity causes spillage of locking solution within a few minutes or hours why was heparin still in the lumen after treatment? Catheters have clamps outside the body. Immediately after injection of the locking solution these clamps are closed and the catheter is capped. No locking solution can be lost from this portion of the catheter. Because, with the exception of concentrated (47%) citric acid (density at room temperature ~1.18 g/mL), locking solutions used clinically are less dense than blood, only part of these solution may spill out if the patient does not lay down horizontally. Also locking solution between the catheter connector and the catheter bend will normally not spill out because this would require tilting of the patient in a position with head down.

Recently, antimicrobial or antibiotic locks have been used successfully for catheter infection prophylaxis19. This corroborates the hypothesis that infections are mostly caused by contamination of the catheter connector: The antimicrobial lock is protected from spillage at the connector site because of the clamps, as described above. In the proximal part of the catheter, spillage of the locking solution may increase the likelihood of clotting5.

**Thixotropic locks**

A solution for the spillage problem has been found by the author and tested in the laboratory20: The thixotropic gel-lock.

The viscosity of conventional (“Newtonian”) fluids is independent of shear which results in a parabolic fluid velocity distribution which has been discussed above. Shear is proportional to the rate of change of the fluid velocity. Laminar flow in cylindrical tubes (figure 2) results in maximal shear at the wall and zero shear in the center.

The viscosity of thixotropic fluids depends on shear: It is maximal without shear and decreases with increasing shear rate. Many thixotropic fluids (mostly gels) are now used in daily life: Hair gel, skin lubricants, toothpaste. For tests I have injected diluted hair-gel: Injection resulted in plug-like flow without spillage. With the end of the catheter dipped in water only minute amounts of the colored thixotropic lock dissolved slowly.

**Thixotropic gel locks do not spill out during injection or by gravity and dissolve only slowly afterwards.**

The thixotropic lock would never be injected into the patient under normal condition. Medical devices, however, must be safe in case of foreseeable user errors. A foreseeable user error is, e.g., over injection or double injection into the same lumen21. For this reason, the lock material must be biocompatible. Gels of this kind are used for many other clinical application and an appropriate gel has been identified with the help of a specialist. The thixotropic gel when injected into fluid through the catheter does not dissolve immediately. In the clinical setting this may result in embolization of the lung. The hazard related to such events depends on the size of the embolus and the time it takes to dissolve. Packing the lock solution in vials or syringes with volumes of 3 mL or less would limit the risk to the injection of 3 mL in case of double injection. The safe limit for air injection has been estimated to be 5 mL for a 50 kg patient with a patent forearm ovale in the heart22. During mechanical thrombolysis of clotted grafts lung emboli have been reported even under normal condition22. Air emboli are clearly within

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**Photo 8 (4551):** In a closed capillary partially filled with a dense colored fluid and a less dense clear fluid the dense fluid will flow to the lower portion of the capillary if the capillary is rotated.

**Photo 9 (5737):** Catheter tip before injection of thixotropic gel lock.

**Photo 10 (5738):** End of injection

**Photo 11 (5740):** 4 sec after previous photo. Gel dissolves slowly. The thin tracing is hardly visible.
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moxonidine and rilmenidine are today preferred because of less adverse reactions. Moxonidine has been shown at a regular dose of 0.4 mg/day to reduce sympathetic overactivity. Currently, moxonidine is used in daily doses of 0.2 to 0.6 mg in the treatment of hypertension. Higher doses (1.8 to 6.0 mg/day) were associated with increased mortality in the MOXCON trial. Rilmenidine may be used in dialysis patients at a dose of 1 mg three times a week. Interestingly, despite its sympathicolytic activity rilmenidine preserves sympathetic responses during mental stress and tilting, with the latter underlining a freedom from postural hypotension on the drug[6]. This aspect may be of relevance for the sympatholytic treatment of hemodialysis patients prone to intradialytic hypotension. In our experience the low-dose use of moxonidine and rilmenidine[11] in patients with CRF is safe. No prospective data on the impact of centrally acting sympatholytic agents in patients with renal insufficiency are available. Since there is a strong rationale for the use of these drugs in CRF, prospective trials should be undertaken. It may be worthwhile to use technologies allowing the determination of sympathetic activity in trials with sympathicolytic inhibitors.

ACE inhibition and AT1 blockade interferes with the central sympathicolytic actions of AII and lowers sympathetic overactivity in CRF patients. Both the ACE inhibitor enalapril[12] and the AT1 receptor blocker losartan reduce sympathetic overactivity, but neither drug normalizes MSNA completely. Preliminary data have shown that daily short dialysis or nocturnal long dialysis reduce MSNA when compared with thrice weekly conventional hemodialysis[13]. Treatment of sleep apnea is an additional means to reduce sympathetic overactivity.

Conclusion

Patients with CRF and patients undergoing hemodialysis treatment show a sustained overactivity of the sympathetic nervous system, which originates from signals rising in the failing kidneys and travelling via afferent renal nerves to cardiovascular centers in the brainstem. The sympathetic overactivity contributes to hypertension and cardiovascular morbidity and mortality in that patient population. Adrenergic receptor blockers, centrally acting sympatheticolytic drugs such as moxonidine and rilmenidine, ACE inhibition and AT1 receptor antagonists, can reduce sympathetic overactivity. Daily short hemodialysis and long nocturnal hemodialysis may reduce elevated sympathetic activity as well. Prospective trials examining the potential impact of beta-blockers and centrally acting sympatholytic drugs on cardiovascular mortality in CRF and hemodialysis patients are very much needed.

REFERENCES


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minutes while it may take days to clear emboli from the lung caused by clots.

The thixotropic lock tested is a hydrogel consisting mostly of water. Diluting this hydrogel by a factor of 2–3 results in loss of the mechanical integrity and dissolution into small particles that do not block vessels and, eventually into molecules that can be cleared from the blood stream. In order to test the time required for dissolution of a thixotropic gel lock into particles smaller than 5 µm thixotropic gel lock material was injected into a fluid circuit in front of a 5 µm filter with 25 mm diameter (~5 cm² surface area). Pressure was measured in front of the filter. When 0.2 mL of lock material was injected, it took 5 minutes until the resulting "embolus" was cleared through the filter as measured by the pressure increase in front of the filter.

In order to compare this result with human physiology the following estimate was made: The human lung contains ~300 Mio alveoles with diameters of 0.2–0.3 mm resulting in a total surface area of ~80 m². This alveoles are surrounded by capillaries. By assuming that the surface area of the capillaries in contact with the alveoles is 80 m² too, the total filtering cross section of the capillaries was estimated to be ~0.5 m² = 500 cm² which is a factor 100 larger compared to the filter surface area used for the test. Risk assessment and hazard analysis is a step wise approach starting with laboratory tests. This thixotropic gel-lock has passed this first test. Demonstration of safety will require animal tests and, eventually clinical tests.

REFERENCES

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