11-1-2013

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Recommended Citation
Yee J. Rise of the Small Machines: Salvation. Advances in Chronic Kidney Disease 2013; 20(6):449-451.

ACKD
Advances in Chronic Kidney Disease
A Journal of the National Kidney Foundation™
Vol 20, No 6, November 2013

EDITORIAL

Rise of the Small Machines: Salvation

If you had not noticed, you are probably working harder than ever to remain as productive as before. Given the ongoing financial and regulatory landscapes in nephrology and medicine, in general, this scenario represents a formula for disaster and self-implosion. More than ever, we must acknowledge and invoke the mantra of former Walt Disney Company cartoonist, Carl Barks: "Work smarter, not harder." Thinking small, not small thinking, portends large advances in nephrology. Machine automation on the small scale will permit us to do this, and technical innovation, particularly in the field of nanotechnology, which uses "machines" that manipulate matter on the scale of 1 to 100 nm to perform specific functions, is our future.

And what is a machine? Classically, it was a mechanical, thermal, or electrical device—an assemblage of typically moving parts, like an automobile, that was unpowered or powered and that yielded a mechanical advantage or reduced the amount of effort required to accomplish a given task compared with the manual effort required by the same task. An archaic definition of a machine is a constructed thing, and this definition and the former apply to nanomachines, which are small machines constructed for a purpose and with high-efficiency yields such that when in high number, performance of dauntingly large tasks is feasible. Nanotechnology is destined to be a key driver for success in clinical nephrology, particularly in the ESRD arena. With this in mind, Dr. William Fissell, MD, graciously accepted this guest editorship of *Advances in Chronic Kidney Disease* entitled "Nanotechnology in Kidney Disease."

As with computing, as mainframe computers have been progressively shrunken into mobile devices, advances in nephrology have proceeded with a reduction in size. Hemodialysis machines, which once occupied nearly the space of a small room, have been tremendously condensed, and one has been created "off-the-shelf" for infant dialysis[1] and another can now be worn for an entire day. In the former circumstance, an English consultant constructed a one-of-a-kind, do-it-yourself hemodialysis machine for his infant patient.[2] In the second instance, the most recent prototype of the wearable artificial kidney by Gura and colleagues[2] has been recognized by the U.S. Food and Drug Administration's 2012 Innovation Challenge program for potential fast track to marketing[3-5] At a clearance of 40 to 50 mL/minute, this 4.5-kg device, worn 24 hours daily, achieves standard weekly Kt/V levels approximating 7, which is clearly superior to any other current dialysis modality, including short daily and nocturnal hemodialysis.

Recently, an even smaller hemodialysis device was created that uses nanotechnology. This device, devised by Kanno and Miki,[6] extends the observations of Uesaka of nanotechnology applied polysulfone membranes,[7] and such a device has potential applicability for implantation, substituting for the function of the natural organs, using convection as the principal cleansing modality. Note that this had been intimated as a possibility as long as a decade ago.[8] In the future, with increasing miniaturization, the wearable artificial kidney has potential to become as popular as the other home-based therapies: short, daily dialysis and peritoneal dialysis.

Miniaturization of sensors could also have broad application in hemodialysis. For example, if sensors could be sterilely apposed to the blood space, the instantaneous determinations of ionized calcium and phosphate concentrations, among other analytes, during extended periods of hemodialysis would provide safety and benefit. Moreover, the readout of such sensors could be used in a servo loop, providing autofeedback to the system for adjustment of these critical analytes, thereby preventing ionized hypocalcemia and hypophosphatemia—the most feared complication of continuous renal replacement therapies that use regional citrate anticoagulation. An ionized calcium sensor has been developed by Yang and colleagues, and it determines ionized calcium

1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2013.09.001

levels nearly instantaneously. With knowledge of mass balances in an extracorporeal circuit, the placement of this sensor would indirectly "measure" plasma ionized calcium. Likewise, a separate sensor that distinguishes citrate anion has been used to determine whether citrate accumulation is occurring during sustained, low-efficiency dialysis, permitting rapid, critical adjustments.[9] The ex vivo modeling of a regional citrate anticoagulation sustained low-efficiency dialysis system was aided and abetted by this sensor technology and ultimately facilitated an enhanced system design that actually does not require ionized calcium.[10]

Further introductions of sensor technology for glucose and cytokine measurements in various body fluids may provide, in the future, widespread capability for the rapid recognition and attenuation of catastrophic clinical consequences, such as hypoglycemia and septic shock. Perhaps other biological sensors would be able to detect clinically undetectable events such as when a hemodialysis or peritoneal dialysis catheter becomes encrusted with the biofilm of microorganisms and when biofilm detachment is imminent. A quorum-sensing sensor in this circumstance might provide guidance for hemodialysis or peritoneal catheter exchanges, removals, and the peremptory use of anti-infectives.[11] In relation to the latter, coupled, spatial, site-specific, nanoparticle-based pharmacotherapy could prove lifesaving. This would be particularly efficacious for the nonwater-soluble antimicrobial agents and for situations in which supratherapeutic local drug levels would be advantageous.[12]

The small machines may also provide nephrologists with water that is purer than that which we have ever afforded our patients. We take pride in the generation of high Kt/V values for our patients; however, the greater the value, the greater the potential exposure to waterborne contaminants that have slipped by our conventional filtration systems and reverse osmosis. Contaminated water supplies must be identified as rapidly as possible. Alternatively, eschewing conventional water supplies would be ideal; however, using ultrapure water is prohibitively expensive for large or small dialysis organizations. Therefore, working smarter is certainly applicable with regard to the acquisition and distribution of pure water. Simply making new the plumbing of an in-center hemodialysis unit is not the answer. Biofouling and biofilm production will simply and inevitably recur—and within days—because of the reality that the source of the water supply is generally extrinsic to the hemodialysis unit.[13]

Nanofilters require less pressure to be effective than conventional filters and surface contact is substantially greater. In addition, cleansing of filters via back-flushing is easier than required of conventional methods.[14] Alumina and other nanofiber materials can be manufactured into nanofilters and devised to remove viruses, bacteria, arsenic, fluoride, heavy metals, and other potentially toxic organic and inorganic colloidal particles at rates faster than those currently attained. It is important to note that the diameter of these carbon nanoporous structures permits low-power flow-through of water molecules, without fouling, but it excludes unwanted pathogens and contaminants.[15] Using and deploying nanotechnology in distressed areas bereft of water or without access to potable water sources is potentially lifesaving. In areas where emergent renal replacement therapy becomes critical, as may transpire after natural disasters such earthquakes and tsunamis, nanotechnology would be indispensable.

Nanotechnology-based gene therapy affords promise for systemic disorders that cause CKD. Dr. Conforti and her team were recently funded by the National Institutes of Health to investigate how nanoscale therapy can alter immune function in the hopes of abrogating the effects of a pathobiological, hyperimmune system as is the case in systemic lupus erythematosus.[16] By gene-targeting a voltage-gated potassium ion channel (Kv) on T cells with nanoliposomes, calcium-based signaling is interdicted, thereby limiting the undesirable amplification of the immune response. This novel and biologically plausible approach could be templated to other autoimmune disorders such as the antineutrophil cytoplasmic antibody-associated vasculitides, among others. Customizable gene-targeting looms within the realm of possibility now that the human genome has been mapped and a multitude of disease-inducing antigens have been, in parallel, delineated.

The aforementioned represents but a trifling of the potential roles that today's and tomorrow's nanoscale machines may fulfill. Thinking smaller may yield large advantages in productivity and cost savings. As always, these advantages are contingent upon discovery, development, and implementation. If appropriate resources are allocated toward the development of nanotechnology, then possibility becomes probability. The rise of the small machines will hopefully become inevitable, and with them, some salvation … for us and our patients.

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Editor-in-Chief

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