Understanding Acute Kidney Injury (AKI), One Patient At A Time

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Background

AKI is an important disease with an annual cost of at least $10 billion in the US. Animal models and basic research have been instrumental in elucidating its molecular mechanisms. However, clinical trials have been slow to translate this knowledge into specific therapies. One well known problem that clinicians face in treating AKI is the variability between patients. Different comorbidities, genetics, epigenetics and degrees of underlying renal dysfunction and many other variables make each patient's AKI unique. Also, the timing of renal injury is often unclear, or there may be repetitive injuries.

The Kidney Research National Dialogue group stressed the importance of better defining clinical phenotypes of AKI in different patient populations (1). They also called for better validation of biomarkers. Engineering tools that could help achieve these goals may augment clinical trials and improve processes of care in the ICU.

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Objective

To use embedded system (small computer) controlled microfluidic urine sampling combined with wireless EMR data collection to automate research on individual patients. The end goals are to augment clinical trials and to allow more patients to be studied in settings with only modest resources such as community hospitals (approximately 4500 of the nation's 5000 hospitals are community hospitals).

Methods: Components

We used tubing and connections designed for microdialysis to create a microfluidic collecting system (FIG. 1). We used fluorocarbon, which is immiscible with water, to create fluidic spacers to partition time-stamped urine samples without cross-contamination. Precise pumping of urine was done with the RP-TX pump (Aquatech, Osaka, Japan), while feedback controlled pumping of the fluorocarbon spacers was done with the Aquatech RP-Q1 pump. For refrigeration, we used a vacuum evacuated reflective glass container (Pope Scientific, Menomonee Falls, WI) to enclose the samples. The container was sealed with R7 insulating foam. It was cooled by a single Peltier thermoelectric chip (Custom Thermoelectric, Bishopville, MD). Efficient heat loss was achieved by using a custom built copper heat pipe with aluminum fins (CCI, Taiwan). Miscellaneous parts for the prototype system were made by an Ultimaker 3D Printer (Ultimaker, Geldermalsen, Netherlands).

Methods: Control System

An off-the-shelf single board computer (SBC, BeagleBone Black ®, Texas Instruments, FIG. 2) was used to control sampling and to monitor fluorocarbon pumping, spacer introduction, bubble tracking and sample cooling. The SBC also will have LEDs to signal faults and system failure. Sample time stamping and temperature tracking were recorded on a Sandisk memory card. EMR data download will be added to the system later. The operating system of the SBC was Linux and the program code was written in C.

FIG. 1

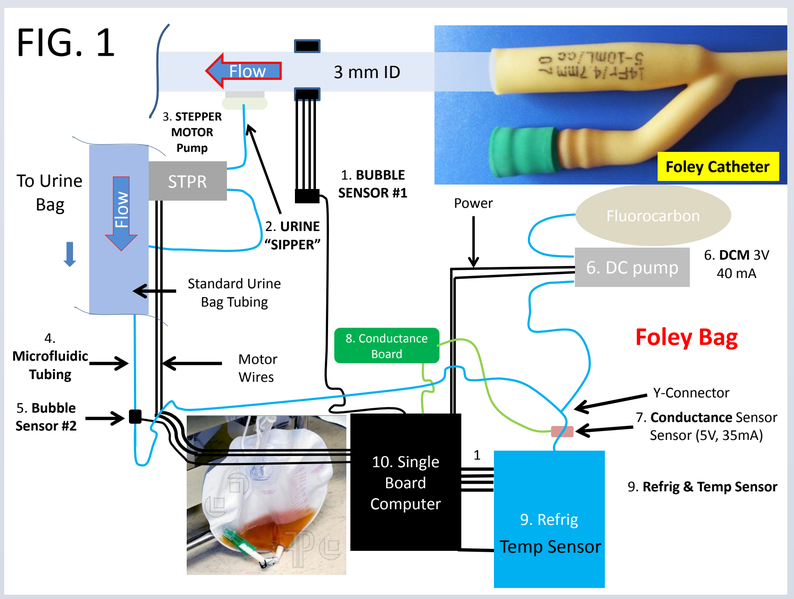


FIG. 2

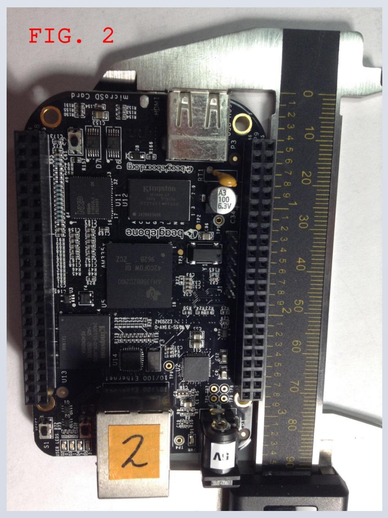


FIG. 3 Discrete samples created with fluorocarbon spacers

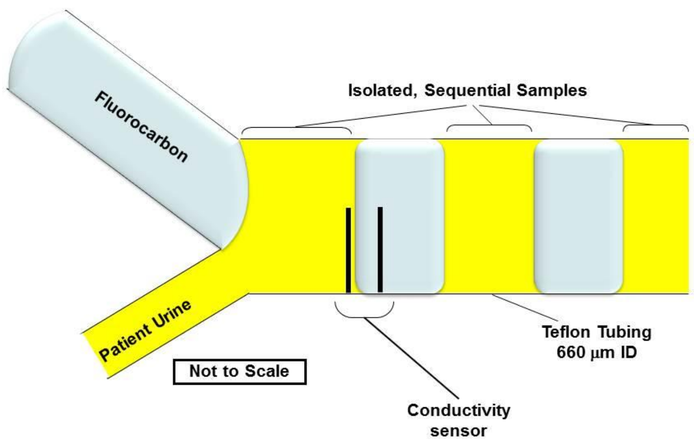
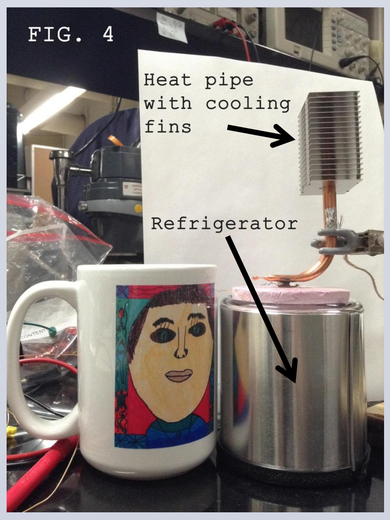


FIG. 4



Results

Results: Sensors

Two bubble sensors (OPTEK Technology, Carrollton, Texas) were used. One tracked interruptions in the urine flow. When they occurred, an analog signal was sent to the SBC and urine pumping was halted until the air passed the collection outlet. The other tracked bubbles within the collecting system to allow compensation in sample size i.e. more urine was collected for a sample that contained air – to keep sample sizes uniform.

Flourocarbon spacers separated samples (FIG. 3). A conduction sensor was used to sense the passage of fluorocarbon (non-conductive) and urine (conductive), through the tubing. This sensor was built from a schematic (2) onto a breadboard and then transferred to a prototype board. PCB Artist ® was used to design a PCB for production.

A highly accurate (0.1 – 0.5 ^{o}C) temperature sensor (TSiC ™ 501F, Innovative Sensor Technology, Ebnat-Kappel, Switzerland) was used to sense the temperature of the sample heat sink. C code was written to turn on the Peltier cooling when temperature exceeds 4^{o} C and to turn it off at 2^{o} C.

Results: SBC

The single board computer responded to bubbles as described above. It also tracked the length of fluorocarbon spacers. Future models will use bar coding. As the spacers moved along a known distance of the tubing, the SBC used time-of-flight calculations to obtain the flow rate within the urine collection system every time a sample spacer passed. This assured that samples were flowing and that the system was functioning properly.

Results: Refrigeration & Sample Capacity

The sample refrigerator was the size of a coffee mug and weighed about 500 grams (FIG. 4). It cooled down a copper conduction bar (3/8 x 3/8 x 1 inch) plus the sample heat sink aluminum rod (round, 1.5 inch diameter, 1 inch length) to 5.1^{o} C in one hour. Future testing will use a more powerful Peltier chip. The temperature of the external heat exchanger stayed below 31^{o} C at all times. The sample capacity was determined to be 1.024 mls, allowing 85 uL of urine collection every hour for 12 hours.

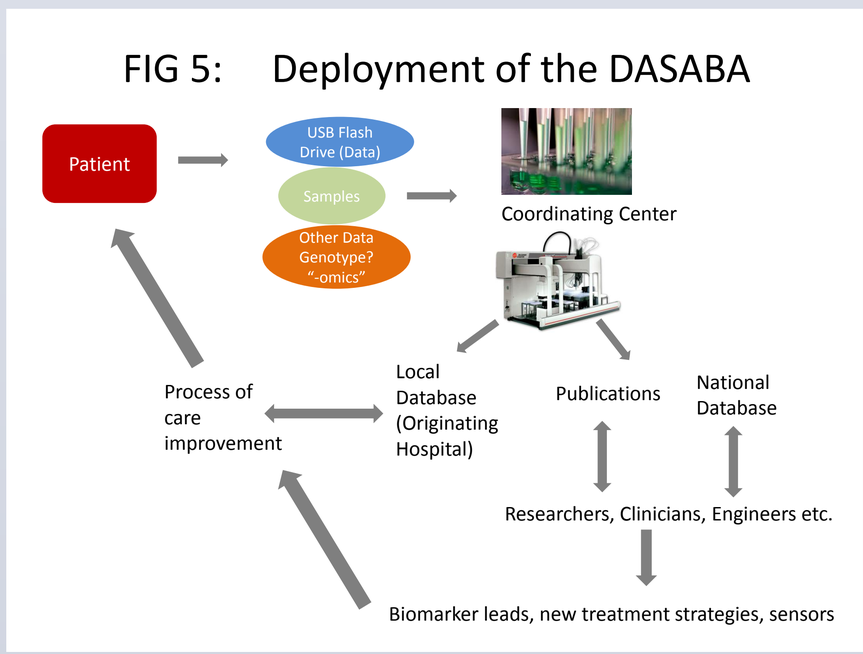
Conclusion

The DASABA is effective for its intended purpose. It uses relatively inexpensive disposable parts, is lightweight, can hang with the urinary bag, and is semi-autonomous, requiring only sample cartridge changes every 12 hours.

Future Work

The immediate goal are: First, construction of the integrated system using Pulse Width Modulation to control power consumption. Second, formal electrical safety testing. Third, identification of a sterilization and packaging partner. Fourth, development of an ejection mechanism to allow semi or fully automated sample ejection e.g. into 96 well plates. Fifth, identification of interested clinical research partners. The current plan is to provide clinical researchers with working prototypes under a evaluation license from Carnegie Mellon University. Sixth, the long range goal is to deploy the DASABA using a "hub and spoke" model with coordinating centers processing samples and data (FIG 5). Seventh, the DASABA is a sensor platform that can be adapted to a variety of uses including with microdialysis to sample interstitial fluid in wounds, skin, brain, CSF, transplanted organs, etc. It can also be used to validate inline sensors with comparison of real-time readings to the samples. Finally, it can be used to analyze biomarker behavior to validate biomarkers in particular populations of patients.

FIG 5: Deployment of the DASABA



References

1. **AKI: A Path Forward.** Bonventre, JV et al. Clin J Am Soc Nephrol 8: 1606–1608

2. **Microscale Experiments Using a Low-Cost Conductance Meter.** Jose H. Bergantin Jr. , Djohn Reb T. Cleofe, and Fortunato Sevilla III. Chemistry Education and Sustainability in the Global Age, Springer Science+Business Media Dordrecht 2013