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Detecting the early onset of hyponatremia: An opportunity for wearable sensors?

Hannah Quinn and James Davis

[1]School of Engineering, Ulster University, Jordanstown, Northern Ireland, UK

Abstract

The electrochemical measurement of sodium ion concentration has a long history and would appear to be ideally placed to serve as the core methodology for sensors that could detect the early onset of hyponatremia. However, there are still many challenges to be overcome – especially when considering elderly end users. This communication highlights the procedural and technological barriers and highlights advances that have been made in attempting to overcome them.

Keywords

Sodium; hyponatremia; ISE; microneedle; sweat; ISF; wearable

1.0 Introduction

Identification of hyponatremia (serum sodium concentration < 135 mmol/L) at an early stage has long been recognised as critical and there is an extensive body of research that underscores its value as a predictor of mortality and morbidity [1,2]. While it is one of the most common electrolyte disorders in a hospitalised population, mild chronic hyponatremia is the more common form encountered in the community [3]. The prevalence of the condition within the geriatric population is particularly concerning as it implicated in cognitive function, gait disturbances, osteoporosis, fractures and falls [3]. The latter is a major health concern with estimates suggesting that 30% of those aged over 65 years and living in the community are liable to suffer a fall at least once per year. This rises to 50% for those patients aged over 80 years. As falls can result in moderate or severe injury that will inevitably restrict their ability to engage in everyday activities, it is little surprise that falls are considered as the first stage of dependence. The latter is supported by the fact that some 40% of elderly patients admitted to hospital are subsequently institutionalised with the mortality rate ranging up to 11% [4]. While there are many "assistive living" sensors that can alert carers or family when a fall has occurred, prevention is clearly a more preferred option. Given the importance of hyponatremia as a risk stratification indicator and the potential to treat hyponatremia, there is a pressing need for point of care sensors that can provide robust measurements of sodium ion concentration. The target patient group, however, presents a unique set of challenges in terms of operational accessibility and technological capability. The aims of this communication are to critically assess how electrochemical sensors could address some of these issues and highlight emerging technologies.

2.0 Commercial Point of Care Systems

There are few commercial technologies to enable direct measurement of electrolyte within a community care scenario. Point of care (POC) systems (i.e. i-Stat™, OPTI Critical Care, EPOC® analysers, HORIBA LaquaTwin Salt meter) can offer discrete analysis [5-7] but are unsuitable for providing periodic/continuous monitoring of the subject's electrolyte balance and the patient would require repeated attention by a suitably qualified nurse / healthcare practitioner. Effective use of such systems would require regular blood sampling and may not be viable given the economic and time pressures on community nursing. Sampling can vary from the extraction of venous blood (blood panel) to finger prick capillary testing. While relatively benign for younger cohorts, the skin of an elderly patient is much thinner and more susceptible to bruising and pain and hence relying on patients to self-administer such tests could generate issues of adherence and competency.

3.0 Wearable Sensors and Smart Technologies

Wearable sensors, in contrast, could offer autonomous sampling and reporting thereby removing both patient and nursing issues and, in many respects, the elderly patient could be viewed as the ideal end user. The ideal is for a minimally invasive sensing system capable of providing real-time or periodic telemetry of sodium level which can thereby enable more timely, and indeed lifesaving interventions. The availability of real-time information would support self-management with connected health (mHealth) reporting allowing specialist oversight within the community. The telemetry aspect is critical allowing predictive modelling of potential trends rather than relying of discrete points. This is highlighted by the fact that a sudden drop in sodium (below 120 mmol/L in 48 h) can lead to cerebral edema [8]. Clearly, a wearable device would be much better placed to provide a more effective warning than waiting for a scheduled appointment for a blood panel to be taken, analysed and assessed.

While commercial smart watches offer a range of physical measurements (i.e. heart rate), biochemical tracking remains within the confines of the laboratory though this may change in the near term with electrolyte monitoring coming to the fore. The measurement of the latter could arguably be considered one of the easier targets given a mature knowledge base relating to the potentiometric detection of Na^+,K^+, Mg^{2+}. There are also key benefits such as the reagentless nature of such sensors, low instrumentational overhead and ease with which they can be combined with smart device electronics. Some of the more recent approaches are compared in **Table 1** with those describing a complete wearable system denoted as “integrated”.

In most cases, the sensors are based on solid contact membranes screen printed onto flexible substrates and rely on conventional sodium receptors such 4-tert-Butylcalix[4]arene-tetra acetic acid tetraethyl ester (Na Ionophore X) . The latter has consistently demonstrated near Nernstian behaviour with little to no interference from other electrolytes (K^+, Ca^{2+}, Mg^{2+} etc) [9-19]. Solid state NASICON type materials have also been explored in the past and variants continue to emerge and while these have been employed in a potentiometric mode, it is worth noting that Suherman et al. (2020) described a voltammetric approach relying on Na^+ insertion in to an iron(III) phosphate modified solid state structure. A preliminary evaluation of the analytical efficacy of the approach has been shown through the analysis of sweat [20].

The emergence and accessibility of laser induced graphene (LIG) brings an additive approach to the electrochemical design strategies [15] and could significantly speed developments with this area. The ability to directly pattern electrode architectures using graphic design software with low cost lasers using flexible polyimide provides an easy route into the wearable sector and stands in marked contrast to the labours and costs associated with conventional screen printed approaches.

Sampling is an issue for any analytical device with the forthcoming wearables almost invariably relying on sweat as the prime biofluid. This overcomes many of the traditional hurdles associated with the complexity of blood and deftly avoids the conflict and discrepancies between direct (whole blood) and indirect (plasma) potentiometry [5-7]. The target consumer for such devices, however, is unlikely to be those identified as being within a clinical risk group but, rather, those engaged in regular sporting activities or intense exercise where they may be at risk of exercise associated hyponatremia (EAH). While the significance of low sodium is clear, the impact of EAH can be considered as a silent killer as it is often difficult to differentiate it from exertional heat illnesses (EHI) due to overlapping symptoms of collapse, dizziness, weakness, and in severe cases mental status changes. Sporting events, endurance races or intense gym exercise can result in participants possessing asymptomatic hyponatremia rates ranging from 5% to 51%. As in the case of clinical hyponatremia, late diagnosis EAH can be fatal [21].

Table 1. Recent developments in potentially wearable sodium ion sensing systems

Electrode Type	Wearable	Integrated Sensor	Sample	Ionophore / Membrane / Reference	Linear Range mol/L	Ref
SPCE Carbon Black	Y	N	SW	Na Ionophore X / PVC PVB Reference	$10^{-4} – 1$	9
SPCE - PEDOT	Y	Y	SW	Na Ionophore X / PVC	10^{-4} - 10^{-1}	10
Au /CNT Film on PI	Y	Y	SW	Na Ionophore X / PVC PVB / Nafion Reference	$10^{-3} – 1$	11
C-Paste Film	Y	Y	SW	$Na_{0.44}MnO_2$	0.2 x 10^{-3}- 21 x 10^{-3}	12
Au - CNT EcoFLex	Y	Y	SB	Na Ionophore X / PVC PVB Reference	$10^{-3} – 1$	13
SWCNT-POT / PET	Y	N	SW	Na Ionophore X / PVC	$10^{-3} – 1$	14
LIG – PEDOT:PSS	Y	Y	SW	Na Ionophore X / PVC	$10^{-4} – 10^{-1}$	15
FET Au/CNT	Y	N	SW	Na Ionophore X / PVC PVB Reference	$10^{-4} – 10^{-1}$	16
FET-CVD Graphene	Y	N	SW	Na Ionophore X / PVC	$10^{-8} – 10^{-1}$	17
SS MN Cu/Pd PEDOT:PSS	Y	Y	ISF	Na Ionophore X / PVC PVB Reference	5x10^{-3}- 2x10^{-1}	18
FET-MN Au/Ag	Y	Y	ISF	Na Ionophore X / PVC PVB Reference	10^{-2}- 1.6x10^{-1}	19

Where: SPCE = Screen printed carbon electrode; PEDOT = poly(3,4-ethylenedioxythiophene); PSS= polystyrene sulfonate; PI = Polyimide; LIG = Laser Induced Graphene; SWCNT = Single walled carbon nanotube; SS = stainless steel; MN = Microneedle; CVD = Chemical vapour deposition; FET = Field effect transistor; PVC = Polyvinylchloride; PVB = Poly viny butyral; POT = poly(3-octylthiophene); SW = Sweat; SB = Saliva and Blood; ISF = Interstitial fluid;

The sampling of sweat however is not without difficulty. Although the core sensing methodology may be well established, collection, transport and indeed removal of the sweat necessitates the introduction of a design complexity that can be prohibitive for commercial adaptation. As such, there will be a question over what is actually being measured – does the sodium concentration reflect the immediate flux or is it cumulative? This reflects whether the collection device is designed for long term application or short term/discrete sampling.

From the perspective of an elderly patient, exercise to induce sweating is unrealistic and the sodium measurement would need to be done while the patient is passive. Sweat collection under such conditions would be at best variable and more likely to be inconsequential thereby removing the analytical efficacy of the device. Although the accessibility and acceptability of the wearable design approach and autonomous measurement capability is advantageous, the reliance on sweat is clearly problematic for the elderly patient.

The unreliability of sweat in this context is compound by the fact that sodium in sweat can be highly variable (typically 10-100 mM) and can be greatly influenced by activity and environmental conditions [22,23]. A critical consideration, especially from a clinical viewpoint relates to how the sweat sodium measurement relates to the systemic concentrations of the ion that influence physiological processes. There is scant literature in this regard and, while it is tempting to suggest that technology has outpaced the available clinical data, it could be argued that only by having the technology can the clinical data be acquired. Interstitial fluid (ISF), in contrast, has an electrolyte concentration similar to that of plasma and therefore offers a stronger clinical correlation [23].

4.0 Microneedle Patches

Transdermal technologies sampling ISF have found some commercial success through the autonomous monitoring of glucose (i.e. Abbott Freestyle). The design and production of microneedles (MN) intended for sensing applications has seen a wide variety of strategies adopted and these have been extensively reviewed [24,25]. Silicone moulds (typically PDMS) facilitate lab scale production and offer an easy route through which to rapidly prototype new MN compositions and thereby refine their properties and performance [25-29]. The micro-moulding technique offers a facile means of modifying the MN composition to include drugs but such methods can also be exploited to enable the production of MN arrays for sensing applications. The viability of this approach was demonstrated through the production of polycarbonate – palladium composite MN sensors [28]. Typical commercial moulds (Micropoint Technologies, Singapore) can provide needle dimensions that range from 200-1000 μm in height (200 μm base x 500 μm pitch). Substitution of the Pd with carbon nanoparticles [29] allows exploitation of detection strategies previously developed at conventional carbon electrodes. More recently, advances in the resolution of 3D printers (with increasingly common 4K UV LCD systems offering XY resolutions of 35-50 μm) have widened the design capabilities further offering direct integration of the needles within custom devices [30,31]. In most cases, the latter are non conductive and require post manufacture modification to enable their sensing capabilities.

A dual sensing MN capable of continuously monitoring both Na^+ and K^+ within ISF has been described by Li et al. (2021) with a near Nernstian response (56 mV/decade) to Na^+ [18]. The Na^+, K^+ ion selective electrodes (ISE) and Ag/AgCl references were all fabricated from 50 μm diameter copper wire which were sequentially treated with the ionophore/membrane components (**Table 1**). All three electrodes were then inserted within a 26 gauge stainless steel needle (outer /inner diameters of 464 μm and 260 μm respectively). It is clear that the preparation of the individual needles is far from compatible with mass manufacturing processes but the performance of the device is nevertheless significant. Coating the Ag/AgCl reference with a cocktail of poly vinyl butyral / NaCl produces a marked insensitivity to varying sample chloride concentrations - a critical consideration for any potentiometric sensor and an approach that is being increasingly adopted [9,11,13,16,8,19]. As is common with most proof of concept MN designs, evaluation is performed in simulated conditions and there remains questions as to long term biocompatibility of the ISE sensing surfaces and its accuracy.

A more scalable option has been reported by Zheng et al. (2022) based on an extended gate field effect transistor (FET) design [19]. In contrast to an earlier Na^+ sensitive FET design based on sweat measurements [16], Zheng and colleagues exploit micro moulding techniques to yield MN patches drop cast coated with ionophore x for Na^+ detection and which sample ISF. The system is exemplary in being one of the few that have progressed to human trials. In this particular case, removal of the MN patch results in pore closure in around 30 minutes but repeated administration over long monitoring periods will inevitably increase the possibility of bacterial ingress and infection. The latter could be especially problematic when considering an elderly cohort already dealing with multiple co-morbid conditions.

5.0 Conclusions

The systems described reside within proof of concept and there are some caveats to consider. The difference between a normal sodium level (135-145 mmol/L) and the hyponatremic threshold (<135 mmol/L) is very small and its ability to reliably distinguish between the two in everyday practice can only be ascertained through validated trials. Nevertheless, the on-body measurement by disposable MN, complimented by intrinsic mechanical flexibility and wireless connectivity clearly highlight a potential path to meeting the requirements of elderly end users.

Declaration of Interest: None

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