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ISFET and Fiber Optic Sensor Technologies: In Vivo Experience for Critical Care Monitoring

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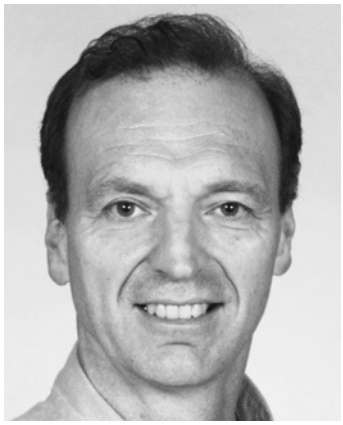
Contents



Bruce A. McKinley is a faculty member of The Methodist Hospital, Department of Surgery, Houston, TX, where he is Director of Translational Research and Bioengineering, Division of Surgical Critical Care and Acute Care Surgery. He received his doctoral degree in Bioengineering from the University of Utah, Salt Lake City, UT, in 1980. He received his M.S. degree in Biomedical Engineering from Iowa State University, Ames, IA, and undergraduate training in Chemical Engineering from Lehigh University, Bethlehem, PA. His work in medical applications of sensors began with his Ph.D. program at the University of Utah, which involved collaboration with electrochemists, bioengineers, and surgeons, under the direction of Drs. Janata, Westenskow, Houtchens, and Moody, to demonstrate the capability of monitoring interstitial electrolytes during shock and resuscitation using early prototype ISFET sensor technology. As a faculty member at the University of Texas, this work continued using then recently developed fiber optic sensor technology with early demonstration of monitoring of brain parenchyma and skeletal muscle pH, PCO_2, and PO_2 in studies of trauma, shock, and resuscitation and monitoring of the interstitium and microperfusion during shock and resuscitation using infrared spectrometry systems to monitor tissue hemoglobin O_2 saturation. Currently, he is involved with computerized clinical decision support as a technique to enable effective clinical research and improve patient care.

1. Introduction

Technologies to provide measurements of (human) biochemistry and physiology developed with analytical chemistry techniques, and with understanding of physiology. Sensors to monitor a microenvironment within a living organism have fascinated physicians and physiologists.[1−18] The capability to monitor some aspect of physiologic process began to appear with in vitro electrochemical sensors for the clinical laboratory. Discrete sensors useful for in vivo monitoring emerged with the earliest in vitro electrochemical sensors.[19]

A discrete sensor, configured as a tethered probe, placed in or near a local environment of interest to provide continuous measurement of the sensed variable, has been an enduring concept.[1−13,20−29] In addition to solid-state temperature and pressure, electrochemistry-based sensors for PO_2, pH, and other specific ions, e.g., K^+ and Ca^{++}, were early examples. Medical applications of sensor technologies have been seen as major market opportunities, and have had varied development efforts. Development and market success, however, has been elusive. In this paper the author reviews these efforts for two innovative sensor technologies that appeared in recent decades: ISFET sensors and fiber optic ('optode') sensors. By realizing the concepts of discrete sensors with micrometer dimensions, these developments effectively revolutionized sensor technology. These developments are primary examples of medical sensor technology that continues to evolve. The markets foreseen for these discrete sensors remain as possibilities.

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2. ISFET Sensor Technology

The ISFET innovation is a generally applicable discrete sensor technology for different electrode sensors of micrometer dimensions. The innovation of the ISFET was

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integrated circuit (IC) based (i.e., solid state) electrode sensors with micrometer dimensions, physical ruggedness, and possibility of manufacture with extreme precision and reproducibility previously unavailable with other electrode technologies. On the basis of emerging IC technology with matrices of independent transistor devices occupying a few square millimeters, the ISFET sensor concept offered the potential of a 'clinical laboratory on a chip' able to be placed safely in a patient. The possible application of continuous monitoring of multiple physiologically important variables was quickly identified.

The theory of ISFET function has been described elsewhere.[30−37] The ISFET concept was based on planar metal oxide semiconductor (MOS) field effect transistor (FET) technology that was being commercialized in the 1970s, primarily as computer memory IC devices. The three material 'metal oxide semiconductor' structure refers to the physical structure of early (and, interestingly, now the very latest) FETs having a metal (aluminum) gate electrode overlying an oxide insulator overlying a semiconductor material. FET device architecture, fabrication methods, and chip surface wire connections were based on the then rapidly developing IC industry technology. The MOSFET structure, metal surface gate overlying insulator and semiconductor with drain and source connections, had been adequately characterized to permit reliable device fabrication. Dimensions of MOSFETs could be specified and a process developed to reliably produce matrices of hundreds of identical devices on a single silicon wafer. The simple MOSFET device modification to create the ISFET was to remove the gate surface metallization and connection and interpose an aqueous solution and reference electrode. Effectively, the reference electrode specified a gate potential to cause the ISFET to function in the nonsaturated region of semiconductor current flow, wherein drain to source current varies directly with gate voltage.

Those variables detected using potentiometric electrode sensor systems would, in concept, use the same reference potential and a single reference electrode. Specific variables would be sensed using ion-selective 'membranes' specifically selective for ions of interest deposited on a planar integrated circuit electrode surface. Such membranes were the basis of ion-selective electrode technology.[38,39] (Nonionic species would be sensed using other selective mechanisms.) The individual sensors would have precise micrometer dimensions and be reproducibly manufacturable.

2.1. Early Prototypes and Concept Realization

Several efforts began in the 1970s that demonstrated sensor function and the possibility of a new sensor technology based on IC devices and technology.[30,32−37,40−43] ISFET chips were designed and fabricated using state of the art materials and methods.[31,34] The multidisciplinary nature of the ISFET brought together several disciplines that had rarely collaborated. The ISFET innovation involved then new electronics engineering with focus on integrated circuit (IC) and semiconductor device design and fabrication, and attracted the attention of classically trained electrochemists.[35,36] The concept of multiple potentiometric sensors of micrometer dimensions as an IC 'chip' recalled the idea of in vivo monitoring of multiple variables simultaneously. This idea attracted the attention of surgical intensivists. Bioengineering, a new collaborative discipline, provided the science and engineering expertise to identify and solve medical instrumentation, materials, and monitoring problems that this new sensor concept engendered. Important advances were made and continued throughout the 1970s and early 1980s in demonstration of ISFET sensors and useable probe designs at several laboratories.[30−32,43−50] Uniquely at the University of Utah (Salt Lake City, UT), science, engineering, and medical expertise combined in the mid 1970s to focus on the ISFET concept as it might be applied to intensive care. As a result of multidisciplinary collaboration, concepts were rapidly realized and early prototype sensors demonstrated.

Original concepts appeared and were proven in the 1970s as large-scale IC fabrication facilities were developing to support the emerging digital computer mass market. The first ISFET sensor to be demonstrated in an electrochemistry/engineering laboratory setting was hydronium ion (pH).[31] Analogous to conventional glass electrodes with SiO_2 H^+-selective 'membranes', the pH ISFET had similar selectivity and sensitivity. In addition to pH, ISFET sensor prototypes demonstrated the capability of other then available ion-selective electrodes. ISFET sensor prototypes were demonstrated for potassium (K^+), calcium (Ca^{++}), sodium (Na^+), ammonium (NH_4^+), and fluoride (F^-) ions.[34,36,37] These potentiometric electrode sensors borrowed ion-selective polymeric membranes in extremely small volumes, which were incorporated in the ISFET structure overlying the thin gate region. Focus on those variables of probable broadest clinical application led to development and demonstration of probes and techniques for sensor placement in anatomic sites likely to provide an indication of physiologic function. Studies to investigate possible applications of these probes were typically done in animal models of shock and resuscitation. A probe design that was used for early studies at the University of Utah is shown in Figure 1.

To the author's knowledge, the first clinically relevant demonstration of polymeric membrane K^+ ISFET function involved intravenous placement of a K^+ ISFET probe and monitoring during IV infusion of KCl, as is commonly done for ICU patients with hypokalemia as part of standard electrolyte replacement therapy.[41] This first demonstration showed stable function of the sensor system placed in the region of the superior vena cava for more than 3 h. Data obtained from in vitro clinical laboratory analysis of serial blood samples confirmed the accuracy of the ISFET sensor system. This and other experiments demonstrated the feasibility and desirability of continuous monitoring of electrolyte variables in physiologic preparations that were very representative of intensive care experiences. These situations are still common and representative of intensive care today.

Of early studies investigating possible applications of K^+ ISFET sensors, those involving sensor placement and monitoring in the interstitial fluid (IF) space of certain tissues (i.e., extravascular, extracellular tissue space) had perhaps the greatest foresight. Animal models of hemorrhagic and burn shock showed clear indication of severe derangement of basic cellular physiology, as monitored by K^+ ISFET sensors placed in skeletal muscle tissue.[41,51] A few years prior to these studies, other basic aspects of cellular physiology during shock and resuscitation had been reported by Shires et al.[2,13,52−54] In these studies, derangements of skeletal muscle cellular membrane potentials and K^+ transport during hemorrhagic shock in primates were measured and reported to be proportional to duration and severity of shock. During this same decade, these processes were able to be monitored with new proximity to cellular physiology using prototype

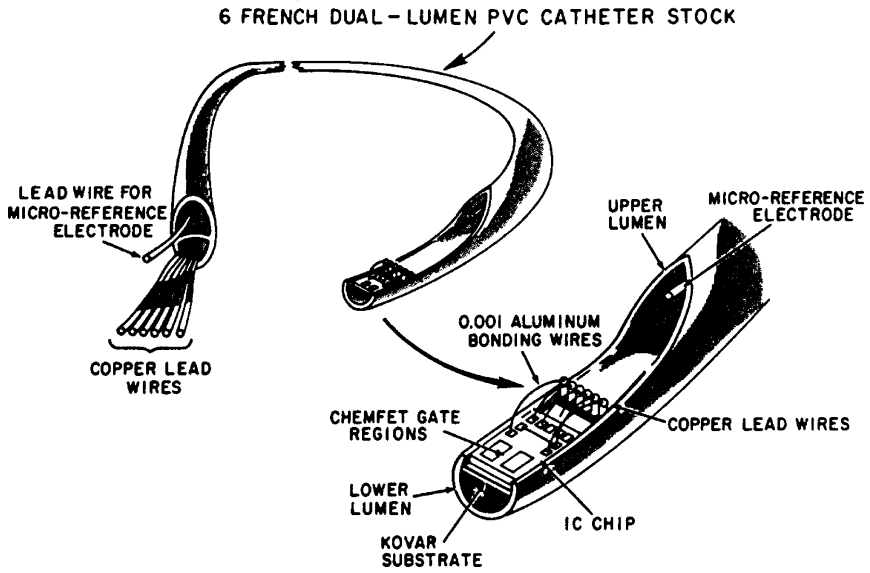


Figure 1. Early ISFET probe design used for studies of medical applications in laboratory animal models of hemorrhagic shock and calcium ion manipulation. Chip with two ISFET devices is shown with wire bonds to prototype copper wire tip connections, prior to encapsulation with epoxy compound. A reference electrode (Ag/AgCl) is depicted in the upper lumen of the catheter. The exposed Ag/AgCl electrode was isolated from protein exposure using a distal hydrogel plug over the catheter port. (Reprinted with permission from ref 51. Copyright 1981 Lippincott Williams & Wilkins.)

ISFET sensors placed adjacent to viable cells in an intact tissue bed. ISFET K^+ probes were also configured to study intracellular dynamics of K^+.[55]

The ability to monitor the IF space had been investigated by others using then conventional glass pH and polymeric membrane ion-selective electrode technology, but investigators were typically limited to muscle surface probe placement.[3,9,14,56] The ISFET probe, incorporating a reference electrode in the same device, provided the capability for minimally invasive, clinically practical placement in viable skeletal muscle beds. A study to investigate the use of ISFET K^+ sensor probes for skeletal muscle IF K^+ activity during hemorrhagic shock and resuscitation found a reproducible, near linear increase of IF K^+ activity during the period of hemorrhage-induced hypotension.[41,51] This finding was consistent with other reports of studies of hemorrhagic shock, including seminal studies of Shires et al.,[13,52,54] and indicated progressive leakage of intracellular K^+ to the interstitial space and failure of extracellular Na^+−intracellular K^+ gradient. After resuscitation, incomplete recovery of IF K^+ was observed, an effect perhaps indicative of inadequate resuscitation.

Figure 2a shows results of an animal experiment involving hemorrhagic shock and resuscitation. Two ISFET K^+ probes, one with central venous placement and one with medial thigh skeletal muscle placement, monitored K^+ activity in blood and IF simultaneously before, during, and after the shock insult (controlled hemorrhage to maintain hypotension with MAP $\approx$ 40 mmHg for 1 h). Interstitial and blood K^+ activities differed significantly in this study. Changes in blood K^+ activity were insignificant during the 1 h of hemorrhagic hypotension. Figure 2b shows composite results from a series of 10 experiments performed using the same protocol. During shock, deterioration of cellular oxidative metabolism, indicated by IF K^+ activity increase, compared to other systemic variables that were monitored, including blood K^+ activity, blood pressure, and heart rate, was especially noteworthy for the following reasons: (1) Blood pressure, a primary variable used to judge (remaining) vascular volume, has compensatory mechanisms that can mask severity of shock or inadequacy of resuscitation. (2) Heart rate and increased extraction of O_2 from blood also compensate for decreased total vascular volume. (3) Skeletal muscle seems to be less sensitive than other tissues to an acute decrease in O_2 delivery, and trans membrane potential is maintained despite a decrease of muscle surface pH, possibly due to glycogen stores and anaerobic metabolism.

ISFET sensors for Ca^{++} activity was a capability demonstrated with a polymeric Ca^{++}-selective membrane placed over the thin gate region of the ISFET device[36,37] (see Figure 1). A study was designed to investigate possible transients in systemic and IF Ca^{++} activity.[57] In dose rate-dependent response, myocardial depression was observed with IV infusion of sodium citrate. Blood Ca^{++} was monitored continuously with a Ca^{++} ISFET placed in the superior vena cava and compared with serial blood sample Ca^{++} activity analyses using a clinical laboratory ion-selective electrode analyzer. Figure 3 depicts results from a series of eight experiments. Blood Ca^{++} activity was observed to decrease to $\sim$1 mEq/L with a dose of citrate administered equivalent to that contained in four units of citrate-preserved blood cells. Myocardial depression, indicated by severely decreased cardiac output, blood pressure, and Ca^{++} activity, and increased pulmonary capillary wedge pressure, recovered but remained depressed for $>$30 min following bolus infusion. It is still common for multiple units of citrate-preserved packed red blood cells (PRBC) to be given rapidly to severely injured patients who are in shock due to hemorrhage upon hospital arrival, during emergency surgery, and during subsequent resuscitation and likely contributes to myocardial depression that can be sustained depending on the dose of citrate. At Level 1 trauma centers in the United States, replacement of lost hemoglobin to regain and sustain systemic O_2 delivery and hemodynamic function often involves volumes of PRBC that exceed 10 units in the first hours of hospitalization.[58]

Further demonstration of the ability to place a small ISFET sensor in an IF compartment involved direct monitoring of

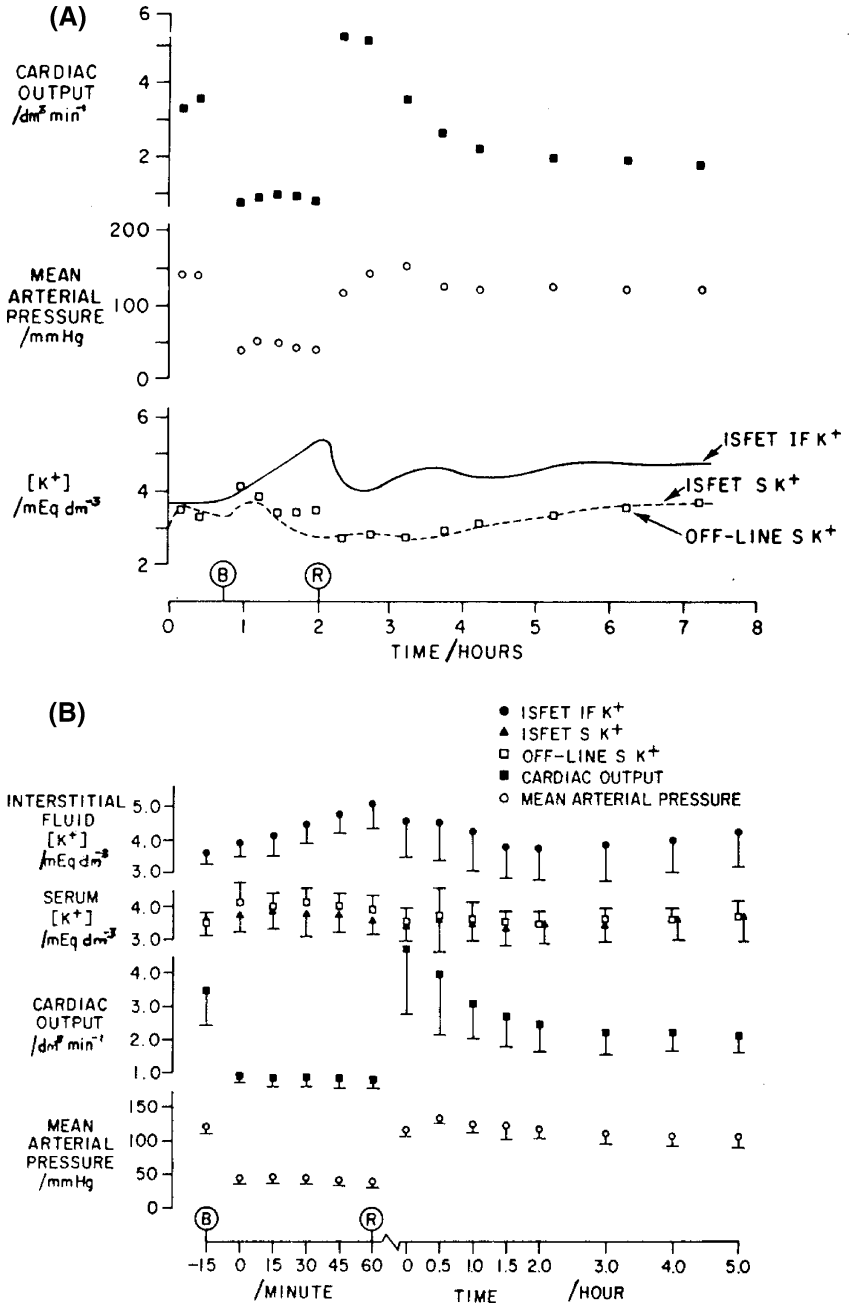


Figure 2. (a) Single hemorrhagic shock experiment results showing continuously monitored interstitial fluid (IF) K^+ activity in skeletal muscle of medial thigh using ISFET K^+ sensor (in probe design depicted Figure 1), continuously monitored blood (serum, S) K^+ activity in superior vena cava using ISFET K^+ sensor (in probe design depicted Figure 1), and independent serial clinical laboratory analyses of blood (serum, S, off line) K^+ activity. Mean arterial pressure and cardiac output measurements depict hemodynamic performance in response to hemorrhage (B), maintained hypotension (shock), and reinfusion of shed blood (R). IF K^+ was observed to increase steadily during shock and decrease with reinfusion of shed blood, while S K^+ changed insignificantly. Agreement of ISFET and off-line S K^+ measurements was also noteworthy. (Reprinted with permission from ref 51. Copyright 1981 Lippincott Williams & Wilkins.) (b) Composite data from 10 hemorrhagic shock experiments showing (mean ± SD) continuously monitored interstitial fluid (IF) K^+ activity in skeletal muscle of medial thigh using ISFET K^+ sensor (15 min intervals), continuously monitored blood (serum, S) K^+ activity in superior vena cava using ISFET K^+ sensor (15 min intervals), and independent serial clinical laboratory analyses of blood (serum, S, off line) K^+ activity. With hemorrhage to produce hypotension (shock), a monotonic increase in IF K^+ activity and an insignificant increase in S K^+ activity were observed; return to near baseline was observed upon reinfusion of shed blood. (Reprinted with permission from ref 51. Copyright 1981 Lippincott Williams & Wilkins.)

myocardial IF Ca^{++} activity.[59] With appropriate surgical exposure of the heart, a Ca^{++} ISFET sensor was placed under the epicardial membrane of the left ventricle of an anesthetized dog without disturbing cardiac function. Ca^{++} activity was manipulated by IV infusion of, first, sodium citrate, to cause hypocalcemia, and then calcium chloride, to cause hypercalemia. Serial femoral artery blood samples were analyzed using a clinical laboratory ion-selective electrode analyzer. The expected responses in the myocardium and blood were recorded in real time. Blood Ca^{++} activity was less than IF Ca^{++} activity during citrate infusion, and the opposite comparison was observed during calcium chloride infusion. Externally imposed changes in blood concentrations were in these experiments, the 'forcing function', with IF Ca^{++} responding with possible moderating effect of phosphorylation-related mechanisms in myocardium to maintain

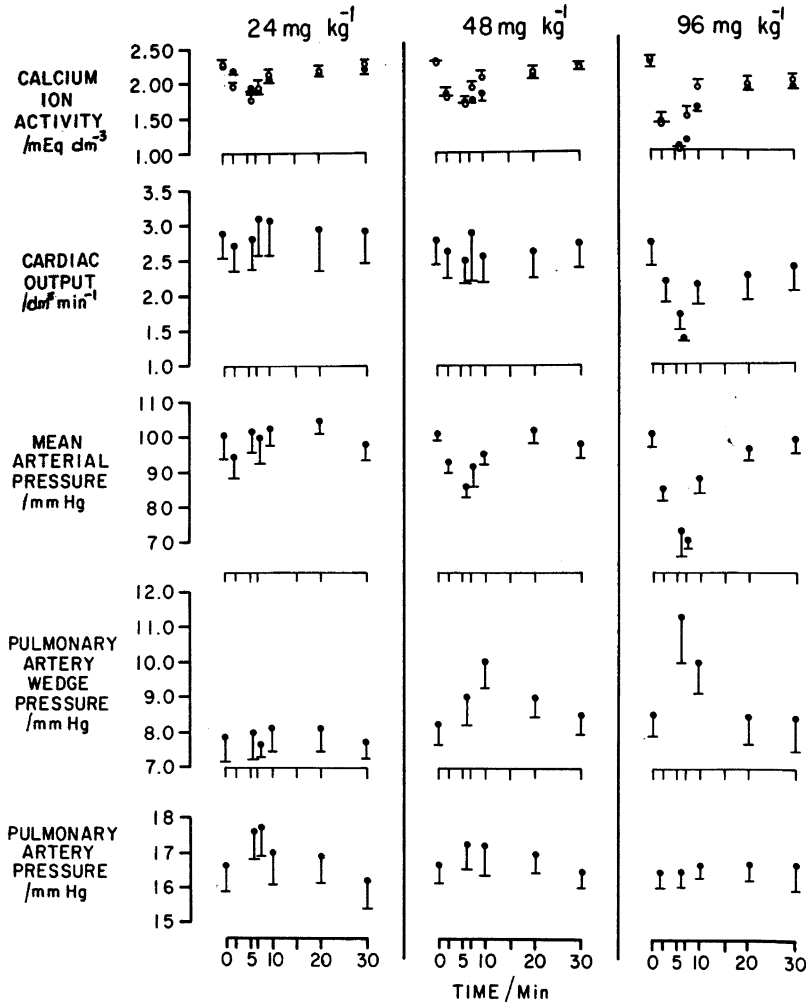


Figure 3. Composite data from eight experiments to study cardiovascular depression associated with sodium citrate (blood preservative agent) administration to simulate rapid blood transfusion (mean ± SEM): off-line (clinical laboratory) analyses of Ca^{++} activity (solid dots, - SEM); continuous central venous blood ISFET Ca^{++} activity (open dots, + SEM); cardiac output, mean arterial pressure, pulmonary artery pressure; pulmonary artery wedge pressure (all - SEM). Cardiovascular depression was observed to be directly proportional to sodium citrate dose rate and inversely proportional to Ca^{++} activity. Rapid return of Ca^{++} activity was observed upon cessation of sodium citrate infusion, likely due to citrate metabolism and release of Ca^{++} ion, correlating with recovery of normal hemodynamic performance. Agreement of ISFET and off-line S Ca^{++} measurements was also noteworthy. (Reprinted with permission from ref 57. Copyright 1981 Lippincott Williams & Wilkins.)

stable Ca^{++} activity in perimyofibrillar IF, despite perfusion of the muscle tissue bed with hypo- or hyper-calcemic blood.

The concept of multiple ISFET sensors on a single IC chip was also realized by the late 1970s.[40,59] IC designs for two ISFET thin gate devices and two conventional MOSFET devices were fabricated (see Figure 1). Individual device dimensions and spacing permitted ISFET sensor encapsulation using previously described techniques. ISFET probes were fabricated with two independently functioning ISFET sensors: one for H^+ and the other for K^+. Analog instrumentation was designed to operate the two sensors simultaneously with biasing achieved using a single reference electrode, also incorporated in the probe. Calibration of both sensors used two solutions of known H^+ and K^+ activities and at two different temperatures to permit temperature compensation using a third device of the same IC, a conventional MOSFET.

With this ISFET probe placed in a surgically exposed gastrocnemius muscle, IF pH and K^+ activity in this skeletal muscle of an anesthetized, mechanically ventilated rabbit were monitored during and after ischemia, induced by temporarily occluding the aorta ~1 cm proximal to the aortic bifurcation to avoid collateral blood supply.[59] Arterial blood samples were obtained for comparison with clinical laboratory ion-selective electrode analyses. During and after ~1 h of ischemia, mirror image symmetry in fluctuations of IF pH and K^+ activity was observed. Skeletal muscle IF pH decreased and K^+ activity increased during ischemia. With release of aortic clamp and reperfusion, recovery toward pre-ischemia baseline occurred. As with studies of IF K^+ activity during hemorrhagic shock, recovery to pre-ischemia IF pH or K^+ did not occur 2 h after the insult.

IF pH and K^+ activity changed with ischemia and reperfusion with a time course that was similar to the canine IF K^+ activity during and after hemorrhagic shock. Reperfusion effects of pH, showing IF pH to differ more from blood (systemic) pH than K^+ activity, demonstrated what is now more commonly understood to be 'washout' of acidemic products of anaerobic metabolism from a large vascular bed after ischemia. Close agreement of IF and systemic K^+ throughout a 5 h experiment is remarkable.

These changes had been observed previously—but separately—by other investigators using similar laboratory preparations and conventional ion-selective (and pH) elec-

trode technology. Simultaneous recordings of skeletal muscle IF pH and K^+ activity at the same site had not been reported. This demonstration of multisensor capability further proved the original ISFET concept of multiple sensors on a single IC and configured in a single, small rugged probe.

2.2. Summary of the First Decade of ISFET Sensor Technology Development

The ISFET as a sensor technology with potential versatility and broad application was recognized in the mid 1970s. In addition to pH, ISFET sensor prototypes demonstrated the capability of other then available ion-selective electrodes. ISFET sensor prototypes were demonstrated for potassium, calcium, sodium, ammonium, and fluoride ions. Prototype sensors were able to be incorporated in probes with dimensions practical for use in direct, continuous monitoring of critically ill patients and in other applications that included dentistry.

The ISFET concept progressed rapidly during the late 1970s. Development of theory, technology, and practical applications advanced simultaneously. The ISFET innovation of a generally applicable discrete sensor technology for different electrochemical sensors of micrometer dimensions was realized by 1980. IC-based ISFET electrode sensors with micrometer dimensions and physical ruggedness previously unavailable with other electrode technologies had been demonstrated. Those variables detected using potentiometric ion-selective electrode sensor systems had been fabricated and demonstrated as ISFET sensors. Multisensor probes had been designed and fabricated. Technical progress occurred at several centers in the United States, Europe, and Japan. In certain settings, the multidisciplinary nature of this innovative sensor technology benefited from electrochemistry, bioengineering, and medical (surgical intensivist) collaboration. Designs of practical ISFET sensor systems were developed, fabricated, and tested for clinically relevant applications.

Early development of a new sensor technology had integrated electrochemistry and electronics engineering disciplines to produce prototype ISFET ICs. Design and development of a practical ISFET probe to optimally use the specific features of small size and ruggedness required electrochemistry, electronics, bioengineering, and medical collaboration. Fabrication of ISFET probes was done manually using materials and techniques in trial and error, typical of early engineering development.

The culmination of these efforts was a very small discrete sensor system able to be placed in specific tissue beds of interest to monitor physiologic processes more directly and reliably than had been possible. The results of these early studies to demonstrate feasibility of this new sensor technology confirmed studies of tissue cellular physiology during hemorrhagic shock and resuscitation that had been reported in the early 1970s. In the United States, this early work was accomplished using scientific grant funding.

The concept of reproducibly manufacturable ISFET sensors and probes commercially available for this purpose, however, was not proven. A new sensor technology seemed ready to be commercialized. Commercialization of ISFET sensor technology proved more elusive than may have been expected by those involved in early conceptualization, development, and demonstration of prototypes. In the United States and elsewhere, funding from commercial entities would be required.

2.3. Summary of ISFET Sensor Development Since 1980

Developments have continued throughout recent decades that have demonstrated sustained interest in ISFET sensor technology.[31] The early 1980s saw several exploratory efforts by major medical product corporations (Critikon (a Johnson & Johnson company), Corning Glass, U.S.; Cordis Europa, The Netherlands; Kuraray, Nihon Kohden, Japan) to develop ISFET sensors toward reproducible, easily manufactured prototypes.[60−67] No U.S. commercial products for medical applications resulted from these efforts to the knowledge of the author, although ISFET pH-based PCO_2 sensors were commercialized for medical applications in Japan (Nihon Kohden), and ISFET pH sensors were developed to manufactured prototypes in The Netherlands (Cordis Europa). ISFET pH sensors are manufactured and used for water, food, brewery, and pharmaceutical process monitoring (Mettler Toledo Inc., Columbus, OH; Honeywell International Inc., Morristown, NJ; Endress+Hauser Group, Reinach, CH). These current ISFET sensors exist as commercial products due to advantages of ruggedness, lack of breakable glass, and sterilizability compared to glass membrane electrodes, and the ability to manufacture a probe that meets the requirements of process monitoring. Similar advantages exist for continuous in vivo monitoring using ISFET sensors in critically ill patients but with probe dimensions that are much smaller than these commercially available process monitoring probes. Of note is the ability to manufacture ISFET pH sensors, the dimensions of which are similar to those of early ISFET prototypes. This capability involves encapsulation of ISFET IC devices without occlusion of ion-sensitive thin gate regions.[45]

A key to the problem of manufacture was encapsulation of parts of planar IC surfaces with ion-sensitive thin gate regions not occluded and able to be exposed to the aqueous solution of interest.[31,45] Eventual hydration and leak between integrated circuit chip SiO_2-exposed gate surface and encapsulation materials was a probable source of instability of the sensors. Long-term stability, though demonstrated over days and likely adequate for medical applications involving relatively short duration monitoring, was unlikely to sustain if packaging in aqueous solution was required. Many designs have appeared that addressed the problem of encapsulation.[31,32,44,45,60−62,64,68−79] An early attempt to address manufacture adapted IC industry tape automated bonding, which provided printed (copper) electrical ('beam') leads in a pattern congruent with ISFET IC bonding pads. The ISFET IC (rectangular cross section; see Figure 1) was positioned between additional tape layers with appropriate adhesive or perforations to anchor and align and, with subsequent application of (thermoset) encapsulant, seal the IC, with the exception of thin gate regions left exposed as a pH sensor or for application of ion-selective membrane.[64] Another approach used conventional thermoset epoxy encapsulant around an ISFET IC placed in a cast form with focused gas jet stream impinging over thin gate regions during curing to prevent flow of epoxy over thin gate regions that would remain exposed.[61] Other reports involve photolithographic IC processing techniques to provide encapsulation as part of ISFET IC fabrication.[68,80] For ISFET pH probe designs for laboratory and food industry process monitoring, manual encapsulation using thermoset epoxy has been devised and micromold techniques incorporating printed circuit electrical leads and elastomeric seals have been used.[45,73]

A related problem encountered early with the Utah in vivo probe design was mechanical stability of the polymeric gel liquid ion-selective membrane placed over the thin gate region of the ISFET device. Convenient polyvinyl chloride and plasticizer formulations of K^+ and Ca^{++} ionophore membrane solution permitted creation of a water-tight seal with an epoxy encapsulant well into which microliter solution volume was deposited using a micropipette and stereomicroscope, but such techniques were difficult to automate. Other methods were devised, e.g., suspended mesh of chemically inert, nonconductive, and mechanically stabilizing polymer,[60] which was, in concept, generalizable to other partial encapsulation techniques. An alternative approach to ion-selective membranes involving functionalized polysiloxanes, able to be covalently linked to IC surfaces and combined with photolithographic techniques, was reported to provide K^+, Ca^{++}, and NO_3^- ISFET sensors.[81]

A key problem for a discrete ISFET sensor system for in vivo monitoring was stable reference potential necessarily provided by a reference electrode. Initial efforts to address this problem were undertaken by researchers at the University of Utah.[40,82,83] A small liquid junction electrode was devised that used saline as internal reference electrolyte and excluded (blood) proteins from the Ag/AgCl equilibrium using a hydrogel barrier. Studies cited above were undertaken with this simple design, which proved adequate for relatively short-term (several hour) experiments. Although systematic study of the performance of reference electrodes for in vivo monitoring as a component of a discrete sensor system was not undertaken for the early studies cited, the problem was addressed as a component of commercial product developments.[75,84−90] The problem of reference electrode design has had continued study as ion-selective electrodes became established as a part of clinical chemistry.[91−97] Alternative methods have been devised to provide proper biasing of the ISFET device and theoretical (Nernstian) electrode response.[31,82] A reference electrode that is integral to a probe is conceptually attractive. 'On chip' reference electrode designs were devised and tested. Various designs provided a liquid junction with micrometer dimensions but otherwise conventional metal halide electrode, and may have offered an adequate compromise between volume of internal reference electrolyte solution (adequate for reference potential stability and duration of probe use; minimal potential for toxic effect due to diffusion or accidental in situ disintegration), exclusion of proteins from the reference potential generating equilibrium reaction, and manufacturable design compatible with ISFET (IC) fabrication technique and medical product sterilization and storage/shelf life requirements.[84−87,89,90,98] Stable reference potential is intended and described, but nonpatent literature reports of performance of such designs are unavailable.

The versatility of the ISFET and chemically sensitive field effect transistor (ChemFET) concept became more apparent with innovations of the early 1980s. Reports continued to reflect the basic nature of the sensor technology.[99−104] Recent reports indicate ongoing development in a wide variety of areas, including cell and tissue culture,[105−108] transcutaneous blood glucose concentration monitoring,[109] enhanced sensitivity glucose sensor,[110] ISFET surface modification for immune function detection,[111] urea sensor designs based on urease enzyme activity,[112,113] organic thin film transistor biosensors,[114] bacterial metabolism and bacteriology for food processing,[115] single nucleotide polymorphism (SNP) detection,[116] protein detection using streaming or zeta potential for immunosensor or biocompatibility applications,[117] and acetylcholinesterase-based ISFET for insecticide detection.[118] Since 1976, nearly 400 U.S. patents have been issued that address ISFET technology.

3. Fiber Optic Sensor Technology

A second discrete sensor technology had its inception during the 1970s. Fiber optic sensors for pH, PCO_2, and PO_2, initially reported in the mid 1970s,[24,26,119,120] appeared to offer many of the same innovation advantages that had been envisioned for ISFET sensors, including extremely small size, reliability, and ease of manufacture. Sensors based on absorbance, fluorescence, and other optical mechanisms are fundamental to much of analytical chemistry. The innovation for discrete fiber optic sensors was incorporation of indicator chemistry at or near the tip of one or a pair of optical fibers. The technology was new and did not seem to involve the complexity of electrode sensors, most specifically a reference electrode. The technology was based on optical signals transmitted via submicrometer diameter optical fibers.

Perceived advantages of optical sensors, compared with electrode sensors (including ISFET), included the following:[121] (1) No need for a reference electrode potential to obtain electrolyte (e.g., pH) measurement. (2) No susceptibility to electrostatic or electromagnetic interference. (3) Potential for better long-term stability in blood or other proteinaceous fluids, probably relating to reference electrode stability. (4) Possibility of multifunction probes of single optical fiber construction based on multiwavelength analysis of mixed indicator sensors and principal of noninteraction of photons of different wavelength sources. (5) Early success of prototype discrete sensor development.

The discrete fiber optic sensor technology had its basis in fluorescence and absorbance chemistry.[122] In concept, absorbance indicators react with the analyte of interest, e.g., H^+, in a reversible equilibrium reaction and change the color of the indicator solution. Indicators, typically weak acids or bases, have different forms (ionized, tautomers) that coexist. The ionized form absorbs certain wavelengths of light. Absorbance of light transmitted through the indicator solution shifts when alterations in concentration or activity of the analyte cause a change in concentration of the indicator forms. Reflected or transmitted light is of the same wavelength or spectral range as incident light. The dye phenol red (phenolsulfonphthalein) is an example of an absorbance indicator that has been developed and used in an optical fiber pH sensor. Another type of optical indicator used fluorescence properties of certain compounds that fluoresce light (emit radiation) upon absorption of light (radiation) from another source, with the wavelength of fluoresced light being greater than that of the absorbed light. Attenuation of fluorescence ('quenching') occurs in proportion to analyte concentration, thus providing a sensor mechanism. Quenching occurs due to radiationless deactivation of excited states of the indicator by electromagnetic interaction of indicator and sensed molecules in a reversible, collisional process that does not consume the analyte. The intensity of fluorescent radiation of a specific wavelength is measured. The dye solvent green 5 (perylene dibutyrate) is a fluorescence indicator that was used in early development of fiber optic PO_2 sensors.

The indicator, therefore, transduces changes in the concentration of the chemical (in the body's fluids) by altering

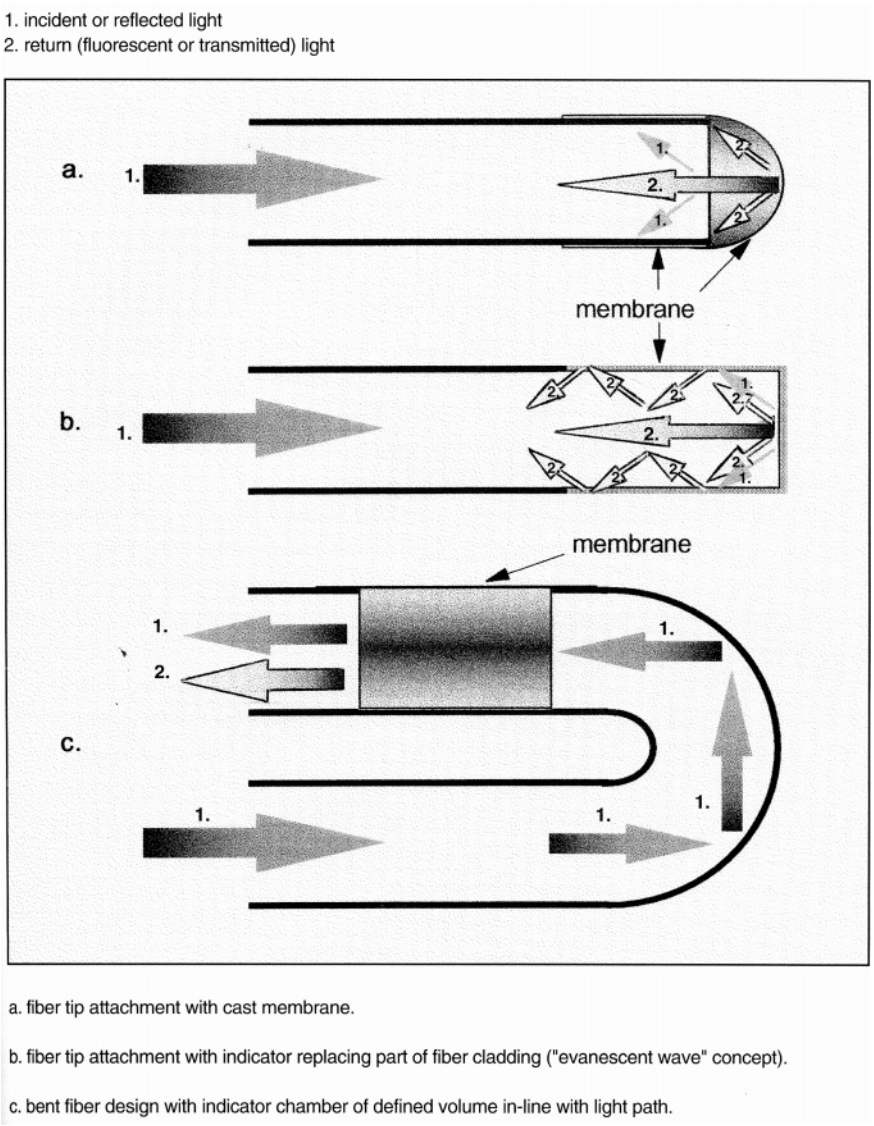


Figure 4. Indicator placement and schematic photon path for different fiber optic sensor designs. (Reprinted with permission from ref 122. Copyright 1994 University HealthSystem Consortium.)

absorbance of source light or changing fluorescence caused by source light. The optical fiber or fibers conduct source light to, and return light from, a small volume of indicator contained within the light path for measurement by remote instrumentation. The term 'optode', analogous to 'electrode', was popularized in the early 1980s. Figure 4 depicts indicator placement in different fiber optic sensor designs and schematic light paths for these designs. The optode sensors that were developed for medical applications were pH, PCO_2, and PO_2. Theory to explain the function of observed sensors was also developed and has been reported elsewhere.[122−127]

Not all reports of fiber optic sensor theory have confirmed an apparent basis of simplicity compared to electrode sensors. Thermodynamic principles applied to fiber optic pH sensors indicate that interphase effects and differences between complex bulk solution and submicroliter volumes of colorimetric indicator isolated in the light path of fiber optic sensors precludes measurement of pH (i.e., hydronium ion activity).[128] Absorbance theory, related to concentrations of indicator conjugate base and conjugate acid, was commonly reported to explain fiber optic pH sensor function.[122,127] For absorbance of incident light by the base form of an indicator dye, A^-, the relative amount (concentration) of A^- varies with pH and is related to transmitted light intensity at an absorption wavelength, assuming uniform properties of the indicator solution. This simplistic approach ignored solute−solvent and solute−solute interactions and interphase surface adsorption effects, which largely determine the intended measured variable, hydrated hydrogen ion activity (not concentration) in the microenvironment of the optode sensor window. This analysis points out the fundamental difference between optical and electrochemical pH sensors. Electrode measurement is a potential difference between the bulk of solution and the bulk of an ion-selective membrane (e.g., hydrated glass for pH), and the potential of the ion species is equal in those two phases. None of the measured potentials is due to adsorbed species, e.g., proteins. Optode measurement of a charged species, e.g., hydronium ion (pH), originates with bulk solution−indicator surface window interaction. Here, the surface activity of the species of interest is related to its corresponding bulk value through its adsorption isotherm, competing adsorption, and surface equilibration effects, including ionic strength, and polyelectrolyte and solvent effects in bulk solution−indicator and indicator−optical fiber surface layers. Effectively, electrode and fiber optic sensor pH measurements are not the same,

and a fiber optic pH sensor does not measure hydronium ion activity but infers pH from optical characteristics of its color indicator. For electrically neutral species PCO_2 and PO_2, effects of activity coefficient variations are much less significant than in ionic sensors, and theory of fiber optic sensor technology based on concentration, and not activity, is consistent with thermodynamic analysis. These analyses do not explain the relatively close agreement of in vivo fiber optic sensor and in vitro pH measurements compared with PO_2 sensors in subsequent clinical trials (see below), but do indicate overly simplistic theoretical justification of early optode sensors.

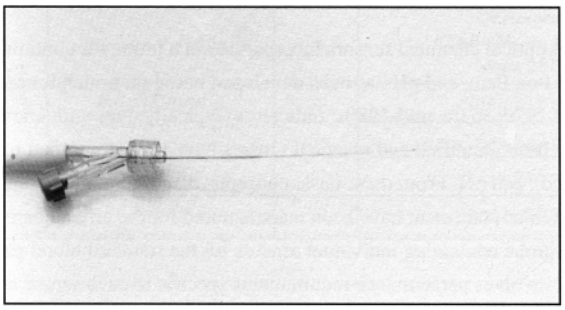
3.1. Development and Commercialization

In contrast to ISFET sensor technology, development of fiber optic sensors began with commercial product focus in the early 1980s and proceeded for 10 years. The product focus was continuous intraarterial blood gas monitoring and became the objective of many development efforts in the United States and Europe. Immediate product focus was motivated by several factors: (1) Sensors for blood gas variables pH, PCO_2, and PO_2 had been demonstrated by early investigators. (2) Fiber optics was seen to be an attractive new technology, and sensor theory, perhaps deceptively simple, was readily understood. (3) Emerging successes of 'high-tech' (i.e., high growth and profit) computer companies motivated new venture funding by corporations, typically medical device and drug companies, and by then new venture capital firms. (4) A market was perceived for blood gas monitoring, a high value clinical laboratory analysis, that seemed clearly defined, to exceed threshold $100M annual revenue needed to sustain interest of investors, and able to be captured with the first product to be developed.

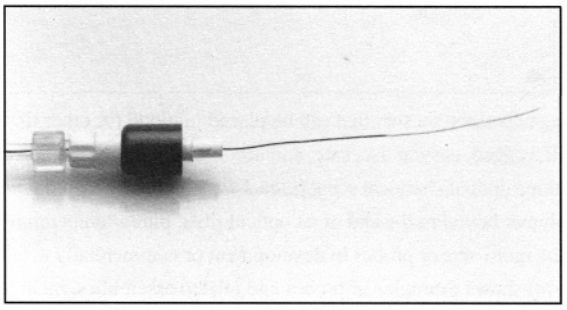
The elegant simplicity of the fiber optic sensor concept apparently involved no principles of electrodes and electrochemistry, and sensor prototypes were demonstrated. With a certain product in mind, a technology rush to market was underway by the mid 1980s.

The product concept, a continuous intraarterial blood gas monitor system comprising an indwelling single-use probe and a bedside instrument, was able to be defined. The essential part of the commercial product that would produce profit was a multisensor, discrete sensor probe that could be manufactured in large numbers at low cost, sold to hospitals at a multiple of manufacture cost, used once and thrown away. Sensor performance was assumed to be adequately stable and rapid in response to consider continuous monitoring, perceived to offer advance in patient care. Access to the patient's blood was required, and was determined to be via a cannula already invading the patient's vasculature for purposes of continuous monitoring of blood pressure. The probe diameter, therefore, needed to be sufficiently small to fit through a conventional disposable peripheral arterial cannula without perturbing the ex vivo blood pressure signal. This requirement could be met with optical fiber technology.

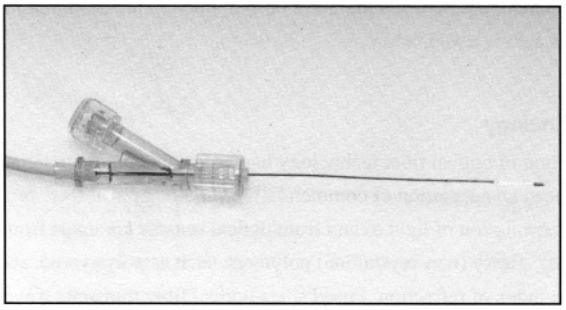
Many development efforts were ongoing throughout the late 1980s. These development efforts led to three competitive continuous intraarterial blood gas monitor systems by the early 1990s: PB3300 Intra-Arterial Blood Gas Monitoring System (Puritan Bennett Inc., Carlsbad, CA), commercially available 1993, production discontinued 1994; Paratrend 7 (Pfizer/Biomedical Sensors Ltd., Highwycombe, U.K.), commercially available 1994−2002; Biosentry System (Optex Biomedical Inc., The Woodlands, TX), commercially available 1994, production discontinued 1995.



a. Puritan Bennett, Inc., PB330™



b. Pfizer/Biomedical Sensors, Ltd., Paratrend 7™ [Note: Po_2 sensor is electrode]



c. Optex Biomedical, Inc., Biosentry™

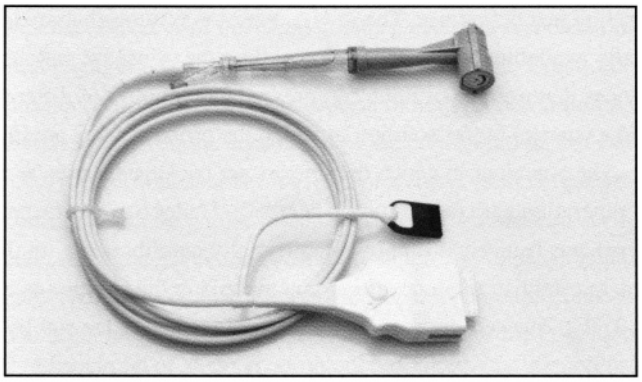
Figure 5. Multisensor indwelling probes with fiber optic sensors for pH, PCO_2, and PO_2, and a thermocouple for temperature measurement and compensation. Probe diameters were ~0.2 mm and designed for sensors to be directly exposed to arterial blood. Connectors were designed to couple with previously placed intraarterial cannula for blood pressure monitoring. (Reprinted with permission from ref 122. Copyright 1994 University HealthSystem Consortium.)

Figure 5 shows photographs of indwelling probes developed for each of these fiber optic sensor systems. Figure 6 shows probes including cable extensions to connect the indwelling probes to bedside instruments, also possibly including a further extension cable ~2 m in length.

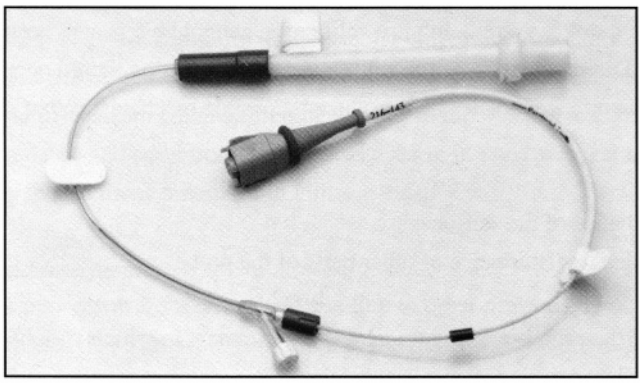
Within a decade of the start of focused product development, 18 years after initial demonstration of the optode, the discrete optode sensor was transformed from prototype to commercial product with FDA clearance to market. Many factors contributed to the limited market success of these systems.

3.2. Clinical Trials and Assessments

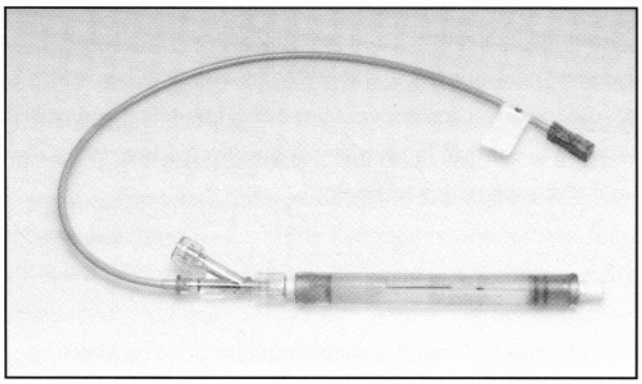
Included in the development efforts were clinical trials of prototype and near commercial systems, and their introduction to clinicians who would use them. Operating rooms and intensive care units were the likely environments for the technology. Typically, the clinical trials were observational and compared continuous intraarterial blood gas monitoring



a. Puritan Bennett, Inc., PB330™



b. Pfizer/Biomedical Sensors, Ltd., Paratrend 7™



c. Optex Biomedical, Inc., Biosentry™

Figure 6. Fiber optic probes including cable extensions to connect the indwelling probes to bedside instruments for operation of multisensor probes for intraarterial blood gas monitoring and display of continuous in vivo data. (Reprinted with permission from ref 122. Copyright 1994 University HealthSystem Consortium.)

and standard clinical laboratory in vitro analyses with the intent of demonstrating equivalence. In vivo monitor data were not used for clinical decision making. As of 1994, when systems had been commercialized, all human use trials reported were limited to groups of <15 patients per hospital. Although there were no reports of complications or patient morbidity due to experimental use of these systems, neither were there reports of cost−benefit analysis.

Tests of four commercially developed systems were reported. The first human use study to be reported included some analysis of clinical use criteria.[129] This study used a system that had been developed extensively but was not commercialized (CDI System 1000, Cardiovascular Devices Inc., Irvine, CA). Prior animal studies were conducted to assess performance and blood compatibility. Several hundred in vitro measurements were shown to agree well with in vivo measurements at times of blood sampling over common clinical ranges of pH, PCO_2, and PO_2. Human studies involved 12 patients and 79 in vitro analyses for comparison (duration of monitoring 3−26 h). A second trial in 14 operating room patients found similarly good in vivo monitor−in vitro analysis agreement (duration of monitoring 2−8 h).

Studies of systems that were commercialized also maintained focus on the continuous intraarterial blood gas monitoring application for which they had been designed. Demonstration of the PB3300 system (Puritan Bennett Inc.) in mechanically ventilated ICU patients at a German university hospital emphasized use of the system in 'routine clinical conditions' (i.e., as a standard clinical monitor subject to no special maintenance or special conditions for proper function than other standard monitors).[130] Probe use for >72 h was reported (range, 8−170 h). Placement via standard 20 gauge cannulae showed no degradation of arterial pressure waveforms. No probe failures occurred. Arterial hypotension, use of vasopressor agents, and core−peripheral temperature differences did not affect agreement of in vivo monitor−standard in vitro analyses. A second trial of the PB3300 system conducted in three U.S. hospitals showed similarly good performance in OR (mean time of monitoring = 6 h) and ICU patients (mean time of monitoring = 46 h) with several hundred in vivo monitor−in vitro sample analyses compared over ranges that included extremes encountered in critically ill patients.[131] In vivo−in vitro comparison data was subjected to 'proficiency testing' used by clinical laboratory regulatory organizations (Health Care Financing Administration Clinical Laboratory Improvement Act) to assess reliability and measure agreement of an analyzer system with results from a peer group of similar analyzers measuring a standard test sample. The data obtained in this study were within the specifications of test sample target−measurement variation, although marginally for PO_2. These studies demonstrated a discrete fiber optic sensor system that was clinically viable.

The Paratrend 7 system (Pfizer/Biomedical Sensors Ltd.) was demonstrated in similar trials with similar success. In ICU patients, a mean duration of monitoring of 43 h (range 10−118 h) showed the ability to monitor pH, PCO_2, and PO_2 for time periods consistent with duration of clinical crises that require intensive care. With this system, 'in vivo recalibration' (adjustment of the system readout) to agree with an in vitro clinical laboratory sample analysis was done at 12 h intervals (but not during periods of blood gas instability, e.g., adjustment of fraction inspired O_2) to correct for presumed sensor drift. A second similar trial in OR patients undergoing cardiopulmonary bypass surgery demonstrated performance during hypothermia (30 °C). In vivo−in vitro agreement was poor for PO_2 but acceptable for pH and PCO_2. Of note, the Paratrend 7 system used an amperometric electrode PO_2 sensor in its first commercially available system.

In work that preceded that of other commercialized systems, the Biosentry System (Optex Biomedical Inc.) had similar results in trials that used a precommercial prototype system. In ICU patients, in vivo monitor−in vitro analysis agreement was acceptable and similar to a comparison of in vitro analyzers (mean monitor duration = 55 h, range 43−68 h).[132] In OR patients, performance was adequate but found

poor in vivo−in vitro agreement for PO_2 during emergence from general anesthesia when PO_2 changes might be rapid and peripheral blood flow could change.[133]

3.3. Issues Identified with Continuous Intraarterial Blood Gas Monitoring

Reports of these trials in the critical care literature demonstrated a new sensor technology that functioned remarkably well in clinical environments for critically ill patients. Continuous intraarterial blood gas monitoring based on fiber optic sensor technology presented a significant advance in physiologic monitoring. Many issues became apparent as a result.[122]

In these clinical trials, many conditions were encountered that would impede general system acceptance for routine clinical use, e.g., sensor calibration, response time and temperature effects, and disagreement of some in vivo−in vitro measurements. The latter issue was one of constant focus throughout efforts to effectively market and sell these continuous intraarterial blood gas monitor systems. In this regard, sensor response times, exact time of sampling, flow variation in the radial artery (typical arterial pressure cannula and probe placement site), and clinical laboratory sample processing systems were examples of factors that could affect in vivo−in vitro analysis agreement. In the eyes of prospective clinician customers, the problem of imprecise agreement of a continuous monitor and the standard clinical laboratory was a persistent issue. Blood gas variables pH, PCO_2, and PO_2 had been marketed as critical physiologic information that require continuous monitoring to better manage critically ill patients, and any disagreement could therefore present a problem.

Clinical (nonideal) situations that were encountered included hemodynamic instability, arterial hypotension, vasoconstriction, and cold extremities (probe temperature up to 7 °C less than body core temperature), all possibly contributing to low blood flow through the peripheral artery of probe placement, and disagreement of in vivo−in vitro analyses. Although limited in size, the initial observational clinical trials did demonstrate remarkably good agreement of in vivo−in vitro analyses, especially pH and PCO_2. PO_2 consistently had the poorest agreement, but arterial PO_2 may be the most 'volatile', subject to the greatest and most rapid changes, and therefore most likely to have the poorest agreement with in vitro analyses of random blood samples.

The cost of any new monitors or equipment was another rapidly growing issue in the early mid 1990s when these continuous intraarterial blood gas monitoring systems became commercially available. None of the clinical trials addressed this issue. Underlying this issue, the benefits of either intermittent, discrete sample analysis or continuous blood gas monitoring had ever been demonstrated or compared, making estimation of the value of one over the other difficult. The cost of the fiber optic sensor systems included the probe and bedside monitor instrument. The latter was especially expensive, having necessarily incorporated expensive optical components to select light of specific wavelength ranges from a broad spectrum source. Bedside monitor instrument prices of $20 000 or greater were problematic. Probe prices of $300 or greater were required due to the cost of manufacture, and were also problematic.

To most potential customers, the cost of the continuous intraarterial blood gas monitor systems seemed much greater than that of standard clinical laboratory systems if the cost of one laboratory blood gas analysis was compared with the cost of one single-use probe. Many other common cost factors for laboratory blood gas analysis (e.g., nursing time required to obtain delayed or lost laboratory results and costs of other monitoring technologies that may provide indications or rationale for obtaining a laboratory blood gas analysis) were typically ignored. The value (benefit/cost ratio) of continuous blood gas data during an acute hypoxic crisis would be very high (could prompt life saving interventions), but probably very low during most of the time a patient is monitored. The cost of two continuous intraarterial blood gas monitor probes during 6 days in an ICU could still be considered a better value than, by crude analogy, the cost of seat belts and air bags in automobiles that are designed to save lives in a crisis.

3.4. Interstitial Fluid Monitoring Using Fiber Optic Sensor Systems

With ongoing controversy over continuous arterial blood gas monitoring, the concept of interstitial fluid (IF) monitoring using this technology began to be investigated. The fiber optic sensor probes were very small in diameter (~0.2 mm), and probe designs that incorporated sensors at or near the probe tip were potentially useful in this application. Monitoring brain parenchyma pH, PCO_2, and PO_2 was the first application to receive focused study.[22,134−138] In studies of patients undergoing neurosurgical procedures, IF pH, PCO_2, and PO_2 were monitored and found to change dramatically.[22,137] In an animal model of cerebral hypoxia and ischemia, differences in systemic and brain parenchyma baseline measurements and dramatic changes in brain parenchyma measurements were demonstrated.[138] These real-time, simultaneous measurements had not been available previously and provided new insight to the effects of changes in brain perfusion on tissue cellular metabolism. Brain parenchyma norms and thresholds for intervention were considered and analyzed.[135,138] As shown in Figure 7, remarkable long-term monitoring was described in one report and demonstrated the possibility of prolonged monitoring throughout typical ICU stay times, similar to blood pressure and, for brain trauma, intracranial pressure.[139] This data confirmed the durability of the sensors and probe designs for IF monitoring. This data also demonstrated ongoing variability of continuous monitoring of basic cellular oxygenation and ventilation variables, and possibility of intervention to preempt and avert potentially disastrous effects of intracranial hypertension due to edema.

A tissue bed of continued interest to many investigators was skeletal muscle, and the same fiber optic sensor technology developed and marketed for continuous intraarterial blood gas monitoring was applicable. Reports in animal models of hemorrhagic shock described the ability to simultaneously monitor IF pH, PCO_2, and PO_2 of skeletal muscle reliably and accurately.[140,141] These reports also depicted clear differences of systemic and IF pH, PCO_2, and PO_2 norms and changes of these variables during and after shock. IF pH was shown to recover much more slowly than IF PCO_2 and PO_2, likely reflecting persistent cellular metabolic perturbation. Similar to studies of brain parenchyma, changes in skeletal muscle IF PCO_2 appeared to reflect the adequacy of perfusion, and, together with IF pH, the presence of anaerobic, or perhaps defective metabolism. A case report of skeletal muscle IF monitored during ICU shock resuscitation using the same fiber optic sensor technol-

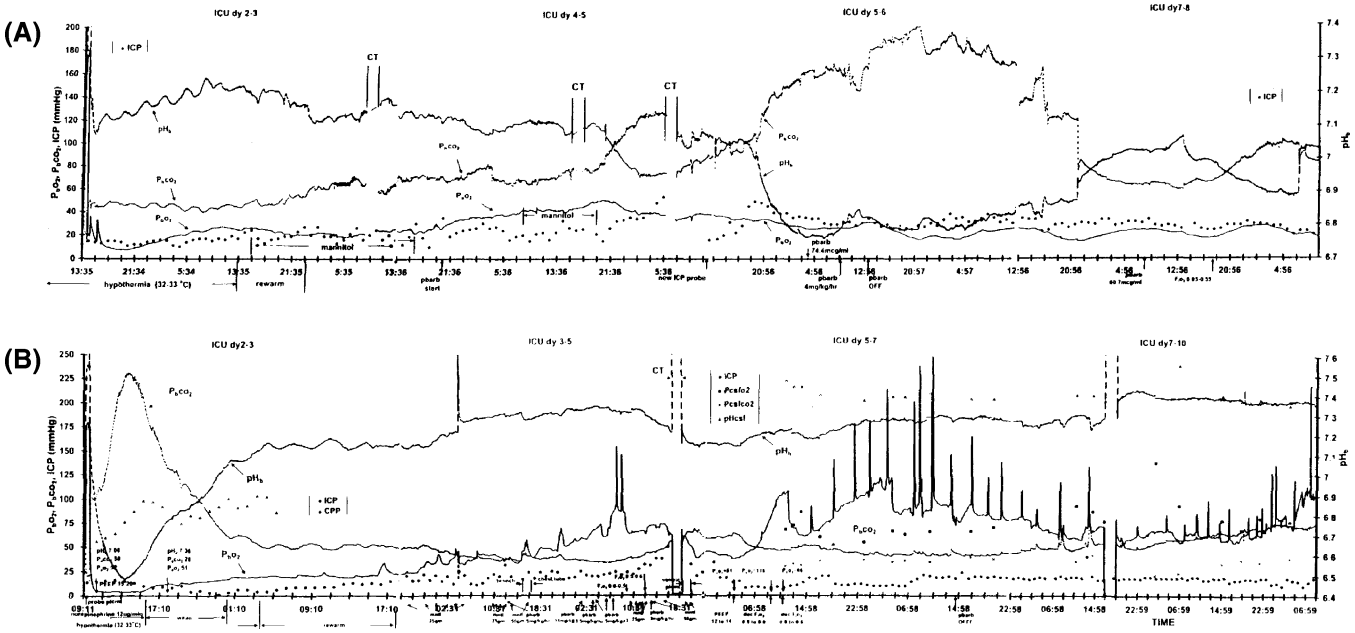


Figure 7. (a) Extended continuous monitor records of patient brain parenchyma interstitial fluid (IF) pH, PCO_2, and PO_2, and intracranial pressure (ICP; hourly) after severe closed head injury during eight successive ICU days. Cyclic oscillation of IF PCO_2 and pH co-incident with hypothermia temperature controller; IF PO_2 increases with start of pentobarbital therapy (ICU day 4); IF pH decrease and IF PCO_2 increase 9 h prior to ICP increase to 50 mmHg (ICU day 4) and 3.5 h prior to second ICP increase (ICU day 5). (Reprinted with permission from ref 139. Copyright 1998 Springer.) (b) Extended continuous monitor records of patient brain parenchyma interstitial fluid (IF) pH, PCO_2, and PO_2, and intracranial pressure (ICP; hourly) after severe closed head injury during 10 successive ICU days: IF $PO_2 = 4$ mmHg, $PCO_2 = 230$ mmHg, pH = 6.48 co-incident with arterial $PCO_2 = 58$ and pH = 7.08, and norepinephrine infusion (ICU day 2); IF PO_2 increase with start of pentobarbital therapy (ICU day 4); IF pH decrease and IF PCO_2 increase 10.5 h prior to ICP increase to 50 mmHg (ICU day 4). (Reprinted with permission from ref 139. Copyright 1998 Springer.) For these studies, brain parenchyma interstitial fluid pH, PCO_2, and PO_2 data was obtained using fiber optic sensor system (Biosentry, Optex Biomedical Inc.) following an institutional review board approved protocol.

ogy and system designed for blood gas monitoring depicted derangements of skeletal muscle IF pH, PCO_2, and PO_2 due to severe shock following massive trauma.[142] Continuous monitoring showed the return of these variables to normal with reestablished stable hemodynamic performance. In these reports, hemodynamic performance was monitored using standard highly invasive pulmonary artery and peripheral artery catheters. The skeletal muscle placement of the fiber optic probe with its multiple pH, PCO_2, and PO_2 and temperature sensors was via percutaneous puncture using a 20 gauge needle and catheter sheath, withdrawn to expose the sensors to IF in viable tissue. This placement technique was minimally invasive, easily accomplished, and of extremely low risk. The authors concluded that skeletal muscle IF (i.e., peripheral tissue) monitoring may provide a more complete picture of shock and resuscitation that do conventional systemic variables, with skeletal muscle IF pH, PCO_2, and PO_2 providing a direct indication of metabolism, respiration, and oxygenation, and an indirect indication of perfusion of peripheral tissue.[142]

3.5. Summary of Fiber Optic Sensor System Development for in vivo Monitoring

By the late 1980s, development of fiber optic sensor systems for intraarterial blood gas monitoring was an international effort and in the United States had involved NIH, national laboratories, major pharmaceutical and device manufacturers, and numerous venture companies. By one estimate, $250 million of private industry and venture funding had been expended from the mid to late 1980s, all with the goal of intraarterial blood gas monitoring. By the early 1990s, three systems were developed, cleared to market by the U.S. FDA, and, for a short time, sold competitively. By the late 1990s, only one of these systems was available, and its use was rarely encountered. Presently, one relatively new fiber optic sensor system designed for IF PO_2 is commercially available and marketed primarily for laboratory animal research (Oxford Optronix Ltd., Oxford, U.K.; www.oxford-optronix.com). Reports of continued development of indicators and sensor systems continue to appear in the literature.[143−145]

4. Factors Affecting the Future of Discrete Sensor Development for in vivo Monitoring

The concept of discrete sensors incorporated in a probe to monitor specific physiologic processes within a patient (or other living subject) has been demonstrated. ISFET and fiber optic sensor technology development in recent decades has provided a wealth of experience and rationale for continued development. The experience has included technology and performance requirements for medical applications of continuous monitoring using discrete sensors incorporated in a probe to provide remote access.

Clinical trials and additional experience with fiber optic sensor continuous arterial blood gas monitor systems stimulated careful consideration of need for and implications of continuous blood gas monitoring. The value added by continuous (blood gas or electrolyte) monitoring over intermittent (clinical laboratory) measurement is not obvious. The need for continuous monitoring of variables is accepted for some variables in clinical critical care. This need has been less well established for those variables traditionally available from the clinical laboratory than for pressure, heart

electrical activity, and certain oxygenation variables, especially arterial blood hemoglobin O_2 saturation (SpO_2; 'pulse oximetry'). These variables, indicative of heart and lung function and of continuous concern in an ICU, may also be monitored because those sensor technologies (invasive blood pressure, Ag−AgCl EKG electrode, hemoglobin O_2 saturation) provide reliable continuous inexpensive measurements.

In general, conditions for continuous monitoring of a sensed variable should include the following: (1) likely to change rapidly and of a magnitude that adversely affects patient physiology; (2) an available, calibrated intervention that affects the measured variable (i.e., a variable that is able to be measured but for which there is no treatment or intervention of research interest would not be a candidate for clinical care); (3) not detectable by other existing techniques; (4) and total response time from decision to obtain a measurement to return an analytical result to be acted upon by a physician and therapy to have an effect should be decreased compared to existing measurement techniques

For remote laboratory-based analyzers, the total response time might be 10 min (including decision to obtain measurement, acquisition of representative sample, transport of sample, processing and analysis, results quality assurance check, and transmit of result to bedside). For a bedside point of care analyzer, total response time might be 5 min. For a discrete sensor-based, continuous in vivo monitor system, total response time (defined using system response time constant to characterize a sensor, e.g., 63% of full response to a step increase in analyte) might also be 5 min, but this system would be more likely to detect important changes of the monitored variables.

Clinical trials of fiber optic sensor-based blood gas monitor systems demonstrated reliable, safe function in ICU settings in patients who were at risk for or who were experiencing respiratory distress and other complications. Other technologies that could still presently be considered to compete with continuous intraarterial blood gas monitoring included the following: (1) physical examination—ability to identify signs or symptoms or likelihood of development of blood gas abnormalities; deemed inadequate to replace blood gas analysis but able to suggest need to obtain blood gas information; (2) pulse oximetry—by the late 1980s, a noninvasive continuous monitor that had become a clinical standard during intraoperative anesthesia and management of critically ill patients; insensitive to changes in $PO_2 > 60$ mmHg, thereby permitting large decreases in arterial PO_2 indicative of deteriorating pulmonary function without affecting hemoglobin O_2 saturation indicated by pulse oximetry; unreliable in patients with poor cutaneous perfusion, e.g., during shock or hypothermia, who could be unstable and likely to suffer sudden decreased oxygenation; (3) capnography—noninvasive continuous monitor of airway end tidal PCO_2 but not specifically indicative of arterial PCO_2, i.e., decreasing end tidal PCO_2, could indicate decreasing cardiac output or increasing alveolar ventilation and not indicative of arterial pH; (4) in vitro (clinical laboratory) arterial blood gas analysis—readily available in hospitals using highly automated analyzers with excellent quality control and rapid, accurate, repeatable analysis; major deficiency is typically prolonged total analysis time from time of sample acquisition to time of results report; (5) in vitro (bedside or point of care) arterial blood gas analysis—accurate, repeatable analysis, available in hospitals, typically in OR or ICU settings where immediate and frequent analysis may be required; self-contained electrode sensor−calibration solution−sample waste modules or single-use disposable electrode sensor modules;[146−151] (6) ex vivo (bedside or point of care) analysis—previously developed in systems using ISFET,[48−50,102,152,153] electrode,[154,155] and fiber optic sensors,[154,155] incorporated in a patient-attached module that are periodically exposed to blood withdrawn from and reinfused to the patient via intravenous or intraarterial catheter and tubing.

For discrete sensor-based continuous monitor systems other than blood gas, other technologies to supplant or cue need for electrolyte analysis include primarily EKG to detect heart rhythm abnormalities, ISFET K^+, and Ca^{++} experience suggests rationale for continuous electrolyte monitoring in many intensive care situations. Bedside point of care analyzers are commercially available to provide random or interval analyses, but rapidity and magnitude of changes in circulating blood volume are common and meet conditions for continuous monitoring as described above.

Decisions to obtain a measurement and with some frequency have been influenced by desire to contain overall patient care cost. The relative value of a continuously monitored variable available intermittently via clinical laboratory analysis must therefore be demonstrated to decrease cost, risk to the patient, and inconvenience of bedside caregivers. In clinical intensive care environments the frequency of essential clinical laboratory measurements tends to increase with perceived severity of a patient's illness. Because risk to the patient is already established with placement of catheters for arterial and venous blood, urine, and upper gastrointestinal tract fluid, the decision for increased frequency of clinical laboratory analysis is unlikely to increase this risk. With increased severity of illness and physician judgment of possibility of survival with certain interventions, cost becomes a secondary factor affecting the frequency of clinical laboratory measurement.[59]

The concept of ex vivo analysis has been pursued, and systems were developed and commercialized. Systems were developed based on early ISFET sensors and measured K^+, Na^+, Ca^{++}, and pH in patient blood with initial focus on intraoperative monitoring during cardiac surgery.[48−50,153] Two systems were commercialized in the early 1990s. A system incorporating fiber optic pH, pCO_2, and pO_2 sensors was found to function reliably in clinical trials involving ICU patients.[156,157] Another system incorporating electrode sensors for pH, pCO_2, pO_2, K^+, Na^+, and hematocrit also functioned reliably in ICU patients.[154,155] Development and commercialization of these ex vivo systems occurred during and after that of intraarterial fiber optic blood gas monitor systems. The electrode system was recently recommercialized (VIA Medical, Austin, TX; www.viamedical.com). Rationale for development of these systems was in part based on the uncertainty of performance (primarily accuracy) and inability to check calibration of intravascular sensors that might be unpredictably compromised by effects of blood protein deposition and clot formation. Further rationale was associated with difficulty in design and manufacture of intravascular probes incorporating multiple sensors of microscopic dimension. Analysis of ex vivo vs in vivo system viability has been based on monitoring of systemic physiology in blood. Described above, focus on intravascular monitoring was a premise that was unsuccessful for fiber optic blood gas systems, whereas, described below, interstitial monitoring was found to be feasible using both ISFET and fiber optic

sensor technologies, and to offer a new mode of physiologic monitoring.

Rationale for continuous data for current clinical laboratory analyses has been described to relate to hospital personnel labor saving in the current environment of cost reimbursement for diseases treated and fixed annual budgets for care of defined patient populations.[59] Instead of multiple discrete sample analyses and the attendant labor involving bedside nurse, clinical laboratory technicians, and sample courier, discrete sensor probes, calibrated and placed once by the bedside nurse, were demonstrated by fiber optic sensor-based continuous blood gas monitor systems described above. The cost to the patient of a multisensor probe, e.g., $300, which would be replaced every 2 or 3 days, would still compare favorably with individual blood gas analyses, e.g., $300 each. If a probe incorporated blood gas and electrolyte sensors, the cost equation would be more favorable for in vivo continuous monitoring. Quality of care, enhanced by continuous monitoring of critical clinical chemical variables, could be favorably affected.

Discrete sensor-based continuous in vivo monitoring is now complemented with information technology in hospital critical care environments. Decision support algorithms could be developed to recognize abnormal trends of individual variables, compare patterns of concurrent variables, interpret abnormalities as possible differential diagnoses, and provide instructions for additional confirmatory analyses and interventions. With the reliability of monitoring systems established, closed loop control would be developed.[158]

4.1. Continuous IF Monitoring

Of the ISFET and optode sensor system experiences, perhaps the greatest advance was demonstration and confirmed utility of IF monitoring as a new mode of monitoring in clinical critical care medicine. Reasons include the following: (1) IF presents compartments that are accessible by small, percutaneously placed probes. (2) Gas partial pressures and ion activities reflect adequacy of blood perfusion and cellular function. (3) Inadequate cellular utilization of delivered substrates is detectable early and adequacy of interventions for improved cellular utilization are able to be monitored.

In large tissue beds, inadequate cellular utilization of delivered substrates is commonly termed 'shock'. Shock is perhaps the most central and resource intense problem that confronts clinical critical care medicine.[12,159] Recognition of shock, resuscitation, and subsequent maintenance of organ system and hemodynamic function are capabilities that have defined clinical critical care of severe trauma and sepsis patient populations. The current state of the art involves measurement of systemic variables to recognize and confirm shock, and to monitor the resuscitation process. Systemically measured variables, including blood pressure, pH, hemoglobin O_2 saturation, and lactate concentration, and derived variables, including base deficit, systemic vascular resistance, and oxygen delivery, have been used clinically as indirect indicators of tissue perfusion, but they do not indicate onset and correction of cellular dysfunction in any particular tissue bed.[160−164]

From ISFET experience, IF K^+ seems to be an indicator of cell function that is appropriate and able to be monitored. In most tissues, especially skeletal muscle which is perhaps most accessible, the large cellular transmembrane gradient between intracellular cytoplasm and extracellular fluid that is the physiologic norm is related to constant O_2-dependent energy supply. An increase in IF K^+, as demonstrated with early ISFET studies of hemorrhagic shock in animal models, is most likely indicative of disruption of O_2-dependent energy supply.[51] IF Ca^{++} monitoring, also demonstrated to be feasible in early ISFET studies, is another variable of potential relevance in monitoring cellular function during shock and resuscitation. Decreased blood Ca^{++} activity was reported in early studies of hemorrhagic and septic shock in animal models,[15,16] and blood and IF Ca^{++} were shown to be decreased by IV citrate infusion comparable to that associated with blood transfusions.[57,59] IF K^+ and Ca^{++} may therefore be more direct indicators of cellular function and detectors of cellular dysfunction than traditional systemic variables, and these variables can be monitored using discrete sensors.

From optode experience, as described previously, IF pH, PCO_2, and PO_2 were studied in animal models of hemorrhagic shock and resuscitation.[140,141] Skeletal muscle was studied as a likely clinically available tissue bed affected by hemorrhage-induced perfusion abnormalities. Comparison of systemic arterial and venous measurements revealed IF pH < venous pH < arterial pH, IF PCO_2 > venous PCO_2 > arterial PCO_2, and arterial PCO_2 > IF PO_2 > venous PO_2, as expected with the tissue bed as the site of cellular respiration and source of acidic metabolic end products. Inverse time courses for IF pH and PCO_2 occurred with hemorrhage, and pH was slowest to recover toward baseline measurements, possibly indicative of integrated metabolic status and its prolonged derangement. Rapidly decreased PO_2 was observed, consistent with decreased perfusion of skeletal muscle (peripheral) tissues and preservation of perfusion of core organs and rapid recovery to measurements that temporarily exceeded baseline with resuscitation. After an hour of shock (MAP $\approx$ 45 mmHg), IF pH $\approx$ 6.9, IF PCO_2 $\approx$ 130 mmHg, and IF PO_2 $\approx$ 5 mmHg, compared with arterial pH $\approx$ 7.1, arterial PCO_2 $\approx$ 35 mmHg, and arterial PO_2 $\approx$ 100 mmHg, were recorded, demonstrating greater proximity of IF measurements to cellular processes than reflected by systemic measurements. In clinical studies of trauma shock resuscitation in which skeletal muscle was monitored during resuscitation, similar arterial−IF−venous gradients and extreme IF measurements were observed.[165] Studies of IF pH, PCO_2, and PO_2 of brain parenchyma in an animal model of ischemia and hypoxia, and clinical studies monitoring effects of therapy after brain trauma, found more extreme measurements of IF pH, PCO_2, and PO_2.[138,166] IF pH, PCO_2, and PO_2 therefore appear to be direct indicators of cellular function and detectors of dysfunction, and were also demonstrated to be reliably monitored using discrete sensors.

The IF studies undertaken with ISFET and, later, optode discrete sensor systems show IF monitoring to be a clinically acceptable technique. Discrete sensor technologies, as described, could open a valuable window of continuous monitoring in critical care medicine. Requirements for IF monitoring of K^+, Ca^{++}, pH, PCO_2, and PO_2 seem to have been clearly met:[59] (1) small probes were able to be placed without disruption or disturbance of the local tissue environment. (2) Sensed variables were able to be monitored in IF environments for many hours to days. (3) With systemic pathology (e.g., hemorrhagic shock, brain injury) and local tissue perfusion changes, sensed variables changed early and with greater sensitivity than conventional systemic param-

eters. (4) The rate and magnitude of changes in sensed IF variables K^+, Ca^{++}, pH, PCO_2, and PO_2 are specific and striking in the presence of shock, or brain injury, to consistently diagnose inadequate perfusion and need for intervention. (5) These sensed IF variables provided timely and reliable responses to interventions to indicate adequacy of response at the tissue level.

Importantly, in critical care settings of trauma and sepsis resuscitation and therapy for brain injury, outcomes are not able to be accurately predicted after resuscitation efforts based on conventional systemic measures. For this reason, the information obtained from continuous IF monitoring using discrete sensor systems could offer greatest utility in monitoring adequacy of resuscitation interventions.

An alternative to direct tissue monitoring that evolved in the 1980s was CO_2 tonometry of mucosa of hollow viscus organs, including stomach and upper gastrointestinal tract.[140,167−175] Using a CO_2-permeable membrane to surround a CO_2 sensor, changes in mucosal interstitial PCO_2 could be monitored by placing a flexible (balloon) tonometer in close proximity to metabolically active mucosal membranes lining the GI tract. Normally highly perfused, the body's response to blood loss or increased skeletal muscle O_2 demand is to shunt blood flow from the GI tract to tissues that require more constant blood flow, causing CO_2 accumulation in the GI mucosa. CO_2 diffusion from intra- to extracellular space and across the permeable membrane to the CO_2 sensor is reliably detected and representative of mucosal interstitial PCO_2. GI mucosal CO_2 tonometry, available commercially beginning in the 1990s, was subjected to many studies and vigorous debate to establish its credibility as an indirect monitor of systemic and organ-specific O_2 delivery and onset of anaerobic metabolism signaling O_2 delivery and perfusion inadequacy. Oral mucosal CO_2 tonometry systems were developed that incorporated an ISFET or fiber optic pH-based PCO_2 sensor. A commercially available system incorporated a fiber optic pH-based PCO_2 sensor, which provided single PCO_2 measurements (Capno-Probe Sublingual Sensor, Nellcor (Tyco Healthcare/Mallinckrodt), Pleasanton, CA; no longer available). Recent reports indicate that continuous measurement of oral mucosal PCO_2 identifies the severity of the volume deficit[176] and may offer a more direct and readily obtainable assessment of tissue perfusion than blood pressure.[177]

Presently, there are two systems commercially available for continuous in vivo monitoring of oxygenation of tissue beds. A highly engineered electrode system was developed and tested in other applications and optimized to monitor brain parenchyma, i.e., brain IF, PO_2 (Licox, Integra LifeSciences Inc., Plainsboro, NJ; www.integra-ls.com).[10,20,28,178,179] The system incorporates a precalibrated electrode PO_2 probe (0.8 mm diameter) and intraparenchyma placement system for use in monitoring brain oxygenation after injury during intensive care for time periods of days. Another technology, near-infrared spectrometry (NIRS), has been developed for noninvasively monitoring tissue hemoglobin O_2 saturation for time periods of days (Inspectra, Hutchinson Technology Inc., Hutchinson, MN; www.htbiomeasurement.com). This technology does not use a discrete sensor that transduces a chemical analyte to electrical or optical signal but monitors IR absorbance by oxygenated hemoglobin (and tissue cytochromes) in skeletal muscle and subcutaneous tissue using a fiber optic probe that attaches to the overlying skin surface.[180,181] In recent clinical trials, the monitored variable, StO_2, has been shown to detect need for early massive transfusion and correlate with outcome in severely injured patients.[182,183] Similar to ISFET and optode sensors, both systems have developed over a period of decades to their present form and function. Of note, these are among the latest monitor systems to become commercially available for intensive care use, and both are designed to monitor tissue and not systemic blood.

4.2. Technology Problems

The requirements of an ideal monitor for use in clinical critical care environments are as follows:[12] (1) a sensor for an essential variable(s) that is accurate and stable for indefinite duration of use; (2) a non- or minimally invasive sensor; (3) a continuous monitor function with the ability to display trend (record of recent measurements with time); (4) a system that is easily used and with measurement display that is easily understood; (5) small size and weight; and (6) ruggedness and transportability.

This list of qualities is attained by very few monitors that are in currently in use. The pulse oximeter is perhaps the foremost example that embodies most of these requirements and is universally affordable throughout the health care systems of the United States and most nations. With new information that would be regarded as essential, e.g., to guide shock resuscitation to an endpoint, new ideals become obvious.

Both ISFET and optode discrete sensor technologies were developed to the extent that features and functions of prototype and commercially available systems did address most of these ideal requirements. Probes were developed that were of 0.5 mm diameter (ISFET) and 0.2 mm diameter (optode). Optode probes were able to be placed percutaneously and without any bleeding in skeletal muscle IF space. Instrumentation systems, designed using early 1990s optical technology, were adequate in their designs. Much improved systems were developed by the late 1990s using new blue light (460 μm) emitting diode (LED) device technology. This single technical development led to electro-optical bedside instruments that were quite compact and transportable and incorporated displays with clearly viewable, easily understood graphical data presentation. Additionally, these latest electro-optical instrumentation systems to be developed, although for an ex vivo a fiber optic sensor system, were affordable (~$2500).[156,157]

Issues encountered with invasive probes or implanted materials include biocompatibility. A device intended to be placed in direct, prolonged contact with blood in a peripheral artery must be non-thrombogenic, nontoxic, sterile and not injurious to the tissue or blood vessel endothelium it will contact. Probe designs for fiber optic sensor systems commercialized in the early to mid 1990s met these requirements. For IF monitoring, these blood compatibility requirements are not applicable because no blood contact occurs. A basic principle of intensive care, especially with evolving infectious agents resistant to antibiotic drugs, is to minimize penetration of skin, upper airway, and other anatomic protective barriers. Compared to intravascular placement, an advantage of percutaneous placement of a small diameter probe in the interstitium, e.g., anterior thigh, tricep, or other skeletal muscle bed, is the lack of blood stream invasion, ease of site preparation, and ability to visually monitor the placement site for development of erythema or presence of blood. Infection of bicep interstitial sites was not reported as a

complication in extensive clinical trials using an electrode PO_2 probe.[20]

Sensor response times have been addressed for ISFET and fiber optic discrete sensors. Optode systems, which balanced sensor response and life times to achieve adequate performance, offered sensor life time duration that was adequate for clinical critical care applications: 72 h was considered a performance requirement; intraarterial blood gas monitoring performance >150 h was reported in clinical trials.[130] Sensor 90% response times for both ISFET (milliseconds) and fiber optic sensor (seconds to 1−3 min) systems were found to be much less than that of physiologic events monitored systemically or in IF compartments.[40,55,122,184]

Inherent to measurement provided by a sensor is accuracy. For continuous in vivo monitoring, accurate measurement provided by a precalibrated sensor is required. Precalibration methods for ISFET and fiber optic sensor systems described were in vitro and relied on characterizing sensor responses over physiologic ranges and specifying sensor measurements in an aqueous solution similar to that of the physiologic (micro) environment into which the sensor would be placed. Typically, two solutions of known gas partial pressures or ion activities bracketing the anticipated (patho)physiologic range were used. Upon placement, it was assumed that precalibration measurements continued to reflect the in vivo physiologic microenvironment. Drift of sensor responses, both baseline and magnitude, is a basic issue for continuous in vivo monitoring, with which sensor access may not be possible without disturbance of the placement site or the sensor. Ex vivo and in vitro systems provide sensor access to check calibration. Provision of in situ recalibration has been addressed using channels and chambers for introduction of calibration fluids but not incorporated in commercial systems.[63] Recent ISFET developments, including options to Si_3N_4 gate regions, may have minimized (pH sensor) drift, and IC device or encapsulation degradation may be monitored by incorporation of other on-chip devices.[45,185,186]

Calibration of sensors prior to placement was a part of prototype ISFET and commercial optode systems operation. Neither ISFET or optode sensors have been fabricated with sufficient uniformity or package shelf life stability to preclude in vitro calibration just before use at patient bedside. Optode sensor system stabilities were characterized sufficiently to predict life time duration, or need for offset adjustment at some reasonable time interval based on representative sample clinical laboratory analysis, and included ports to permit (blood) sample acquisition at the placement site for independent clinical laboratory analysis.[122]

The question of accuracy has been addressed in studies of ISFET and fiber optic sensor systems in systemic blood of laboratory and clinical trials by comparing samples from the sensor microenvironment, as described above, and these studies have provided the best evidence that continuous in vivo monitoring is accurate and reliable in blood. IF, i.e., extravascular and extracellular, environments are arguably less complex and more favorable than intravascular blood for sensor placement and monitoring. Effects of protein or cell adsorption on in vivo sensor systems, e.g., ISFET ion-selective membrane or reference electrode surfaces, in either blood or IF have not been studied systematically to the author's knowledge. Related effects have been studied in commercial clinical laboratory (in vitro) systems, and reports confirm complexity of in vivo electrolyte and protein interaction.[96,187,188] Empirical data, including blood and IF, provide convincing evidence of continuous in vivo monitoring capability for discrete blood gas and electrolyte sensors.

The foremost problem, and the most obvious, for ISFET and optode discrete sensor systems is low-cost manufacture involving liquid and polymeric components with micrometer dimensions. To the knowledge of the author, these problems have not been adequately resolved, or if they had, a commercially viable product would be presently available. For ISFET sensors, insulation−encapsulation of part of an IC chip and exposure of the thin gate region or incorporation of liquid or gel ion-selective membrane material over the thin gate region has been the essential challenge. Recent developments that have been cited include:[45] prefabricated microhousing assemblies; sensor fabrication using epoxy molds; photolithographic process to incorporate nonplanar structure; and elastomeric sealant materials. These developments have provided encouraging manufactured prototypes of single-sensor probes as small as ~1−2 mm diameter with ruggedness much greater than that of conventional (glass membrane pH) electrodes. Discrete ISFET sensors manufacturable in large volume and suitable for in vivo monitoring are not yet reported. For ISFET sensor systems, a technical solution of this problem appears to preclude commercial endeavors for the high-price, high-volume medical market. For optode sensor systems, automation of processes was foreseeable with manufacturing methods developed by the early 1990s.

5. Summary

ISFET and fiber optic sensors progressed rapidly from concept to reality in less than a decade, specifically for medical applications. Both technologies realized the concepts of discrete sensors with micrometer dimensions, and with potential for manufacture of a high-technology, low-cost monitor to dramatically improve medical care. Much was learned with these developments, and these technologies are principal examples of medical sensor technology that continues to evolve.

Both ISFET and fiber optic sensors are basic technologies with broad applicability, including many sensors and sensor mechanisms and many potential applications. Development of these two sensor technologies progressed very differently. ISFET sensors progressed with continued demonstration of new sensors and mechanisms with engineering prototypes developed to study and confirm feasibility of applications. Based mostly on scientific grant and minimally on private funding, this progressed rapidly throughout the 1970s and early 1980s with the resulting demonstration of sensors for hydrogen, potassium, calcium, sodium, ammonium, and fluoride ions and, with broader ChemFET technology, developments of other families of sensors, and development of sensor theory and mechanism. Fiber optic sensors, from earliest demonstrations of pH and PO_2 sensors, focused medical drug and device corporations on the blood gas variables, pH, PCO_2, and PO_2, and on a perceived market for continuous intraarterial blood gas monitoring. Developments of commercial products resulted and, as described, had limited market success for many reasons.

ISFET and fiber optic sensor systems were found to be useful for continuous monitoring of interstitial fluid compartments of tissue beds. Skeletal muscle and brain parenchyma are tissue beds in which reliable monitoring was demonstrated and found to have probable clinical importance. With ISFET sensors in prototype probes, interstitial fluid monitor-

ing of pH, K^+, and Ca^{++} was investigated with early success. Fiber optic pH, PCO_2, and PO_2 sensor systems designed for intraarterial blood gas monitoring were used for interstitial fluid monitoring and further demonstrated capability and probable clinical utility of interstitial fluid monitoring. Interstitial fluid monitoring appears to be a mode of monitoring that should be pursued in clinical critical care medicine, and ISFET and fiber optics sensor systems offer feasibility.

The information obtained from continuous interstitial fluid monitoring using ISFET or fiber optic sensor systems could offer greatest utility in monitoring adequacy of shock resuscitation interventions. Recognition, resuscitation, and prevention of shock is perhaps the most central and resource intense problem that continues to confront clinical critical care medicine.[12,59,159] As demonstrated with continuous monitoring of ISFET or fiber optic K^+, Ca^{++}, pH, PCO_2, and PO_2 sensor systems, these variables may be more direct indicators of cellular function and detectors of cellular dysfunction than traditional systemic variables, e.g., blood lactate concentration or base deficit. The probe designs and sensor systems permitted bedside placement for continuous interstitial fluid monitoring of these variables with little restriction of patient access by clinicians. Experiences with these two sensor technologies have demonstrated capability and probable clinical importance in monitoring the interstitial fluid space of tissue beds.

The developments of both sensor technologies progressed rapidly from basic scientific research and development of theoretical understanding to engineering prototypes and development of practical understanding. Technical problems have precluded a commercially viable medical product. ISFET pH sensors are commercially available for various applications in water, food, and drug process monitoring, but the foremost problem for both ISFET and fiber optic sensor systems, and that most obvious for medical applications, is low-cost manufacture involving liquid and polymeric components with micrometer dimensions.

6. Conclusion

ISFET and fiber optic sensor developments since the 1970s have realized the concept of monitoring clinically important problems in critically ill patients. The ability to continuously monitor physiologic processes of viable cells in tissue beds has also been demonstrated. ISFET and fiber optic sensor technologies have had different development directions since their inceptions, but both have been and continue to be pursued with similar interest. Rapid early progression and developments that continue to show the enduring interest in the concept of discrete sensors to monitor otherwise invisible physiologic processes. It seems likely that these technologies will continue to provide insight into physiology as technical problems are incrementally resolved. These sensor technologies have both been used to demonstrate IF monitoring, a possible new window of continuous monitoring in critical care medicine. The breakthrough of a viable commercial product that provides a new mode of continuous monitoring for clinical critical care seems probable. With the future as the cradle of past developments,[189] the medical markets foreseen for these sensor technologies remain as possibilities.

7. References

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