Green Plasma Disappearance Rate in Critically Ill Patients." Chest 122: 1715-20, 2002.

A number of public domain systems exist that utilize a single irradiation source, such as a fiber optic cable connected to a laser and an associated separate detector, such as a CCD camera or spectrophotometer. The laser emitter and fluorescence detector have been further associated with endoscopic devices. Even simpler densitometric systems have likewise existed for some time, with such systems relying on the absorption of ICG in the 805-810 nm range. An ear densitometer produced by the Waters Co. of Rochester, Minnesota is advertised as being capable of in vivo measurement of ICG absorbance, but in the aforementioned higher doses.

In light of the marginally useful devices available for continuous monitoring of liver or other organ function using a circulating analyte, the present disclosure provides the advantages of a useful non-invasive system. Thus, in application for United States Patent Serial No. 12/418,866, to which priority is claimed, a generally non-invasive technique for screening for measuring the concentration of a circulating analyte is disclosed. The present disclosure provides advantages that will be apparent. This results in one or more intensity versus time curves, representing an analyte concentration resulting from metabolism of the indicator through the circulatory system, i.e. by the lungs, brain, kidney or other organs.

Implementation of the transcutaneous detection system for accurate detection of a circulating indicator allows monitoring of the decay of a circulating indicator in the blood, and thus allows for monitoring of organ function with relatively low doses of indicator.

BRIEF SUMMARY

~~According to a first aspect of the present invention, there is a system for measuring the concentration of a liver activity analyte that is predominantly removed from the circulating blood by the liver and that contains a fluorescent moiety that can be excited to emit fluorescence through irradiation by excitation photons in wavelength range known to induce fluorescence in said fluorescent moiety of a liver activity indicator analyte, comprising providing an indicator delivery system having an outlet located in a blood vessel of the patient in blood flow communication with the heart; providing at surface of the skin of a human subject one or more sources of excitation photons in wavelength range known to induce fluorescence in said fluorescent component of liver activity indicator; providing at the surface of the skin of a human subject and in alignment with a fraction of the emitted fluorescence photons excited by the source of excitation photons one or more detectors to measure the intensity of emitted fluorescence photons from the liver activity indicator; and providing a monitor/controller responsive to said one or more detectors to record the time-varying relative concentration of the liver activity indicator by recording the time-varying fluorescence signal level. a sensor comprising a photodiode emitter energizable to generate light at the excitation radiation~~

~~wavelength and a photodetector which is filtered for response substantially only to the fluorescence emission, providing a transmissive sensor positionable to sense the presence of at least a portion of the blood-borne indicator flowing within a blood vessel at arterial vasculature of one or more symmetrically paired distal locations of the patient and having one or more outputs corresponding with the instantaneous concentration of indicator at such blood vessel vasculature; providing a monitor/controller having a display and responsive to said actuation to commence measuring the relative concentration of blood concentration of a liver activity indicator in the blood, responsive to a sensor output to display one or more metrics reflecting indicator concentrations to determine the nature of liver function.~~

According to a first aspect of the present invention, there is provided a non-invasive system for assaying the liver function of a mammalian patient using an analyte that is predominantly removed from the circulating blood by the liver and that contains a fluorescent moiety that can be excited to emit fluorescence through irradiation by excitation photons in an appropriate wavelength range, comprising: an analyte delivery assembly having an outlet locatable in a blood vessel of the patient and in blood flow communication with the heart; at least one non-invasive optical sensor positionable along a skin surface of the patient to detect the presence of at least a portion of the analyte as it flows through underlying arterial vasculature, the at least one non-invasive optical sensor comprising a plurality of laser diode emitters located along one side of a tissue location of the patient and energizable to emit light at a first wavelength that will transcutaneously excite the analyte, and a like number of photodetectors located along an opposite side of the tissue for detecting the concentration-indicating intensity of fluorescing photons that will be emitted by the analyte at a second wavelength as a result of excitation light from the emitters being transmitted through the subject tissue and underlying vasculature; one or more sensor outputs corresponding with the instantaneous concentration of analyte flowing through said vasculature at the sensor location; and a monitor/controller having a display, the monitor/controller programmed: to cue actuation of the indicator delivery assembly; to measure, after a predetermined dwell period, the time-varying relative concentration of analyte in the blood over some length of time by repeatedly recording a time-varying analyte fluorescence signal level; to calculate an analyte exponential decay coefficient using the recorded analyte concentration vs. time data; and to determine and indicate the quality of liver function using at least the calculated analyte exponential decay coefficient.

~~According to the second aspect of the present invention, there is a sensing array apparatus comprising (a) a plurality of sources of excitation photons and photodetector pairs for measuring the fluorescence emitted by a fluorescent moiety of a liver activity indicator analyte; b) said sources of excitation photons providing an excitation light source emitting a first wavelength for excitation of a liver activity indicator within the tissues of a patient body, said emitters transmitting the excitation~~

~~light through a collimator lens having a collimating channel aligned with an optical path interference filter, said collimating channel and interference filter located intermediate between said sources of excitation photons and photodetector; and (c) said photodetectors providing for measuring the intensity of the fluorescent light emitted at a second wavelength from the fluorescent moiety of the liver activity indicator analyte; and, (d) a support system of a plurality of array support arms; wherein the array support arms of the support system allow positioning of the sensing array apparatus on the exterior of the patient body, whereupon activation of one or more of the sources of excitation photons transmit excitation light through tissue of the patient, thereby exciting liver activity indicator analyte present in said tissue, said photodetectors thereby measuring the intensity of light emitted by excited liver activity indicator analyte.~~

According to a second aspect of the present invention, there is provided a kit of consumable materials for use by a non-invasive system for assaying the liver function of a mammalian patient, the kit comprising: an indicator delivery tubing system including a valve, syringe connectors, a flow sensor and a sterile intravenous injector; one or more doses of liver activity indicator reagent as a shelf stable material; a diluent for preparing the dose of liver activity indicator reagent for injection or for delivering an indicator bolus; and a dose of nonreactive blood compatible clearing reagent for completing the injection.

~~According to the third aspect of the present invention, there is a kit supplying consumable materials necessary for quantifying liver function comprising: a) an indicator delivery tubing system providing a valve, syringe connectors, a flow sensor and sterile intravenous injector; b) one or more doses of liver activity indicator reagent as a shelf stable material; c) a diluent for preparing the dose of liver activity indicator reagent for injection or for delivering an indicator bolus; and d) a dose of nonreactive blood compatible clearing reagent for completing the injection.~~

~~According to the fourth aspect of the present invention, there is a method for measuring the relative concentration over time of a liver activity indicator in the circulating blood stream, comprising the steps: a) selecting a liver activity indicator analyte that is predominantly removed from circulating blood by the liver said analyte further comprising a fluorescent moiety that can be excited to emit fluorescence through irradiation by excitation photons in wavelength range known to induce fluorescence in said analyte; b) positioning about the skin of a human subject one or more emitter/detector arrays for emitting excitation photons in a given wavelength range known to induce fluorescence in said fluorescent moiety of the liver activity indicator analyte, said emitter in alignment with one or more detectors configured to measure the intensity of emitted fluorescence photons from the liver activity indicator analyte; c) recording the relative concentration over time of the liver activity indicator analyte that has been injected into the blood stream of a human subject, by recording time varying fluorescence signal level; and d)~~

~~calculating a liver activity metric according to Formula 1, whereby the relative liver activity of the patient is displayed in a report.~~

According to a third aspect of the present invention, there is provided a non-invasive method for assaying the relative concentration over time of a liver activity analyte in e a circulating blood stream, comprising the steps: providing an analyte delivery assembly having an outlet locatable in a blood vessel of a patient and in blood flow communication with the heart; positioning at least one non-invasive optical sensor along a skin surface of the patient to detect the presence of at least a portion of the analyte as it flows through underlying arterial vasculature, the at least one non-invasive optical sensor comprising a plurality of laser diode emitters located along one side of a tissue location of the patient and energizable to emit light at a first wavelength that will transcutaneously excite the analyte, and a like number of photodetectors located along an opposite side of the tissue for detecting the concentration-indicating intensity of fluorescing photons that will be emitted by the analyte at a second wavelength as a result of excitation light from the emitters being transmitted through the subject tissue and underlying vasculature; providing one or more sensor outputs corresponding with the instantaneous concentration of analyte flowing through said vasculature at the sensor location; and providing a monitor/controller having a display, the monitor/controller is programmed for: cueing actuation of the indicator delivery assembly; commencing measurement, after a predetermined dwell period, the time-varying relative concentration of analyte in the blood over some length of time by repeatedly recording a time-varying analyte fluorescence signal level; calculating an analyte exponential decay coefficient using the recorded analyte concentration vs. time data; and determining and indicating the quality of liver function using at least the calculated analyte exponential decay coefficient.

The present system discloses using a transcutaneous detection system to measure the quantity of a circulating detection agent in the blood, and thereby measure the decay of concentration due to liver function. The present system utilizes a variation of the previously disclosed system, method and apparatus for detecting and quantifying right-to-left pulmonary shunts. The preferred indicator, which is employed, is indocyanine green (ICG) dye, which will fluoresce when exposed to an appropriate wavelength of higher energy light, for example, a laser in the near infrared region. The procedure is under the control of a monitor/controller having a visual display and capable of providing a cue to the operator. A vein access catheter is employed in connection with a peripheral vein

~~We claim:~~CLAIMS

1. A non-invasive system for ~~measuring the concentration of a~~ assaying the liver function of a mammalian patient using an ~~activity~~ analyte that is predominantly removed from the circulating blood by the liver and that contains a fluorescent moiety that can be excited to emit fluorescence through irradiation by excitation photons in an appropriate wavelength range ~~known to induce fluorescence in said fluorescent moiety of a liver activity indicator analyte~~, comprising:

~~providing~~ an ~~indicator~~ analyte delivery ~~system~~ assembly having an outlet ~~located~~ locatable in a blood vessel of the patient and in blood flow communication with the heart;

~~providing at surface of the skin of a human subject one or more sources of excitation photons in wavelength range known to induce fluorescence in said fluorescent component of liver activity indicator;~~

~~providing at the surface of the skin of a human subject and in alignment with a fraction of the emitted fluorescence photons excited by the source of excitation photons one or more detectors to measure the intensity of emitted fluorescence photons from the liver activity indicator; and~~

at least one non-invasive optical sensor positionable along a skin surface of the patient to detect the presence of at least a portion of the analyte as it flows through underlying arterial vasculature, the at least one non-invasive optical sensor comprising a plurality of laser diode emitters located along one side of a tissue location of the patient and energizable to emit light at a first wavelength that will transcutaneously excite the analyte, and a like number of photodetectors located along an opposite side of the tissue for detecting the concentration-indicating intensity of fluorescing photons that will be emitted by the analyte at a second wavelength as a result of excitation light from the emitters being transmitted through the subject tissue and underlying vasculature;

one or more sensor outputs corresponding with the instantaneous concentration of analyte flowing through said vasculature at the sensor location; and

~~providing a monitor/controller responsive to said one or more detectors to record the time-varying relative concentration of the liver activity indicator by recording the time-varying fluorescence signal level.~~

~~a sensor comprising a photodiode emitter energizable to generate light at the excitation radiation wavelength and a photodetector which is filtered for response substantially only to the fluorescence emission.~~

~~providing a transmissive sensor positionable to sense the presence of at least a portion of the blood-borne indicator flowing within a blood vessel at arterial vasculature of one or more symmetrically paired distal locations of the patient and having one or more outputs corresponding with the instantaneous concentration of indicator at such blood vessel vasculature;~~

~~providing~~ a monitor/controller having a display, ~~and responsive to said~~ the monitor/controller programmed:

(1) to cue actuation of the indicator delivery assembly;

(2) to ~~commence~~ measure, after a predetermined dwell period, ~~measuring~~ the time-varying relative concentration of ~~blood concentration of a liver activity indicator~~ analyte in the blood over some length of time by repeatedly recording a time-varying analyte fluorescence signal level~~, responsive to a sensor output~~;

(3) to calculate an analyte exponential decay coefficient using the recorded analyte concentration vs. time data; and

(4) to determine and indicate the ~~nature~~ quality of liver function using at least the calculated analyte exponential decay coefficient.

2. The system of claim 1 wherein the ~~skin surface is~~ at least one sensor is adapted for location on one or more of the ear, the finger of the hand, the neck, the leg, or the arm of the patient.

3. The system of claim 1 wherein the ~~skin surface is at paired distal~~ at least one sensor is adapted for location ~~comprising~~ on both ears, paired fingers, paired locations on the hands, paired toes, paired locations on the feet, paired locations on the legs, or paired locations on the arms of the patient.

4. The system of claim ~~3~~ 1 wherein the ~~paired distal location is the ears~~monitor/controller is further programmed to calculate one or more liver activity metrics selected from the group of plasma disappearance rate and residual fractional analyte concentration, using the calculated analyte exponential decay coefficient.

5. The system of claim 1 ~~in which~~ wherein the monitor/controller ~~publishes the~~ is further programmed to display a measure of relative indicator concentration decay as a multitude of function of time curves ~~and the derived exponential decay coefficient, plasma disappearance rate, and residual relative concentration at 15 minutes after injection of the indicator~~.

6. The system of claim 1 ~~in which information is desired concerning a patient concerning~~ wherein one or more of the derived analyte exponential decay coefficient, plasma disappearance rate, and residual relative concentration are calculated for a patient having a medical condition comprising one or more of poisoning, trauma, sepsis, ~~pre-operative screening, post-operative recovery,~~ cirrhosis, hepatitis, or for the purpose of pre-operative screening, post-operative recovery, or organ transplant.

7. The system of claim 1 in which the liver activity ~~indicator~~ analyte is indocyanine green dye.

8. The system of claim 1 ~~in which the sensor further comprises a sensor array with transmission mode sensing in which the sensor array comprises two or more pairs of emitters of excitation photons and fluorescence detectors of the fluorescent analyte of liver activity~~ wherein the monitor/controller is programmed to characterize a given liver as normal when the calculated plasma disappearance rate is equal to or greater than 15% per minute, and to characterize a given liver as diseased or otherwise compromised when the calculated plasma disappearance rate is between 4% and 10% per minute.

9. The system of claim ~~8 further comprising~~ 1 wherein said emitters and photodetectors ~~optionally~~ are energizable in a sequence of ~~such~~ emitter-detector pairs or are energizable simultaneously, and wherein the monitor/controller is ~~responsive~~ programmed to elect one or more ~~of that~~ emitter-detector pair exhibiting an average detection signal output of highest intensity.

10. The system of claim ~~1~~ 4 ~~in which the light path of excitation photons is arranged with an aspheric collimating lens, and the light path of emitted fluorescent photons to the photodetector is arranged with a collimator plate and an interference filter~~wherein the monitor/controller is further programmed to determine and indicate the quality of liver function using one or more of the calculated plasma disappearance rate and the residual fractional analyte concentration.

11. The system of claim 1 wherein the ~~excitation source emits photons in a wavelength range of from about 750 to 820 nanometers~~monitor/controller is further programmed to display one or more of the derived analyte exponential decay coefficient, plasma disappearance rate, and residual fractional analyte concentration at a time 15 minutes after injection of the analyte.

12. The system of claim ~~3 whereby~~ 1 wherein the at least one non-invasive optical sensor ~~array positionable at paired distal locations further comprises two fluorescence sensing array fixtures with sensing array arms,~~ is removeably attached to a headband.

13. The system of claim 1 wherein the ~~apparatus of the system is configurable for use with a subject that is a laboratory animal, a zoological specimen, a cat, a dog, an elephant, an ape, a horse, or a human~~ predetermined dwell period is between two minutes and three minutes.

14. The system of claim 1 ~~in which~~ wherein:

the indicator delivery assembly comprises a flexible elongate delivery tube extending between proximal and distal ends, an auxiliary catheter coupled in fluid transfer relationship with the distal end defining the outlet, ~~a~~ an indicator flow ~~initiation~~ detector coupled in fluid transfer relationship with the proximal end and adapted to derive signals corresponding with the commencement and termination of fluid flow through the system, and a three-way valve connected upstream to the sensor, a first indicator containing syringe coupled in indicator flow relationship with the valve and actuateable to cause indicator to flow through the valve, and a second isotonic saline fluid containing syringe coupled in fluid flow relationship with the valve and actuateable to cause isotonic saline to flow through the valve.

15. The system of claim 1 wherein the length of time over which the monitor/controller measures the time-varying relative concentration of analyte in the blood is between 10 minutes and 20 minutes. ~~A sensing array apparatus comprising~~

~~(a) a plurality of sources of excitation photons and photodetector pairs for measuring the fluorescence emitted by a fluorescent moiety of a liver activity indicator analyte;~~

~~b) said sources of excitation photons providing an excitation light source emitting a first wavelength for excitation of a liver activity indicator within the tissues of a patient body, said emitters transmitting the excitation light through a collimator lens having a collimating channel aligned with an optical path interference filter, said collimating channel and interference filter located intermediate between said sources of excitation photons and photodetector; and~~

~~(c) said photodetectors providing for measuring the intensity of the fluorescent light emitted at a second wavelength from the fluorescent moiety of the liver activity indicator analyte; and,~~

(d) a support system of a plurality of array support arms;

wherein the array support arms of the support system allow positioning of the sensing array apparatus on the exterior of the patient body, whereupon activation of one or more of the sources of excitation photons transmit excitation light through tissue of the patient, thereby exciting liver activity indicator analyte present in said tissue, said photodetectors thereby measuring the intensity of light emitted by excited liver activity indicator analyte.

16. The sensing array apparatus system of claim 15 wherein the plurality of sources of excitation photons and photodetector pairs are three laser diode emitter and photodetector pairs monitor/controller measures the time-varying relative concentration of analyte in the blood at five second intervals.

17. The system of claim 15 5 wherein said sensor assembly further comprises: a first collimator having a collimating channel aligned with an optical path and located intermediate the other surface of the scaphoid fossa of the ear and an interference filter, and a second collimator having a collimating channel aligned with an optical path and located between the interference filter and the photodetector the slope of a given function of time curve indicates the level of liver enzymatic activity for a corresponding given period of time.

18. A kit supplying of consumable materials necessary for quantifying use by a non-invasive system for assaying the liver function of a mammalian patient, the kit comprising:

a) an indicator delivery tubing system providing including a valve, syringe connectors, a flow sensor and a sterile intravenous injector;

b) one or more doses of liver activity indicator reagent as a shelf stable material;

c) a diluent for preparing the dose of liver activity indicator reagent for injection or for delivering an indicator bolus; and

d) a dose of nonreactive blood compatible clearing reagent for completing the injection.

19. The kit of claim 18 further comprising a an indicator flow initiation sensor detector that further comprises an capable of detecting indicator flow initiation sensor with a circuit that in communication and of communicating with a monitor controller monitor/controller of the non-invasive system, the indicator flow detector adapted responds to a query determining report the number of indicator injections a flow initiation sensor has cued detected thereby and that is to become automatically disabled for repeat use after a some

~~testing procedure~~ predetermined time period or predetermined number of detected indicator injections.

20. A non-invasive method for ~~measuring~~assaying the relative concentration over time of a liver activity ~~indicator~~analyte in ~~the~~ a circulating blood stream, comprising the steps:

~~a) selecting a liver activity indicator analyte that is predominantly removed from circulating blood by the liver said analyte further comprising a fluorescent moiety that can be excited to emit fluorescence through irradiation by excitation photons in wavelength range known to induce fluorescence in said analyte;~~

~~b) positioning about the skin of a human subject one or more emitter/detector arrays for emitting excitation photons in a given wavelength range known to induce fluorescence in said fluorescent moiety of the liver activity indicator analyte, said emitter in alignment with one or more detectors configured to measure the intensity of emitted fluorescence photons from the liver activity indicator analyte;~~

~~c) recording the relative concentration over time of the liver activity indicator analyte that has been injected into the blood stream of a human subject, by recording time-varying fluorescence signal level; and~~

~~d) calculating a liver activity metric according to Formula 1,~~

~~whereby the relative liver activity of the patient is displayed in a report~~

providing an analyte delivery assembly having an outlet locatable in a blood vessel of a patient and in blood flow communication with the heart;

positioning at least one non-invasive optical sensor along a skin surface of the patient to detect the presence of at least a portion of the analyte as it flows through underlying arterial vasculature, the at least one non-invasive optical sensor comprising a plurality of laser diode emitters located along one side of a tissue location of the patient and energizable to emit light at a first wavelength that will transcutaneously excite the analyte, and a like number of photodetectors located along an opposite side of the tissue for detecting the concentration-indicating intensity of fluorescing photons that will be emitted by the analyte at a second wavelength as a result of excitation light from the emitters being transmitted through the subject tissue and underlying vasculature;

providing one or more sensor outputs corresponding with the instantaneous concentration of analyte flowing through said vasculature at the sensor location; and

providing a monitor/controller having a display, the monitor/controller is programmed for:

(1) cueing actuation of the indicator delivery assembly;

(2) commencing measurement, after a predetermined dwell period, the time-varying relative concentration of analyte in the blood over some length of time by repeatedly recording a time-varying analyte fluorescence signal level;

(3) calculating an analyte exponential decay coefficient using the recorded analyte concentration vs. time data; and

(4) determining and indicating the quality of liver function using at least the calculated analyte exponential decay coefficient.