(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2014 (16.10.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/166504 A1

(51) International Patent Classification:
A61B 5/0205 (2006.01) *A61B 5/0468* (2006.01)

(21) International Application Number:
PCT/DK2014/050094

(22) International Filing Date:
11 April 2014 (11.04.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2013 70206 11 April 2013 (11.04.2013) DK

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/166504 A1

(54) Title: METHOD AND DEVICE FOR PREDICTING FLUID RESPONSIVENESS OF PATIENTS

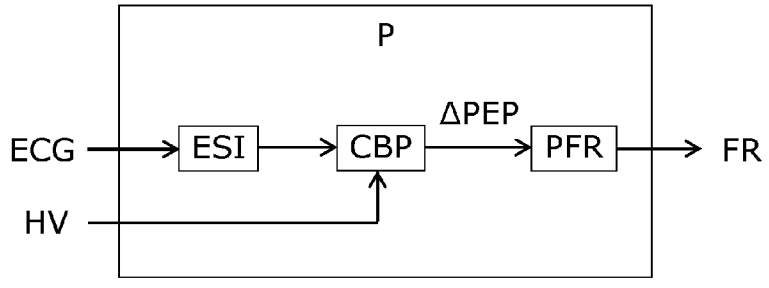

Fig. 1

(57) Abstract: The invention provides a device and a method for predicting fluid responsiveness of a subject, e.g. a patient suffering from sepsis. Input data indicative of cardiac beat performance of the subject, e.g. ECG and/or data indicative of a preload dependent hemodynamic variable, is used to identify spontaneous extra systoles. A measure of cardiac beat performance, e.g. a change in pre-ejection period (PEP) or systolic blood pressure (SBP) in response to the extra systole compared to a baseline PEP, in relation to the identified extra systole is calculated. In response thereto, an indication of predicted fluid responsiveness of the subject is generated. A reliable fluid responsiveness prediction based on data available in existing intensive health care monitoring equipment.

METHOD AND DEVICE FOR PREDICTING FLUID RESPONSIVENESS OF PATIENTS

FIELD OF THE INVENTION

The invention relates to the field of medical devices. More specifically, the invention provides a software method and a device for predicting fluid responsiveness of patients. The method is intended for but not limited to hemodynamically unstable patients.

BACKGROUND OF THE INVENTION

Reliable fluid responsiveness monitoring has been sought for decades. A patient group specifically in need of reliable fluid responsiveness prediction monitoring is septic patients. In Denmark, 12,000 patients develop sepsis, and they subsequently develop acute circulatory compromise due to loss of intravascular fluid caused by dehydration and/or leaky capillareies or due to acute heart failure. Treatment is either restoring the intravascular volume by fluids, i.e. optimize cardiac preload, or administering heart stimulating and/or vasoactive drugs such as adrenalin. Around 2,000 of the Danish patients die, partly due to inadequate hemodynamic management, which is caused by inadequate monitoring that can lead the physicians towards the correct treatment.

Other patient groups also have a need for reliable fluid responsiveness prediction monitoring, e.g. pre-, peri-, and postoperative patients.
The fluid responsiveness question is essential because fluids might be a sufficient treatment of hemodynamically unstable patients and inotropic drugs work better if the volume status is optimized and choosing the wrong treatment leads not only to mistreatment and perhaps deteriorating effects such as pulmonary edema, it also delays definitive therapy.

Traditionally used preload estimates such as central venous pressure (CVP) are unreliable and has led to more functional approaches, such as passive leg raising methods and dynamic variables in relation to controlled mechanical ventilation, e.g. pulse pressure variation, PPV.

Dynamic variable monitoring is a concept that repeatedly has provided convincing results. The monitoring is in many ways optimal, since it is continuous and based on already acquired minimally invasive data. Unfortunately, dynamic variables are limited to controlled mechanically ventilated patients and it is even limited to an increasing extent due to influence of tidal volume and, typically as a consequence, respiratory frequency. Tidal volume needs to be at least 8-10 ml/kg for dynamic variables to be reliable, and the recommended tidal volume for most septic patients – if at all ventilated – is around 6 ml/kg. In addition, weaning from mechanical ventilation should be considered as soon as possible for these patients, and even support ventilation mode (used in the weaning phase) renders dynamic variables unreliable. Thus, for the vast majority of critically ill patients, dynamic variables do not seem to be applicable for fluid responsiveness prediction with the present ventilator guidelines. A crossectional study on 311 critically ill patients (of which 100 suffered sepsis) from 26 French ICUs showed that PPV is applicable in only 2-3% of patients. Dynamic variables are today mainly useful in the operating rooms, in the first few post-operative hours following major surgery and in the initial hours after intubation of critically ill patients. Consequently, no reliable continuous monitoring technique exists for most critically ill patients, and it has never existed for spontaneously breathing patients.

Yet, the fundamental physiological idea of dynamic variables, i.e. a varying preload, is fascinating. In lack of ventilator treatment, different interventional approaches, such as passive leg raising (PLR) methods, have been investigated with reasonable results. However, the interventional nature of this approach and the need for reliable cardiac output (CO) monitoring are obstacles for PLR use, and it would be preferable if reliable minimally invasive or non-invasive monitoring that did not require an intervention were available for these patients in line with dynamic variables.

In conclusion, at present, physicians do not have a reliable tool for determining where on the Frank-Starling curve 97% of critically ill patients are located. Thus, the physicians do not know whether to treat such patients by administering fluids or inotropic/vasoactive drugs, or in other words, whether such patients are fluid responsive.

SUMMARY OF THE INVENTION

Thus, according to the above description, it may be seen as an object of the present invention to provide a method (e.g. for implementing in software) and a device for non-invasively or minimally invasively and still reliably predicting, or at least assisting in predicting, how a patient will respond to fluid administration. Preferably, the method and device are suited for continuous and automatic monitoring.

In a first aspect, the invention provides a fluid responsiveness prediction system arranged to predict fluid responsiveness of a subject, wherein the system comprises

- input means (e.g. an input unit) arranged to receive input data indicative of cardiac beat performance, and optionally heart rate, obtained from a subject, and
- a processor arranged
    - to identify extra systoles in response to the input data,
    - to calculate a measure of cardiac beat performance, such as to calculate a change in a measure of cardiac beat performance, in relation to the identified extra systole, in accordance with the input data, and
    - to generate an indication of predicted fluid responsiveness of the subject in response to said measure of cardiac beat performance.

The invention is based in the insight that (spontaneous) extra systoles, which most people experience frequently, induce a convenient intermittent physiologic preload change, which can be used to extract a measure that allow prediction of fluid responsiveness of a subject. Especially, such extra systoles introduce a cardiac preload change, which can be used to derive a measure of a change in cardiac beat performance, e.g. change in pre-ejection period (ΔPEP) or systolic blood pressure (ΔSBP). Such change in pre-ejection period has been shown to provide a tool for prediction of fluid responsiveness of a ventilated patient, see e.g. [*"Automated pre-ejection period variation indexed to tidal volume predicts fluid responsiveness after cardiac surgery", S.T. Vistisen et al., Acta Anaesthesiol. Scand. 2009, Vol. 53, pages 534-542*]. The invention is surprising in view of the fact that arrhythmias, such as frequent extra systoles, are a limitation regarding ventilation induced dynamic variables because they interfere with the induced

cycling changes in preload and attempts have been made to reject extra systoles from analysis when calculating dynamic variables.

An extra systole in itself induces an intermittent preload shift: The post ectopic beat (PEB) represents a heart beat with increased preload – a reversible fluid challenge. Experiments performed on pigs and a clinical observational study on post-cardiac sutgery patients (which is both described later), have indicated that the occurrence of an extra systole provides a convenient preload varying mechanism which can be used to predict fluid responsiveness, i.e. identify the Frank-Starling curve slope at the current Frank-Starling curve operating position, see further explanation later.

The proposed system is convienient for use in (but not limited to) patients seen in emergency departments and intensive care units (ICUs) , since the data indicative of cardiac beat performance is normally available in the form of Electro Cardio Graphy (ECG) data, and e.g. pulseoximetry and/or continuous blood pressure data. Thus, without further invasive or non-invasive measurement means, it is possible to predict fluid responsiveness of such patients by simply performing an algorithm on the available continuously monitored data indicative of cardiac beat performance. When (spontaneous) extra systoles are detected, a measure of fluid responsiveness can be generated, thus assisting physicians in choosing the correct treatment of the patients, such as hemodynamically unstable patients.

Extra systoles are normally divided into two groups, supraventricular extrasystoles and ventricular extrasystoles. If preferred, it is possible to provide an algorithm arranged to detect which group an extra systole belongs to, and thus treat the two groups differently, e.g. by discarding one of the types for further processing, if preferred.

Also, it is to be understood that it is possible and may be advantageous to utilise the mentioned hemodynamic variables in relation to the ectopic beat and the heart beat following the post-ectopic beat for a correction of the primary part of the method, analysis of the ectopic beat. In addition, ECG morphology in relation to the post-ectopic beat may be advantageous to consider in relation to correction.

In the following, various embodiments will be described.

It may be preferred to provide an algorithm that can detect extra systoles and provide the additional cardiac beat performance information, e.g. cardiac preload data, based on one single data input signal. This may be done based on data e.g. from a pulseoximetry device or an arterial blood pressure device. Even though detection of extra systoles may be carried out without use of the ECG curve, ECG is the preferred signal from which to detect the occurrence of an extra systole.

However, in other embodiments it may be preferred to use two (or more) different types of input data which may be available in existing (intensive care)monitoring equipment, and may be based on different types of monitoring measurements on the subject. In one embodiment the input means can receive

- first input data indicative of an ECG obtained from a subject, and to receive
- second input data indicative of a hemodynamic variable estimating cardiac beat performance, or indicative of a hemodynamic signal from which at least one hemodynamic variable estimating cardiac beat performance can be estimated, and

wherein the processor is arranged

- to identify extra systoles in response to the first or second input data,
- to calculate a measure of cardiac beat performance in relation to the identified extra systole, in accordance with the first or second input data, and
- to generate an indication of predicted fluid responsiveness of the subject in response to said measure of cardiac beat performance.

Especially, the indication of predicted fluid responsiveness may be generated by comparing cardiac beat performance at the post ectopic beat with cardiac beat performance at a number of preceeding and/or following sinus beats.

Especially, it may be preferred that the input data comprises data indicative of induced changes in a cardiac preload dependent hemodynamic variable. Hereby, it is possible to determine a measure of the Frank-Starling curve slope for the

subject's present Frank Starling curve operating position, and thus provide a reliable prediction of fluid responsiveness of the subject when a (spontaneous) extra systole occurs.

In one embodiment, the input data comprises data indicative of a hemodynamic variable estimating cardiac beat performance on a heart beat to heart beat basis in relation to baseline heart beats preceeding or following at least one of: an ectopic beat, a post-ectopic beat, and a heart beat immediately following a post-ectopic beat. Especially, a change in cardiac beat performance in response to the extra systole may be derived. E.g. by calculating a change from a baseline cardiac beat performance to a cardiac beat performance in response to the extra systole's post ectopic beat. A baseline cardiac beat performance may be calculated as an average or other statistical measure of heart beat to heart beat performance for a number, e.g. 5-10 normal (sinus) heart beats, preceding and/or following an extra systole.

In one embodiment, the input data comprises data indicative of at least one of cardiac beat performance variables. Such cardiac beat performance could be, but is not limited to: a systolic arterial blood pressure, an arterial pulse pressure, a time derivative of arterial pressure upstroke (dP/dt), a pre-ejection period (PEP), a measure of cardiac stroke volume, a hemodynamic characteristics of the plethysmographic curve, a measure of cardiac stroke work, and a measure of blood flow. Thus, several possible types of data indicative of cardiac beat performance may be used for the prediction, particularly a preload dependent cardiac beat performance variable.

Especially, the input data may comprise data indicative of at least one of: morphological characteristics derived from a plethysmographic curve comparable to the ones mentioned above for the arterial blood pressure curve, a direct measure of cardiac stroke volume, an indirect measure of cardiac stroke volume, a preload dependent hemodynamic characteristic of the plethysmographic or arterial pressure curve, a direct or indirect measure of cardiac stroke work, and a direct or indirect measure of blood flow, a direct or indirect hemodynamic characteristic.

Especially, the input data may comprise a direct or indirect hemodynamic characteristic derived from a sensor capable of performing measuring a bioimpedance or a bioreactance.

Especially, the input means may be arranged to receive data from a pulseoximetry device and/or a blood pressure device. The processor is then preferably arranged to derive a measure of blood pressure variation, or a measure of a temporal variation in the signal, in response to the data from the device. In a variation, the processor may additionally be arranged to identify extra systoles based on the data from the device.

In a preferred embodiment, the processor is arranged to calculate a PEP in response to the input data, e.g. in response to data from a pulseoximetry device or an arterial blood pressure device. Especially, the PEP may be calculated as a time from an R spike in a received ECG data, until a time where a measure of arterial blood pressure acceleration reaches a local maximum.

In a preferred embodiment, the processor is arranged to calculate a measure of change in pre-ejection period (ΔPEP) or systolic arterial blood pressure (ΔSBP) in relation to the identified extra systole. ΔPEP and ΔSBP have been verified in animal experiments and in an observational clinical setting to provide a reliable measure of fluid responsiveness when induced by an extra systole. Especially, ΔPEP or ΔSBP may be calculated as a difference between a measure of baseline PEP or SBP and a measure of PEP or SBP determined in response to the identified extra systole's post ectopic beat. The processor may then compare the calculated ΔPEP or ΔSBP with a predetermined reference value, and to generate the indication of predicted fluid responsiveness of the subject accordingly.

In one embodiment, the processor may be arranged to discard an identified extra systole, if a coupling interval is more than a predetermined fraction of a baseline heart beat interval (RR interval). 'Coupling interval' is understood as the period from a normal cardiac heart beat (normal contraction where the sinus node in a non-prematurely manner initiates the normal beat) and the extra systole (premature beat). Especially, an extra systole may be discarded, if said fraction is more than 95%, such as more than 90%, such as more than 85, such as more

than 80%. In case the fraction is too large, the extra systole will not be associated with a sufficient cardiac preload change, and thus not provide information allowing a reliable fluid responsiveness prediction. In the same manner, the processor may be arranged to detect multiple consecutive extra systoles, and to discard generation of an indication of fluid responsiveness, if multiple consecutive extra systoles are detected, because the preload shifts may become too chaotic.

One system embodiment comprises an ECG device arranged to obtain ECG data on the subject. Especially, the processor may be housed within said ECG device. Such embodiment can be based on an existing ECG device, where the processor according to the invention is the processor available in existing equipment, which is programmed to perform according to this invention. In the same manner, the system may comprise e.g. a blood pressure measurement device or another device from which it is possible to extract cardiac beat performance variables from a subject.

In a second aspect, the invention provides a method for predicting fluid responsiveness of a subject, the method comprising

- providing input data indicative of cardiac beat performance of the subject,
- identifying extra systoles in response to the input data,
- calculating a measure of cardiac beat performance, such as a measure of a change in cardiac beat performance, in relation to the identified extra systole, in accordance with the input data, and
- generating an indication of predicted fluid responsiveness of the subject in response to said measure of cardiac beat performance.

In a third aspect, the invention provides a computer program product having instructions which when executed by a processor cause the processor to perform the method according to the second aspect.

Especially, the computer program product may be arranged to cause the processor to store data ECG and other related data at least 5-10 heart beats before and after the identified extra systoles in memory, so as to allow later analysis of fluid responsiveness of the patient, e.g. by a request of a user. Alternatively, or additionally, the computer program product may cause the

processor to update a fluid responsiveness prediction in response to data from the patient continuously, e.g. outputting a prediction result estimate using a number and/or text and/or a grapic symbol on a display, and/or using an audible output. Especially, the fluid responsiveness prediction result may be updated each time a new extra systole is identified, thus creating new data for a prediction calculation.

Especially, such computer program product may be generated for updating of software on existing patient montoring equipment.

Especially, the method may compare the measure of change in cardiac beat performance with a predetermined reference value, and generate an indication of predicted fluid responsiveness of the subject in accordance with said comparison.

It is appreciated that the same advantages and embodiments described for the first aspect apply as well for the second and third aspects. Further, it is appreciated that the described embodiments of the first, second and third aspects can be intermixed in any way between the mentioned aspects.

BRIEF DESCRIPTION OF THE FIGURES

The invention will now be described in more detail with regard to the accompanying figures of which

Fig. 1 illustrates a block diagram of one embodiment,

Fig. 2 illustrates, for example data, graphs for ECG and arterial blood pressure variations,

Fig. 3-5 show graphs illustrating results of experiments performed on pigs,

Fig. 6 illustrate a diagram of steps in a method embodiment

Fig. 7 illustrates in the middle panel the Frank-Starling curve, i.e. the relation between cardiac preload and stroke volume, and

Figs. 8a and 8b show overall results of a study performed on human patients.

The figures illustrate specific ways of implementing the present invention and are not to be construed as being limiting to other possible embodiments falling within the scope of the attached claim set.

DETAILED DESCRIPTION OF EMBODIMENTS

FIG. 1 illustrates a block diagram of basic parts of a system embodiment with a processor or processor system P arranged to receive two input data streams: Electro Cardio Graphy data ECG, as well as data indicative of a hemodynamic variable HV, e.g. data from an oximetry or arterial blood pressure device. Thus, both such data ECG and HV are normally available as monitoring data for ICU patients, and thus no extra measurement devices are required to perform the invention in a preferred embodyment.

The processor P is programmed to perform algorithms ESI, CBP, PFR, serving to resulting in the generation of an output in the form of a fluid responsiveness result FR. It is to be understood that this result can be communicated in various ways, e.g. displayed on a display screen, or in other ways so as to be able to assist a physician in deciding how to apply the best treatment of the patient.

An algorithm ESI serves to identify extra systoles by monitoring the ECG data (or possibly the HV data alone). The hemodynamic variable data HV are applied to an algorithm CBP used to calculate a baseline cardiac beat performance measure, preferably Pre-Ejection Period (PEP) or systolic arterial blood pressure (SBP), as an average of e.g. 5-10 normal heart beats. When an extra systole is detected, PEP or SBP is calculated in response to the extra systole, and a change in PEP or SBP (ΔPEP or ΔSBP) is calculated as a difference between the baseline PEP or SBP and the PEP or SBP associated with the post-ectopic beat of the extra systole. Based on the ΔPEP value, an algorithm PFR generates a prediction of fluid responsiveness FR e.g. by comparing with a stored reference value, thereby determining if it is likely that the patient is fluid responsive or not.

It is to be understood that the algorithms ESI, CBP, PFR could be implemented in software in existing intensive care monitoring equipment, especially an ECG monitor and/or an arterial blood pressure monitor.

FIG. 2 illustrates an example of data allowing calculation of a Pre-Ejection Period (PEP), namely ECG data (upper graph), and arterial blood pressure in the form of a blood pressure curve (middle graph). The lower graph shows arterial blood pressure acceleration (lower graph), i.e. the second time derivative of the blood pressure.

PEP is defined as the time interval (period) between electrical depolarization of the myocardium, Q spike in the ECG, and opening of the aortic valve. As such, PEP is the period of isovolumetric contraction. Because the R spike is much easier to automatically detect with software algorithms, this fiducial point in the ECG may be used for definition of PEP beginning. Likewise, it is not possible to detect the exact timing of aortic valve opening with peripheral measurements, e.g. radial artery pressure or plethysmographic curve. The vascular transit time of the pressure signal is nearly 100 ms from aorta to the radial site. Yet, since the current invention relies on changes in PEP and vascular transit time is at best minimally affected by preload changes, it is still possible to use the peripheral site to detect this. Thus, PEP end may be defined as the timing of systolic upstroke in arterial blood pressure or plethysmographic curve. For an automatic detection of this, maximal acceleration is used. The maximal acceleration detects the upstroke slightly after the pressure begins to increase, and, provided reasonable signal pre-processing, such local maximal acceleration is easily found automatically by detecting the time where there is a peak in the blood pressure acceleration. This is acceptable since the detection is the same for each heart beat and since PEP changes and not absolute PEP values are the scope. The example data illustrated in FIG. 2, are seen to result in a PEP of approximately 150 ms.

In the following, a verification of the invention will be described, namely an experiment performed on 10 Danish female landrace pigs, where extrasystoles were provoked with a pacemaker. The experiment was approved by the Danish National Animal Ethics Committee (journal number 2012/561-195).

The animals (weight range: 38-40 kg) were premedicated intramuscularly with midazolam (0.5 mg/kg), ketamine (5 mg/kg), and atropine (0.5 mg). Anaesthesia was induced with propofol (3 mg/kg) and fentanyl (1 ug/kg) and maintained with propofol (10 mg/kg/hour) and fentanyl (0.5 mg/kg/hour). The animals were intubated and mechanically ventilated. We significantly reduced respiratory blood pressure variations by setting tidal volume low (always less than 5.5 ml/kg) and respiratory frequency high (approximately 30 breaths/min) titrated to keep arterial pH at 7.4. Positive end-expiratory pressure (PEEP) was 5 cmH_2O. From pilot testing, dynamic variables appeared not to be significantly larger with these ventilator settings compared with reported values from spontaneously breathing pigs exposed to a similar experimental protocol. Ringer acetate was infused (10 ml/kg) during the instrumentation period. At the end of the experiment, the animals were euthanized with pentobarbital.

Four venous sheets were placed in left (2) and right (2) external jugular veins. One sheet was used for drug and Ringer acetate administration as well as for pulmonary artery catheterisation. Another sheet was used for blood withdrawal and subsequent volume expansions (see below). The final two sheets were used for two 5-French four-pole pacing catheters, of which one was placed in the right atrium, the other at right ventricular apex for induction of supraventricular and ventricular extra systoles, respectively. Placement was guided by X-ray and validated from ECG throughout the experiment.

An arterial catheter was placed through a sheet in a femoral artery and used for arterial blood sampling as well as continuous monitoring of arterial pressure (AP). A pulse oximeter was placed and securely fixed on the animal's tale. Three lead ECG was monitored. ECG (lead II), AP, and plethysmographic curves were continuously sampled at 300 Hz throughout the experiment and continuous CO, HR and mean arterial pressure (MAP) was sampled every minute by monitor dedicated software (S/5 Collect, General Electric, Datex-Ohmeda Division, Instrumentarium Corp., UK).

The main experiment began with a basic data registration. After that, the pacing protocol was executed (see below) and then, four intravascular volume shifts were performed, of which each was followed by the pacing protocol. The first was a

controlled bleeding of 25% estimated blood volume (660 ml for all pigs) performed during 15-20 minutes (*hypovolaemia*). The blood was bleed into a bag with anticoagulants and saved for the second volume shift, retransfusion. In an attempt to reach a more clinically relevant level after retransfusion, we transfused 500 ml blood (19% of estimated blood volume) because pigs autotransfuse from the spleen following bloodletting. In previous studies, pigs were generally fluid unresponsive when reaching the subsequent "normovolaemic level" following replacement of all depleted blood.

In the following, we refer to the volaemic level reached after retransfusion of 500 ml blood as *normovolemia*. The two last volume shifts were each done as a volume expansion with 500 ml hydroxyethyl starch 130/0.4 in 0.9% NaCl and we refer to them as *hypervolaemia* and *extreme hypervolaemia*.

At baseline and after each volume shift, atrial pacing was initiated in the following way: The pacer determined RR intervals and we manually set an initial coupling interval at 50-100 ms below the observed RR interval. After the first induced extra systole, the coupling interval was decreased by 10 ms for the next paced extra systole, which was induced 10 heart beats later. The pacer continued in that scheme until refractoriness was reached or the aortic valve had not opened at the ectopic beat (EB) for approximately 10 consecutive induced extra systoles. At that point, we changed to ventricular pacing and paced following the same scheme.

In this section the signal processing will be described. The three curves sampled at 300 Hz were digitally upsampled offline to 1000 Hz as previously described, see [*Vistisen ST, Koefoed-Nielsen J, Larsson A. Automated pre-ejection period variation predicts fluid responsiveness in low tidal volume ventilated pigs. Acta Anaesthesiol Scand 2010; 54: 199-205*]. The upsampling was performed for the sake of temporal resolution (1 ms) and, briefly, it was done using zero padding in the fast Fourier transformed frequency domain followed by an inverse Fourier transform leading to a 1000 Hz signal. The upsampled ECG was filtered with a 2nd order high-pass filter with cut-off frequency at 10 Hz to reduce T spike amplitude. R spike detection was done with a simple threshold algorithm with subsequent maximal value search for exact R spike position. Thresholds were the same for each pig but varied between pigs. Blood pressure and plethysmographic curves

were 2nd order low-pass filtered with cut-off frequency at 25 Hz. When detecting the PEP, however, the cut-off frequency was 10 Hz. All signal processing and subsequent data analysis was carried out in Matlab (Mathworks Inc., USA).

The detected RR interval time series were visually inspected to identify all useful PEBs. PEBs were considered useful, if none of the heart beats since the previously induced extra systole were arrhythmic. Investigating pilot data, we saw that coupling intervals close to the baseline heart rate did not change cardiac performance much at the PEB. This led to the decision that only extra systoles with coupling intervals reduced 20% or more compared to the baseline heart rate were used for fluid responsiveness prediction. Additionally, we subdivided the analyses of extra systoles in two scenarios: Those extra systoles where any ejection was observed at the EB and those, where no ejection occurred at the EB.

For each PEB, we detected PEP from the blood pressure, using the maximal 2nd derivative of the curve, PEP from the plethysmographic curve (with the same method), pulse pressure (PP), systolic pressure (SP), and maximal slope of the blood pressure upstroke (dP/dt). Each of these variables was compared with their averaged reference value: Median value of the four sinus heart beats preceding the EB, effectively mean of the 2nd and 3rd largest value among these four reference value representatives. For PEP and SP, both relative and absolute changes were derived. PEP was calculated both from arterial pressure (AP) and the plethysmographic curve (Pleth). Only relative changes were extracted for PP and dP/dt, leading to the terms shown in Table 1.

$\Delta_{PEB,\ abs}PEP_{AP}$	(PEP at sinus beat)-(PEP at PEB); (ms) derived from AP curve
$\Delta_{PEB,\ rel}PEP_{AP}$	((PEP at sinus beat)-(PEP at PEB))/(PEP at sinus beat); (%) derived from AP curve
$\Delta_{PEB,\ abs}PEP_{Pleth}$	(PEP at sinus beat)-(PEP at PEB); (ms) derived from Pleth curve
$\Delta_{PEB,\ rel}PEP_{Pleth}$	((PEP at sinus beat)-(PEP at PEB))/(PEP at sinus beat); (%) derived from Pleth curve
$\Delta_{PEB,\ abs}SP$	(SP at PEB)-(SP at sinus beat); (mmHg)
$\Delta_{PEB,\ rel}SP$	((SP at PEB)-(SP at sinus beat))/(SP at sinus beat); (%)
$\Delta_{PEB}PP$	((PP at PEB)-(PP at sinus beat))/(PP at sinus beat); (%)
$\Delta_{PEB}dP/dt$	((dP/dt at PEB)-(dP/dt at sinus beat))/(dP/dt at sinus beat); (%)

Table 1.

Abbreviations and corresponding explanations for the variables used for fluid responsiveness prediction are:PEB, post-ectopic beat; abs, absolute difference between variable at normal sinus beat and variable at PEB, PEP, pre-ejection period; AP, arterial pressure curve; rel, relative difference between variable at normal sinus beat and variable at PEB, Pleth, plethysmographic curve; SP, systolic pressure; PP, pulse pressure; dP/dt, maximal slope of systolic upstroke in AP.

An improvement in PEP is a decreasing PEP as opposed to SP, PP, and dP/dt. For the sake of identical operational sign and eased interpretation, we choose to calculate all the $\Delta_{PEB,\ xx}PEP_{xx}$-values after the scheme $PEP_{sinus\ beat}$-PEP_{PEB}, whereas the other variables (e.g. SP changes) were calculated as SP_{PEB}-$SP_{sinus\ beat}$; in short: a reversal of the operational sign for the $\Delta_{PEB,\ XX}PEP_{XX}$-values. Stroke volume (SV) was calculated as CO/heart rate. CVP and pulmonary artery occlusion pressure (PAOP) was obtained prior to each volume expansion.

It was not possible to make power calculations for the present study. The primary outcome was to evaluate the fluid responsiveness predictive value of different variables (Table 1) from both supraventricular and ventricular extra systoles. Fluid responsiveness was defined as an increase in SV of 15% or more following volume expansion.

Hemodynamic characteristics at baseline and the four volaemic levels (hypovolaemia, normovolaemia, hypervolaemia, and extreme hypervolaemia) were analysed with ANOVA for repeated measures using Stata (StataCorp LP, USA). Assumptions for the model (normality, equal variance as well as normality of model residuals) were tested with QQ plot inspection and Bartlett test. In presence of detected differences, Bonferroni corrected post hoc testing was used to identify differences between volaemic levels (10 tests performed, $p<0.005$ considered significant). In case of violations of the model, we refrained from making further post hoc testing and reported only summary statistics.
The predictive value of the PEB induced changes in variables were analysed with receiver operating characteristics (ROC) curves. Extra systoles from hypovolaemia, normovolaemia, and hypervolaemia were used to predict the hemodynamic effect of the subsequent volume expansion. Characteristics from each eligible PEB entered this analysis. Thus, ROC analysis assumptions are

violated (independence assumption) and we merely used the analysis to report sensitivity and specificity and to find optimal thresholds, not to compute comparative statistics. Sensitivity, specificity, and corresponding thresholds are reported for ROC areas > 0.65. Data are represented as mean (standard deviation), $p<0.05$ was considered significant when not Bonferroni correcting.

Table 2 presents the results in terms of the overall hemodynamic characteristics from the experiment. Data are presented as mean (standard deviation). *: $p<0.005$ from "Baseline", §: $p<0.005$ from "Hypovolemia", #: $p<0.005$ from "Normovolemia", ¤: $p<0.005$ from "Hypervolemia". CO, cardiac output; SV, stroke volume; SvO_2, mixed venous oxygen saturation; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; HR, heart rate. $: Model assumptions not met by HR, thus no post hoc testing performed.

	Baseline	Hypovolemia	Normovolemia	Hypervolemia	Extreme hypervolemia
CO (l/min)	3.8 (0.6)	2.9 (0.5)*	3.9 (0.4)§	4.3 (0.5)§	4.5 (0.6)*§
SV (ml)	58.7 (9.5)	40 (11)*	60.5 (8.6)§	65.7 (7.5)*§	65.7 (7.5)*§
SvO_2 (%)	65.7 (7.2)	53.4 (8.8)*	67.3 (4.8)§	69.3 (6.2)§	69.4 (7.8)§
MAP (mmHg)	88.9 (13.2)	66.4 (12.7)*	80.4 (11.4)*§	86.4 (14.6)§	91.1 (14.2)§#
PAOP (mmHg)	6.5 (1.8)	4 (1.8)*	6.8 (1.4)§	8.7 (1.5)*§#	12.4 (1.8)*§#¤
CVP(mmHg)	3.8 (1.8)	1.8 (1.6)*	4.1 (1.7)§	6.8 (1.9)*§#	9.7 (1.6)*§#¤
HR (min^{-1}) $	*66.9 (15.5)*	*76.8 (17.5)*	*65.7 (9.4)*	*66.1 (6)*	*68.2 (7.4)*

Table 2

HR data did not comply with statistical model assumptions (variance was not equal across volaemic levels). All tested hemodynamic variables were significantly

altered by the controlled bleeding and all variables but MAP returned to baseline level following retransfusion. Concerning HR, nine of ten pigs increased HR with controlled bleeding and for nine of ten pigs HR fell again following retransfusion. Fluid responsiveness was encountered for all but one pig following blood retransfusion and for one pig following the first colloid volume expansion.

The usefulness of PEBs varied considerably. This was mainly caused by the occurrence of spontaneous extra systoles but also – for ventricular extra systoles – because the refractory period at low coupling intervals was not long enough in some cases to prevent the underlying sinus node rhythm from inducing QRS complexes, i.e. no sinus beats fell out despite the ventricular extra systole. In fact, in six of the ten animals, this phenomenon was encountered before the pacing protocol had reached the "no-ejection-at-EB" level, mostly, throughout the experimental protocol. Therefore we refrained from analysing the data, where no ejection occurred.

Table 3 reports how many PEBs (with preceding EB ejection) were eligible from each pig at each volaemic level for both atrial and ventricular extra systoles. It indicates how much data from each animal has entered the receiver operating characteristics (ROC) analysis.

	Baseline		Hypo		Normo		Hyper		Extreme hyper	
	SVE	VE	SVE	VE	SVE	VE	SVE	VE	SVE	VE
Pig1	28	25	12	14	20	5	0	20	22	18
Pig2	16	8	19	3	19	6	30	11	23	20
Pig3	19	41	20	27	9	28	21	22	32	25
Pig4	27	15	23	5	15	6	22	17	27	5
Pig5	25	11	20	12	20	19	24	22	22	20
Pig6	23	18	19	15	26	15	25	11	25	17
Pig7	31	12	16	0	27	6	30	9	19	14
Pig8	35	19	31	6	32	0	19	11	20	15
Pig9	18	10	13	11	14	8	3	3	4	7
Pig10	23	18	5	0	1	8	10	8	13	13
Used for ROC analysis			178	93	183	101	184	134		

Table 3

Fig. 3 shows PEP changes related to the EB and the PEB from a representative pig in which ventricular extra systoles were induced. PEP was improved (shortened) considerably more at the PEB, when the pig was hypovolaemic (and in this case

also fluid responsive) compared to the two other volaemic levels (not associated with fluid responsiveness).

Fig. 4 shows, how $\Delta_{PEB,\ abs}PEP_{AP}$ from ventricular extra systoles from all animals was related to SV changes following volume expansion. The vertical line indicates the global optimal $\Delta_{PEB,\ abs}PEP_{AP}$ threshold (6 ms) for fluid responsiveness prediction.

Fig. 5 shows the corresponding ROC curve presenting an area under the ROC curve of 0.84. The optimal 6 ms threshold corresponded to a sensitivity of 71% and specificity of 77%.

Sensitivity and specificity values of the variables in Table 1 from both atrial as well as ventricular extra systoles are seen in Table 4, which shows that PEB characteristics from ventricular extra systoles were generally superior to those from atrial extra systoles in predicting fluid responsiveness. Classification characteristics for CVP were: Area under ROC curve: 0.89, sensitivity of 100%, specificity of 65% at a threshold of 4.5 mmHg. Classification characteristics for PAOP were: Area under ROC curve: 0.90, sensitivity of 100%, specificity of 65% at a threshold of 7.5 mmHg. Optimal thresholds, sensitivities, and specificities are reported for ventricular extra systoles with areas under the ROC curve (AUCs) above 0.65.

AUCs	AUC, atrial	AUC, ventricular	Optimal thresholds (ventr. extra systoles)	Sens/spec (ventr. extra systoles)
$\Delta_{PEB,\ abs}PEP_{AP}$	0.63	0.84	6 ms	77%/71%
$\Delta_{PEB,\ rel}PEP_{AP}$	0.59	0.81	3.9 %	76%/71%
$\Delta_{PEB,\ abs}PEP_{Pleth}$	0.64	0.79	3 ms	71%/70%
$\Delta_{PEB,\ rel}PEP_{Pleth}$	0.59	0.77	1.4 %	70%/69%
$\Delta_{PEB,\ abs}SP$	0.5	0.75	0 mmHg	55%/90%
$\Delta_{PEB,\ rel}SP$	0.61	0.70	0 %	55%/89%
$\Delta_{PEB}PP$	0.54	0.60	Not calculated	Not calculated
$\Delta_{PEB}dP/dt$	0.63	0.69	27%	53%/89%

Table 4

The hypothesised physiologic mechanism exists for ventricular extra systoles: Cardiac performance is generally more improved at the ventricular extra systolic PEB when the heart is fluid responsive as compared to when it is fluid unresponsive. However, the mechanism was not as clear for supraventricular extra systoles.

Whether derived from the AP curve or from the Pleth curve, the family of $\Delta_{PEB,\ xx}PEP_{xx}$ variables from ventricular extra systoles' provided an approximate 70-75% sensitivity and specificity and adequate ROC areas around 0.8, whereas the PEB changes in "pressure variables" offered good specificity (around 90%) on the expense of sensitivity (around 55%) with lower ROC areas around 0.7. Due to the independence violation for ROC analysis, the current study is primarily considered hypothesis confirming and encourages further research on ventricular extra systoles in both the clinical and experimental setting.

CVP and PAOP offered high classification rates, however for clinical use, CVP and PAOP can be considered less relevant. Both $\Delta_{PEB,\ abs}SP$ and $\Delta_{PEB,\ rel}SP$ had a fair area under the ROC curve but the optimal threshold was 0 (% and mmHg) and even associated with a low sensitivity. This may be attributed to the diastolic pressure characteristics of the PEB. On the other hand, $\Delta_{PEB}dP/dt$ was considerably larger than 0% and with optimal threshold at 27%.

The reason why variables derived from supraventricular extra systoles were not useful for fluid responsiveness prediction was difficult to tell from data. The compensatory pause is longer for ventricular extra systoles compared to supraventricular extra systoles and could theoretically create a "stronger signal" that could better separate responders from non responders. However, the classification performance differences between the two types of extra systoles appeared to be explained by differences in cardiac performance at PEBs during fluid unresponsiveness: A variable like $\Delta_{PEB,\ abs}PEP_{AP}$ was generally higher at supraventricular extra systoles compared to ventricular extra systoles under that condition. This appeared not to be explained by the differences in eligible PEBs between the two types of extra systoles.

An important issue for the clinical applicability of the presented extra systole method is prevalence of extra systoles. Extra systoles are generally considered benign and prevalent in both diseased and healthy subjects but prevalence increases with age and heart disease. 76% of non-hospitalised elderly women (aged 65 or more) and 88% of non-hospitalised elderly men have one or more ventricular extra systoles during 24 hour ECG recordings, and nearly 40% of men aged > 80 years have more than 15 ventricular extra systoles hourly. Their prevalence is however not well investigated among critically ill patients, but it can be expected that prevalence is higher for this patient group compared to healthy volunteers. As such, analysing extra systoles appears a feasible semi-continuous monitoring method.

The overall conclusion from the experiment is that analysis of cardiac beat performance at the extra systolic PEB may contribute to predicting fluid responsiveness reliably in patients where dynamic variables are not useful and where ventricular extra systoles are prevalent.

A subsequent clinical study performed on human patients, further validated the method. That study was an observational study on post-cardiac surgery patients, mainly scheduled for coronary artery bypass grafting (CABG) surgery and/or valvular replacement surgery. The setting for this study was the first post-operative 24h following surgery. Patients scheduled for a volume expansion on clinical grounds were followed in an observational manner. Most of the followed patients were mechanically ventilated and most patients encountered cardiac pacing. All patients had cardiac output monitored with a Swan-Ganz catheter (pulmonary artery catheter).

Patients were followed if they received 500 ml fluids, either artificial colloids, albumin or crystalloid fluids. Infusion times > 30 mins excluded volume expansions performed with crystalloids, and infusion times > 60 mins excluded volume expansions performed with colloids or albumin.

Data were considered for analysis if other hemodynamic interventions/circumstances were not initiated/encountered during the volume expansion or in the period where data were inspected for the occurrence of extra

systoles, e.g. changes in anesthesia and/or vasoactive drugs, changes made to PEEP level, and Trendelenbourg positioning. Net bleeding of > 100 ml blood during the volume expansion also excluded the recording for further analysis. When a volume expansion was performed and met the inclusion criteria, extra systoles seen maximally 30 min prior to the initiation of volume expansion were identified and used for analysis.

Extra systoles with at least 10 sinus beats prior to and following an extra systole were considered for analysis because these sinus beats were used for calculation of a baseline for PEP, SBP and other variables (median value). Sinus beats both before and after the extra systole was used for baseline calculation because slow (low frequency) autonomic rythms (changing e.g. SBP) are better corrected for in this manner. Among the eligible extra systoles, a median value was extracted for ΔPEP, ΔSBP and other Δ-variables.

In the study, both atrial (supraventricular) and ventricular extra systoles were eligible for analysis. The preliminary study results revealed that ΔSBP was a promising and the most interesting variable based on data from 20 patients.

Figs. 8a and 8b illustrate the results of the study.The data set of 20 patients is comprised by data acquired from a previous study primarily investigating fluid responsiveness prediction with dynamic variables but where extra systoles were found retrospectively (7 patients) and a study dedicated for validating the present method (in the time of writing, 13 patients). Among the 6 patients not responding to the volume expansion, no patients presented an extrasystolic induced ΔSBP above 3.5% prior to the volume expansion (100% specificity). On the other hand, only 3 out of the 14 patients responding to volume expansion, presented an extrasystolic induced ΔSBP below 3.5% (79% sensitivity). Area under the receiver operating characteristic (ROC) curve was 0.82. For ΔPEP, sensitivity and specificity were 86% and 67%, respectively, with ROC area of 0.71.

In preliminary conclusion, whether derived from arterial or ventricular extra systoles, the ΔSBP variable appears very interesting in the clinical setting of the investigating patient group (post-cardiac suregery patients). The fact that atrial extra systoles also appeared promising may be an advantage to the method

regarding eased detection and applicability. In the back ground population, atrial extra systoles are more prevalent than ventricular extra systoles. The ΔSBP "sibling" variable that can be detected from the plethysmographic curve was not as interesting as the ΔSBP variable derived from the arterial blood pressure signal, e.g. partly because only 13 data points were available for this recording.

FIG. 6 illustrates a method embodiment according to the invention. The method comprises receiving ECG data R_ECG, e.g. from an ECG device, and receiving data indicative of a blood pressure curve R_BPC, e.g. from a pulseoximetry device. E.g. 5-10 baseline heart beats can be used to calculate a baseline cardiac beat performance comprising calculating e.g. a baseline Pre-Ejection Period (PEP), C_BPEP. It is to be understood that the method can be performed on a stored data set, or it can be implemented so as to real-time monitor a patient where ECG and pulseoximetry data are continuously received at a pre-defined sample rate. Thus, e.g. calculating baseline values can be performed as a moving average, or the like, or it can be performed on stored data, once an extra systole is detected. When an extra systole is identified ESI in the ECG data, an optional step of verifying the extra systole V_ES can be performed, e.g. resulting in discarding the extra systole for further processing, if it does not fulfil a predetermined set of criteria, e.g. including being within a pre-defined coupling inverval ratio, and/or if the extra systole forms part of multiple extra systoles. If the extra systole is accepted for further processing, a PEP is calculated in response to the extra systole, and subsequently calculating a change in PEP, C_ΔPEP as a difference between the baseline PEP and the calculated PEP in response to the extra systole. This ΔPEP is then compared with a reference value C_RV, and finally based on this comparison, a fluid responsiveness prediction result is generated G_FR.

It is to be understood that the final fluid responsiveness prediction result can be communicated to a physician or other medical staff in various ways, e.g. including the use of a graphical symbol and/or text and/or numbers and/or colors presented on a display device. Especially, the fluid responsiveness prediction result can be communicated as part of an existing intensive care monitoring display.

Fig. 7 illustrates an example of a Frank-Starling curve, middle graph, together with arterial data versus time for from two patients exhibiting extra systoles.

Below and above the Frank-Starling curve, data from two patients exhibiting extra systoles are shown. The extra systoles were recorded prior to a fluid administration in both patients. It can be seen that a patient responding to subsequent fluid expansion with an increase in cardiac output of 34% (upper blood pressure panel) also showed a significant increase in systolic blood pressure (SBP) at the extrasystolic post-ectopic beat compared with the surrounding sinus beats. On the other hand, another patient not exhibiting an improved SBP at the post-ectopic beat (lower blood pressure panel), did not respond to fluid expansion (CO changed 4% after fluid expansion).

To sum up, the invention provides a device and a method for predicting fluid responsiveness of a subject, e.g. a patient suffering from sepsis. Input data indicative of cardiac beat performance of the subject, e.g. ECG and/or data indicative of a preload dependent hemodynamic variable, is used to identify spontaneous extra systoles and to measure the extra systolic induced changes in cardiac beat performance, e.g. a change in pre-ejection period (PEP) or systolic arterial blood pressure (SBP) in response to the extra systole compared to a baseline PEP or SBP derived from several surrounding sinus beats.. In response thereto, an indication of predicted fluid responsiveness of the subject is generated. A reliable fluid responsiveness prediction based on data preferably available in existing intensive care monitoring equipment.

Although the present invention has been described in connection with the specified embodiments, it should not be construed as being in any way limited to the presented examples. The scope of the present invention is to be interpreted in the light of the accompanying claim set. In the context of the claims, the terms "including" or "includes" do not exclude other possible elements or steps. Also, the mentioning of references such as "a" or "an" etc. should not be construed as excluding a plurality. The use of reference signs in the claims with respect to elements indicated in the figures shall also not be construed as limiting the scope of the invention. Furthermore, individual features mentioned in different claims, may possibly be advantageously combined, and the mentioning of these features in different claims does not exclude that a combination of features is not possible and advantageous.

CLAIMS

1. A fluid responsiveness prediction system arranged to predict fluid responsiveness of a subject, wherein the system comprises

- input means arranged to receive input data (HV, ECG) indicative of cardiac beat performance obtained from a subject, and

- a processor arranged
  - to identify extra systoles (IES) in response to the input data,
  - to calculate (CBP) a measure of cardiac beat performance (ΔPEP), such as a measure of a change in cardiac beat performance, in relation to the identified extra systole, in accordance with the input data, and
  - to generate (PFR) an indication of predicted fluid responsiveness (FR) of the subject in response to said measure of cardiac beat performance (ΔPEP).

2. System according to claim 1, wherein the input means is arranged to receive
- first input data (ECG) indicative of an Electro Cardio Graphy obtained from a subject, and to receive
- second input data (HV) indicative of a hemodynamic variable estimating cardiac beat performance, or indicative of a hemodynamic signal from which at least one hemodynamic variable estimating cardiac beat performance can be estimated, and

wherein the processor is arranged
- to identify extra systoles in response to the first or second input data,
- to calculate a measure of cardiac beat performance (ΔPEP) in relation to the identified extra systole, in accordance with the second input data, and
- to generate an indication of predicted fluid responsiveness (FR) of the subject in response to said measure of cardiac beat performance (ΔPEP).

3. System according to claim 1 or 2, wherein the input data comprises data indicative of a cardiac preload dependent hemodynamic variable.

4. System according to claim 2 or 3, wherein the second input data comprises at least one of: a measure of arterial blood pressure, and data representing a plethysmographic curve.

5. System according to any of the preceding claims, wherein the input data comprises data indicative of a hemodynamic variable estimating cardiac beat performance on a heart beat to heart beat basis in relation to baseline heart beats preceeding at least one of: an ectopic beat, a post-ectopic beat, and a heart beat immediately following a post-ectopic beat.

6. System according to any of the preceding claims, wherein the input data comprises data indicative of at least one of: a systolic arterial pressure, an arterial pulse pressure, a time derivative of arterial pressure upstroke, a pre-ejection period, a measure of cardiac stroke volume, a hemodynamic characteristics of the plethysmographic curve, a measure of cardiac stroke work, and a measured blood flow.

7. System according to any of the preceding claims, wherein the input data comprises data indicative of at least one of: morphological characteristics derived from a plethysmographic curve comparable to the ones mentioned above for the arterial blood pressure curve, a direct measure of cardiac stroke volume, an indirect measure of cardiac stroke volume, a preload dependent hemodynamic characteristic of the plethysmographic or arterial pressure curve, a direct or indirect measure of cardiac stroke work, and a direct or indirect measure of blood flow, a direct or indirect hemodynamic characteristic.

8. System according to any of the preceding claims, wherein the input data comprises a direct or indirect hemodynamic characteristic derived from a sensor capable of performing measuring a bioimpedance or a bioreactance.

9. System according to any of the preceding claims, wherein the input means is arranged to receive data from a pulseoximetry device, and wherein the processor is arranged to derive a measure of hemodynamic variation in response thereto.

10. System according to any of the preceding claims, wherein the input means is arranged to receive data from an arterial blood pressure device, and wherein the processor is arranged to derive a measure of hemodynamic variation in response thereto.

11. System according to any of the preceding claims, wherein the processor is arranged to calculate a pre-ejection period (PEP) in response to the input data.

12. System according to any of the preceding claims, wherein the processor is arranged to calculate a measure of change in pre-ejection period (ΔPEP) in relation to the identified extra systole.

13. System according to claim 12, wherein the processor is arranged to compare the calculated change in pre-ejection period (ΔPEP) with a predetermined reference value, and to generate the indication of predicted fluid responsiveness of the subject accordingly.

14. System according to any of the preceding claims, wherein the processor is arranged to calculate a measure of change in systolic arterial blood pressure (ΔSBP) in relation to the identified extra systole.

15. System according to claim 14, wherein the processor is arranged to compare the calculated change in systolic arterial blood pressure (ΔSBP) with a predetermined reference value, and to generate the indication of predicted fluid responsiveness of the subject accordingly.

16. System according to any of the preceding claims, wherein the processor is arranged to discard an identified extra systole, if a coupling interval is more than a predetermined fraction of a baseline heart beat interval.

17. System according to any of the preceding claims, wherein the processor is arranged to detect multiple consecutive extra systoles, and to discard generation of an indication of fluid responsiveness, if multiple consecutive extra systoles are detected.

18. System according to any of the preceding claims, comprising an Electro Cardio Graphy device arranged to obtain Electro Cardio Graphy data on the subject, wherein the processor is housed within said Electro Cardio Graphy device.

19. System according to any of the preceding claims, comprising a blood pressure measurement device arranged to obtain blood pressure measurement data on the subject.

20. System according to any of the preceding claims, wherein the indication of predicted fluid responsiveness is generated by comparing cardiac beat performance at the post ectopic beat with cardiac beat performance at a number of preceeding and/or following sinus beats.

21. Method for predicting fluid responsiveness of a subject, the method comprising

- receiving input data (R_ECG, R_HV) indicative of cardiac beat performance of the subject,

- identifying extra systoles (IES) in response to the input data,

- calculating a measure of cardiac beat performance (C_ΔPEP), such as a measure of a change in cardiac beat performance, in relation to the identified extra systole, in accordance with the input data, and

- generating an indication of predicted fluid responsiveness (G_FR) of the subject in response to said measure of cardiac beat performance.

22. Computer program product having instructions which when executed by a processor cause the processor to perform the method according to claim 20.

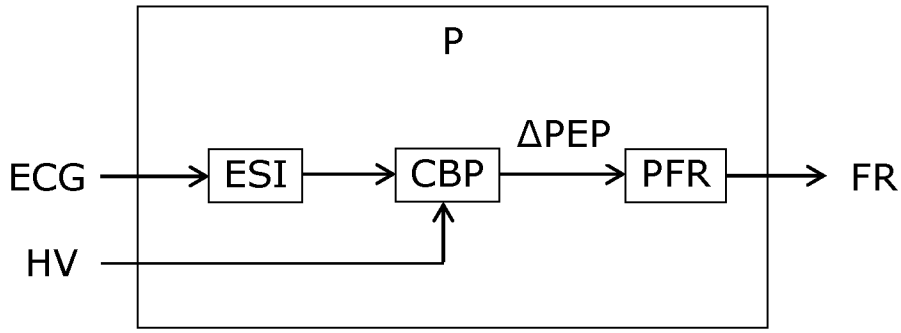
P
ECG
ESI
CBP
ΔPEP
PFR
FR
HV

Fig. 1

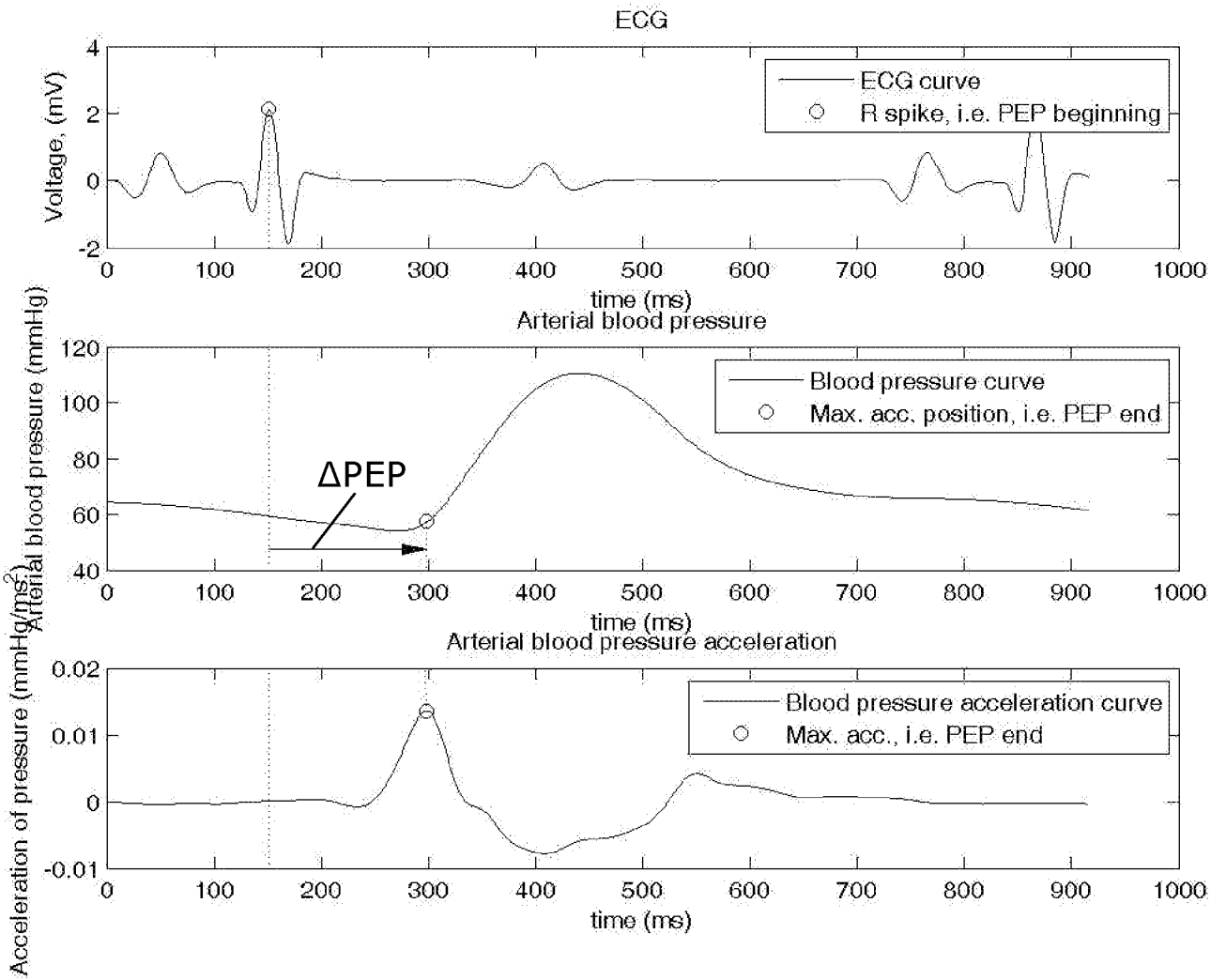
ECG
Voltage, (mV)
ECG curve
R spike, i.e. PEP beginning
time (ms)
Arterial blood pressure
Arterial blood pressure (mmHg)
Blood pressure curve
Max. acc. position, i.e. PEP end
ΔPEP
time (ms)
Arterial blood pressure acceleration
Acceleration of pressure (mmHg/ms²)
Blood pressure acceleration curve
Max. acc., i.e. PEP end
time (ms)

Fig. 2

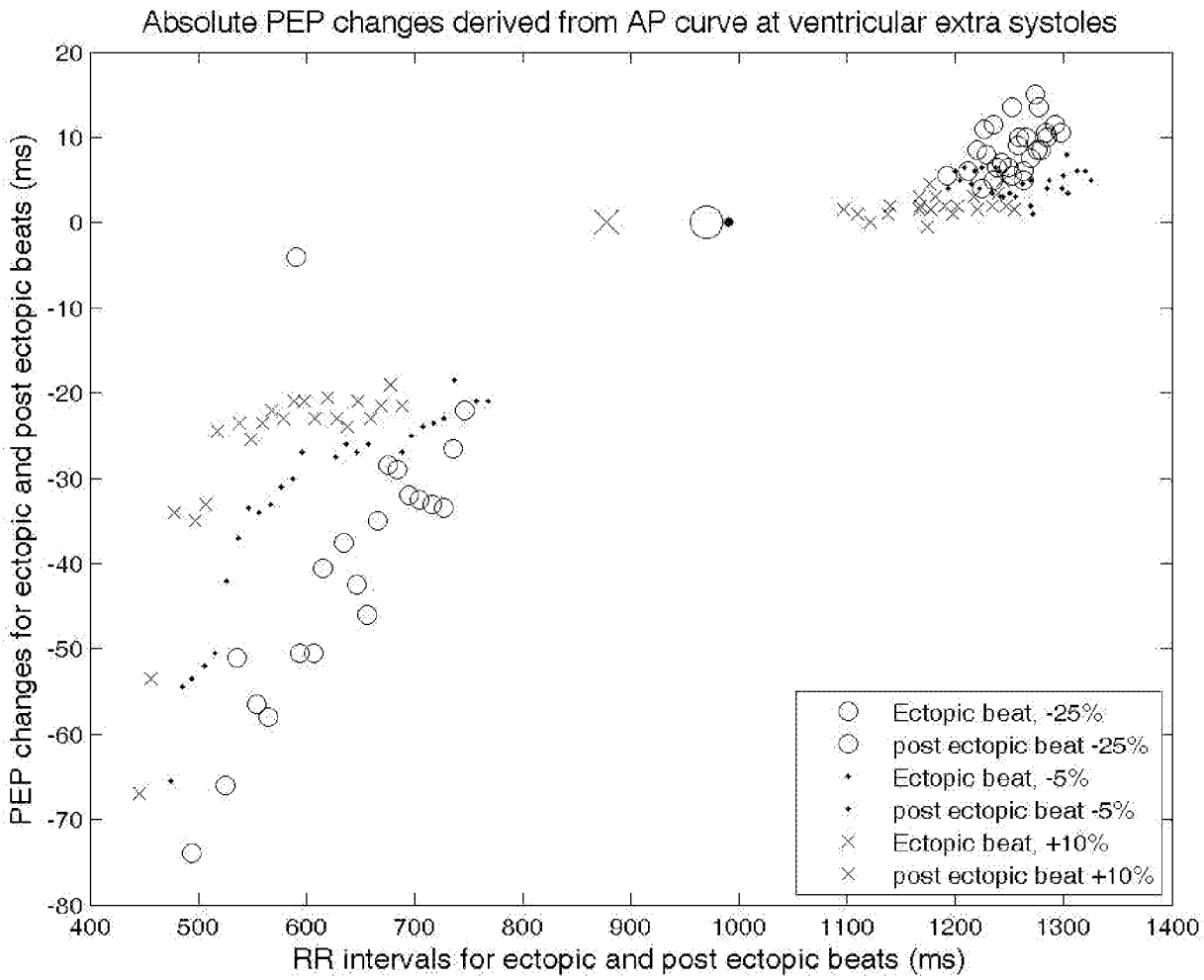
Absolute PEP changes derived from AP curve at ventricular extra systoles
PEP changes for ectopic and post ectopic beats (ms)
RR intervals for ectopic and post ectopic beats (ms)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
400
500
600
700
800
900
1000
1100
1200
1300
1400
Ectopic beat, -25%
post ectopic beat -25%
Ectopic beat, -5%
post ectopic beat -5%
Ectopic beat, +10%
post ectopic beat +10%

Fig. 3

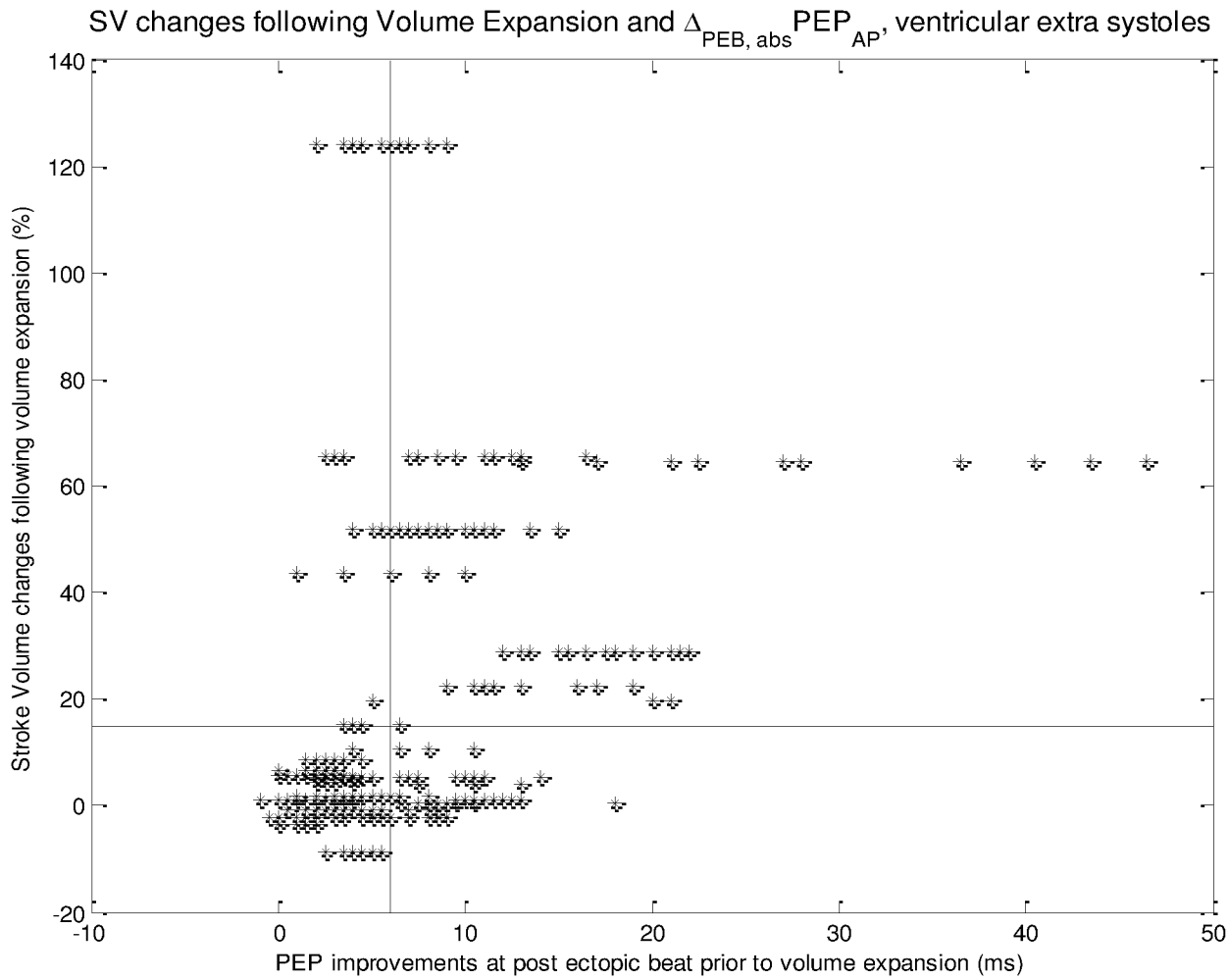
SV changes following Volume Expansion and $\Delta_{PEB, abs}PEP_{AP}$, ventricular extra systoles
Stroke Volume changes following volume expansion (%)
PEP improvements at post ectopic beat prior to volume expansion (ms)
140
120
100
80
60
40
20
0
-20
-10
0
10
20
30
40
50

Fig. 4

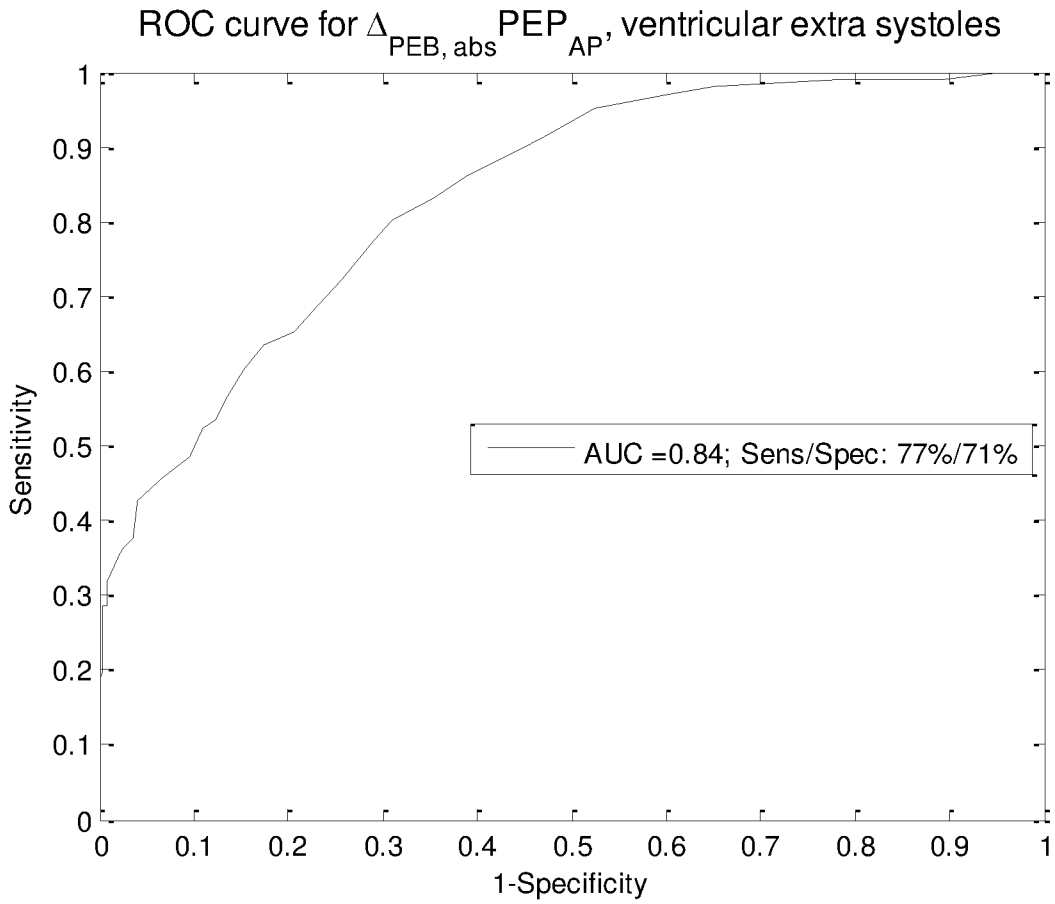
ROC curve for $\Delta_{PEB, abs}PEP_{AP}$, ventricular extra systoles
Sensitivity
1-Specificity
AUC =0.84; Sens/Spec: 77%/71%
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Fig. 5

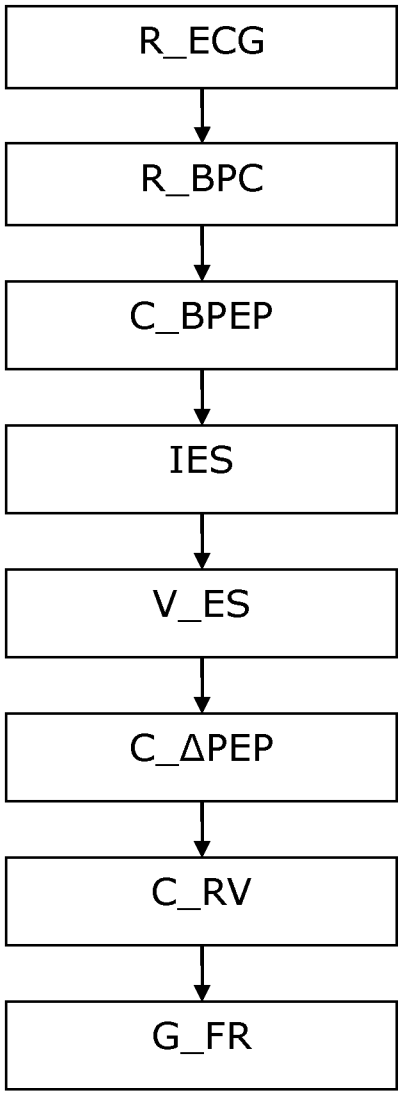

FIG. 6

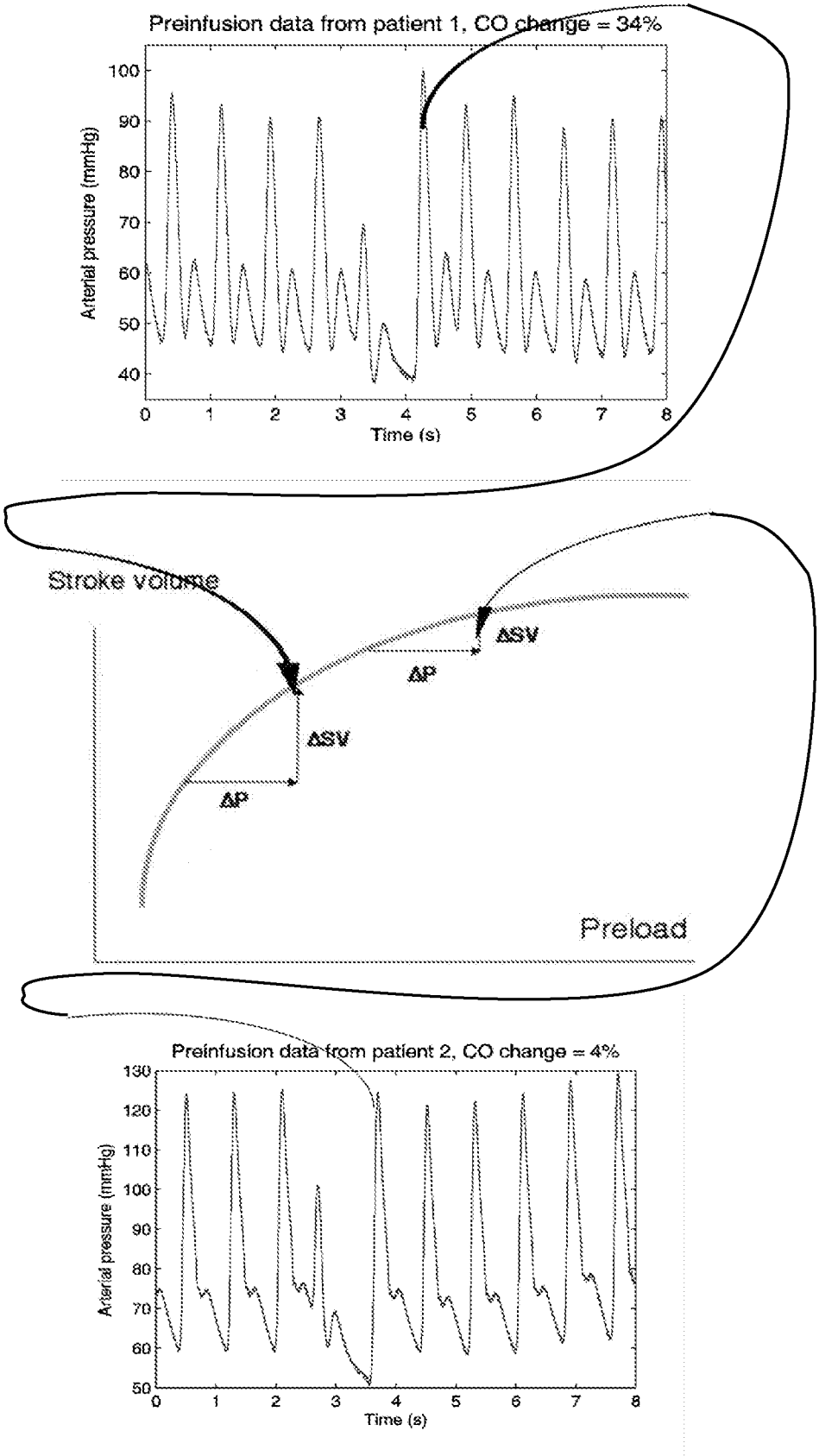
Preinfusion data from patient 1, CO change = 34%
Arterial pressure (mmHg)
Time (s)
Stroke volume
ΔSV
ΔP
ΔSV
ΔP
Preload
Preinfusion data from patient 2, CO change = 4%
Arterial pressure (mmHg)
Time (s)

FIG. 7

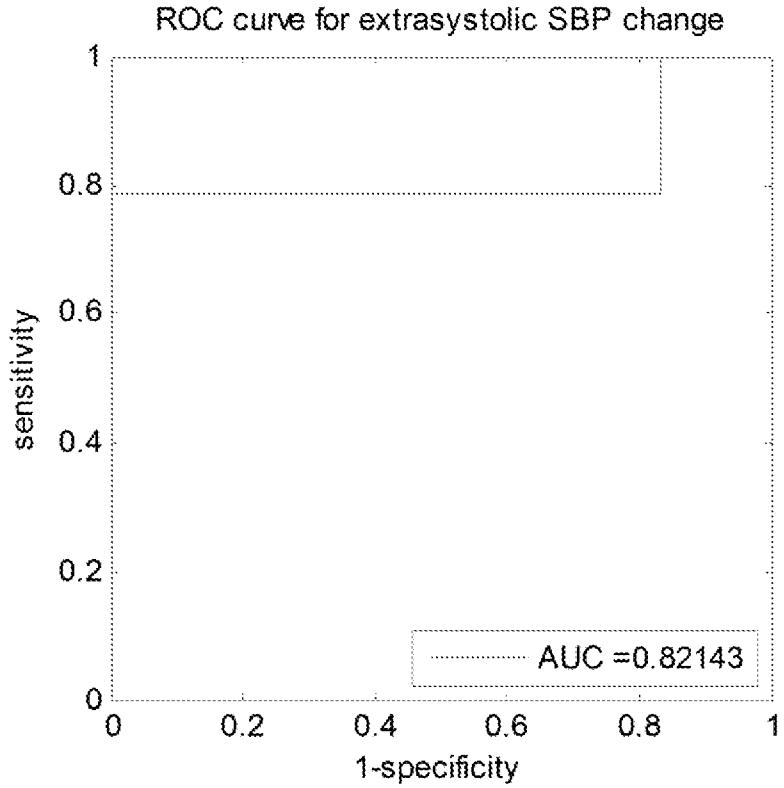
ROC curve for extrasystolic SBP change
sensitivity
1-specificity
AUC =0.82143
0
0.2
0.4
0.6
0.8
1

FIG. 8a

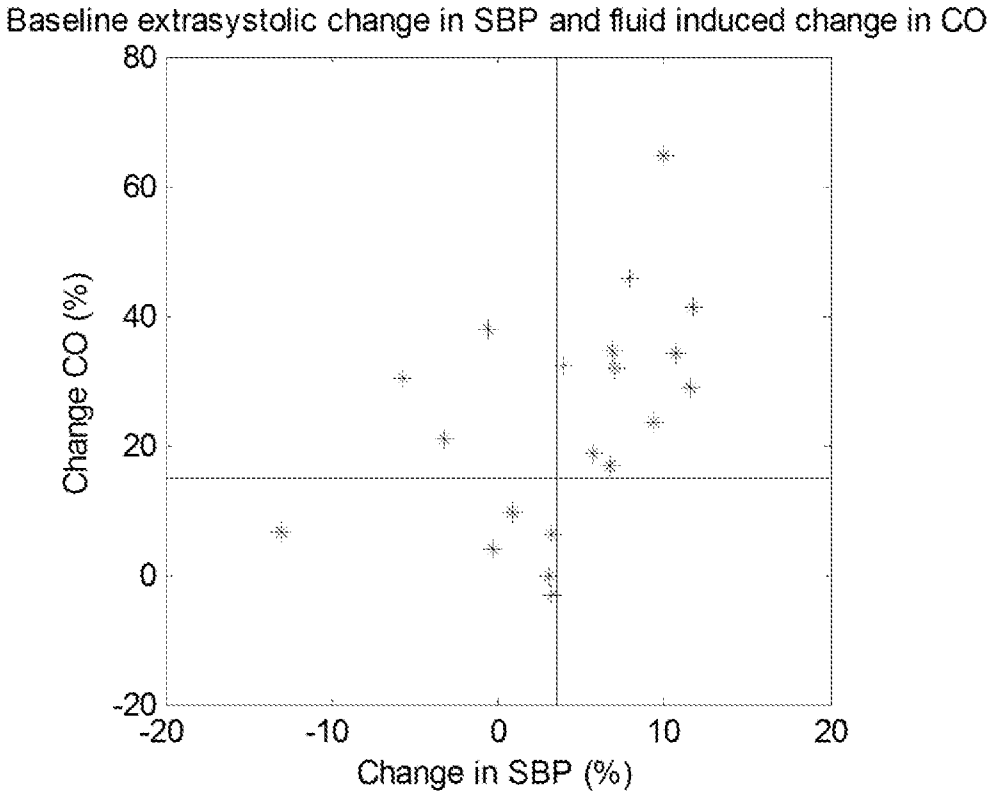
Baseline extrasystolic change in SBP and fluid induced change in CO
Change CO (%)
Change in SBP (%)
80
60
40
20
0
-20
-20
-10
0
10
20

FIG. 8b

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2014/050094

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/0205 A61B5/0468
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SALVATORE PALA ET AL: "Comparisons of predictors of fluid responsiveness in major surgery", THE EFFECT OF APPLIED COMPRESSIVE LOADING ON TISSUE-ENGINEERED CARTILAGE CONSTRUCTS CULTURED WITH TGF-BETA3, IEEE, 28 August 2012 (2012-08-28), pages 3128-3130, XP032463602, ISSN: 1557-170X, DOI: 10.1109/EMBC.2012.6346627 page 3128, section "Introduction" page 3129, section "B. Indices of fluid responsiveness" -----	1-22
Y	US 2004/186525 A1 (BURNES JOHN E [US] ET AL) 23 September 2004 (2004-09-23) paragraph [0013] ----- -/--	1-22

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2014	25/06/2014

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2014/050094

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 1 813 187 A1 (UP MAN GMBH & CO MED SYSTEMS K [DE] IPRM INTELLECTUAL PROPERTY RIG [CH) 1 August 2007 (2007-08-01) paragraphs [0004], [0007], [0019], [0020]; figure 1	1-21
A	WO 2009/023713 A2 (EDWARDS LIFESCIENCES CORP [US]; HATIB FERAS [US]; DERDERIAN LINA [US];) 19 February 2009 (2009-02-19) page 8, line 8 - line 17	1-21

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Information on patent family members

International application No
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