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***Validation of a New Method for Stroke Volume
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Validation of a New Method for Stroke Volume Variation Assessment: a Comparison with the PiCCO Technique

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Abstract: This paper proposes a novel, simple and minimally invasive method for stroke volume variation assessment using arterial blood pressure measurements. The arterial blood pressure signal is reconstructed using a semi-classical signal analysis method allowing the computation of a parameter, called the first systolic invariant $INVS_1$. We show that $INVS_1$ is linearly related to stroke volume. To validate this approach, a statistical comparison between $INVS_1$ and stroke volume measured with the PiCCO technique was performed during a 15-mn recording in 21 mechanically ventilated patients in intensive care. In 94% of the whole recordings, a strong correlation was estimated by cross-correlation analysis (mean coefficient=0.9) and linear regression (mean coefficient=0.89). Once the linear relation had been verified, a Bland-Altman test showed the very good agreement between the two approaches and their interchangeability. For the remaining 6%, $INVS_1$ and the PiCCO stroke volume were not correlated at all, and this discrepancy, interpreted with the help of mean pressure, heart rate and peripheral vascular resistances, was in favor of $INVS_1$.

Key-words: Arterial blood pressure, first systolic invariant, PiCCO, semi-classical signal analysis, stroke volume variation

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Validation d'une nouvelle méthode pour l'estimation du volume d'éjection systolique: comparaison avec le PiCCO

Résumé : Cet article propose une nouvelle méthode pour l'estimation du volume d'éjection systolique par des mesures de pression artérielle. Le signal de pression est reconstruit à l'aide d'une méthode d'analyse semi-classique permettant le calcul d'un paramètre, appelé le premier invariant systolique $INVS_1$. On montre que $INVS_1$ est linéairement relié au volume d'éjection systolique. Afin de valider cette approche, une comparaison statistique entre $INVS_1$ et le volume d'éjection systolique mesuré par la technique PiCCO a été effectuée pour un enregistrement de 15 minutes pour 21 patients mécaniquement ventilés et en soins intensifs. Pour 94% de l'enregistrement complet, une forte corrélation a été estimée par une analyse cross-corrélation (coefficient moyen=0.9) et une régression linéaire (coefficient moyen =0.89). Une fois la relation linéaire vérifiée, un test de Bland-Altman a montré une bonne correspondance entre les deux approches et leur interchangeabilité. Pour les 6% restant, $INVS_1$ et le volume d'éjection calculé par PiCCO n'ont pas été corrélés, et cette différence, interprétée à l'aide de la pression moyenne, de la fréquence cardiaque et des résistances vasculaires périphériques a été en faveur de $INVS_1$.

Mots-clés : Pression artérielle, premier invariant systolique, PiCCO, analyse semi-classique du signal, variations du volume d'éjection

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1 Introduction

Hemodynamic monitoring is crucial for critical care patient management. A recent international consensus conference recommended against the routine use of static preloaded measurements alone to predict fluid responsiveness [2], and dynamic assessment now seems more useful. Several studies have documented the ability of respiratory stroke volume variation (*SVV*) to predict the fluid responsiveness in hemodynamically compromised patients [8]-[13]. Measuring respiratory *SVV* requires a continuous monitoring of stroke volume (*SV*) which can be obtained using invasive or non-invasive methods. Current invasive methods used have the disadvantage of requiring the insertion of a central venous catheter and the calibration of the cardiac output measure with a cold isotonic sodium chloride bolus (PiCCO technology) [3] or a lithium chloride bolus (LiDCO technology) [9]. An alternative method, which does not require venous catheter insertion or calibration has been proposed (FloTrac Vigileo) [5], but several clinical studies have pointed out its poor agreement with reference techniques [12], [16]. Esophageal echo-doppler is the main non-invasive method, calculating aortic blood flow from the echo-derived aortic diameter and the doppler-derived aortic blood velocity [11]. Nevertheless, this technique has potential contraindications, such as esophageal varices or esophageal surgery, and several limitations: for instance, it measures the blood flow in the descending aorta and not the whole cardiac output. Moreover, the precision of the measurement depends on accurate probe positioning, which is not always easy to obtain [4]. Thus, each of the above methods has its own drawbacks, and there is still a need for an easily applicable, minimally invasive, accurate and affordable method to estimate *SVV*.

Due to the fact that Arterial Blood Pressure (ABP) can be measured using minimally invasive or noninvasive methods, the idea of estimating *SV* from ABP has captured scientists for a long time. Thus, many methods have been developed and whose objective is to find a relation between one or several parameters characterizing the shape of the pressure and *SV* or cardiac output (*CO*), see for instance [7], [15], [22], [23] and the references quoted there. These

methods, which are based on some models of systemic circulation, are called pulse contour methods. A comparison between some of the pulse contour methods has been proposed in [1], [26], [27], [29]. The simplest model supposes a proportionality between CO and the Mean Arterial Pressure (MAP). Other approaches, based on windkessel models, link SV to different lumped parameters such as pulse pressure, the systolic and diastolic pressures [7]. However these approaches consider the arterial system as a lumped system which appears not sufficiently accurate. So, other methods resulting from distributed arterial models use the pressure area so that SV is often supposed to be proportional to the area under the systolic part of the pressure curve. Corrected versions of this relation have been also proposed [15]. However, this approach requires detecting the end of the systole which is completely nontrivial, particularly in peripheral ABP waveforms. Moreover, approaches taking into account the nonlinear aspects of the arterial system have been proposed, for example modelflow [28], but some studies have revealed the poor efficiency of this method in a number of cases [24].

In this paper we introduce a novel technique for SVV assessment using ABP measurements. This method is based on the analysis of ABP with a new signal analysis method that was recently proposed in [21], and called Semi-Classical Signal Analysis (SCSA). The new spectral parameters provided by SCSA, eigenvalues and invariants, have already given promising results in some other applications, as summarized in the following.

On the one hand, we assessed their ability to discriminate between different situations. In the first situation, nine heart failure subjects were compared to nine healthy subjects. In the second situation, eight highly fit triathletes were compared before and after training. SCSA parameters always provided more significant results than classical parameters, regarding temporal as well as spectral parameters ([20], [21]). On the other hand, we tested the ability of the invariants to represent physiological parameters of great interest, particularly SVV , in two well-known conditions: the head-up 60 degrees tilt-test and the handgrip-test [21]. Let us focus on the first invariants. The first global invariant (INV_1) is, by definition, the mean value of the ABP signal, which is a standard parameter in clinical practice. The first systolic ($INVS_1$) and diastolic ($INVD_1$) invariants are less obvious. They result from the decomposition of the pressure into its systolic and diastolic parts. In particular, $INVS_1$ corresponds to the integral of the estimated systolic pressure with SCSA. Referring to the pulse contour method stating that the area under the systolic part of the pressure curve is proportional to SV as described above, one can show that $INVS_1$ variations give information on SVV .

We study in this paper the correlation between $INVS_1$ and measured SVV using a reference method; the PiCCO technique. The PiCCO technique uses the pulse contour method with a calibration by a transpulmonary thermodilution and is considered a reliable technique. In what follows, we present the experimental protocol and recall some basic aspects of the SCSA method. We introduce $INVS_1$ and its relation to SVV . Then, we present statistical results on 21 patients' recordings.

2 Materials and Methods

This prospective study was conducted in the 16-bed medical-surgical intensive care unit (ICU) of the Sud-Francilien General Hospital (Evry, France).

2.1 Patients

- **Inclusion criterion:** all mechanically ventilated patients whose cardiac output was continuously monitored with a transpulmonary thermodilution catheter (PiCCO, Pulsion Medical Systems, Munich, Germany) were included, except those satisfying the following excluding criteria. PiCCO is routinely used in this unit to monitor hemodynamically compromised patients.
- **Exclusion criteria:** patients presenting cardiac arrhythmias or breathing spontaneously were excluded because the SVV is not applicable for such patients.
- **Protocol:** all patients were sedated with midazolam and fentanyl in dosages that were titrated to achieve full adaptation to the ventilator. Ventilator settings were as follows: volume assist-control mode; tidal volume (V_t), 6ml/kg ideal body weight; breathing rate, 20 cycles/minute; inspiratory/expiratory ratio, $\frac{1}{2}$; and FiO_2 adjusted to maintain transcutaneous oxygen saturation in blood 94%. Positive end-expiratory pressure (PEEP) was set at $5\text{cm H}_2\text{O}$ but some hypoxemic patients required an increase in PEEP to $10\text{cm H}_2\text{O}$ during the data acquisition, to improve arterial oxygenation. The increase in PEEP was left to the discretion of the attending physician, as well as the adaptation of vasoactive drugs dosages, adjusted to maintain an adequate circulatory status during the protocol.

2.2 Data acquisition

One-lead electrocardiogram, arterial pressure, and respiratory flow signals were recorded during a 15-min period using a Biopac 100 system (Biopac systems, Goleta, CA, USA). All data were sampled at 1000Hz and stored on a hard disk. Cardiac output was calibrated just before the data acquisition with a cold isotonic sodium chloride bolus of 20 ml. Then, CO and peripheral vascular resistances (PVR) were delivered every 30 seconds during the 15-min period.

2.3 Signal analysis

Signal processing was performed using the Scilab and Matlab environments at the French National institute for Research in Computer Science and Control (INRIA-Sisyphe team).

A Semi-Classical Signal Analysis method

In this section, we introduce the SCSA technique and some results of its application to ABP analysis. We also show the relation between $INVS_1$ and SVV .

The SCSA principle Let $y : t \mapsto y(t)$ be a real valued function representing the signal to be analyzed such that:

$$\begin{aligned} y &\in L^1_1(\mathbb{R}), \quad y(t) \geq 0, \quad \forall t \in \mathbb{R}, \\ \frac{\partial^m y}{\partial x^m} &\in L^1(\mathbb{R}), \quad m = 1, 2, \end{aligned} \quad (1)$$

with,

$$L^1_1(\mathbb{R}) = \{V \mid \int_{-\infty}^{+\infty} |V(t)|(1 + |t|)dt < \infty\}. \quad (2)$$

The main idea in the SCSA consists in interpreting the signal y as a multiplication operator, $\phi \rightarrow y \cdot \phi$, on some function space. Then, instead of the standard Fourier Transform, we use the spectrum of a regularized version of this operator, known as the Schrödinger operator in $L^2(\mathbb{R})$, for the analysis of y :

$$H(h; y) = -h^2 \frac{d^2}{dt^2} - y, \quad (3)$$

for a small $h > 0$. The SCSA method is better suited to the analysis of some pulse shaped signals than the Fourier Transform [21].

In this approach, the signal is a potential of the Schrödinger operator $H(h; y)$. We are interested in the spectral problem of this operator which is given by:

$$-h^2 \frac{d^2 \psi}{dt^2} - y\psi = \lambda \psi, \quad t \in \mathbb{R}, \quad (4)$$

where $\lambda, \lambda \in \mathbb{R}$ and $\psi, \psi \in H^2(\mathbb{R})$ ¹ are respectively the eigenvalues of $H(h; y)$ and the associated eigenfunctions. Under equation (1), the spectrum of $H(h; y)$ consists of:

- a continuous spectrum $\lambda \geq 0$,
- a discrete spectrum composed of negative eigenvalues. There is a non-zero, finite number N_h of negative eigenvalues of the operator $H(h; y)$. We put $\lambda = -\kappa_{nh}^2$ with $\kappa_{nh} > 0$ and $\kappa_{1h} > \kappa_{2h} > \dots > \kappa_{nh}$, $n = 1, \dots, N_h$. Let ψ_{nh} , $n = 1, \dots, N_h$ be the associated L^2 -normalized eigenfunctions [21].

The SCSA technique consists in reconstructing the signal y with the discrete spectrum of $H(h; y)$ using the following formula:

$$y_h(t) = 4h \sum_{n=1}^{N_h} \kappa_{nh} \psi_{nh}^2(t), \quad t \in \mathbb{R}. \quad (5)$$

Here, the parameter h plays an important role. As h decreases, the approximation of the signal improves. However, as h decreases, the number of negative eigenvalues N_h increases and hence the time required to perform the computation increases. So, in practice, what we are looking for is a value of h that provides a sufficiently small estimation error with a reduced number of negative eigenvalues. We summarize the main steps for reconstructing a signal with the SCSA as follows [21]:

¹ $H^2(\mathbb{R})$ denotes the Sobolev space of order 2

1. Interpret the signal to be analyzed y as a potential of the Schrödinger operator $H(h; y)$ (3) ;
2. compute the negative eigenvalues and the associated L^2 -normalized eigenfunctions of $H(h; y)$;
3. compute y_h according to equation (5) ;
4. look for a value of h to obtain a good approximation with a small number of negative eigenvalues.

ABP analysis with the SCSA Now, we introduce some results on the application of the SCSA to ABP analysis. We denote by P the ABP signal and $\hat{P}$ its estimation with the SCSA such that:

$$\hat{P}(t) = 4h \sum_{n=1}^{N_h} \kappa_{nh} \psi_{nh}^2(t), \quad (6)$$

where $-\kappa_{nh}^2$, $n = 1, \dots, N_h$ are the N_h negative eigenvalues of the Schrödinger operator $H(h; P)$ and ψ_{nh} the associated L^2 -normalized eigenfunctions.

The ABP signal was estimated for several values of the parameter h and hence N_h . Fig.1 illustrates measured and estimated pressures for one beat of an ABP signal and the estimated error with $N_h = 9$. Signals measured at the aorta (invasively) and at the finger (non invasively) respectively were considered. We point out that 5 to 9 negative eigenvalues are sufficient for a good estimation of an ABP beat [17], [19].

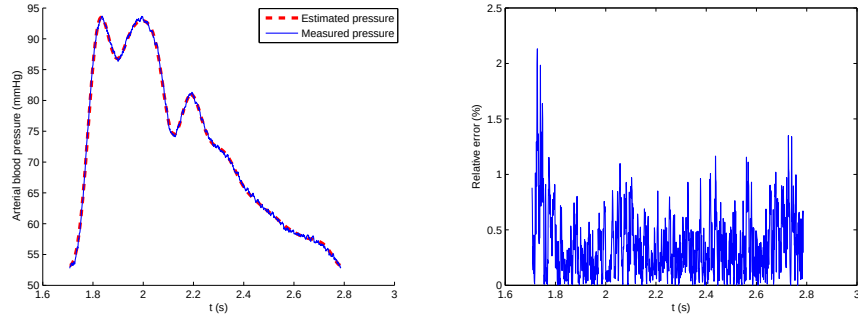
One application of the SCSA to ABP signals consists in decomposing the signal into its systolic and diastolic parts. This application was inspired by a reduced model of ABP based on solitons solutions of a Korteweg-de Vries (KdV) equation ² proposed in [10], [18]. As described in [17], [21], the idea consists in decomposing (6) into two partial sums: the first one, composed of the N_s ($N_s = 1, 2, 3$ in general) largest κ_{nh} and the second composed of the remaining components. Then, the first partial sum represents rapid phenomena that predominate during the systolic phase and the second one describes slow phenomena of the diastolic phase. We denote by $\hat{P}_s$ and $\hat{P}_d$ the systolic pressure and the diastolic pressure respectively estimated with the SCSA. Then we have:

$$\hat{P}_s(t) = 4h \sum_{n=1}^{N_s} \kappa_{nh} \psi_{nh}^2(t), \quad (7)$$

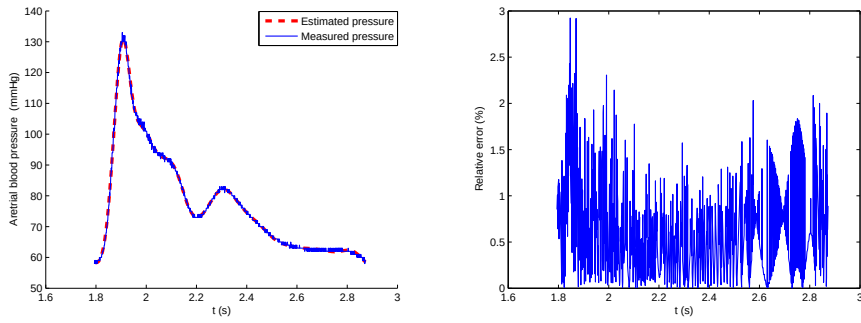
$$\hat{P}_d(t) = 4h \sum_{n=N_s+1}^{N_h} \kappa_{nh} \psi_{nh}^2(t). \quad (8)$$

Fig.2 shows measured pressure and estimated systolic and diastolic pressures respectively. We notice that $\hat{P}_s$ and $\hat{P}_d$ are respectively localized during the systole and the diastole.

²Solitons are solutions of some non-linear partial derivative equations like the KdV equation



(a) Aorta



(b) Finger

Figure 1: Estimation of the pressure at the aorta and the finger level with the SCSA and $N_\chi = 9$. On the left, the estimated and measured pressures. On the right, the relative error

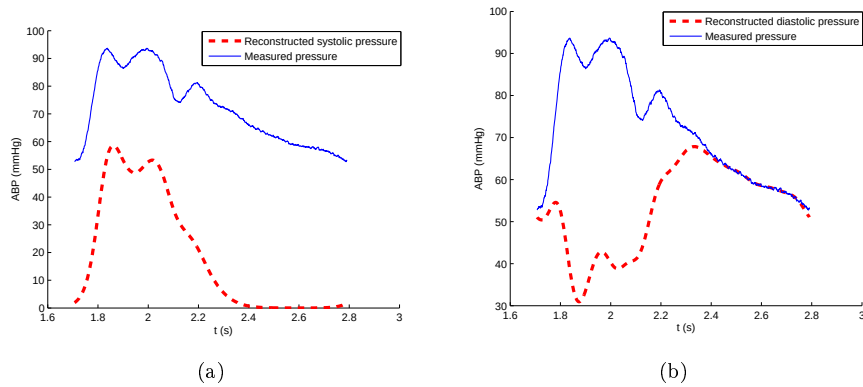


Figure 2: (a) Estimated systolic pressure, (b) Estimated diastolic pressure

SCSA parameters As seen previously, the SCSA technique provides a new description of the ABP signal with some spectral parameters which are the negative eigenvalues and the so called invariants³. The latter consist in some momentums of the κ_{nh} , $n = 1, \dots, N_h$. So we define the first two global invariants by:

$$INV_1 = 4h \sum_{n=1}^{N_h} \kappa_{nh}, \quad INV_2 = \frac{16}{3}h \sum_{n=1}^{N_h} \kappa_{nh}^3. \quad (9)$$

Systolic ($INVS_{1,2}$) and diastolic ($INVD_{1,2}$) invariants are deduced from the decomposition of the pressure into its systolic and diastolic parts and are then given by:

$$INVS_1 = 4h \sum_{n=1}^{N_s} \kappa_{nh}, \quad (10)$$

$$INVS_2 = \frac{16}{3}h \sum_{n=1}^{N_s} \kappa_{nh}^3, \quad (11)$$

$$INVD_1 = 4h \sum_{n=N_s+1}^{N_h} \kappa_{nh}, \quad (12)$$

$$INVD_2 = \frac{16}{3}h \sum_{n=N_s+1}^{N_h} \kappa_{nh}^3. \quad (13)$$

$INVS_1$ for SVV estimation We will see here how $INVS_1$ is related to SV . For this purpose, we recall one approach of the pulse contour methods that supposes proportionality between SV and the area under the systolic part of the pressure curve as described in the introduction. We denote this area by P_{sa} (see fig.3). So we have:

$$SV_{PC} = kP_{sa}, \quad (14)$$

where k is a positive real and SV_{PC} is the stroke volume estimated with the pulse contour method.

Referring to (7) and (10), and remembering that ψ_{nh} are L^2 -normalized, we have:

$$INVS_1 = \int_{-\infty}^{+\infty} \hat{P}_s(t) dt. \quad (15)$$

So, $INVS_1$ refers to the area under the systolic curve $\hat{P}_s$. Thus, one can remark that both P_{sa} and $INVS_1$ describe the area under the systolic pressure but they may not be equal because the detection of the end systole in the two cases is not the same (see fig.2.a and fig.3). Indeed, while P_{sa} is computed by detecting the dicrotic notch which is completely non trivial in peripheral ABP waves, $INVS_1$ results from a nonlinear model of ABP based on solitons that considers the propagation of the pulse wave [10], [18] as was described in section II.C.1.b. We can write the following relation between the two areas:

$$INVS_1 = P_{sa} + b, \quad (16)$$

³We call these parameters invariants because they are related to the Korteweg-de Vries invariants in time

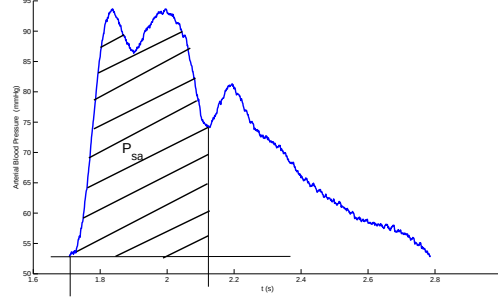


Figure 3: Area under the systolic part of the pressure curve used to estimate SV

where $b \in \mathbb{R}$ represents the difference between the two areas. Then, we get:

$$INVS_1 = aSV_{PC} + b. \quad (17)$$

with $a = \frac{1}{k}$. Hence, $INVS_1$ and SV_{PC} are linearly related.

Resulting time series used to compare $INVS_1$ to PiCCO stroke volume

On top of $INVS_1$, two vascular time series were analyzed: the heart rate (HR) was computed from the pulse interval (PI), which is the distance between two systolic occurrences; MAP was calculated from the systolic and diastolic values. All data were resampled at 4 Hz, by the interpolation of a third order spline function to obtain equidistant data and to guarantee their synchronization. They were then averaged over 15 seconds and delivered every 30 seconds, like the PiCCO protocol. PiCCO cardiac output was divided by HR to give a stroke volume (SV_{PiCCO}). According to the relation between $INVS_1$ and SV , $INVS_1$ was subsequently called SV_{SCSA} when it was estimated with the linear equation (17): $SV_{SCSA} = aSV_{PiCCO} + b$. Thus, in addition to the SV_{PiCCO} and SV_{SCSA} , temporal relations with HR , MAP and PVR time series were analyzed to help interpret SV behavior in case of a divergence between SV_{PiCCO} and SV_{SCSA} .

2.4 Statistical analysis

1. Cross-correlation analysis.

The cross-correlation analyzes the temporal similarity between two time series by estimating the correlation between one time series at time t and the other at time $t \pm x$ lags (in samples) [25]. A cross-correlation was performed between SV_{PiCCO} and $INVS_1$ time series averaged every 30 seconds. Cross-correlation coefficients were computed using the Matlab `xcorr` function (The MathWorks, Inc) after subtracting the means from

the time series. Cross-correlation coefficients were computed for all lags $(-30; +30)$, each lag corresponding to a 30-second interval. The correlation coefficients of the unlagged data stand at the midpoint (lag 0). A 5% level of probability for the correlation coefficients was considered significant (Bravais-Pearson table). An average estimate of the correlation over all the subjects was allowed after homogeneity tests (non significant z-test and Jarque-Bera test) [14]. The individual correlation coefficients were averaged for each lag.

2. Linear regression.

According to the proportional relation between SV_{PiCCO} and $INVS_1$ (equation (17)), a linear regression analysis was applied, using SigmaStat. This analysis provides the Pearson R coefficient, which measures the degree of linear correlation between the two estimates, and the parameters of the linear equation (17), a and b . So, they allow an estimation of the stroke volume SV_{SCSA} using (17). This transformation is required before using the Bland-Altman test.

3. Bland-Altman method.

Unlike the first two approaches which are not affected by differences in units or the nature of results, the Bland-Altman method analyzes the agreement between two estimates of the same variable [6]. Thus, we used SV_{SCSA} instead of $INVS_1$, and moreover, SV_{SCSA} variations to compare them to SV_{PiCCO} variations ($\Delta := SVV_{PiCCO} - SVV_{SCSA}$ with $SVV_{PiCCO} = SV_{PiCCO}(n) - SV_{PiCCO}(n-1)$ and $SVV_{SCSA} = SV_{SCSA}(n) - SV_{SCSA}(n-1)$). The mean difference between SVV_{PiCCO} and SVV_{SCSA} (mean Δ) is plotted against the average of the two volume variations. Mean Δ which represents the bias between the two methods, and the 95% confidence interval ($[CI_{inf}\Delta \quad CI_{sup}\Delta]$) gives the variation of the values of one method compared to the other.

3 Results

3.1 Patients

The 21 patients recordings were analyzed over 900 seconds, representing about 30 averaged values, except one recording, analyzable only for the first 16 averaged values. In order to illustrate the main results, we choose the first three subjects in Table 1, representing various conditions: subject one was submitted to PEEP changes (fig.8), subject two was submitted to noradrenaline dose changes (fig.9), subject three had no change in ventilatory parameters nor in drugs (fig.10).

Table 1: Cross-correlation and linear regression coefficients between SV_{PiCCO} and $INVS_1$

Subject	Number of values	Cross correlation	Linear regression
1	30	0.99	0.98
2	30	0.97	0.97
3	30	0.97	0.97
4	30	0.96	0.96
5	30	0.96	0.96
6	30	0.95	0.95
7	30	0.95	0.95
8	30	0.93	0.94
9	30	0.91	0.91
10	30	0.91	0.89
11	30	0.90	0.89
12	30	0.90	0.90
13	30	0.86	0.85
14	30	0.85	0.77
15	30	0.85	0.86
16	30	0.85	0.85
17	21	0.84	0.87
18	30	0.82	0.83
19	16	0.82	0.82
20	30	0.77	0.77

The subjects (col. 1) are listed in the decreasing order of cross-correlation coefficients. Col. 2 indicates the number of measurements delivered every 30-second per subject, according to the PiCCO protocol and representing a 900 seconds analysis. Col. 3 and 4 stand for coefficients of cross-correlation (mean: 0.90 ± 0.01 at lag 0) and linear regression (mean: 0.89 ± 0.01). Subject 21 and the last third of Subject 17, whose $INVS_1$ and SV_{PiCCO} were not correlated at all (coefficient < 0.1), were discarded from the table. The last part of Subject 19 was discarded before analysis because of a PiCCO dysfunction.

3.2 Cross-correlation analysis

Table 1, column three, shows the coefficients of cross-correlation in decreasing order. The amount of well correlated measures represents 94% of the all recordings. Because of an obvious divergence between SV_{PiCCO} and $INVS_1$ (coefficients < 0.1), Subject 21 and the third part of Subject 17 were discarded from the table. Thus, they represent only 6% of discrepancy among all the recordings. Fig.4 and fig.5 respectively represent the time series of HR , MAP , PVR , $INVS_1$ and SV_{PiCCO} for subjects 21 and 17.

Fig.6 represents the cross-correlation coefficients of the 20 remaining subjects (dashed lines). As homogeneity was verified, averaged values were also plotted ($-\bullet-$). The vertical axis depicts the correlation coefficients. The horizontal axis depicts the lag, in number of 30-second averaged values of one time series on another. The correlation coefficients of the unlagged data are plotted at horizontal midpoint (lag 0). The two symmetrical continuous lines represent critical

Table 2: Bland-Altman test results

Subject	$Min\Delta$	$CI_{inf}\Delta$	$Max\Delta$	$CI_{sup}\Delta$
1	-.0056	-.0074	.0048	.0077
2	-.0026	-.0037	.0034	.0039
3	-.0030	-.0036	.0022	.0037
4	-.0043	-.0057	.0043	.0056
5	-.0034	-.0039	.0044	.0040
6	-.0048	-.0052	.0045	.0053
7	-.0059	-.0072	.0043	.0072
8	.0005	-.0009	.0009	.0009
9	-.0037	-.0051	.0046	.0050
10	-.0047	-.0055	.0042	.0057
11	-.0073	-.0114	.0095	.0115
12	-.0070	-.0096	.0068	.0096
13	-.0044	-.0072	.0078	.0079
14	-.0018	-.0031	.0023	.0032
15	-.0029	-.0053	.0060 *	.0054
16	-.0022	-.0026	.0026 *	.0030
17	-.0033	-.0041	.0024	.0046
18	-.0081	-.0100	.0079	.0094
19	-.0016	-.0045	.0035	.0046
20	-.0054	-.0080	.0079	.0080

$\Delta = SVV_{PiCCO} - SVV_{SCSA}$ with $SVV_{PiCCO} = SV_{PiCCO}(n) - SV_{PiCCO}(n-1)$ and $SVV_{SCSA} = SV_{SCSA}(n) - SV_{SCSA}(n-1)$. $Min(\Delta)$ and $max(\Delta)$ stand for the minimal and maximal values of Δ respectively. CI is 95% confidence interval of the agreement limits of Δ ; $[CI_{inf}\Delta, CI_{sup}\Delta]$. * means that all the values are inside $[CI_{inf}\Delta, CI_{sup}\Delta]$ except 1 value greater than $CI_{sup}\Delta$ for two subjects.

r values for a level 5 of probability (Bravais-Pearson table). The greatest correlation stands at lag 0 for all the remaining subjects (mean correlation= 0.90; $sem = 0.01$; $p = 0.00001$). This result shows an excellent temporal similarity between the successive measures, indicating that they change in the same way over time.

3.3 Linear regression

Table 1, column four, shows the R coefficients of linear regression. Cross-correlation and R coefficients are strongly correlated (0.95 at Spearman rank order correlation test). The mean coefficient, equal to 0.89 shows a great degree of linearity between the two methods. Fig.7 shows the plots of linear regression for the first three subjects.

3.4 Bland-Altman method

Fig.7 shows the Bland-Altman plots for the first three subjects. Differences in the two mean SVV ($SVV_{PiCCO} - SVV_{SCSA}$) are plotted against the mean of the two SVV ($\frac{SVV_{PiCCO} + SVV_{SCSA}}{2}$). Continuous lines respectively stand

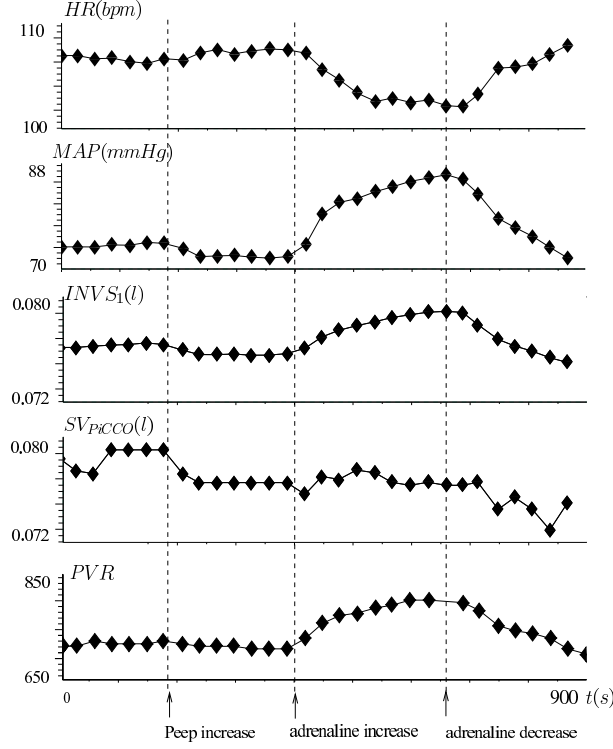


Figure 4: Cardiovascular time series of subject 21, submitted to ventilatory and pharmacological changes. The lack of correlation between $INVS_1$ and SV_{PiCCO} (cross-correlation coefficient=0.039) is in favor of $INVS_1$. Before increasing PEEP, nothing happens, HR , MAP , PVR are stable, thus no SV change can be expected. Nevertheless, SV_{PiCCO} decreases then increases while $INVS_1$ remains quite stable. During increasing adrenaline, increasing PVR is accompanied, as expected, by increasing MAP and decreasing HR . An increase in SV is also expected, which is done by $INVS_1$ while SV_{PiCCO} remains quite stable.

for the mean of differences Δ between the two results, and the 95% confidence interval. Each dot stands for the difference between SVV measured by the two methods. In the three cases, mean Δ is equal to 0 and all values are within the two 95% confidence intervals. Table 2 gives results for all the subjects. When comparing $\min(\Delta)$ to $CI_{inf}\Delta$ (columns 1 and 2) and $\max(\Delta)$ to CI_{sup} (columns 3 and 4), one can see that all values are inside $[CI_{inf} \ CI_{sup}]$ except one value greater than $CI_{sup}\Delta$ in two subjects (*). These global results allow us to conclude that a good proximity exists between the two methods with the same order of dispersion and that they are interchangeable.

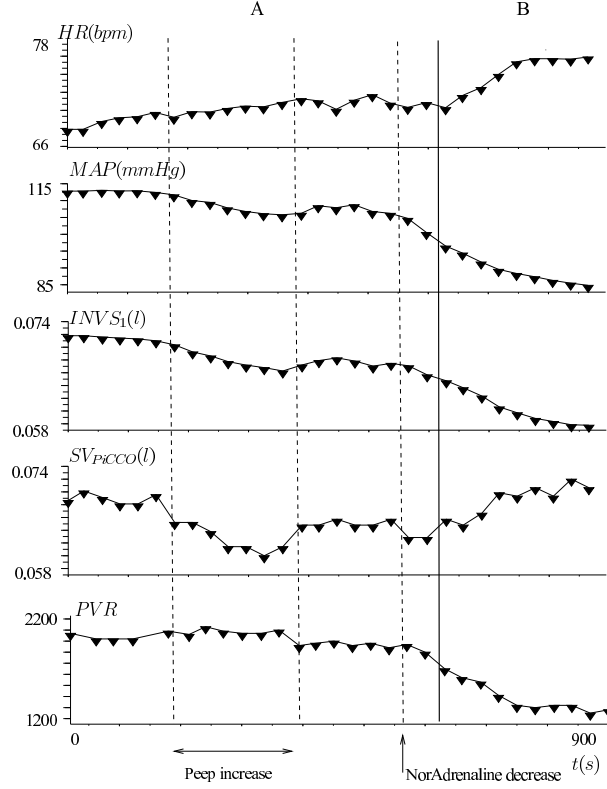


Figure 5: Cardiovascular time series for subject 17, submitted to ventilatory and pharmacological changes. $INVS_1$ and SV_{PiCCO} are strongly correlated (cross-correlation coefficient = 0.84) during period A, and they are divergent during period B. Decreasing noradrenaline is naturally accompanied by decreasing PVR and MAP and increasing HR . A decrease in SV is also expected, which is done by $INVS_1$ while SV_{PiCCO} strongly increases.

4 Discussion

A new method for a simple and minimally invasive SVV estimation from ABP measurements has been validated in this study. The ABP signal is reconstructed with a semi-classical signal analysis method SCSA which enables the decomposition of the signal into its systolic and diastolic parts. Some spectral parameters, that give relevant physiological information, are then computed and especially the first systolic invariant $INVS_1$, given by the area under the estimated systolic pressure curve. Thus, we have shown that $INVS_1$ yields reliable SVV assessment.

So, in order to validate this approach, we compared $INVS_1$ estimated from ABP measurements with SV measured with a reference method: the PiCCO technique. Three statistical methods were applied for this validation: cross-correlation analysis, linear regression and the Bland-Altman test. Among the 315 minutes duration of all the 21 recordings, 94 % presented a very high correlation between $INVS_1$ and SV_{PiCCO} . The mean coefficient was equal to 0.9

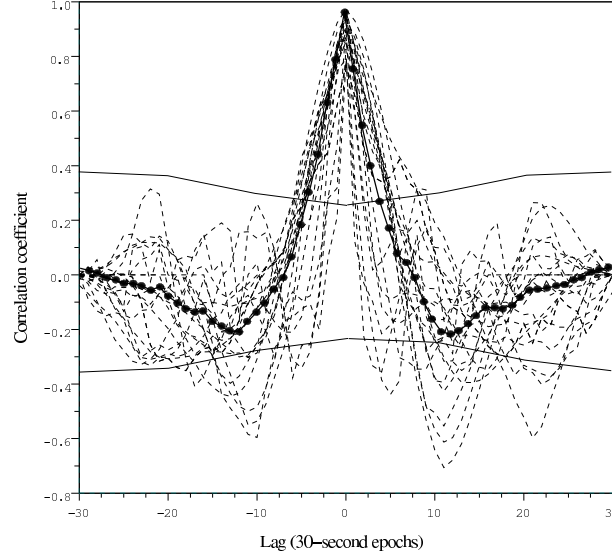


Figure 6: Cross-correlation between the 30-second averaged SV_{PiCCO} and $INVS_1$ values in 20 subjects. Each line (dashed) stands for a subject; the strong line ($-\bullet-$) represents the average of the 20 subjects; continuous lines represent critical r values for a 5% level of probability (Bravais-Pearson table). The vertical axis depicts the correlation coefficients. The horizontal axis depicts the lag, in number of 30-second measures, of one time series on another. The correlation coefficients of the unlagged data are shown at horizontal midpoint (lag 0). All time series are exactly synchronized, with a mean correlation coefficient equal to 0.9 at lag 0 ($p=0.00001$).

for cross-correlation, and equal to 0.89 for linear regression. The remaining 6% without correlation, concerned two subjects: all of subject 21 and the last third of subject 17. This discrepancy, interpreted with the help of the synchronized HR , MAP , PVR time series, can be explained by the following remarks:

- For subject 21 (fig.4), before increasing PEEP, nothing happens, HR , MAP , PVR are stable, thus no SV change can be expected. Nevertheless, SV_{PiCCO} decreases then increases while $INVS_1$ remains quite stable. During increasing adrenaline, increasing PVR is accompanied, as expected, by increasing MAP and decreasing HR . An increase in SV is also expected, which is done by $INVS_1$ while SV_{PiCCO} remains quite stable.
- For the last third of subject 17 (fig.5, B), decreasing noradrenaline is naturally accompanied by decreasing PVR and MAP and increasing HR . A decrease in SV is also expected, which is done by $INVS_1$ while SV_{PiCCO} strongly increases.

The divergence between $INVS_1$ and SV_{PiCCO} is in favor of $INVS_1$ for these two subjects.

On the 94% recordings with well correlated $INVS_1$ and SV_{PiCCO} , the Bland-Altman test showed a very good agreement between the two approaches

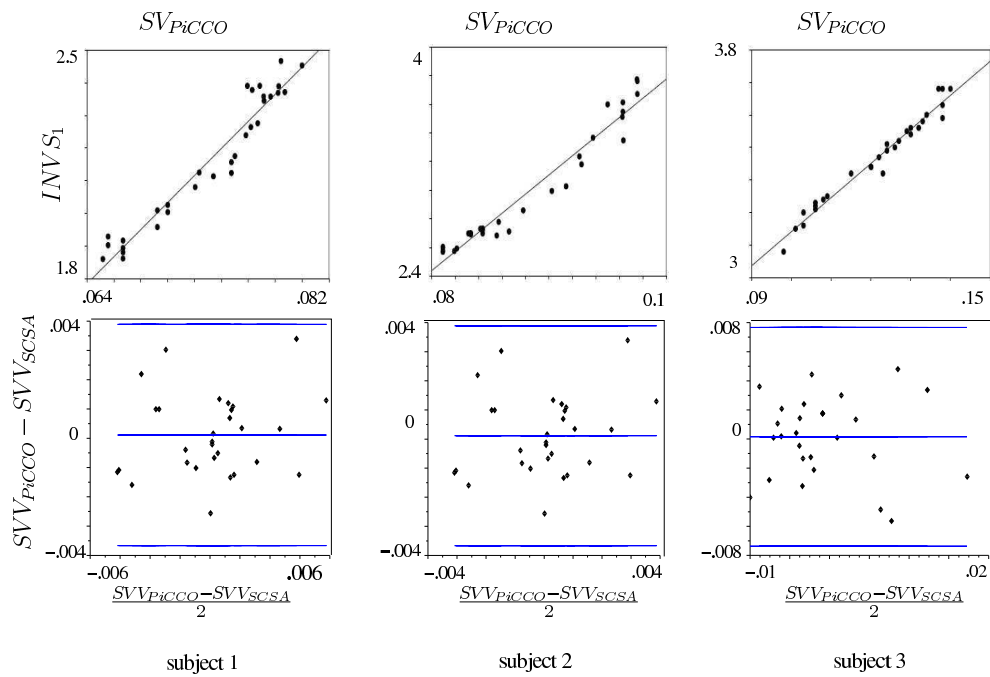


Figure 7: Linear regression plots (at the top) and Bland-Altman plots (at the bottom) for the three first subjects. The coefficient of correlation is greater than .95 for each of them, meaning a strong linear relation. All the differences in SVV_{PiCCO} and SVV_{SCSA} are included in the 95 % confidence interval for each of them, meaning a good agreement between the two methods.

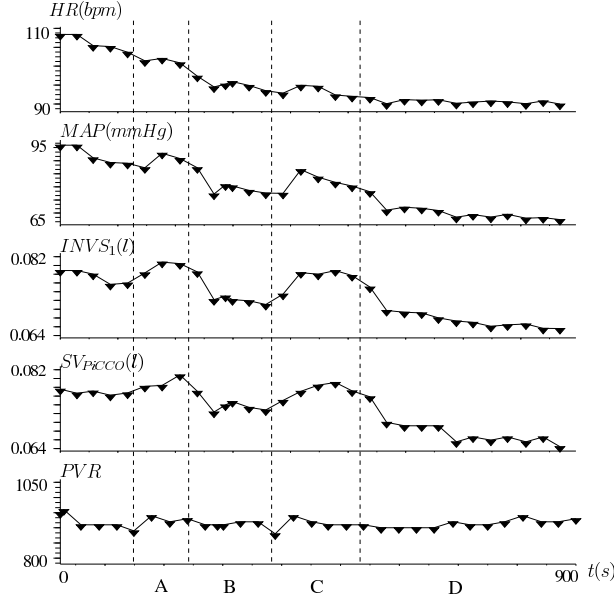


Figure 8: Cardiovascular time series of subject 1, submitted to Positive End Expiratory Pressure changes. A: decreasing PEEP; B: increasing PEEP; C: decreasing PEEP; D: increasing PEEP. $INVS_1$ and SV_{PiCCO} are strongly correlated (cross-correlation coefficient = 0.99).

and demonstrated their interchangeability. It is worth noticing that this agreement is obtained in unstable hemodynamic and/or noisy conditions which prove the robustness of the SCSA method. Several great ventilatory or pharmacological changes are illustrated in fig.8, fig.9 and fig.10 but also by the non averaged time series in fig.11. A noisy condition is illustrated by subject 3 on the right. Despite a raw PI (top right) disturbed by extra-systoles and artefacts, $INVS_1$ (bottom right) is well estimated.

Therefore, this study shows that SCSA is a reliable method for SVV assessment and more suitable in the two cases of divergence. The good agreement between the two approaches could be explained by the fact that the main idea in the SCSA technique is quite similar to the PiCCO and consists in using the area under the systolic part of the pressure curve. However, the detection of the end systole with the SCSA is different from the pulse contour approach. Indeed, while the pulse contour approach uses an algorithm to detect the dicrotic notch, the SCSA uses an ABP model based on solitons that takes into account nonlinear phenomena, as described in section II.C.1.b. This difference could explain the greater reliability of SCSA when discrepancies between the two approaches appear. Moreover, this explanation agrees with the observation of the raw ABP signal for subject 17: its shape is very different between the first and last part of the recording.

Finally, unlike the PiCCO technique which needs periodic calibration by a thermodilution technique, SCSA is easier to use, requiring less equipments, only for ABP measurements. It is much less invasive and could be totally

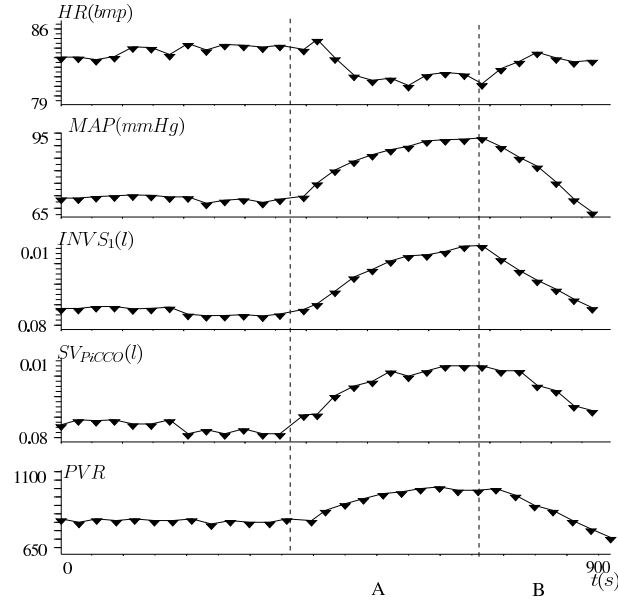


Figure 9: Cardiovascular time series of subject 2, submitted to a vasoactive drug. A: increasing noradrenaline; B: decreasing noradrenaline. $INVS_1$ and SV_{PiCCO} are strongly correlated (cross-correlation coefficient = 0.97).

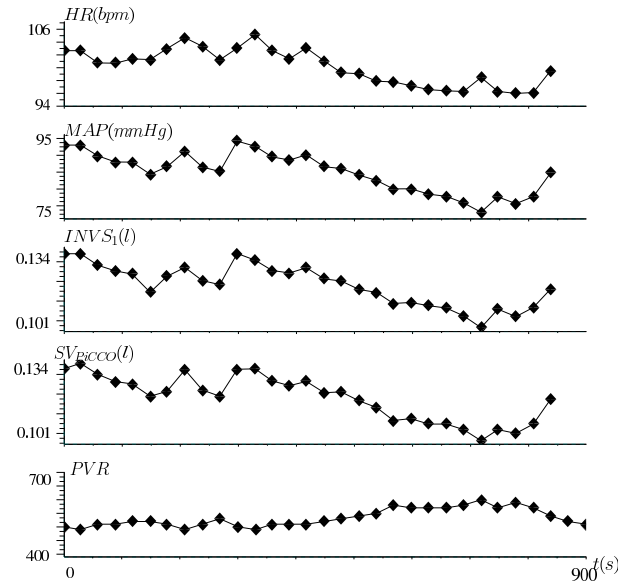


Figure 10: Cardiovascular time series of subject 3, without any change in ventilatory or pharmacological condition. $INVS_1$ and SV_{PiCCO} are strongly correlated (cross-correlation coefficient = 0.97).

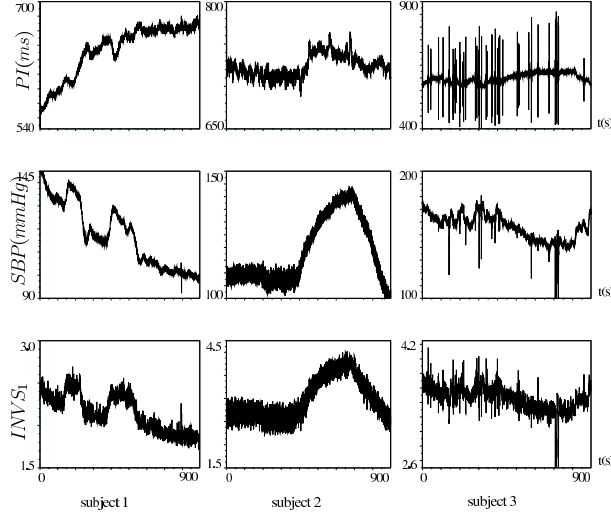


Figure 11: Pulse interval (PI), Systolic Blood Pressure (SBP) and $INVS_1$ time series for the three first subjects with a strong correlation between SV_{PiCCO} and $INVS_1$. The $INVS_1$ is precisely estimated despite unstable hemodynamic conditions (subjects 2 and 3) and noisy conditions such as extra-systoles and artefacts (subject 3).

noninvasive if we used a FINOMETER device, for instance. This latter point, already experimented in our previous studies [21], should be a new perspective for a simple non-invasive SVV assessment.

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