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Real-Time, Minimally Invasive, Beat-to-Beat Estimation of End-Systolic Volume Using a Modified End-Systolic Pressure-Volume Relation

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Abstract: Intensive care management of cardiovascular disease and dysfunction, a major and growing issue, would benefit from improved synthesis of continuously monitored, information rich catheter waveforms into clear, relevant cardiac metrics. Volume measurements are rarely taken in intensive care, but advances have been made in approximating cardiac stroke volume using pressure measurements. This paper proposes a method for the minimally invasive, real-time, beat-to-beat estimation of end-systolic volume, with the goal of providing further insight into cardiac volume behavior and access to important metrics such as cardiac preload. This method relies on a modified end-systolic pressure-volume relation, aortic pressure and heart rate data and a brief echocardiography calibration. The method was validated across 11 pigs and 2 protocols, encompassing the progression of sepsis and a variety clinical procedures employed in the management of sepsis. The method demonstrated consistently strong correlation coefficients, with a mean of $R = 0.82$, and low estimation error, with a mean absolute percentage error of 13.3%. This method thus allows effective estimation of end-systolic volume, providing a more complete picture of cardiac behavior in an intensive care environment in which volume measurements are rarely taken. As such, the method has the potential to benefit clinical decision making and management of cardiovascular disease and dysfunction.

Keywords: Biomedical Systems, Medical Applications, Biomedical Control, Medical Systems, Least-Squares Estimation

1. INTRODUCTION

Cardiovascular disease and dysfunction (CVD) is a major and growing health issue, responsible for significant social and economic costs globally. In 2013, CVD was responsible for 31% of global deaths, and in 2010, global expenditure on CVD ($863 billion USD) was equivalent to 1.39% of gross world product for that year (Roger et al., 2012). These figures are set to rise, driven by an aging population. As such, there is a clear need to reduce incidences of inadequate or incorrect diagnosis of cardiac disturbances in the Intensive Care Unit (ICU), which contribute to increased length of stay, cost, and mortality (Angus et al., 2001, Pineda et al., 2001).

Management of CVD in the ICU typically occurs in an information rich environment, provided by a variety of instruments including catheters placed near the heart that directly measure arterial and venous pressure waveforms. However, despite the abundance of information provided by such instruments, their use is not necessarily associated with improved clinical outcomes (Frazier and Skinner, 2008, Chatterjee, 2009). Control and management of CVD in the ICU requires better real-time synthesis of clear biological markers to make this information rich and complex system easier to interpret.

Examples of such biological markers are preload and afterload. Afterload serves as an indicator of the pressure downstream from the left ventricle, and is sensitive to alterations in valve function and arterial tone (Hall, 2010). Afterload is approximated in the ICU via the typically measured, resulting aortic pressure (P_{ao}) (Kelly et al., 1990). Preload, representing the loading conditions upstream from the heart, is sensitive to venous blood pressure and return, which are in turn sensitive to circulatory volume and venous tone (Hall, 2010). Preload is typically represented by End-Diastolic Volume (V_{ed}) (Michard et al., 2003), but this value is not typically measured in the ICU as the required instrumentation is too invasive. As a result, clinical approximation is difficult. In fact, volume and flow measurements, in general, are rarely taken in the ICU (Kamoi et al., 2014), resulting in a relative abundance of pressure measurements, but an incomplete picture of cardiac behaviour.

Recent work has provided a means of approximating the beat-to-beat cardiac stroke volume (SV) under typical ICU instrumentation (Kamoi et al., 2014). SV provides a beat-to-beat indicator of the how much heart volume is changing, but must be combined with a beat-to-beat absolute maximum or minimum value to provide a more complete picture of cardiac volume behaviour, and thus allow approximation of cardiac

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preload. There is thus a need to relate either End-Systolic (V_{es}) or End-Diastolic (V_{ed}) Volume to existing pressure measurements. An existing and frequently used example of such relationship is the End-Systolic Pressure-Volume Relation (ESPVR) (Senzaki et al., 1996, Grossman et al., 1977, Crottogini et al., 1988). However, this relation relies upon several subject specific parameters that are measurable in an experimental environment, but too invasive to measure clinically.

The focus of this paper is to investigate the viability of using a modified ESPVR to provide a beat-by beat approximation of V_{es}, allowing, in concert with *SV,* approximation of V_{ed} (preload) and a more complete picture of cardiac volume behaviour. This modified ESPVR relies on continuous heart rate and aortic pressure data, and initial parameters being fixed during a brief (10 heartbeat) echocardiography calibration during which non-invasive volume measurements are available (Lang et al., 2015). These short echocardiography readings are becoming increasingly available in a clinical environment (Vieillard-Baron et al., 2008). This method, if able to effectively track V_{es} through changing patient behaviour and condition over a sustained period of monitoring, has the potential to aid in the provision of a more complete picture of cardiac behaviour under normal ICU instrumentation. This outcome provides additional information and metrics to aid real-time clinical management and decision making, potentially improving clinical outcomes.

2. METHODS

2.1 Experimental Protocols

Eleven male, pure Piétrain pigs weighing 18.5 to 29 kg were subject to two distinct protocols approved by the Ethics Commission for the Use of Animals at the University of Liège, Belgium. The pigs were sedated, anaesthetised and mechanically ventilated (GE Engstrom CareStation) with a baseline positive end-expiratory pressure (PEEP) of 5 cmH_2O. The heart was accessed via a median sternotomy, and an admittance pressure-volume catheter (Transonic, NY, USA) with a sampling rate of 250 Hz inserted into the left ventricle. Proximal aortic pressure was continually sampled using a pressure catheter (Transonic, NY, USA) with a sampling rate of 250 Hz.

To ensure a diverse range of cardiac states was exhibited, several procedures were performed:

- **Protocol 1:** A single infusion of endotoxin (lipopolysaccharide from E. Coli, 0.5 mg/kg injected over 30 minutes) to induce septic shock, which drives a change in afterload conditions and is associated with a large variety of effects including an inflammatory response and capillary leakage that may lead to hypovolemia, global tissue hypoxia and cardiac failure (Nguyen et al., 2006).
- **Protocol 2:** An infusion of dobutamine over a period of 30 minutes. Dobutamine directly increases contractility in order to improve cardiac output, and is a key component in hemodynamic resuscitation in patients with severe sepsis (Dellinger et al., 2008).
- **Protocols 1 & 2:** Several Positive End-Expiratory Pressure (PEEP) driven recruitment manoeuvres (RMs), both pre- and post- endotoxin/dobutamine infusion, which drive a change in preload conditions and are typically associated with a decrease in mean blood pressure and cardiac output (Jardin et al., 1981).
- **Protocols 1 & 2:** One to four infusions of 500 mL saline solution over 30 minute periods, pre- and post-endotoxin/dobutamine infusion, simulating fluid resuscitation therapy, another key component of hemodynamic resuscitation in patients with severe sepsis, which itself results in a change in circulatory volume (Vincent and Gerlach, 2004).

2.2 ESPVR

The ESPVR is typically expressed (Sagawa, 1981):

$$P_{es} = E_{es} \times (V_{es} - V_0) \quad (1)$$

where P_{es} is the end-systolic pressure, V_{es} the end-systolic volume, E_{es} the end-systolic elastance and V_0 the ventricular volume at zero pressure. This relationship represents the ventricular volume corresponding to a given ventricular pressure when the heart is fully contracted (end-systole).

The exact nature of E_{es} is somewhat controversial. It has been argued that it is constant for a given contractility (Suga et al., 1973), though there is evidence that suggests it varies as a result of loading conditions (Burkhoff et al., 1993, Baan and Van Der Velde, 1988). As the intent is to be able to track V_{es} through changes in contractility, a fixed value for E_{es} is clearly not appropriate for ICU monitoring, or for an experimental data set encompassing sepsis and dobutamine where contractility is directly varied dramatically due to condition and drug therapy.

2.3 Proposed Method

While a number of the components of ESPVR are not measured under typical ICU instrumentation, it is possible to replace these values with physiologically similar and more easily obtained measurements. ESPVR is thus re-factored:

$$P_{DN} = E_{es} \times (V_{es} - V_d) \quad (2)$$

Where:

- P_{es} is replaced by P_{DN} (Dicrotic notch pressure in the aorta), as the aorta sits directly downstream from the left ventricle, thus aortic and left-ventricular pressure are very similar (with a slight difference due to aortic valve resistance) during systole. As real-time aortic pressure is typically available in the ICU, P_{DN} provides a readily available surrogate for P_{es}.

- V_0 is replaced by V_d (Ventricular Dead Space Volume), as the two are often used interchangeably, and have similar physiological roles and values (Sagawa, 1981, Stevenson et al., 2012b, Stevenson et al., 2012a). V_d can be more easily estimated than V_0, via a relationship with baseline V_{es} (Davidson et al., 2017):

$$V_d = 0.48 \times V_{es}(Baseline) \quad (3)$$

Finally, the fact that E_{es} changes as patient contractility, and potentially loading conditions, vary, needs to be accounted for. The decision was made to approximate E_{es} using a power relationship with Heart Rate (HR) for several reasons. First, changes in HR and E_{es} are staple cardiovascular system responses to changing conditions (Hall, 2010). As continuous monitoring of HR in the ICU is commonplace, it provides a partial, if incomplete, picture of cardiovascular system response, which is typically sympathetic with changes in E_{es}. Second, a power relationship was selected as it suits a sympathetic relationship and is sufficiently simple, provided the exponent is fixed *a priori*, that it can be uniquely determined during a 10 heartbeat echocardiography calibration. Thus, this relationship captures, in a simplified manner, physiological elements and suits the need for method simplicity and ease of use. The fully modified ESPVR relationship reads:

$$V_{es} = \frac{P_{DN}}{E_C \times HR^n} + V_d \quad (4)$$

with n to be determined and then fixed *a priori*. Thus, in the model implementation, P_{DN} and HR are inputs that are measured every heartbeat, ^{n} is fixed *a priori*, and V_d and E_c are fixed for the duration of monitoring during the calibration phase, where V_{es} is being measured. The results section presents an assessment of the increase in errors associated with the transition from a subject specific to an *a priori* value of n.

2.4 Analysis

Linear least squares, performed using MATLAB (R2014a, 64-bit) and the 'lsqlin' function, was used to determine a subject specific exponent n that minimised method errors for each of the 11 pigs (E_c can be analytically determined for a given n during the echocardiography calibration, and is thus a dependent parameter). The overall process for determining the approximate beat-to-beat V_{es} curve using the *a priori* exponent was as follows:

1. Determine V_d (Eq. 3) and E_C (Eq. 4) from a 10 heartbeat 'calibration' period where V_{es} is measured, simulating an echocardiography reading.
2. Determine V_{es} for each subsequent heartbeat based on the fixed values (V_d and E_C) and heartbeat specific measured values (HR and P_{DN}).

Overall evaluation of the effectiveness of the method was accomplished in several ways:

- Using Pearson's correlation coefficients (R), which allow evaluation of the method's capability to capture trends in V_{es} over the course of the two protocols investigated, and thus provide benefits in monitoring patient condition.
- Using the absolute percentage error for each pig, which allows an evaluation of the ability of the method to accurately approximate the exact value of V_{es}, and thus the suitability of this method for use as a component of a larger model.
- Via direct visual evaluation of the trendlines, which is only possible due to the relatively small number of subjects (11), but does provide a means of evaluating the temporal and procedure based variations in method effectiveness.

A comparison across these metrics was made between V_{es} curves estimated using subject specific n, and V_{es} curves estimated by the *a priori* fixed n, which provides an indication of how much method accuracy is lost in the reliance on an *a priori* exponent. Overall, this analysis was conducted over 11 individuals across two protocols, encompassing a total of 166,659 heartbeats of data.

3. RESULTS

Table 1 provides an overview of the subject specific exponents, n, provided by linear least squares, along with the associated correlation coefficients and error values for tracking V_{es}. As can be seen, the correlation coefficients are high, with a mean of 0.83. Further, overall error values are relatively low, except for Pig D4 and the 75th percentile error for Pig D5. It is also interesting to note the generally higher error values for protocol 2 (dobutamine, Pig D-) compared to protocol 1 (sepsis, Pig S-). It was decided, for simplicity, to set the *a priori* value of n to 3 based on these results.

Table 1. Tracking V_{es} with Subject Specific n: Correlation Coefficients and Errors, median (25th perc. – 75th perc.)

Pig	Exponent (n)	Correlation (R)	Abs. Percentage Error, %
Pig S1	3.06	0.93	1.7 (0.9 - 3)
Pig S2	4.02	0.94	2.9 (1.5 - 4.8)
Pig S3	2.06	0.87	4.6 (2.2 - 7.2)
Pig S4	2.72	0.8	4.7 (2.1 - 8.2)
Pig S5	4.27	0.81	2.3 (0.9 - 7.7)
Pig D1	1.8	0.87	12.2 (3 - 26.7)
Pig D2	1.93	0.88	11.5 (5.8 - 22)
Pig D3	3.24	0.85	19.3 (9.9 - 34.4)
Pig D4	4.16	0.67	31.8 (15.9 - 49.1)
Pig D5	3.55	0.91	15.7 (5.6 - 82.6)
Pig D6	0.98	0.6	6.6 (2.8 - 13.2)
Mean	2.89	0.83	10.3 (4.6 - 23.5)

Table 2 provides an overview of the correlation coefficients and error values associated with tracking V_{es} using an *a priori*

exponent $n = 3$, as would be done clinically. Overall, there is only a slight increase in error, from 10.3% to 13.3% (mean of medians), and slight decrease in correlation coefficients, from $R = 0.83$ to $R = 0.82$ (mean). There is only once case (Pig D6) in which there is a large increase in error between Tables 1 and 2. The notable difference in error values between the sepsis and dobutamine protocol pigs is also present in Table 2.

Table 2. Tracking V_{es} with *a priori* $n = 3$: Correlation Coefficients and Errors, median (25^{th} perc. – 75^{th} perc.)

Pig	Correlation (R)	Abs. Percentage Error, (%)
Pig S1	0.94	1.8 (1.0 - 3.2)
Pig S2	0.91	6.4 (4.6.0 - 9.8)
Pig S3	0.84	4.5 (2.7.0 - 7.4)
Pig S4	0.79	4.7 (2.1.0 - 8.1)
Pig S5	0.8	4.2 (2.2.0 - 7.8)
Pig D1	0.81	14.8 (3.6.0 - 28.5)
Pig D2	0.84	15.2 (9.6.0 - 23.3)
Pig D3	0.86	19.3 (9.5.0 - 35.6)
Pig D4	0.71	33.7 (17.1.0 - 48.9)
Pig D5	0.92	18.4 (7.5.0 - 85.3)
Pig D6	0.66	23.3 (12.2.0 - 28.2)
Mean	0.82	13.3 (6.6.0 - 26)

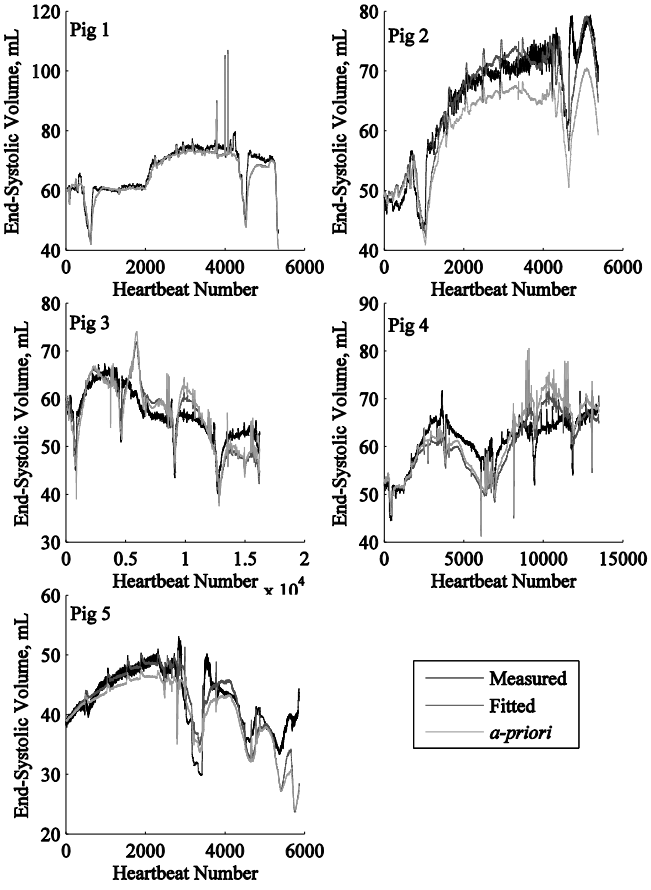

Fig. 1. End-Systolic Volume trends and tracking for protocol 1 (sepsis)

Figures 1 and 2 visualise the approximation of V_{es} for each subject across both protocols. It is clear, there is a diverse range of subject specific responses to the various elements of each protocol, which are generally effectively tracked by the method with only a minor decrease in performance when shifting from a subject specific to an *a priori* exponent value. The sharp, vertical, and long term changes in V_{es} exclusive to Figure 2 demonstrate the effect of dobutamine in rapidly altering cardiac behaviour. In contrast, V_{es} in Figure 1 tends to change more gradually as sepsis develops over the course of the experiment. These latter results indicate the method accurately captures expected, induced changes in V_{es}, and does so in a subject specific fashion, capturing subject specific response to condition and care.

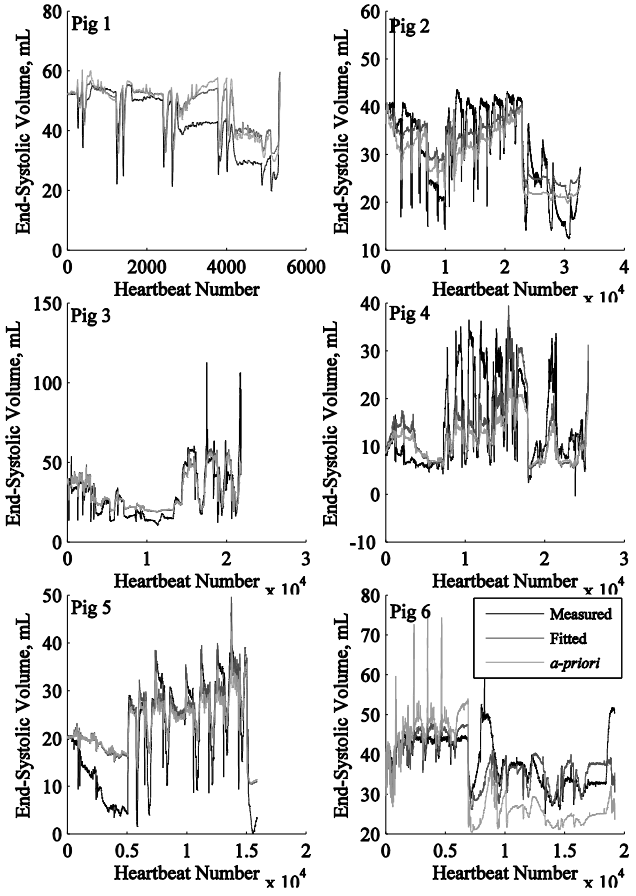

Fig. 2. End-Systolic Volume trends and tracking for protocol 2 (dobutamine)

4. DISCUSSION

As seen in Table 2, the correlation coefficients across all 11 pigs and 2 protocols are reliably good, with a mean of 0.82 and minimum of 0.66. This result suggests that the method is able to effectively capture trends in V_{es}. The ability to track trends in V_{es} allows, in concert with SV, for tracking of preload which is important for patient diagnostics and monitoring purposes. That these high correlation coefficients are sustained across 11 subjects and 2 protocols encompassing elements such as sepsis

and dobutamine, which dramatically alter cardiac function, provides a good initial validation of the method.

While the ability to track trends is important for monitoring changes in patient condition, the ability to approximate the actual value of V_{es} is important for the method to be used as a component of larger models, and in providing a more complete picture of cardiac volume behaviour in the ICU. Table 2 show that the method is able to continuously estimate the value of V_{es} relatively effectively, with a mean median error of 13.3%, and mean 75th percentile error of 26.0%. Again, this accuracy is sustained over a number of subjects and a pair of different and demanding clinical protocols, suggesting the method is able to adapt to both short and long term changes in patient condition due to disease or drug therapy.

Despite the considerable variation in the subject specific values of n, which range from 0.98 (Pig D6) to 4.27 (Pig S5), the use the *a priori* $n = 3$ results in only a relatively minor increase in error and decrease in correlation coefficients. A comparison between Tables 1 and 2 shows the largest decrease in correlation coefficient is a relatively minor reduction from $R = 0.87$ to $R = 0.81$. A similar comparison of error values shows minor increases in error between Table 1 and 2 in most cases, with the only major increase occurring for Pig D6. Pig D6 had the lowest subject specific exponent ($n = 0.98$), and Figure 2 shows $n = 3$ causes an overestimation of the decrease in V_{es} that results from a dobutamine infusion (at about heartbeat 7000). However, the method still predicts the direction of change correctly, and given the ability of the method to capture dobumatine shifts accurately for the other 5 pigs in Figure 2, this case seems to be an exception, rather than the rule.

There is a distinct increase in error values, though not a concordant decrease in R values, from Protocol 1 (sepsis) to the Protocol 2 (dobutamine). While the overall error values for both data sets are within acceptable levels, this shift does imply some level of condition dependency on the part of the method. One possibility is that dobutamine, which causes an artificial and externally administered alteration of cardiovascular behaviour, results in a shift in the sympathetic relationship between HR and E_{es}. While the method is still able to capture trends accurately, the exact magnitude of the patient response to dobutamine is difficult to predict, as in Pig D6, resulting in the observed increased error. This outcome would suggest the ability of the method to estimate the value of V_{es} would benefit from recalibration after the administration of drugs such as dobutamine, though the method performs well enough, regardless.

There are a couple of limitations to this study that should be noted. First, the proposed method does require an echocardiography calibration to provide subject specific initial parameters. While echocardiography is non-invasive, and becoming increasingly commonplace in the ICU (Vieillard-Baron et al., 2008), the method still cannot be implemented entirely without an increase in the workload of clinicians. Second, the method was validated across a limited data set. While effort was made to ensure the experimental protocols encompassed a variety of procedures, conditions and drugs with a variety of effects, this still represents only a fraction of the range of cardiac behaviour possible in an ICU. As such, further validation over more diverse data sets and subjects is needed.

Specifically, there are several interventions that specifically alter either HR or contractility. Examples include inotropes, which increase contractility and were part of the validation, and vagus nerve stimulation (De Ferrari et al., 2011), which decreases HR. The method's ability to adapt to inotropes, albeit with some increase in error, suggests that the method is capable of tracking changes through such interventions. Further, given that such interventions are instigated by a clinician, it would be relatively easy to recalibrate the method directly after an intervention should the method be shown to require it.

5. CONCLUSION

Management of CVD in the ICU would benefit from better extraction of relevant cardiac metrics from the wealth of data regularly available in such an environment. A method was developed to allow clinical approximation of V_{es} beat-to-beat, using a modified ESPVR, brief echocardiography calibration and continuous P_{ao} and HR data. This method was validated across 11 pigs and 2 protocols, covering sepsis, dobutamine infusion, recruitment manoeuvres and fluid infusions. The method was found to be able to track trends in V_{es} effectively across both protocols, with a mean correlation coefficient of $R = 0.82$. The method was also able to approximate the exact value of V_{es} effectively, with a mean-median absolute percentage error of 13.3%, though these errors were consistently higher for the protocol involving dobutamine than sepsis. Overall, this method, combined with an existing method that provides SV, allows for a more complete picture of cardiac volume behaviour to be established in the ICU, including metrics such as preload. This has the potential to benefit clinical management and decision making around CVD in the ICU.

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