

Electrocardiogram R-wave is an Unreliable Indicator of Pulse Wave Initialization

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Abstract: Pulse wave velocity (PWV) measurements are commonly used to evaluate a patient's arterial stiffness, an indicator of cardiovascular dysfunction. PWV is usually calculated by measuring the pulse transit time (PTT) over a known distance through the arteries. In an experimental study on animals, it is straight forward to measure the PTT using two pressure catheters a known distance apart in the central arteries. However, in a clinical setting it is uncommon for such a direct invasive method to be used. This study aims to identify whether a surrogate measure of PTT could be found without the need for an external device and without being additionally invasive. The aim is to use the time between the R-wave of an electrocardiogram (ECG), and the pulse wave passing one pressure catheter (rPTT), both of which are common in critical care. The analysis was performed using data from four porcine experiments (Pietrain Pigs, 20-29kg) in which ECG, aortic arch pressure and abdominal aortic pressure were measured simultaneously over a range of induced hemodynamic conditions including recruitment manoeuvres (RM), fluid admission and dobutamine admission. From the measured data, the correlation of rPTT and PTT was calculated for each pig and condition. The overall results showed varied correlations across the pigs ($r^2 = 0.07$ to 0.75). The variability is suspected to be due to two main causes, the first being pig specific response to the interventions. The second cause leading to poor correlation is suspected to be the pre-ejection period (PEP), the time following the ECG R-wave but before ejection of blood from the ventricle. The analysis showed that rPTT was an unreliable measure of PTT and a poor surrogate.

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1. INTRODUCTION

Pulse wave velocity (PWV) is clinically useful for determining a patient's arterial stiffness and is an indicator for possible future cardiovascular dysfunction (Laurent et al. 2006; Blacher, Asmar, et al. 1999). A stiffer artery expands less under flow induced pressure and thus dissipates less energy, leading to the pulse wave traveling faster. PWV has also been used as a parameter in models for determining/estimating other physiology with varied success (Kamoi et al. 2015; Fung et al. 2004; Pitson et al. 1994). PWV is commonly measured using pulse transit time (PTT), the time it takes for a wave front generated by the heart to travel between two arterial sites, a known distance apart (Millasseau et al. 2005; Kamoi et al. 2015; Dogui et al. 2011; Loukogeorgakis et al. 2002; Payne et al. 2006; Laurent et al. 2006). The wave front is often identified as the foot of an arterial pressure waveform.

The 'gold standard' PWV measure for arterial stiffness is measured from the common carotid artery to the femoral artery (Laurent et al. 2006). However, measures between other arterial sites are common, depending on whether a local or regional PWV measure is desired (Laurent et al. 2006). In a clinical setting it is often most relevant to measure PTT along the aortic pathway (Blacher, Guerin, et al. 1999; Laurent et al. 2006).

In an experimental setting, particularly those using animals as a substitute for human patients, it is easy to measure PTT directly using invasive means. In a clinical setting it is more desirable to minimise invasion to patients and hence devices which measure PTT and PWV using minimal invasion are favoured.

This study aims to identify whether a surrogate measure of PTT could be found without the need for any external or additionally invasive devices. The intention is to use metrics

that are already commonly measured for other purposes in an intensive care unit (ICU), such as electrocardiogram (ECG). An ECG measurement is non-invasive and common in hospital care. The perceived risk is the ECG R-wave signifies the start of ventricular contraction, rather than the onset of blood ejection. For a short time following the R-wave the heart contracts isovolumetrically and no blood is ejected, the duration of this event is known as the pre-ejection period (PEP) (Pitson et al. 1994; Payne et al. 2006). The ECG signal could be used with only a single arterial pressure catheter, which is also common in critical care and the ICU. This would remove the need for a second arterial catheter, located more central to the heart, which is more invasive and less common than ECG.

In a previous study, the time between an ECG R-wave and succeeding foot of a pressure waveform, was termed rPTT (Payne et al. 2006); for consistency this paper uses the same notation. However, it should be noted that rPTT is not just a pulse transit time measurement, it is instead made up of both the PTT, from the aortic valve to a downstream arterial site, and PEP.

If rPTT and PTT show good correlation over a range of hemodynamic states, rPTT may be used to simplify clinical measures and models that rely on PTT. Hence, this study investigates how well rPTT correlates with a traditional beat to beat measure of PTT, using pressure measurements from two arterial sites in various hemodynamic conditions.

2. METHODS

2.1. Porcine Trials and Measurements

This study uses data from experiments performed on pigs at the Centre Hospitalier Universitaire de Liège, Belgium. All experimental procedures, protocols and the use of data in this study were reviewed and approved by the Ethics Committee of the University of Liège Medical Faculty.

Experiments were performed on 7 healthy, pure pietrain pigs, weighing between 20–29kg. Of the 7 pigs, Pigs 2, 3, 6 and 7 are analysed as part of this paper. The other pigs were excluded due to differences in experimental protocol and in some places abnormalities in the captured data. The pigs were administered with ketamine (20mg/kg) and diazepam (1mg/kg) prior to conducting the protocols of the experiment. Anaesthesia was induced and maintained by continuous infusion of sufentanil (0.5µg/kg/hour) and sodium pentobarbital (3mg/kg). Each pig was intubated via a tracheotomy and ventilated using a Draeger Evita2 ventilator (Draeger, Lubeck, Germany).

Left ventricular pressure and volume were directly measured using 7F micromanometer-tipped admittance catheters (Transonic Scisense Inc., Ontario, Canada) inserted into the ventricle through the right carotid artery. Pressure waveform

measurements were captured at the aortic arch and abdominal aorta with 7F pressure catheters (Transonic Scisense Inc., Ontario, Canada). The catheters were inserted into the aortic arch through the left carotid artery and into the abdominal aorta through the femoral artery, respectively. All cardiovascular and respiratory data were sampled at 1000Hz.

2.2. Hemodynamic Modification

During the experiments, each pig underwent several step-wise positive end-expiratory pressure (PEEP) recruitment manoeuvres (RM). Increases in PEEP reduce systemic venous return to the right heart and increase pulmonary resistance. Thus, left ventricle preload decreases, leading to lower arterial pressure and a reduction in stroke volume (SV) (Luecke & Pelosi 2005), and an expected increase in PTT. RMs involved increasing PEEP with 5cmH₂O steps to a maximum of 15cmH₂O for Pig 7 and 20cmH₂O for Pigs 2, 3 and 6.

The experiment also included multiple administrations of fluid boluses. These boluses were administered in 180ml steps ranging from 0ml to 720ml / 900ml for Pigs 7 / 2, 3 and 6, respectively. This aimed to increase the blood volume and as a consequence increase the arterial pressure and SV, while decreasing PTT for the pigs that were fluid responsive.

The experiment also involved administering a continuous dobutamine infusion to modulate contractility. Dobutamine increases contractility of the heart and can also act as a vasodilator (Ruffolo 1987; Ellender & Skinner 2008). It is commonly used in clinical settings to increase cardiac output (CO) as a result of increased contractility (Ruffolo 1987; Ellender & Skinner 2008). The effect of dobutamine on PTT was harder to predict, as the increase in CO could lead to a shorter PTT. However, the vasodilation could counter this effect, depending on the level of subject specific response to inotrope admission.

2.3. Data Selection Summary

Four stages were considered as part of the analysis: a control, followed by three hemodynamic modifications outlined in Section 2.2. The *control* stage was when a pig was at rest following anaesthesia, but before any hemodynamic modifications were applied. The second stage was a RM where the data analysed was that captured during the maximum PEEP, labelled *high PEEP* in Section 3 tables. The particular RM used occurred before any fluids or dobutamine were introduced. The third stage was *high fluids*, the time following each pig's final 180ml bolus admission, taking it to its highest introduced fluid state. The final stage was during the admission of *dobutamine*, which for Pig 6 was infused at a rate of 2.5 µg/kg/min while Pigs 2, 3, and 7 were infused at 5 µg /kg/min.

2.4. Identification of rPTT and PTT

In this study, PTT was measured as the time between the arrival of a foot of the pressure waveform at the catheter in the aortic arch and then the catheter in the lower abdominal aorta. The foot of the waveform for each beat was identified as the observed measurement nearest the intersection of two tangent lines, one line from the minimum pressure for a given beat, the other from the maximum positive pressure gradient, occurring during systole. Example feet of the waveforms are shown in Figure 1.

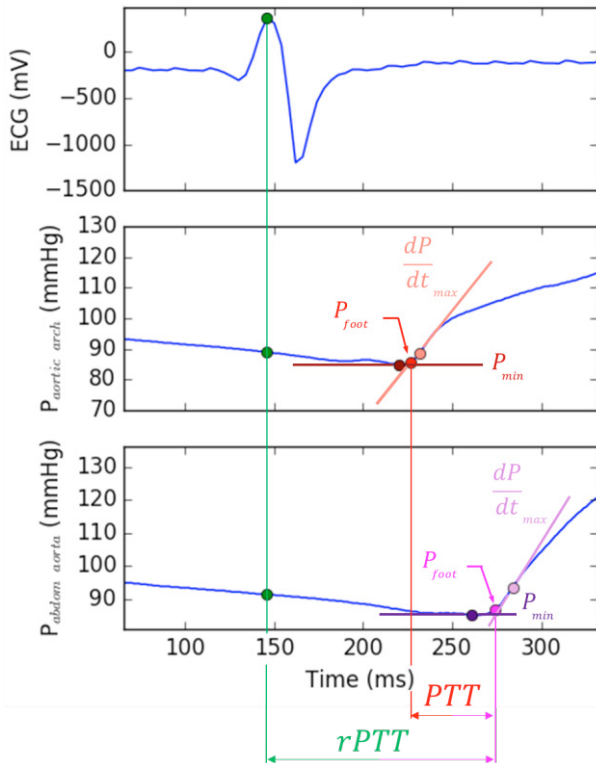


Figure 1: Example of how rPTT and PTT are determined, including identification of the feet of the pressure waveforms.

This method is consistent with previous published studies (Payne et al. 2006; Kamoi et al. 2015) and was found to be more reliable than simply taking the minimum pressure of a beat to be the foot, particularly for pigs and events where the pressures were low.

In this study, rPTT is the time between the ECG R-wave and the foot of the pressure waveform, measured in the abdominal aorta. The R-wave was the simplest of points to identify given its prominence in the ECG waveform.

2.5. Data Analyses

Each stage outlined in Section 2.3 was first analysed separately for each pig. For each beat, the PTT and rPTT were identified using the method shown in Figure 1. Once all

beats of a stage were analysed, PTT and rPTT means and standard deviations were found. Analysing each stage individually allowed the variability due to a particular hemodynamic modification to be measured. Next the variability in rPTT due to variability in PTT was measured using linear regression and the coefficient of determination (r^2). This method gives a measure of the strength of relationship between the two variables. The r^2 values physical represents the percentage of the total variation in rPTT described by the variation in PTT.

Once each stage analysis was complete, the stages were concatenated and an overall analysis was complete. By concatenating the data of each stage a wider range of PTT was observed and hence a more holistic picture of the relationship between rPTT and PTT was found. The means, standard deviations and correlation coefficients for each pig were then compared in order to see subject variability of PTT and rPTT. The results of this analysis are found in Section 3.

3. RESULTS

Each stage contains between 71 and 687 beats, with high PEEP typically representing the fewest beats, while dobutamine and high fluids accounted for the most. The mean and standard deviation of PTT and rPTT for each pig and stage are summarised in Table 1. The coefficient of determination of each stage and for each pig is shown in Table 2. Figure 2-5 shows each stages PTT vs rPTT data and the overall coefficients of determination for each pig.

Table 1: Per pig stage specific statistics. Data is given as mean and (standard deviation) in milliseconds (ms)

Pig No.	Mean and (Standard Deviation) of PTT & rPTT (ms)							
	Control		High PEEP		High Fluids		Dobutamine	
	PTT	rPTT	PTT	rPTT	PTT	rPTT	PTT	rPTT
Pig 2	66.9 (1.6)	136.2 (2.6)	65.1 (2.0)	139.8 (3.3)	69.5 (2.6)	163.9 (2.8)	58.2 (1.5)	106.3 (1.6)
Pig 3	56.4 (1.1)	106.8 (1.7)	55.8 (1.0)	106.0 (2.3)	57.4 (1.1)	112.1 (1.7)	57.6 (1.2)	113.9 (2.2)
Pig 6	46.3 (0.8)	128.2 (3.6)	44.7 (0.8)	130.2 (3.9)	44.6 (0.9)	136.2 (2.4)	45.7 (0.8)	126.8 (2.1)
Pig 7	103.6 (1.3)	152.5 (3.8)	112.4 (2.2)	166.1 (4.5)	99.8 (1.9)	154.4 (4.1)	96.7 (3.8)	161.8 (9.9)

Table 2: PTT vs rPTT Coefficients of Determination for each pig and each stage.

Pig No.	Coefficient of Determination (r^2 value)				
	Control	High PEEP	High Fluids	Dobutamine	Overall
Pig 2	0.35	0.11	0.46	0.04	0.75
Pig 3	0.47	0.16	0.45	0.38	0.38
Pig 6	0.003	0.33	0.21	0.02	0.07
Pig 7	0.57	0.51	0.60	0.85	0.21

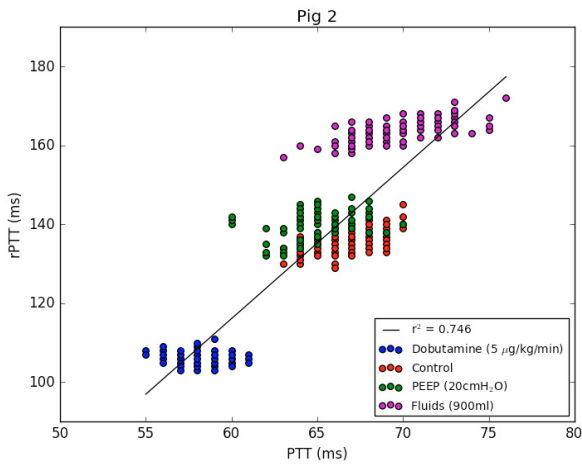


Figure 2: Relationship between PTT & rPTT for Pig 2 over all four stages.

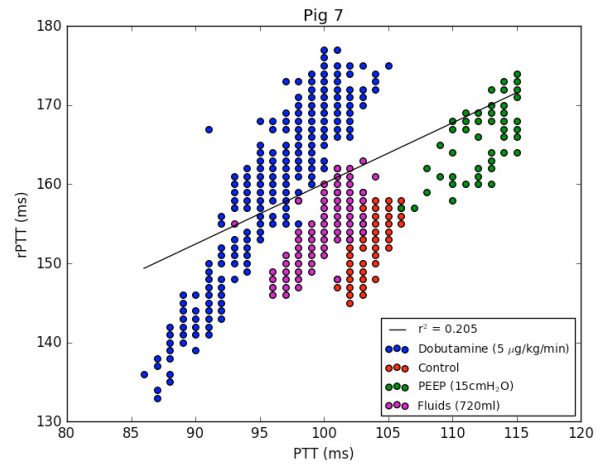


Figure 5: Relationship between PTT & rPTT for Pig 7 over all four stages.

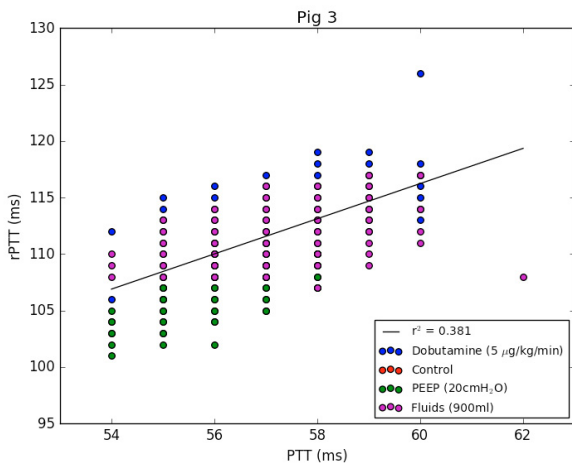


Figure 3: Relationship between PTT & rPTT for Pig 3 over all four stages.

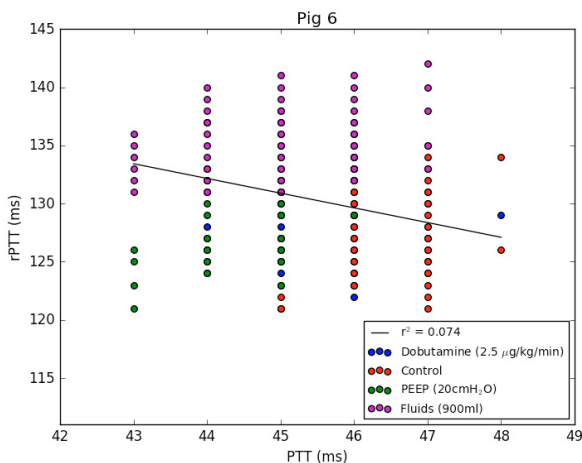


Figure 4: Relationship between PTT & rPTT for Pig 6 over all four stages.

4. DISCUSSION

4.1. Correlation outcomes

Table 2 shows the overall coefficients of determination range from $r^2 = 0.07$ to 0.75 , indicating an inconsistent correlation between PTT and rPTT across the pigs. Poor correlation results suggest that variation in PTT only accounts for a small fraction of the variation in rPTT, as described in Section 2.5.

4.2. Response to Interventions

In general all pigs showed only minor changes in PTT as a result of the different interventions, although Pigs 2 and 7 did give the widest range of results. One observation is that lower r^2 values were observed in pigs who did not appear to respond to the intervention of each stage. Table 1 shows that when intervention was applied to Pig 6, only very small changes in PTT and rPTT were observed, relative to the other pigs. Figures 4 and 5 illustrate this outcome with Pig 6's data for each stage overlapping ($r^2 = 0.074$), while Pig 7 shows response to intervention through the change in PTT over each event ($r^2 = 0.205$).

Another observation is the effect of intervention appears to be specific to each pig. For example, Figure 2 shows fluid admission having a significant effect on Pig 2, while the other pigs show less of a response. It is possible that Pigs 3, 6 and 7 are simply fluid unresponsive. It has been shown in both experimental and clinical settings that a significant number of critically ill patients are not fluid responsive (Marik 2013; Marik 2010; Young 2004; Michard & Teboul 2002). The best method for measuring fluid responsiveness is still debated (Ceconi et al. 2014) and such an analysis was not conducted for this study. This makes drawing conclusions on the effect of fluid admissions on PTT and rPTT difficult.

During the control portion of the experiment, Pig 6 had a mean abdominal aortic pressure measurement of 105mmHg,

within expected physiological ranges for healthy pigs (102 ± 9.3 mmHg) (Hannon et al. 1990); while Pig 3 was significantly higher at 118.3mmHg and Pigs 2 and 7 were more than 5 standard deviations from the mean (148.8mmHg and 53mmHg, respectively). Similarly, Pigs 2, 3 and 7 showed stronger correlations, while also being more responsive to the interventions. It is possible the initial healthy state of Pig 6 simply lead to the body responding to the different treatments by adjusting to maintain its equilibrium.

4.3. Pre-ejection Period and its effect on rPTT

Where the higher end of r^2 values were observed, there is still a significant proportion of the variation in rPTT that is not explained by the variation in PTT. The remaining variation in rPTT must come from the time following the ECG R-wave, but before ejection of blood from the ventricle occurs. The ECG R-wave is the peak of the QRS complex and corresponds to ventricle depolarization, which initiates the chemical and mechanical onset of contraction. Once contraction is underway, the aortic valve is initially closed; during this period contraction is often thought of in the ideal case as being isovolumetric (Smith et al. 2005; Pironet et al. 2013; Guyton & Hall 2006).

As mentioned in Section 1, the combined electromechanical delay and isovolumetric contraction is known as the pre-ejection period (PEP) (Payne et al. 2006). The end of the PEP is defined as the aortic valve opening time (Pitson et al. 1994), which occurs when the ventricle pressure exceeds the aortic pressure. At this point the pulse wave begins its path past the catheter in the aortic arch. Thus, for any given beat in the pig experiments, the difference between rPTT and PTT should be the PEP plus a slight delay due to the aortic catheter being positioned in the aortic arch, which is set back slightly from the aortic valve.

Looking at Table 1, the difference between rPTT and PTT ranges from 49ms (Pig 7; control) to 94ms (Pig 2; high fluids). The aortic catheter was positioned close the aortic valve, suggesting a large range of PEP values of similar magnitude to the PTT observations, which is consistent with other literature using both human and animal subjects (Payne et al. 2006; Talley et al. 1971; Newlin & Levenson 1979). Furthermore, the bias caused by PEP has been observed before in studies utilizing the ECG R-wave as its initial indicator of contraction (Loukogeorgakis et al. 2002; Pitson et al. 1994; Fung et al. 2004). Hence, even modest variation in the PEP independent of PTT could explain the lack of a strong relationship between rPTT and PTT.

Variation in PEP poses an issue if rPTT was to be used as a less invasive surrogate for PTT measured using pressure measurements at two arterial sites. One solution is to measure rPTT over a longer distance so that the proportion of PEP to PTT is reduced (Fung et al. 2004). While this approach

would not remove the PEP bias, it would serve to reduce the effects of varying PEP on a PTT estimate based on rPTT. However, a common clinical motivator for calculating PTT was the determination of arterial stiffness, which increases as people age and is a predictor of future cardiovascular outcomes (Laurent et al. 2006; Blacher, Asmar, et al. 1999). The aorta is less stiff than the peripheral arteries, but shows a much larger change in stiffness over a human's lifetime. Therefore, the aorta is the desired regional stiffness when making cardiovascular diagnostic predictions (Laurent et al. 2006; Nichols 2005; Nichols et al. 2011). Including the periphery in estimations of PTT from rPTT could lead to an overestimate in aortic arterial stiffness and incorrect diagnostic information.

There is scope still to analyse the relationship between PEP and PTT. If a strong relationship exists, one that appears to be population specific, it would be possible to measure rPTT and estimate PTT as a result. Else if PEP and PTT have a strong patient-specific correlation, rPTT may be limited to estimating Δ PTT. Finally, if PEP appears to be independent of changes in PTT, without an accurate measure of PEP, rPTT would be an unreliable substitute for the true pulse transit time.

The large range of rPTT-PTT observed across the four pigs suggests PEP is likely to be specific to each pig. Given the variability of rPTT, it seems likely that PEP will not show a strong relationship with PTT. Speculation aside, this analysis is still being conducted and remains to be validated over a larger, continuing trial with further subjects.

5. CONCLUSION

The weak relationship found between PTT and rPTT suggests much of the variation in rPTT cannot be attributed to PTT. Although direct analysis of PEP is not shown in this study, the time difference between rPTT and PTT, for which a significant proportion is attributed to PEP, showed little consistency between pigs and intervention stages. As a result, this work comes to a similar conclusion to that completed by Payne et al 2006. Specifically, despite advances in processing, rPTT is unsuitable as a direct measure of PTT and is also a poor surrogate.

However, this conclusion does not render rPTT entirely useless. Further analysis needs to be completed to understand the relationship between PEP and PTT. If this relationship exists in strength, there is still the possibility of at least measuring changes in PTT by monitoring rPTT.

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