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Quantitative Waveform Measures of the Electrocardiogram as Continuous Physiologic Feedback During Resuscitation with Cardiopulmonary Bypass

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Abstract

Background—There are few if any real-time physiologic measures that currently provide feedback during resuscitation from cardiac arrest. Such measures could be used to guide therapy not simply based on process guidelines but on the physiologic response of the patient from moment to moment. To this end, we applied an existing technology – quantitative waveform measures (QWMs) of the ventricular fibrillation (VF) electrocardiogram (ECG) – as a continuous measure of myocardial response to reperfusion with cardiopulmonary bypass (CPB) after prolonged cardiac arrest.

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Disclosures

Dr Menegazzi and Dr Sherman are co-inventors of a quantitative measure of the ventricular fibrillation electrocardiogram waveform, the VF Scaling Exponent, which has been patented and subsequently licensed to Medtronic, Inc.

Conflict of Interest Statement

Drs Menegazzi and Sherman are co-inventors of the VF Scaling Exponent, an ECG waveform analysis measure that has been patented and licensed to Medtronic, Inc. Both receive royalty money through this licensing agreement. Neither Dr Menegazzi nor Dr Sherman holds any other financial interests in Medtronic, Inc.

There are no further conflicts to disclose.

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Methods—Sixteen domestic, mixed-breed swine were sedated, anaesthetized and paralyzed. Mechanical ventilation with room air was provided. Large diameter bypass catheters were placed in the right external jugular vein and right femoral artery for cardiopulmonary bypass (CPB). VF was induced with a 3-second 100mA transthoracic shock and left untreated for 15, 20, 25, or 30 minutes, followed by 10 minutes of centrifugal pump CPB (Bard CPS). Continuous Lead II ECG was recorded with an electronic data acquisition system (Power Lab, ADInstruments). Four QWMs representing 4 signal characteristics of the VF ECG were calculated in 5-second windows throughout the course of untreated VF and resuscitation with CPB.

Results—Four animals were assigned to each VF duration group. QWM recovery was inversely correlated with untreated VF duration, and was drastically reduced above 20 minutes of untreated VF. Return of spontaneous circulation (ROSC) was highly unlikely after 20 minutes of untreated VF.

Conclusion—QWMs of the VF ECG provided a real-time metric of myocardial electrophysiologic response to reperfusion with CPB. Resuscitation from greater than 20 minutes of untreated cardiac arrest was unlikely. QWMs may be useful for titrating CPB duration before defibrillation and assessing CPR quality independently of process guidelines.

Introduction

During cardiac arrest and resuscitation, the patient is largely an ischemic black box. The most proximate physiologic response to the primary treatments for cardiac arrest – CPR and defibrillation – is return of spontaneous circulation (ROSC). However, in the window between identification of cardiac arrest and the end of resuscitation, we have little information about the impact of resuscitation efforts. Considering the length of this window, the criticality of the therapy, and the ability of providers to vary the parameters of CPR or administer drugs, it is disappointing that physiologic feedback to guide resuscitation is still not widely utilized. This is not for a lack of understanding. For instance, it is known that myocardial energy stores rapidly deplete over time during untreated cardiac arrest¹, metabolites such as lactate accumulate², and there is systemic hypoxia and tissue stunning³. Similarly, while there is still much to be learned about CPR, it is believed that CPR impedes or reverses some effects of global ischemia⁴, that the impact of CPR is dependent on the effectiveness of the perfusion that it provides^{5, 6}, and that the success of defibrillation is related to the delivery of CPR^{7, 8}. Despite this knowledge, by current treatment protocols it is still usually impossible to update the prognosis of a pulseless patient as therapies are being administered due to a lack of meaningful physiologic feedback. Resuscitation guidelines instead focus on provider processes such as chest compression rate, compression depth, and shock delivery parameters such as peri-shock pause⁹, all of which have been correlated with patient outcomes but none of which are calibrated to individual patients' physiologic response.^{10–12}

Two areas of investigation that have shown potential for providing feedback during resuscitation are end-tidal carbon dioxide measurement and ECG analysis.^{13, 14} However, to date the translation of these findings into practice has been limited and further work is needed to refine these measures for real-time assessment of the effect of interventions. In this study, we attempted to further address the need for physiologic feedback during resuscitation by applying an existing non-invasive, ECG analysis technology in a novel way. Quantitative waveform measures (QWMs) of the ventricular fibrillation (VF) electrocardiogram (ECG) have shown utility for predicting rescue shock success in animal and human studies^{15–21} and have been correlated with depletion of myocardial energy stores during untreated VF.²² We examined the trajectory of QWMs during prolonged VF followed by resuscitation using cardiopulmonary bypass (CPB) as a model of high quality or

“ideal” reperfusion therapy. Secondly, we estimated the relationship between duration of untreated VF, QWM evolution, and ROSC during resuscitation.

Methods

The Institutional Animal Care and Use Committee at the University of Pittsburgh approved this study.

Sixteen mixed-breed, domestic swine with an average mass of 26.5kg were sedated with ketamine (10mg/kg) and xylazine (4mg/kg). A surgical plane of anesthesia was achieved by bolus administration of alpha chloralose (50mg/kg) through an ear vein cannula, followed by maintenance infusion of the same (10mg/kg/hr). The animals were intubated with a 5-0 cuff endotracheal tube, and then paralyzed with an initial 4mg bolus of pancuronium. A left-side cut-down was performed to gain access to the left femoral vein and artery, into which 9F introducers were placed. Micromanometer-tipped catheters (Millar Instruments, Houston, TX) were placed in the right atrium and aorta via the femoral introducers for central pressure monitoring. Coronary perfusion pressure during CPB was calculated as the difference between these aortic and right atrial pressures. Surface electrodes were placed corresponding to Lead II ECG and connected to a commercial signal amplifier (DAM-50, WPI, Inc, Sarasota, FL). Central pressures and ECG signal were monitored and recorded continuously (Power Lab, AD Instruments, Sydney, Australia).

The experimental CPB scheme consisted one arterial in-flow and one venous outflow. The right femoral artery and right external jugular vein were exposed, and a 14F stainless steel-tipped catheter and an 18F coil-reinforced catheter were placed, respectively. The catheters were clamped off with tube-occluding forceps until the initiation of CPB. The bypass circuit was driven by a centrifugal pump head in line with a hollow fiber oxygenator (Affinity NT, Medtronic, Inc, Brooklyn Park, MN). The circuit was primed with 0.9% normal saline, and the air mix delivered to the oxygenator was 50% oxygen. The circuit was pre-heparinized with 225U heparin per kg body mass. Animals did not receive any heparin prior to initialization of CPB. The approximate total circuit priming volume was 800mL. A water-circulating heat exchanger provided temperature control for the bypass circuit, with an activation temperature of 34°C; thus animals were allowed to become passively hypothermic when CPB began. Temperature means and ranges are reported with our results. Control of all circuit components was managed through a Bard CPS Cardiopulmonary Bypass System (C.R. Bard, Inc), incorporating flow, temperature, and gas mixture controls.

Animals were assigned to groups receiving 15, 20, 25 or 30 minutes of untreated VF, which was induced by a single 3-second 100mA transthoracic shock with a frequency of 60Hz. After the prescribed duration of untreated VF, the bypass circuit was completed, and perfusion was initiated at a peak flow rate of approximately 3 liters per minute. Approximately 500mL of additional unheparinized priming fluid were added to the circuit to maintain vessel patency. All animals received 10 minutes of bypass flow, followed by defibrillation attempts, if the ECG rhythm was VF. Defibrillation attempts were delivered q1 minute with an energy of 150J in a biphasic truncated exponential waveform (M-Series, Zoll Medical Corp., Chelmsford, MA) until return of spontaneous circulation or 20 minutes of failed resuscitation. ROSC was defined ad hoc as conversion of VF to a pulsatile rhythm lasting greater than one minute. All animals attaining ROSC regained pulses with a systolic blood pressure of greater than 80mmHg and remained stable for at least 20 minutes. During shock delivery, CPB flow was suspended long enough to delivery a shock and ascertain the outcome. CPB was resumed after failed shocks and discontinued after successful shocks. Heparin (225U/kg) was re-administered if indicated by periodic Activated Coagulation Time

assay (I-Stat, Abbott Point of Care, Inc, Princeton, NJ). Animals surviving to 20 minutes were euthanized with 40mEq intravenous KCl.

Continuous ECG recordings sampled at 1000Hz from the untreated VF and 10-minute bypass periods were down-sampled to 250Hz and divided into sequential 5-second windows for analysis. All windows were reviewed for artifact, and in general, ECG artifact related to the mechanical activity of the CPB unit was found to be both minimal and consistent. The following measures were calculated for each window to create a sequential curve of each measure for the entire duration of untreated VF and CPB: Amplitude Spectrum Area (AMSA), Detrended Fluctuation Analysis (DFA), Median Slope (MS) and Logarithm of the Absolute Correlations (LAC). The particular QWMs used in this study were chosen to account for 4 distinct, though related, signal properties underlying the derivation of QWMs: frequency, fractal dimension, slope, and autocorrelation. Descriptions of the calculation methodology for each measure have been reported in detail previously.^{4, 6-9} For all calculations, we utilized custom programs written and executed in MATLAB (R2009a, The Mathworks, Inc.).

Our principle outcomes of interest were QWM values, ROSC, and the ratio of each QWM at start of VF to its value after 10 minutes of CPB (recovery proportion). Repeated measures ANOVA was used to compare QWM values at key experimental time points. ANOVA was used to compare QWM values between animals with different untreated VF durations at the end of untreated VF and at the end of the 10-minute bypass phase. Statistical calculations were performed in Stata 11 (StataCorp, College Station, TX) using an alpha level of 0.05. Best-fit lines of the average recovery proportion curves (Microsoft Excel 12, Redmond, WA.) were used to explore the relationship between recovery proportion, time, and untreated VF group.

Results

Descriptive group variables and outcomes are enumerated in Table 1. The VF duration groups did not differ by sex, weight or core temperature. The overall mean (SD) temperature was 37.8 (1.3) at the start of VF, 38.2 (1.4) at the start of CPB, and 35.3 (1.1) after 10 minutes of CPB. Mean (SD) arterial blood pressure across all groups during CPB was 57mmHg (8.82). All animals in the 15-minute group and 3 of 4 animals in the 20-minute group attained ROSC. Only 1 of 4 animals in the 25-minute group was successfully resuscitated. No animals in the 30-minute group regained pulses. All animals with ROSC went on to survive for 20 minutes. When the VF duration groups were dichotomized, animals sustaining 15 or 20 minutes of untreated VF were nearly 50 times more likely to be successfully resuscitated than animals in the 25 or 30-minute groups (OR = 49.0, 95% CI: 2.53, 948.62; $p = 0.01$). All animals in the 15 and 20-minute groups exhibited a rhythm of VF after 10 minutes of CPB reperfusion. Two animals in the 25-minute group and only 1 animal in the 30-minute group exhibited VF after 10 minutes of CPB. The remaining animals exhibited asystole or an aberrant wide-complex pulseless electrical activity (PEA) rhythm. Open-chest examination of the heart of one animal in this PEA rhythm suggested slow organized contraction of the right ventricle coupled no left ventricular activity. Figure 1 shows piecewise traces from sample ECG segments in each of the 4 VF duration groups.

Smoothed, VF duration group-averaged traces of each of the 4 quantitative measures over the course of untreated VF and the 10-minute CPB reperfusion period are shown in Figure 2. In general, all 4 measures deteriorated during untreated VF. For LAC, AMSA, and MS, this corresponded to a progressive decrease; for DFA, the resultant trend was a progressive increase. At the onset of CPB, the trajectory of each measure was generally reversed, driving each QWM toward its original value at the start of untreated VF. Table 2 shows the mean

values of each QWM at key experimental time points. In general, individual QWMs differed between the start of untreated VF, the start of CPB, and the end of CPB resuscitation, reflecting a steep rise or fall during untreated VF and some degree of recovery during CPB. At the end of CPB, recovery of each QWM tended to decrease along with increasing duration of untreated VF. That is to say, animals in the 15 and 20min groups tended to recover a higher proportion of their baseline QWMs than animals in the 25 and 30min groups. Slope of the QWM curves during CPB differed between the 4 QWMs, suggesting differential responsiveness of these measures to the effects of reperfusion. Table 3 shows the time to QWM recovery for individual measures, based on the fitted QWM-versus-time regression lines. Only animals in the 15 and 20min groups fully recovered their baseline QWMs, and this did not occur for all measures. Figure 3 shows the minute-by-minute recovery proportion for one QWM (for figure clarity, only MS is shown) for all VF duration groups with cubic regression lines overlaid.

Discussion

There are two general findings that stand out among our results. The first is the three-way relationship between duration of untreated VF, reperfusion, and evolution of QWMs. We observed the deterioration of QWMs over untreated VF durations up to 30 minutes, and after providing reperfusion with CPB, we observed differential physiologic response based on VF duration expressed in QWMs. QWM response was progressive, suggesting a cumulative effect on the myocardium. These observations were consistent across the four QWMs.

Secondly, we observed a 20-minute threshold after which resuscitation was unlikely, a finding that in turn was reflected in differential QWM recovery after a fixed duration of CPB reperfusion. In support of this threshold, a recent study considering the limits of conventional resuscitation therapies in a swine model of cardiac arrest arrived at an estimate of 13 minutes when survival with intact neurological function was the outcome of interest, and 15 to 17 minutes when the outcome was ROSC.²³ The same study also utilized CPB as the method of reperfusion, suggesting a high degree of comparability with our own. Kern et al demonstrated that open-chest cardiac massage similarly has a threshold for resuscitation of approximately 20 minutes.²⁴

These two general findings make a case for QWMs as real-time measures of physiologic status and response during resuscitation. One may envision an application of QWMs as direct measures of CPR quality that view physiology independently of CPR process. However, because QWMs are surrogates for physiologic processes, they may be best interpreted in terms of their change. We propose an adaptation of current QWM-based shock prediction technology to show trends in QWMs during CPR or CPB. Further work is necessary to understand the sensitivity of QWMs under all relevant conditions and modes of resuscitation. This includes an understanding of the effects of rate, depth, and pauses.

As depicted in Figure 1, in this study we also had a glimpse at the relationship between three cardiac arrest ECG rhythms: VF, asystole, and PEA. Asystole as we observed it was often the consequence of sustained ischemia and was reversible if treated prior to 25 minutes. In these animals, reperfused asystole gave rise to coarse VF amenable to rescue shock, but exactly why reperfusion after 20 minutes did not consistently convert asystole to a shockable rhythm is not clear. Despite this uncertainty, our model does suggest that CPB reperfusion may have a role to play in addressing this rhythm. Further uncertainty arises when considering the two instances of PEA that resulted after reperfusion. It may be that conduction abnormalities and myocardial stunning manifest in this non-perfusing rhythm in the face of even very effective reperfusion. Our observation of right heart activity and left heart stasis during this rhythm, while limited and anecdotal, supports this notion.

Finally, our study provides needed basic science insight into the nascent field of resuscitation with CPB. In this study we have demonstrated that QWMs can be applied to animals undergoing CPB without complication from ECG artifact present during CPR. We have also shown that reperfusion effect can be monitored with respect to changes in QWMs throughout bypass. If CPB is used to stabilize a pulseless patient in the field prior to or during transport to hospital, QWMs may provide prognostic information relevant to treatment decisions downstream, such as coronary catheterization and cessation of resuscitation efforts.

Our study has several limitations, the most critical of which is the difficulty of generalizing of our findings to humans. We used an established swine model of prolonged VF that has been shown to display ROSC rates similar to human OHCA.²⁵ However, we utilized young, healthy animals with electrically induced VF, a combination of pre-arrest condition and arrest etiology that deviates from most cardiac arrests in humans. At least one previous study suggests that ischemic VF and electrically induced VF result in similar trends in QWMs.²⁶

Another significant limitation of our study is the lack of long-term survival or neurologic status outcomes. Ultimately, the utility of our findings hinges on the contribution that they make to improving survival to hospital discharge and neurologic status. In this sense, we regard our study as preliminary and hope that it sets the stage for further research.

Lastly, while we assert that QWM may be a useful measure of physiologic response to resuscitation interventions, in this study we did not test QWMs during CPR. Previous studies have demonstrated a relationship between CPR, coronary perfusion pressure, and QWMs.^{14, 27} However, our study provides a look at the most extreme durations of untreated VF, coupled with what is likely to be the clearest picture yet of the effects of reperfusion thereafter.

Conclusion

QWMs deteriorated during untreated VF and recovered after onset of CPB reperfusion. Duration of untreated VF was inversely correlated with recovery of QWMs during CPB. Only animals with 20 minutes or less of untreated VF completely recovered at least one QWM after CPB reperfusion. Twenty minutes of untreated VF appeared to be the temporal limit after which both recovery of QWMs and resuscitation became unlikely. QWMs may have utility for providing physiologic feedback during resuscitation and could serve as a real-time CPR effectiveness measure.

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Figure 1. Sample ECG Traces at Key Experimental Time Points

A. Early coarse VF converts over 15 minutes to lower amplitude, lower frequency VF.

B. Early coarse VF converts over 20 – 30 minutes to asystole.

C. 15-minute VF converts over 10 minutes of CPB resuscitation to coarse VF.

D. 20-minute asystole converts over 10 minutes of CPB resuscitation to coarse VF.

E. 25–30 minute asystole converts over 10 minutes of CPB resuscitation to asystole with visible atrial artifact.

F. 25–30 minute asystole converts over 10 minutes of CPB resuscitation to irregular, wide complex PEA.

Figure 2. Continuous Time Course of QWMs Throughout Untreated VF and Subsequent Resuscitation with CPB

15VF – Animals with 15 minutes of untreated VF, 20VF – Animals with 20 minutes of untreated VF, 25VF – Animals with 25 minutes of untreated VF, 30VF – Animals with 30 minutes of untreated VF.

Figure 3.
Recovery Proportion of Median Slope QWM Over Time for 10 minute Resuscitation with CPB

Table 1

Descriptive Variables and Outcomes by VF Duration Group

VF Duration Group	% Female	Weight Mean (SD)	ROSC	Survival	Pre-CPB Rhythm	Post-CPB Rhythm
15 min n = 4	50.0	27.1 (0.6)	4/4	4/4	VF: 2/4 PEA: 0/4 Asystole: 2/4	VF: 4/4 PEA: 0/4 Asystole: 0/4
20 min n = 4	100.0	26.7 (0.8)	3/4	3/4	VF: 0/4 PEA: 0/4 Asystole: 4/4	VF: 4/4 PEA: 0/4 Asystole: 0/4
25 min n = 4	100.0	27.3 (1.8)	1/4	1/4	VF: 0/4 PEA: 0/4 Asystole: 4/4	VF: 2/4 PEA: 1/4 Asystole: 1/4
30 min n = 4	50.0	25.9 (0.7)	0/4	0/4	VF: 0/4 PEA: 0/4 Asystole: 4/4	VF: 1/4 PEA: 1/4 Asystole: 2/4

Table 2

QWM Measures at Key Experimental Time Points, Mean (SD)

VF Duration Group	Start VF	Start CPB	End CPB
AMSA			
15 min (p < 0.001)	10.61 (0.26)	8.69 (0.26)	10.40 (0.32)
20 min (p < 0.001)	10.64 (0.35)	8.14 (0.50)	10.19 (0.85)
25 min (p = 0.001)	10.44 (0.09)	7.77 (0.45)	8.90 (0.22)
30 min (p < 0.001)	11.22 (0.30)	7.62 (0.57)	8.32 (1.05)
	p < 0.01	p < 0.05	p < 0.01
DFA			
15 min (p < 0.01)	0.152 (0.090)	0.707 (0.324)	0.125 (0.110)
20 min (p < 0.001)	0.095 (0.015)	0.736 (0.102)	0.198 (0.224)
25 min (p < 0.05)	0.287 (0.320)	0.797 (0.026)	0.383 (0.100)
30 min (p < 0.05)	0.104 (0.044)	1.00 (0.330)	0.689 (0.408)
	p = NS	p = NS	p < 0.05
LAC			
15 min (p < 0.05)	6.05 (0.16)	4.72 (0.86)	5.93 (0.38)
20 min (p < 0.001)	5.93 (0.06)	3.83 (0.81)	6.40 (0.73)
25 min (p < 0.001)	5.87 (0.12)	3.39 (0.46)	5.10 (0.17)
30 min (p < 0.001)	6.16 (0.18)	3.71 (0.67)	5.09 (0.69)
	p < 0.05	p = 0.11	p < 0.05
MS			
15 min (p < 0.01)	203.18 (36.80)	26.64 (12.88)	177.59 (58.38)
20 min (p < 0.01)	202.59 (15.93)	12.50 (2.32)	169.12 (104.98)
25 min (p < 0.001)	194.90 (22.54)	9.66 (3.03)	31.10 (15.90)
30 min (p < 0.001)	215.55 (41.76)	8.68 (2.83)	30.51 (38.13)
	p = NS	p < 0.05	p < 0.01

Table 3
Fitted Recovery Timing of QECG Measures by VF Duration Group, Minutes from Start of CPB

	Fitted Time to Maximum Observed Recovery (Minutes)				Fitted Time to Full Recovery (Minutes)			
	AMSA	DFA	LAC	MS	AMSA	DFA	LAC	MS
VF Duration Group								
15 min	10.0	8.95	8.82	7.27	--	5.37	5.93	5.50
20 min	8.10	10.00	10.00	10.00	--	--	7.03	--
25 min	8.18	10.00	9.67	10.00	--	--	--	--
30 min	7.55	9.50	8.98	9.18	--	--	--	--