Original Article

The Clinical Utility of Continuous QT Interval Monitoring in Patients Admitted With COVID-19 Compared With Standard of Care: A Prospective Cohort Study

Wael Alqarawi, MD,^a David H. Birnie, MBChB, MD,^a Mehrdad Golian, MD,^a
Girish M. Nair, MBBS, MSc, FHRS,^a Pablo B. Nery, MD,^a Andres Klein, MD,^a
Darryl R. Davis, MD, FHRS,^a Mouhannad M. Sadek, MD, FHRS,^a David Neilipovitz, MD,^b
Christopher B. Johnson, MD,^c Martin S. Green, MD,^a and Calum Redpath, MBChB, PhD^a

^a Arrhythmia Service, Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

^b The Ottawa Hospital, Ottawa, Ontario, Canada

^c Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

ABSTRACT

Background: QT interval monitoring has gained much interest during the COVID-19 pandemic because of the use of QT-prolonging medications and the concern about viral transmission with serial electrocardiograms (ECGs). We hypothesized that continuous telemetry-based QT monitoring is associated with better detection of prolonged QT episodes. **Methods:** We introduced continuous cardiac telemetry (CCT) with an algorithm for automated QT interval monitoring to our designated COVID-19 units. The daily maximum automated heart rate-corrected QT (Auto-QTc) measurements were recorded. We compared the proportion of marked QTc prolongation (Long-QTc) episodes, defined as QTc $\geq$ 500 ms, in patients with suspected or confirmed COVID-19 who were admitted before and after CCT was implemented (control group vs CCT group, respectively). Manual QTc measurement by electro-

RÉSUMÉ

Introduction : La surveillance de l'intervalle QT a suscité beaucoup d'intérêt durant la pandémie de la COVID-19 en raison de l'utilisation de médicaments prolongeant l'intervalle QT et les préoccupations quant à la transmission virale par les électrocardiogrammes (ECG) en série. Nous avons posé l'hypothèse que la surveillance en continu de l'intervalle QT par télémétrie était associée à une meilleure détection des épisodes de prolongation de l'intervalle QT.

Méthodes : Nous avons introduit la télémétrie cardiaque en continu (TCC) à l'aide d'un algorithme de surveillance automatisée de l'intervalle QT dans nos unités de COVID-19. Les mesures automatisées quotidiennes de l'intervalle QT corrigé (auto-QTc) en fonction de la fréquence cardiaque maximale ont été enregistrées. Nous avons comparé la proportion des épisodes de prolongation marquée de

The COVID-19 pandemic has brought multiple challenges to the health care system. One of which is the use of QT-prolonging medications with no clear evidence to guide monitoring.¹ Although clinicians are familiar with managing patients taking QT-prolonging medications, the current situation is different in 3 respects. First, combination therapy of 2 or more proarrhythmic anti-COVID-19 therapies is not uncommon and carry a greater risk of ventricular arrhythmias.^{2,3} Second, direct myocardial injury seen with COVID-19 has been shown in basic and clinical studies to increase the susceptibility to QT prolongation.^{4,5} Third, the usual practice

of performing serial electrocardiograms (ECGs) to monitor QT interval is being discouraged because of the risk of viral transmission, which limits the use of previously recommended protocols.⁶ As such, it is critical to find an alternative practical and safe method of monitoring the QT interval in these patients. Automated QT interval monitoring using continuous cardiac telemetry (CCT) systems is an appealing alternative because of the minimal contact with patients and its potential ability to detect episodes of transient QT prolongation that could be missed with intermittent QT measurements. We hypothesized that continuous QT monitoring with CCT for patients admitted to critical care units with COVID-19 would detect more episodes of prolonged QT than standard of care.

Received for publication June 14, 2020. Accepted July 16, 2020.

Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

Corresponding author: Dr Wael Alqarawi, University of Ottawa Heart Institute, 40 Ruskin St, H-1285A, Ottawa, Ontario K1Y 4W7, Canada. Tel.: +613-696-7402; fax: +1-613-696-7123.

E-mail: WAlqarawi@ottawaheart.ca

See page 597 for disclosure information.

Methods

This was a single-centre prospective cohort study that included consecutive patients admitted to critical care units affiliated with The Ottawa Hospital (5 units) with confirmed or suspected COVID-19 between April 7 and May 9, 2020.

physiologists was used to verify Auto-QTc. Charts were reviewed to describe the clinical response to Long-QTc episodes.

Results: We included 33 consecutive patients (total of 451 monitoring days). Long-QTc episodes were detected more frequently in the CCT group (69/206 [34%] vs 26/245 [11%]; $P < 0.0001$) and ECGs were performed less frequently (32/206 [16%] vs 78/245 [32%]; $P < 0.0001$). Auto-QTc correlated well with QTc measurement by electrophysiologists with an excellent agreement in detecting Long-QTc ($\kappa = 0.8$; $P < 0.008$). Only 28% of patients with Long-QTc episodes were treated with recommended therapies. There was 1 episode of torsade de pointes in the control group and none in the CCT group.

Conclusions: Continuous QT interval monitoring is superior to standard of care in detecting episodes of Long-QTc with minimal need for ECGs. The clinical response to Long-QTc episodes is suboptimal.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.⁷ See [Supplemental Table S1](#) for the STROBE checklist.

On April 28, 2020, CCT was implemented in all critical care units receiving COVID-19 patients at The Ottawa Hospital. Patients receiving CCT were considered the active group (CCT group) and those admitted before CCT were considered controls (control group). Patients were followed until discharge or death. This quality improvement initiative was granted an exemption by the Ottawa Health Science Network Research Ethics Board.

CCT group

Patients admitted after the implementation of CCT were attached to a cardiac monitor connected electronically to servers at the Arrhythmia Monitoring Centre at the University of Ottawa Heart Institute. The QT interval monitoring algorithm previously validated by Philips was used.⁸ Briefly, this system measures heart rate-corrected QT intervals (QTc) every 30 minutes and displays the results in a table attached to the daily report, which was then posted on the electronic medical record. Bazett's formula is used for heart rate correction.⁹ No correction for wide QRS is used. The end of the T wave is determined by a novel algorithm that measures vertical distances from a line connecting the peak of the T wave to a heart rate-adjusted point forward in time. The point with the maximum vertical distance is considered the end of the T wave.⁸ A 15-second ECG strip at the time of the maximum QTc measured in 24 hours was attached to the report. [Supplemental Figure S1](#) shows an example of such a report. Intermittent ECGs were performed in this group at the discretion of the treating team. For the purpose of this study, the daily maximum QTc provided by the system is called automated QTc (Auto-QTc).

l'intervalle QTc (QTc long), définie par un intervalle QTc ≥ 500 ms, chez les patients montrant une suspicion de COVID-19 ou ayant la COVID-19 qui avaient été admis avant et après la mise en place de la TCC (groupe témoin vs groupe de TCC, respectivement). La mesure manuelle de l'intervalle QTc par les électrophysiologistes a été utilisée pour vérifier les mesures auto-QTc. Nous avons passé en revue les dossiers pour décrire la réponse clinique aux épisodes de QTc long.

Résultats : Nous avons sélectionné 33 patients consécutifs (total de 451 journées de surveillance). Les épisodes de QTc long étaient détectés plus fréquemment dans le groupe de TCC (69/206 [34 %] vs 26/245 [11 %]; $p < 0,0001$) et les ECG étaient moins fréquemment effectués (32/206 [16 %] vs 78/245 [32 %]; $p < 0,0001$). Les mesures auto-QTc corrôlaient bien avec les mesures manuelles du QTc par les électrophysiologistes et montraient une excellente concordance dans la détection de QTc long ($\kappa = 0,8$; $p < 0,008$). Seuls 28 % des patients ayant des épisodes de QTc long ont reçu les thérapies recommandées. Il y a eu une épisode de torsade de pointes dans le groupe témoin et aucun dans le groupe de TCC.

Conclusions : La surveillance en continu de l'intervalle QT est supérieure à la norme de soins dans la détection des épisodes de QTc long et exige peu d'ECG. La réponse clinique aux épisodes de QTc long est sous-optimale.

Control group

Patients admitted before the implementation of CCT received the standard of care, which consisted of standard bedside telemetry without automated QT measurements and intermittent ECG monitoring at the discretion of the treating team. All ECGs were reviewed and the recorded QTc intervals were collected (ECG-QTc).

Data collection

Data on baseline characteristics including age, sex, comorbidities, QT-prolonging medications, QTc recorded on ECG at admission, and baseline serum K, Ca, Mg, and creatinine levels were collected. Patients with at least 1 positive nasopharyngeal swab were labelled as "confirmed COVID-19" and the rest were labelled as "suspected COVID-19." QT-prolonging antimicrobial therapy for confirmed COVID-19 patients were recorded. Electronic medical records were reviewed for all patients daily to record the QTc, the number of ECGs performed, and whether there was death or torsade de pointes (TdP). Auto-QTc for the CCT group and ECG-QTc for the control group (when available) were used to report daily maximum QTc.

In days with marked QTc prolongation (Long-QTc), defined as Auto-QTc ≥ 500 ms in the CCT group and ECG-QTc ≥ 500 ms in the control group, additional data were collected and included K, Ca, and Mg levels, medication adjustment (defined as stopping QT-prolonging medications), and electrolytes supplementation.

Outcomes

The prespecified primary outcome of the study was the proportion of new Long-QTc episodes (≥ 500 ms) in each group. Secondary outcomes were episodes of (TdP), the proportion of ECGs performed during the monitoring period, and the proportion of Long-QTc episodes that were

associated with guideline-recommended clinical response including medication adjustment or electrolyte supplementation.¹ Progress notes were reviewed to record whether Long-QTc episodes were documented in notes by any physician.

Automated QTc validation

Two cardiac electrophysiologists (Eps) (W.A. and C.R.) blinded to the Auto-QTc over-read a total of 66 consecutive measurements (32% of all Auto-QTc) using a predefined protocol. [Supplemental Figure S2](#) shows an example of manual QT measurement:

- Tangent method to determine the end of T-wave.¹⁰
- Bazett's formula for heart rate correction.⁹
- Averaged QTc for 5 consecutive beats in atrial fibrillation.¹¹
- Adjusted QTc for wide QRS: adjusted QTc = QTc - (QRS - 120).¹²

Statistical analysis

A formal, *a priori* calculation of sample size was carried out before collecting data. We estimated the proportion of Long-QTc to be 30% and 10% in the CCT group and control group, respectively.¹³ A sample size of 62 monitoring days in each group was calculated, which provides an 80% power to detect a statistically significant difference. Because of the uncertainty about the agreement between Auto-QTc and EP-QTc in detecting Long-QTc, we continued collecting data until we had > 62 monitoring days with EP-QTc measurements.

Continuous data were reported as median (interquartile range) and categorical data as numbers (percentages).

Wilcoxon rank sum test, χ^2 test, and Fisher exact test were used when appropriate to analyze outcome data. We used mixed effect multivariate logistic regression modelling to adjust for important confounders. Age was categorized into 2 groups on the basis of previous literature (≥ 68 and < 68 years).¹³ Correlation and agreement between Auto-QTc and EP-QTc were assessed with Pearson correlation coefficient (r) and κ statistics, respectively. Analyses were performed using SAS (version 9.4, SAS Institute, Inc, Cary, NC) and P values of < 0.05 were considered statistically significant.

Results

We included 33 patients with 451 monitoring days: 14 patients (206 monitoring days) in the CCT group and 19 patients (245 monitoring days) in the control group.

Patient characteristics

[Table 1](#) includes a summary of patient characteristics. Patients in the control group were older and had more confirmed COVID-19 cases whereas the CCT group had more female patients. Both groups had comparable comorbidities, baseline electrolyte levels, baseline QTc on ECG, and similar proportions of patients receiving QT-prolonging medications. Only 1 patient had QTc > 500 ms at baseline and was in the CCT group.

QT-prolonging antimicrobial therapy for confirmed COVID-19 included hydroxychloroquine/azithromycin combination in 3 patients, hydroxychloroquine alone in 1 patient, and azithromycin alone in 5 patients including the patient in the CCT group. In-hospital mortality was similar between the groups.

Table 1. Patient characteristics

	Control group (n = 19)	CCT group (n = 14)	<i>P</i>
Age, years	67 (57-74)	56 (41-63)	0.036*
Female sex	4 (21)	7 (50)	0.136
Confirmed COVID-19 status	8 (42)	1 (7)	0.046*
PMH			
CAD	2 (11)	1 (7)	1.0
AF	3 (16)	1 (7)	0.62
HTN	11 (58)	4 (29)	0.158
CHF	3 (16)	3 (21)	1.0
DM	8 (42)	2 (14)	0.131
Stroke	1 (5)	1 (7)	1.0
Depression	3 (16)	0 (0)	0.244
CKD	1 (5)	1 (7)	1.0
Cirrhosis	1 (5)	2 (14)	0.561
COPD	2 (11)	3 (21)	0.629
Creatinine, $\mu\text{mol/L}$	80 (62-95)	99 (71-247)	0.075
K, mmol/L	4.2 (3.7-4.6)	4.2 (3.9-5)	0.289
Mg, mmol/L	0.8 (0.8-0.9)	0.9 (0.7-1.1)	0.156
Ca, mmol/L	2.1 (2-2.2)	2.1 (1.7-2.2)	0.333
Receiving QT-prolonging medications	5 (26)	4 (29)	0.886
QTc on admission ECG, ms	445 (428-478)	445 (431-490)	0.614
Average length of stay, days	10 (9-12)	10 (6-19)	0.828
In-hospital death	6 (32)	4 (29)	1.0

Data are presented as median (interquartile range) or number (percentage).

AF, atrial fibrillation; CAD, coronary artery disease; CCT, continuous cardiac telemetry; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; PMH, medical history.

*Significant P value.

Proportions of new marked Long-QTc

Long-QTc was more frequently detected in the CCT group compared with the control group (69/206 [34%] vs 26/245 [11%]; $P < 0.0001$). Because important factors were not balanced between the 2 groups, we performed a sensitivity analysis adjusting for these factors (age, sex, COVID status, and the number QT-prolonging anti-COVID 19 therapies). Being in the CCT group remained significantly associated with Long-QTc (adjusted odds ratio, 4.10; 95% confidence interval, 2.47–6.83; $P < 0.0001$). Two patients in each group had a single episode of Long-QTc and the rest had repeated episodes.

Also, because auto-QTc did not correct for wide QRS, we performed a second sensitivity analysis excluding patients with wide QRS. The CCT group remained significantly associated with more episodes of Long-QTc (63/199 [31%] vs 10/216 [14%]; $P < 0.0001$).

Proportion of ECGs performed

ECGs were performed less frequently in the CCT group compared with the control group (32/206 [16%] vs 78/245 [32%]; $P < 0.0001$).

Clinical response to new marked Long-QTc

Overall, 27/95 (28%) Long-QTc episodes were associated with electrolyte supplementation and none were associated with medication adjustment. Extended electrolytes were checked in 71/95 (75%) of Long-QTc episodes. There was no difference between the 2 groups in checking or supplementing extended electrolytes. In 37 episodes of Long-QTc where the Mg level was < 1 mmol/L, only 17 (46%) had Mg supplementation.^{1,6,13,14} Table 2 depicts outcomes associated with each group and Figure 1 shows clinical response to Long-QTc episodes.

One episode of TdP was observed in the control group and none in the CCT group. ECG-QTc was 577 ms after the TdP episode and 565 ms 1 day earlier. Extended electrolytes were checked and supplemented on both days, but no medication adjustment was made (the patient was receiving propofol, which was not stopped).

Auto-QTc validation

There was strong correlation between Auto-QTc and EP-QTc ($r = 0.8$; $P < 0.0001$) and excellent agreement in

detecting Long-QTc ($\kappa = 0.8$; $P < 0.008$). The sensitivity of Auto-QTc in detecting any episode of EP-QTc ≥ 500 ms was 100% and the specificity was 84%. The difference between Auto-QTc and EP-QTc was assessed in 66 pairs and showed that Auto-QTc overestimated QTc by a median of 3 ms (interquartile range, 0–40 ms). Figure 2A shows the distribution of this difference and Figure 2B is a dot plot diagram of all 66 paired measurements. Because Auto-QTc overestimated QTc compared with EP-QTc, we performed a sensitivity analysis excluding Auto-QTc that was not validated by EP (ie, comparing EP-QTc vs ECG-QTc). The difference in the proportion of Long-QTc between the 2 groups remained significant (23/66 [35%] vs 26/245 [11%]; $P < 0.0001$).

Discussion

Our study showed that continuous QT interval monitoring detects more episodes of prolonged QTc than standard of care. Also, the institution of CCT was associated with a reduction in the number of ECGs being performed, which is likely because of the availability of continuous QT monitoring for serial ECGs, notwithstanding potential residual confounding. Our findings have important clinical implications for COVID-19 and, potentially, non-COVID-19 patients who are treated with medications that are either known to be proarrhythmic or with an uncharacterized risk profile.

QT interval monitoring is the first step in the effort to mitigate the risk of ventricular arrhythmias in hospitalized patients.⁶ Although there are no clear recommendations to guide choosing the best strategy of QT monitoring, performing serial ECGs is the most common practice.^{6,13} This strategy, however, has several limitations. First, it neglects the dynamic nature of the QT interval.¹⁵ Sympathetic tone, hormones, medications, and electrolytes influence the QT interval and are highly variable during the course of the day of any hospitalized patient.^{16,17} This explains why intermittent QT monitoring could miss periods of prolonged QT interval even if done daily. Second, the best time to assess QT interval after administration of any QT-prolonging medications is often unknown because the degree and timing of QT prolongation varies depending on the pharmacokinetics of the medication used, route of administration, and renal and hepatic function of the patient.⁶ This is particularly challenging when higher doses or new combinations of known proarrhythmic medications are used such as the use of high-dose

Table 2. Outcome data per group

	Control (n = 245 days)	CCT (n = 206 days)	P
Episodes of Long-QTc	26/245 (11)	69/206 (34)	$< 0.0001^*$
Daily ECGs performed during monitoring period	78/245 (32)	32/206 (16)	$< 0.0001^*$
Episodes of Long-QTc during which extended electrolytes were checked [†]	20/26 (77)	51/69 (74)	0.763
Any clinical response to Long-QTc [†]	5/26 (19)	22/69 (32)	0.223
Physician notes documenting Long-QTc	2/26 (8)	0 (0)	0.073
Episodes of TdP	1 (0.4)	0 (0)	1.0

Data are presented as n (%) except where otherwise noted.

CCT, continuous cardiac telemetry; ECG, electrocardiogram; Long-QTc, marked QTc prolongation of ≥ 500 ms; TdP, torsade de pointes.

* Significant P value.

[†] These were only assessed in episodes of Long-QTc.

Figure 1. (A) Clinical response to marked prolongation in QTc and (B) Mg replacement during episodes of marked QTc prolongation.

hydroxychloroquine and the combination of azithromycin/hydroxychloroquine during the current COVID-19 pandemic.^{3,18} Last, performing serial ECGs mandates additional contact with infected patients, which is particularly disadvantageous in patients with a highly infectious disease like COVID-19.

Although continuous QT monitoring is appealing, one needs to be cautious not to rely on the automated QTc readings provided by the monitoring system without validation. Indeed, our study showed that the automated QTc systematically overestimates manual QTc measurement by EPs. This is likely the result of using different methods to identify the end of the T wave and the failure of automated QTc measurements to adjust for wide QRS. However, this should not preclude using automated QTc measurements in daily practice because it could be used as a “screening” tool to identify QTc measurements that need to be verified by physicians. This is supported by the high sensitivity of automated QTc in detecting any episode of QTc ≥ 500 ms. Moreover, many experts recommend initiating electrolyte supplementation and stopping QT-prolonging medication at a threshold lower than 500 ms.^{1,12} As such, most episodes

detected using the automated QTc measurement in our study likely fall in the category of episodes that deserve intervention.

Regardless of the strategy and method of QT interval monitoring used, one can only expect improvement in clinical outcomes if episodes of prolonged QTc are treated properly. Despite numerous recent publications recommending preventative measures in patients with prolonged QTc, most episodes with marked QTc prolongation in our study were not treated with these measures.^{1,12,19,20} This suggests that simply reporting the prolonged QTc is not enough to alert the primary team. Akin to the automated infectious disease consultation for *Staphylococcus* bacteremia and the automated notification of critical lab values used in many institutions, efforts to establish clinical pathways to better manage episodes of prolonged QTc are necessary.^{21,22} Jain et al.²³ developed a protocol in which ECGs from COVID-19 patients were tagged for expedited review. An automated phone consult by the electrophysiology service was then initiated for any patient with prolonged QTc. This led to identifying significant numbers of prolonged QTc episodes and instituting relevant interventions. Future studies will need to examine whether

Figure 2. (A) Box plot of the difference between automated QTc measurement (Auto-QTc) and manual QTc measurement by an electrophysiologist (EP-QTc) and (B) dot plot diagram of Auto-QTc and EP-QTc measurements.

these interventions lead to more adherence to recommended therapies and, more importantly, improvement in clinical outcomes.

Most patients in our study had more than 1 episode of marked QTc prolongation during their admission. This is likely because these patients have factors such as age, sex, ethnicity, and/or genetic variants that predispose them to prolonged QTc every time they are re-exposed to a risk factor.²⁴⁻²⁷ Only 1 of these episodes was associated with TdP, which is in line with previous reports.^{3,28,29} It is critical that this is not used to lighten our concerns about QTc prolongation. Although there are multiple risk factors for TdP, prolonged QTc is the single most important modifiable risk factor than can be treated effectively with low-risk interventions. As such, we should continue every effort to find the best strategy of preventing, detecting, and treating episodes of QTc prolongation.

Our study has several limitations. First, this was not a randomized clinical trial. However, differences in the baseline characteristics of and disease severity are unlikely to explain our results and that was supported by our adjusted analysis. Second, our results are specific to the QT interval monitoring algorithm by Philips, which might not be generalizable to other systems. The lack of QTc correction for wide QRS is an important limitation of this system. However, the difference between the 2 groups remained significant after excluding patients with wide QRS. As discussed previously, a strategy of using the automated system as a screening tool for marked QTc prolongation is practical and safe. Similarly, our study only included patients admitted to critical care units. These patients, however, typically receive more monitoring than patients admitted to non-critical care units and, as such, this is unlikely to bias the result away from the null. Last, the small number of ECGs performed in the CCT group prevent any meaningful analysis to correlate Auto-QTc with ECG-QTc. However, this is not necessary because manual QTc measurement from telemetry strips is a well accepted method that is endorsed by all relevant organizations and is been used in studies on hospital-acquired QTc prolongation.^{6,13,30}

In conclusion, we report herein an improvement in detecting episodes of marked QTc prolongation with the use of continuous QT monitoring in a cohort of patients with suspected or confirmed COVID-19. Screening QTc intervals with an automated QTc algorithm is feasible. Efforts to improve adherence to recommended therapies of prolonged QTc episodes is needed.

Acknowledgements

The authors thank Sali Khalaf (research assistant at the University of Ottawa Heart Institute) for her substantial contribution to data collection.

Funding Sources

This project was supported by a grant from the Division of Cardiology at the University of Ottawa Heart Institute.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2020.07.012>.