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Original Article

QT dispersion in patients with chronic and advanced heart failure: Is it only a methodological problem?

Kronik ve ileri evre kalp yetmezliği hastalarında QT dispersiyonu: Sadece metodolojik sorun mu?

Omer YILDIZ*

Koc University Hospital, Cardiology Department, Istanbul / TURKEY

Abstract

Aim: QT dispersion is a potential predictive marker for ventricular tachyarrhythmia events and sudden cardiac death (SCD). However, prior investigations on the prognostic value of QT dispersion in patients with chronic heart failure (CHF) have shown conflicting results. Therefore, the present study aims to assess the prognostic value of QT dispersion in patients with CHF.

Material and Methods: A total of 66 patients with CHF (LVEF ≤35%, functional class NYHA II/III) were included in the study. Baseline ECG recording, Holter monitoring, equilibrium radionuclide ventriculography, and cardiopulmonary exercise test were carried out in all patients. Findings of the patients who experienced SCD group during the follow-up were compared with survivors.

Results: Over 36.7 ± 11.7 months follow-up, 10 patients (7 of 10 with SCD) died, and 3 patients underwent cardiac transplantation. Mean heart rate (101 ± 23 vs. 81 ± 12bpm, p <0.006) and NHYA class (2.6 ± 0.5 vs. 2.0 ± 0.7; p <0.03) were significantly higher, and LVEF (16 ± 4 vs. 27 ± 8%, p <0.006) was significantly lower in the SCD group. No significant differences between the two groups were found for peak VO2 (13.6 ± 7.4 vs. 17.2 ± 5.8ml/kg/min, p =0.138), heart rate variability (88 ± 51 vs. 133 ± 59ms, p =0.059) and QT dispersion (88 ± 51 vs. 90 ± 35ms, p =0.089).

Conclusions: Present findings indicate that in patients with chronic and advanced heart failure, both a decreased LVEF and increased heart rate but not QT dispersion provide predictive information on SCD.

Keywords: QT dispersion; heart failure; prognosis; mortality.

Corresponding Author*: Ömer Yıldız, Koc University Hospital, Cardiology Department, Istanbul / TURKEY
E-mail: oyildiz@kuh.ku.edu.tr.
ORCID: 0000-0002-3632-3405
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ÖZ

Amaç: QT dispersiyonu ventriküler taşiaritmi ve ani kardiyak ölüm (AKÖ) olayları için potansiyel bir belirteçtir. Ancak, kronik kalp yetmezliği (KKY) olan hastalarda QT dispersiyonunun prognostik değeri üzerine yapılan önceki araştırmalar çelişkili sonuçlar göstermiştir. Bu çalışma, ileri evre KKY olan hastalarda QT dispersiyonunun prognostik değerini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya 66 ileri evre KKY olan hasta (sol ventriküler ejeksiyon fraksiyonu (SVEF) ≤%35, fonksiyonel sınıf NYHA II/III) dahil edildi. Tüm hastalarda başlangıçta EKG kaydı, holter monitörizasyonu, radyonüklid ventrikülografi ve kardiyopulmoner egzersiz testi yapıldı. Takip sırasında AKÖ grubu olan hastaların bulguları sağ kalanlarla karşılaştırıldı.

Bulgular: Toplam 36,7 ± 11,7 ay üzerinde takipte, 10 hasta (7'sinde AKÖ) öldü ve 3 hastaya kalp nakli uygulandı. Ortalama kalp atış hızı (101 ± 23'e karşı 81 ± 12/dk., p <0,006) ve NHYA sınıfı (2,6 ± 0,5'e karşı 2,0 ± 0,7; p <0,03) anlamlı olarak daha yüksekti ve SVEF (16 ± 4'e karşı %27 ± 8, p <0,006) AKÖ grubunda anlamlı olarak daha düşüktü. Zirve VO2 (13,6 ± 7,4'e karşı 17,2 ± 5,8ml/kg/dk, p =0,138), kalp hızı değişkenliği (88 ± 51'e karşı 133 ± 59msn, p =0,059) ve QT dağılımı (88 ± 51'e karşı 90 ± 35msn, p =0,089) değerlerinde iki grup arasında anlamlı fark izlenmedi.

Sonuç: Mevcut bulgular, ileri evre KKY olan hastalarda AKÖ riski açısından azalmış SVEF ve artmış kalp hızının istatiksel olarak anlamlı olduğunu, QT dispersiyonunun ise anlamsız öngörücü bilgi sağladığını göstermektedir.

Anahtar Kelimeler: QT dispersiyonu; kalp yetmezliği; prognoz; mortalite.

Introduction

With the ageing of the population, the incidence and prevalence of heart failure continue to increase [1]. Despite remarkable progress in the pharmacological and device therapy of chronic heart failure (CHF), the prognosis of the patients remains poor. Less than 50% of patients with CHF survive after four years [2]. Up to 50% of the deaths are unexpected sudden cardiac death (SCD), which is assumed to be associated with arrhythmias like ventricular tachycardia and fibrillation [3-4]. Despite increased efforts, there is to date no specific method for detecting patients with CHF predisposed to potentially lethal ventricular arrhythmias.

Efforts to define the ventricular repolarization disorders from the surface electrocardiogram can be traced back to the 1960's [5]. Mirvis is the first to report on a significant spatial variation in QT intervals in patients with acute myocardial infarction and healthy individuals [6]. Since then there has been a rising interest in so-called QT dispersion. Since the QT dispersion has been suggested as a marker for ventricular repolarization inhomogeneity; it is assumed as a possible prognostic clinical tool in the detection of future life-threatening ventricular arrhythmias and death [3]. The prognostic benefit of QT dispersion has been investigated in several cardiovascular diseases, particularly for patients with congenital QT syndromes [3]. Previous studies on the prognostic value of QT dispersion in CHF patients have shown conflicting results [3,7-9]. Hence, the present study focuses on evaluating the prognostic value of QT dispersion in patients with chronic and advanced heart failure.

Material and Methods

The study group included 66 patients aged ≥18 years with chronic and advanced heart failure (LVEF ≤35% and a functional class of the New York Heart Association (NYHA) II-III who were referred to a tertiary academic medical centre for the management of heart failure and/or to be evaluated for heart transplantation (HTx) from November 1995 to June 2000.

Patients with atrial fibrillation, pacemaker rhythm, significantly measured QT prolongation (corrected QT-interval > 460ms or 500ms with bundle branch block), receiving a class I or class III antiarrhythmic drug, unable to perform cardiopulmonary exercise test (CPx), severe non-cardiac diseases and poor recording quality, as well as patients unable or unwilling to participate, have been excluded. Informed consent was obtained from all patients. The ethics committee of our institution approved the study protocol.

In all patients, a digitized 12 leads standard ECG (PC ECG software, Dr. Vetter, Baden Baden) was recorded under physical resting conditions in supine position. Later, an experienced observer manually evaluated the digitized 12 lead standard ECG on the screen. In all 12 leads, the QT interval was measured from the beginning of the QRS complex to the visual return of the T-wave to the isoelectric line. When a U-wave was present, the nadir between T-wave and U-wave was defined as the offset of T-wave. For each sinus beats, QT dispersion was

calculated utilizing a computer software (PC ECG software, Dr. Vetter, Baden Baden). The mean QT dispersion value was calculated from the obtained measurements of QT dispersion using a computer program specially developed in-house for the differentiated analysis of the data.

Holter monitoring was performed in all patients to define the heart rate variability and mean heart rate. The heart rate variability was evaluated with time domain analysis and the standard deviation of the normal-to-normal intervals (SDNN) was included in the present analysis. An equilibrium radionuclide ventriculography was performed in all patients to determine the left ventricular ejection fraction (LVEF) at rest using a multicrystal gamma camera (Orbiter, Siemens, Erlangen). For the quantitative determination of the O2 uptake at maximum load (peak VO2), a CPx was performed on a bicycle ergometer (Ergoline, Jaeger, Würzburg) in a semi-recumbent position in all patients.

The primary endpoint of the study is the occurrence of SCD (death within one hour of the onset of symptoms). Since no direct pathophysiological relationship was described between QT dispersion and dying from progressive pump failure, it was evaluated as an endpoint without analyzing in a separate group.

Statistical Analysis

The results are presented as mean ± standard deviation (SD) unless otherwise stated. Differences between the patients who survived and who experienced SCD in the using the follow-up period were tested with Student's t-test for independent samples or when more than two patient groups exist using ANOVA (analysis of variance with subsequent student Newman-Keuls test and Bonferroni t-test). P value <0.05 was considered as statistically significant.

Results

The characteristics of the study patients are summarized in Table 1.

Diabetes mellitus was present in 21 patients (32%) and 16 patients (24%) suffered from renal insufficiency in the stage of compensated retention. Four patients (6%) had both concomitant diseases. Figures 1-4 compare the QT dispersion values with the NYHA classification, LVEF, peak VO2, and SDNN. There were no significant differences in QT dispersion between NYHA classes I, II, and III (Fig. 1). In patients with LVEF ≤20%, QT dispersion was also not significantly different from the patients with LVEF >20% (Fig. 2). Likewise, patients with peak VO2 ≤14ml/kg/min showed similar QT dispersion values to patients with peak VO2 >14ml/kg/min (Fig. 3). In patients with a low heart rate variability (SDNN ≤65ms), the QT dispersion was not significantly different from the patients with an SDNN >65ms (Fig. 4).

Tab. 1: Clinical characteristics of the patients included in the mean QT dispersion analysis (n = 66)

Characteristic	Value
Basic data	
Age (years)	52.1±12.4
Gender	
Male	53 (80 %)
Female	13 (20 %)
Etiology	
Non-ischemic CHF	44 (67 %)
Ischemic CHF	22 (33 %)
Medications	
ACE inhibitors or angiotensin II receptor antagonists	57 (86 %)
Diuretics	17 (26 %)
Cardiac glucosides	38 (58 %)
Antiarrhythmics	4 (6 %)
Beta-receptor blockers	26 (39 %)
Cardiovascular implantable electronic device	
Implantable cardioverter defibrillator	8 (12 %)
Hemodynamic and corresponding parameters	
LVEF (%)	25 ± 10
Systolic blood pressure (mmHg)	119 ± 26
Diastolic blood pressure (mmHg)	83 ± 16
Mean heart rate (beats/min)	82 ± 21
Parameters of functional resilience	
Peak VO2 (ml/kg/min)	16.7 ± 5.9
NYHA class	
I	13 (19.7 %)
II	29 (43.9 %)
III	24 (36.4 %)
Neurohumoral parameter	
Heart rate variability, SDNN (ms)	129.2 ± 59.8
QT dispersion (ms)	90 ± 34

The values are shown as mean ± standard deviation or as number (percent)

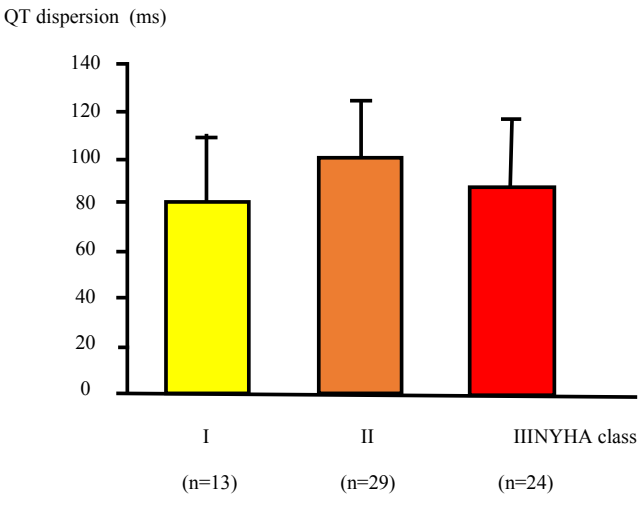

Figure 1: QT dispersion depending on NYHA class (mean ± standard deviation; total collective n = 66).

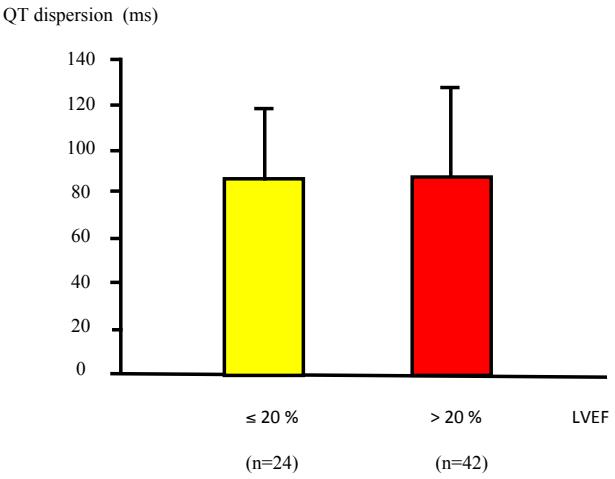

Figure 2: QT dispersion depending on the left ventricular ejection fraction (LVEF) (mean ± standard deviation; total collective n = 66, differences between groups not significant).

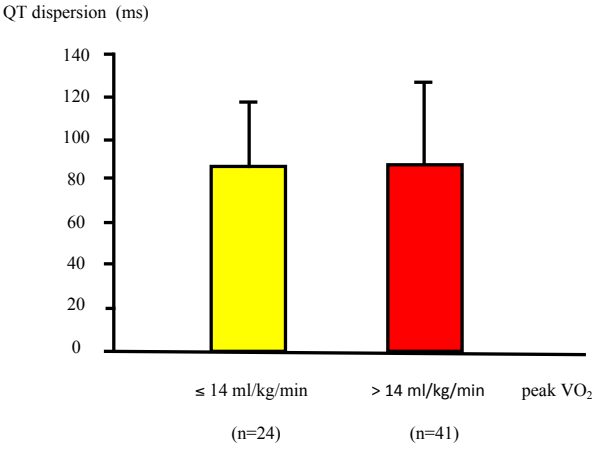

Figure 3: QT dispersion depending on the peak VO2 (mean ± standard deviation; total collective n = 66, in one patient no data available, differences between groups not significant).

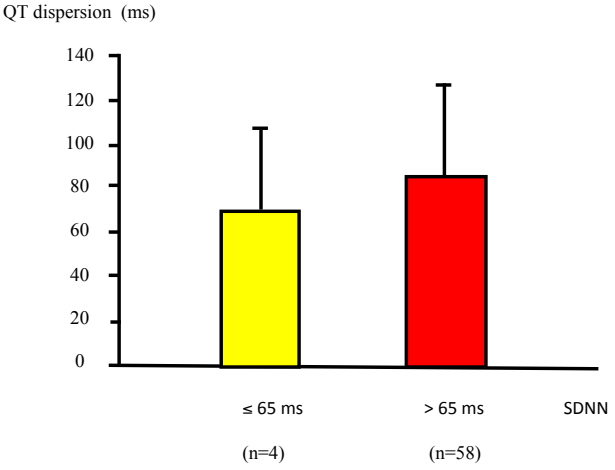

Figure 4: QT dispersion depending on the heart rate variability (SDNN) (mean ± standard deviation; total collective n = 66, no data available from 4 patients, differences between groups not significant).

Patients with ischemic CHF (n =22) and non-ischemic CHF (n =44) differed significantly with respect to age (57.8 ± 8.9 and 48.0 ± 13.0 years respectively; p =0.002), maximum oxygen intake under physical exertion (13.7 ± 4.0 and 18.2 ± 6.1ml/kg/min, respectively; p =0.003), and mean heart rate (76 ± 20 and 87 ± 17 beats/min respectively; p=0.023). Their LVEF (27.9 ± 7.1 and 23.6 ± 10.9% respectively; p =0.112), and QT dispersion (99 ± 40 and 85 ± 30m/s, respectively; p=0.116) were similar to each other (Table 2). Beta-blocker (61% vs. 30%, respectively) and ACE inhibitor/ angiotensin II receptor blocker (91% vs. 84%, respectively) usage were more frequent in ischemic CHF then non-ischemic patients. For all other characteristics, no significant differences were found between the two patient groups.

Tab. 2: Comparison between clinical characteristics of patients with ischemic CHF and non-ischemic CHF

Characteristic	Ischemic CHF (n=22)	Non-ischemic CHF (n=44)	p Value
Age (years)	57.8 ± 8.9	48.0 ± 13.0	0.002
Peak VO2 (ml/kg/min)	13.7 ± 4.0	18.2 ± 6.1	0.003
Mean heart rate (beats/min)	76 ± 20	87 ± 17	0.023
LVEF (%)	27.9 ± 7.1	23.6 ± 10.9	0.112
QT dispersion (ms)	99 ± 40	85 ± 30	0.116

The values are shown as mean ± standard deviation or as number (percent).

During a mean follow-up period of 36.7 ± 11.7 months, ten patients died, which corresponds to 15.2% (all percentages related to the total collective n =66). The one-year mortality rate of the total study population was approximately 8%. Seven patients (10.6%) died of SCD (on average, after 16.6 ± 13.9 months). After an observation period of 33.0 ± 12.7 months, two (3%) patients developed acute cardiac pump failure with immediate consequences of death. One patient (1.5%) died after an observation period of 11 months of the immediate consequences of lymphoma. HTx procedure was performed on three patients after an observation period of 17.7 ± 11.0 months. In the case of the HTx patients, only the observation period up to the transplant date was evaluated. Four (4%) of 10 deceased patients had previously suffered cardiac decompensation, i.e., without immediate death. The fifty-three survivors (80.3%) were observed for 35.0 ± 11.3 months. For the endpoint related analyses, three groups were formed; group 1: patients with SCD (n=7), group 2: survivors (n=53), group 3: deceased patients without SCD (n=3).

Using variance analysis (ANOVA), the three groups were simultaneously compared; mean heart rate in the group of patients with SCD was significantly higher than in survivors. Also, LVEF was significantly lower than in survivors. Only tendentially but not significantly elevated was the NYHA functional class in patients with SCD compared to survivors. Furthermore, systolic blood pressure tended to be lower in patients with SCD than in the survivors. On the other hand, there were no significant differences between the three groups with concerning QT dispersion and the other parameters given in Table 3.

Tab. 3: Comparison between clinical characteristics of patients with sudden cardiac and death from other causes and survivors

Characteristics	Sudden cardiac death n=7 (Group 1)	Survivor n=56 (Group 2)	p Value (Groups 1 vs. 2)	Death from other cause n=3 (Group 3)	p Value (Groups 1,2 and 3 among each other)
Age (years)	50 ± 11	52 ± 22	0.80	53 ± 22	0,92
Male	6 (85.7 %)	44 (78.6%)		3 (100%)	
Female	1 (14.3 %)	12 (21.8%)		0	
Non-ischemic CHF	3 (42.9%)	38 (67.9%)		2 (66.7%)	
Ischemic CHF	4 (57.1%)	18 (32.1%)		1 (33.3%)	
Systolic blood pressure (mm Hg)	109 ± 12	123 ± 21	0.09	101 ± 5	0.056
Diastolic blood pressure (mm Hg)	79 ± 12	85 ± 12	0.21	76 ± 12	0.24
Mean heart rate (beats/min.)	101 ± 23	81 ± 12	p < 0.006	92 ± 40	only Group 1 vs. 2 *p < 0.03
NYHA class	2.6 ± 0.5	2.0 ± 0.7	p < 0.03	2.5 ± 0.7	0.059
LVEF (%)	16 ± 4	27 ± 8	p < 0.006	21 ± 15	only Group 1 vs. 2 *p < 0.018
Peak VO2 (ml/kg/min)	13.6 ± 7.4	17.2 ± 5.8	0.138	15.0 ± 1.4	0.28
SDNN (ms)	88 ± 51	133 ± 59	0.059	153 ± 74	0.13
QT dispersion (ms)	88 ± 51	90 ± 35	0.089	89 ± 44	0.99

The values are shown as mean values ± standard deviation or as number (percent)
p < 0.05 in comparison of patients with sudden cardiac death vs. survivors
*p < 0.05 = in simultaneous 3-group comparison using ANOVA

In addition to this simultaneous comparison of all patients in the study, the groups "SCD" and "survivors" were compared statistically concerning the significance of the QT dispersion directly utilizing the t-test. In this two-group comparison, patients with SCD were again found to have a significantly higher mean heart rate and lower LVEF as well as a higher NYHA functional class. Furthermore, a decreased SDNN were observed. Finally, no significant differences were found for QT dispersion, peak VO2, and other parameters listed in Table 3 between patients with SCD and survivors.

Discussion

The present paper demonstrates that QT dispersion has no prognostic value in terms of SCD in patients with advanced CHF due to ischemic or idiopathic dilated cardiomyopathy.

This outcome of the present study is in agreement with some [4,10,11] but yet in conflict with other investigations [7,8,12,13]. In the past, many studies showed that CHF patients with increased QT dispersion are prone to life-threatening cardiac arrhythmias and SCD. Nevertheless, results of other studies were inconsistent. In recent decades, attempts have been made in several investigations utilizing multivariate survival analysis to define the prognostic value of QT dispersion on mortality for patients with CHF. Only for patients with dilated cardiomyopathy and QT dispersion >80ms Galinier et al [8] indicated to have a prognostic value for both sudden death and arrhythmic death, while for patients with CHF due to ischemic heart failure had no prognostic value. An early publication showed that in patients with ischemic cardiomyopathy (within 2 to 9 days after myocardial infarction) had prognostic information for both QT dispersion and corrected QT (QTc) dispersion in terms of all-cause mortality [14]. They detected, however, extensive overlap in QT dispersion between non-survivors and survivors, reducing the utilization of the prognostic relevance. Previous research demonstrated that 14 patients with CHF and QT dispersion >140ms waiting for cardiac transplant died before transplantation, meaning that increased QT dispersion yield prognostic information [15]. Another former investigation (with small sample size) found that the corrected JT dispersion and relative QT dispersion (standard deviation of QT dispersion divided by mean x100) comprise independent prognostic value in 34 patients with idiopathic or ischemic dilated cardiomyopathy who suffered from ventricular tachyarrhythmia or sudden death [16]. Rotterdam study demonstrated that during a mean follow-up of 4 years healthy older (aged 55 years) subjects with QTc dispersion >60ms (vs >39ms) had a two-fold increased risk of SCD [17].

This inconsistency in the results of the studies mentioned above is not apparent, but many factors may bias the outcomes. A previous study demonstrated that QT dispersion is not a direct indicator of ventricular depolarization disorders, but solely a rough marker of T-wave morphology [18]. Evaluation of the T-wave morphology by T loops may be a more accurate description of heterogeneity of the cardiac action potential. So far, there are only a few studies that have shown a satisfying

reproducibility of QT dispersion, [19] but several studies have demonstrated high inter-and intra-observer variability of QT dispersion [14,20]. Furthermore, the unreliable determination of T-wave offset is the main technical difficulty in measuring the QT dispersion [18,21]. Also, the relatively small value of the QT dispersion compared to the QT interval is a problem. Since a relatively small error in QT measurement leads to increased error in QT dispersion [22]. Another one is that due to sympathovagal balance, the QT-dispersion has a diurnal variation [23]. Thus, QT dispersion measurements obtained at different times should not be compared.

Several scientific articles utilizing multivariate analysis demonstrated no prognostic value of QT dispersion for mortality in patients with CHF. To justify the use of multivariate survival analysis, however, requires many endpoints which was also absent in the present study [24].

The discrepancy in the predictive power of QT dispersion concerning mortality between the previous and the present study may be in the various methodology of studies providing a compelling explanation for differences of the outcomes.

Study limitations

The limitations of the present investigation include its observational characteristics and the implementation at a single tertiary centre. Since, patients with advanced CHF and severe symptoms represented by NYHA functional class IV are unable to perform CPx examination, they were not included in the present work compared to previous studies [7-9]. This exclusion may also bias the prediction of SCD, so that QT dispersion was not significantly increased in advanced CHF patients and SCD compared to survivors. As no healthy volunteers were included in the present study, it cannot be clarified whether the patients had pathologically altered levels of QT dispersion. Due to the lack of differences in the mean values between advanced CHF patients with SCD and survivors, no further statistical analysis of the prognostic relevance utilizing Cox regression was performed. In future studies with larger study groups, the prognostic value of QT dispersion should be further examined, in particular for patients with ß-blocker therapy, who were relatively low in this analysis.

Conclusions

In the present work, both decreased LVEF and increased heart rate, but not QT dispersion revealed a significant association in advanced CHF patients, and SCD compared to survivors. Since no precise definition of QT dispersion has been agreed to date, there are various methods of QT dispersion measurement limiting the comparability of the scientific papers. Thus, standardization techniques and more precise measurement are necessary to assess and compare QT dispersion in future researches.

Declaration of conflict of interest

The author has no conflicts of interest to declare. The author received no funding for this work.

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