

QT dispersion during hypobaric hypoxia

Alçak basınç ortamında oluşan akut hipoksinin QT dispersiyonu üzerine etkisi

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ABSTRACT

Objective: Hypoxia is one of the major concerns in aviation. Clinical hypoxia has been shown to increase QT dispersion (QTd). We aimed to examine QTd during hypobaric chamber training to observe the effect of hypobaric hypoxia on QT dispersion.

Methods: A total of 38 healthy male aviators volunteered to take part in this longitudinal study. Subjects' electrocardiograms were recorded by 12-lead digital Holter device before, during, and after hypobaric exposure at simulated altitude of 30,000ft. Data from 23 of the subjects, aged 27.91±6.02 years (range 22–39) was used. QT intervals were measured manually. QT dispersion and heart rate adjusted QTd (QTcd) were calculated for each subject. Statistical significance of changes in parameters was analyzed using the Friedman test. Comparison of pre-post exposure clusters was made using Dunn's test.

Results: QT dispersion values were as following: prehypoxic 64.09±8.39 ms, hypoxic 50.35±11.06 ms and posthypoxic 59.83±9.06 ms (Median: 64, 50, 60; Mean rank: 2.65, 1.28, 2.07) (p=0.0001 for prehypoxic–hypoxic, p=0.046-prehypoxic-posthypoxic, and p=0.002 for posthypoxic-hypoxic). Heart rate values were as following: prehypoxic 74.09±6.43 beats/min, hypoxic 127.1±17.39 beats/min, and posthypoxic 95.17±11.35 beats/min (Median: 75, 122, 92; Mean rank: 1, 3, 2) (p=0.0001 for prehypoxic–hypoxic, prehypoxic–posthypoxic, and posthypoxic–hypoxic). The change in QTd and HR during hypobaric chamber exposure was statistically significant but, the change in QTcd was not (p<0.001, p<0.001, p>0.1, respectively).

Conclusion: From the findings of present study, it is not possible to directly comment on the validity of QTd in revealing arrhythmogenic predisposition of healthy subjects exposed to hypobaric hypoxia. The relationship between QT dispersion and hypobaric hypoxic exposure is not clear, particularly when QTd is corrected for the increased heart rate. QT dispersion measurement has not been proven a reliable and practical method to show arrhythmia predisposition during a hypobaric hypoxic exposure in healthy individuals. (*Anadolu Kardiyol Derg 2008; 8: 266-70*)

Key words: Electrocardiography, altitude chamber, flight, aviation, hypoxia, ventricular repolarization

ÖZET

Amaç: Hipoksi havacılıkta karşılaşılabilecek önemli sorunlardan biridir. Klinik hipoksi elektrokardiyogramda en uzun ve en kısa QT mesafesi arasındaki fark yoluyla hesaplanan QT dispersiyonunda (QTd) artışla kendini gösterir. Bu çalışmada hipobarik hipoksi ortamını yansıtan alçak basınç odası eğitiminin QT dispersiyonu üzerine etkisinin araştırılması amaçlanmıştır.

Yöntemler: Bu longitudinal çalışmaya 38 sağlıklı gönüllü katıldı. Otuzbin ft. yüksekliğe eşdeğer basınçta hipoksi eğitimine giren kişilerden hipoksi öncesi, hipoksi esnasında ve hipoksi sonrasında digital Holter yoluyla 12 derivasyonlu elektrokardiyogram çekildi. Yaş ortalaması 27.91±6.02 yıl (yaş aralığı: 22–39 yıl) olan 23 denekten ancak uygun veri alınabildi. Diğer 15 uçucu, kayıtlarının parazitli olmasından dolayı çalışmaya dahil edilmedi. Elde edilen ritm örnekleri manuel olarak değerlendirildi. Her bir kişi için QT aralıkları, kalp hızı ve düzeltilmiş QTd değerleri manuel olarak ölçüldü. Değerler arasındaki farklar Friedman testiyle, hipoksik maruziyet öncesi-sonrası karşılaştırmalar Dunn testi ile değerlendirildi.

Bulgular: QT dispersiyon değerleri hipoksi öncesi (prehipoksik) 64.09±8.39 msn, hipoksik 50.35±11.06 msn ve hipoksi sonrası (posthipoksik) 59.83±9.06 msn (mediyan: 64, 50, 60; ortalama rank: 2.65, 1.28, 2.07) (sırasıyla prehipoksik–hipoksik, prehipoksik-posthipoksik ve posthipoksik–hipoksik; p=0.0001, p=0.046, p=0.002); kalp hızı değerleri 74.09±6.43 atım/dak, 127.1±17.39 atım/dak ve 95.17±11.35 atım/dak (mediyan: 75, 122, 92; ortalama rank: 1, 3, 2) (sırasıyla prehipoksik–hipoksik, prehipoksik-posthipoksik ve posthipoksik–hipoksik; p=0.0001, p=0.0001) olarak bulundu. Alçak basınç eğitimi esnasında QTd ve kalp hızında oluşan değişiklik istatistiksel olarak anlamlı fakat kalp hızı ile korele edilerek ölçülen düzeltilmiş QT dispersiyonu anlamlı değildi (sırasıyla p<0.001; p<0.001; p>0.1).

Sonuç: Çalışmamızda hipobarik hipoksi maruziyetinde kalp hızı ve QT dispersiyonunda anlamlı derecede değişiklik olduğu ancak düzeltilmiş QT dispersiyonunda bu anlamlı değişikliğin oluşmadığı görüldü. Sonuç olarak QTd ölçümünün sağlıklı deneklerde hipobarik hipoksi maruziyetinde aritmi predispozisyonunu göstermede güvenilir ve pratik bir yöntem olarak kullanılamayacağı görüldü. (*Anadolu Kardiyol Derg 2008; 8: 266-70*)

Anahtar kelimeler: Elektrokardiyografi, alçak basınç odası, uçuş, havacılık, hipoksi, ventriküler repolarizasyon

Introduction

Hypoxia is one of the major concerns in aviation, because it can potentially affect aviators by disrupting the intracellular oxidative process and impairing cellular functions. The cardiovascular response to hypoxia is to increase cardiac output; heart rate increases due to the reflex responses of carotid and aortic chemoreceptors as well (1).

It has been supposed that hypoxemia increases the risks of tachyarrhythmia in patients affected by respiratory failure directly or indirectly by increasing the sympathetic activity, which affects the performance of the left ventricle (2). Additionally, increased heterogeneity of ventricular repolarization has been reported to contribute to the development of serious ventricular arrhythmias. One way to assess increased dispersion of repolarization is the measurement of QT dispersion (QTd) which is the inter-lead differences between the longest and shortest QT intervals in the standard 12-lead electrocardiogram (ECG) (3).

Clinical hypoxia has been shown to cause an increase in QTd and is suggested to be an early marker of a blood gas mediated electropathy in patients with chronic obstructive airway disease (4, 5). Similarly, changes in the QTd of healthy subjects after exercise have been reported as well (6). However, the acute effects of hypobaric hypoxia on ventricular repolarization and risk of arrhythmia in healthy subjects have not been yet elucidated.

In this study we examined QTd during hypobaric chamber training to determine the effect of simulated hypobaric hypoxia on QTd of healthy subjects.

Methods

A total of 38 healthy male aviators volunteered to take part in this longitudinal study. Data of 23 subjects, aged 27.91 ± 6.02 years (range 22–39 years) were determined to be useful for inclusion in this study. Fifteen subjects were excluded from the study because their ECG recordings were not readable due to the interference in the chamber.

All subjects passed aviation medical examinations and were fit for flight duties. They did not have any cardiac or respiratory problems. None of them had taken medications in the three days period prior to the chamber training. All participants gave their informed consents.

A multiplace hypobaric chamber (ETC, Southampton, PA) was used for hypoxia training.

Electrocardiograms were recorded by 12-lead digital Holter device (CardioScan, Dms-Service Llc, NV) from the beginning to the end of the hypobaric chamber flight. The recordings were then transferred to a computer for offline analysis. Three 10 second ECGs were obtained for each subject; the first was at the ground level (2700 ft; prehypoxic); the second at the end of the hypoxic period (hypoxic); and the final was recorded 20 sec. after recovery from hypoxia (posthypoxic) at a simulated altitude of 30.000 feet. Effective performance time (EPT) values of each subject were recorded (7). All recordings were made during actual hypoxia training session; normal chamber procedures were not changed for study purposes.

Evaluation of QT dispersion

A cardiologist, blinded to subjects' data, manually measured the QT intervals from the onset of the QRS to the end of the T wave. RR and QT intervals were measured in as many of the 12 leads as possible. The lead was not included if the end of the T wave could not be identified. Only ECG recordings with ≥ 8 different analyzable leads were accepted. Heart rate adjusted QT (QTc) was calculated, by Bazett's formula: $QTc = QT / \sqrt{RR}$ (8). The QT dispersion was defined as the difference between the maximum and minimum QT values. Accordingly, the dispersion of QTc (QTcd) was defined as the difference between the maximum and minimum QTc values.

Statistical Analysis

Statistical analyses were performed by using SPSS® for Windows® 10.0 (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean \pm SD, median and mean rank values. Statistical significance of changes in parameters was analyzed using the Friedman test. Comparison of pre-post exposure clusters was made using Dunn's test. The correlation of age, EPT, and smoking with QTd, QTcd, HR and the difference of these values before and after hypoxic exposure were also analyzed. Pearson and Kendall tau b correlation coefficient was used as appropriate.

Results

Table 1 shows values for EPT and prehypoxic, hypoxic and posthypoxic QTd, QTcd and HR. All subjects' EPTs were within the suggested limits (9) with a minimum of 60 sec to a maximum of 200 sec. QT dispersion values were 64.09 ± 8.39 ms, 50.35 ± 11.06 ms and 59.83 ± 9.06 ms (prehypoxic, hypoxic, and posthypoxic, respectively); HR values were 74.09 ± 6.43 beats/min, 127.1 ± 17.39 beats/min and 95.17 ± 11.35 beats/min (prehypoxic, hypoxic, and posthypoxic, respectively).

The change in QTd, QTcd and HR due to hypoxia and after recovery from hypoxia was analyzed with Friedman test (Table 2). The change in QTd and HR during hypobaric chamber exposure was statistically significant ($p < 0.001$ and $p < 0.001$, respectively) but, the change in QTcd was not ($p > 0.1$). Since QTd and HR showed significant changes, further analysis of these parameters were made using Dunn's test by paired comparison of

Table 1. Descriptive parameters for EPT, QTd, QTcd, and HR

Variables	Mean	Std. Dev.	Median	Min.	Max.
EPT, sec	144.8	36.5	147.5	60	200
QTd prehypoxic, ms	64.09	8.4	64	48	84
QTd hypoxic, ms	50.35	11.06	50	28	80
QTd post hypoxic, ms	59.83	9.06	60	28	76
QTcd prehypoxic, ms	71.16	9.82	71.85	54	93
QTcd hypoxic, ms	73.17	16.65	70.73	37	110
QTcd post hypoxic, ms	75.48	13.09	77.16	31	101
HR prehypoxic, beats/min	74.09	6.43	75	64	88
HR hypoxic, beats/min	127.1	17.4	122	106	175
HR posthypoxic, beats/min	95.17	11.35	92	75	123

EPT- Effective performance time, HR- heart rate, QTd- QT interval dispersion, QTcd- heart rate adjusted QT interval dispersion

prehypoxic-hypoxic, posthypoxic-prehypoxic and posthypoxic-hypoxic results. There was a significant change in HR for all three clusters ($p < 0.001$, $p < 0.001$, and $p < 0.001$) and in QTd for hypoxic-prehypoxic comparison ($p < 0.001$).

The correlation of age, EPT, and smoking with QTd, QTcd, HR and the difference of these values before and after hypoxic exposure are shown in Table 3. Posthypoxic QTd and QTcd, and the difference in QTd and QTcd values between posthypoxic and prehypoxic periods were correlated with EPT.

Discussion

Our study demonstrated that simulated hypobaric hypoxia changed QTd but did not make a significant change in QTcd.

Although being quite different from clinical hypoxia, it is well known that one of the first responses to hypobaric hypoxia is increased heart rate as a result of carotid and aortic chemoreceptor stimulation (1).

Table 2. Effects of hypoxia on QT dispersion and heart rate in healthy subjects

Ranks	Test Statistics(*)		
	Mean	N	23
	Rank	Chi-Square	21.956
QTdpre, ms	2.65	Df	2
QTdhyp, ms	1.28	Asymp. Sig.	<0.001
QTdpost, ms	2.07	(*) Friedman Test	
	Mean	N	23
	Rank	Chi-Square	4.261
QTcdpre, ms	1.65	Df	2
QTcdhyp, ms	2.13	Asymp. Sig.	0.119
QTcdpost, ms	2.22	(*) Friedman Test	
	Mean	N	23
	Rank	Chi-Square	46.000
HRpre, beats/min	1.00	Df	2
HRhyp, beats/min	3.00	Asymp. Sig.	<0.001
HRpost, beats/min	2.00	(*) Friedman Test	
	Z(**)	Asymp. Sig. (2-tailed)	
QTdhyp – QTdpre	-3.668(†)	<0.001	
QTdpost – QTdpre	-1.995(†)	0.046	
QTdpost – Qtdhyp	-3.151(‡)	0.002	
HRhyp - HRpre	-4.198 (#)	<0.001	
HRpost – Hrpre	-4.199 (#)	<0.001	
HRpost - HRhyp	-4.200(†)	<0.001	

(**) Dunn post test
(†) Based on positive ranks.
(‡) Based on negative ranks.
HRpre- prehypoxic heart rate, HRhyp- heart rate at hypoxic period, HRpost -posthypoxic heart rate, QTdpre- prehypoxic QT interval dispersion, QTdhyp- QT interval dispersion at hypoxic period, QTdpost- posthypoxic QT interval dispersion, QTcdpre- prehypoxic heart rate adjusted QT interval dispersion, QTcdhyp- heart rate adjusted QT interval dispersion at hypoxic period, QTcdpost- posthypoxic heart rate adjusted QT interval dispersion

In a study of baroreflex responses at sea level and at altitude, Knudtson et al. found that a resetting of the baroreflex responses occurred during hypobaric hypoxia, which resolved by oxygen administration. They conclude that the change in the baroreflex responses results from hypoxia; and reduced ambient pressure per se has no influence on the carotid baroreflex control of heart rate (10).

Hypoxia may alter ventricular repolarization and QT dispersion in several ways: hypoxia severity is not the same over different regions of the ventricle; in some regions cellular adenosine triphosphate (ATP) decrease results in activation of ATP sensitive potassium channels; stress under hypoxia may increase beta adrenergic signaling and the resulting cAMP (adenosine monophosphate)-dependent phosphorylation of some potassium channels and calcium channels may shorten the action potential and QT interval (11-13).

On the clinical hypoxia side, Tirlapur et al. studied ECGs of patients with chronic obstructive airway disease. During the night when the patients' basal arterial oxygen saturation fell, their QT interval became longer, as well as producing widespread electrocardiographic changes. The authors proposed that hypoxemia had a direct toxicity on the heart and might have been potentially arrhythmogenic in patients with chronic obstructive airway disease (5).

However, either in real flight or in physiological training sessions hypoxic effect normally does not last long enough to show the same arrhythmogenic effect which can be seen in

Table 3. The correlation of age, EPT, and smoking with QTd, QTcd, HR and the difference of these values before and after hypoxic exposure.

		Age	EPT	Smoking†
	N	23	22	23
EPT, sec	r	-0.478(*)	1	0.270
	p	0.025	.	0.088
Smoking†	r	0.384(*)	0.270	1
	p	0.026	0.088	.
QTd posthypoxic, ms	r	-0.358	0.482(*)	-0.161
	p	0.093	0.023	0.315
QTcd posthypoxic, ms	r	-0.435(*)	0.481(*)	-0.285
	p	0.038	0.023	0.070
Heart Rate posthypoxic, beats/min	r	-0.424(*)	0.279	-0.190
	p	0.044	0.209	0.233
QTd3_1β	r	-0.284	0.512(*)	-0.205
	p	0.189	0.015	0.201
QTcd3_1β	r	-0.335	0.543(**)	-0.225
	p	0.118	0.009	0.152

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
† Kendall tau b correlation coefficient
Difference between hypoxic and prehypoxic
β Difference between posthypoxic and prehypoxic
φ Difference between posthypoxic and hypoxic
EPT- effective performance time
HR- Heart rate
QTd- QT interval dispersion
QTcd- heart rate adjusted QT interval dispersion

clinical cases. Another important difference is, instead of chronic patients we used healthy aviators as our subjects. Our aim in this study was to find out whether or not hypobaric hypoxic exposure resulted in a similar change in QT dispersion.

The period of time from the loss of sufficient oxygen until the subject is no longer able to perform the task in a safe or efficient manner is called EPT. In our subject group, EPT levels were within NATO (9) limits (minimum 1–2 min) with a value of 144.8 ± 36.49 sec. (range 60 sec–200 sec). QT dispersion decreased from prehypoxic level of 64.09 ± 8.4 to hypoxic level of 50.35 ± 11.06 and increased to posthypoxic level of 59.83 ± 9.06 . However, QTcd increased from a baseline level of 71.16 ± 9.82 to 73.17 ± 16.65 because of hypoxia and increased more in the recovery period to 75.48 ± 13.09 . Further analysis of QTd and HR changes between prehypoxic, hypoxic, and posthypoxic intervals showed a significant change in HR between all exposure intervals and in QTd between the hypoxic and prehypoxic interval.

The change observed in HR is a well-known effect of hypoxia. Our results were consistent with the previous findings that HR increases greatly with a hypoxic exposure and decreases after supplemental oxygen is breathed. Although the changes in HR and QTd were significant, QTcd was not. This recalls discussions about the validity and significance of QTd measurements, in which it is strongly advised that the change in QTd might be the result of the change in HR and therefore had to be corrected. Interestingly, in the present study, HR adjusted QTd did not show a significant change. Roukema et al. (6) found similar results in QTd of healthy controls after exercise. Although QTd decreased, QTcd increased slightly after exercise.

Another finding is presence of a significant correlation between EPT and: posthypoxic QTd; posthypoxic QTcd; and the difference between their posthypoxic-prehypoxic values. Since EPT at the same time gives the duration of hypoxic exposure, this correlation may be attributable to hypoxic duration and not necessarily the subject's hypoxia tolerance.

Day et al. (14) reported that, in patients with QT prolongation, QTd differentiated patients with ventricular tachycardia from those without a history of ventricular tachycardia. They proposed that QTcd could be useful as a marker of heterogeneous repolarization and, hence, of ventricular electrical instability.

Several studies have shown that an increased QTd and/or QTcd could be a marker for arrhythmic events, myocardial infarction, and sudden death (15-17). QT dispersion after exercise has been shown to be a useful indicator for identifying those patients with significant cardiac stenosis in the absence of exercise induced ischemic symptoms (18). Roukema et al. (6) reports that QTd is greater at peak exercise in ischemic heart disease patients, as well.

However, not all of the studies have supported this idea. Many authors have pointed out the difficulties of measuring QT, as well as common measurement errors in QT dispersion determination. Automated, as well as manual measurements have also been criticized for having measurement errors (19-21). In a study that examined the value of QTd in a large group of (37,579) male subjects, it was concluded that QTd was a weak predictor for cardiovascular mortality and methodologically limited (22).

Limitations of the study

Major limitations of the present study were interferences on the data recording and difficulties of measuring QT. Interferences on data recording are not anticipated in a patient population. However, during hypobaric chamber training the subjects are not inactive. During the prehypoxic period inside and outside observers explain the signs and symptoms of hypoxia. Also, the subjects have some degree of conversation with each other and with observers. In the hypoxic period besides the increasing heart rate, the subject begins filling out a test page, communicates with the observer, and puts his oxygen mask on and takes it off. All these activities and the running hypobaric chamber system serve as sources of interference. However, the evaluator tried to derive as much data as he could. When it was impossible to acquire QT interval data, the case was excluded.

Conclusion

From the findings of the present study, it is not possible to directly comment on the validity of QTd in revealing arrhythmogenic predisposition of subjects exposed to hypobaric hypoxia. The relation between QT dispersion and hypobaric hypoxic exposure is not clear, particularly when QTd is corrected for the increased heart rate. Our results are not consistent with the previous studies of clinical hypoxia and QT dispersion (2, 5). One possible reason could be the relatively short duration of and the rapid exposure to the hypobaric environment compared to long duration of clinical hypoxia. Another possible cause could be the differences between the subject population since our subjects were a mix of healthy aviators and others were patients with important systemic diseases and possible metabolic disorders.

In conclusion, QTd measurement has not been proven to be a reliable and practical method to show arrhythmia predisposition during a hypobaric hypoxic exposure in healthy individuals.

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