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# Hyperbaric oxygen therapy reduces the risk of QTc interval prolongation in patients with diabetes and hard-to-heal foot ulcers

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ABSTRACT

*Aims:* Heart rate corrected QT (QTc) interval prolongation is a risk factor associated with increased mortality. Hyperbaric oxygen therapy (HBO) has previously been shown to have acute beneficial effects on QTc dispersion. The aim of this study was to evaluate long-term effects of HBO on QTc time in diabetic patients with hard-to-heal foot ulcers.
*Methods:* In a prospective, double-blinded placebo-controlled study, patients were randomized to 40 treatment sessions with either HBO or air (placebo), at 2.5 ATA. Patients fulfilling >35 completed treatment sessions were included in the evaluation.
*Results:* Of the initial 75 patients (38 HBO/37 placebo), two were excluded due to pacemaker use. Baseline characteristics were similar between groups. At the 2-year follow-up, QTc time was significantly shorter in the HBO compared to the placebo group (438 vs. 453 ms, $p < 0.05$). Further, fewer HBO treated patients had a QTc time >450 ms (22 vs. 53 %, $p < 0.02$). This difference seemed to be caused by a significant prolongation of the QTc interval in the placebo group (427 (419–459) at baseline vs. 456 ms (424–469) after 2 years), whereas no significant change was seen in HBO treated patients.
*Conclusions:* HBO treatment might protect against QTc prolongation in this high-risk diabetic population.


## Introduction

Diabetic foot ulcers (DFU) are a major health problem and an important risk factor for morbidity and mortality among people with diabetes mellitus (Brownrigg et al., 2012). This excess mortality has in part, been explained by an increased burden of traditional cardiovascular risk factors, such as hypertension, myocardial infarction, heart failure, renal dysfunction and smoking. However, these risk factors cannot fully explain this excess mortality risk, and lately studies have demonstrated an association between heart rate corrected QT interval (QTc) and all-cause and cardiovascular mortality in the general population (Goldberg et al., 1991; Montanez, Ruskin, Hebert, Lamas, & Hennekens, 2004) as well as in people with diabetes (Christensen et al., 2000; Cox et al., 2014; Fagher & Londahl, 2013). Several factors, i.e. hereditary disorders, coronary heart disease, cardiac autonomic neuropathy and microvascular disease, may all contribute to QTc prolongation (Dekker, Schouten, Klootwijk, Pool, & Kromhout, 1994; Festa, D'Agostino, Rautaharju, Mykkanen, & Haffner, 2000; Macfarlane, McLaughlin, Devine, & Yang, 1994).

Systemic hyperbaric oxygen therapy (HBO) is a medical treatment for hard-to-heal diabetic foot ulcers that has been demonstrated to increase oxygenation in hypoxic tissue and enhance microvascular function (Faglia et al., 1996; Game et al., 2012; Kalani, Jorneskog, Naderi, Lind, & Brismar, 2002; Londahl, Katzman, Nilsson, & Hammarlund, 2010). Further, HBO may also have acute beneficial effects on QT dispersion, as demonstrated in a study by Kardesoglu et al. (2008), and this might have a protective effect on the risk for ventricular arrhythmias and sudden death. Whether HBO therapy has any long-term effect on QTc time has to our knowledge previously not been studied. The aim of this study was to evaluate long-term effects of HBO on QTc time in diabetic patients with multiple complications.

## Materials and methods

Design and procedures of the randomized, double-blinded, placebo-controlled Hyperbaric Oxygen Treatment in Diabetic Patients with Chronic Foot Ulcers (HODFU) study evaluating effects of HBO in patients with chronic diabetic foot ulcers, have been reported in detail previously (Londahl et al., 2006; Londahl et al., 2010). The outcomes for the group receiving HBO were compared with those of the group receiving treatment with hyperbaric air (placebo). The study was performed in an

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ambulatory setting and study treatment was given as an adjunct treatment at a multi disciplinary foot clinic.

Patients provided signed informed consent before any study related procedure was performed. The study was approved by the Ethics Committee, Lund University, and was conducted according the Declaration of Helsinki. It is registered on clinicaltrials.gov, registration number NCT00953186.

All participants in the HODFU study were diabetes patients with at least one foot-ulcer below the ankle, with duration of at least 3 months, treated at a multidisciplinary foot clinic.

Before inclusion patients were evaluated regarding the possibility for vascular surgical intervention and only patients with adequate peripheral circulation or patients without reconstructable peripheral arterial disease were included. Exclusion criteria were presence of contraindication for HBO treatment (Londahl et al., 2006; Londahl et al., 2010), (i.e., severe pulmonary disease, untreated thyrotoxicosis, pneumothorax, ongoing treatment with cisplatin, doxorubicin or disulfiram, women in fertile age not receiving adequate anti-conception therapy) or patients with known malignancy, a history of stroke or myocardial infarction within 30 days, misuse of alcohol or other drugs, acute infection (C-reactive protein >30 mg/l), declined general condition and patients participating in other clinical trials.

Patients were randomized to 40 treatment sessions (90 minutes long, five days a week for eight weeks) with either oxygen or air, at 2.5 absolute atmospheres (ATA) in a hyperbaric chamber. Randomization was stratified according to arterial toe blood pressure ≤ 35 mmHg/>35 mmHg and done in blocks of ten using sealed and numbered opaque envelopes.

All HODFU study participants fulfilling the per-protocol requirement of at least 36 completed study treatment sessions were included for analysis. Patients with a ventricular stimulating pacemaker, making it impossible to calculate a correct QTc interval, were excluded from the present ECG evaluation study.

All patients were evaluated with standard 12-lead resting ECG, using a Siemens ECG machine (Siemens Elema, Solna, Sweden) before randomization and at two-year follow-up visit. The QT interval, defined as the time between the beginning of the Q wave and the end of the T-wave represents the duration of the electrical depolarization and repolarization of the ventricular walls of the myocardium (Rautaharju et al., 2009). Depending on the ECG configuration the end of the T-wave was defined as either the point where the downslope of the T wave cross the isoelectric line or the onset of the U-wave in presence of a T-U junction or the onset of the P-wave in presence of a T-P junction. It was calculated using the validated Sicard 440/740 ECG computer-analysis program (Megacart version 3 V4, 7/2.38/23; Siemens Elema) (Macfarlane et al., 1990; Willems et al., 1991), and was then corrected for heart rate using Bazett's formula to get the QTc interval. In this study QTc prolongation was defined as a QTc value >440 milliseconds (ms) (Algra, Tijssen, Roelandt, Pool, & Lubsen, 1993; Tentolouris et al., 1997). We also evaluated the cut-point of 450 ms, since this alternative level also is used in the literature (Cox et al., 2014; Rautaharju et al., 2009). Two researchers independently evaluated all ECGs in a blinded manner.

Laboratory data were analyzed at the local certified laboratory at Helsingborg hospital. Hyperlipidemia was defined as total cholesterol >5.0 mmol/l, LDL-cholesterol >2.5 mmol/l or on-going prescription of a cholesterol-lowering drug. Estimated glomerular filtration rate (eGFR) was calculated from plasma creatinine level using the modification of diet in renal disease (MDRD) equation (Levey et al., 2006). eGFR <60 ml $min^{-1}$ 1.73 $m^{-2}$ was considered to indicate renal impairment. Nephropathy was considered present in case of a Urine to Albumine Ratio (UACR) >30 mg/g (or 3,5 mg/mmol) on 2 separate occasions. Hypertension was defined as systolic blood pressure ≥140, a diastolic blood pressure ≥90 or prescription of a blood pressure-lowering drug.

Vital statuses of all participants were determined from the Swedish National Death Registry.

*Statistical analysis*

Statistical analyses were performed using SPSS (IBM, IL, USA) version 20. Continuous data are given as median and interquartile range (IQR) and categorical variables as percentages. To assess differences between groups Mann-Whitney U-test were used for continuous variables and Chi-squared test were used for categorical data. For paired comparisons before and after treatment Wilcoxon's signed rank test (continuous variables) and Mc Nemar's test (categorical variables) were performed. A two-tailed p-value <0.05 was considered as statistical significant.

## Results

A total number of 75 patients fulfilled at least 36 completed treatment sessions and were included in the study (Fig. 1); 38 were randomized to HBO and 37 to placebo. Two patients were excluded due to pacemaker use. Baseline characteristics of the remaining 73 patients (38 HBO, 35 placebo), with a median age of 70 (61–77) years, are given in Table 1. There were no differences in traditionally cardiovascular risk factors between groups at baseline and QTc time was similar in patients randomized to HBO (426 (410–440) ms) and placebo (426 (419–458)). Further, no difference was found in prescription pattern of drugs with hypoglycemic action or drugs with known QTc prolonging effect between groups. After two years, follow-up data from the 61 remaining patients were evaluated (Fig. 1). By then, QTc time was significantly shorter in the HBO group as compared to the placebo group, 438 (425–453) vs. 456 (424–469) ms, $p < 0.05$. This difference seemed to be caused by a significant prolongation of the QTc interval in the placebo group (427 ms (419–459) at baseline vs. 456 ms (424–469) after 2 years, whereas no significant change was seen in HBO treated patients (426 ms (412–439) vs. 438 ms (425–453) (Fig. 2).

The proportion of patients with prolonged QTc interval >440 ms and >450 ms were lower two years after HBO (Table 2A) compared to placebo (Table 2B).

## Discussion

People with diabetes are at a higher risk for cardiovascular disease and all-cause mortality compared to a general population and this risk is even higher among patients with a history of a DFU (Brownrigg et al., 2012). However, this excess risk cannot fully be explained by a higher prevalence of cardiovascular disease (CVD) or known CVD risk factors (Regidor et al., 2012). Lately, several studies have indicated the importance of long QTc time, a well-known predictor for malignant arrhythmias and death, as a predictor of all-cause mortality in patients with diabetes (Cox et al., 2014; Fagher & Londahl, 2013). QTc prolongation is more frequently found in patients with diabetes than in non-diabetic patients (Festa et al., 2000). The mechanism behind the higher prevalence of prolonged QTc time among people with diabetes is not fully understood, but possible contributors could be a higher incidence of myocardial infarctions as well as presence of cardiac autonomic neuropathy, factors known to be associated with QTc prolongation (Festa et al., 2000; Tentolouris et al., 1997). Further, it is also known that QT interval is prolonged during hypoglycemia (Landstedt-Hallin, Englund, Adamson, & Lins, 1999).

Early intervention with improved metabolic control reduces the risk of developing microvascular complications, including neuropathy (American, 2014; UKPDS, 1998), but in patients with manifest neuronal dysfunction there is to our knowledge no effective method or treatment to enhance nervous function.

HBO is a therapy used in the management of chronic diabetic foot ulcer management to increase tissue oxygenation and improve wound healing (Faglia et al., 1996; Kalani et al., 2002; Londahl et al.,

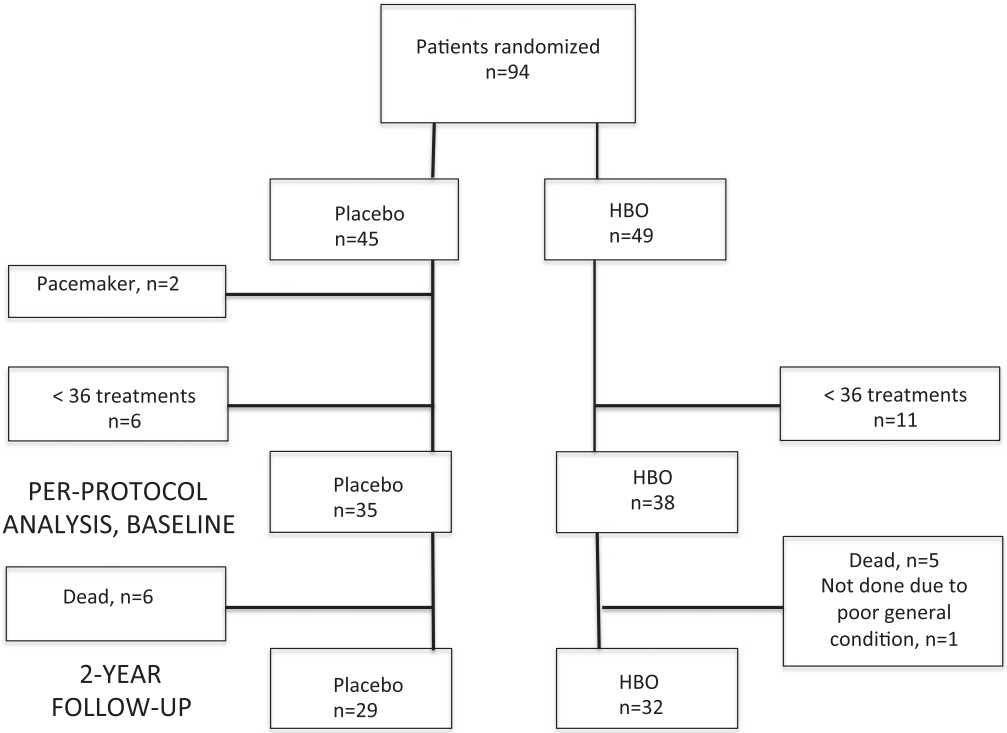


**Fig. 1.** Flow chart of patients included in the HODFU study at start and number of patients included in the per-protocol analysis at baseline and at 2-year follow-up.

2010). Our results indicate that HBO therapy might have a protective long-term effect on QTc prolongation.

**Table 1**
Baseline characteristics and medical treatment of patients fullfilling at least 36 out of 40 HBO/placebo treatment sessions. Categorical data are given as percentages and continuous data as median and interquartil range. p Values <0.1 are given as figures, otherwise n.s. is stated.

| *Baseline characteristics* | HBO | Placebo | p Value |
|---|---|---|---|
| | n = 38 | n = 35 | |
| Age (years) | 67 (55–75) | 71 (64–79) | n.s |
| Sex male/female (%) | 76/24 | 89/11 | n.s |
| Diabetes type 1/2 (%) | 26/74 | 29/71 | n.s |
| Creatinine (μmol/l) | 87(67–140) | 102 (77–141) | n.s |
| eGFR (ml $min^{-1}$ 1.73 $m^{-2}$) | 66 (41–99) | 63 (40–82) | n.s |
| eGFR <60 ml $min^{-1}$ 1.73 $m^{-2}$ (%) | 39 | 40 | n.s |
| QTc time (milliseconds) | 426 (410–440) | 426 (419–458) | n.s |
| Diabetes duration (years) | 23 (10–33) | 20 (16–36) | n.s |
| HbA1c (%) | 7.9 (6.9–8.9) | 8.1 (7.0–9.1) | n.s |
| HbA1c (mmol/mol) | 63 (52–74) | 65 (53–76) | |
| Coronary/ congestive heart disease (%) | 40 | 51 | n.s |
| Stroke (%) | 16 | 14 | n.s |
| Atrial fibrillation (%) | 21 | 34 | n.s |
| Hypertension (%) | 76 | 74 | n.s |
| Hyperlipidemia (%) | 87 | 89 | n.s |
| Nephropathy (%) | 89 | 83 | n.s |
| Dialysis (%) | 5 | 3 | n.s |
| Smoking (ever) (%) | 68 | 69 | n.s |
| Ankle brachial index | 0.76 (0.57–1.13) | 0.79 (0.62–1.01) | n.s |
| Toe blood pressure (mmHg) | 50 (30–85) | 52 (30–75) | n.s |
| Toe blood pressure <35 mmHg (%) | 30 | 33 | n.s |
| TCPO2 (mmHg) | 45 (32–55) | 53 (39–70) | n.s |
| *Medical Treatment (%)* | | | |
| Insulin | 90 | 91 | n.s |
| Metformin | 13 | 14 | n.s |
| Sulfonylurea | 16 | 20 | n.s |
| Quinolones | 8 | 9 | n.s |
| Statins | 66 | 66 | n.s |
| Beta-blockers | 34 | 43 | n.s |

We know from earlier studies that neuronal regulation of the heart progressively decreases with age, a process that seems to be aggravated in patients with diabetes, plausibly due to autonomic neuropathy (Kuo et al., 1999; Macfarlane et al., 1994; Mangoni, Kinirons, Swift, & Jackson, 2003; Masaoka, Lev-Ran, Hill, Vakil, & Hon, 1985). A few previous studies have indicated that HBO could have acute beneficial effects on autonomic nerve function. Kardesoglu et al. demonstrated in a small study of 30 patients with diabetes undergoing HBO therapy for non-healing foot ulcers a significant

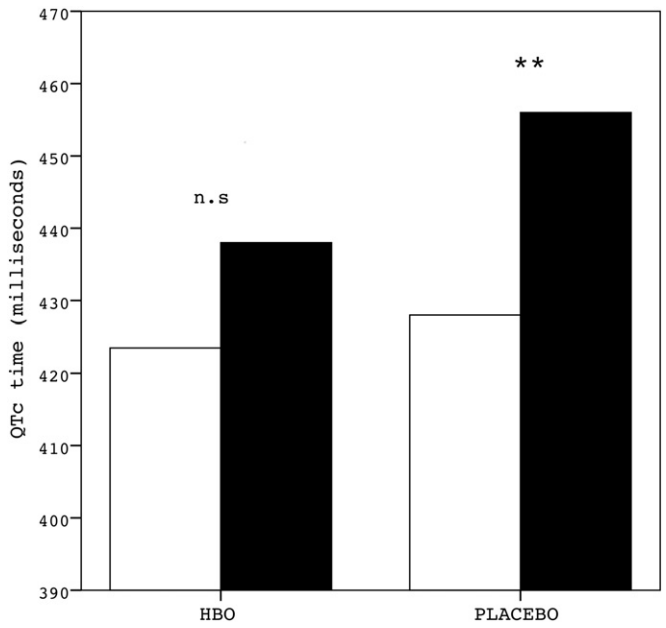


**Fig. 2.** Median QTc-time at baseline (white bars) and at two-year follow-up (black bars) in patients treated with hyperbaric oxygen therapy and placebo, respectively. ** $p < 0.01$.

**Table 2A**
ECG evaluation before and 2 years after treatment with HBO. Categorical data are given as percentages and continuous data as median and interquartile range. p Values <0.1 are given as figures, otherwise n.s. is stated.

| *HBO group, n = 32* | Baseline | 2 year follow-up | p-value |
|---|---|---|---|
| QTc time (milliseconds) | 424 (411–438) | 438 (425–453) | n.s |
| Heart rate (beats/min) | 78 (67–88) | 75 (66–85) | n.s |
| QTc >440 ms (%) | 16 | 38 | 0.065 |
| QTc >450 ms (%) | 16 | 25 | n.s |

decrease in QTc dispersion after 10 HBO sessions (2 weeks), although mean QTc time did not change significantly (Kardesoglu et al., 2008). Further, in a prospective study by Sun et al., evaluating heart rate variability in patients with diabetic foot ulcers undergoing HBO therapy, there was an increase in heart rate variability after 4 weeks of HBO therapy, compared to an age-, sex- and disease-matched control group not receiving HBO therapy, and they suggested that HBO might enhance the sympathovagal balance of the heart (Sun, Yang, & Kuo, 2006). However, Sun et al. did not evaluate QTc time. Further, Lund et al. suggested in a study of 10 healthy volunteers, that HBO treatment immediately influences and increases parasympathetic tone (Lund et al., 1999), with a significant increase in respiratory arrhythmia during HBO. They could however not differentiate whether the effect was caused by oxygen therapy or pressure in this small study, nor did they analyze QTc time. In a Cochrane review from 2011 evaluating effects of adjunctive HBOT in the treatment of acute coronary syndrome, there was some evidence found from small trials to suggest that HBO is associated with a reduction in the risk of death, the volume of damaged muscle, the risk of major adverse coronary events and time to relief from ischaemic pain. However, the number of studies and patients included were small and the author's conclusion was that routine application of HBOT to these patients cannot be justified from this review (Bennett, Lehm, & Jepson, 2011). Our prospective randomized double-blinded placebo-controlled study, evaluating long-term effects of HBO therapy compared to hyperbaric air in patients with diabetes and hard-to-heal foot ulcers indicates that HBO treatment might attenuate QTc interval prolongation. Two years after treatment fewer patients in the HBO, compared to the placebo group, had a prolonged QTc interval and this difference seemed to be related to a progress in QTc time in the placebo group. This prolongation was not seen in patients receiving HBO.

We can only speculate on the mechanisms behind our findings. The etiology of neuropathy in diabetes is not fully understood, but there is strong evidence that impaired blood flow and tissue hypoxia plays a major role in developing neuronal dysfunction (Cameron, Eaton, Cotter, & Tesfaye, 2001). The fact that microvascular changes are involved in diabetic neuropathy was first recognized in a human biopsy study by Fagerberg in 1959, demonstrating structural changes such as thickening and hyalinization of the small interneuronal vessels walls from people with neuropathy (Fagerberg, 1959). These changes, caused by capillary basal membrane thickening, pericyte degeneration and endothelial cell hyperplasia, were in a study by Malik et al. markedly increased in nerve capillaries compared to skin capillaries and did strongly correlate with the degree of clinical signs (Malik et al., 1989).

**Table 2B**
Electrogardiographic data before and after treatment with placebo. Categorical data are given as percentages and continuous data as median and interquartil range. p Values <0.1 are given as figures, otherwise n.s. is stated.

| *Placebo group, n = 29* | Baseline | 2 year follow-up | p Value |
|---|---|---|---|
| QTc time (milliseconds) | 426 (419–458) | 456 (424–469) | 0.010 |
| Heart rate (beats/min) | 74 (62–80) | 73 (65–85) | n.s |
| QTc >440 ms (%) | 31 | 59 | 0.008 |
| QTc >450 ms (%) | 28 | 52 | 0.016 |

The plausible importance of hypoxia as a major contributor to neuropathy can be implicated as non-diabetic patients with chronic hypoxia developing neuropathy with neuropathological changes similar to those seen in diabetes (Malik et al., 1990). In a study by Carrington et al., reduced motor nerve conduction velocity was both associated with decreased transcutaneous oxygen levels ($TcPO_2$) and increased mortality, suggesting a similar etiological mechanism between neuropathy and hypoxia (Carrington et al., 2002). Thus, improved microcirculation might preserve neural function, including cardiac autonomic function, thereby avoiding further detoriation of the QTc-time. Also, improved microcirculation in cardiac tissue might per se be involved.

### *Strengths and limitations*

There are both strengths and limitations in our study. Despite the limited number of patients, our data are reasonably robust as the study is designed as a randomized double-blinded placebo controlled study. We can conclude that the effect is not related to the hyperbaric pressure per se, since there was a significant difference in progress of the QTc interval between the study groups. The low number of participants might enhance the influence of other potential causes of QTc prolongation on our results. However, baseline characteristics were similar and we did not find any difference in prescription patterns of common drugs with a known QTs prolonging action (for instance beta-blockers and quinolones) between groups. We cannot answer the question whether HBO has any beneficial effects on peripheral neuropathy, since we didn't collect quantitative data on this, but our study might provide a clinical basis for larger studies in the future to answer this question and to confirm our present findings.

Despite these limitations, our study is to our knowledge the first to demonstrate that HBO therapy might have a protective effect on long-term progression of the QTc interval among patients with diabetes.

## Conclusions

In conclusion, HBO seems to have a protective effect on QTc prolongation in patients with diabetes and chronic foot ulcers.

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## References

Algra, A., Tijssen, J. G., Roelandt, J. R., Pool, J., & Lubsen, J. (1993). Contribution of the 24 hour electrocardiogram to the prediction of sudden coronary death. *Br Heart J*, *70*, 421–427.

American, Diabetes A. (2014). Standards of medical care in diabetes-2014. *Diabetes Care*, *37*(Suppl. 1), S14–S80.

Bennett, M. H., Lehm, J. P., & Jepson, N. (2011). Hyperbaric oxygen therapy for acute coronary syndrome. *Cochrane Database Syst Rev*, CD004818.

Brownrigg, J. R., Davey, J., Holt, P. J., Davis, W. A., Thompson, M. M., Ray, K. K., et al. (2012). The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. *Diabetologia*, *55*, 2906–2912.

Cameron, N. E., Eaton, S. E., Cotter, M. A., & Tesfaye, S. (2001). Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia*, *44*, 1973–1988.

Carrington, A. L., Shaw, J. E., Van Schie, C. H., Abbott, C. A., Vileikyte, L., & Boulton, A. J. (2002). Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? *Diabetes Care*, *25*, 2010–2015.

Christensen, P. K., Gall, M. A., Major-Pedersen, A., Sato, A., Rossing, P., Breum, L., et al. (2000). QTc interval length and QT dispersion as predictors of mortality in patients with non-insulin-dependent diabetes. *Scand J Clin Lab Invest*, *60*, 323–332.

Cox, A. J., Azeem, A., Yeboah, J., Soliman, E. Z., Aggarwal, S. R., Bertoni, A. G., et al. (2014). Heart rate-corrected QT interval is an independent predictor of all-cause and cardiovascular mortality in individuals with type 2 diabetes: the Diabetes Heart Study. *Diabetes Care*, *37*, 1454–1461.

Dekker, J. M., Schouten, E. G., Klootwijk, P., Pool, J., & Kromhout, D. (1994). Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. *Circulation*, *90*, 779–785.

Fagerberg, S. E. (1959). Diabetic neuropathy: a clinical and histological study on the significance of vascular affections. *Acta medica Scandinavica. Supplementum*, *345*, 1–97.

Fagher, K., & Londahl, M. (2013). The impact of metabolic control and QTc prolongation on all-cause mortality in patients with type 2 diabetes and foot ulcers. *Diabetologia*, *56*, 1140–1147.

Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., et al. (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care*, *19*, 1338–1343.

Festa, A., D'Agostino, R., Jr., Rautaharju, P., Mykkanen, L., & Haffner, S. M. (2000). Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. *Am J Cardiol*, *86*, 1117–1122.

Game, F. L., Hinchliffe, R. J., Apelqvist, J., Armstrong, D. G., Bakker, K., Hartemann, A., et al. (2012). A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*, *28*(Suppl. 1), 119–141.

Goldberg, R. J., Bengtson, J., Chen, Z. Y., Anderson, K. M., Locati, E., & Levy, D. (1991). Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). *Am J Cardiol*, *67*, 55–58.

Kalani, M., Jorneskog, G., Naderi, N., Lind, F., & Brismar, K. (2002). Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. *Journal o8 Diabetes Complications*, *16*, 153–158.

Kardesoglu, E., Aparci, M., Uzun, G., Suleymanoglu, S., Uz, O., Onem, Y., et al. (2008). Hyperbaric oxygen therapy decreases QT dispersion in diabetic patients. *Tohoku J Exp Med*, *215*, 113–117.

Kuo, T. B., Lin, T., Yang, C. C., Li, C. L., Chen, C. F., & Chou, P. (1999). Effect of aging on gender differences in neural control of heart rate. *Am J Physiol*, *277*, H2233–H2239.

Landstedt-Hallin, L., Englund, A., Adamson, U., & Lins, P. E. (1999). Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. *J Intern Med*, *246*, 299–307.

Levey, A. S., Coresh, J., Greene, T., Stevens, L. A., Zhang, Y. L., Hendriksen, S., et al. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*, *145*, 247–254.

Londahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care*, *33*, 998–1003.

Londahl, M., Katzman, P., Nilsson, A., Hammarlund, C., Sellman, A., Wykman, A., et al. (2006). A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. *J Wound Care*, *15*, 457–459.

Lund, V. E., Kentala, E., Scheinin, H., Klossner, J., Helenius, H., Sariola-Heinonen, K., et al. (1999). Heart rate variability in healthy volunteers during normobaric and hyperbaric hyperoxia. *Acta Physiol Scand*, *167*, 29–35.

Macfarlane, P. W., Devine, B., Latif, S., McLaughlin, S., Shoat, D. B., & Watts, M. P. (1990). Methodology of ECG interpretation in the Glasgow program. *Methods Inf Med*, *29*, 354–361.

Macfarlane, P. W., McLaughlin, S. C., Devine, B., & Yang, T. F. (1994). Effects of age, sex, and race on ECG interval measurements. *J Electrocardiol*, *27*, 14–19 (Suppl.).

Malik, R. A., Masson, E. A., Sharma, A. K., Lye, R. H., Ah-See, A. K., Compton, A. M., et al. (1990). Hypoxic neuropathy: relevance to human diabetic neuropathy. *Diabetologia*, *33*, 311–318.

Malik, R. A., Newrick, P. G., Sharma, A. K., Jennings, A., Ah-See, A. K., Mayhew, T. M., et al. (1989). Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. *Diabetologia*, *32*, 92–102.

Mangoni, A. A., Kinirons, M. T., Swift, C. G., & Jackson, S. H. (2003). Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis. *Age Ageing*, *32*, 326–331.

Masaoka, S., Lev-Ran, A., Hill, L. R., Vakil, G., & Hon, E. H. (1985). Heart rate variability in diabetes: relationship to age and duration of the disease. *Diabetes Care*, *8*, 64–68.

Montanez, A., Ruskin, J. N., Hebert, P. R., Lamas, G. A., & Hennekens, C. H. (2004). Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Intern Med*, *164*, 943–948.

Rautaharju, P. M., Surawicz, B., Gettes, L. S., Bailey, J. J., Childers, R., Deal, B. J., et al. (2009). AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*, *53*, 982–991.

Regidor, E., Franch, J., Segui, M., Serrano, R., Rodriguez-Artalejo, F., & Artola, S. (2012). Traditional risk factors alone could not explain the excess mortality in patients with diabetes: a national cohort study of older Spanish adults. *Diabetes Care*, *35*, 2503–2509.

Sun, T. B., Yang, C. C., & Kuo, T. B. (2006). Effect of hyperbaric oxygen on cardiac neural regulation in diabetic individuals with foot complications. *Diabet Med*, *23*, 360–366.

Tentolouris, N., Katsilambros, N., Papazachos, G., Papadogiannis, D., Linos, A., Stamboulis, E., et al. (1997). Corrected QT interval in relation to the severity of diabetic autonomic neuropathy. *European Journal of Clinical Investigation*, *27*, 1049–1054.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, *352*(1998)., 837–853.

Willems, J. L., Abreu-Lima, C., Arnaud, P., van Bemmel, J. H., Brohet, C., Degani, R., et al. (1991). The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med*, *325*, 1767–1773.