

The effect of intensive diabetes treatment on resting heart rate in type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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Abbreviations:

DCCT: Diabetes Control and Complications Trial
EDIC: Epidemiology of Diabetes Interventions and Complications Study
RHR: resting heart rate
SBP: systolic blood pressure

ABSTRACT

Objective: Cardiovascular disease is a major cause of morbidity and mortality in individuals with type 1 diabetes. Resting heart rate (RHR) is a risk factor for cardiovascular disease in the general population and case-control studies have reported a higher RHR in individuals with type 1 diabetes. In individuals with type 1 diabetes there is a positive correlation between HbA1c and RHR; however, no prospective studies have examined whether a causal relationship exists between HbA1c and RHR. We hypothesized that there is an effect of intensive diabetes treatment, aimed at achieving normal HbA1c levels, on RHR in individuals with type 1 diabetes.

Research Design and Methods: 1,441 individuals with type 1 diabetes who participated in the Diabetes Control and Complications Trial (DCCT) had their RHR measured biennially by ECG during the DCCT, and annually for ten years during the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study.

Results: During the DCCT, intensive treatment was associated with lower mean RHR than conventional treatment, both in adolescents (69.0 vs. 72.0 beats per minute; 95% CI 62.8-75.7 and 65.7-78.9, respectively, $p=0.013$) and adults (66.8 vs. 68.2; 95% CI 65.3-68.4 and 66.6-69.8, respectively, $p=0.0014$). During follow-up in EDIC, the difference in RHR between the treatment groups persisted for at least 10 years ($p<0.0001$).

Conclusions: Compared with conventional therapy, intensive diabetes management is associated with lower RHR in type 1 diabetes. The lower RHR with intensive therapy may explain, in part, its effect in reducing cardiovascular disease, recently demonstrated in type 1 diabetes.

Cardiovascular disease is the major cause of mortality in individuals with diabetes (1, 2) and consumes the majority of the health care expenditures attributable to diabetes in the US (3). Resting heart rate (RHR) is a risk factor for cardiovascular disease and mortality in the general population (4-13). For example, after adjustment for other risk factors the odds ratio for all cause-mortality during 36 years of follow-up of individuals with hypertension in the Framingham Heart Study was 1.98 (95% CI 1.52-2.59) for males and 1.87 (95%CI 1.37-2.56) for females for each heart rate increment of 40 beats/min (8). Case-control studies have reported a higher RHR in individuals with type 1 diabetes compared to age-matched controls (14). In a study of 44 monozygotic twins discordant for type 1 diabetes (with a mean duration of type 1 diabetes of 14 years), RHR in the type 1 diabetes twin was on average 8 beats per minute higher than in the non-diabetic co-twin ($p < 0.0005$) (15). Cross-sectional studies have reported an association between HbA1c and RHR in individuals with type 1 diabetes, with poor glycemic control being positively associated with RHR in a study of 148 children with type 1 diabetes (16). However, there was no association between change in HbA1c and change in RHR over a one year follow-up (16). These studies suggest that type 1 diabetes results in higher RHR. Further, the correlations observed with glycemia suggest that the level of metabolic control plays an important role in influencing RHR. However, there have been no prospective studies of intensive diabetes treatment (focused on improved glycemic control) on RHR in individuals with type 1 diabetes. We have examined whether intensive diabetes treatment, aimed at achieving glycemic levels as close to the non-diabetic range as possible, affects RHR using data collected during the Diabetes Control and Complications Trial (DCCT) and its

follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC). Specifically, we hypothesized that: (i) RHR at DCCT baseline is associated with the duration of type 1 diabetes prior to entry into the study and glycemic control; (ii) there is an effect of intensive therapy, compared with conventional therapy, during DCCT on RHR; (iii) any demonstrable effect of intensive therapy on RHR will be explained by differences in glycemic control between intensive and conventional therapy; (iv) any effect of intensive vs. conventional therapy on RHR during the DCCT will continue during the EDIC follow-up, supporting the metabolic memory phenomenon that has been demonstrated for other complications.

RESEARCH DESIGN AND METHODS

Subjects

The inclusion and exclusion criteria for the DCCT and the treatment protocol have been described in detail (17). Briefly, 1,441 subjects with type 1 diabetes between 13 and 39 years of age were recruited into the DCCT between 1983 and 1989. The primary prevention cohort consisted of 726 subjects with no retinopathy, a urinary albumin excretion rate < 40 mg per 24 hours and diabetes duration 1 to 5 years. The secondary intervention cohort consisted of 715 subjects who had non-proliferative retinopathy, urinary albumin excretion rate ≤ 200 mg per 24 hours and diabetes duration of 1 to 15 years. As part of the screening for the DCCT, individuals were excluded if they had hypertension (defined by systolic ≥ 140 or diastolic ≥ 90 mm Hg), a history of symptomatic ischemic heart disease, or the presence of major ECG abnormalities suggestive of coronary heart disease, specifically myocardial infarction (17). Subjects in the primary prevention and secondary intervention cohorts were randomly assigned to either intensive or

conventional treatment arms, and assessed for complications at frequent follow-up visits. The intensive and conventional treatment groups maintained a separation of median HbA1c level of about 2 percentage points throughout the follow-up period (7.1% vs 9.0%; $p < 0.001$). Baseline characteristics of participants have been provided elsewhere (15). The DCCT was terminated in 1993, after a mean duration of follow-up of 6.5 years and one year ahead of schedule, when the principal study questions concerning treatment effects had been answered. In 1994, 1,375 DCCT subjects (96% of the surviving cohort), 687 from the intensive arm and 688 from the conventional arm, agreed to participate in the EDIC follow-up study which included annual examinations measuring diabetic complications (18). Glycosylated hemoglobin (HbA1c) was measured by high performance liquid chromatography in a central laboratory at baseline and then quarterly during the DCCT and annually during EDIC (19). For the analysis at DCCT baseline and during DCCT treatment, individuals < 18 years of age at DCCT baseline ($n=195$) (20) were analyzed separately from those ≥ 18 years because of a negative relationship between age and RHR during adolescence. All subjects were analyzed together during EDIC since all were > 18 years at the start of EDIC.

Resting heart rate

Twelve lead resting ECGs were obtained at DCCT baseline, every 2 years (up to 8 years) during DCCT, at DCCT closeout, and annually during EDIC, according to the DCCT Manual of Operations (Chapter 18) (15). ECGs were obtained by certified technician or research nurse at 29 clinics and read according to the revised Minnesota Code (21) (22) at the Central ECG Reading Unit (University of Minnesota: under the direction of Dr. Richard S. Crow). In brief, at least one full minute of ECG tracing was obtained

consisting of five seconds of each of the leads (I, II, III, aVR, aVL, aVF, V1-V6). An internal quality control surveillance program entailed the duplicate masked evaluation of 10% of ECGs and was used to estimate the reproducibility of the grading system. During EDIC, 90% of ECGs scheduled were obtained, and 95% of those were coded as having no technical difficulties for Minnesota scoring. The coding procedure involved duplicate independent coding and tabulation with adjudication of disagreed codes by the supervisor. There were four levels of quality control procedures used: 1) training and repeat testing of coders; 2) daily inter-coder independent comparisons; 3) internal re-circulation of records; and 4) errors detected during serial comparison. RHR was obtained by measuring 3 complete R-R intervals from lead I to the nearest 0.5 mm and then converted to rate per minute (21). RHR from ECGs with the following Minnesota codes (atrial fibrillation (8-3-1); atrial flutter (8-3-2); supraventricular rhythm (8-4-1); second degree AV block (6-2-1/2); ventricular rhythm (8-2-2); and electronic pacemaker (6-8)) were considered missing for the analysis.

Statistical

General linear models were used for the analysis of DCCT baseline for patients < 18 years, while generalized estimating equations were applied for subjects ≥ 18 years because of the violation of normality of RHR. For the repeated measures of RHR during DCCT and EDIC, analyses were performed using mixed linear models under the intent-to-treat assumption. All analyses used $\ln(\text{RHR})$. The DCCT treatment analysis adjusted for DCCT baseline RHR: the EDIC analysis adjusted for DCCT closeout RHR as EDIC baseline.

$\ln(\text{RHR})$ was regressed against variables selected from the literature (23, 24, 25, 26) measured at DCCT baseline, including: age, sex, duration of type 1

diabetes, eligibility HbA1c, clinic, smoking status, systolic blood pressure (SBP), triglycerides, HDL-cholesterol, stimulated C-peptide, ethnicity (white, non-white), body mass index (BMI), alcohol (yes/no), caffeine consumption, exercise, clinical neuropathy classification (27, 28), R-R interval variation, Valsalva ratio (29), DCCT treatment group, and cohort. Medication use (ACE inhibitor, β -blockers, calcium-channel antagonists) reported at each year during EDIC was included in the EDIC analysis as time dependent covariates. Medication use was not reported during the DCCT.

In the multivariate analyses, variables with $p < 0.05$ were considered significant and are mentioned in the results section: non-significant variables are not mentioned unless relevant. Interactions were not included in the models, except to determine whether treatment effects differed over time and to calculate the corresponding least square means. The assumptions of normality and constant variance were not violated based on the distribution of residuals and the residual vs. predicted plot, respectively. To determine whether the treatment effect in DCCT could be explained by differences in HbA1c, updated mean $\ln(\text{HbA1c})$ was calculated during DCCT and used as a time dependent covariate. For the EDIC analysis, the mean DCCT $\ln(\text{HbA1c})$ for all the visits during the DCCT was calculated for each individual, and the length of time in DCCT was included. The difference in the sum of squares regression for treatment groups adjusted and unadjusted for mean $\ln(\text{HbA1c})$ as described above were used to calculate the fraction of the treatment effect explained by HbA1c (30). Smoking status and exercise status reported at each year during the DCCT and EDIC were added to the DCCT and EDIC analyses as time dependent covariates, respectively, to determine if the treatment effect could be explained by the addition of these variables. RR-variation at DCCT closeout was also

added to the EDIC analysis, in addition to HbA1c, smoking status and exercise status to determine if it provided any additional explanation of the treatment effect. The treatment effect explained by these additional variables in the DCCT and EDIC analyses were calculated similarly to HbA1c as mentioned above. The procedure of Holm (31) was used to correct for multiple comparisons. All statistical analyses were performed using SAS V 8.2 (Cary, NC).

RESULTS

Average duration in DCCT was 7.0 ± 2.0 (mean \pm SD) years for subjects < 18 years of age and 6.0 ± 1.6 years for those ≥ 18 years. DCCT baseline variables are provided in Table 1 in the Appendix, separately by age group and assigned treatment. Significant differences between treatment groups were found in HDL cholesterol ($p=0.0110$) for adolescents; and in stimulated C-peptide ($p=0.0299$) and systolic blood pressure ($p=0.0048$) for adults at DCCT baseline. All the other variables listed in Table 1 were similar between treatment groups. The number of subjects, RHR measures in each time period, and the unadjusted RHR values by categorical covariates at DCCT baseline, during DCCT and during EDIC are provided in Table 2 in the Appendix, again with the values during DCCT provided separately for subjects < 18 and ≥ 18 years of age. The unadjusted RHR values by medication usage are provided in Table 3 in the Appendix. The unadjusted RHR values by time during DCCT and EDIC are provided in Tables 4 and Table 5 in the Appendix, respectively. The least square means for the treatment groups over time during the DCCT (provided separately for subjects < 18 and ≥ 18 years of age) and during EDIC are presented in Figure 1. There were a total of 18,960 RHR measures obtained throughout the study.

DCCT Baseline analysis for Subjects <18 years of age

General linear models were used for the analysis of DCCT baseline for patients <18 years. F-tests were used to determine statistical significance. At DCCT baseline, RHR was significantly associated with exercise ($p=0.027$). Univariate t-tests were performed to determine which exercise levels differ from one another using a Holm adjustment; however, a significant difference could not be detected at the univariate level, which may be due to the small sample size. RHR was negatively associated with RR variation ($p=0.0062$) and positively associated with SBP ($p=0.0010$). Contrary to one of our hypotheses, there was no significant association between DCCT baseline RHR and HbA1c ($p=0.11$) or type 1 diabetes duration ($p=0.59$). There was no significant difference in RHR by treatment group at DCCT baseline ($p=0.15$). The relatively small size of the <18 year old cohort may have limited our ability to establish a relationship with some of the variables examined.

DCCT Baseline analysis for Subjects ≥ 18 years of age

Generalized estimating equations were applied for subjects ≥ 18 years because of the violation of normality of RHR. Score Chi-square tests were used to determine statistical significance. At DCCT baseline, RHR was significantly higher in females than males ($p<0.0001$), higher in smokers ($p=0.0071$), lower in those who drank alcohol ($p=0.040$) and lower in those who reported hard or strenuous exercise compared to moderate exercise (overall $\chi^2=12.94$, 3df, $p=0.0048$). RHR was positively associated with triglycerides ($p=0.0004$), HbA1c ($p=0.0019$), duration of type 1 diabetes ($p=0.0007$), and SBP ($p=0.0022$), while negatively associated with RR variation ($p<0.0001$). Again, there was no significant difference between treatment groups ($p=0.82$).

Analyses of RHR during DCCT for subjects <18 years of age at baseline

Mixed linear models under the intent-to-treat assumption were used for RHR during DCCT. During the DCCT, RHR was significantly higher in the group randomly assigned to conventional than in the group assigned intensive therapy ($p=0.013$, least-squares mean =72.0 (95% confidence interval (CI) 65.7-78.9) and 69.0 (62.8-75.7), respectively). RHR was also higher in females than males ($p=0.0004$), and increased over time ($p=0.0001$). However, the difference between treatment groups did not change over time. DCCT RHR was significantly positively associated with both DCCT baseline RHR ($p<0.0001$) and caffeine consumption ($p=0.028$). There was no significant association between RHR during DCCT and baseline HbA1c ($p=0.44$).

Analyses of RHR during DCCT for subjects ≥ 18 years of age at baseline

As in the younger age group, subjects randomly assigned to conventional therapy had higher RHR than those receiving intensive therapy ($p=0.0014$, least-squares mean =68.2 (95%CI 66.6-69.8) and 66.8 (65.3-68.4), respectively). RHR increased over time during DCCT ($p<0.0001$). Females had higher RHR than males ($p<0.0001$), as did those in the secondary compared to primary cohort ($p=0.010$). DCCT RHR was also positively associated with the following DCCT baseline variables: RHR ($p<0.0001$), HbA1c ($p=0.0001$), stimulated C-peptide ($p=0.040$), and SBP ($p=0.0008$).

In both age groups, including the updated mean $\ln(\text{HbA1c})$ during DCCT in the model resulted in the treatment effect on RHR no longer being significant ($p=0.61$ for <18 year old group, $p=0.075$ for ≥ 18 group). This longitudinal measure of HbA1c explained 96% of the treatment effect on RHR in the <18 year old group, and 69% of the treatment

effect in the ≥ 18 group. When smoking status and exercise status were added to the model as time dependent covariates, neither variable was found to be statistically significant for the < 18 group ($p=0.38$ and $p=0.11$), respectively. However, for the ≥ 18 group, exercise status was statistically significant ($p=0.002$) and the p -value for the treatment effect increased to $p=0.29$ compared to $p=0.08$ when the longitudinal measure of HbA1c was included alone. Those who reported hard exercise had a statistically lower resting heart rate than those who reported mild ($p=0.001$) or moderate ($p=0.002$) exercise. The longitudinal measure of HbA1c and exercise status together explained 90% of the treatment effect on RHR in the ≥ 18 group.

Analysis of RHR during EDIC

Both age groups were analyzed together during follow-up in EDIC because all were > 18 years. $\ln(\text{RHR})$ during EDIC continued to be significantly higher in those who were randomly assigned to conventional compared to intensive treatment group in the DCCT ($p<0.0001$, least-squares mean= 68.0 (95%CI 66.5-69.6) and 66.6 (65.2-68.1), respectively). It also was higher in females than males ($p=0.024$), and was higher in smokers ($p=0.0051$). EDIC RHR was positively associated with DCCT closeout RHR ($p<0.0001$), and variables measured at DCCT baseline, including triglycerides ($p=0.050$), HbA1c ($p=0.0001$), BMI ($p=0.033$), systolic blood pressure ($p=0.045$) and negatively with RR variation ($p=0.024$) and age ($p<0.0001$). RHR differed over time during EDIC ($p<0.0001$); however, the former treatment effect did not change over time. Specifically, significant former DCCT treatment effects were observed throughout EDIC: the difference in RHR between intensive and conventional treatment remained at years 1 through 4 ($p=0.001$); years 5 through 9 ($p<0.005$); and at year 10 ($p<0.01$). Of the 12,844 RHR measures

during EDIC, 2,336 (18%) were measured while an individual was taking an ACE inhibitor, 208 (2%) during β -blocker treatment, and 384 (3%) while receiving a calcium-channel blocker. Of these medications, only treatment with beta-blockers showed a significant association with RHR, with a lower RHR when they were being taken ($p<0.0001$).

When the mean value of all $\ln(\text{HbA1c})$ levels in DCCT was included in the mixed model, along with duration in DCCT, the former DCCT treatment groups still had significantly different RHR during EDIC ($p=0.0062$). In this model, 53% of the former DCCT treatment effect on RHR was explained by the mean DCCT $\ln(\text{HbA1c})$. Further, after the addition of the DCCT closeout RR variation, and the time dependent covariates for smoking status and exercise status to the prior model, 69% of the treatment effect was explained by the DCCT $\ln(\text{HbA1c})$ ($p<0.0001$), DCCT closeout RR variation ($p=0.0008$), smoking status ($p=0.0007$) and exercise status ($p<0.0001$). Those who reported mild exercise had a statistically higher resting heart rate than those who reported moderate ($p=0.0006$), hard ($p=0.0035$) or strenuous ($p=0.029$) exercise. RHR was also higher in smokers and negatively associated with DCCT closeout RR variation. Furthermore, the DCCT treatment group effect still remained significant ($p=0.0228$).

CONCLUSIONS

The major results of this study support and extend the association of diabetes with faster RHR and of higher levels of glycemia with RHR previously demonstrated in cross-sectional studies. A significant treatment effect of intensive therapy on RHR occurred as early as two years after the initiation of DCCT interventions (the earliest measure after randomization) in both age groups and continued through DCCT closeout. HbA1c

during DCCT accounted for 96% of the treatment group effect in the <18 year old age group, and 69% of the effect in those ≥ 18 years of age at baseline. When HbA1c levels were included in the analyses, the treatment effects in both age groups were no longer significant. When the time dependent covariates for smoking status and exercise status were included in both models, exercise status was statistically significant ($p=0.0021$) for the ≥ 18 group only in addition to HbA1c. HbA1c and exercise together explained 90% of the treatment group effect in those ≥ 18 years of age at baseline.

After DCCT closeout, the former intensive therapy was associated with significantly lower RHR up to EDIC year 10, consistent with long-term benefits of former intensive therapy, known as imprinting or metabolic memory (32, 33). Although inclusion of the overall mean $\ln(\text{HbA1c})$ during DCCT accounted for 53% of the former treatment group differences during EDIC, the treatment groups remained significantly different ($p=0.0062$), implying that mechanisms other than those strongly correlated with mean HbA1c during DCCT account for at least part of the imprinting phenomena. Further, after the addition of the DCCT closeout RR variation, and the time dependent covariates for smoking status and exercise status to the prior model, 69% of the treatment effect was explained by the DCCT $\ln(\text{HbA1c})$ ($p<0.0001$), DCCT closeout RR variation ($p=0.0008$), smoking status ($p=0.0007$) and exercise status ($p<0.0001$) and the treatment effect continued to remain statistically significant ($p=0.0228$). In individuals ≥ 18 years at DCCT baseline, baseline RHR was positively associated with eligibility HbA1c, diabetes duration, triglycerides, and significantly different between genders; however these associations were not observed in individuals <18 years of age at DCCT baseline. Other variables, such as exercise level, RR variation and systolic

blood pressure were associated with RHR in both age groups at baseline.

The mechanisms by which intensive diabetes therapy results in lower RHR compared with conventional therapy are not clear, but include at least in part glycemic exposure or measures strongly correlated with it. It is possible that the higher RHR in individuals with conventional treatment of type 1 diabetes is a reflex hemodynamic response to reduced stroke volume. This could result from either diastolic dysfunction or change in blood volume. However, no direct measures of diastolic function or blood volume have been made in this study. Previous analyses have shown that there was no significant effect of intensive treatment on diastolic blood pressure during DCCT in either cohort. For systolic blood pressure, individuals randomized to intensive therapy had significantly higher blood pressure than conventionally treated individuals in the primary ($p<0.01$) but not in the secondary cohort ($p=0.62$) (34). Alternatively, there may be direct mechanisms by which glycemic exposure results in the changes in RHR, such as the effects of intensive therapy on the autonomic nervous system demonstrated during DCCT (29). However, when RR variation measured at DCCT closeout was included in the model for the analysis of RHR during EDIC, the former treatment group effect remained significant, implying that there are other mechanisms apart from direct effects on the autonomic nervous system (as measured by RR variation) that result in persistence of the treatment effect on RHR. Studies have reported positive associations between fasting insulin levels and RHR (35, 36). Although insulin levels were not measured during the DCCT, insulin doses were significantly higher in the intensive than conventional treatment groups (37), and would be predicted to reduce the differences in RHR noted between the intensive and conventional treatment groups.

No studies have addressed whether RHR is a risk factor for cardiovascular disease or mortality in individuals with type 1 diabetes although the effect in the general population is well established (see Introduction). Also, the clinical relevance of a 2-3 beat/min difference in RHR is unknown. The results of the current study lead to a series of questions including whether RHR is associated with sub-clinical measures of cardiovascular disease (34, 38). In the Pittsburgh Epidemiology of Diabetes Complications Study, RHR at baseline was significantly higher in those who progressed to overt nephropathy, compared to those who did not progress (82 ± 12 , 73 ± 10 (mean \pm SD) respectively, $p=0.002$) (39). Recent DCCT/EDIC results have shown that subjects who experienced hard CVD outcomes ($n=83$) had borderline higher RHR at DCCT baseline than those without CVD ($n=1358$), 70 ± 12 vs 68 ± 11 , ($p=0.073$) (40). The cumulative difference in the covariate-adjusted heart beats between an individual randomized to intensive vs. conventional therapy with

duration in DCCT of 6 years and 10 years in EDIC results in 7.3 fewer months of heart beats for individuals ≥ 18 and 7.6 for those < 18 years.

In summary, the DCCT/EDIC study has shown that prior intensive treatment during the DCCT period, compared to conventional treatment, results in a slightly though significantly decreased resting heart rate for up to 10 years of follow-up after the randomized treatment difference in HbA1c had dissipated. This effect is largely explained by the difference in HbA1c that existed during the DCCT. Whether the lower resting heart rate per se confers a benefit in terms of future CVD events or mortality remains to be seen, as follow-up of the cohort continues.

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Figure 1 Legend.

Least-squares means and 95% confidence intervals for resting heart rate separately by treatment. **A:** during DCCT for subjects <18 years, **B.** during DCCT for subjects ≥ 18 years, **C.** during EDIC for all subjects. Solid circles indicate intensive treatment during DCCT; open circles indicate conventional treatment during DCCT. Details of the models used at DCCT baseline, during DCCT treatment, and during EDIC are provided in the Methods. For the DCCT, the difference in treatment groups was statistically significant; (<18 years ($p=0.013$), ≥ 18 years ($p=0.0014$)) and the treatment group by time interaction was not statistically significant (<18 years ($p=0.19$); ≥ 18 years ($p=0.10$)). For EDIC, the difference between treatment groups was statistically significant; years 1 through 4 ($p=0.001$); years 5 through 9 ($p<0.005$); and at year 10 ($p<0.01$).

