Risk of Aborted Cardiac Arrest or Sudden Cardiac Death During Adolescence in the Long-QT Syndrome

Jenny B. Hobbs, MD
Derick R. Peterson, PhD
Arthur J. Moss, MD
Scott McNitt, MS
Wojciech Zareba, MD, PhD
Ilan Goldenberg, MD
Ming Qi, PhD
Jennifer L. Robinson, MS
Andrew J. Sauer, BS
Michael J. Ackerman, MD, PhD
Jesaja Benhorin, MD
Elizabeth S. Kaufman, MD
Emanuela H. Locati, MD, PhD
Carlo Napolitano, MD
Silvia G. Priori, MD, PhD
Jeffrey A. Towbin, MD
G. Michael Vincent, MD
Li Zhang, MD

THE HEREDITARY LONG-QT SYNDROME (LQTS) is characterized by prolonged ventricular repolarization and an increased risk for ventricular tachyarrhythmias (torsades de pointes) and sudden cardiac death.1 The clinical course of LQTS is influenced by many factors, including sex,2,4 congenital deafness,7 prior cardiac events,1,10 family history,7 QT-interval length,1,2,4,7,8 and genotype.3,4,9,10 Previous investigations have evaluated the effect of these factors on cardiac events (syncope, aborted cardiac arrest, and sudden cardiac death), with syncope the predominant end point in almost all of the prior studies.

Using the large LQTS cohort derived from the International Long QT Syndrome Registry who were alive at age 10 years and were followed up during adolescence until age 20 years. The registry enrollment began in 1979 at 5 cardiology centers in the United States and Europe.

Main Outcome Measures Aborted cardiac arrest or LQTS-related sudden cardiac death; follow-up ended on February 15, 2005.

Results There were 81 patients who experienced aborted cardiac arrest and 45 who had sudden cardiac death; 9 of the 81 patients who had an aborted cardiac arrest event experienced subsequent sudden cardiac death. Significant independent predictors of aborted cardiac arrest or sudden cardiac death during adolescence included recent syncope, QTc interval, and sex. Compared with those with no syncopal events in the last 10 years, patients with 1 or 2 or more episodes of syncope 2 to 10 years ago (but none in the last 2 years) had an adjusted hazard ratio (HR) of 2.7; (95% confidence interval [CI], 1.3-5.7; P<.01) and an adjusted HR of 5.8 (95% CI, 3.6-9.4; P<.001), respectively, for life-threatening events; those with 1 syncopal episodes in the last 2 years had an adjusted HR of 11.7 (95% CI, 7.0-19.5; P<.001) and those with 2 or more syncopal episodes in the last 2 years had an adjusted HR of 18.1 (95% CI, 10.4-31.2; P<.001). Irrespective of events occurring more than 2 years ago, QTc of 530 ms or longer was associated with increased risk (adjusted HR, 2.3; 95% CI, 1.6-3.3; P<.001) compared with those having a shorter QTc. Males between the ages of 10 and 12 years had higher risk than females (HR, 4.0; 95% CI, 1.8-9.2; P=.001), but there was no significant risk difference between males and females between the ages of 13 and 20 years. Among individuals with syncope in the past 2 years, β-blocker therapy was associated with a 64% reduced risk (HR, 0.36; 95% CI, 0.18-0.72; P<.01).

Conclusions In LQTS, the timing and frequency of syncope, QTc prolongation, and sex were predictive of risk for aborted cardiac arrest and sudden cardiac death during adolescence. Among patients with recent syncope, β-blocker treatment was associated with reduced risk.
LONG QT SYNDROME

Syndrome Registry, we identified the effect of various clinical factors and therapeutic interventions on the risk of aborted cardiac arrest and sudden cardiac death during the high-risk adolescent period.

METHODS

Study Population

Patients were drawn from the International Long QT Syndrome Registry. Informed consent was obtained for all participants enrolled in the registry or from parents or guardians of minors. The study was approved by the University of Rochester Medical Center Institutional Review Board. A baseline 12-lead electrocardiogram was obtained at the time of enrollment with measurement of RR, QT, and Bazett-corrected QTc intervals. Clinical data including demographics, personal and family history of disease, therapy, and history of cardiac events were obtained as previously reported, and follow-up was updated yearly. Genetic testing was performed on 1627 members of 221 families enrolled in the registry. The LQTS genotype was determined using standard mutational analytic techniques involving 5 established genetic laboratories associated with the International Long QT Syndrome Registry.

Members of the registry who survived to age 10 years were eligible for inclusion in the study if they met at least 1 of the following criteria: (1) QTc 450 ms or longer, (2) QTc from 420 to 450 ms with syncope before age 10 years; or (3) QTc from 420 to 450 ms with an LQTS mutation by genetic testing. Thirty-nine participants who had had an aborted cardiac arrest before they were 10 years old were excluded because they already experienced a life-threatening event. Also excluded were 1027 individuals from families with known LQTS mutations but did not have their family's LQTS mutation. The exclusion of such individuals might involve rare patients with an undetected second mutation. The final study group consisted of 2772 participants (1140 probands and 1632 first- and second-degree relatives) who met the entry criteria at age 10 years.

Follow-up was closed on February 15, 2005. Those younger than age 20 years on the date follow-up was closed were censored at the time of their last contact. Those who were lost to follow-up were also censored at the time of their last contact. If someone was enrolled in the registry after reaching 10 years, past history was obtained retrospectively from birth to their enrolled age, and ongoing clinical information was obtained at yearly intervals thereafter. In these individuals, we used the historical clinical information from before age 10 years and the follow-up information to age 20 years if they had not otherwise been censored for any of the above reasons. Among those between age 10 and 20 years, 3 patients died from non-LQTS causes, 52 were lost to follow-up and censored at the time of their last contact, and 557 were younger than age 20 years when the follow-up was closed. Long QT syndrome genotype information was available for 722 participants in the study group.

Predictor and Outcome Variables

Candidate risk factors identified in previous studies included sex, congenital deafness, syncope, family history of any cardiac event, QTc length, and genotype. Syncope, which was evaluated in a time-dependent manner, was defined as transient loss of consciousness that was abrupt in onset and offset. Syncope was evaluated in a time-dependent manner. The total number of syncopal events and the timing of these events in relation to the observed end point were recorded. Treatment for LQTS (initiated at the discretion of each patient's attending physician) was also noted.

The primary end point was time to aborted cardiac arrest, (requiring external defibrillation as part of the resuscitation) or LQTS-related sudden cardiac death (death abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep), whichever occurred first between ages 10 and 20 years (after the 10th and before the 21st birthday). Descriptive information regarding the terminal event was obtained from first-degree relatives and from autopsy examination, if performed. The LQTS Registry did not use an adjudication committee for event classification, but rather, relied on the LQTS physician-investigators associated with each enrolling center to categorize the end point events according to the aforementioned criteria.

Statistical Analysis

Univariable relationships between survival and the clinical characteristics were assessed using Cox proportional hazards models. Stratified and unstratified multivariable Cox models, allowing for time-dependent covariates, were fit to estimate the adjusted hazard ratio (HR) of each factor as a predictor of a first life-threatening cardiac event during adolescence, adjusted for the others. Syncope and β-blocker therapy were modeled as time-dependent covariates.

The proportional hazards assumption was assessed by interacting each of the major covariates with time (age) with a nonsignificant interaction indicating that the hazards were proportional. The only covariates that did not meet the proportional hazards assumption was male vs female sex. To relax the assumption of proportional hazards for sex over the entire age range of 10 to 20 years, separate nonparametric baseline hazard functions were allowed for males and females by stratification. Then, to summarize the sex effect, sex was modeled in an unstratified model as a time-dependent covariate (via an interaction with time), allowing for different HRs among those aged 10 to 12 and 13 to 20 years.

Main-effect variables were included if the appropriate likelihood ratio test met the 2-tailed .05 level of significance, whereas a more stringent 2-tailed .01 level was used for the inclusion of interactions. Once the significance of
the predictors was established, the penalized log-partial likelihood was used as a goodness-of-fit criterion for non-nested models to compare and select functional forms for predictors, including selecting thresholds for QTc, recent syncopal time windows, and age groups for age-specific sex effects. The predicted survival functions from a sex-stratified time-independent Cox model, using only syncopal history and β-blocker status at age 10 years (ignoring syncopal events and changes in therapy after age 10 years) along with QTc, were used to estimate the cumulative 10-year event rates for risk groups defined at age 10 years. Grouped jackknife estimates of standard errors were compared with the standard large-sample estimates in order to determine whether adjusting our inferences for the potential dependencies due to family membership appeared necessary.11

Analyses were performed using SAS software version 9.1.3 (SAS Institute Inc, Cary, NC). All P values are 2-tailed.

RESULTS

Population Characteristics

Clinical characteristics are presented in TABLE 1. The overall use of β-blockers at 10, 13, 16, and 20 years of age was 10%, 12%, 14%, and 14%, respectively. None of the 10 patients who had received an implantable cardioverter defibrillator before age 10 years experienced a life-threatening event during adolescence.

Time-Dependent Multivariable Cox Model

During follow-up, 81 patients experienced aborted cardiac arrest and 54 had sudden cardiac death; 9 of the 81 patients who had an aborted cardiac arrest experienced a subsequent sudden cardiac death. Using model-fit statistics, we found that the most predictive threshold for QTc prolongation in this population was 530 ms. Other cut points ranging from 480 to 600 ms, by 10 ms intervals, were somewhat less significant (although mostly significant at the .05 level), as was modeling QTc as a continuous variable. As shown in TABLE 2 and TABLE 3, patients with a QTc greater than 530 ms were more than twice as likely to experience an event compared with those with a QTc less than 530 ms. Similar though slightly less significant results were obtained when using the more traditional QTc threshold of 500 ms.

In addition to QTc, time-dependent syncope and β-blocker therapy (both considered as time-dependent covariates), and sex were each significantly related to the risk of life-threatening events (aborted cardiac arrest or sudden cardiac death) during adolescence (Table 2). Both the timing and frequency of recent syncopal events were related to risk. Those with syncope more than 10 years ago were not at significantly increased risk compared with those who had experienced syncope in the past 2 years.

### Table 1. Population Characteristics

<table>
<thead>
<tr>
<th>Study Population (N = 2772)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, No. (%)</td>
</tr>
<tr>
<td>QTc, mean (SD), ms</td>
</tr>
<tr>
<td>Congenital deafness, No. (%)</td>
</tr>
<tr>
<td>Family history of cardiac event, No. (%)</td>
</tr>
<tr>
<td>Syncope only before age 10 y, No. (%)</td>
</tr>
<tr>
<td>Therapy before age 10 y, No. (%)</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Pacemaker</td>
</tr>
<tr>
<td>LCTG</td>
</tr>
<tr>
<td>ICD</td>
</tr>
<tr>
<td>LQTS mutations</td>
</tr>
<tr>
<td>LQT1</td>
</tr>
<tr>
<td>LQT2</td>
</tr>
<tr>
<td>LQT3</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>First life-threatening event from age 10-20 y, No. (%)</td>
</tr>
<tr>
<td>Aborted cardiac arrest</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
</tr>
</tbody>
</table>

### Table 2. Time-Dependent Multivariable Cox Model: Risk of Aborted Cardiac Arrest or Sudden Cardiac Death (Ages 10-20 Years)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent syncope vs no syncope in past 10 y 1 Syncopal event in past 2-10 y and no events within 2 y</td>
<td>9</td>
<td>2.7 (1.3-5.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2-10 y and no events within 2 y</td>
<td>29</td>
<td>5.8 (3.6-9.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 Syncopal event in past 2 y</td>
<td>26</td>
<td>11.7 (7.0-19.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2 y</td>
<td>20</td>
<td>18.1 (10.4-31.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QTc ≥530 ms</td>
<td>51</td>
<td>2.3 (1.6-3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Males aged 10-12 y vs age-matched females*</td>
<td>19</td>
<td>4.0 (1.8-9.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Time-dependent β-blocker therapy for those with recent syncope†</td>
<td>10</td>
<td>0.36 (0.2-0.7)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

### Table 3. Time-Dependent Multivariable Cox Model: Risk of Sudden Cardiac Death (Ages 10-20 Years)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent syncope vs no syncope in past 10 y 1 Syncopal event in past 2-10 y and no events within 2 y</td>
<td>5</td>
<td>4.2 (1.7-10.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2-10 y and no events within 2 y</td>
<td>13</td>
<td>6.2 (3.0-12.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 Syncopal event in past 2 y</td>
<td>8</td>
<td>8.2 (3.4-19.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2 y</td>
<td>9</td>
<td>15.0 (6.2-36.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QTc ≥530 ms</td>
<td>26</td>
<td>3.1 (1.8-5.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Males aged 10-12 y vs age-matched females*</td>
<td>8</td>
<td>11.6 (1.4-94.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Time-dependent β-blockers for those with recent syncope†</td>
<td>4</td>
<td>0.49 (0.2-1.4)</td>
<td>.18</td>
</tr>
</tbody>
</table>

*Between the ages of 13 and 20 years, there was no significant difference in risk between the sexes.
†β-Blocker therapy was significant only among those who had experienced syncope in the past 2 years.
pared with those who never had syncope. Therefore, these 2 groups were combined to form a reference group of all patients without syncope in the past 10 years. Compared with this reference group, those with 1 episode of syncope between 2 and 10 years ago (but none in the last 2 years) were at an increased risk for events, with an even greater risk for those with 2 or more syncopal episodes in this period. The HRs for 1 and 2 or more syncopal events in the last 2 years (“recent syncope”) contributed even greater risk. Of note, among those patients in whom genotype was known, multivariable analysis detected no significant association between genotype and life-threatening events.

In the entire study population, β-blocker use had a marginally significant risk-reducing effect (adjusted HR, 0.69; 95% confidence interval [CI], 0.5-1.1; \(P = .08\)). A prespecified interaction between β-blocker use and high-risk participants with recent syncope displayed a significant 64% reduction in risk for those with recent syncope (Table 2). Among those who had not experienced recent syncope, β-blocker use was not associated with reduced risk (adjusted HR, 1.2; 95% CI, 0.7-2.0; \(P = .62\)).

Sex increased risk in an age-dependent manner. Among those aged 10 to 12 years, males had 4 times the risk of females of the same age, whereas there was no significant sex difference among those aged 13 to 20 years (Table 2). Congenital deafness, family history of cardiac events, LQTS genotype, and treatment with a pacemaker, implantable cardioverter defibrillator, or left cervicothoracic sympathetic ganglionectomy were not independently predictive of events.

Multivariable analysis was also performed using time to sudden cardiac death as the sole end point, and the results were similar (Table 3). The effect of β-blockers showed similar trends when using only sudden cardiac death as the end point, but the effect was not significant in any group, including those with recent syncope (HR, 0.49; 95% CI, 0.2-1.4; \(P = .18\)), those without recent syncope (HR, 1.3; 95% CI, 0.6-2.9; \(P = .48\)), and the entire study sample (HR, 0.95; 95% CI, 0.5-1.8; \(P = .88\)). Males aged 10 to 12 years continued to display increased risk compared with age-matched females in the sudden cardiac death–only analysis. Again, there was a weaker sex-related difference in risk between the sexes for the 13- to 20-year age group (HR, 1.6; 95% CI, 0.2-0.8; \(P = .16\)).

**Figure.** Cox Model–Based Time to First Aborted Cardiac Arrest or Sudden Cardiac Arrest Between Ages 10 and 20 Years for Females with Long-QT Syndrome

Event rates are based on estimates from the time-independent Cox model (see “Methods” section). Only the 2 highest and lowest risk groups are shown in order to display the entire range of event rates. Males are at higher risk than females earlier in adolescence, with a range of risk at age 20 years similar to those for females.

**Time-Independent Multivariable Cox Model**

The nature of the time-dependent Cox model prevents assessment of absolute risk or cumulative event rates based only on the covariate pattern at the time origin. Therefore, to obtain an estimate of the 10-year event rates experienced by individuals in a given risk stratum at age 10 years, we created a time-independent Cox model substituting syncopal history and β-blocker status at age 10 years (ignoring syncopal events and changes in therapy after age 10 years) in place of their time-dependent counterparts. The relative HRs for this model were similar to those found in the time-dependent analysis. The grouped jackknife estimates of all standard errors (not shown) were within 3% of the standard large-sample estimates, indicating that any dependencies due to family membership were negligible, perhaps due to the low probability of observing multiple events within any given family. The survival functions predicted by this time-independent Cox model were then used to assess the 10-year event rates for each risk group defined at age 10 years. Representative curves depicting the range of risk and the effect of β-blocker therapy in females are shown in the Figure. For males, the range of risk was 3% to 32% and β-blockers reduced risk from 32% to 12% in the very high-risk group.

**COMMENT**

To the best of our knowledge, this is the largest LQTS study to date and is the first to identify risk factors specific for aborted cardiac arrest and sudden cardiac death in the high-risk adolescent period. Our findings indicate that the timing and frequency of recent syncope, the degree of QTc prolongation, and sex are independent predictors of life-threatening events in adolescents with LQTS. Assessment of these 3 factors can be easily performed during a routine office visit, can be used to risk-stratify patients with suspected LQTS, and should be helpful in guiding treatment decisions.
β-Blocker therapy was associated with 64% risk reduction in high-risk participants. Those in the “very high risk” group experienced, on average, a 1% per year life-threatening event rate between the ages of 10 and 20 years despite β-blocker therapy (Figure). Implantable cardioverter defibrillator and/or left cervicothoracic sympathetic ganglionectomy is a consideration for this high-risk group.12,13

Our findings with regard to the changing effects of sex over time expanded on those of Locati et al, who demonstrated that males were more likely than females to experience a first cardiac event before age 15 years, with females at higher risk thereafter. One explanation for the age-dependent effect of sex is that males (both with and without LQTS) experience a shortening of the QTc during adolescence.14-16 Although the mechanism for this finding remains unknown, some evidence suggests that androgens may shorten QTc,17,18 while estrogens appear to decrease potassium-channel density in the myocardium.19,20 However, in our current study, sex was associated with life-threatening events even after adjustment for QTc. It is therefore likely that additional unidentified factors contribute to the complex relationship between age and sex in LQTS during adolescence.

We detected no significant independent association between genotype and life-threatening events. At first glance, this is surprising given that several previous publications have identified strong genotype-specific effects.3,4,9,10,21 The disparity between our findings and those of previous investigators may be explained, in part, by our use of a more specific end point that excludes syncope. These findings suggest that genotype may play a larger role in predicting syncope than aborted cardiac arrest or sudden cardiac death. In addition, although prior studies evaluated risk factors for the first event after birth, our focus was on life-threatening events during adolescence, after survival to age 10 years. This allowed us to identify clinical risk factors like the timing and frequency of syncope during childhood and adolescence that are likely to be influenced by genotype.3,4,9,10,16 Because LQTS has variable penetrance,22,23 it stands to reason that clinical factors (ie, a patient’s phenotype) would provide a more accurate representation of disease severity than genotype. At birth, however, when the full clinical phenotype is not yet manifest, the predictive information provided by genotype may be more important.

It is also possible that the absence of a genotype effect was due to limited power. Only 26% of the participants were genotyped, and just 4% of the genotyped individuals experienced a life-threatening event. Similar limitations may also apply to the nonsignificant risk observed for congenital deafness and the lack of significant risk reduction associated with implantable cardioverter defibrillators and left cervicothoracic sympathetic ganglionectomy in the multivariable Cox models for these factors were also of low frequency.

Not surprisingly, β-blocker therapy was predictive of a reduced risk of aborted cardiac arrest and sudden cardiac death in high-risk but not low-risk individuals. Still, the use of β-blocker therapy for all LQTS patients, especially the LQT1 and LQT2 subtypes, remains prudent, particularly considering their demonstrated efficacy at reducing the incidence of syncope.3 In the sudden cardiac death–only model, β-blockers failed to display any significant effect, even among those with recent syncope. It is unclear if the failure of β-blockers to reduce the risk of sudden cardiac death is a true-negative finding or related to limited power from a low frequency of sudden cardiac death events.

In summary, we identified 3 important factors for estimating the risk of life-threatening events in adolescent patients with suspected LQTS: timing and frequency of recent syncope, the duration of the QTc interval, and sex. This clinically oriented risk-stratification approach might serve as a useful guide for prophylactic treatment decisions to reduce the risk of sudden death in patients with LQTS during the high-risk teenage years.

Author Affiliations: Cardiology Unit of the Department of Medicine (Drs Hobbs, Moss, Zareba, Goldenberg, Moss, McNitt and Sauer, and Ms Robinson), the Departments of Biostatistics and Computational Biology (Dr Peterson), and Pathology (Dr Qi), University of Rochester Medical Center, Rochester, NY; Departments of Medicine, Pediatrics, and Molecular Pharmacology, Mayo Clinic College of Medicine, Rochester, Minn (Dr Ackerman); Department of Cardiology, Bikur Cholim Hospital, Jerusalem, Israel (Dr Benhorin); The Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio (Dr Kaufman); Cardiovascular Laboratory, Department of Pediatric Cardiology, Baylor College of Medicine, Houston, Tex (Dr Towbin); and Department of Pediatrics, University of Utah School of Medicine, Salt Lake City (Drs Vincent and Zhang).

Author Contributions: Dr Moss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hobbs, Peterson, Moss, McNitt, Zareba, Kaufman, Towbin, Vincent.

Acquisition of data: Moss, McNitt, Zareba, Qi, Robinson, Benhorin, Kaufman, Napolitano, Priori, Towbin, Vincent.

Analysis and interpretation of data: Hobbs, Peterson, Moss, McNitt, Zareba, Goldenberg, Qi, Sauer, Ackerman, Benhorin, Locati, Towbin, Vincent, Zhang.

Drafting of the manuscript: Hobbs, Peterson, Moss, Towbin.

Critical revision of the manuscript for important intellectual content: Hobbs, Peterson, Moss, McNitt, Zareba, Kaufman, Towbin, Vincent, Zhang.

Statistical analysis: Hobbs, Peterson, Moss, McNitt, Zareba, Benhorin, Locati.

Obtained funding: Moss, Towbin.

Administrative, technical, or material support: Moss, Qi, Robinson, Sauer, Towbin, Vincent.

Study supervision: Moss, Goldenberg, Towbin.

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REFERENCES


Interpretation is not (as some people assume) an absolute value, a gesture of mind situated in some timeless realm of capabilities. Interpretation must be evaluated . . . . Like the fumes of the automobile and of heavy industry which befoul the urban atmosphere, the effusion of interpretation of art today poisons our sensibilities. In a culture whose already classic dilemma is the hypertrophy of the intellect at the expense of energy and sensual capability, interpretation is the revenge of the intellect upon art.

—Susan Sontag (1933-2004)