Marked Variability in Susceptibility to Ventricular Fibrillation in an Experimental Commotio Cordis Model

Alawi A. Alsheikh-Ali, MD, MS; Christopher Madias, MD; Stacey Supran, MA; Mark S. Link, MD

**Background**—Precordial blows in sports and daily activities can trigger ventricular fibrillation (VF) (commotio cordis). Whereas chest wall blows are common, commotio cordis is rare. Although factors such as timing, location, orientation, and energy of impact are critically important, we also hypothesize that there is individual susceptibility to commotio cordis. Using our model of commotio cordis, we evaluated individual animal susceptibility to VF induction and assessed animal characteristics that might be involved.

**Methods and Results**—This retrospective analysis included 139 juvenile swine (weight, 8 to 54 kg) that were anesthetized and placed prone in a sling to receive chest wall strikes with a ball propelled at 30 to 40 mph. Each animal received a minimum of 4 impacts directly over the cardiac silhouette, all timed to a narrow vulnerable window during cardiac repolarization. Of 1274 total impacts, 360 impacts (28%) resulted in VF. There was wide variability in individual animal susceptibility to VF. In 38 animals, none of the impacts resulted in VF (range, 4 to 18 impacts per animal). The majority of animals (91; 65%) were induced into VF with 30% of the strikes. In fact, only 19 animals (14%) had 50% occurrence of VF with chest wall impacts, and only 7 (5%) had 80% occurrence of chest impacts that induced VF.

In the animal-based analysis, individual correlates of VF included animal weight, mean impact velocity, mean left ventricular pressure generated by the blow, mean QRS duration, mean QTc, and QTc variability. In multivariable analysis, mean left ventricular pressure generated by the blow, mean QRS duration, and QTc variability remained significant correlates of risk, and number of impacts gained statistical significance such that animals with more impacts were less susceptible to VF.

**Conclusions**—Swine display a wide range of individual vulnerability to VF triggered by chest wall impact, with a distinct minority being uniquely susceptible. Mild abnormalities in cardiac depolarization and repolarization might underlie this susceptibility. Such individual susceptibility may also be present in humans and contribute to the rarity of commotio cordis. (Circulation. 2010;122:2499-2504.)

**Key Words:** commotio cordis ■ death, sudden ■ cardiac arrhythmia ■ ventricular fibrillation

The induction of ventricular fibrillation (VF) and sudden cardiac death (SCD) by blunt, nonpenetrating blows to the chest wall is known as commotio cordis.1–4 Commotio cordis is most frequently observed in young individuals, with an estimated incidence of 10 to 20 events per year in the United States. Chest blows that trigger such catastrophic events often occur in the setting of athletic activities but can also transpire during activities of daily living unrelated to sport. However, although chest blows are a common daily occurrence, SCD resulting from such blows is unusual. The rare incidence of this condition is attributed to a necessary confluence of multiple factors that include a chest blow of certain energy and direction, occurring directly over the heart, with an appropriately hard and compact object timed to a narrow window of vulnerability during ventricular repolarization.5–9 However, in addition, it is also possible that the uncommon occurrence of commotio cordis is in part due to variability in individual susceptibility to the induction of VF by a chest blow. It is unlikely that susceptibility to commotio cordis will ever be systematically studied in humans. Therefore, in the present analysis, we utilize our extensive experience with an animal model of commotio cordis to examine heterogeneity in individual susceptibility to VF induction and to assess animal characteristics that might be involved.

**Clinical Perspective on p 2504**

**Methods**

**Design**

The present study is a retrospective analysis of the incidence of VF with chest blows in our experimental model of commotio cordis and the ECG characteristics before the chest blow.5–8,10,11 Because multiple impacts were necessary to ascertain individual susceptibility, in the present analysis only animals with ≥4 control chest wall impacts were included. We excluded from the present analysis
animals that were administered any pharmacological agents other than anesthetics. Animals in this analysis included those from the prior experimental protocols: energy limits of commotio cordis (n=4 animals),7 resuscitation and automated external defibrillators in commotio cordis (n=15 animals),12 chest protector studies (n=35 animals),13 colchicine (n=6 animals),13 stretch-activated channels (n=6 animals),16 sites of impact (n=12 animals),6 and 61 animals in protocols not yet published.

Animal Model and Experimental Protocol
In conformity with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care, the Institutional Animal Care and Use Committee of Tufts Medical Center (Boston, Mass) approved the research protocol. Male domesticated swine (weight, 8 to 54 kg) were anesthetized with ketamine and inhaled isoflurane.5,6,14 Animals were intubated and placed on a respirator, and general anesthesia was maintained throughout the experiment with isoflurane (2% isoflurane gas in 100% oxygen gas). Millar Mikrotip (Houston, Tex) pressure catheters were introduced into the left ventricle via the femoral artery. ECG tracings and left ventricular pressures were recorded continuously with the use of an analog-to-digital converter (Chart software; AD Instruments, Mountain View, Calif). Recordings were sampled at 2000 Hz, not filtered, and saved on a laptop computer. Each animal was placed prone in a sling to approximate physiological cardiac anatomy and hemodynamics. Chest blows were directed toward the anatomic center of the left ventricle as identified by transthoracic echocardiography. VF was defined as polymorphic ventricular arrhythmia requiring defibrillation (Figure 1). If VF occurred after a chest blow, the animal was immediately defibrillated. After each episode of VF, the animal’s blood pressure, heart rate, and left ventricular ejection fraction (by echocardiography) were monitored. If these parameters returned to the baseline levels, repeat impacts were delivered.

Susceptibility to VF
For this analysis, we included animals that received at least 4 qualifying impacts. A qualifying impact was defined as an impact delivered at 30 to 40 mph over the cardiac silhouette and timed to a narrow window of vulnerability 10 to 40 ms before the peak of the T wave. For each animal, susceptibility to VF was defined as the proportion of qualifying impacts resulting in VF. Computer-stored ECG tracings from all qualifying impacts were reviewed. Characteristics analyzed for individual susceptibility included the following: animal weight, number of impacts, order of impacts, specific timing of impact within the vulnerable window, velocity of impact, peak left ventricular pressure generated by the impact, and heart rate, QRS duration, corrected QT interval (QTc), and QTc variability before the impact. With the use of Bazett’s formula, QTc was calculated on the basis of measurements obtained with electronic calipers. QTc variability was defined as the difference between the maximal and minimal QTc in an individual animal. QTc variability was measured over 49±33 minutes. All ECG measurements were performed by a single investigator.

Analytical Plan
To describe the heterogeneity in individual animal susceptibility to VF, we used summary statistics of central tendency and dispersion (median and 25th and 75th percentiles) with a visual display of the distribution of susceptibility in the form of a histogram. To examine the relationship between animal/impact characteristics and susceptibility to VF, 2 separate analyses were performed. In an animal-based analysis, we used simple linear regression to examine the association between animal characteristics and susceptibility to VF. In a separate impact-based analysis, we used multilevel logistic regression, specifically the generalized estimating equations method of the SAS GENMOD procedure, to account for repeated measures in each animal. A P value of <0.05 was considered statistically significant. All analyses were performed in SAS 9.1 (SAS Institute Inc, Cary, NC).

Results
Individual Susceptibility to VF
A total of 139 animals receiving a total of 1274 impacts were included in the present analysis. The median number of impacts per animal was 6 (25th and 75th percentiles, 5 and 13). Overall, 360 impacts (28%) resulted in VF. There was wide variation in individual animal susceptibility to VF, with a median of 20% (25th and 75th percentiles, 0% to 40%; range, 0% to 100%; Figure 2). The majority of animals (91; 65%) were induced into VF with <30% of the strikes. In 38 animals, none of the impacts resulted in VF (range, 4 to 18 impacts per animal). Only 19 animals (14%) had >50% VF with chest wall impacts, including 7 (5%) with >80% VF with chest wall impacts and only 3 animals with 100% VF (range, 4 to 16 impacts per animal).

Characteristics Associated With Susceptibility to VF

Animal-Based Analysis
Weight (P=0.02), mean velocity of impact (P=0.001), mean peak left ventricular pressure generated by the blow (P=0.0007), mean QRS duration (P=0.0001), mean QTc (P=0.0028) and QTc variability (P=0.0025) were individual correlates of VF (Table). Animals who were more susceptible to VF had significantly longer QRS and QTc intervals (Figure 3). With the use of linear regression, there was found to be a significant relationship between the mean QTc and individual animal susceptibility to VF, such that each 10-ms increment in mean QTc was associated with a 1.3% (95% confidence limits, 0.5% to 2.1%) increase in susceptibility to VF (P=0.0028). Animals with no VF had a mean QTc interval of 417±49 ms compared with those with 100% VF of 499±41 ms. In multivariable analysis, peak left ventricular pressure (P=0.0008), QRS duration (P=0.01), and QTc variability (P=0.005) remained significant correlates of risk, whereas number of impacts gained statistical significance (P=0.008) such that animals with fewer impacts were more susceptible to VF.

Impact-Based Analysis
In impacts that triggered VF, significant correlates of VF included animal weight (odds ratio [OR]=0.96 per kg; P=0.004), velocity of impact (OR=1.18 per mph; P<0.0001), peak left ventricular pressure (OR=1.003 per mm Hg; P<0.0001), QRS duration (OR=1.03 per ms; P=0.035), and QTc (OR=1.007 per ms or 1.07 per 10 ms; P=0.001). The QTc in the preceding beat was significantly longer in impacts that resulted in VF compared with the corresponding interval in impacts that did not result in VF (median, 456 [25th and 75th percentiles, 426 and 483, respectively] versus 437 [25th and 75th percentiles, 398 and 468, respectively] milliseconds; P<0.0001). In multivariable analysis, velocity (OR=1.14 per mph; P=0.002) and peak left ventricular pressure (OR=1.002 per mm Hg; P=0.04) remained significant, whereas QTc remained marginally significant (OR=1.04 per 10 ms; P=0.097) and impact order gained significance (OR=0.97 per impact; P=0.004) such that VF became less likely with each successive impact.
Figure 1. Chest blow induces VF in an animal with a longer QTc but not in an animal with a shorter QTc. Top, An animal with a preimpact QTc of 477 ms is struck by a 40-mph lacrosse ball, and VF is induced. This animal received 16 impacts, all resulting in VF. Bottom, An animal with a preimpact QTc of 347 ms is struck by a 40-mph lacrosse ball without induction of VF. This animal had no episodes of VF with 6 impacts.
Discussion

On the basis of this extensive analysis of nearly 1300 impacts in 139 animals, there is clear individual susceptibility to chest wall blow–induced VF. Despite a suspicion that certain children might be uniquely susceptible to commotio cordis, these data are the first to demonstrate such individual vulnerability. In these experiments, in which the variables for the induction of VF were optimized, the majority of animals were relatively resistant to VF, and only a very select minority were uniquely vulnerable. Clues as to why individual susceptibility exists are seen in cardiac depolarization and repolarization, in that prolonged QRS and QTc intervals were associated with heightened susceptibility to induced VF.

Despite the multitude of chest impacts that occur in sports, commotio cordis is only reported 10 to 20 times annually in the United States. The rare occurrence of this devastating condition is certainly due in part to the necessary confluence of multiple biological and mechanical variables necessary for VF induction with a chest impact. Experiments utilizing our animal model have revealed these variables to include the appropriate timing of the impact during a narrow window of cardiac repolarization, achievement of the proper impact energy, the location of impact directly over the heart, and the hardness of the impact object. The present analysis of control impacts in our model demonstrates the previously unrecognized biological variable of individual animal susceptibility to VF induction by chest blows. This individual susceptibility to commotio cordis evident in swine might also be present in humans.

Individual susceptibility to SCD in other conditions has been described and has only recently been explored more extensively. Early epidemiological data demonstrate that a family medical history of SCD increases the risk of SCD in an individual, independently of the risk of coronary artery disease. However, the exact nature of how and why this occurs is only now being elucidated with techniques to evaluate the genome. Subclinical individual genetic variations carried in single nucleotide polymorphisms likely underlie these susceptibilities in the predisposition to SCD. For example, in the Seattle Cardiac Arrest Blood Study, genetic variations in $\beta_2$-adrenergic receptors and angiotensin-converting enzyme–related pathways were shown to be associated with the risk of SCD. Increased risk was evident in homozygotes for the Gln27 allele and the AGTR2 allele, whereas decreased risk was observed in individuals with the AGTR1 allele. In individuals with prior myocardial infarctions, the angiotensin-converting enzyme D and AT1 alleles are associated with higher risk of ventricular arrhythmias.

Table. Unadjusted Analysis of Factors Associated With the Induction of VF in an Experimental Model of Commotio Cordis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P: Animal-Based Analysis</th>
<th>P: Impact-Based Analysis</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.02</td>
<td>0.004</td>
<td>0.96 per kg</td>
</tr>
<tr>
<td>Velocity</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>1.18 per mph</td>
</tr>
<tr>
<td>No. of impacts</td>
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<td>Not used for this analysis</td>
<td>0.59</td>
</tr>
<tr>
<td>Impact order</td>
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<td>0.48</td>
<td>0.12</td>
</tr>
<tr>
<td>Timing of impact†</td>
<td>Not used for this analysis</td>
<td>&lt;0.0001</td>
<td>1.003 per mm Hg</td>
</tr>
<tr>
<td>Peak LVP</td>
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<td>0.0007</td>
<td>0.035 per ms</td>
</tr>
<tr>
<td>Mean peak LVP</td>
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<td>0.77</td>
</tr>
<tr>
<td>Heart rate</td>
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<td>0.085</td>
<td>1.03 per ms</td>
</tr>
<tr>
<td>Mean heart rate</td>
<td>Not used for this analysis</td>
<td>0.0001</td>
<td>0.035 per ms</td>
</tr>
<tr>
<td>QRS</td>
<td>Not used for this analysis</td>
<td>0.001</td>
<td>1.07 per 10 ms</td>
</tr>
<tr>
<td>Mean QRS</td>
<td>Not used for this analysis</td>
<td>&lt;0.0001</td>
<td>1.07 per 10 ms</td>
</tr>
<tr>
<td>QTc</td>
<td>Not used for this analysis</td>
<td>0.0028</td>
<td>0.0025</td>
</tr>
<tr>
<td>Mean pre-QTc</td>
<td>Not used for this analysis</td>
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<td>0.0025</td>
</tr>
<tr>
<td>QTc variability</td>
<td>Not used for this analysis</td>
<td>0.0028</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

*The impact-based analyses above are from the multilevel model.
†All impacts were within the vulnerable window of 10 to 40 ms before T wave peak; this analysis is of time within this vulnerable window.

Figure 2. Variation in individual animal susceptibility to VF. The bar graph demonstrates that the majority of animals are relatively resistant to chest wall blow–induced VF, whereas a very small minority are uniquely susceptible. Of 139 animals, only 3 had VF induced with 100% of impacts. Ninety-one animals had VF induction with <30% of strikes. Thirty-eight animals had no VF inductions.

Figure 3. Animals more susceptible to VF had significantly longer QTc intervals. Animals with no VF had a mean QTc of 417±49 ms compared with those with ≥75% VF (mean QTc of 464±47 ms) and 100% VF (mean QTc of 499±41 ms).
Genetic variations in the nitric oxide synthase 1 adapter protein, which modulates the QT interval,21,22 and variants of the KCNQ1 and SCN5A gene are associated with an increased risk of SCD.23,24 However, these aforementioned genetic variations are not likely to be observed before SCD because of lack of symptoms and clinical findings in the affected individuals. It is possible that these or other subclinical single nucleotide polymorphisms underlie susceptibility to VF with chest wall impact.

It was not unexpected that abnormalities in cardiac repolarization are associated with an increased susceptibility to commotio cordis, given the requirement for the chest impact to occur during a vulnerable portion of repolarization. However, the finding that a prolonged depolarization increases the risk of VF is unexpected. Abnormalities in repolarization are known hallmarks of monogenetic diseases in which individuals are at risk of sudden arhythmic death. In the long-QT syndrome, which includes at least 10 well-defined genetic conditions, males are at increased risk for SCD.32–34

In the Brugada syndrome, genes encoding for the SCN5A, a sodium channel involved in repolarization, create the abnormal repolarization substrate.25,28–30 It is likely that genetic polymorphisms that affect an individual’s risk of commotio cordis are present and might be involved in cardiac depolarization or repolarization. Whether these polymorphisms are similar to those discussed above will likely never be elucidated given the rarity of commotio cordis. Although it is likely that much of the male predilection for commotio cordis is related to the higher prevalence of male participation in ball sports, there might also be some modification by gender-related hormones or processes or conceivably X-linked recessive genetic mutations influencing susceptibility to commotio cordis. This gender modification is also seen in other disorders. In the Brugada syndrome, males are at increased risk for SCD compared with females.31 In the long-QT syndrome, males appear to be at greater risk for SCD when they are younger than 15 years, whereas in adulthood, females have an increased risk of SCD.32–34

Limitations
The QTc is only a rough measure of repolarization and provides no data on specific genetic polymorphisms that are potentially relevant to commotio cordis. However, it is not likely that the specific polymorphisms involved in commotio cordis will ever be elucidated in humans, given the rarity of the condition. In addition, although the unadjusted association between the QT interval and susceptibility to VF in commotio cordis was statistically significant, the strength of the association (both in the animal-based and impact-based analyses) was relatively weak. Therefore, other factors such as those involved in depolarization are likely also involved in the heterogeneity of individual susceptibility to VF in commotio cordis. Anesthetic agents themselves might affect the QT interval, as well as the susceptibility to VF with chest wall impact. However, the use of specific anesthetic agents was consistent in all protocols, and therefore this limitation is likely minimized.

Conclusion
In this experimental model of commotio cordis, there is wide variation in individual vulnerability to VF triggered by chest wall impact. This individual susceptibility might be carried in subclinical single nucleotide polymorphisms and might also be modulated by gender. The individual vulnerability to chest wall impact is also possibly present in humans and has clinical implications for individuals succumbing to commotio cordis.

Sources of Funding
This study was supported by the Louis J. Acompora Foundation North American National Operating Committee on Standards for Athletic Equipment.

Disclosures
Dr Link has a patent on a chest protector that is designed to reduce the risk of sudden death with chest wall impact. This chest protector is licensed to Cascade Sports and is not discussed in this article.

References


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