these failed procedures, an additional analysis was stated a priori in detail in the statistical analysis plan prior to unblinding in which the lowest (i.e., worst) CFR from the prior ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) substudy (0.55) was imputed to those patients with a failed procedure. When patients with a failed procedure were included in the analysis, no difference was seen between bivalirudin and eptifibatide in the primary end point (median of 1.43 for bivalirudin vs. 1.33 for pooled eptifibatide arms, p = 0.13). To comply with the requests of the reviewers, however, the analysis in the published report included only patients with a successful PCI and does not account for patients with a failed procedure. Given the potential for clopidogrel pretreatment to confound the efficacy outcomes in the trial, randomization in the trial was stratified by clopidogrel pretreatment, and it was prespecified that the key analyses would be adjusted for clopidogrel pretreatment. In a prespecified analysis, there was a significant interaction term between clopidogrel pretreatment and the randomization arm with respect to the end point of death or myocardial infarction (MI) (p = 0.031 for interaction between clopidogrel pretreatment and randomization arm). Among patients treated with clopidogrel for ≤6 h before angiography, the risk of death/MI was significantly lower among patients treated with eptifibatide compared with bivalirudin (5.0% vs. 10.3%, n = 548, p = 0.022). In the smaller cohort of 309 patients treated with clopidogrel for >6 h, no significant difference existed in the incidence of death/MI between eptifibatide and bivalirudin (9.5% vs. 6.1%, p = 0.31). Among troponin-positive patients treated for ≤6 h with clopidogrel, the risk of death/MI was significantly lower among patients treated with eptifibatide (4.1%, n = 197 vs. 13.2%, n = 106, p = 0.003).

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Taser Research in Pigs Not Helpful

Two reports in a 2006 issue of JACC cite studies of the effects of Taser shocks in porcine “models.” Nanthakumar et al. (1) reported the results of 150 discharges at various body locations in 6 pigs, concluding that there may be increased risks for dysrhythmias, especially under conditions of adrenergic stress. Lakkireddy et al. (2) reported the results of shocks in 5 pigs before and after cocaine infusions, using a device designed to mimic the Taser X-26 model. Cocaine increased the ventricular fibrillation (VF) threshold in these pigs, suggesting cocaine may be protective for Taser-related VF risk in humans.

Efforts to study the human effects of Taser shocks by substituting pigs appear to have little rationale or necessity. Important anatomical and electrophysiological differences between humans and pigs make pigs poor surrogates for human responses to cardiac drugs and electrical discharges. Additional confounders include the use of anesthesia, controlled laboratory conditions, repetitive shocks in animals smaller than humans, and inability to interview the subjects about symptoms caused by their Taser exposures.

Nanthakumar et al.’s (1) finding of increased Taser-associated dysrhythmia risk in pigs contrasts with a 2005 study in healthy human volunteers (3), and is not supported by a review of many thousands of Taser outcomes in police uses and in human volunteers (4). Lakkireddy et al.’s (2) conclusion contradicts the known effects of cocaine on dysrhythmia risk in humans (5,6).

The effects of Taser shocks in humans may not be completely understood, but the useful information to date is from studies in humans receiving shocks under various circumstances. Conflicting and inconsistent results from studies in pigs and other animals have muddied rather than clarified the picture. No scientific or ethical justification exists for such studies when much species-specific information is available and could be expanded (7).

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REFERENCES

Electronic Control Devices and the Clinical Milieu

In a 2006 issue of the Journal, Nanthakumar et al. (1) presented a study of Taser ECDs (electronic control devices) using 6 pigs averaging 50 kg (110 lb). Research on these devices is important as they are rapidly changing the practices of law enforcement in North America and the United Kingdom with over 620 uses per day. The ECD delivers its short, motor-neuron capturing pulses through a pair of small darts (or barbs) attached by very fine wires. Darts were positioned subcutaneously to maximize current through a pair of small darts attached by very fine wires.

The researchers then infused epinephrine and delivered 16 ECD applications—again in the worst-case position. They had one case of ventricular fibrillation (VF) from these 16 applications. The investigators concluded that these devices may have cardiac risks. Although we recognize the solid reputations of the researchers and the quality review process of JACC, we have concerns about the applicability of this conclusion to the clinical setting. The first concern lies with the implicit assumption that the rhythm with a police “in-custody death” is VF. The ECDs are involved in 30% to 32% of in-custody deaths (J. Ho, unpublished data, 2006) (4,5). However, studies have not reported a single case in which the presenting rhythm was VF when an ECD was used. A study of 162 consecutive in-custody deaths found that, whereas there was a significant association of impact weapons with sudden death, the ECDs were never (0 of 50; p = 0.001) associated with a sudden collapse. This would seem to eliminate electrically induced VF as the cause of death.

The one anecdote, cited in Nanthakumar et al. (1), of possible electrically induced VF was misreported with material omissions (6). A violent subject exhibiting all the signs of excited delirium was briefly subdued with a short ECD discharge. Paramedics were present and found a normal pulse and respiration after the ECD discharge. After a 14-min delay, the subject collapsed and probably had an ideoventricular rhythm. After an aggressive therapy of 3 defibrillation shocks along with atropine and epinephrine, the subject finally had the VF strip shown in the published anecdote. A total of 23 min elapsed between the ECD application and the published VF strip.

Our second concern has to do with the timing of the shocks with the epinephrine infusion. The study does not mention any delay between the time of infusion and the ECD application. Although perhaps counterintuitive, epinephrine reduces the VF threshold only for the first few minutes (7). After that there is a supratachyphylaxis, and the VF threshold is increased significantly above the baseline. This timing is concordant with the clinical scenario. Typically, an individual exhibits violent agitation with hyperactivity (8) for several minutes, and third parties call for help. The police require 5 to 15 min to arrive before they can apply any restraint device. At this point, the adrenergic tone has been elevated for several minutes. An epinephrine infusion minutes before an ECD shock would appear to give results opposite of those seen with the clinical scenario.

Finally, we would draw attention to the results of the Cleveland Clinic study published in the same issue of the Journal (9). This study used significantly higher exposures (total shock charge of approximately 2,000 five-second weapon discharges per pig versus about 50 for the Nanthakumar et al [1]) and also evaluated the risk of the induction of ventricular arrhythmias. The investigators found no induction of arrhythmias except at a high multiple of the device output and that cocaine increased this safety margin even further. That would appear to be more consistent with the clinical results in which no objectively documented VF has occurred in 610,000 police uses of these devices.

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Reply

We thank Drs. Pippin and Kroll et al. for their interest in our work (1). We disagree with the notion that experimental models are never of any use in understanding and in studying arrhythmias. Most of the work on mechanisms of fibrillation and defibrillation, including studies in cardiac arrest, have been conducted in guinea pigs, rats, pigs, and dogs. Readers of JACC are quite aware of the