Anesthesiology
1997; 86:265

In Reply:—The case we reported described the use of transesophageal atrial pacing (TAP) to drive an internal dual chamber pacemaker. This allowed normalization of a chaotic heart rate and efficient synchronization of intraaortic balloon pumping (IABP). The electrical signal generated by the TAP was sensed by the atrial wire of the internal pacemaker, which subsequently activated ventricular pacing. The electrocardiographic signal obtained consisted, then, in an atrial spike, generated by the TAP, followed by a ventricular spike, generated by the internal pacemaker. Finally, the IABP (Datascope System 90, Datascope, Paramus, NJ) was triggered in a dual-chamber pacing mode. The situation described by Roth is quite different, because the TAP has been used solely to directly trigger the IABP. Although an interesting topic, atrial pacing triggering of IABP was not the purpose of our communication. In addition, it has to be noted that, contrary to models 95 and 97, the IABP Datascope System 90 is not designed to permit isolated atrial pacing triggering. It is not surprising, therefore, that the TAP activity was not recognized by the IABP or was recognized as ventricular activity with subsequent inadequate timing. Why the Datascope System 95 did not recognize the TAP spike while in atrial pacing triggering mode in the second case reported by Roth is unclear, and does not meet our personal experience with this material.

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(Accepted for publication October 18, 1996.)

Anesthesiology
1997; 86:265

In Reply:—Thank you for giving Datascope the opportunity to respond to this exchange of correspondence regarding transesophageal atrial pacing as a trigger for intraaortic balloon pumps (IABP).

The result of proper triggering and timing is the synchronization of intraaortic balloon (IAB) inflation and deflation action with left ventricular contraction. When available, the R-wave is the preferred method of IABP triggering. However, Datascope pumps provide the ability to alternatively trigger from ventricular pacing pulses as precursors to ventricular stimulation and contraction.

No Datascope IABP has ever been designed to trigger off the atrial pacing pulse, due to vagaries of A-V pacing intervals and the potential dissociation of atrioventricular activity. Our newest pump consoles (System 95 and 97) provide a "Pacer A" mode. This mode is only invoked to *reject* large atrial pacing artifact that may compete with depressed QRS complexes during R-wave triggering (*i.e.*, after cardioplegia). Triggering on an atrial pacing stimulus will result in both early inflation and early deflation of the IAB. The longer the atrioventricular pacing delay, the earlier the timing will occur.

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(Accepted for publication October 18, 1996.)

Anesthesiology
1997; 86:265-6

Is Pentobarbital Analgesic in the Rat Formalin Test?

To the Editor:—In an interesting article, Gilron and Coderre[1] demonstrated lack of analgesic effect of systematically administered pentobarbital in the rat formalin test, contradictory to our results that showed that pentobarbital produces preemptive analgesia *via* activation of $GABA_A$ receptors.[2] To make this issue even more complex, another group of investigators reported hyperalgesic effects of pentobarbital in this test.[3,4] Although the mechanism for this discrepancy is unclear, we raise a few issues missed by Gilron and Coderre.

First, whether pentobarbital produces analgesia appears critically dependent on the dose administered. In our study, the preemptive analgesic state was created by doses of pentobarbital sufficient to produce loss of righting reflex (16–20 $mg \cdot kg^{-1}$).[2] However, the smallest dose (10 $mg \cdot kg^{-1}$), which did not produce loss of righting reflex in any animal, was slightly hyperalgesic,[2] in agreement with Abbott *et al.*[3] showing hyperalgesia by a subhypnotic dose (10 $mg \cdot kg^{-1}$). In the study by Gilron and Coderre, where pentobarbital failed to show analgesia, even rats receiving the largest dose (20 $mg \cdot kg^{-1}$) did not lose righting reflex, indicating that this dose was

relatively smaller than our largest dose when the sensitivity of animals to pentobarbital is taken into account. Because pentobarbital is antinociceptive at the spinal level while suppressing the descending inhibitory system supraspinally,[5] we speculate that increasing doses produce a continuum of effects from disinhibition to suppression of the spinal nociceptive system, resulting in hyperalgesia to analgesia.

The second, and perhaps more intriguing, issue is that pentobarbital appears to differentially affect various pain-related behaviors in the formalin test. Injection of formalin provokes several distinct behaviors, including favoring, lifting, licking, and flinching of the injected paw. We used flinching as a measure of pain and demonstrated pentobarbital-induced preemptive analgesia.[2] In contrast, others used the weighted scoring system involving favoring, lifting, and licking, and failed to show an analgesic effect.[1,3,4] In this regard, it is noteworthy that intrathecally administered muscimol, a $GABA_A$ agonist, also selectively attenuates formalin-induced flinching while having no effect on the weighted pain score.*

In fact, such differential alterations in formalin-evoked pain behaviors are not unique to agents with $GABA_A$ agonist properties. Accumulating evidence suggests that several other classes of agents also cause dissociation among various pain-related behaviors in the formalin test. For example, amphetamine reduces the weighted pain score while leaving flinching unaffected.[3] Naloxone, although not generally accepted as an analgesic, inhibits licking but does not alter and may increase flinching.[6] It is a matter of great controversy which of these behaviors or their combination is the best measure of formalin-induced pain.[3,6] However, the problem may really lie in the fact that, when dealing with animal models of pain, researchers have predominantly focused on the intensity of pain but have rarely evaluated the quality of pain. Obviously, this approach is too simplistic, because we know pain is a multifactorial phenomenon, at least clinically. That a number of unrelated classes of agents exert such diverse and differential influences on pain behaviors strongly indicate that these drugs may change the quality of pain in a different fashion, resulting in nonuniform alterations in pain behaviors. In our clinical practice, we ask the patient not only "how much does it hurt?" but also "how does it hurt?". Then, why not ask the same questions to animals? We believe considerations on the quality of pain are essential to thoroughly understand and to add more clinical relevance to animal models of pain. To this end, we believe investigation on the differential effects of pharmacologic interventions on various pain-related behaviors is a highly promising strategy.[7]

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(Accepted for publication October 31, 1996.)

* Kaneko M, Hammond DL: GABA acting at $GABA_A$ receptors in the spinal cord limits the second, but not the first phase response to formalin in the rat. Presented on August 20, 1996, at the 8th World Congress on Pain, Vancouver, Canada.

Anesthesiology
1997; 86:266–7

In Reply:—Goto *et al.* continue an interesting discussion regarding conflicting results among the cited studies. As they reiterate, evidence exists to support the dose dependency of barbiturates on nociceptive behavior. This phenomenon appears to be due to a dose-related progression starting from suppression of descending inhibitory systems (hyperalgesic effect) to suppression of spinal nociceptive mechanisms (analgesic effect). For this reason, differences in behavioral effects of GABAminergic anesthetics that have variable pharmacokinetic/pharmacodynamic (PK/PD) profiles must be interpreted with caution. Goto *et al.* suggest that, in our study, the lack of analgesic effect with pentobarbital may be due to the possibility that the dose used produced roughly equal suppression of both descending inhibitory and spinal nociceptive systems. Although this is a feasible hypothesis, it should be noted that the purpose of our study paradigm is to measure persistent pain during phase 2, which is thought to be an expression of spinal sensitization produced by noxious stimulation during phase 1. The timing and dosing of drugs used in our study was designed to maximize drug effect during phase 1, in an attempt to prevent spinal sensitization while allowing for anesthetic recovery, so as to eliminate or at least minimize residual drug effect during