Title: MYOCARDIAL MYOSIN ISOENZYME SHIFTS AND THE EFFECTS OF HALOTHANE ON CARDIAC CONTRACTILITY IN NON-INSULIN TREATED SPONTANEOUSLY DIABETIC RATS

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Introduction: Cardiomyopathy unrelated to coronary macroangiopathy is a well-recognized complication of diabetes, with evidence of widespread asymptomatic involvement in humans. Prominent as a potential etiologic factor is the shift in cardiac myosin isoenzymes which has been documented in both chemically induced and spontaneous diabetes in rats. We have demonstrated more rapid and more complete isoenzyme shifts in diabetic BB/W rats, a strain which develops spontaneous euthyroid diabetes, than in chemically induced diabetic rats. Preliminary observations while dealing with these spontaneously diabetic rats indicated to us that they may be more sensitive to the myocardial depressant effects of the potent inhalational anesthetics than non-diabetic rats. We therefore sought to evaluate the relative myocardial depressant effects of halothane in spontaneously diabetic, myosin isoenzyme shifted rat hearts.

Methods: Cardiac myosin isoenzymes were analyzed by native gel electrophoresis from 16 3.5-5 month old, 225-275 g male diabetic BB/W rats maintained without insulin for 9-28 days. These animals received daily subcutaneous injections of 9 ml Ringer's lactate and 1 meq solution bicarbonate. The animals were chronically hyperglycemic (blood glucose 532 ± 12 mg/dl) and acidotic (bicarbonate 16.7 ± 1.8 meq/l; pH 7.06- 7.30) despite chronic bicarbonate therapy. In addition, six non-insulin treated diabetic rats and four non-diabetic age matched BB/W rats were killed and their hearts removed for in vitro myocardial contractility studies. Following removal, each heart with a portion of the aorta was rapidly transferred to an isolated heart perfusing apparatus. The hearts were perfused with Krebs bicarbonate solution. Once attached to the apparatus a force displacement transducer was attached to the apex of the heart with suture and a preload of 5 g was placed on the heart. Once normal contractions were established control measurements were made of heart rate (HR), tension time index (TTI), peak systolic tension (PST), and time to peak tension (TPT). Following this, each heart was perfused with Krebs solution equilibrated with 1% or 2% halothane and the contractility measurements repeated.

Results: Of the 16 diabetic animals in which isoenyzmes were determined, 15 showed an essentially complete myosin isoenzyme shift from the normal V1 to the V3 form. Examination of the data showed that this shift began by 12 days following the discontinutation of insulin and was essentially completely shifted by 16 days. As can be seen in Figures 1 through 4, diabetic hearts demonstrated significantly lower contractility performance compared to normal hearts.

Discussion: The shift in myosin isoenzymes in the diabetic rat heart is associated with significant contractile impairment in the normal and anesthetized state. Surprisingly, in this preparation, in the nonanesthetized state the diabetic heart was capable of maintaining normal heart work, i.e., TTI (Fig 1) and reaching normal PST (Fig 2). However, the diabetic heart rate (Fig 3) and TPT (Fig 4) were significantly reduced compared to normal hearts. In addition, halothane caused significant reductions in all measured contractile parameters in diabetic hearts that were dose dependent and were more pronounced than in non-diabetic hearts. We conclude that in the spontaneously diabetic rat diabetes is associated with a shift in myosin isoenzyme types and results in increased susceptibility to the myocardial depressant effects of halothane.

Fig 1

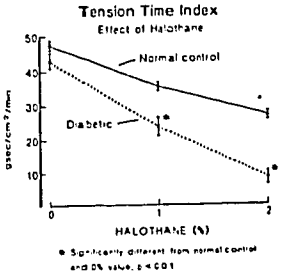

Fig 2

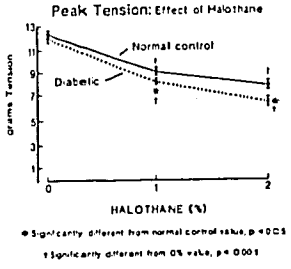

Fig 3

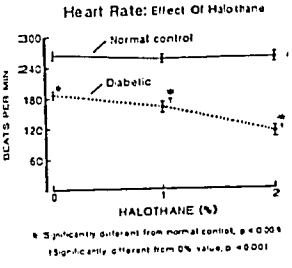

Fig 4