INTRODUCTION. Although the effects of halothane (HA) on the rate of protein synthesis has been studied in other organ systems,1 2 3 to our knowledge this has not been studied in the heart. Our purpose was to investigate the relationship of HA dose to rate of protein synthesis in the isolated, perfused rat heart. As a means of identifying a possible mechanism of HA effects, perfusions were done in the presence and absence of insulin, a known modulator of protein synthesis.

METHODS. A total of 60 male Sprague-Dawley rats (321 ± 28 g) were studied. Animals were killed instantly by decapitation in the absence of anesthesia, as recommended by our Institutional Animal Care and Use Committee. Hearts were then rapidly (within 20 sec) excised. Perfusions were of the Langendorf type, in which the heart does no external work, but ejects against a controlled pressure. Aortic pressure was held constant at 65 mm Hg at all times during the perfusions for all hearts. A recirculating Krebs-Henseleit buffer at low volumes (12 cc total) was utilized, modified to include 0.1% bovine serum albumin, normal serum concentrations of 19 amino acids, and 0.40 mM phenylalanine. Uniformly racilabelled [U-14C] phenylalanine ([14C] PHE) was added after 5 min of recirculating perfusion for first hour rates of protein synthesis, and after 65 min for second hour rates. As outlined in Table 1, perfusions were performed in either the presence or absence of insulin (0.4 mU/ml) at several HA concentrations. Measured HA vapor was administered with QH2O (95:5) and equilibrated with the buffer by diffusion in the oxygenator circuit. HA concentrations were intermittently confirmed at the outlet of the oxygenator, using mass spectrometry (MGA 1100). At the conclusion of each perfusion, hearts were clamped between aluminum blocks cooled in liquid nitrogen (LN2). Frozen heart pellets were pulverized in a mortar and pestle cooled in LN2. Heart proteins were purified and washed with perchloric acid. The washed pellets were dissolved in 0.3 N NaOH, and an aliquot counted by liquid scintillation spectrophotometry for Incorporated radioactivity. A second aliquot was assayed for protein content.

Protein synthesis data are presented as DPM of 14C PHE incorporated per milligram protein per hour (DPM/mg protein-hr) for the different perfusion conditions. Data were normalized for small differences in radioactivity concentrations in the buffer. Differences between rates of protein synthesis across groups were analyzed for statistical significance using the two sample t-test, with α=0.05.

RESULTS. Results are shown in Table 2. For the first hour, in the presence of insulin, rates of protein synthesis were unchanged for all concentrations of halothane studied, when compared to controls. During the second hour, in the presence or absence of insulin, rates of protein synthesis were similarly unchanged for any HA concentration studied, when compared to controls. There was a significant decrease in rates of protein synthesis in the hearts without insulin versus those with insulin during the second hour (p<0.05 for controls, 1.5% HA, and 4.0% HA).

DISCUSSION. Our results for rates of myocardial protein synthesis in the presence of HA show no significant change in the presence of anesthetics, under the specific conditions of our study. This finding is significant, since studies of lung,1 liver,2 and human lymphocytes,3 all show an Immediate, dose-dependent, and reversible inhibition of protein synthesis by HA. This suggests that the mediator of protein synthesis in the heart may differ from that in other organs.

Insulin has been found to increase protein synthesis by promoting faster rates of both peptide chain initiation and elongation, an effect that is more pronounced during the second hour of a perfusion. The faster rates of protein synthesis seen in the presence of insulin in this study are consistent with results reported earlier.4 However, since a differential effect of halothane in the presence or absence of insulin was not seen in the present study, it appears that HA does not interfere with the insulin effect under the conditions of this study.

HA in whole animal models has been shown to decrease myocardial cyclic AMP (cAMP).5 On the other hand, increased rates of protein synthesis in perfused hearts under conditions of elevated aortic pressures (120 mm Hg) have been linked with elevations in levels of cAMP, an effect which can be blocked by methacholine.6 From these two findings, one could expect a decrease in protein synthesis in the presence of HA; the absence of an effect suggests that under the conditions of a constant aortic pressure of 60 mm Hg, cAMP modulation of myocardial protein synthesis may be minimal, and becomes Important under conditions which stretch the myocardium (i.e., at higher aortic pressures). Cyclic AMP levels under these perfusion conditions, as well as studies under different conditions, are needed to further elucidate HA effects on myocardial metabolism.