## REFERENCES

1. MacKenzie AE, Allen G, Lahey D, Crossan M, Nolan K, Mettler G, Worton RG, MacLennan DH, Korneluk R: A comparison of the caffeine halothane muscle contracture test with the molecular genetic diagnosis of malignant hyperthermia. ANESTHESIOLOGY 75:4–8, 1991
2. MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG: Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature 343:559–561, 1990
3. Levitt RC, Meyers D, Fletcher JE, Rosenberg H: Molecular genetics and malignant hyperthermia. ANESTHESIOLOGY 75:1–3, 1991


*(Accepted for publication December 27, 1991.)*

Anesthesiology
76:660–661, 1992

*In Reply:*—In our recent publication,[1] the results of a molecular genetic analysis of a large malignant hyperthermia (MH) kindred were reported. It was demonstrated that complete linkage between inheritance of a restriction fragment length polymorphism (RFLP) in the ryanodine receptor (RYR1) gene and the MH phenotype was contingent upon alteration of the thresholds defining positive *in vitro* contracture tests (IVCT). Hopkins *et al.* have speculated that if these altered thresholds were applied to the data in an earlier publication first reporting RYR1–MH linkage,[2] such linkage would not have been demonstrated. We believe that Hopkins *et al.* are correct in their assertion. However, we are uncertain what implications we are to derive from this point.

In the study reported in reference 1, the IVCTs were carried out in one laboratory, whereas in the reference 2 study, they were performed in another. Potential false positive diagnoses of probable normal individuals were identified in reference 1 but not in reference 2. No problem was noted in the diagnoses of MH individuals in either paper. The origin of the false positives may lie with normal variations of contracture response in the family in reference 1, or it may be a laboratory-specific phenomenon. Regardless of the origin, we are unclear how the presence of false positivity in some but not all MH kindreds renders the evidence for RYR1–MH linkage invalid. Nonetheless, Hopkins *et al.* go on to state that based on their experience in testing 2,300 patients for MH susceptibility (presumably IVCTs), no conclusions regarding the linkage of MH and RYR1 can or should be made from the data in references 1 and 2. It is not readily apparent why performing a physiologic assay (albeit 2,300 times) is helpful in the assessment of the accuracy of what is primarily a genetic test. We believe that determination of the validity of linkage for each MH family can most readily be effected by collecting IVCT data and then assaying for cosegregation of positive IVCT results with one of the many RYR1–RFLP alleles that have been defined. We also believe that the *a priori* rejection of RYR1–MH linkage because of a postulated methodologic flaw is unwarranted. Should such weaknesses exist, they will emerge with the analysis of kindreds large enough to support or refute genetic linkage, such as that studied in reference 1.

Assertions for or against RYR1–MH linkage will ultimately be borne out or refuted by additional studies in this area. In this regard, a transcriptionally significant RYR1 mutation has recently been linked to MH in five breeds of swine,[3] resulting in a lod score of 102 with a recombinant fraction of 0.0.[4] The reappearance of the mutation across the species barrier in a human family in whom it was observed to cosegregate with MH[5] makes almost incontestable the conclusion that mutations in the RYR1 gene cause at least some forms of MH in humans.

We do not believe, however, that all inherited forms of human MH are based in the RYR1 gene. MH has been associated with a variety of other neuromuscular diseases,[6] of which myotonic dystrophy (separated from RYR1 on chromosome 19[7]) and Duchenne muscular dystrophy, on the X chromosome, are but two examples. Moreover, absence of linkage of RYR1 to MH has been recently observed in some MH kindreds.[8,*] The common causal feature in MH is undoubtedly lack of regulation of calcium within skeletal muscle cells. This might result from a series of mutations in a series of proteins in the sarcoplasmic or endoplasmic reticulum, the plasma membrane, or other organelles whose common feature is to diminish the ability of muscle cells to regulate intracellular calcium. Since there is now evidence of at least one RYR1 mutation causing MH,[5] and since there is a physiologic rationale for the involvement of defects in the ryanodine receptor in MH, in those family cases where RYR1–MH linkage cannot be established, research should be directed toward determination of whether the IVCT is in error or whether linkage indeed lies with an alternate gene.

* Deufel T: Personal communication.

ALEX MACKENZIE, M.D., PH.D.
*Assistant Professor*
*Division of Genetics*
*Department of Paediatrics*
*University of Ottawa*
*Children's Hospital of Eastern Ontario*
*401 Smyth Road*
*Ottawa, Ontario, Canada K1H 8L1*
DAVID H. MACLENNAN, PH.D.
*J. W. Billes Professor of Medical Research*
*Banting and Best Department of Medical Research*
*University of Toronto*
*C. H. Best Institute*
*112 College Street*
*Toronto, Ontario, Canada M5G 1L6*


## REFERENCES

1. MacKenzie AE, Allen G, Lahey D, Crossan ML, Nolan K, Mettler G, Worton RG, MacLennan DH, Korneluk R: A Comparison of the caffeine halothane muscle contracture test with the molecular genetic diagnosis of malignant hyperthermia. ANESTHESIOLOGY 75:4–8, 1991
2. MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, Frodis W, Britt BA, Worton RG: Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature 343:559–561, 1990
3. Fujii J, Otsu LK, Zorzato F, De Leon S, Khanna VK, Weiler J, O'Brien PJ, MacLennan DH: Identification of a mutation in the porcine ryanodine receptor that is associated with malignant hyperthermia. Science 253:448–451, 1991

4. Otsu K, Khanna VK, Archibald AL, MacLennan DH: Co-segregation of porcine malignant hyperthermia and a probable causal mutation in the skeletal muscle ryanodine receptor gene in backcross families. Genomics 11:744–750, 1991
5. Gillard EF, Otsu K, Fujii J, Khanna VK, De Leon S, Derdemezi J, Britt BA, Duff CL, Worton RG, MacLennan DH: A substitution of Cysteine for Arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia. Genomics 11:751–755, 1991
6. Brownell AKW: Malignant hyperthermia: relationship to other disease. Br J Anaesth 660:303–308, 1988
7. MacKenzie AE, Korneluk RG, Zorzato F, Fujii J, Phillips M, Iles D, Wieringa B, Le Blond S, Bailly J, Willard HF, Duff C, Worton RC, MacLennan DH: The human ryanodine receptor gene, its mapping to 19q13.1, placement in a chromosome 19 linkage group and exclusion as the gene causing myotonic dystrophy. Am J Hum Genet 46:1082–1089, 1990
8. Levitt R, Nouri N, Jedlicka AE, McKusick VA, Marks AR, Shutack JG, Fletcher JE, Rosenberg H, Meyers DA: Evidence for genetic heterogeneity in malignant hyperthermia susceptibility. Genomics 11:543–547, 1991

*(Accepted for publication December 27, 1991.)*

Anesthesiology
76:661, 1992

## Use of a Capnometer to Detect Leak of Carbon Dioxide during Laparoscopic Surgery

*To the Editor:*—In laparoscopic surgery, carbon dioxide is insufflated into the abdominal cavity to make space for the procedure. Sometimes a leak in one of the connectors or orfices of the instruments allows the distending gas to escape and results in poor visibility. Localization of the leak is not always straightforward, and operating time is lost. Capnography can be used to solve this problem by having the surgeon examine the suspected sites with a sterile end of a gas sampling tube. The capnometer will sense the leaking carbon dioxide, and the indicator will rise to the top of its scale.

PERTTI PESONEN, M.D.
*Department of Anesthesiology*
PEKKA LUUKONEN, M.D.
*Department of Surgery*
*Mehilainen Hospital*
*P Hesperiankaty 17*
*00260 Helsinki, Finland*

*(Accepted for publication January 2, 1992.)*

Anesthesiology
76:661–662, 1992

## Afterload Dependence of Postischemic Myocardium

*To the Editor:*—The study by Buffington and Coyle[1] on the load dependence of postischemic myocardium provides valuable data on the residual functional capacity after perfusion is reestablished. As pointed out by the authors, the marked decrement in the contractile response of the postischemic myocardium to increases in preload, compared with its control response, is of great interest and importance. The authors also contend that the response of the postischemic myocardium to changes in afterload is not different from the control response and suggest that afterload reduction therapy would not be expected to have the same particular benefit as when this type of therapy is used in cardiac failure.

In fact, the data support the opposite conclusion. The authors base their conclusion on the fact that the *slope* of the relationship between systolic wall thickening and mean arterial pressure (MAP) was the same for control and postischemic myocardium (fig. 2 of their paper). However, although the slopes of these relationships are parallel, the absolute values of the data are different; at all combinations of left atrial pressure and MAP, the systolic thickening of the postischemic myocardium is less. As a result, the *percent* improvement in systolic wall function as MAP is reduced from 110 to 70-mmHg is much greater in the postischemic myocardium than in the control state. This is borne out by the data of tables 1 and 2 from the paper, which present systolic wall thickening as a percent of end-diastolic thickness or in absolute units (millimeters), respectively.

TABLE 1. Recalculated Data from Tables 1 and 2[1]

| | Preload ($cmH_2O$) | Control (% increase) | Postischemic (% increase) |
|---|---|---|---|
| Table 1 data | 3 | 7.1 | 17.6 |
| | 6 | 26.7 | 38.9 |
| | 9 | 18.9 | 57.9 |
| Table 2 data | 3 | 11.1 | 25.0 |
| | 6 | 33.3 | 53.3 |
| | 9 | 21.9 | 56.2 |

Using the mean values presented in these tables (either as percents or absolute units), we have calculated the percent *increases* in thickening as MAP is decreased from 110 to 70 mmHg at different left atrial pressures; the data are for the test zone before (control) and postischemia. Percent increases (table 1) were calculated as follows:

$$\frac{\text{systolic thickening at 70 mmHg MAP} - \text{systolic thickening at 110 mmHg MAP}}{\text{systolic thickening at 110 mmHg MAP}} \times 100$$

It can be seen that the postischemic myocardium demonstrates a much greater relative improvement in systolic wall thickening with decreases in MAP from 110 to 70 mmHg than does the control state. Thus, the trends in the data suggest that the increased sensitivity of the failing heart to afterload and the value of afterload reduction therapy are concepts that also apply to the postischemic myocardium. Statistical tests of these trends would require analysis of the paired control and postischemic data for individual animals.