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Finger Blood Pressure

To the Editor:—I congratulate Gibbs and colleagues[1] for their timely evaluation of the Finapres™ to measure accurately mean arterial pressure and for the form in which they chose to present the results. In addition to the bias and accuracy of the measurements, they show the frequency, magnitude, and duration of the discrepancies between the Finapres™ and radial artery mean arterial pressure measurements. Had these researchers used regression analysis or calculated the correlation coefficient between the two sets of measurements, they would have reached the opposite conclusions, as have others.[2] However, the statement, "It is hoped that future improvements in engineering design will lead to greater reliability of FIN measurements" is overly optimistic. The idea of measuring blood pressure accurately and noninvasively and in a finger is very alluring; unfortunately, it has been known for some time that finger blood flow and pulse pressure are regulated by sympathetic vasoconstriction.[3] Nijboer and Dorlas,[4] using finger and ear plethysmograms in anesthetized patients, found that whereas the pulse pressure on the pinna of the ear was minimally affected by sympathetic stimulation (laryngoscopy, surgical stimulation, *etc.*), pulse pressure on the finger was influenced greatly by such events. Therefore, although the finger could be a good place to measure peripheral vascular response to sympathetic stimulation, it is not a good place to assess the general state of the circulation.

Do we need noninvasive measurement of blood pressure in dangerously sick patients? If we do, the carotid, femoral, or radial artery areas should be used. Technically, it should not be difficult to develop the proper transducer; however, its placement will require great attention to detail, a rare commodity in clinical situations.

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Inconsistency of Data Linking the Ryanodine Receptor and Malignant Hyperthermia Genes

To the Editor:—We read the article by MacKenzie and colleagues[1] with great interest. However, we found the rationale behind the evidence for linkage between the malignant hyperthermia (MH) and ryanodine receptor (RYR) genes tortuous, if not entirely circular.

The original paper by MacLennan *et al.*[2] suggesting the RYR gene as a candidate gene for MH produced a lod score of 4.2. This degree of linkage was obtained using *in vitro* contracture test (IVCT) thresholds for the phenotyping of MH susceptibility similar to those that produced no linkage with the RYR gene in the pedigree described by MacKenzie *et al.* If the revisions to the threshold values of the IVCT suggested by MacKenzie *et al.* were applied to the patients in the paper by MacLennan *et al.*, it is difficult to imagine that linkage between the RYR gene and MH could still be demonstrated.

From our experience of testing more than 2,300 patients for MH susceptibility, we believe that no conclusions regarding the linkage of MH and the RYR gene can or should be made from the data presented by MacLennan *et al.* or MacKenzie *et al.* This view is based on their use of the *combined* halothane and caffeine test with its high false positive rate (11% in our unpublished series; see also the editorial by Levitt *et al.*[3]) and, in the case of MacKenzie *et al.*, by the use of a 1% halothane test, which lacks the sensitivity of tests using 2% or 3% halothane.

Great care must be taken in selecting those families suitable for genetic studies, and the papers by these Canadian groups highlight the need for the full reporting of IVCT methods and results (*i.e.*, the degree of muscle contraction in response to the stated concentration of caffeine and of halothane) in all studies investigating the genetics of MH. Also, because of the likelihood that MH is a heterogenous disorder,[3] data from more than one family should not be pooled without good reason.

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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.

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