An update on malignant hyperthermia diagnostics and anaesthetic machine preparation for patients at risk in Africa

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The EMHG first published its protocol for an in vitro contracture test (IVCT) in 1984¹ and this has ever since formed the bedrock of clinical diagnosis and phenotyping. In 2015² the EMHG published the updated guidelines for investigation of malignant hyperthermia susceptibility. Evidently the rigour of the IVCT stood the test of time and was used in more than 10 000 individuals worldwide to define their MH risk, representing an example of preventative medicine and improved patient safety.

The IVCT is a clinically useful and robust test³ that is sensitive and specific. The initial point estimate for specificity of 94% could possibly be explained by the use of atrophied muscle, because muscle sampled during ipsilateral joint arthroplasty was included.³ The reported point estimate for sensitivity of the IVCT was 99%. On closer examination of the single patient (case 4) who reduced the sensitivity from 100% to 99%, it was found that the authors misapplied the Larach Clinical Grading Scale (LCGS)⁴ which specifically excludes rigidity on emergence of general anaesthesia as an indicator of MH. The LCGS score for this patient should have been 35, therefore excluding the patient from the category of “almost certain” MH used to determine the sensitivity of the test. This was possibly a case of iatrogenic hyperthermia and febrile convolution in an infant who had received atropine before surgery and overly enthusiastic warming during surgery.

The robustness of the IVCT was further evident from its use to phenotype members of MH families in molecular genetic studies, firstly with the linkage analysis that identified RYR1 as the major locus implicated in MH⁵, ⁶ and later with the second locus CACNA1S⁷ providing further evidence for the involvement of interacting gene products. STAC3 is the most recent gene associated with MH.⁸ A homozygous STAC3 mutation has been linked to Native American myopathy and MH susceptibility in one Native American family.⁹

The complex nature of the genetics of MH, which would not have been realized without the IVCT, has been confirmed further by early results of next-generation sequencing in MH families.¹⁰¹¹¹² Once an MH-causative mutation has been identified in an MH index patient, the family can be screened for this mutation and all the relatives carrying this mutation will be considered MH susceptible. Unfortunately 50% of MHS individuals do not carry potentially pathogenic variants in the known MH-associated genes, resulting in a rather low sensitivity of MH genetic testing.¹³

Currently the presence of rare variants in RYR1, CACNA1S and STAC3 also has a low specificity. While there are more than 200 reported RYR1 variants associated with MH, only 42 RYR1 and 2 CACNA1S variants are accepted as MH causative (www.emhg.org) and can be used in diagnostic genetic testing for MH. It is also important to note that these causative mutations are population specific and the patients from African origin are most likely to be negative for these causative mutations described in Caucasian patients. If the specific variants in the African population have been identified, it, needs to be shown to produce functional changes compatible with a pathogenic role in appropriate model cell systems.¹⁴ Currently we do not have a laboratory in South Africa that does functional studies and calcium handling.

Because of the complex nature of MH genetics, a negative genetic test result cannot be used to rule out MH susceptibility and patients with negative genetic results should be offered in vitro contracture testing to confirm their MH-negative status.

Before the establishment of in vitro contracture testing¹⁵, persistently raised serum creatine kinase (CK) concentration was documented in association with MH susceptibility and proposed as a diagnostic test. The utility of resting CK concentration is, however, limited because of a lack of sensitivity and specificity.¹⁶ However, in patients with so-called idiopathic hyperCKaemia, investigation of MH susceptibility may be warranted after other causes have been excluded by a full neurological examination.¹⁷ As with patients with rhabdomyolysis, the neurologist should liaise with an MH testing centre, where any muscle biopsy should be carried out to also do IVCT and histology.

Criteria for patient referral

The most common reasons for referral for investigation of MH susceptibility² are listed in Table 1.
The diagnostic pathway for investigation of MH susceptibility

The diagnostic pathway for investigation of MH susceptibility is explained in the following flow chart published by the EMHG.²

![Flow Chart](https://via.placeholder.com/150)

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it is evident that because of the rebound phenomenon, residual emission of anaesthetic vapour still occurs. It is also impossible to give a fixed time for purging to create a safe, clean machine as the amount of vapour absorbing parts in each make and model of anaesthetic machine differs. Therefore, the time it takes to purge the machine to get the vapour concentration in the fresh gas system to less than 5 ppm differs as well. It is recommended that after lengthy purging, fresh gas flow remains above 10 L/min throughout the anaesthetic.

Alternatively, activated charcoal filters (ACFs) can be used to prepare the anaesthetic machine to deliver a trigger-free general anaesthetic to MH susceptible patients or to patients with increased risk of developing an MH crisis. ACFs can clean the anaesthetic machine in 90 seconds, irrespective of the specific make or model.

Recommendations on the use of activated charcoal filters are summarised in Table 2.

Table 2. Recommendations on the use of activated charcoal filters in preparing an anaesthetic machine for a malignant hyperthermia susceptible patient.

<table>
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<th>Recommendations</th>
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<tr>
<td>1. Remove vaporisers from the anaesthetic machine.</td>
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<td>2. Flush the circuit for 90s with oxygen or air @ 10 L/min using the ventilator with a 2 litre test lung attached.</td>
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<td>3. Change the full breathing circuit and soda lime while maintaining flushing @ 10 L/min (the ventilator is left unchanged).</td>
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<td>4. Insert ACFs on both inspiratory and expiratory ports of the breathing circuit.</td>
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<td>5. Maintain FGF of 10 L/min for 90 minutes from the beginning of the anaesthetic.</td>
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<td>6. After 90 minutes it is safe to reduce the FGF to 3 L/min.</td>
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<td>7. Then ACFs can be used at 3 L/min until a total of 12 hours has elapsed from the commencement of the anaesthetic.</td>
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<td>8. After 12 hours ACFs need to be replaced.</td>
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<td>9. ACFs are single-use items.</td>
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<td>10. Single ACF can be placed in only the inspiratory limb but if misplaced accidentally in expiratory limb, it will be completely ineffective. Because of this potentially dangerous situation, it is recommended that ACFs be used as a pair, one in each limb.</td>
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Conclusion

Being able to determine potential malignant hyperthermia patients’ real risk after so many years without an IVCT laboratory definitely improves the standard of care in South Africa. Additionally, the in vitro contracture testing facility could also be contributing to the DNA mapping of population groups with undefined causative MH variants. The availability of activated charcoal filters gives anaesthesiologists an option of expediting and improving anaesthetic machine preparation for malignant hyperthermia susceptible patients. References