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In Reply:

Regarding the number of letters Dr. Kempen produced in the past years, his comment relative to our study about perioperative use of statins[1] might be useful for understanding perioperative effect of chronic cardiac treatment.

The first part of the comment was related to the inclusion of variables in the propensity score. We did not include the variable "Year of surgery" in the propensity score because it did not predict the presence of statins. A better understanding of the method would have allowed consideration that patients' medical history might have changed during the year in question, and that the expected effect of this covariable on the probability of being treated by statins was implicitly characterized by other variables that were already included in the propensity score.

As we have shown, the adjustment of the propensity score provided a very good balance between statin users and control subjects. The inclusion of the year of surgery would not have improved the propensity score, as well as the other variables mentioned in the comment. The second part of the comment was related to the surgical characteristics. The rate of endograft procedures remained constant, and as low as 7% during the study period. This low rate, associated with the high experience of the surgeons, probably explains why we did not observe any conversion to open procedures. Endograft treatment was not associated with statin use. Furthermore, although probably not outlined clearly enough, these patients were not included in the analysis, because the rate of postoperative major adverse events is recognized as being lower.

The difference between abdominal and lumbar approach was not associated with the preoperative use of statins, when the other variables were taken into account. In fact, it might be obvious for most of us that some surgical characteristics are predictors of postoperative adverse events. However, the question is to know whether these events are associated with the use of statins. This is the aim of propensity score, *i.e.*, to estimate the probability of receiving the treatment of interest given the other covariates.

In randomized controlled trials, treatment allocation is at random, meaning that the probability of receiving the experimental treatment is 0.5 for each patient. Conversely, for propensity score analysis, the probability of receiving the experimental treatment, given the other covariates, is identical for each patient. However, because some unknown and underlying covariables might operate, a propensity score analysis should not conclude about causality. Consequently, randomized controlled trials will always remain the gold standard.

Finally, the comment of Dr. Kempen underlines the need for education about modern statistical methods. We fully agree upon the role of propensity score methodology in exploring drug effects as well as in the need of review articles for emergent and complex statistical methodology.

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Relevance and Value of a Morphine Immunoassay as a Diagnostic Aid for Neuromuscular Blocking Drug-induced Anaphylaxis

To the Editor:

Neuromuscular blocking drugs (NMBDs) are the major cause of episodes of immediate hypersensitivity during the perioperative period.[1] The detection of liberated mast cell tryptase[2] is used to confirm an anaphylactic event; skin prick testing with all currently used unconjugated NMBDs, followed by intradermal tests if necessary, is central to identifying the culprit, as well as cross-reacting drugs. Identification of the implicated NMBD(s) is important for providing safe anesthesia for the patient in the future. Although skin tests remain the diagnostic tool of choice, their sensitivity and specificity have at times been questioned. Serum immunoglobulin E (IgE) antibody assays are often used in cases involving skin test-negative or equivocal reactors or when skin tests are unreliable or unavailable, making these tests useful adjuncts to skin and tryptase tests. They are also valuable when applied to sera taken at the time of the reaction, to preoperative serum samples, and serum taken before or after death.[3] The IgE assay in inhibition form can sometimes help in identifying and providing immunochemical insights into cross-reacting drugs.[3,4] After extensive testing over many years on hundreds of serum samples, a morphine-solid phase was shown to be superior to NMBD-solid phases and other selected solid phases for the detection of NMBD-reactive IgE antibodies, and its use, along with the tryptase and skin tests, was strongly advocated as the best diagnostic combination of

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examinations to confirm a true IgE-mediated reaction to a NMBD.[3,5]

The value of the morphine immunoassay as a test for the detection of NMBD-reactive IgE antibodies is the subject of a recent study by Laroche *et al.*[6] An initial response to the work could be statement of the precept "better late than never." To expand on this, one needs to draw attention to a historic perspective that the paper does not provide. Although the study is entitled "Evaluation of a *new* routine diagnostic test …" (my emphasis) the test is not new in the sense that it originates from a morphine immunoassay applied to detect NMBD allergic sensitivity over 20 yr ago[7] and stems directly from a large study over a decade ago in which the assay was used to examine sera from 347 patients who experienced an adverse reaction during anesthesia.[5] Describing the assay as new gives a wrong impression; describing the assay as "a new *commercial* routine diagnostic test" or an "improved" test (if that is what it turns out to be) might perhaps be more correct.

A false claim in the paper, and one that has been repeated in the French NMBD-anaphylaxis literature for many years, attributes the introduction of a choline solid phase support for the detection of NMBD-reactive IgE antibodies to research results published in the early 1990s. Choline chloride was used in one of the studies[8] and *p*-aminophenylphosphorylcholine in the other.[9] The presence of a charged phosphate group and a hydrophobic aromatic ring in the choline derivative *p*-aminophenylphosphorylcholine introduces unnecessary structures and potentially opens the door to unwanted interactions with antibodies with specificities unrelated to substituted ammonium ions. The reasons for using choline to detect IgE antibodies instead of succinylcholine and other NMBDs containing quaternary ammonium ions, together with a method of preparation, were provided in detail in two previous articles.[10,11] The two later studies[8,9] introduced no conceptual advancement.

A common error of loose terminology is perpetuated in the study by Laroche *et al.*[6] In discussing the complementary structures recognized by NMBD-reactive IgE antibodies, the quaternary ammonium ion is often referred to in the literature as the IgE-binding determinant despite our ignorance in most cases of the origin and precise ammonium group specificity of the antibodies.[3] In the initial antibody combining site studies on sera from NMBD-allergic patients, cross-reactive tertiary as well as quaternary ammonium ions on a range of different drugs and chemicals were identified as IgE-binding (allergenic) determinants.[4,12] These determinants were therefore collectively described as substituted ammonium ions[12] rather than simply quaternary ammonium ions and that terminology should continue to be used. The commercial morphine immunoassay is called the quaternary ammonium morphine (QAM) test although morphine contains a monomethyl tertiary ring nitrogen, some NMBDs contain tertiary as well as quaternary ammonium groups, and the assay detects IgE-reactive tertiary as well as quaternary ammonium structures.

Despite these criticisms, the study by Laroche *et al.*[6] is an overdue but welcome reminder of a specific, sensitive, and labor-saving procedure with a predictive value that is quite good. The test should be particularly appropriate as a backup for routine skin tests and in cases where clinical data indicate NMBD-induced anaphylaxis but skin tests prove negative, unreliable, or cannot be carried out. Widespread application of the morphine immunoassay together with carefully compiled case histories, serum tryptase determinations, and skin tests currently offers the best combination of examinations needed for successful diagnosis, and the IgE assay promises to identify some previously undetected NMBD-induced allergic reactions.[5,6] Until further significant advances are made in our understanding of the origin of NMBD sensitization and the consequent IgE antibody-combining site specificities,[3] or an improvement in the form of a new and/or novel diagnostic test is pioneered, routine application of these four diagnostic approaches currently offers the clinician the best chance of achieving a correct diagnosis.

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In Reply:

We thank Dr. Baldo for his interest in reading our article "Evaluation of a New Routine Diagnostic Test for Immunoglobulin E (IgE) Sensitization to Neuromuscular Blocking Agents."[1] Dr. Baldo is a pioneer in the study of immunologic mechanisms of the sensitization to neuromuscular blocking agents. His group has been the first in demonstrating the presence of IgE reacting against drugs containing quaternary and tertiary ammonium in patients sensitized against muscle relaxants, using quaternary and tertiary chemical compounds coupled to epoxy-Sepharose.[2,3] We confirmed these results 3 yr after their previous observation, using the same procedure.[4,5] We disagree with Dr. Baldo's comment "the French NMBD [neuromuscular blocking drug]-anaphylaxis literature for many years attributes the introduction of a choline solid phase support for the detection of NMBD-reactive IgE antibodies to research results published in the early 1990s," and we did cite eight of Dr. Baldo's publications. We invite him to read our recent review on this topic, which clearly chronicles his contribution in the field.[6]

In our experience, the use of the epoxy-Sepharose solid phase was problematic for diagnostic use, and this led us to subsequently improve a quaternary ammonium Sepharose-radioimmunoassay, which shared superiority in several aspects[7]: the epoxy-Sepharose procedure provided a much lower coupling efficiency of the chemical compound than the quaternary ammonium Sepharose reactive phase, with consequences in the sensitivity of the assay; and the epoxy-Sepharose procedure introduced an aliphatic hydrophobic chain between the Sepharose gel and the coupled drug, which could produce a nonspecific binding of hydrophobic IgE.[8] In contrast, the choline is directly coupled to Sepharose by an ether bond, with a high coupling efficiency and no addition of any aliphatic chain, in the quaternary ammonium Sepharose assay. These differences may explain that the quaternary ammonium Sepharose-radioimmunoassay produces higher sensitivity and specificity than the epoxy-Sepharose method, in our experience.[7] We would also like to point out that the radioimmunoassay with aminophenylphosphorylcholine was as efficient as the quaternary ammonium Sepharose-radioimmunoassay, in our hands.[9] Finally, the diagnostic value of the choline solid phases used in France[7,9] has been carefully evaluated and used in many clinical studies; these studies explain that they have been recommended by the European Network of Drug Allergy and the French Society for Anaesthesia and Intensive Care.[10]

The concept of using a morphine solid phase to bind neuromuscular blocking agent (NMBA)-specific IgE is not new[11] and was used in Dr. Baldo's laboratory for years.[12] However, this homemade assay was not available outside Australia. In contrast, the assay that we evaluated is the first commercial test using morphine as a sensitive marker to detect NMBA-specific IgE and is available to any specialized laboratory worldwide. This is why the word "new" was associated with "routine" in the title of our article. The morphine-based assay may have some limitations for its predictive value.[1] For example, Florvaag *et al.* demonstrated a high prevalence of IgE antibodies against morphine in Norwegians, probably in relation to the high consumption of pholcodine-containing syrups in this country.[13]

Dr. Baldo found questionable the name used to designate the assay we tested (quaternary ammonium, morphine), according to the nature of the ammonium ions responsible for NMBA allergy. The topic of our article was the clinical evaluation of a diagnostic test measuring sensitization to NMBA, and we have not discussed in any great detail the allergenic epitopes involved in NMBA allergy. We agree with Dr. Baldo that quaternary as well as tertiary ammonium ions are recognized by IgE from NMBA-allergic patients. This implicates that the positive charge on the nitrogen is essential for IgE antibody recognition, not primarily whether the nitrogen is quaternary or tertiary. The terminologic use of quaternary ammonium ions in NMBA allergy probably has its origin from the fact that all NMBAs contain at least one quaternary ammonium ion. We agree that the current terminology was not stringent. However, the proposed use of "substituted ammonium ions" as a generic term is less specific, because it also includes secondary and primary ammonium ions. The most prudent use of terminology when referring to NMBA epitopes should be "quaternary and tertiary ammonium ions." Finally, the commercial test for IgE antibodies against NMBA described in our article is actually not marketed as a quaternary ammonium test but as "c260 morphine," thus reflecting the actual antigen on the solid phase.

We appreciate that ultimately Dr. Baldo does agree with our conclusion that this commercial test for NMBA sensitization is a useful diagnostic tool.

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