SSEPs and prognosis in postanoxic coma: Only short or also long latency responses?

To the Editor: We read with interest the article by Zandbergen et al.¹ Over 15 years ago, we found that absence of the N20 potentials within 24 hours after cardiac arrest excludes recovery of cognition^{2,3} and several other groups have confirmed our experience. The prognostic significance of the N20 potential is not the same in traumatic coma, however,⁴ and we have seen several adults who recovered cognition after head trauma despite bilateral absence of N20 on initial recordings.

The article by Zandbergen et al. also shows that evoked potentials do not clarify the outcome of those patients after arrest in whom the N20 potentials are preserved. Only well-focused, repeated clinical examination is adequate to define the outcome. No other neurophysiologic test or imaging technique is more reliable than repeated bedside clinical testing in this group of patients.

Diederik Zegers de Beyl, *Bruxelles, Belgium*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We appreciate the contributions of Zegers de Beyl et al. to the evaluation of SSEP for prognosis in postanoxic coma. However, only structured reviews of all relevant studies could demonstrate the predictive value of the absence of the N20 potential to have sufficient statistical reliability for use in clinical practice.^{5,8}

In patients with preserved N20 potentials, not only clinical testing, but also EEG and biochemical testing may be useful to identify additional patients with poor prognosis.⁹ We agree with Dr. Zegers de Beyl that the absence of the N20 potential in other conditions leading to coma is not as reliable to indicate a poor prognosis as in patients with postanoxic coma.^{6,7}

E.G.J. Zandbergen, J.H.T.M. Koelman, R.J. de Haan, A. Hijdra, for the PROPAC-Study Group, *Amsterdam, The Netherlands*

Disclosure: The authors report no conflicts of interest.

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Volunteering for early phase gene transfer research in Parkinson disease

To the Editor: We read with interest the article by Kim et al. on patient willingness to participate in hypothetical medical research.¹ They found no correlation between risk perception (RP) and risk tolerance (RT) and showed these risk parameters independently predicted willingness to participate.

Kim et al. quantified the OR for willingness to participate at 1.087 for each one-point increase in RT score and 0.912 for each one-point increase in RP score. Using these values, a table displaying the effect of compounding these independent OR was constructed, which illustrates the relative likelihood of willingness to participate based upon individual RP and RT scores. An arbitrary value of 1 was assigned to an individual with RP and RT scores of 50.

Table The effect of compounding independent OR

Risk tolerance score	Risk perception score		
	25	50	75
25	1.242	0.1242	0.01242
50	10	1	0.1
75	80.489	8.0489	0.80489

As shown, an individual with an RP score of 25 and an RT score of 75 is over 6,000 times more likely to participate than an individual with an RP score of 75 and an RT score of 25. This difference in likelihood to participate challenges the comment by Kim et al. that “Tolerance of risk associated with willingness to participate seems rational and ethically unproblematic.”¹

Is the decision to participate “rational” when the likelihood to participate is determined by subjective individual interpretation

of situational RP and RT? Is tolerance of risk “ethically unproblematic”? If you were a passenger in an airplane approaching bad weather, would you prefer that your pilot have a high RP score and low RT score or a low RP score and a high RT score? The concepts and roles of RP and RT in individual choice have been examined in automobile drivers and aircraft pilots, individuals in whom interpretation of risk has obvious consequences for others.²

Similarly, risk-taking preferences of subjects can have consequences for their families, investigators, and medical research sponsors. The work of Kim et al. is intriguing and presents concepts of risk that have received too little attention in the area of subject recruitment and selection in human research and experimentation.

Jack E. Riggs, Laurie Gutmann, Gerald R. Hobbs, *Morgantown, WV*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: Riggs et al. object to our statement, “Tolerance of risk associated with willingness to participate seems rational and ethically unproblematic.” Their objection is based on an analogy with airline safety and on a quantitative point, but both arguments are problematic.

Their analogic argument about an airline pilot is misplaced because the normative role of RT in airline safety is different from the informed consent context. For duly reviewed and approved research studies involving gene transfer for PD, the effect of a potential subject’s RT on his or her willingness to participate is ethically unproblematic because, at the point of deciding whether to participate in research, it is precisely the individual’s preferences and values that ought to matter. At that point, it is a matter of personal values and preferences of the potential subjects. Of course, their decision may indeed have an impact on those around them, but one would hope that it is the subject’s preferences that have priority since it is he or she who takes on the risk of neurosurgery and gene transfer.

The quantitative argument of Riggs et al. is problematic because it combines the effects of RP and RT; this approach magnifies the effects and increases the drama but misses the normative distinction between RT and RP. The independent effect of RT in the informed consent setting is ethically unproblematic because, as noted already, it reflects personal values and preferences and indeed is the very thing that ought to matter in informed consent decisions. As for the effect of RP, since it is something that can be more or less accurate and not merely a subjective preference, the ethics of its impact should be evaluated primarily on its accuracy. The goal in informed consent ought to be to improve accuracy of RP and to allow subjects to exercise their preferences regarding risk.

Syncope in migraine: The population-based CAMERA study

To the Editor: We read with interest the article by Thijs et al. on syncope in migraine.¹ These authors found a higher lifetime prevalence of syncope, frequent syncope, and symptoms of orthostatic intolerance among migraineurs compared to control subjects as reported by the patients, without finding objective evidence of autonomic system (ANS) dysfunction when measured by the autonomic reactivity tests. Our clinical experience suggests a clinical correlation at least as frequent as that reported.

We believe that several factors in the study design may have contributed to an underestimation of the presence of ANS dysfunction signs in migraineurs. First, the cases and controls were somewhat older (mean age 48 ± 8 years) than the typical patients with postural orthostatic tachycardia syndrome (POTS) and orthostatic intolerance, which commonly occur in women 15 to 50 years of age.² By selecting an older population of patients with migraine, the investigators may have failed to capture potential cases of migraineurs with POTS and other forms of ANS dysfunction.

Second, the orthostatic blood pressure and heart rate measurements in this study were performed while patients remained on antihypertensive medications. The use of some antihypertensive medications, such as beta-blockers, may blunt the orthostatic blood pressure and heart rate response and therefore may produce unreliable autonomic reactivity test results.³

Finally, cardiovascular measurements of supine, standing, and post-venipuncture blood pressure and heart rate may not have been sufficiently sensitive in detecting subtle ANS disturbance that may occur in migraineurs, as determined by previous investigators.^{4,5} Other tests of ANS function that were not performed in this study, such as Valsalva maneuver, resting rate variation during deep breathing, sustained hand grip, and head-up tilt test, may have been more informative in identifying subtle signs of ANS dysfunction in migraineurs.

For example, one study found a statistically significant elevated diastolic blood pressure and lowered resting rate variation during deep breathing, as well as a lower Valsalva ratio, which was not statistically significant, in disabled migraine patients compared to controls.⁴ Another study of migraineurs also found signs of ANS dysfunction when using Valsalva maneuver, sustained hand grip, and head-up tilt test.⁵ Further research in this area is needed.

Svetlana Blitshteyn, William P. Cheshire, Jr., *Jacksonville, FL*

Disclosure: The authors report no conflicts of interest.

To the Editor: The recent report by Thijs et al.¹ demonstrated in a population-based study a significantly higher prevalence of syncope in patients with history of migraine, and found no difference in the prevalence of POTS and orthostatic hypotension (OH) between migraineurs and controls. Certain aspects of this study deserve attention.

The authors described controls as "those who had indicated that they had no severe headaches interfering with daily activities and who had rated any headaches they had as 0 on the pain scale. This effectively excluded people with chronic daily headaches and cluster headache."¹ However, the authors did not emphasize that "people with minor migraine or an occasional tension headache might have been included" among controls, as the authors of an

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Disclosure: The authors report no conflicts of interest.

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earlier study on the same cohort of patients stated in their report.⁶ This is an important omission.

Moreover, how many controls had migraine? And how many controls with OH or POTS had migraine? If migraine and autonomic dysfunction, manifesting as OH or POTS, share a common pathophysiologic mechanism, then the inclusion of migraineurs among controls would decrease the likelihood of detecting differences in the prevalence of OH and POTS between patients and controls.

The authors state that the diagnosis of migraine in 863 cases was based on the 2004 International Headache Society (IHS) criteria.⁷ However, a previous report by the same study group on brain lesions in migraineurs indicated using the 1988 IHS criteria to diagnose migraine.^{6,8} The two cohorts of patients appear to be the same in the two reports,^{1,6} but the number of migraineurs and the prevalence of migraine with aura are the same in the two reports, despite using different criteria. Even minor changes in the IHS criteria can result in the exclusion of a small percentage of cases of migraine.⁹

Finally, the authors did not report 95% CI and OR. The reporting of CI and OR data is valuable for a better understanding of the range and level of observed differences. To illustrate this point, we calculated the 95% CI for the difference (15%) in prevalence of syncope between patients and controls (46% vs 31%) to be 6% to 25%. The OR was 1.93, with 95% CI = 1.26 to 2.97. Hence, a migraineur has nearly twofold increased odds of having syncope than controls, but this risk could be close to one or up to nearly threefold. One wonders what the OR and CI for the prevalence of syncope would be if migraineurs were excluded from the control group?

Imad T. Jarjour, E. O'Brian Smith, *Houston, TX*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: Drs. Blitshteyn and Cheshire raise several points suggesting our study may have underestimated the prevalence of autonomic dysfunction in migraine. Overall, it should be noted that our study was population-based and not a patient population recruited from a headache clinic.

First, whether the relatively high age in our study (mean age 48 ± 8 years, range 30 to 60 years) may have missed POTS cases is debatable. POTS indeed typically presents between the ages of 15 and 50 years. Only limited information is available on the prognosis of POTS, which suggests that it tends to persist for many years¹⁰; if so, cases would still have been present.

Secondly, antihypertensive medication may affect cardiovascular reactivity measures, but a lowered responsivity seems more likely to result in falsely abnormal results rather than falsely normal results. Such medication may cause clinically relevant OH. Regardless, there were reasons not to exclude subjects with antihypertensive medication: migraineurs with frequent headaches may use antihypertensive medication for migraine prevention, so excluding them would cause exclusion of disabling migraine. Besides this, the use of antihypertensive medication did not differ significantly between patients and controls, and did not affect the prevalence of syncope.

Finally, the use of additional tests such as a Ewing battery may have resulted in the identification of subtle and subclinical abnormalities. However, this was not the purpose of our study. We focused on syncope as a clinically relevant expression of autonomic dysfunction, and not on autonomic alterations in any form.

We accordingly chose to perform tests that would have a more direct relation to the onset of syncope and that could be applied in the context of a large population-based study.

We agree that more extensive cardiovascular measurements are useful to study migraine, and would suggest that these be directed at the reasons for the increased prevalence of syncope and orthostatic intolerance.

We also thank Drs. Jarjour and Smith for their comments. They state that we omitted a statement concerning the control group from an earlier article on the CAMERA study. In our publication in JAMA 2004, we stated that the control definition “effectively excluded people with chronic daily headaches and cluster headache, but people with minor migraine or an occasional tension headache might have been included.”⁶

First, let us stress that “minor migraine” does not feature in the classification system of the IHS; the sentence was added on a reviewer’s request, presumably to indicate putative uncertainty regarding the groups. Whereas this uncertainty might indeed hold true for the partially paper three-step diagnostic procedure,¹¹ it has no consequences for the current study.

The random inclusion of participants for the CAMERA study from the larger sample involved a detailed, structured telephone interview. We again asked all 481 subjects about previous and current headaches and when necessary corrected the previous classification. Only 3% of subjects were reclassified, most due to developed migraine headache for the first time in the 3 to 5 years in between, or due to changes in migraine subtype. This double-checking makes us confident that the control subjects did not have current or previous migraine fulfilling IHS criteria.

Jarjour and Smith are correct that in 2004 the IHS classification was updated. However, criteria for diagnoses 1.1 and 1.2.1, pertinent to our study, were not changed between the 1988 and 2004 editions.^{7,8} Finally, we agree that CI or OR add information. As for how the OR would behave if migraineurs were excluded

from the control group, we can lay Drs. Jarjour and Smith’s fears to rest: there were none.

R.D. Thijs, M.C. Kruit, M.A. van Buchem, M.D. Ferrari, L.J. Launer, J.G. van Dijk, *Leiden, the Netherlands*

Disclosure: The authors report no conflicts of interest.

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Correction

Phenotype-genotype correlation in Dutch patients with myoclonus-dystonia

In the Brief Communication “Phenotype-genotype correlation in Dutch patients with myoclonus-dystonia” by M.C.F. Gerrits et al. (*Neurology* 2006;66:759–761), there were two errors in table 1. The mutation in Case 6 is given as IVS7+2C>T but should be IVS7+2T>C, leading to the same amino acid change. The protein in Case 7 is described as p.Q286fsX297, but after re-sequencing must be L295fsX297, as shown in the corrected table below. The authors apologize for these errors.

Case	SGCE mutation	Protein	Exon
1	c.619-20delAG	p.R207fsX215	5
2	c.179A>C*	p.H60P	2
3	c.856C>T	p.Q286X	7
4	c.304C>T	p.R102X	3
5	c.808T>C	p.W270R	6
6	IVS7+2T>C	diff. splicing	intron
7	c.885insT	L295fsX297	7

* De novo mutation.

SGCE = ϵ -sarcoglycan gene.

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Correction

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