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Regional Block and Cancer Recurrence: Too Early to Tell

To the Editor:—We read with much interest the recently published study by Exadaktylos *et al.*[1] Their retrospective cohort study identified a beneficial relation between paravertebral block and cancer recurrence in women undergoing breast cancer surgery. The authors opined that regional anesthesia might help to maintain normal perioperative immune function and reduce the risk of tumor recurrence and metastases. If these findings are real, it would be the first demonstration that anesthesia *per se* protects from cancer recurrence—a true revolution.

However, before such conclusions can be drawn, a number of limitations of this study should be addressed. Although some were discussed in the excellent accompanying editorial by Ochroch *et al.*,[2] some major ones seem to have gone unnoticed.

First, the authors state that prognostic factors and particularly the Nottingham Prognostic Score were similar in both groups. As a consequence, the smaller number of cancer recurrence and metastases observed in the paravertebral group seems to be due to the inherent benefits of the regional technique. However, the Nottingham Prognostic Score is not a measure of the propensity for tumor recurrence or metastasis.[3] It has never been validated as such. Only axillary node extension and histologic grade of the tumor have been demonstrated to do this. There is evidence from the literature suggesting that patients with high-grade (grade III) histologic breast tumors undergoing surgery are more at risk of recurrence and metastasis than patients with lower grades.[4,5] Reanalyzing the study data of Exadaktylos *et al.*,[1] it seems that 54% of patients in the nonblock group compared with 42% of patients in the paravertebral block group had high-grade breast tumors and increased risk of cancer recurrence. Had categorical variables from the histologic grades been compared as is recommended,[6] with the chi-square test (and not the Mann–Whitney U test for nonnormally distributed numerical variables), it would have been found that patients in the nonblock group had poorer prognosis at a P value less than 0.001.

Second, the authors assume a cause–effect phenomenon between the predictor (the anesthetic technique) and the outcome (cancer recurrence or metastasis). However, the opposite may be true here: The outcome may have caused the predictor to occur. Treatment allocation seemed to be mainly influenced by the anesthesiologist's decision to use a paravertebral block. A block may not have been offered to patients in whom it was not indicated (*e.g.*, patients with extensive metastases, recurrent or bilateral breast tumors).[7] As a consequence, patients with extensive, recurring, or bilateral tumors were less likely to have a paravertebral block. Cancer recurrence might have guided the choice of the anesthetic technique and not the opposite. This effect–cause phenomenon is recognized bias of cross-sectional, case–control, and retrospective cohort studies.[8] There are some well-known examples in the literature, such as the protective effect of tobacco smoking against Parkinson disease or the deleterious effect of low levels of blood cholesterol in cancer patients.[9,10] In both cases, presumed consequences (Parkinson disease–cancer) are actually causes of lower tobacco smoking and blood cholesterol.

Finally, in the study of Exadaktylos *et al.*,[1] paravertebral blocks were performed by the same anesthesiologist, and all such cases were performed by the same surgeon and managed by the same oncologist. What about the "nonblock" cases? Were the latter patients managed by a range of surgeons and oncologists, perhaps with different approaches to treatment? There may be other explanations as to why the latter patients had poorer outcomes.[11]

In conclusion, the only study design able to reliably answer whether paravertebral block really protects from breast cancer recurrence is a randomized controlled trial. This should be done as soon as possible before an unproven hypothesis becomes a standard of practice in breast cancer surgery.

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In Reply:—We thank Drs. Haller and Myles for their comments regarding our article.[1] They suggest that a reanalysis comparing our paravertebral and general anesthesia groups treating histologic grade as a categorical factor shows the groups to differ on histologic grade, thus implying an overlooked problem with confounding.

This is simply not the case: A chi-square analysis comparing the groups on histologic grade III *versus* the combined I/II, as suggested, leads to a P value of 0.19 (not the < 0.001 stated by Haller and Myles). This is less significant than the $P = 0.16$ that we reported when considering the variable to be ordinal. The primary reason is that there is a loss of information on histologic grade by collapsing the first and second levels, which is why we analyzed all three categories. Furthermore, our analysis using the Mann–Whitney test is a more powerful way to detect group differences on severity because it uses the natural ordering, as opposed to simply considering the grades as nominal categories such as red, white, and blue, as the chi-square test does.

Most importantly, adjustment for histologic grade in our multivariable analyses of cancer recurrence obviates concern for the potential con-

founding due to this factor. Our results are thus interpreted as the hazard ratio of recurrence for paravertebral *versus* general anesthesia for patients at the same histologic grade, and similarly for other factors in the model. This sort of multivariable analysis compensates for small, or even moderate, imbalances at baseline. We adjusted for this factor because of the retrospective nature of the study, even though we did not have evidence of it being a true confounder because it was not associated with the treatment groups ($P = 0.16$) or the outcome ($P = 0.25$), both of which are required by the classic definition of confounding.

As specified in the article, a single surgeon performed all cases in both groups. And again as specified, all paravertebral anesthesia was performed by a single anesthesiologist (D.J.B.), who also performed some of general anesthesia alone cases. The remainder were performed by three other attending anesthesiologists. The cases were similar, and the primary determinant of anesthetic type was assignment to D.J.B., who was the only anesthesiologist in the group familiar with the paravertebral technique.

The substantial limitations of observational studies are well known and were discussed in our article. For example, we specified: "Patients were not randomized and clinical care was not standardized, so that selection bias and the effects of unmeasured confounding variables cannot be excluded. For example, patients in the general anesthesia group had slightly larger tumors, smaller margins, and higher chemotherapy rates than patients in the paravertebral group, factors that could affect mortality, although these differences did not reach statistical significance. Relevant information such as the amount of morphine given and the type of chemotherapy used in each group was not available in the records."

Under no circumstances should a small retrospective study be the basis for practice, and we suggested no such thing in our report. In contrast, the conclusion of our article was that "this study should be viewed as generating a hypothesis and an estimated effect size for future large randomized controlled trials, which are being planned and which will require several years for execution and analysis." A prospective trial is now in progress (ClinicalTrials.gov No. NCT00418457).

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Heme as a Playmaker in the Regulation of the Nitric Oxide System

To the Editor:—We read with great interest the article by Tsai *et al.*[1] In this article, the authors presented a laboratory investigation in which they showed that heme oxygenase-1 (HO-1) induction significantly inhibits type 2 cationic amino acid transporter expression and L-arginine transport in lipopolysaccharide-stimulated macrophages. The authors further suggested that this effect may be related to the activation of nuclear factor erythroid 2–related factor 2 and inhibition of nuclear factor κB. After we read this analysis, it occurred to us that some points may be added to the discussion.

The authors showed that lipopolysaccharide treatment resulted in a significant increase in type 2 cationic amino acid transporter expression and this effect was reversed by concomitant treatment with hemin (fig. 1). However, there are no data indicating the effect of hemin treatment on nitric oxide formation. These set of experiments could have rendered the authors' conclusions stronger; in fact, heme may act as a pro-oxidant molecule, thus leading to an increased expression of the inducible isoform of nitric oxide synthase, which in turn leads to increased nitric oxide production. In this case, hemin, although resulting in a significant decrease in type 2 cationic amino acid transporter expression and activity, may still induce the release of nitric oxide. In addition, heme serves as prosthetic group of inducible isoform of nitric oxide synthase, and thus heme treatment may result in an increased synthesis of the enzyme. Different HO-1 inducers, such as $SnCl_2$ or cobalt-protoporphyrin, could have added more information because they potently induce HO-1 without increasing intracellular heme levels. In this regard, we and other authors previously showed that HO-1 induction by using cobalt-protoporphyrin or gene targeting modulates intracellular heme level, thus regulating the synthesis of heme-dependent proteins such as nitric oxide synthases, cyclooxygenases, nicotinamide adenine dinucleotide phosphate oxidase, and cytochrome P-450.[2,3] These observations may be consistent with previous work performed by the same authors[4] showing that propofol treatment resulted in a concomitant reduction of both the inducible isoform of nitric oxide synthase and type 2 cationic amino acid transporter expression. In this regard, we also showed that propofol may act as an inducer of HO-1 *via* activation of the nuclear factor-κB pathway.[5] Another point that we believe needs to be raised is in regard to the authors' choice of adding hemin immediately after lipopolysaccharide stimulation, thus not permitting a strong preinduction of HO-1 activity, which would have allowed increased carbon monoxide levels and a reduction of the intracellular heme pool. Interestingly, the authors also showed that tin protoporphyrin, a strong inhibitor of HO activity, results in a significant increase of HO-1 protein (even though in the Results section it was indicated that tin protoporphyrin did not increase protein expression) and partial reversion of hemin effects. The molecular mechanism underlying this effect is still unclear, and several hypotheses may be carried out. One is that HO activity inhibition after tin protoporphyrin treatment results in increased intracellular heme level after strong HO activity inhibition, thus leading to increased HO-1

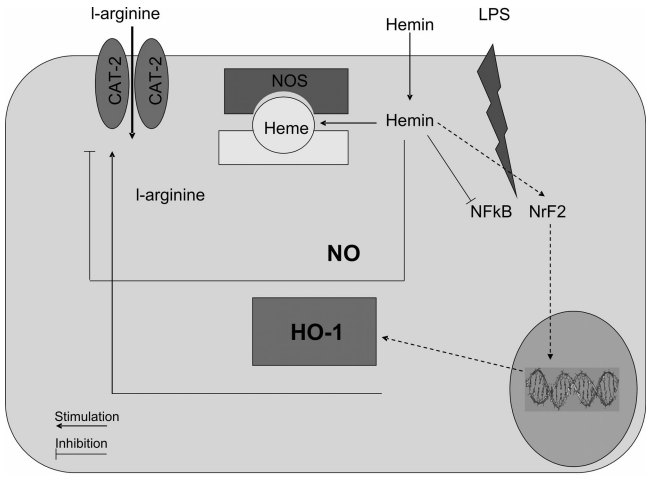

Fig. 1. Schematic representation of possible mechanisms involved in the interaction between heme and the nitric oxide system. CAT-2 = type 2 cationic amino acid transporter; HO-1 = heme oxygenase 1; LPS = lipopolysaccharide; NFκB = nuclear factor κB; NOS = nitric oxide synthase; Nrf2 = nuclear factor erythroid 2–related factor 2.