To the Editor:

Which Factors Should Be Taken into Account?

In a recent article in CHEST (October 2011) Slowik et al described the effect of secondhand smoking on elastine breakdown products, desmosine and isodesmosine (D/I). The authors concluded that exposure to secondhand smoke causes a significant rise in plasma D/I and, therefore, may be as dangerous and harmful as active smoking on tissue matrix and lung parenchyma.

We applaud the authors’ attempt to show that passive smoking is indeed harmful. Nevertheless, we have a few comments on the study design.

First, it is unclear why the authors chose to examine two cohorts. The composition between the two cohorts differed greatly. The first cohort, which included a group of nonsmokers, passive smokers, and smokers, consisted of women with the average age ≈30 years. The second cohort, again including a group of nonsmokers, passive smokers, and smokers, consisted of both men and women with average ages of 35, 41, and 57 years, respectively. The question arises as to whether the observed difference between the cohorts (in passive smokers and smokers) is confounded by age and sex differences.

Second, it is unknown which test subjects were former smokers. Previous investigations show that former smokers with COPD continue to have high D/I content. It is speculative whether the same effect can be found in former smokers without COPD. In this study, it is not clear whether the former smokers are included, nor is it clear whether smokers, including any former smokers, received pulmonary function testing in order to rule out COPD.

Finally, the high pressure liquid chromatography-mass spectrometry/mass spectrometry method is reliable, provided the use of an internal standard (such as deuterated desmosine) is used. Slowik et al chose not to use an internal (deuterized) standard but instead used the average of two measurements. In doing so, the internal validation and the results may have been compromised.

D/I remains an interesting marker for the evaluation of elastine breakdown. However, its role remains small in contemporary literature. More research must follow if the use of D/I is to gather significance. A validated method, with an internal standard, for the measurement of D/I remains a mandate.

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References

Secondhand Smoke Exposure Effect on Elastin Degradation Markers

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Response

To the Editor:

I thank Dr Spanbrouck and colleagues for their comments on our recent article in CHEST.1 We chose two cohorts for the study because we had the opportunity to do so and could not predict the results. In fact, as pointed out, the cohorts were quite different in composition in terms of sex predominance and age variations and showed results, consistent in both cohorts, of significant increases in plasma levels of desmosine and isodesmosine (D/I) in subjects exposed to secondhand smoke. We are not aware of data showing differences between men and women in levels of D/I in normal subjects. There may be a relation between aging and increases in D/I in plasma in normal subjects, but we have not observed such a correlation in the current data available to us or in currently published studies. Larger series of studies of normal subjects of various ages may show such a relation to age, which has been suggested in aging rats.2

None of the secondhand smoke-exposed subjects were former smokers. The active smokers in both cohorts were free of respiratory symptoms and were considered to be in normal health. The measurements of D/I in the subjects exposed to secondhand smoke were not only an average of two analyses but were based on recoveries of known amounts of spiked samples of plasma. This greatly improved accuracy and repeatability. Subsequent analyses using the pyridoline standard3 showed acceptable similarities when compared with our previously published measurements.

A stable deuterium isotope, which is not yet available, is the ideal internal standard. We are in the process of synthesizing this standard (Yamada et al, unpublished data, November 2011). The deuterium used in the reference cited by the respondents was made by ion exchange reaction, which is not stable during hydrolysis. As pointed out, I agree that D/I remain an interesting marker for the evaluation of elastin breakdown and have so stated in a recent publication.4

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Risk of Teratoma Formation After Transplantation of Induced Pluripotent Stem Cells

To the Editor:

I read with great interest the article by Yang et al1 in a recent issue of CHEST (November 2011), which clearly demonstrates that IV administration of induced pluripotent stem (iPS) cells reduces endotoxin-induced acute lung injury in mice. Regarding the possibility of teratoma formation2 after transplantation of iPS cells, I have several concerns from the viewpoint of human clinical application in the future.

First, it would be interesting to know the reason why there would be no teratoma formation in the present study. Recently, it has been revealed that mouse iPS cell-derived cells have immunogenicity and can be rejected immunologically, even when transplanted into syngenic mice,3 because several genes are found to be overexpressed in teratomas, which will induce immune responses. On the other hand, it has been shown that embryonic stem (ES) cell-derived cells have no immunogenicity and can be engrafted as teratomas. In the present study, it is not clear whether the lack of teratoma formation is attributable to the types of cells the authors used or the method they used to inject cells. Control experiments, either by using ES cells or by direct intratracheal injection, would clarify this point.

Second, it would be safer to inject differentiated cells rather than undifferentiated iPS cells in order to avoid potential teratoma formation. Recently, there has been a commentary by Okita et al4 against the article describing immunogenicity of iPS cells.5 The commentary mentioned that, for human medical applications, iPS-derived cells (ie, differentiated cells), but not iPS cells themselves (ie, undifferentiated cells), would be injected into patients. Based on this philosophy, is there the same efficacy, even when differentiated cells from iPS cells would be administered into mice with endotoxin-induced acute lung injury?

Finally, as mentioned by the authors, because autologous iPS cells would be hardly available for patients with acute lung injury, allogeneic iPS or ES cells should be applied. How about allogeneic transplantation in mice? The use of immunosuppressants for allotransplantation would be prohibited because...