A computed method for noninvasive MRI assessment of pulmonary arterial hypertension

To the Editor: In a recent article, Laffon et al. (2) presented a new method to noninvasively assess pulmonary arterial hypertension using magnetic resonance phase-contrast velocity quantification. For screening purposes, it would be very useful to estimate pulmonary arterial pressure (Ppa) noninvasively, and any attempt in this direction should therefore be appreciated. The article by Laffon et al., however, raises serious questions.

Their article elaborates on an earlier article (1), in which the ratio of pressure wave velocity divided by peak systolic velocity (averaged across the vessel cross section), $c/U_{\text{max}}$, is related to pulse pressure, which in turn is correlated with Ppa. In the recent article (2), an attempt is made to improve the method in two ways: 1) $U_{\text{max}}$ and the maximal vessel cross-sectional area ($S_{\text{max}}$), which is needed for calculation of $c$, are “normalized” with respect to body height, weight, and heart rate, and 2) the explicit model between the ratio $c/U_{\text{max}}$ and pulse pressure is abandoned. Instead, however, Laffon et al. directly relate Ppa to the normalized $U_{\text{max}}$ and $S_{\text{max}}$ via expression of them in polynomial terms.

The first issue we would like to comment on is the normalization procedure. Laffon et al. (2) do not describe in detail how the normalization procedure is used for the normalization procedure. Thus, in total, 24 parameters (related to each patient), improves the accuracy of MRI to noninvasively estimate pulmonary arterial pressures.

Another issue that we would like to address is the resulting expression of polynomial terms given in Eq. 6. From their Eqs. 7–11, it follows that no less than 16 parameters are used to relate Un and Sn to Ppa. In addition, another eight parameters are used for the normalization procedure. Thus, in total, 24 parameters are estimated from a data set of only 31 patients! It seems surprising, then, that no greater correlation ($r > 0.92$) was found between measured and calculated Ppa, as the number of degrees of freedom for finding an optimal solution is huge. Unfortunately, Laffon et al. do not elaborate on their optimization algorithm, making firm conclusions impossible.

Finally, we would like to comment on the study design. It is rather curious that the same population is used for parameter estimation and for validation without any statistical correction. Validation using bootstrapping or a design with a separate validation group would have been preferred.

In summary, we seriously doubt the mathematical basis of the method for noninvasive estimation of pulmonary arterial pressure and have fundamental questions regarding the study design. It is, however, not our intention to exclude the possibility of noninvasive estimation of pulmonary arterial pressure. On the contrary, in our view, the ideas underlying the presented method are interesting and deserve to be studied more carefully.

REFERENCES

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REPLY

To the Editor: We read with great interest the letter about our paper (4) by Lankhaar et al., who are actively involved in the field of noninvasive functional imaging, including that for the pulmonary circulation (3). It appears that the comments by Lankhaar et al. may be related to the fact that the basic principles of our proposed method were not fully taken into account. These principles are as follows: 1) to directly compute combinations of limited polynomial series of physical parameters ($U_{\text{max}}$ and $S_{\text{max}}$) instead of developing a model analysis; 2) to correct, i.e., to “normalize” physical parameters by means of biophysical parameters (patient’s height, weight, and heart rate) that may act as perturbations; and 3) to optimize constants of both polynomial series and normalization vs. catheterization.

Therefore, the first issue of the normalization procedure should be considered as follows. We deliberately use noninteger powers of biophysical parameters, as previously done for computing body surface area (BSA) (1): BSA ($\text{cm}^2$) = 71.84
[height (cm)$^{0.725} \times$ weight (kg)$^{0.425}$]. Note that, in this latter example, the dimension of the product [height (cm)$^{0.725} \times$ weight (kg)$^{0.425}$] is not that of a surface (in cm$^2$), and, likewise, its physical meaning may thus appear curious to some authors. The dimension of the constant 71.84 enables one to get that of a surface in the second member of the equation. In Eqs. 12 and 13 of our paper (4), similar constants do not necessarily appear because constants appearing in Eqs. 7 and 8 and Eqs. 9–11 implicitly include these constants. In addition, a similar normalization procedure is used to optimize the $^{18}$F-labeled 2-fluoro-2-deoxy-D-glucose standard uptake value in PET imaging (2). More generally, regarding the relevance of noninteger dimensions, the amazingly up-to-date 88-yr-old paper of Du Bois and Du Bois (1) and the more recent fractals theory clearly establish this point.

The second issue deals with polynomial development and degrees of freedom. The selected polynomial series are presented in Eqs. 7 and 8 and Eqs. 9–11 in the manner that they were actually computed: $p_1[y(U_n)]$ and $p_2[z(v(S_n))]$, respectively. Terms in polynomial series developments of Eqs. 7–11 are obviously not independent parameters. In the proposed method, the actual number of independent parameters remains limited to five: two physical and three biophysical. Moreover, when half-integer powers of the same independent physical parameters $U_{\text{max}}$ and $S_{\text{max}}$ are used in Eqs. 12 and 13 ($U_{\text{max}}^{0.5}$ and $S_{\text{max}}^{1.5}$), the accuracy of the method, i.e., the estimation of computed mean $P_{\text{pa}}$ vs. mean $P_{\text{pa}}$ from catheterization, is improved.

Finally, as suggested in the last issue raised by Lankhaar et al., we did validate the method in a “separate” group of patients since the method was initially designed in a subset of the series (the first 10–15 patients) and published polynomial series and normalization that were optimized in a larger series of 31 patients.

In conclusion, we trust that the mathematical basis of the computed method of noninvasive MRI estimation of pulmonary arterial hypertension and the study design are now clearer. We fully agree with the comment from Lankhaar and colleagues about the interest of the method and the need for further investigations.

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