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Letter to the Editor

Reply to "Putting the patient first: The validity and value of surface-based electrical impedance myography techniques"

We appreciate the letter by Rutkove et al. (2021) to Sanchez et al. (2021) and agree with the points that he and his colleagues make about the value of surface electrical impedance myography (EIM). We also agree that in our discussion, we were unfairly critical of surface EIM methods, their validity deserving further acknowledgment. To clarify, the purpose of making the analogy between an EIM test and a nerve conduction velocity test is to exemplify the modeled relationship between an observation made during an EIM test and the *causal factor* generating such observation. Also, it illustrates the added value of providing *standardized* in lieu of *non-standardized* absolute (i.e., not relative) outcomes, regardless of whether these test outcomes represent a *true* measure or not of an actual physiological phenomenon. As for the latter, we already discussed in Sanchez et al. (2021) (Section 4) that both EMG and nerve conduction studies do not provide *true* measures since their outcomes are affected by the volume conduction properties of muscle, which is the sole topic of discussion in Sanchez et al. (2021).

Also discussed in Sanchez et al. (2021), surface impedance techniques can be dependent on the muscle/limb size. As the authors rightfully pointed out in their comment, it does not necessarily have to be something negative. Our argument was made in relation to lacking a model to interpret the causal factors originating these changes. Case in point, assuming the limb as a cylindrical muscle conductor, one can use a model relating the muscle lean cross-sectional area (lCSA) to the change of surface resistance ΔR measured along the limb Δx and the "averaged" electrical conductivity of the volume conductor σ. In this model, we have two *unknown causal factors* generating surface resistance values: the electrical conductivity property of muscle and the volume of muscle. To estimate the former, one could use an indirect assessment to quantify muscle lCSA first. For example, Bachasson et al. (2021) used quantitative magnetic resonance imaging (MRI) to assess muscle lean cross-sectional area first to then compute analytically the conductivity solving the following "*inverse problem*"

$$\sigma = \frac{\Delta x}{\Delta R \cdot \mathrm{lCSA}_{\mathrm{MRI}}}, \tag{1}$$

and reported *absolute*, *standardized* values for the conductivity property that ranged from 0.82 S/m at 50 kHz to 1.16 S/m at 350 kHz. Bachasson and colleagues then used this newly computed in vivo human conductivity values to predict muscle lCSA from the analysis of surface resistance data *only* from healthy participants and patients with severe muscle wasting and fatty degeneration. The authors then used the same model to solve the following "*inverse problem*"

$$\mathrm{lCSA} = \frac{\Delta x}{\Delta R \cdot \sigma} \tag{2}$$

and found strong agreement of lean muscle volumes estimated with Eq. 2 against MRI with a prediction error <10%. Note this muscle volume predictions from surface impedance data were possible thanks to having used MRI on the first place together with a model. Also, muscle volume predictions were obtained from a painless, non-ionizing and quick surface impedance test that did not require a specialized facility or the labor-intensive segmentation of different tissue compartments within images, these clear advantages over other more cumbersome methods to obtain the same information such as dual-energy X-ray absorptiometry or MRI.

Would a statistical model be able to outperform lean volume predictions based on the biophysical model above? Potentially, machine learning approaches are especially well suited for predictive modeling, however, the physiological interpretation might be obscured. Also, to make a fair comparison, both models should have the same number of parameters. *Would a relative or absolute change in a surface EIM test be useful to follow up a condition causing progressive muscle degeneration?* Absolutely, we acknowledged this. The point made in Sanchez et al. (2021) (Section 3.2) is that concomitant diseased-induced changes in *unknown* muscle conductivity values and limb/muscle size could lead to unpredictable surface resistance changes. The reader can see this using the same model but now solving the "*forward problem*"

$$\Delta R = \frac{\Delta x}{\sigma \cdot \mathrm{lCSA}} \Rightarrow \begin{cases} \sigma \downarrow \text{ and } \mathrm{lCSA} \downarrow & \rightarrow \Delta R \uparrow \\ \sigma \downarrow \text{ and } \mathrm{lCSA} \uparrow & \rightarrow ? \\ \sigma \uparrow \text{ and } \mathrm{lCSA} \downarrow & \rightarrow ? \\ \sigma \uparrow \text{ and } \mathrm{lCSA} \uparrow & \rightarrow \Delta R \downarrow \end{cases} \tag{3}$$

To be sure, a surrogate assessment of muscle lCSA (e.g., using MRI as in Bachasson et al. (2021)) could help to determine if resistance changes recorded with a surface EIM test were caused by pathological alterations affecting the electrical conduction property of muscle using Eq. 1 (i.e., the actual scientific hypothesis supporting EIM), overall muscle lean volume (e.g., as quantified by MRI), or both. *In patients with muscle wasting, would needle EIM approach be useful as a surface EIM test at predicting muscle lean volume*? We do not think so since a needle impedance measurement measures a confined muscle volume near the electrodes.

Also, it is paramount to emphasize that unlike surface EIM where we have a good technical understanding thanks to the large body of work that has been performed over the years, comparatively, less is known about needle EIM: the state of art of the technique is very much in its early stages of development with the limitations that this entails. The reader must be aware that a number of important questions still remain to be answered that will

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determine its final utility. In addition to the limitations discussed in Sanchez et al. (2021) and practical concerns raised in Rutkove et al. (2021), contact impedance artifacts due to the relatively small size of the needle could be even more severe than a surface measurement where the electrodes are much larger. Also, the impact to in vivo data of the intrinsic biological variability of muscle still needs to be determined. Further research is warranted to assess if as a result of the relatively small distance between motor units and the needle electrodes themselves, the electrical current applied for EIM measurement could potentially activate muscle near the focal region, this not being a concern for surface EIM approaches. These limitations are just the tip of the iceberg, future work will help shed light to these questions and surely new concerns will arise, these now not being possible to fully grasp due to our current lack of knowledge.

Technical and practical comparisons aside, we believe surface and needle EIM methods are here to stay and a promising future awaits for both from a scientific and clinical point of view. Sanchez et al. (2021) provides an overview of the limitations and strengths of each technique which will allow us to keep improving EIM and its clinical use to continue offering the prospect of providing valuable patient outcomes.

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Disclosure

Dr. Sanchez holds equity in Haystack^{Dx}, Inc., a company that develops clinical needle impedance technology for neuromuscular evaluation. The company has an option to license patented needle impedance technology where the author is named an inventor. He also holds equity and serves as Scientific Advisory Board Member of Ioniq Sciencies, Inc., a company that develops clinical impedance technology for early lung cancer detection. Dr. Sanchez serves as Scientific Advisory Board Member of B-Secur, Ltd., a company that develops wearable ECG and impedance technology. He consults for Myolex, Inc., a company that develops surface EIM technology. The company has an option to license patented surface impedance technology where the author is named an inventor. Dr. Sanchez also serves as a consultant to Impedimed, Inc., a company that develops clinical impedance technology. The company patented impedance technology where the author is named an inventor. He also serves as consultant to Texas Instruments, Inc., Happy Health, Inc., and Maxim Integrated, Inc., companies that develop impedance related technology for consumer use.

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