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EDITORIAL

Translational research in acute respiratory distress syndrome

Investigación traslacional sobre el síndrome de dificultad respiratoria aguda

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Dear Editor,

Translational research (TR) or ''bench to bedside research'' is defined as the ''process of transformation of knowledge through successive fields of research from a basic science discovery to public health impact''.[1] TR should be considered a type of pragmatic and patient-centered research, whose main aim is to reduce the time lag between the problem identification and its solution.

In TR, the first step is to have a clear definition of the disease and the problem. Recently, the importance of linking clinical manifestations (syndrome) to pathological findings with the aim to define a specific disease has been highlighted.[2,3] Identifying physiopathological mechanisms that link this relation (clinical–pathological) allows to understand the disease, identify subcategories and recognize therapeutic targets. In reference to the problem, it sometimes seems that identifying it is an easy or fast process, but nothing could be furthest from the truth. Selecting the problem implies the answer to the following questions: (a) Is it possible to address the problem with the intellectual, logistic and economic resources available for the researcher? (feasibility) and (b) which scientific, social and economic impact could the research have? (interest or relevance).

The second step is to enunciate the hypothesis. In several cases, experiments in humans are not possible. However, animal models allow us to partially simulate certain human conditions. In other words, animal models are a simplification of the human reality that permits to focus the attention on a specific event (or a few events) and reduces the influence of confusion factors. How similar to the human disease the animal model should be mainly depends on which question researchers want to answer. In all experimental conditions, it is necessary to have a reference by which to assess the efficacy of an intervention. This reference, which is indeed more important than the intervention itself, derives from at least two groups: controls and sham. The former are animals that only differ from the experimental group in that they receive a placebo. All the animals are prepared similarly [e.g. anesthesiated, operated, etc.], but then the researcher randomizes each one to the intervention or placebo groups. The latter are animals on which investigators apply the same preparation than on the control group, but which do not receive any intervention nor placebo. On the one hand, the control group allows to know the specific effect of the intervention since both groups share the same confusion variables. On the other, the sham group ensures that the scientific data reflect the effect of the experiment itself, and this is not merely a consequence of the procedure. Finally, if preclinical studies are positive and there is enough evidence in favor of the new treatment (or solution for the problem), this should be evaluated at the bedside and, if effective, incorporated to the clinical practice.

Acute respiratory distress syndrome (ARDS) is a cataclysmic syndrome. Diffuse alveolar damage (DAD), the histological hallmark for the acute phase,[4] is present in only 48% of ARDS patients.[5] Furthermore, it has been recently

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demonstrated that patients with ARDS and DAD present a different outcome from patients with ARDS but without DAD.[5,6] One of the most important problems in relation to ARDS is the lack of effective pharmacological treatments, despite positive results in preclinical studies. This dissonance may be due to the fact that animal models do not represent ARDS or that the population on which the treatment is tried out is incorrect.[7] For example, clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population because the effect of an intervention is over targets (e.g. molecules, pathophysiologic pathways or anatomical structures) which should be present in the sample in which the intervention is evaluated. For that reason, it is only possible to lump patients who share the same. However, when the target is present only in a subset of patients, the population has to be splinted and the intervention must be tried out only on the subgroup which presents the target. Enrichment is the word used to describe the procedure of selecting subgroups of patients in which detection of an intervention effect is more likely than it would be in an unselected population.[7] Biomarkers are currently the most useful way to enrich a specific population.[8]

In this issue of *Medicina Intensiva*, Cano et al.[9] use an elegant translational experiment to address the effect of a restrictive versus a liberal strategy of fluid management in a two-hit rabbit model of lung injury. Despite both strategies influence the outcome (wet and dry lung weight ratio [WW/DW]) several differences are evident. The liberal arm is associated to a decrease in the dynamic compliance and a bigger increase in WW/DW, as well as in the corrected aortic flow time than the restrictive strategy. Likewise, a trend to increase the total inspiratory work of breath, expiratory airway resistance and histology lung injury is reported in association to the liberal arm. On the contrary, the cardiac index is significantly reduced only in the restrictive arm. As a conclusion, Cano et al.[9] mentioned that preemptive hemodynamic intervention by restricting the administration of fluids significantly slowed the progression of pulmonary edema and the decrease in pulmonary compliance. These interesting results provide a physiopathological explanation for the finding of the clinical study *Fluid and Catheter Treatment Trial (FACTT)*,[10] which included 1001 ALI/ARDS patients. The FACTT study found that the conservative fluid protocol improves several secondary end-points but not the primary end-point (60 days mortality).[10] As it was mentioned earlier on,[5] less than a half of FACTT participants could have been expected to present the ARDS histological hallmark (DAD) and the rest, a group of heterogeneous entities such as pulmonary embolism, fibrosis or atelectasis.[5] For this reason, based on the results of Cano et al.,[9] an intriguing question is what would have happened if the FACTT cohort had been enriched in DAD? In other words, was the effect of restrictive fluid in the FACTT study diluted by the lack of enrichment in DAD? One of the targets for restrictive fluid protocol may be the disrupted alveolar capillary barrier function.[11] But, is this target shared by ARDS patients with and without DAD? This question should have a direct impact on the design of future ARDS studies since it could determine which patients could be lumped and which patients should be splinted.

As a conclusion, Cano et al.[9] use a refined animal model to explain what had been observed at the bedside with ARDS patients. This can be regarded as a clear example of TR, which could be considered one of the most powerful strategies to accelerate the long and winding process from ''bench to beside''.

Conflict of interest

The author express that don't have conflict of interest to declare.

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