overextend the conclusions and implications of their work, it could be tempting to assume that the limited impact of the pedometer-based intervention extends to other settings. Before arriving at that premature conclusion, it should be clear that, as the authors explain, the addition of pedometers still confers benefits when used outside of rehabilitation programs. Equally important, improving outcomes of pulmonary rehabilitation in the direction of increasing physical activity could still be achieved with the use of pedometers, but only if they are just a component of a more comprehensive behavioral intervention. Although simple and elegant interventions, such as the one presented by Nolan and colleagues (10), using the available, easy-to-implement, elegant, and everyday smaller wearable technology, are very appealing, improving physical activity in COPD will require either more complex approaches or continuing to try simple innovative interventions, like the one tested by the authors—at least until we learn more about the physical and behavioral determinants of inactivity (18), something that will remain elusive if our professional organizations, research granting agencies, and journals do not make rehabilitation research, education, and implementation a priority. ■

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What's in a Number? Platelet Count Dynamics as a Novel Mediator of Acute Respiratory Distress Syndrome Survival

The mortality rate for acute respiratory distress syndrome (ARDS) remains unacceptably high, and efforts to reduce mortality through drug therapy have been repeatedly unsuccessful (1, 2). One factor that may limit efforts to find effective new therapies is the lack of proven causal intermediates in ARDS. If a marker were demonstrated to mediate a portion of ARDS mortality risk, then efforts to target that marker would be a rational strategy for future ARDS therapeutic development. Taking an example from coronary

artery disease (CAD), the utility of plasma low-density lipoprotein (LDL) cholesterol is not only that LDL serves as a risk factor for CAD but also that strategies to modify LDL are likely to improve CAD outcomes. In contrast, although numerous potential markers have been associated with ARDS outcome, the relationship between each marker and outcome is far from certain, and the mechanism underlying each marker's association remains unclear (3). Statistical methods known as causal inference approaches have been proposed to disentangle correlation from causation within human observational data, yet these methods have been applied infrequently to ARDS (4).

In this issue of the *Journal*, Wei and colleagues (pp. 1353–1361) present a causal mediator analysis of a novel quantitative trait, the decline in platelet count, on ARDS mortality using variants in the gene leucine-rich repeat–containing 16A (*LRRC16A*) (5). In essence, mediation analysis analyzes the role of a mediator, such as platelet count, in the relationship between an exposure of interest, such as a genetic variant, and an outcome, such as ARDS (6). Elegantly, the use of a genetic variant as the exposure of interest in mediation analysis obviates the typical requirement for a control of possible exposure–outcome confounding, because the exposure (e.g., possessing a variant in *LRRC16A*) clearly preceded the studied outcome (e.g., ARDS) (6). The investigators focused on platelet abundance as a potential mediator, because platelets influence both impaired coagulation and the excessive inflammatory response observed in ARDS (7, 8). Beyond their classic role in the regulation of hemostasis, platelet activation in ARDS influences host immune responses, resulting in the release of immunomodulatory mediators, increased neutrophil migration, and decreased endothelial membrane integrity (8, 9). In earlier work, investigators demonstrated that thrombocytopenia is a risk factor for ARDS development and for ARDS-related mortality (10). The gene *LRRC16A* had been implicated as a quantitative trait locus regulating platelet count during health, and Wei and colleagues confirmed the genetic contribution of *LRRC16A* to baseline platelet count in a critically ill population at risk for ARDS (4). Using a similar mediation analysis to that in the present article, they demonstrated that a *LRRC16A* missense single-nucleotide polymorphism (SNP) associated with ARDS risk and that the risk was partially mediated through baseline platelet count at intensive care unit (ICU) admission, with lower platelet counts being a risk factor for ARDS. The present article asks whether genetic regulation of platelet abundance also contributes to ARDS mortality and uses a mediation analysis to detect the proportion of ARDS mortality risk explained by a change in platelet abundance.

In a stepwise process, the authors first examined numerous potential platelet phenotypes for association with ARDS mortality and determined that baseline platelet count, delta platelet count at 7 days, and delta platelet count at 28 days all associate with mortality. They next tested the association between five *LRRC16A* coding variants and ARDS mortality and identified one missense SNP, rs9358856, that associated with mortality (5). Importantly, rs9358856 is distinct and not highly linked to rs7766874, the *LRRC16A* variant previously reported to mediate a portion of ARDS risk via lower baseline platelet count (4). The mortality-associated SNP rs9358856 was associated with delta platelets at either 7 or 28 days but not with baseline platelet count. Finally, the formal causal mediation analysis determined a significant causal indirect effect of rs9358856 on improved ARDS survival that was mediated through attenuated decline in platelets over the first 7 or 28 days in the ICU (5). Between 11 and 18% of the effect of rs9358856 on improved ARDS survival could be explained by an attenuated platelet decline. In complementary analyses, the authors used whole blood gene expression in a subpopulation with genotyping to demonstrate that (*1*) rs9358856 associates with reduced *LRRC16A* expression, (*2*) baseline *LRRC16A* expression inversely associates with baseline platelet count, and (*3*) higher baseline *LRRC16A* expression correlates with a higher delta platelet count. Taken collectively, these findings suggest that *LRRC16A*-mediated decline in platelet count after ICU admission may explain a portion of ARDS survival and that rs9358856 seems to be a functional SNP.

Beyond the elegant use of a mediation analysis, the study by Wei and colleagues is important in that it identifies platelet decline as a novel intermediate variable for ARDS survival and a potential target warranting future testing for ARDS therapy (5). There has been strong interest in therapeutically targeting platelet activity in ARDS. Although the LIPS-A (Lung Injury Prevention Study with Aspirin) study did not find a reduced risk of ARDS for high-risk subjects randomized to aspirin therapy over placebo, there are ongoing efforts to target platelets for ARDS therapy (11–13). The gene expression data in the present manuscript strengthens the candidacy of rs9358856 as a functional variant and may contribute to our understanding of platelet homeostasis. The authors postulate that this missense SNP may affect platelet structure, function, or longevity via altered F-actin polymerization (14), although further work is needed to better elucidate these possibilities.

One important limitation of this study is that the platelet phenotypes investigated included only quantitative assessments of platelet count as potential mediators for the relationship between *LRRC16A* variation and ARDS outcome (5). It remains unknown whether the conferred mortality risk associated with a decline in platelet count reflects decreased platelet production, increased platelet consumption, or platelet sequestration, for instance in the pulmonary circulation (15). Furthermore, the platelet count does not fully characterize the variety of platelet functions that may influence ARDS outcome. Platelet activation plays a crucial role in ARDS pathogenesis, including contributions to hemostasis, angiogenesis, microvascular coagulopathy, increased capillary permeability, and recruitment of inflammatory cells (7, 9, 16). Additional studies are necessary to further clarify the mechanisms in which platelets serve as causal agents. This study also warrants replication of both the genetic variant and causal mediation in populations with different ARDS risk factors and of diverse ancestry. In addition, functional studies of *LRRC16A* may help to describe further the mediating effects of platelets in the relationship between genetic variants and ARDS. The finding that platelet count decline accounted for less than 20% of the observed rs9358856–reduced mortality association leaves the majority of this association unexplained and requires further elucidation.

In summary, Wei and colleagues have focused attention on platelet count dynamics as an important intermediate phenotype for ARDS mortality (5). If we can better understand the mechanisms

underlying this relationship, including effects on both platelet quantity and function, then a strategy to mitigate platelet decline may merit investigation as a novel ARDS therapy. ■

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Learning Health Care System: Pragmatic Comparison of Crystalloid Choice in a Medical Intensive Care Unit

Electronic health records (EHRs) have now been in widespread use throughout the United States. It is expected that the application of EHRs will improve everyday clinical practice, assure patient safety, and facilitate research. In reality, not all of the promises of EHRs have been fulfilled. Through extensive use, weaknesses of the current generation of EHRs were brought to the forefront, such as poor user interface, implementation difficulties, the time required to use them, and others (1). In the intensive care unit (ICU), EHR use is not only time consuming but also burdened by an ever-increasing amount of irrelevant data, potentially impeding safe patient care (2). The potential benefits of EHRs in ICU practice do exist, but they have yet to be fully exploited (3). One particularly promising area is in facilitating comparative effectiveness research (4) and fulfilling the National Academy of Medicine goal of a learning health care system (5). Pragmatic comparative effectiveness trials compare the effects of a number of treatments used in real-world practice on clinical outcomes to guide decision-making (4). Administration of intravenous fluids is a ubiquitous medical intervention in the treatment of critically ill patients, but the choice of particular type of solution has been a matter of debate (6).

In this issue of the *Journal*, Semler and colleagues (pp. 1362–1372) present a well-designed pragmatic trial in which they address the question of the type of intravenous crystalloid therapy in the medical ICU in regard to adverse effects (7). The SALT (Isotonic Solution Administration Logistical Testing) randomized trial was designed as a cluster-randomized, multiple-crossover study of 974 critically ill patients treated in a tertiary care medical ICU during a 4-month period. The aims of the trial were to compare the saline to balanced crystalloid treatment and at the same time to assess the feasibility of performing a large pragmatic randomized trial using the capabilities of EHRs.

The study showed no significant differences in the incidence rate of acute kidney injury (AKI), renal replacement therapy, or death between the treatment groups. Prior observational studies