

# From Berlin to Kigali: the sobering journey of acute respiratory distress syndrome

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What do Berlin, Kigali, and acute respiratory distress syndrome (ARDS) have in common? Berlin is the capital of Germany, brimming with attractiveness, science, culture, and a great lifestyle after the re-unification 25 years ago. Kigali is the largest city in Rwanda as well as its capital since the country's independence in 1962, located at an altitude of 1,560 m. ARDS is characterized by dysregulated inflammation, inappropriate accumulation of leukocytes, uncontrolled activation of coagulation, and alveolar barrier disruption (1), often resulting in a life-threatening impairment of pulmonary gas exchange with hypoxemia, hypercapnia, and respiratory acidosis. The main causes of ARDS are direct (pneumonia, aspiration of gastric content) or indirect injuries (sepsis, massive transfusion, multi-trauma, peritonitis, pancreatitis). In European countries, the incidence of ARDS was estimated to be 50 cases per 100,000 person years, corresponding to approximately 40,000 cases per year for a country like Germany (2). ARDS is often associated with multiple-organ failure. A broad scenario of acute interventions for ARDS therapy have been investigated and recommended in recent years, but evidence that all these measures can decrease mortality is still limited (3). Mortality remains as high as 40–50% in major series (4).

In 1994, a European-North American consensus conference introduced a 'simple' catalogue for the definition of ARDS and, at the same time, a differentiation from acute lung injury (ALI) was carried out as follows: ratio of arterial oxygenation to fractional inspiratory oxygen concentration ( $\text{PaO}_2/\text{FIO}_2$ -ratio)  $<200$  (ALI  $<300$ ), bilateral radiographic opacities without evidence for (exclusively) cardiac origin, acute onset (5). A presence or level of positive end-expiratory pressure (PEEP) was not addressed.

In the following years, increasing activities in basic and clinical science in terms of pathophysiology, inflammation cascades, epidemiology, and the (deleterious) effects of mechanical ventilation to the injured lung were observed. Simultaneously, the critique on the 'simple' ARDS definition grew: the accuracy of the assessment of ARDS was seen as limited and the absence of a mandatory PEEP level for the classification of oxygenation impairment was criticized.

In 2011, during the Annual Congress of the European Society of Intensive Care Medicine in Berlin, an expert group created a new definition of ARDS (6). The main changes were: (I) a recommendation of three levels of three categories based on the degree of hypoxemia, whether mild, moderate or severe. Consequently, the term 'ALI' went 'overboard'; (II) the onset within 1 week of a known insult; (III) a minimum level of PEEP ( $\geq 5$  cm  $\text{H}_2\text{O}$ ); and (IV) an objective evaluation to help rule out hydrostatic edema (e.g., echocardiography). The new Berlin definition was evaluated on a cohort of  $>3,000$  patients and found to be valuable.

As it turned out, even the Berlin definition found critics, but on a high intellectual and somewhat exaggerated level (7). On the other hand, thinking outside the high-income box, a more severe objection regarding the validity of the Berlin definition comes from Kigali, Rwanda. Riviello and co-workers (8) estimated the incidence and outcome of ARDS at the university teaching hospital at Kigali. They screened every adult patient in the hospital for 6 weeks, and collected data on demographics and ARDS risk factors, predominantly by lung ultrasonography. The first (unsurprising) result was that the Berlin definition could not be applied in most patients due to the inaccessibility of

mechanical ventilators, arterial blood gas diagnostics, and chest radiography. Consequently, the authors had to modify the ARDS definition to a Kigali version: the requirement of PEEP was deleted and a  $\text{PaO}_2/\text{FIO}_2$  ratio was replaced by a  $\text{SPO}_2/\text{FIO}_2$  ratio (9) using pulse oximetry (hypoxemia cut-off  $\leq 315$ ). Cardiac function was assessed by anamnesis or (when available) by echocardiography. The further main results were that 42 patients (median age 37 years) of 1,046 hospital admissions (4%) met the Kigali criteria for ARDS, 39% of ARDS patients were admitted to the ICU, and the mortality was 50%. The medico-political message of this important scientific contribution is that the Berlin definition is not applicable or is likely to underestimate the incidence of ARDS in low-income countries that represent a large part of the world and, furthermore, may result in estimates of only 'treated incidence' in high-income countries.

The study by Riviello *et al.* (8) poses severe reflections and some 'meta-questions':

- Is it possible, in the era of increasing high-tech medicine, to define diseases and/or assess grades of disease severity with validity and accuracy throughout the world when technical devices, lab values, and 'sophisticated' measurements are necessary, but not available to all?
- Science claims regarding the worldwide compatibility of results, cooperative projects, guidelines, and exchange of scientific data by international journals, symposia, and workshops: is it an illusion that scientists always speak about the same topic?
- Do we have to accept that first-world medicine (from high-income countries), second-world medicine (from advanced developing countries), and third-world medicine (from low-income countries) involve such different bases of scientific and clinical medicine that a 'true' cooperation is in far future?

Some conclusions or challenges for future global studies (10) can be drawn or postulated: on the one hand, different definitions of diseases or the severity of diseases around the world will counteract the globalization of science, which is necessary and unstoppable. On the other hand, it is not possible to work with definitions not applicable in parts of the world, or, when applied, producing invalid results. Where is the compromise and how can we go on? The Kigali study is a landmark study for a global approach to respiratory science and medicine: (I) it places the focus on daily life circumstances in a resource-constrained country with typical impacts for diagnosis and therapy, which are far away from the standard of industrialized countries;

(II) the study is an important step for the improvement of systematic health technology trials (i.e., investigations on medical informatics systems) (11), which are necessary to understand (and improve) pathways of care in countries with a relatively weak health infrastructure and limited healthcare; (III) although the Kigali modification of ARDS requires validation before widespread use, there is no doubt that scientists, clinicians, and healthcare specialists are called up to start projects and to stimulate further cooperation in reflecting on and refining an ARDS definition that can be used in all high-income and low-income countries.

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### Footnote

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