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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardio-Pulmonary-Renal Interactions

A Multidisciplinary Approach

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ABSTRACT

Over the past decade, science has greatly advanced our understanding of interdependent feedback mechanisms involving the heart, lung, and kidney. Organ injury is the consequence of maladaptive neurohormonal activation, oxidative stress, abnormal immune cell signaling, and a host of other mechanisms that precipitate adverse functional and structural changes. The presentation of interorgan crosstalk may include an acute, chronic, or acute on chronic timeframe. We review the current, state-of-the-art understanding of cardio-pulmonary-renal interactions and their related pathophysiology, perpetuating nature, and cycles of increased susceptibility and reciprocal progression. To this end, we present a multidisciplinary approach to frame the diverse spectrum of published observations on the topic. Assessment of organ functional reserve and use of biomarkers are valuable clinical strategies to screen and detect disease, assist in diagnosis, assess prognosis, and predict recovery or progression to chronic disease. (J Am Coll Cardiol 2015;65:2433–48) © 2015 by the American College of Cardiology Foundation.

The concept of organ crosstalk refers to the complex biological communication and feedback between different organs, mediated via mechanical, soluble, and cellular mechanisms. Although crosstalk is essential to maintain body homeostasis, pathological states in 1 or more organs can lead to functional and structural dysfunction in other organs. The classification of cardiorenal syndromes has been expanded into 5 subtypes. Types 1 and 2 involve acute and chronic cardiovascular disease scenarios leading to acute kidney injury (AKI) or accelerated chronic kidney disease (CKD). Types 3 and 4 describe AKI and CKD, respectively, leading primarily to heart failure (HF), although it is possible that acute coronary syndromes, stroke, and arrhythmias could be cardiovascular disease outcomes in these forms of CRS. Finally, CRS type 5 describes a systemic insult to both the heart and the kidneys, such as sepsis, where both organs are injured simultaneously in persons with previously normal heart and kidney function at baseline. Pulmonary-renal syndromes represent heterogeneous clinical entities, described by a combination of diffuse alveolar hemorrhage on the basis of pulmonary capillaritis in conjunction with glomerulonephritis as well as acute respiratory distress syndrome (ARDS) associated with AKI in the absence of hematuria. Hepatorenal syndrome can involve the development of functional cardiopulmonary changes and AKI in patients with advanced liver failure (acute or chronic) and is beyond the scope of this review.

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

ARDS = acute respiratory distress syndrome

BNP = B-type natriuretic peptide

CKD = chronic kidney disease

CPRI = cardio-pulmonary-renal interactions

FGF = fibroblast growth factor

GFR = glomerular filtration rate

HF = heart failure

LV = left ventricular

PH = pulmonary hypertension

CARDIO-PULMONARY-RENAL INTERACTIONS: NEED FOR DEFINITION OF A SYNDROME?

With growing knowledge of interdependent feedback mechanisms involved in the heart, lung, and kidney crosstalk, the descriptive classification of a syndrome can represent a framework for exploring epidemiology, pathophysiology, detection, and management. Because of the complicated courses of hospitalization and the high mortality of patients with involvement of all 3 organs, an integrative approach is needed. The sequence of organ involvement can vary depending on the acuity and nature of the underlying disorder. Many patients with disorders of 1 organ (e.g., CKD) die of complications of the other (e.g., HF) before the first organ's failure reaches its fullest extent, or the dysfunction of every organ may develop slowly until a "collapse" is reached and full-blown decompensation occurs. That is, each dysfunctional organ has the ability to initiate and perpetuate mutual injury through hemodynamic, neurohormonal, and cell signaling feedback mechanisms, while multiple episodes of acute (on chronic) decompensation may lead to reciprocal end-organ disease progression (**Central Illustration**). Given the multitude of contributing factors and the time sequence of events in cardio-pulmonary-renal interactions (CPRI), it is challenging to identify the underlying pathophysiological mechanisms and develop a strategy for diagnostic and therapeutic intervention. This review summarizes recent advances in our understanding of CPRI.

LUNG IN ORGAN CROSSTALK: THE PULMONOLOGIST'S VIEW

Open to environmental influence, the lung is a highly immunologic organ, representing a gateway to the environment. The lung has critical pathophysiological connections to the failing heart and kidney (**Figure 1A**).

LUNG INJURY, ABNORMAL CELL SIGNALING, AND OXIDATIVE STRESS. The lung conducts gas exchange via 3 mechanisms: ventilation, diffusion, and perfusion. Any imbalance can cause respiratory disturbance, which can be compensated to a certain degree by hyperventilation, greater oxygen extraction from blood by the tissues, and increased cardiac output, depending on the organ's functional reserve. In both noncardiogenic and cardiogenic pulmonary edema, fluid accumulation in the fissure and alveolar spaces can be seen as a result of increased pulmonary capillary permeability, elevated intravascular hydrostatic pressure, low colloid osmotic pressure, and insufficient lymphatic drainage (1). Changes to the alveolar-capillary barrier can induce an inflammatory cascade and oxidative stress of the pulmonary microcirculation, which results in cycles of alveolar wall injury predisposing and/or aggravating lung injury (**Figure 1B**) (2). Invasive and noninvasive measurements include analysis of pulmonary edema fluid, exhaled breath condensate (pH, arachidonic acid derivatives), proinflammatory cytokines (interleukin [IL]-1β, -2, -6, -8, -12, and -17; interferon gamma; and tumor necrosis factor [TNF]-α), anti-inflammatory cytokines (IL-4, -5, -10, and -13 and TGF-β), and chemokines (IL-8, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1β), reactive oxygen and nitrogen species, and exhaled nitric oxide (3,4). The concept of subclinical lung injury (e.g., due to previous smoking) takes into account that even asymptomatic events can lead to increased future susceptibility to respiratory failure events, and new diagnostic techniques may provide early detection (5,6).

Circulating factors have been implicated in the pathogenesis of pulmonary inflammation following renal and hepatic ischemia/reperfusion injury in animal models and humans (7-9). In ischemic AKI, experimental studies demonstrate increased pulmonary vascular permeability, cellular apoptosis, alveolar hemorrhage, and leukocyte trafficking due to the production and/or decreased clearance of mediators of lung injury (2). Intraluminal neutrophils contribute through phagocytosis and release of mediators, including reactive oxygen species and proteases, and activation of dendritic cells, augmenting the immune response. Pro-inflammatory cytokines produced by renal tubular cells as well as white blood cells include TNF-α and IL-1β and -6. Conversely, there are counterbalancing cell signaling peptides, including the anti-inflammatory IL-10, which has been shown to reduce lung injury in experimental models (2). Delayed recovery of kidney function may impair resolution of lung inflammation post-AKI (10). The altered mechanisms for water transport in pulmonary edema are described in detail in the "Uremic Lung" section.

MECHANICAL VENTILATION AND ARDS. Mechanical ventilation increases intrathoracic pressure and produces adverse hemodynamic effects that are opposite to normal spontaneous ventilation. Mechanical ventilation compresses pulmonary vasculature, which may result in increased right ventricular afterload and diminished cardiac output, leading to hypotension