MINERVA ANESTESIOL 2004;70:233-7

Pathophysiology of severe pulmonary hypertension in the critically ill patient

G. VIA[1], A. BRASCHI[2]

Pulmonary hypertension (PH) is a threatening condition that can be associated with a great variety of both pulmonary and extrapulmonary diseases. In all forms of severe PH the pulmonary vascular bed looses its physiological features of a "high flow-low pressure system", putting an increased afterload on the right ventricle (RV). Acute pulmonary hypertension in the intensive care unit often represents a clinical problem secondary to acute respiratory failure, left heart failure, pulmonary embolism, or decompensation of prior PH by concurrent pulmonary or cardiovascular disease. Right ventricular failure (acute cor pulmonale) occurs when relevant increases in pulmonary vascular resistance overwhelm its compensatory mechanisms, both abruptly on a previously normal RV, or gradually on a chronic cor pulmonale. This review addresses the main pathophysiolocal aspects of severe PH, focusing on the hemodynamic derangements occurring in the setting of acute cor pulmonale, and emphasizing the role of ventricular interdependance (the way right ventricular failure greatly affects diastolic and systolic function of the left ventricle), the risk of RV ischemia (the end stage of RV failure) and systemic organ hypoperfusion (caused by antegrade and retrograde heart failure). The understanding of the peculiar features of this type of cardiovascular insufficiency is necessary to both provide effective monitoring and adequate supportive therapy.

Key words: **Pulmonary hypertension - Critically ill - Cor pulmonale - Right ventricular failure - Acute respiratoty distress syndrome - Pulmo-nary embolism.**

Address reprint requests to: Dr. G. Via, c/o Servizio di Anestesia e Rianimazione I, IRCCS Policlinico San Matteo, Piazzale Golgi, 27100 Pavia, Italy. E-mail: gcvia@libero.it.

[1]Unit of Anesthesia and Resuscitation I, IRCCS San Matteo Polyclinic, Pavia, Italy
[2]Section of Anesthesiology and Resuscitation, University of Pavia, Pavia,

The normal pulmonary circulation is characterized by pressure and resistance 80-90% lower than those of the systemic circulation, and it thus can be defined as a "high flow-low pressure system", where up to three- to fourfold increases of cardiac output can be tolerated without significant increases of pulmonary artery pressure. Besides, pulmonary vascular resistance (PVR) decreases in healthy subjects when blood flow rises[1,2]. The low vascular tone of pulmonary circulation (even if highly reactive to hypoxemia and endogenous constrictors)[3] determines thus physiologically an independence of pulmonary arterial pressure (PAP) and cardiac output (CO). Pulmonary hypertension (PH) determines the loss of this relation[4], and mean PAP values greater than 20 mmHg at rest are usually considered a marker of this condition in the adult patient.

TABLE I. —*Pathophysiological mechanisms resulting in PH.*

Vasoconstriction	Hypoxia, hypercarbia, COPD, ARDS
Pulmonary venous hypertension	Mitral disease, left ventricular failure
Pulmonary macro- or microvascular disease, ARDS, obstruction	Thromboembolic disease, pulmonary embolism, sickle cell pulmonary edema, DIC
Pulmonary vascular obliteration	Primary PH, pulmonary vasculitis, interstitial lung disease
Increased pulmonary blood flow	Ventricular/atrial septal defects, patent ductus arteriosus, sepsis

Pulmonary hypertension is often secondary to a great variety of cardiopulmonary diseases, acting on the pulmonary circulation in different ways. Long-standing, chro-

Pathogenesis of ph in critical care medicine

Many pathological conditions, both pulmonary or extrapulmonary in origin, can eventually result in PH (Table I) with different mechaninsms. Patients treated in the intensive care unit (ICU)[5] usually:

A) have developed acute PH as a consequence of acute respiratory failure (ARDS, ALI), sepsis, left heart failure, pulmonary embolism, persistent PH of the newborn.
B) experience decompensation of a chronic form of PH, either because of superimposing respiratory or cardiovascular disease, or as severe evolution of their basic pulmonary or cardiac pathological process (as in cardiac surgery and lung transplantation).

From a pathophysiological point of view, with great impact on the treatement of the underlying cause and on prognosis, the increase of resistance to flow in the pulmonary vascular bed can be consequence of a functional process (reactive arterial vasoconstriction; vascular engorgement; compression; contribution of high intrathoracic pressures in mechanical ventilation)[6-9] or of structural nature (vascular remodeling, i.e. obliteration, both primary or in response to volume/pressure overload or inflammatory/toxic process; vascular obstruction by deposition of fibrin or microemboli, or by macroemboli[10-13]), being the latter obviously related to a lesser degree of reversibility, also because morphological modifications require the time of a long standing PH to develop.

Cardiovascular effects of PH

Regardless of the actual mechanism(s) involved, PH adversely affects both respiratory and cardiovascular function. The features of gas exchange impairment in PH[14,15] will not be addressed in this paper, which instead focuses on the peculiar cardiovascular derangements produced by the sudden, or anyway no longer tolerated, increased afterload put by severe PH on the right ventricle (RV). This pathological condition is defined as Acute Cor Pulmonale (Decompensated Chronic Cor Pulmonale, in the setting of a preexistent PH). A sudden mild increase in PAP induces no major hemodynamic consequences on a previously normal RV function, by promoting an adaptation (through dilation compensating for a possible reduction in its ejection fraction). Neither does a gradual increase in PAP to higher values, adding to progressive dilation the compensatory mechanism of RV hypertrophy. But if the mean PAP exceeds values around 40 mmHg in the non-adapted RV (or even less in a previously otherwise dysfunctioning RV) or anyway gets over the limit of compensation of an adapted RV in chronic PH, RV failure ensues, potentially leading to cardiogenic shock. While RV dysfunction secondary to pulmonary venous hypertension (in end-stage cardiomiopathies, heart transplant, mitral disease) is part of biventricular failure, massive pulmo-

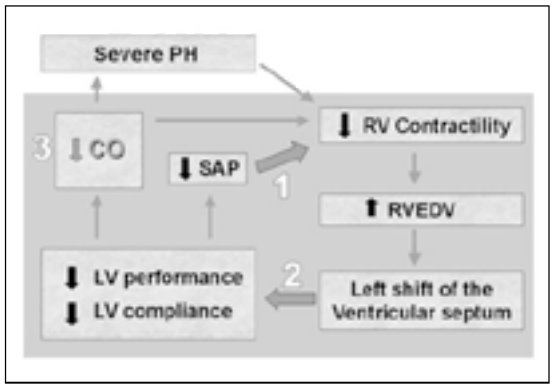

Figure 1. — The vicious circle of RV failure in the setting of cor pulmonale. Enclosed in the grey shaded area are the hemodynamic derangements taking part to the circle. Numbers from 1 to 3 emphasize the key points of the pathological process. PH = pulmonary hypertension, RV = right ventricle, RVEDV = RV end diastoli volume, LV = left ventricle, SAP = systemica arterial pressure, CO = cardiac output.

nary embolism and acute respiratory distress syndrome (ARDS) represent the 2 main causes of acute cor pulmonale in the adult[16-18] (according to an echocardiographic definition)[19], and persistent pulmonary hypertension of the newborn the most frequent in pediatrics.

The vicious circle of RV failure

Even though knowledge of the hemodynamic features of acute cor pulmonale exists since many years[20,21], only the clinical use of echocardiography has yield over recent years a thorough understanding of RV failure in this setting[22]. In decompensated chronic cor pulmonale or acute cor pulmonale, right ventricular failure breaks out a threatening vicious circle in which 3 crucial mechanisms represents the key points of both monitoring and potential therapeutic correction (Figure 1).

Understanding of these key points, gives answer to the following questions.

Why does systemic arterial pressure become crucial in the evolution of RV failure? The right and the left ventricles are two serial pumps, and the RV is perfused by the left ventricle (LV) throughout the entire cardiac cicle at a pressure gradient physiologically produced by the difference between aortic bulb pressure and coronay sinus pressure (RV end diastolic pressure, RVEDP). In severe PH, the systemic features of the pulmonary circulation and the increased RV intracavitary pressures render RV perfusion mainly a diastolic phenomenon depending greatly on diastolic systemic arterial pressure (being the other term of the gradient, RVEDP, greatly increased): the threat of severe PH is thus RV ischemia, leading to cardiogenic shock[23].

How does RV dysfunction deeply condition LV performance? In severe PH, the RV dilates, losing its triangular shape (in the 4 chamber echocardiographic view) for a more rounded one. In the fixed pericardial space, RV dilation happens at the expense of the other ventricle, with a proportional reduction in LV diastolic dimension[24]. A septal diplacement or flattening thus occurs (meaning a loss of the physiological constant interventricular septal convexity toward the RV troughout the whole cardiac cicle), imparing LV relaxaton[25]. RV afterloading also produces an abnormal and characteristic septal motion, due to changes in RV contraction, that becomes stronger (as far as it can stand the elevated afterload) and longer than normal[26] (Figure 2). As a result, when the LV starts to relax, RV contraction continues, reversing the trans- septal pressure gradient and causing the septum to bulge toward the LV (Figures 2A, 2B and 2C). Abnormal septal position is maintained during diastole and can even increase at end diastole, due to possible concurrent RV volume overload (Figures 2B and 2D). At the onset of systole, LV contraction restores the normal trans-septal gradient and sets the septum back to its flattened position 19. This pathological septal motion (named paradoxical septal motion, because of the inter-

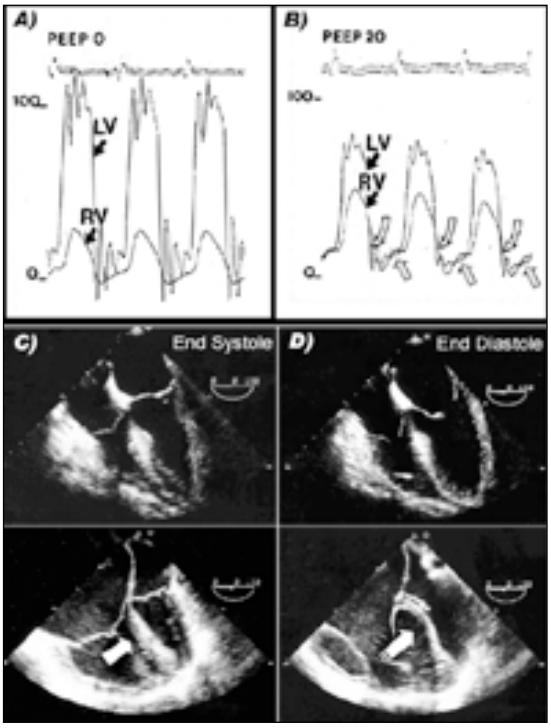

Figure 2. — Acute Cor Pulmonale produced by application of an elevated PEEP level during mechanical ventilation of a patient with prior normal RV function (A). Simultaneous Right (RV) and Left (LV) heart catheterization show a subsequent (B) dramatic increase in RV systolic pressure (i.e. PAPs), reduction of systemic arterial pressure, and a longer RV contraction, with end systolic RV pressure exceeding end systolic LV pressure (empty curved arrows, shaded areas). The trans septal gradient is maintained in mesodiastole (RV and LV pressure equalization), but volume overload may produce a further shift of the gradient towards the left (empty straight arrows, shaded areas). Echocardiographic equivalent (TEE 4 chamber view) of this phenomenon in another patient with decompensation of chronic cor pulmonale. Left panels (C) show what happens at end systole in this heart (down) compared to a normal heart (up): septal flattening and leftward shift (septum paradoxus) is evident (arrow), in addition to RV enlargement and Right atriomegaly. The same hearts are shown in right panels (D) at end diastole: further leftward septal shift (arrow) occurs because

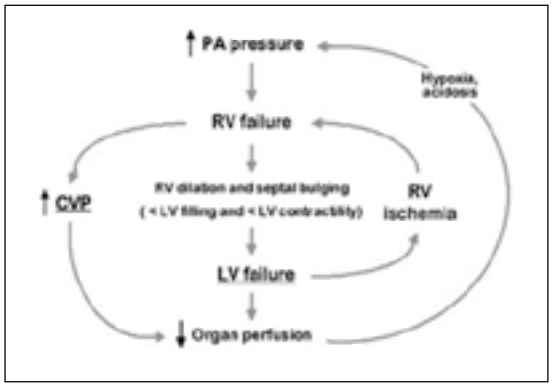

Figure 3. — The role of ventricular interdipendence in enhancing the vicious circle of RV failure. Pulmonary hypertension, the primum movens, also is promoted by the effects of reduced organ perfusion.

ventricular septum moving parall and not opposite to the LV posterolateral wall, as it should be) may also potentially interfere with LV ejection, producing dynamic obstruction of its outflow tract. The whole phenomenon of this pathological ventricular interaction (reduced preload, diastolic dysfunction, systolic impairment, of the LV) is named ventricular interdependence[22-27].

How is the overall effect of RV failure on CO and organ perfusion determined? The significant reduction in cardiac output in acute cor pulmonale adds to systemic venous congestion (both for reduced RV contractility and for tricuspid regurgitation, always associated), with exponential detrimental effect on organ perfusion (Figure 3)[28,29].

Therapeutic hints in PH

High RV filling pressure (traditional volume loading in RV infarction treatment) restores normal hemodynamics only if pulmonary vascular resistance is normal and RV contractility is not markedly reduced[28]. Successful management must thus include:

A) reduction of pulmonary afterload, when possible (pulmonary vasodilators, better if selective, with non-systemic action);

B) augmentation of contractile strength (inotropes effective on RV myocardium: dobutamine, isoproterenol, epinephrine, PDI), decreasing RV size with improved LV filling; Maintenance of aortic blood pressure, especially if

high fixed pulmonary resistance is present (vasopressors may augment RV performance when coronary perfusion pressure is reduced by increased RV end diastolic pressure) [29,30].

Riassunto

Fisiopatologia dell'ipertensione polmonare grave nel paziente con patologia in atto

L'ipertensione polmonare rappresenta una condizione pericolosa che si può associare a una grande varietà di patologie sia polmonari che extrapolmonari. In tutte le forme di ipertensione polmonare di grado severo, il letto vascolare polmonare perde le sue caratteristiche fisiologiche di "sistema ad alto flusso e a bassa pressione", determinando un aumento del postcarico a livello del ventricolo destro. Presso l'unità di terapia intensiva, l'ipertensione polmonare acuta spesso rappresenta una problematica clinica secondaria all'insufficienza respiratoria acuta, allo scompenso cardiaco sinistro, all'embolia polmonare o allo scompenso di una pregressa ipertensione polmonare a causa di una concomitante patologia polmonare o cardiovascolare. Lo scompenso del ventricolo destro (cuore polmonare acuto) si verifica quando un importante aumento delle resistenze vascolari del polmone superano i suoi meccanismi di compenso, sia improvvisamente a livello di un ventricolo destro precedentemente normale, che gradualmente in un quadro di cuore polmonare cronico. La presente review analizza i principali aspetti fisiopatologici dell'ipertensione polmonare di grado severo, concentrando l'attenzione sulle alterazioni emodinamiche che si verificano nel quadro clinico del cuore polmonare acuto e sottolineando il ruolo dell'interdipendenza ventricolare (il meccanismo attraverso cui lo scompenso del ventricolo destro condiziona in grande misura la funzionalità diastolica e sistolica del ventricolo sinistro), il rischio di ischemia del ventricolo destro (lo stadio terminale dell'insufficienza ventricolare destra) e l'ipoperfusione sistemica degli organi (causata dall'insufficienza cardiaca anterograda e retrograda). La comprensione delle caratteristiche peculiari di questo tipo di insufficienza cardiovascolare è necessaria al fine di fornire sia un efficace monitoraggio che una adeguata terapia di supporto.

Parole chiave: Ipertensione polmonare – Malattia critica - Cuore polmonare - Insufficienza ventricolare destra - Sindrome da distress respiratorio - Embolia polmonare.

References

1. Pappert D, Falke KJ. Pulmonary hypertension. Pathophysiology and causes. In: Webb A, Shapiro M, Singer M editors. Oxford Textbook of Critical Care. Oxford: Oxford University Press, UK; 1999. p. 280-3.
2. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: pathophysiology and anesthetic approach. Anesthesiology 2003; 99:1415-32.
3. McCulloch KM, Docherty CC, Morecroft I, MacLean MR. EndothelinB receptor-mediated contraction in human pulmonary resistence arteries. Br J Pharmacol 1996;119:1125-30.
4. Enson Y. Pulmonary hypertension and its consequences. In: Baum GL, Wolinsky E, editors. Textbook of pulmonary diseases. Boston: Little Brown; 1989. p.5.
5. Mc Laughlin W. Severe pulmonary hypertension: critical care clinics. Crit Care Clin 2001;17:453-67.
6. Marshall BE, Hanson CW, Frasch F, Marshall C. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 2. Pathophysiology. Intensive Care Med 1994; 20:379-89.
7. Zapol W, Snider M. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977;296:476-80.
8. Flick MR, Matthay MA. Pulmonary edema and acute lung injury. In: Murray JF, Nadel J, editors. Textbook of respiratory medicine. 3rd ed. Philadelphia: WB Saunders Company; 2000. p.1575-629.
9. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP. Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology 1990;72:966-70.
10. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336:111-7.
11. Gaine S. Pulmonary hypertension. JAMA 2000;284:160-8.
12. Zapol W, Jones R. Vascular components of ARDS. Clinical pulmonary hemodynamics and morphology. Am Rev Respir Dis 1987;136:471-4.
13. Leeman M. The pulmonary circulation in acute lung injury: a review of some recent advances. Intensive Care Med 1991;17:254-60.
14. Zwissler B, Messmer K. Pulmonary vascular obstruction. In: Webb A, Shapiro M, Singer M editors. Oxford Textbook of Critical Care. Oxford: Oxford University Press, UK, 1999. p. 287-91.
15. Wilson EP, White RA. Pulmonary embolus. In: