

Letter to the editor

Acute life-threatening reversible pulmonary vasoconstrictive reaction to bleomycin chemotherapy demonstrating the clinical application of ePLAR – echocardiographic Pulmonary to Left Atrial Ratio



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Lung toxicity arising from the chemotherapeutic agent bleomycin typically manifests a spectrum of chronic pulmonary syndromes including interstitial pneumonitis, hypersensitivity pneumonitis, eosinophilic pneumonia and progressive interstitial fibrosis. We report a rare case of acute pulmonary hypertension associated with bleomycin administration, which emphasises the clinical relevance and applicability of the recently described, non-invasive echocardiographic parameter ePLAR (echocardiographic Pulmonary to Left Atrial Ratio).

Right heart catheterisation has historically remained the gold standard for distinguishing *pre-capillary pulmonary hypertension* (high mean pulmonary pressure, normal pulmonary wedge pressure), from *post-capillary pulmonary hypertension* (elevated pulmonary wedge pressure). The echocardiographic parameter, ePLAR, is a non-invasive method of predicting the pressure gradient across the pulmonary vasculature [1,2]. This parameter is calculated from the maximum tricuspid regurgitation continuous-wave Doppler velocity (m/s) divided by the transmitral E-wave septal: mitral annular DTI e'-wave ratio ($ePLAR_{(m/s)} = TRV_{max(m/s)}/E/e'$) – See Fig. 1A. Increasing ePLAR values suggest increasing trans-pulmonary gradient (TPG), whilst lower ePLAR values indicate elevated left heart pressures as the driver for elevated pulmonary pressures.

A 70-year-old man was diagnosed with Hodgkin's lymphoma requiring six cycles of systemic chemotherapy with doxorubicin, bleomycin, vincristine and dacarbazine. Baseline cardiac and respiratory

function tests were normal 2 days prior to chemotherapy. Left and right ventricular function was preserved (EF 62%, TAPSE 30 mm/s). Right ventricular systolic pressure (RVSP) was calculated at 24 mmHg, with normal estimated left atrial filling pressure ($E/e' 11$). Trans-pulmonary flow characteristics were normal as demonstrated by an ePLAR of 0.22 m/s (normal range for age 0.24 ± 0.09 m/s) [1].

Immediately after the first cycle of chemotherapy, the patient sustained a sudden hemodynamic and respiratory collapse associated with confusion, rigidity, pyrexia (42°) and faecal incontinence. The medical emergency team was alerted and he was transferred promptly to ICU with a presumed reaction to bleomycin. Fluid and ventilatory resuscitation was undertaken. Emergency therapy with IV paracetamol, piperacillin/tazobactam and vancomycin was administered, though subsequently blood cultures taken at the time were negative. Troponin T rose from 43 ng/ml at baseline to 293 ng/ml immediately post-reaction, returning to 196 ng/ml 7 hours after the reaction.

Emergency echocardiography was performed approximately one hour after the bleomycin infusion. This study showed new moderate tricuspid regurgitation and pulmonary hypertension with a moderately elevated right ventricular pressure (RVSP 54 mmHg, TRV_{max} 3.44 m/s, estimated right atrial pressure 8 mmHg) and a calculated ePLAR of 0.54 m/s, suggesting markedly elevated trans-pulmonary gradient (See Fig. 1 B&C). Left heart Doppler parameters suggested low left atrial filling pressures ($E/e' 6.3$), consistent with poor trans-pulmonary transit and shock. The electrocardiogram showed sinus rhythm and global T-wave inversion. CT pulmonary arteriography, however, ruled out acute pulmonary embolus (PE).

The patient recovered over 12 h, no longer requiring inotropic or respiratory support. A second echocardiogram 60 h after the reaction showed partial normalisation, with a mildly elevated RVSP (43 mmHg) and a mildly elevated ePLAR of 0.38 m/s. Late echocardiography 6 days after the reaction showed complete normalisation of all parameters with a normal RVSP (24 mmHg) and an ePLAR of 0.24 m/s. A diagnosis of an acute reversible severe vasospastic pulmonary reaction to bleomycin chemotherapy was made.

Bleomycin is an antibiotic with antineoplastic properties, first isolated in 1966 from a strain of *Streptomyces verticillus*. Bleomycin is utilised as part of cytostatic therapy for numerous malignancies such as lymphomas, Hodgkin's and non-Hodgkin, germ cell tumours, and squamous

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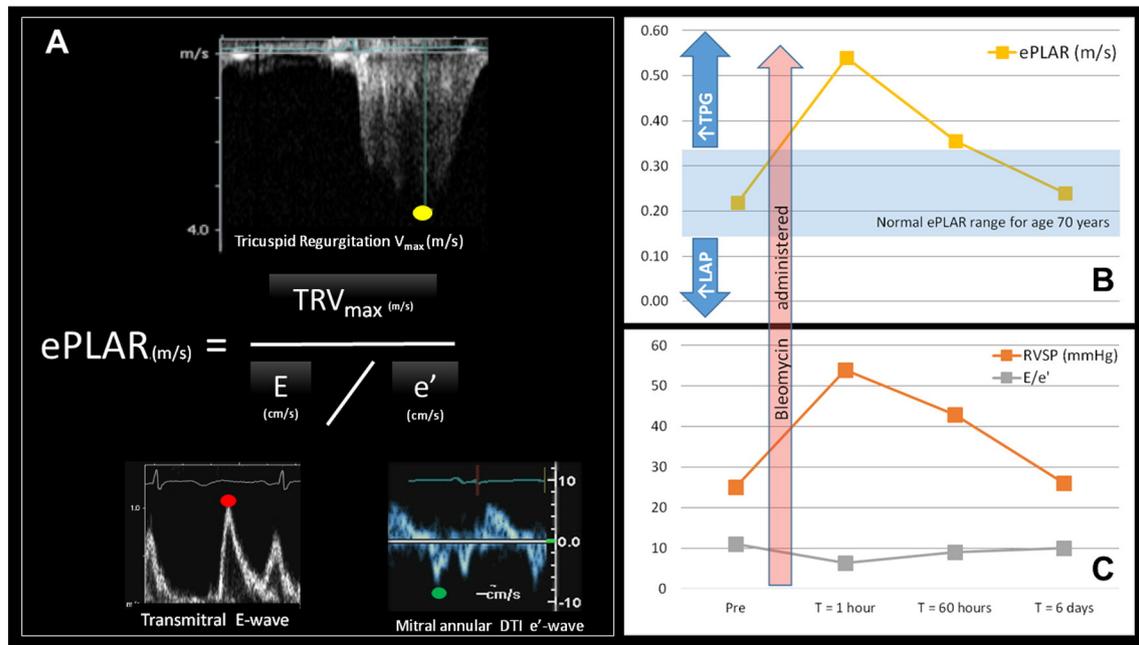


Fig. 1. A. The ePLAR (m/s) consists of three parameters – peak tricuspid regurgitation continuous-wave Doppler velocity (m/s) divided by the transmitral peak pulsed-wave Doppler E wave (cm/s): peak Doppler Tissue Imaging mitral septal annular e'-wave (cm/s). B & C. Echocardiographic data obtained pre, 1-h post, 60-h post and 6-days post reaction to bleomycin chemotherapy. Prior to bleomycin therapy, all parameters were normal (RVSP 24 mmHg, E/e' 11 – see C, ePLAR 0.22 m/s – see B). At 60 min post bleomycin, there was a dramatic increase in RVSP to 54 mmHg with a fall in E/e' to 6.3 (see C). This was associated with a substantial increase in ePLAR to 0.54 m/s (see B), consistent with an abrupt increase in trans-pulmonary gradient. Over the ensuing days, all parameters returned linearly towards normal.

cell carcinomas of the head and neck [3]. It exerts its antitumor effect by chelating and oxidising ferrous (Fe^{2+}) to ferric ions (Fe^{3+}), reducing oxygen to free radicals. These induce tumour cell death by producing single and double strand breaks in DNA. Bleomycin is excreted by the kidneys unchanged in the first 24 h following administration. Additionally, bleomycin is inactivated by the enzyme bleomycin hydrolase, which is present in all tissues with relative deficiencies in the skin and lung [3]. This spatial difference accounts for the greater levels of toxicity seen in these organs. The mechanism by which bleomycin produces lung injury is yet to be elucidated but likely pertains to oxidative damage, bleomycin hydrolase deficiency, and the production of inflammatory cytokines [4,5].

Bleomycin related pulmonary toxicity occurs in approximately 10% of patients and presents initially with dyspnoea, cough, and pyrexia [6, 7]. Pneumonitis can progress to fibrosis and death up to 6 months after discontinuation of bleomycin [8]. Fibrosis is mediated by lymphocytes and macrophages secreting tumour necrosis factor [3,9]. Risk factors include renal impairment, supplemental oxygen exposure, radiation therapy, age >40 years, cigarette smoking and a cumulative dose of bleomycin >300 000 IU [9]. Hypersensitivity pneumonitis is not dose related and occurs within days to weeks of exposure [9]. The diagnosis is based upon radiological evidence of parenchymal patchy infiltrates, often misdiagnosed as lung metastases, and either bronchoalveolar lavage eosinophilia or histopathology. Systemic glucocorticoids are used as therapy provided infection has been excluded [6]. Our patient did not exhibit eosinophilia during his admission.

In the acute setting, bleomycin has yet to be associated with an acute pulmonary hypertensive reaction, which is a well-recognised complication of several pharmaceutical therapies and recreational drugs, with documented increased pulmonary vascular resistance, right heart failure and death. Therapeutic drugs including interferons, tyrosine kinase inhibitors and appetite suppressant medications such as aminorex, fenfluramine, and benflores, have been associated *pre-capillary* pulmonary hypertension, although confirming causality is challenging [10]. Recreational drugs including amphetamines and cocaine are also associated with pulmonary hypertension, owing to

their pharmacological similarities to fenfluramine. As in our case, ePLAR could prove valuable in detecting the nature of such drug reactions with pulmonary hypertension. Acute pulmonary embolus (PE) is another potentially catastrophic event which could have explained this man's cardiorespiratory collapse. Raised ePLAR values have been demonstrated in acute sub-massive PE, consistent with abruptly elevated TPG, in the absence of acutely increased pulmonary artery pressure [2].

The association of bleomycin and acute hemodynamic and respiratory collapse reactions has not been previously described in the literature. This patient demonstrates a life-threatening case of acute reversible pulmonary hypertension. It highlights the clinical applicability of ePLAR, which suggested abruptly elevated trans-pulmonary gradient in the setting of new moderate pulmonary hypertension. PE clearly needed to be excluded – and was. This case illustrates how this new parameter ePLAR may be applied to delineate pulmonary vascular events to guide appropriate management.

Conflict of interest

All authors have no conflict of interest.

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