Clinical Investigation

Sodium Nitroprusside in Patients With Mixed Pulmonary Hypertension and Left Heart Disease: Hemodynamic Predictors of Response and Prognostic Implications

HOONG SERN LIM, MD, FRCP, AND ALEX ZAPHIRIOU, MRCP

Edgbaston, Birmingham, UK

ABSTRACT

Background: Mixed pulmonary hypertension (PH) in heart failure (HF) is defined by transpulmonary gradient ≥ 12 and/or pulmonary vascular resistance (PVR) ≥ 240 dyne/s/cm^{-5}, but diastolic pressure gradient (DPG) ≥ 7 mmHg has been proposed more recently. We evaluated the acute hemodynamic response to sodium nitroprusside (SNP) specifically in relation to the proposed DPG criterion ≥7 mmHg and the prognostic significance of response to SNP in patients with mixed PH and advanced HF.

Methods: Ninety-eight consecutive patients with advanced HF and mixed PH underwent cardiac catheterization and acute SNP infusion. Baseline hemodynamic parameters included transpulmonary gradient, PVR, DPG, and pulmonary capacitance (PCap). Hemodynamic response to SNP was defined as a reduction in PVR of at least 20%. The composite endpoint was death/heart transplantation/mechanical circulatory support.

Results: Sixty of the 98 patients were SNP responders. SNP resulted in significant reductions in filling pressures and PVR and increase in stroke volume and PCap. DPG (not baseline PVR) was significantly associated with hemodynamic response to SNP on logistic regression analysis. The sensitivity and specificity of a DPG ≥7 mmHg to identify nonresponders to SNP were 74% and 97%, respectively. At median follow-up of 218 (148–324) days, 13 and 19 patients of the SNP responders and nonresponders, respectively, met the composite endpoint (P = .021 by log-rank test). Hemodynamic response to SNP and PCap were independently associated with the composite outcome of survival free from transplantation/mechanical circulatory support.

Conclusion: Baseline DPG ≥ 7 mmHg is associated with poor PVR response to SNP. PVR response to SNP and PCap are associated with a more favorable prognosis in patients with advanced HF and mixed PH. (*J Cardiac Fail 2016;22:117–124*)

Key Word: Vasodilator.

Background

Pulmonary hypertension (PH) is common in patients with advanced heart failure (HF). In most cases, PH in left heart disease reflects passive elevation in left-sided filling pressures. However, some patients develop functional and/or structural abnormalities (abnormal vasoconstriction and/or remodeling) of the pulmonary vasculature in addition to passive PH—so-called mixed (or reactive) PH—leading to a disproportionate rise (and fall) in pulmonary artery pressures in response to changes in left-sided filling pressures. Mixed PH is currently defined by elevated pulmonary vascular resistance (PVR) ≥ 3 Wood units and transpulmonary gradient (TPG) ≥ 12 mmHg in association with an elevated mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure (PAWP) > 15 mmHg.[1] These criteria for mixed PH in HF were based on published ranges in the normal population.[2] However, there are inherent limitations to TPG and PVR measurements, prompting calls for the use of diastolic pressure gradient (DPG).[3,4] A recent report has suggested a DPG of ≥7 mmHg to identify patients with superadded pulmonary vascular abnormalities in mixed PH.[5]

There are significant limitations in the current resting TPG and PVR criteria in defining mixed PH. First, these criteria

From the University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK.

Reprint requests: Hoong Sern Lim, MD, FRCP, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2TH, UK. Tel: +44 121 371 3994; Fax: +44 121 371 4045. E-mail: sern.lim@uhb.nhs.uk.

Manuscript received April 3, 2015; revised manuscript received October 25, 2015; revised manuscript accepted October 27, 2015.

See page 124 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2015.10.018

have limited specificity for distinguishing passive from reactive PH. This was well-illustrated by Naeije et al,[6] who reported *proportional* reduction in pulmonary artery and PAWP s in patients with HF who underwent transplantation, despite baseline TPG and PVR that would meet the criteria for mixed PH. Second, the elevated TPG and PVR in mixed PH may be mediated by abnormal vasoconstriction, pathological pulmonary vascular remodeling, or both. The former may respond acutely to vasodilators, but resting TPG and PVR criteria have poor sensitivity and specificity for response to vasodilators. This is evident from several studies that have reported on the acute improvements in pulmonary hemodynamics with vasodilators in some patients despite TPG and PVR levels above the criteria for mixed PH.[7–9] The criterion of DPG ≥ 7 mmHg has not been studied in relation to the response to vasodilators.

Sodium nitroprusside (SNP) is a potent vasodilator that can acutely reduce left ventricular afterload, improve cardiac filling pressures, reduce mitral regurgitation, and increase cardiac output in patients with HF.[10] The improvement in left-sided filling pressures reduces pulmonary artery pressures proportionately in passive PH, although pulmonary vasodilatation may also contribute to the reduction in pulmonary artery pressure.[11] Hence, PH related to abnormal vasoconstriction may respond acutely to SNP; in contrast, the presence of structural remodeling of the pulmonary vasculature would be expected to limit the hemodynamic response to SNP ("fixed" PH).[12,13] This has formed the basis for the assessment of candidacy for heart transplantation,[14,15] but the prognostic significance of fixed PH is not clear.

Hence, this study aimed to: (1) describe the acute hemodynamic response to SNP in patients with HF and mixed PH, as defined by contemporary criteria of resting PVR ≥ 3 Wood units (or 240 dyne/s/cm^{-5}) and/or TPG of ≥12 mmHg; (2) evaluate the response to SNP in relation to the proposed DPG criterion of ≥7 mmHg; and (3) assess the prognostic significance of response to SNP in patients with mixed PH and advanced HF. We hypothesized that a DPG ≥ 7 mmHg is a sensitive and specific criterion for poor hemodynamic response to SNP (fixed PH) and that poor response to SNP is associated with worse clinical outcomes.

Methods

Study Design and Patient Population

This is a retrospective analysis of prospectively collected data on consecutive ambulant patients with HF (New York Heart Association class III or IV) who underwent in-hospital assessment for heart transplantation between December 2010 and April 2014 at University Hospital Birmingham NHS Foundation Trust (Birmingham, United Kingdom). Patients with congenital heart disease or severe cardiogenic shock requiring inotropic support or urgent mechanical circulatory support (including intra-aortic balloon pump) were excluded from this study. Patients with significant contraindications, other causes of PH (eg, chronic thromboembolic disease), or who are "too well" for transplantation would not undergo in-hospital assessment/cardiac catheterization and were not included. Baseline demographic data, including information on the medical history and current use of medications, were collected from all the patients at the time of heart transplant assessment. The investigations/procedures were performed in accordance with our institution's protocol for assessment for heart transplantation and approval from the NHS Research Ethics Committee was not required.

Transthoracic Echocardiography

Transthoracic echocardiography was performed in accordance with standard guidelines. The left ventricular end-systolic, end-diastolic volumes, and ejection fraction were obtained by Simpson's method from 2-dimensional apical images. The tricuspid annular plane systolic excursion was measured by M-mode in the apical view as a measure of right ventricular (RV) function. Mitral and tricuspid regurgitation was quantified by Doppler in accordance with current recommendations.[16]

RV diameter was measured at the mid-RV level. Restrictive transmitral filling pattern was defined by a E/A ratio of >2 and/or an E wave deceleration time of <140 ms[17] (eg, in patients with atrial fibrillation).

Right Heart Catheterization

Right atrial, RV, pulmonary artery. and PAWPs were recorded with a balloon-tipped catheter. The pulmonary artery and PAWP measurements were taken at end-expiration over at least 2 respiratory cycles including at least 5 beats using the Series IV Physio-Monitoring and Information System (Witt Biomedical; Melbourne, Australia). The position of the catheter was confirmed on fluoroscopy and the pressure waveform. Left heart catheterization was not performed routinely, but an arterial line was inserted for blood pressure monitoring and arterial blood gas sampling. Cardiac output and changes on infusion of SNP were measured by the Fick method with serial pulmonary artery and systemic arterial blood gas analyses. Resting oxygen consumption (VO_2) was taken from the cardiopulmonary exercise test performed on the morning before right heart catheterization for the calculation of cardiac output, assuming no change in VO_2 with SNP infusion. Duplicate blood gas sampling was performed routinely, with a <10% difference in 89 of the 98 cases and a <15% difference in all 98 patients, which is consistent with previous reports.[18]

TPG was calculated as: mean pulmonary artery—mean PAWP. PVR in Woods units was calculated as: TPG/cardiac output. Pulmonary artery capacitance (PCap) was calculated as stroke volume/pulmonary artery pulse pressure. DPG is defined as the difference between pulmonary artery diastolic pressure and mean PAWP in mmHg and measured on pullback with balloon deflation.

Nitroprusside Infusion and Definition of Response

Historically, our program has used SNP infusion in patients undergoing assessment for heart transplantation if there was evidence of mixed PH and left heart disease, which was