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Nitric Oxide Attenuates Arterial Pulse Wave Reflection in a Vasodilator Responding Pulmonary Arterial Hypertension Patient

Running title: NO reduces wave reflection in IPAH

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Pulmonary arterial hypertension is characterized by distal vasoconstriction, vascular remodeling, microvascular injury and thrombosis leading to increased pulmonary vascular resistance (PVR) and elevated mean pulmonary arterial pressure (PAPm). A small subset (<10%) of patients with idiopathic pulmonary arterial hypertension (IPAH) respond profoundly (≥10 mmHg drop in PAPm to ≤40 mmHg with stable or increased cardiac output) to acute vasodilators, such as inhaled nitric oxide (NO)[1]. These patients have an excellent prognosis when treated with high-dose calcium channel blockers[1]. The principal disease mechanism in this rare subtype of IPAH may be vasoconstriction with limited vascular remodeling. Here, we describe for the first time how inhaled NO influences arterial pulse wave propagation in such a vasoreactive IPAH patient.

The patient was a 33-year-old woman undergoing right heart catheterization, which was performed using a dual-tipped pressure and Doppler flow sensor wire to acquire simultaneous pressure and flow velocity measurements in the right pulmonary artery at rest and during NO inhalation (20 PPM). Wave intensity analysis (with and without subtraction of reservoir pressure) and pressure separation were performed[2, 3].

During vasoreactivity testing, PAPm and PVR decreased (31 → 17 mmHg and 4.1 →1.0 Wood Units, respectively), while arterial compliance and cardiac output increased (3.1 → 6.5 mmHg·ml and 5.6 → 6.6 l/min, respectively). Arterial pulse wave velocity (PWV) decreased (5.1 → 3.1 m/s) indicative of decreased vessel stiffness. The energy the pulse wave (FCW in Figure 1) generated by right ventricular ejection increased consistent with improved cardiac performance, while wave reflection index (WRI), defined as the ratio of the reflected wave energy (BCW in Figure 1) to FCW energy, decreased (54 → 13%). The reflection time (Δt in Figure 1) lengthened and the apparent reflective site, calculated by multiplying PWV by Δt /2, was 15 – 17 cm downstream of the measurement site. Forward (P_f) and backward (P_b) pressures and the P_b/P_f ratio decreased (66 → 39 %) in response to NO. Qualitatively similar results were observed when analysis was performed using excess pressure (after subtracting reservoir pressure from the measured pressure).

Vasoconstriction and arterial stiffening compromise wave transmission between the proximal and distal vasculature leading to increased reflection. Reflected waves arriving during systole augment pressure and impede flow and therefore impose an additional load on the contracting ventricle. During NO challenge, wave reflection reduced indicative of improved energy transmission properties. Reflections also arrived later, probably due to the lower PWV. The estimated apparent reflective site likely corresponds to the level of pulmonary small arteries or arterioles, where NO exerts its dominant effect suggesting that improved pulse wave transmission results from vascular smooth muscle relaxation. WRI is minimal (<5%) in individuals without pulmonary vascular disease[2]. It is noteworthy that, despite normalization of PAPm and PVR during NO challenge, there was some residual WRI (13%). This may be attributable to underlying vascular remodeling and/or incomplete vasodilatation.

This extent of attenuation in arterial pulse wave reflection in response to an intervention has not been witnessed previously in man. In another study, wave reflection remained unchanged despite of a mild decrease in PVR during NO challenge, it may be relevant that this study cohort had severely elevated pulmonary pressures (PAPm: ~63 mmHg)[4]. Large wave reflection was present in untreated and chronically treated PAH patients, even in patients with mild PAH[2]; and substantial wave reflection persisted in patients with chronic thromboembolic pulmonary hypertension following pulmonary endarterectomy despite decreased PAPm and PVR (Su et al, unpublished data, 2018). Therefore, the pronounced reduction in wave reflection during NO inhalation may suggest near-normal pulmonary vascular structure in vasoreactive IPAH with the predominant abnormality being vasoconstriction of the pulmonary arterioles.

In conclusion, in response to NO, arterial pulse wave energy increased, PWV decreased and reflection decreased. Clearly, the results from this single case study cannot be extrapolated to other vasoreactivity testing agents or to all NO responders. Nevertheless, it provided a unique insight into arterial wave behavior in vasoreactive IPAH.

Conflict of interest: None

References

1. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk NA, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz CA, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo BL, Albert BJ, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis ZJ. 2015 esc/ers guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur. Heart J*. 2016;37:67-119
2. Su J, Manisty C, Parker KH, Simonsen U, Nielsen-Kudsk JE, Mellemkjaer S, Connolly S, Lim PB, Whinnett ZI, Malik IS, Watson G, Davies JE, Gibbs S, Hughes AD, Howard LS. Wave intensity analysis provides novel insights into pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *J. Am. Heart Assoc*. 2017;6:e006679
3. Bouwmeester JC, Belenkie I, Shrive NG, Tyberg JV. Wave reflections in the pulmonary arteries analysed with the reservoir-wave model. *J. Physiol*. 2014;592:3053-3062
4. Huez S, Brimioulle S, Naeije R, Vachiery JL. Feasibility of routine pulmonary arterial impedance measurements in pulmonary hypertension. *Chest*. 2004;125:2121-2128

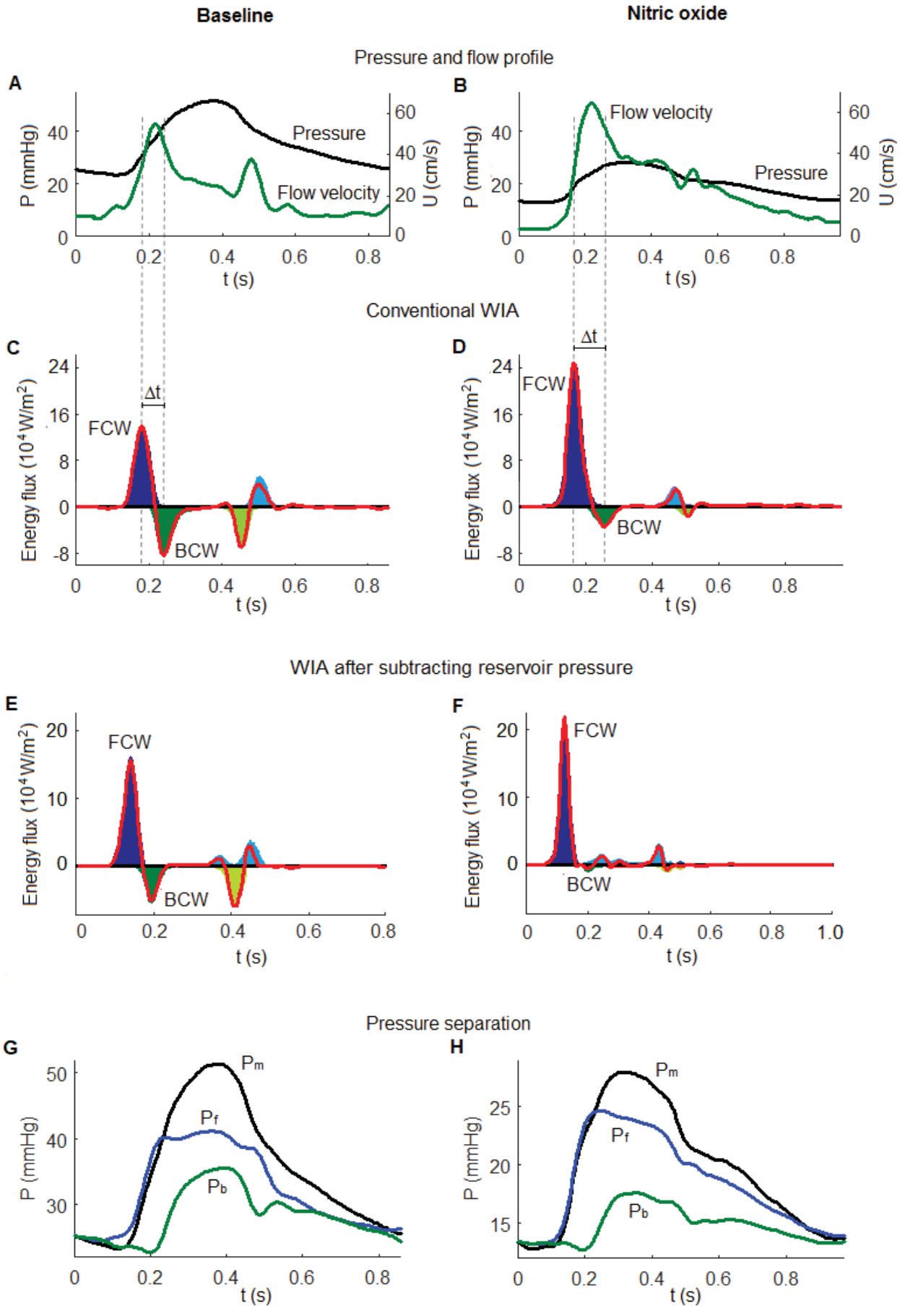
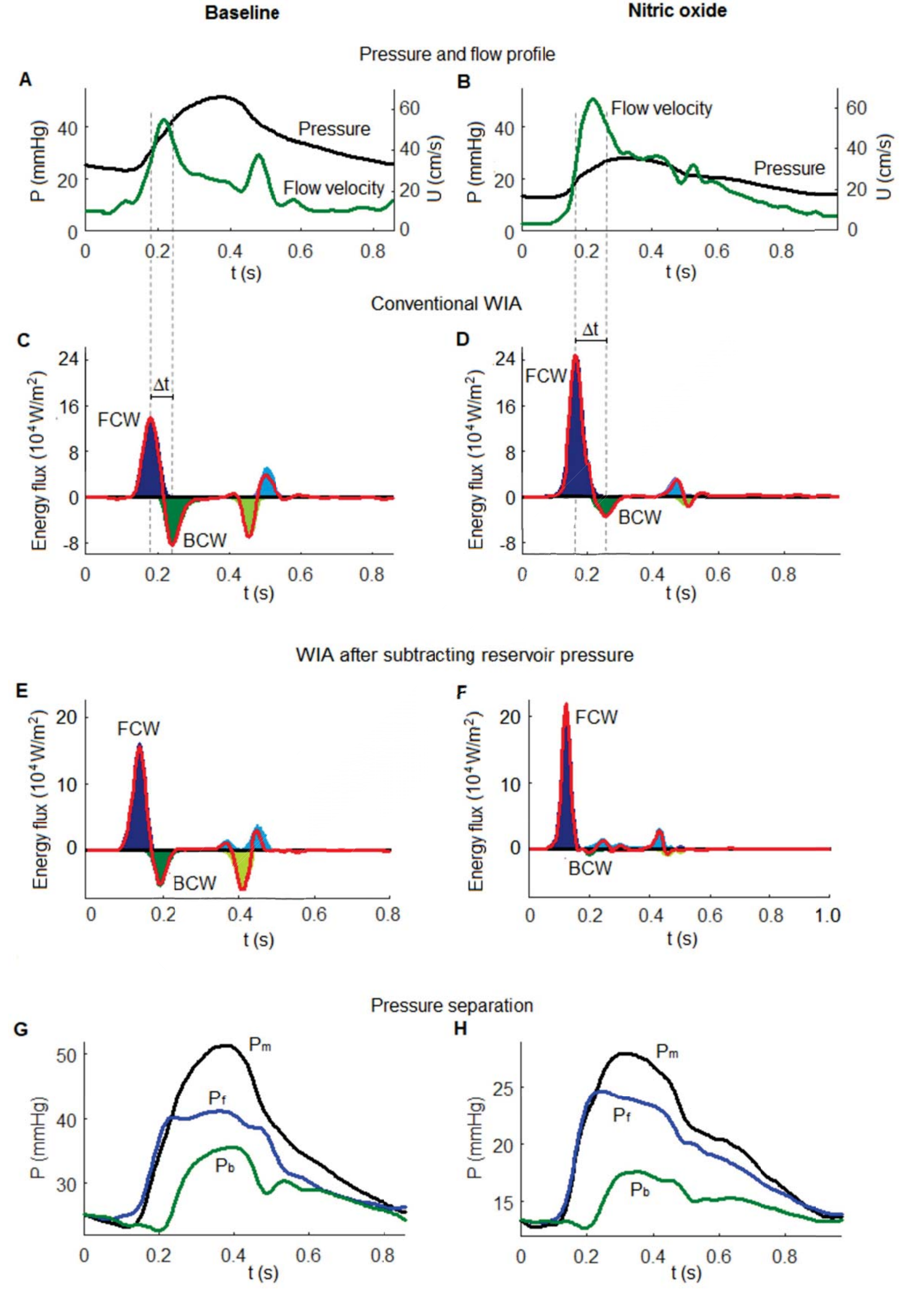


Figure 1. Analyses of Pulmonary Arterial Wave Propagation

By analyzing the incremental changes in pressure and flow velocity (A & B), wave intensity analysis (C & D) determines the origin (forward versus backward), type (compression versus decompression) and timing of the arterial pulse waves and the energy carried by the waves per cross sectional area of the artery. Forward compression wave (FCW, dark blue) was observed in early systole; it increased the pressure and flow and was related to right ventricular ejection. Backward compression wave (BCW, dark green) was observed in mid-systole; it decreased the flow while increasing the pressure and can be ascribed to reflection of the preceding FCW caused by impaired energy transmission between the proximal and distal vasculature. In late systole, forward decompression wave (light blue) was observed; it decreased the pressure and flow and corresponded to right ventricular relaxation. The observed backward decompression wave (light green) in late systole was most likely related to velocity signal artefact attributed to axial movement of the catheter. A potential limitation of separating wave intensity into their forward and backward components is that it depends on the estimated pulse wave velocity, which may be inaccurate if the reflection site is close to the site of measurement. Conversely, net wave intensity is not subjected to this problem and therefore, the contour of the net wave intensity profile is highlighted in red. .
When performing WIA using the excess pressure (E & F, after subtracting the reservoir pressure from the measured pressure), similar wave intensity patterns was observed. Pressure separation (G & H) deconstructs the measured pressure (P_m) waveform into forward (P_f) and backward (P_b) pressures. Note that the ratio of the magnitude of BCW to FCW and the ratio of peak P_b to P_f reduced substantially during nitric oxide vasoreactivity testing, while the reflection time (Δt) increased.


Baseline
Nitric oxide
Pressure and flow profile
A
B
P (mmHg)
U (cm/s)
Pressure
Flow velocity
t (s)
Conventional WIA
C
D
Δt
FCW
BCW
Energy flux (10⁴W/m²)
WIA after subtracting reservoir pressure
E
F
Pressure separation
G
H
Pm
Pf
Pb