8. Pullamsetti SS, Perros F, Chelladurai P, Yuan J, Stenmark K. Transcription factors, transcriptional coregulators, and epigenetic modulation in the control of pulmonary vascular cell phenotype: therapeutic implications for pulmonary hypertension (2015 Grover Conference series). *Pulm Circ* 2016;6:448–464.
9. Gamen E, Seeger W, Pullamsetti SS. The emerging role of epigenetics in pulmonary hypertension. *Eur Respir J* 2016;48:903–917.
10. Meloche J, Potus F, Vaillancourt M, Bourgeois A, Johnson I, Deschamps L, *et al*. Bromodomain-containing protein 4: the epigenetic origin of pulmonary arterial hypertension. *Circ Res* 2015;117:525–535.
11. Mumby S, Gambaryan N, Meng C, Perros F, Humbert M, Wort SJ, *et al*. Bromodomain and extra-terminal protein mimic JQ1 decreases inflammation in human vascular endothelial cells: implications for pulmonary arterial hypertension. *Respirology* 2017;22:157–164.
12. Chabert C, Khochbin S, Rousseaux S, Veyrenc S, Furze R, Smithers N, *et al*. Inhibition of BET proteins reduces right ventricle hypertrophy and pulmonary hypertension resulting from combined hypoxia and pulmonary inflammation. *Int J Mol Sci* 2018;19:E2224.
13. Piquereau J, Boet A, Péchoux C, Antigny F, Lambert M, Gressette M, *et al*. The BET bromodomain inhibitor I-BET-151 induces structural and functional alterations of the heart mitochondria in healthy male mice and rats. *Int J Mol Sci* 2019;20:E1527.
14. Van der Feen DE, Kurakula K, Tremblay E, Boucherat O, Bossers GP, Szulcek R, *et al*. Multicenter preclinical validation of BET inhibition for the treatment of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2019;200:910–920.
15. Picaud S, Wells C, Felletar I, Brotherton D, Martin S, Savitsky P, *et al*. RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. *Proc Natl Acad Sci USA* 2013;110:19754–19759.
16. Galdeano C, Ciulli A. Selectivity on-target of bromodomain chemical probes by structure-guided medicinal chemistry and chemical biology. *Future Med Chem* 2016;8:1655–1680.
17. Chiang CM. Nonequivalent response to bromodomain-targeting BET inhibitors in oligodendrocyte cell fate decision. *Chem Biol* 2014;21:804–806.
18. Nicholls SJ, Ray KK, Johansson JO, Gordon A, Sweeney M, Halliday C, *et al*. Selective BET protein inhibition with apabetalone and cardiovascular events: a pooled analysis of trials in patients with coronary artery disease. *Am J Cardiovasc Drugs* 2018;18:109–115.
19. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, *et al*. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation* 2013;127:1128–1138.
20. Zhang X, Lee HC, Shirazi F, Baladandayuthapani V, Lin H, Kuiatse I, *et al*. Protein targeting chimeric molecules specific for bromodomain and extra-terminal motif family proteins are active against pre-clinical models of multiple myeloma. *Leukemia* 2018;32:2224–2239.

Reply to Piquereau and Perros and to Pullamsetti and de Jesus Perez

From the Authors:

In a recent issue of the *Journal*, we reported results from the first multicenter, preclinical study to show the therapeutic benefits of the BET (bromodomain and extraterminal motif) inhibitor RVX208 in multiple animal models of pulmonary arterial hypertension (PAH) (1). In their letter to the editor, Piquereau and Perros raised concerns about the potential cardiotoxic effects of BET inhibitors in patients with PAH based on published data demonstrating structural and functional alterations of the heart in healthy rodents treated with the pan-BET inhibitor I-BET-151 (2). A contrast must be drawn between highly potent, nonselective BET inhibitors such as I-BET-151, which are under development for oncology indications, and RVX208, which is a BD2-selective BET inhibitor with lower potency that has an excellent cardiovascular (CV) safety profile to date. A series of phase 2 studies evaluating RVX208 in a total of 789 patients with CV disease recently demonstrated a >40% reduction in major CV events (3). RVX208 is currently being evaluated in a phase 3 clinical trial involving 2,425 patients with high-risk type 2 diabetes and coronary artery disease (ClinicalTrials.gov identifier: NCT02586155). This study is being monitored by an independent data and safety monitoring board, which recommended that the study should continue as per protocol. To date, the total exposure in patients with high-risk CV disease is approaching 2,000 subjects, with no heart failure signal identified. To ensure the safety of the drug in the context of right ventricular dysfunction, we conducted experiments in a rat model of increased ventricular afterload induced by pulmonary artery banding. Treatment with RVX208 was not accompanied by deleterious effects, and, on the contrary, promoted the ventricular response to increased afterload (1). Combined, these results affirm a favorable safety profile of RVX208 for use in patients with PAH and PAH-associated right ventricular dysfunction and support the establishment of a clinical trial. Finally, as pointed out by Pullamsetti and de Jesus Perez, a comprehensive understanding of how domain- and isoform-selective BET inhibition can regulate specific transcriptional and biological responses will further refine its applications in the clinical arena. ■

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References

1. Van der Feen DE, Kurakula K, Tremblay E, Boucherat O, Bossers GP, Szulcek R, *et al*. Multicenter preclinical validation of BET inhibition for the treatment of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2019;200:910–920.
2. Piquereau J, Boet A, Péchoux C, Antigny F, Lambert M, Gressette M, *et al*. The BET bromodomain inhibitor I-BET-151 induces structural and functional alterations of the heart mitochondria in healthy male mice and rats. *Int J Mol Sci* 2019;20:1527.
3. Nicholls SJ, Ray KK, Johansson JO, Gordon A, Sweeney M, Halliday C, *et al*. Selective BET protein inhibition with apabetalone and cardiovascular events: a pooled analysis of trials in patients with coronary artery disease. *Am J Cardiovasc Drugs* 2018;18:109–115.

Check for updates

Early Use of Norepinephrine for Sepsis: Promising Results That Require Confirmation

To the Editor:

Permpikul and colleagues demonstrated in a randomized controlled study that norepinephrine initiated early in the management of sepsis with arterial hypotension increased the rate of shock control at 6 hours (1). This result has potentially clinically significant consequences because it could alter the management of resuscitation in patients with sepsis and septic shock. However, some points regarding catecholamine use in this study should be noted.

First, it could be highlighted that epinephrine dose is more important than expected according to the 2012 and 2016 Surviving Sepsis Campaign guidelines (2, 3): 20% of patients in the placebo group were treated with epinephrine and 17.4% in the norepinephrine group. In contrast, De Backer and colleagues reported a maximum of 1.5% of patients with shock (mainly from septic origin) treated with open-label epinephrine (4). Prescription of epinephrine is most often limited to arterial hypotension that is refractory to high doses of norepinephrine (2, 3). However, in the present study, the maximum doses of norepinephrine prescribed do not seem to justify epinephrine initiation, as the 75% interquartile range in the control group was 0.15 μg/kg/min. In contrast, in the HYPRESS (Hydrocortisone for Prevention of Septic Shock) study (5), which included patients with sepsis, the average dose of norepinephrine in the control group was 0.4 ± 0.8 μg/kg/min.

Second, open-label norepinephrine was started in the placebo group 2.5 hours after inclusion, i.e., after 30 ml/kg of fluid expansion. At this time point, mean arterial pressure was, as expected, lower in the placebo group than in the norepinephrine group. However, despite this difference in mean arterial pressure, in Figure E3B in the online supplement of Reference 1, the slopes (representing the amount of norepinephrine per kilogram) are parallels between 2.5 and 5.75 hours, despite a persistent lower mean arterial pressure in the placebo group. Logically, a substantial steepening of the slope was expected in order to more quickly reach a mean arterial pressure above 65 mm Hg. This could suggest a vasopressor under resuscitation in the control group.

Third, it should be also be acknowledged that the case mix in this study, which had a high proportion of urinary tract infections, cannot be compared with European or North American case mixes in which pneumonias were most often predominant (5). Similarly, in the present study, the nurse-to-patient ratio was 1:3 in the ward, whereas in some countries, this ratio is applied in ICUs.

Finally, the results of the present study are promising but need to be confirmed in multicenter trials. ■

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References

1. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER): a randomized trial. *Am J Respir Crit Care Med* 2019;199:1097–1105.

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