CrossTalk:

Rebuttal from:

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Cornwell et al. (2018) provide irrefutable arguments that the human circulation is able to survive on lower arterial oscillations than the normal arterial pulsatility. Thus, we agree that a key aim for future research will be to determine the *optimal* amount of pulsatility for each individual CF-LVAD patient. To ultimately achieve a personalized therapeutic target, the optimal balance between LVAD device settings (including its effects on native heart function) and the patient's pre-existing peripheral arterial health will need to be considered. At present, the consistently low pulsatility in CF-LVAD patients is, in our opinion, still of concern. Despite an impressive improvement in CF-LVAD outcomes with the HeartMate 3 device (Mehra *et al.*, 2017; Mehra *et al.*, 2018), approximately 8-10% of patients still experience disabling stroke (Colombo *et al.*, 2018). The precise role of arterial pulsatility in these patients is currently not known. Notwithstanding, our own observations suggest that patients with similar CF-LVAD settings can have different arterial pulsatility (Castagna *et al.*, 2017), indicating the necessity to examine not just the local cerebral haemodynamics but also the transmission of energy across the whole circulation (Webb *et al.*, 2012).

The consideration of comorbidities that may be partially responsible for stroke is indeed important. Taking on our opponents' argument, we propose that some of those comorbidities could in fact be a strong indication of a wider, systemic cardiovascular problem, that may reflect inadequate pulsatility in multiple organs, not just the brain. Indeed, the prevalence of cortical microbleeds in 97% of CF-LVAD patients, macrovascular bleeding events in 40-50%, including gastrointestinal bleeding in >25%, suggests a common haemodynamic origin (Yoshioka *et al.*, 2017; Mehra *et al.*, 2018).

Perhaps most importantly, we think it is essential to extend the elegant previous findings based upon mean blood velocities and mean arterial pressure to the measurement of pulsatility (Cornwell

et al., 2014; Cornwell *et al.*, 2015). For example, the same mean pressure and mean flow velocity can be underpinned by different pulsatility. These specific mechanical oscillations will stimulate the mechanoreceptors and possibly the baroreceptor, as well as the endothelium-derived release of nitric oxide (Nakano *et al.*, 2000). Thus, while cerebral autoregulation provoked by a stressor that does not alter pulsatility might be preserved in CF-LVAD patients, it is conceivable that the chronic exposure to a low pulsatile load might narrow the range of adequate functional responses in the event of a stressor of pulsatile nature.

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References

Castagna F, Stöhr EJ, Pinsino A, Cockcroft JR, Willey J, Reshad Garan A, Topkara VK, Colombo PC, Yuzefpolskaya M & McDonnell BJ. (2017). The Unique Blood Pressures and Pulsatility of LVAD Patients: Current Challenges and Future Opportunities. *Curr Hypertens Rep* **19,** 85.

Colombo PC, Mehra MR, Goldstein DJ, Estep JD, Salerno C, Jorde UP, Cowger JA, Cleveland JC, Uriel N, Sayer G, Skipper ER, Downey FX, Ono M, Hooker R, Anyanwu AC, Givertz MM, Mahr C, Topuria I, Somo SI, Crandall DL & Horstmanshof DA. (2018). Comprehensive Analysis of Stroke in the LongTerm Cohort of the MOMENTUM 3

Study: A Randomized Controlled Trial of the HeartMate 3 Versus the HeartMate II Cardiac Pump. *Circulation* **In press**.

Cornwell W, Tarumi T, Lawley J & Ambardekar AV. (2018). CrossTalk opposing view: Blood flow pulsatility in left ventricular assist device patients is NOT essential to maintain normal brain physiology. *J Physiol*.

Cornwell WK, 3rd, Tarumi T, Aengevaeren VL, Ayers C, Divanji P, Fu Q, Palmer D, Drazner MH, Meyer DM, Bethea BT, Hastings JL, Fujimoto N, Shibata S, Zhang R, Markham DW & Levine BD. (2014). Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. *J Heart Lung Transplant* **33,** 1295-1303.

Cornwell WK, 3rd, Tarumi T, Stickford A, Lawley J, Roberts M, Parker R, Fitzsimmons C, Kibe J, Ayers C, Markham D, Drazner MH, Fu Q & Levine BD. (2015). Restoration of Pulsatile Flow Reduces Sympathetic Nerve Activity Among Individuals With Continuous-Flow Left Ventricular Assist Devices. *Circulation* **132,** 2316-2322.

Mehra MR, Goldstein DJ, Uriel N, Cleveland JC, Jr., Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y & Investigators M. (2018). Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med* **378,** 1386-1395.

Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC, Jr., Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW, Salerno C & Investigators M. (2017). A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* **376,** 440-450.

Nakano T, Tominaga R, Nagano I, Okabe H & Yasui H. (2000). Pulsatile flow enhances endothelium-derived nitric oxide release in the peripheral vasculature. *Am J Physiol Heart Circ Physiol* **278,** H1098-1104.

Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U & Rothwell PM. (2012). Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke* **43,** 2631-2636.

Yoshioka D, Okazaki S, Toda K, Murase S, Saito S, Domae K, Miyagawa S, Yoshikawa Y, Daimon T, Sakaguchi M & Sawa Y. (2017). Prevalence of Cerebral Microbleeds in Patients With Continuous-Flow Left Ventricular Assist Devices. *J Am Heart Assoc* **6**.