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Letter to the Editor

Response to letter to the editor: 'Left ventricular flow in the presence of aortic regurgitation'

We would first and foremost like to thank Drs. Yoganathan and Okafor for their general interest and ensuing letter regarding our recent original work on left ventricular flow subject to aortic regurgitation (Di Labbio and Kadem, 2018). We certainly appreciate their commendment of the experimental methodology used in our work which represents an important step forward in the simulation and understanding of aortic regurgitation, building upon the *in vivo* work of Stugaard et al. (2015), the associated editorial of Pedrizzetti and Sengupta (2015) as well as our own primary *in vitro* work on the subject (Raymondet et al., 2016; Di Labbio and Kadem, 2016; Ben-Assa et al., 2017).

As commended by Drs. Yoganathan and Okafor, our work represents the first time-resolved study of the intraventricular flow in the case of incremental aortic regurgitation, possessing roughly 10 times the temporal resolution found in Stugaard et al. (2015) and Okafor et al. (2017). Unlike the recent *in vitro* study of Okafor et al. (2017), which was unknown to us at the time, our study also includes an atrial kick mechanism (responsible for *A* wave filling) that is decoupled from the ventricular relaxation mechanism (responsible for *E* wave filling). The mechanical independence of the atrial kick from the ventricular relaxation is critical in simulating a disease like aortic regurgitation *in vitro* as the regurgitation should occur forcefully during the *E* wave and only passively during the *A* wave. Mechanical coupling of the atrial kick and ventricular relaxation mechanisms as in Okafor et al. (2017) will result in excessive and prolonged regurgitation, an artifact which is entirely avoided in our work. Furthermore, we must also stress that our work is novel in another respect. Here, chronic aortic regurgitation is studied incrementally for the first time, namely how the intraventricular flow behaves when the left ventricle has had the opportunity to adapt to different grades of the disease. This is very much unlike the *in vivo* experiments of Stugaard et al. (2015) on anesthetized dogs and the *in vitro* simulations of Okafor et al. (2017) which investigate acute aortic regurgitation; i.e., how a healthy heart responds to sudden regurgitation.

To address the first point raised by Drs. Yoganathan and Okafor, it should first be understood that the eloquent *in silico* work of Pedrizzetti, Domenichini and Tonti (2010) addresses the issue of the change in mitral inflow orientation arising from replacement of a patient's native mitral valve (i.e., there is no aortic regurgitation). In so doing, the mitral inflow is naturally directed slightly more toward the ventricle center and, by consequence, the part of the induced vortex ring which is typically largely dissipated against the adjacent ventricular wall is permitted to grow and occupy the majority of the ventricular volume in the vicinity of its apex. Our work demonstrates vortex reversal by an altogether different and previously unexplored fluid dynamic mechanism. Here, the regurgitant jet generates a vortex of its own rotating counter to that generated by the mitral inflow. As the severity of the chronic regurgitation worsens, the regurgitant jet-driven vortex dominates the ventricular volume more and more. This is shown schematically in Fig. 1 and clearly depicted when comparing Figs. 4 and 5 as well as the associated Supplementary Videos 1–3 in our article. Additionally, in our recent work (Di Labbio et al., 2018), we track the motions of the mitral and regurgitant jet-driven vortices and demonstrate how their motion organizes material in the left ventricle. In response to the question as to how this reversal can be defined, there are several ways. The most obvious way, of course, is by visual inspection and was done by Pedrizzetti et al. (2010). However, in addition to a visual inspection of the velocity fields, we opted to quantify the reversal by computing the circulation within the left ventricle which is precisely what is depicted in Fig. 6. By computing the circulation, we should expect positive values if the overall rotation is in a counter-clockwise sense and vice versa. Albeit, in our study as well as in the study of Pedrizzetti et al. (2010), there tends to be two dominant vortices present in the ventricle. This is where such a definition becomes more powerful as the more dominant vortex ought to also drive the sign of the circulation. In our study, the regurgitant jet-driven vortex rotates in the counter-clockwise sense and as the regurgitation worsens the circulation tends toward positive values (refer to the diastolic portion of Fig. 6).

In response to the second point, the aorto-mitral angle certainly plays an important role in dictating the resulting left ventricular fluid dynamics in the case of aortic regurgitation, be it chronic or acute. Given the wide variability of this angle reported in the human population (Veronesi et al., 2009, 2013; Tsang et al., 2013; Bai et al., 2014; Varghese et al., 2014; Bapat et al., 2015; Bruggink, 2015) and the fact that it is also variable throughout a cardiac cycle (Goetz et al., 2003, 2006; Timek et al., 2003), this is a highly relevant question in the case of aortic regurgitation that deserves further study. In our work, the angle between the mitral and aortic valve axes is 14° or, in other words, the aorto-mitral angle is approximately 166°, representing the more obtuse end of the spectrum; see Di Labbio et al. (2018) as well as Fig. 2 in that article. There is no particular reason why we selected the more obtuse end since our ultimate intention has always been to investigate the full range of angles. In fact in our initial experiments we used an angle of 158° and obtained similar results (Raymondet et al., 2016; Di Labbio and Kadem, 2016; Ben-Assa et al., 2017). The behavior we observe must therefore be sustained for a moderate range of angles. In general, one may consider the two extremes. In the limit where the left ventricular outflow tract is parallel to the mitral inflow (representing an aorto-mitral angle of 180°), we have two parallel jets interacting in the left ventricle. We

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expect the results will resemble the interactions between free, parallel, in-plane jets (cf. Bisoi et al., 2017 and the references therein), particularly between those having different velocities (Fujisawa et al., 2004). In fact, the results reported in our work bare some visual resemblance to these studies already (cf. also Di Labbio et al., 2018), in addition to that of Soong et al. (1998) who investigate two parallel jets interacting within a channel. At the opposite end of the spectrum, where the left ventricular outflow tract is perpendicular to the mitral inflow (aorto-mitral angle of 90°) or where the aorto-mitral angle is acute, we have the collision of two jets. However, given that the regurgitant jet emanates first, we cannot suggest the interaction to be anything like that observed in Houser et al. (2018) since in that study, a vortex ring is simply forced to collide with an established jet and is quickly destroyed. Instead, the mitral inflow may not even have the opportunity to generate a full vortex ring of its own during the *E* wave and the flow may resemble that in Fig. 1 of Pedrizzetti and Sengupta (2015) for example.

With regard to the third point, the intraventricular flows captured in this work are time-resolved acquisitions of single cardiac cycles. The benefit of such an approach is obvious and fundamental to particle image velocimetry, we are looking at the flow as it is, including any fluctuations that may be present. In our work, the use of 10 samples was to merely show the consistency and high degree of repeatability of the experiments and, by consequence, of the reported results; we refer the authors to Di Labbio et al. (2018) for an additional demonstration of this fact. Nonetheless, Drs. Yoganathan and Okafor raise an interesting point regarding the difference between viscous dissipation computed from a phase-averaged flow field (as in phase-contrast magnetic resonance imaging) to that computed from a time-resolved flow field acquired from a single cardiac cycle. By phase-averaging, as in Okafor et al. (2017), these fluctuations are inherently filtered out and this results in an underestimation of viscous dissipation (Di Labbio and Kadem, 2019). Essentially, in the case of the data acquired in our work, we can report that phase-averaging the intraventricular flow grossly underestimates viscous energy dissipation, particularly in the presence of aortic regurgitation. With more severe regurgitation, the turbulent fluctuations (Di Labbio et al., 2018) become increasingly important in the calculation of viscous dissipation, and therefore by phase-averaging there is a depreciation in the computed viscous dissipation. In fact in Di Labbio and Kadem (2019), we have shown that the error in the total viscous energy loss per cardiac cycle when computed from phase-averaged flow fields increases monotonically with regurgitation severity and can be as large as 80%.

As per the final point, in our study, the atrial kick does not seem to substantially contribute to the viscous dissipation, as clearly shown in Fig. 7 of Di Labbio and Kadem (2018), even though it is directly observable in the flow field as we show more extensively in Di Labbio et al. (2017, 2018). This may be due to the effects of the regurgitant jet overshadowing any contribution to the viscous dissipation from the atrial kick. Whether this is truly the case *in vivo* certainly requires further investigation as the study of Stugaard et al. (2015), although quite novel and insightful, lacks the temporal and spatial resolution necessary to accurately resolve the variation of the viscous dissipation in time; in fact, the same is true for the results reported in Okafor et al. (2017) in terms of temporal resolution. Additionally, this all goes without saying that the calculation of the viscous dissipation in two dimensions lacks the gradients involving the out-of-plane direction, and so it is not yet understood whether this commonly used plane is truly representative of the viscous dissipation characteristics of the full three-dimensional flow state in the left ventricle.

Conflict of interest statement

No conflict of interest to declare.

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