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Editorial

The first paper in the September 2019 issue of CVET, authored by Dr. Changfu Wu from the Center for Devices & Radiological Health, Food and Drug Administration (FDA), raises a number of important questions. The round robin study conducted under the auspices of the International Standards Organization (ISO) Working Group on Cardiac Valve Substitutes, was spearheaded by Dr. Wu. Dr. Wu is a lead reviewer for heart valve substitutes at the FDA. For transparency, I am (APY) the chair of the ISO working group. Data sets were generated by thirteen International Laboratories (see their named listing in the publication), each having at least 10 years of experience in such experimental protocols; and considered to be, ''EXPERTS''. In other words, these laboratories do such measurements on a weekly basis. The results of each laboratory were kept blinded from the other twelve participants, including Dr. Steve Rhetta who conducted the measurements at the FDA, as well as Dr. Dasi and me. Only Dr. Wu at the FDA knows the ''owners'' of each of the 13 plus data sets.

The study concludes that there are significant variations (coefficient of variation ranging from 7.7% to 45.5%) in the results of nominal hydrodynamic performance metrics required for the assessment and regulatory approval of surgical heart valve substitutes. This finding is ''astounding/shocking'' and very disconcerting. ***Because of significant ''scientific discrepancies'', mainly due to experimental protocols, certain laboratories in this round-robin study were requested to re-do their measurements.*** According to the great Philosopher, Dr. Boz: *How do laboratories who conduct such experimental protocols on a daily basis, create such* ***''confusion''*** *about the functional performance of* ***Life Saving Heart Valve Substitute Devices****?* With 40 plus years of experience conducting such measurements, I will together with Dr. Dasi lay out our scientific opinions and recommendations.

For the studies described in this paper, the primary piece of equipment is a ''Pulse Duplicator''. A pulse duplicator is a device used to simulate the pressure and flow characteristics of the left or right heart including the immediate upstream and downstream vessels. There are a number of commercial pulse duplicators as well as ''home''/custom designed ones. All of them involve a pump, compliance, inductance, and resistance circuits each tuned to ensure set pressure and flow conditions. Due to the complexity of the physiology of the human heart and the nature and sensitivity of pressure-flow dynamics to the ventricular and vascular coupling, a pulse duplicator cannot and should not be treated as a ''turnkey'' piece of equipment. In my 40 plus years of working with pulse duplicators, I know them to be ''idiosyncratic machines'' that need careful attention to tuning and operation. For example, different pumps (piston or bladder etc.) will have different compliance and resistance settings to yield the ''same'' operating conditions of cardiac output and mean afterload pressure. Without careful attention to detail, the resulting waveform shapes across various pulse duplicators for the same valve will significantly vary due to differing flow and pressure wave dynamics. In some cases, the same pulse duplicator may result in different waveforms if the valve is not seated properly each time or a different component is used (e.g. change in valve chamber or tubing connecting the flow loop components). Looking at the coefficient of variation, the least coefficient of variation occurred in quantifying the effective orifice area (EOA) at 7.7 to 21.6% while the most occurred in mean pressure gradient at 14.7 to 45.5%. The variation in regurgitant fraction was between 10.1 and 32.8%. Such large variation in pressure gradient can only be explained by large variations in the peak pressure gradient and the shapes of the pressure gradient curves, which in turn implies that very large and significant variations in the flow waveforms (peak flow and true systolic durations) occurred across these experiments. Figure B2 and the comparison of the large variations in flow curves between the valves is proof.

Beyond these variations in input conditions for the valve, which result in different pressure and therefore pressure gradient waveforms, it is generally assumed that all of these variations are ''taken out'' by the EOA equation, which will yield a flow independent result. On the contrary, it is known that the EOA equation is flow dependent because the pressure gradient and pressure recovery phenomena are sensitive to Reynolds number. The location of pressure taps relative to how the pressure is recovering in each of these pulse duplicators may very well be different leading to sig-

nificant differences in calculated EOA. The sensitivity of this equation to pulsatile unsteady flow conditions is another major factor that needs further investigation.

In addition, current pulse duplicators have associated instrumentation such as: physiologic pressure transducers and amplifiers; physiologic flow probes and flowmeters; high speed cameras; flow field measurement systems such as particle image velocimetry (PIV) and laser Doppler velocimetry (LDV). These associated equipment items require hardware and software data collection systems.

Therefore, the ''operator'' of a pulse duplicator and associated pieces of equipment needs to understand cardiac physiology and associated fluid mechanic concepts (such as pressure wave propagation and reflection in blood vessels, pressure gradients and pressure recovery across orifices and valves, and ventricular fluid mechanics). Understanding the software is also critical, and cannot be treated as a black box. For instance the final metrics of hydrodynamic performance are strongly dependent on what the software defines as the time domains—often defined by cross-over points of flow and pressure curves. They also need to be knowledgeable in sophisticated data and statistical analysis methodologies.

These skill sets in our opinion require a minimum of a MS degree in Biomedical, Mechanical, Chemical or Aerospace Engineering. The overall manager for such a test laboratory should have a MS with a number years (at least 3 years) of experience, or a Ph.D. in similar fields.

Furthermore it should be noted, that the impact of variations in pulse duplicator waveforms on global hydrodynamic parameters, such as EOA and regurgitant fraction, may be less than the impact on more localized and more critical characteristics such as velocity, shear stress, vorticity, turbulence kinetic energy etc. These localized flow characteristics are important to understanding valve related blood damage that leads to hemolysis and thromboembolic complications including leaflet thrombosis in bioprostheses. Further studies are clearly necessary to capture the sensitivity of local flow characteristics. Given these variations, end users should incorporate comparisons with benchmark or control valves to ensure reproducibility of the setup when characterizing new devices.

The results of this round robin study, conducted by the ISO Cardiac Valves standards working group, clearly point to the fact that the current mentality in the heart valve industry is to ***''obtain results''*** that satisfy the minimum requirements as stated in the standards. Therefore, it is important that regulatory bodies around the world should rigorously scrutinize in detail the hydrodynamic data provided by manufacturers. In their review of these data, ***the regulatory bodies should look beyond results that ''pass the minimum requirements''!***

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