Cardiovascular Engineering and Technology, Vol. 10, No. 3, September 2019 *(© 2019)* pp. 423–436
https://doi.org/10.1007/s13239-019-00416-3

Evaluating the Performance of Cardiac Pulse Duplicators Through the Concept of Fidelity

REYNALDO A. RODRIGUEZ, KIRAN H. DELLIMORE, and JACOBUS H. MÜLLER

Biomedical Engineering Research Group, Mechanical & Mechatronic Engineering, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa

(Received 26 June 2018; accepted 22 April 2019; published online 30 April 2019)

Associate Editor Ajit P. Yoganathan oversaw the review of this article.

Abstract

Introduction—The advanced design techniques used in modern prosthetic heart valve (PHV) development require accurate replication of the entire cardiac cycle. While cardiac pulse duplicator (CPD) design has a direct impact on the PHV test data generated, no clear guidelines exist to evaluate the CPD's performance. In response to this, we present a method to quantitatively assess CPD performance.

Materials and Methods—A method to establish the fidelity of CPDs was formulated based on the pressure/time relationship and the error related to this relationship's target. This method was applied to assess the performance of a custom-made CPD. The performance evaluation included the assessment of the motion control system and overall repeatability of pressure measurements using a St Jude Epic 21 mm aortic valve.

Results—The CPD's motion control system had an average root mean square error (RMSE) beat-to-beat tracking accuracy of 0.046 ± 0.008 mm. Assessment of the pressure measurements yielded a repeatability of $< 2.4 \pm 0.9$ mmHg RMSE beat-to-beat differential pressure. The combination of pressure and its location within a heartbeat (fidelity) was within 5.0% of the individual targets for at least 95% of heartbeats.

Conclusion—Fidelity can be used to objectively quantify the performance of various aspects of CPDs and to identify the cause of unexpected PHV or CPD behaviour. It also enables comparisons to be made among various CPDs in terms of overall performance. This approach may enable standardization of the assessment of CPD performance in the future.

Keywords—Heart valve testing, Cardiac pulse duplicator, Fidelity, *In vitro* hemodynamics, Prosthetic heart valves, Performance assessment.

Address correspondence to Jacobus H. Müller, Biomedical Engineering Research Group, Mechanical & Mechatronic Engineering, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa. Electronic mail: cobusmul@gmail.com

INTRODUCTION

The first documented cardiac pulse duplicators (CPDs) appeared in the mid-1950s and were intended to gain insights into physiological cardiac and valvular function as well as studying the effects of heart valve pathologies.[8,10,14,19] Shortly thereafter, with the advancement in surgical valve replacements in the early 1960s, a growing interest in CPDs was sparked to test valve replacements.[4,9] Some of the early CPDs had the capability of adjusting the systolic fraction and stroke volume (SV) to some extent but still did not provide much flexibility in terms of ventricular control. Due to strong interest in the field and the rapid evolution of prosthetic heart valves (PHVs) during the 1960s and 1970s, the ISO5840 standard was released in 1984 in order to guide and regulate the PHV market by describing the requirements for the commercialisation of PHVs. Through successive releases, the ISO5840 standard has included guidelines on the testing protocol for the implantable devices and on specifications for the equipment used to perform the testing. Understandably, the information given with respect to testing equipment intended to assess the performance of the PHV under pulsatile flow is limited to the hardware specifications that it must meet. To date no details are included to evaluate the equipment's performance.[12,13]

While specifications and performance may seem similar at first sight it is important to recognise that devices meeting specifications may still not perform satisfactorily, given the complexity and flexibility of modern CPDs which include the capability to program modifications to their pumps' action. The nature of PHV testing makes it difficult to distinguish PHV performance from that of the testing equipment. It should also be emphasized that the data produced by

CPDs are *perceived* PHV performance. D'Avenio *et al.*[7] already noted this when they attempted to compare the Sheffield CPD to the RWTH Aachen CPD using the same PHV. They concluded that the design of the hydraulic loop has a measurable effect on PHV performance and that its design must be considered when interpreting PHV test results. As with any evolving field, the ISO5840 standard lags behind of the technology in terms of guidance and its development has been retrospective: guidelines are updated and regulations are specified once the technology has been in widespread use for a few years. Consequently and partly due to the fact that ISO5840 does not define stringent testing protocols, the area of CPD performance has received little formal attention by the research community. Thus, currently there are no answers to important questions such as:

- How is a CPD's performance quantified?
- How can the Performance of two different CPD designs be objectively compared?
- How does a CPD's design affect perceived PHV performance?

However, both numerical and experimental PHV studies, utilizing techniques such as computational fluid dynamics (CFD), fluid–structure interaction (FSI) and particle image velocimetry (PIV), are increasingly focusing on investigating physical phenomena taking place within the PHV or its vicinity throughout the whole heartbeat.[11,15,18] As a result, it is important to replicate the cardiac cycle more accurately than called for by the current ISO5840-3:2015 standard in order to initialise and/or validate models. Furthermore, it is accepted that *In vitro* PHV behaviour is not directly comparable to the *in vivo* situation.[6,16] This reinforces the idea that there is merit in attempting to replicate the physiological conditions as closely as possible in an *In vitro* environment in order to improve the PHV design process. With this in mind and considering that the above questions are not yet answered, it can be demonstrated experimentally that the measured PHV performance can be affected by various aspects of a CPD. These include the hydraulic loop geometry and wetted materials, the control system, the implementation of lumped parameter controls, measurement locations as well as the data acquisition and analysis software.

While methods and data for the validation of CPDs have been reported,[2,22,34] there is a dearth of literature on approaches to quantify CPD performance. Furthermore, no open literature could be found that directly compares two CPDs to each other by using the same PHV samples and test parameters (D'Avenio *et al.*[7] intended to do this but ultimately their work fulfilled this purpose only partially because they did not use identical test parameters in both CPDs). The lack of a standardised assessment for the performance of CPDs means that the evaluation of a few specific parameters such as systolic pressure (P_{syst}), diastolic pressure (P_{dias}) and mean arterial pressure (MAP) could allow a CPD to appear competent based on a simple validation test. Foregoing a well-designed CPD performance assessment without the use of more complex CPD performance indicators could result in skewed or biased PHV test data being accepted as a reliable representation of PHV performance. These CPD performance indicators include those based on time, those spanning specific portions of the cardiac cycle, those derived from measured data and/or those resulting from combinations of basic parameters. Thus, credible and unbiased PHV performance results can only be obtained once overall CPD performance has been thoroughly tested and proven.

In order to evaluate and present performance metrics which should prove useful in assessing and comparing CPDs, irrespective of design, this study proposes the concept of fidelity to objectively quantify CPD performance. The concept of fidelity is then demonstrated by testing a commercially available PHV on a custom-made CPD and analysing the generated data according to the proposed protocol.

MATERIALS AND METHODS

Apparatus

The concept of fidelity was tested on a custom made CPD, designed and built at Stellenbosch University. Since PHV performance is affected by all aspects of the CPD's design, a brief description of both hardware and software is given.

Mechanical Description

A custom made 90 mm diameter piston pump with a maximum stroke of 30 mm pressurised the working fluid, a solution of 20% glycerol by volume (refer to Fig. 1). The dynamics of the working fluid could be altered by introducing a variable amount of air into the ventricular compliance chamber, which was directly connected to the pump's cylinder, and by restricting flow with the ball valve which separately connected the pump to the ventricle.

Pressure from the working fluid caused the flexible silicone ventricle to collapse which in turn pressurised the blood analogue fluid in the ventricle and initiated one directional flow due to the arrangement of the mitral and aortic valves. The blood analogue consisted

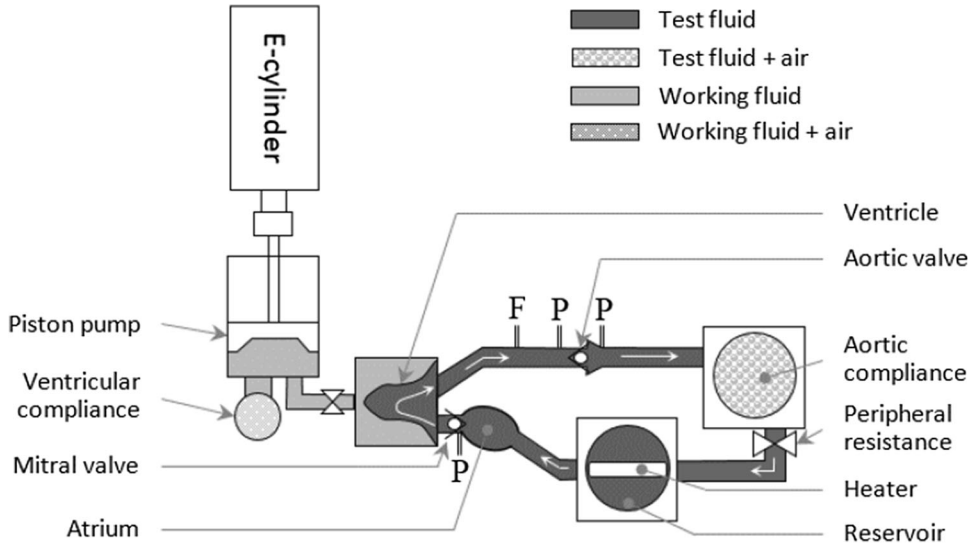

FIGURE 1. Physical layout of the CPD (top view). *F* flowmeter, *P* pressure sensor.

of a previously researched solution of 48% glycerol and 52% distilled water (by mass) to which sodium chloride was added to form a 0.9% saline solution. At 37 °C this resulted in a dynamic viscosity of 3.2 cP and a density of 1111.8 kg/m[3][26] relating to whole blood with a haematocrit level in the range of 40–45%.[32] The flowmeter connected the ventricle to the tubular test section where the aortic valve was positioned. The test section discharged into the acrylic aortic root compliance chamber, where a variable amount of air could be introduced with a hand pump. The peripheral resistance needle valve was attached to the aortic root compliance chamber and was manually adjusted to obtain appropriate systolic, diastolic and mean arterial pressure values. Flow from the peripheral resistance valve was returned to the reservoir which contained a submersible 300 W heater (RS Components, Corby, United Kingdom) and a PT100 resistance temperature detector (USTA1P-PS1A D = 3 mm/L = 30 mm, Unitemp, South Africa). The level of fluid in the reservoir was used to set mean atrial pressure or preload. The atrium was connected to the reservoir and was made of a latex balloon so it could collapse quickly, supplying the ventricle with fluid for the next stroke. The mitral valve was mounted in a housing which allowed the atrium to interface with the ventricular chamber. The test section (from the flowmeter to the aortic root compliance chamber) was made of clear acrylic to allow for observation and PIV measurements. Pressure taps were positioned in the mitral valve's housing (15 mm behind the mitral valve) as well as 50 mm upstream and downstream of the aortic valve. The 50 mm offset avoids measurement in potentially turbulent flow regions near the test valve.

Control Approach

A SEW MoviDrive (MDX61B0015-5A3-4-00, SEW Eurodrive GmbH & Co KG, Bruchsal, Germany) was used to control an electric cylinder with a 150 mm stroke (SEW CMS50 M/KY/RH1 M/SM1) which drove the piston pump. Although the electric cylinder has a stroke of 150 mm, only 20 mm were used to drive the pump. The motion of the ventricle pump was achieved through a cascaded feedback control loop approach consisting of two control loops: a speed control loop executed by the SEW MoviDrive following a proportional-integral-derivative (PID) position control loop executed by a National Instruments (NI) myRIO (myRIO 1950, National Instruments, Texas, USA). The overall electrical design is described diagrammatically in Fig. 2.

A control waveform was graphically or numerically designed on the personal computer (PC) to represent the instantaneous volume of the ventricle. The PC planned the path for the electric cylinder based on the selected stroke volume and heart rate. The path was a waveform composed of position setpoints for the whole heartbeat which was sent to the NI myRIO. The

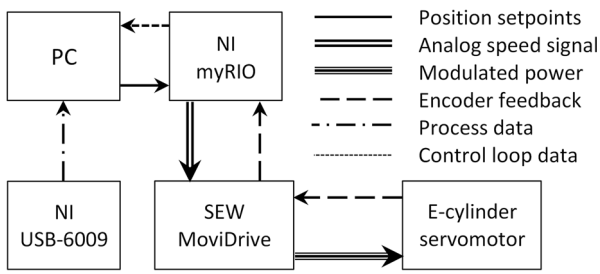

FIGURE 2. Signal flow between the physical components of the system.

NI myRIO iterated through these position setpoints feeding them to the position control loop at a variable rate based on the heart rate and the number of positions per heartbeat selected by the user. The position control loop calculated the position of the pump's piston using the encoder signal from the electric cylinder's servomotor (routed through the SEW MoviDrive) and computed an output which was sent to the MoviDrive (in the form of a − 10 to 10 V analog signal) representing the speed needed to achieve the next requested position in time. Due to the hardware characteristics of the SEW MoviDrive, the best performance was achieved when a setpoint was sent to the MoviDrive every 1 ms. The motion design and overall control program, which ran on the PC, were written using NI LabVIEW while the position controller and hardware handling were programmed in NI LabVIEW RT (Real Time) and runs on the NI myRIO.

Due to the fact that the position controller commanded the speed controller, the two controllers were tuned separately. The speed controller was tuned first by sending a sine wave of varying frequencies and amplitudes to the SEW MoviDrive. The operating points that were checked included frequencies equivalent to 60, 70, 90, 120, 180 and 200 bpm with displacements ranging from 37.5 to 300 mm. The speed/time relationship was assessed using the encoder feedback from the electric cylinder's servomotor and tuning was carried out in real time by minimising the mean square error between the setpoint sine wave and the encoder's feedback. Once the speed controller was optimally tuned, the position controller was tuned in a similar fashion, by feeding a sine wave (in this case representing position) to the position controller. Based on physiological values,[31] three operating conditions were tuned using cardiac outputs (CO) equivalent to rest (CO = 5 L/min) for a normal individual, moderate exercise (CO = 16.8 L/min) and extreme physical strain (CO = 24 L/min) which represents the maximum cardiac output that the CPD can generate (Table 1).

To better handle the large variations in setpoints resulting from the wide operating conditions, a PID constant scheduling system was implemented in the position controller. PID scheduling allowed the controller to adjust its behaviour based on the requested cardiac output, becoming more reactive as cardiac output increased. This solution resulted in a smooth and accurate response over cardiac outputs ranging from 3.5 to 24 L/min.

The test fluid's temperature was controlled independently from the rest of the CPD. The submersible heater and the temperature sensor were connected to a Delta DTA PID temperature controller (Delta Electronics, Taiwan) which maintained the temperature at 36 ± 0.5 °C. No agitation was necessary because the heater and sensor were placed in the stream created by the fluid returning to and exiting the reservoir.

Data Acquisition

The NI myRIO did not have the required resolution for the acquisition of the analog pressure and flow signals (as stipulated by the ISO5840-3:2015)[13] which led to the use of a separate data acquisition (DAQ) card (USB-6009, National Instruments, Texas, USA). The variables measured by the DAQ card were ventricular, aortic and atrial pressure as well as aortic flow rate. All transducers were set up for current output and each was measured by the DAQ *via* a 500 Ω precision resistor (PAPTF56500R00BYEK, Vishay Intertechnology, Inc., Pennsylvania, USA). Data from all transducers were acquired at 1000 Hz. This ensured that enough signal detail was captured to enable detection of water hammer effects and perform calculations related to the pulse wave velocity. A Wika A-10 (WIKA Alexander Wiegand SE & Co. KG, Klingenberg, Germany) was connected to each pressure tap. The pressure transducers had a range of 0–1 bar (0–750.062 mmHg) and exhibited a maximum error of ± 1.659 mmHg during calibration. All corrections were applied during data acquisition. The flowmeter consisted of a Siemens Sitrans Mag 5100 W DN15 flow tube with a Siemens Mag 5000 signal converter (Siemens AG, Berlin, Germany). The custom made acquisition software provided beat by beat graphical feedback as well as basic analytical information such as

TABLE 1. Test conditions used for tuning the CPD, based on data from Vinet *et al.*[31]

Physical condition	Rest	Exercise (moderate)	Exercise (maximal)
HR (bpm)	70 (71 ± 15)	140 (146 ± 12)	189 (189 ± 12)
SV (mL)	71 (81 ± 23)	120 (119 ± 22)	128 (128 ± 23)
CO (L/min)	5.0 (5.7 ± 2.2)	16.8 (17.6 ± 3.3)	24.2 (24.3 ± 4.6)

Literature values are included in brackets.
HR heart rate, *SV* stroke volume, *CO* cardiac output.

minimum, maximum and mean pressures as well as flow rate.

Performance Evaluation

In the context of this evaluation, fidelity (discussed in detail later) was defined as a combined measure of hydrodynamic accuracy and repeatability. Thus, these two properties were initially tested individually to provide basic validation of the experimental setup. This ensured that the fundamental behaviour of the CPD was acceptable and that the subsequent fidelity tests were based on reliable data. However, the accuracy of the control system in relation to piston motion was established first because piston velocity was the only way to generate flow. The resistance and compliance controls then converted flow to pressure predictably so it was only necessary to assess accuracy from a control point of view. Therefore, the following section details the methodology used to assess the performance of the control system without hydrodynamic considerations. Subsequently, the repeatability and fidelity tests were carried out and evaluated from a hydrodynamic point of view using a St Jude Medical Epic 21 mm aortic valve (SJM E100-21A; St Jude Medical, Inc., Minnesota, USA) in a blood analogue. The rest conditions presented in Table 1 (HR = 70 bpm, SV = 71 mL) were used with P_{syst}/P_{dias} = 120/80 mmHg.

Control System Behaviour

The response of the control system was assessed separately to eliminate uncertainties related to the electromechanical performance of the pump when evaluating the CPD's overall hydrodynamic performance. Tracking ability was quantified by computing the root mean square error (RMSE) between the control waveform and the measured position of the electric cylinder for five consecutive cycles. This was done beat-to-beat for five consecutive heartbeats and the standard deviation for the individual RMSEs was then calculated. Using this approach instead of calculating a single RMSE for all five beats provides a more reliable indication of random beat accuracy. Since in this application the ability to closely reproduce the control signal is more important than when the control signal is reproduced (lag time), the accuracy was assessed in terms of the effective tracking error. Due to the type of controller used and the nature of the system the process will always lag the control signal by a few milliseconds. Therefore, the effective tracking error was found by aligning the process value and the control signal during post processing through minimisation of the RMSE, which yielded the lag time. When multiplied by the area of the pump's piston, the phased RMSE provides an indication of the mean instantaneous ventricular volume error when compared to a randomly selected point within the control waveform. Based on Table 1, rest, moderate and maximal exercise conditions (with an equivalent cardiac output of 5.0, 16.8 and 24.2 L/min, respectively), were verified using this process. The same (morphological) control waveform, shown in Fig. 4 as "Setpoint" was used for all three tests. The parameters of each test were set as per Table 1.

Repeatability

Ultimately, the only variables of interest generated during CPD tests are hydrodynamic. Therefore, repeatability of the CPD as a test instrument was assessed hydrodynamically rather than from the perspective of a controller's response. Two repeatability notions were employed: intra-test and inter-test repeatability. Intra-test repeatability is based on pressure measurements of five consecutive heartbeats. It is established by calculating the standard deviation of the RMSEs between the differential pressures of a baseline heartbeat and the following five individual heartbeats. To evaluate inter-test repeatability it is necessary to perform another test, a large number of heartbeats after the first test (without adjusting any parameters) and to determine a second intra-test repeatability value using the original baseline heartbeat as a reference. The two intra-test measurements result in a recording of ten heartbeats, fulfilling the requirements of the current pulsatile test protocols[13] but more heartbeats could be used if desired. Inter-test repeatability is determined by the average of the two standard deviations of the two tests. Therefore, an inter-test repeatability value of zero indicates perfect repeatability. Repeatability within a group of consecutive heartbeats is based on the individual standard deviation values. Figure 3 explains the concept diagrammatically. Two measurements were taken, approximately 2500 heartbeats (35 min) apart, without modifying any test parameters. The baseline heartbeat used to obtain these results was recorded immediately before the first test (T1).

Fidelity

As repeatability cannot account for accuracy, the idea of fidelity was introduced in an effort to provide a single metric that can be used to judge the CPD's performance in terms of both of these properties. This was challenging due to the fact that in this case accuracy contains an element of time (the correct amplitude must be generated at the correct time step within a cycle) and this must then be evaluated over multiple cycles. Fidelity was therefore not defined as a measure

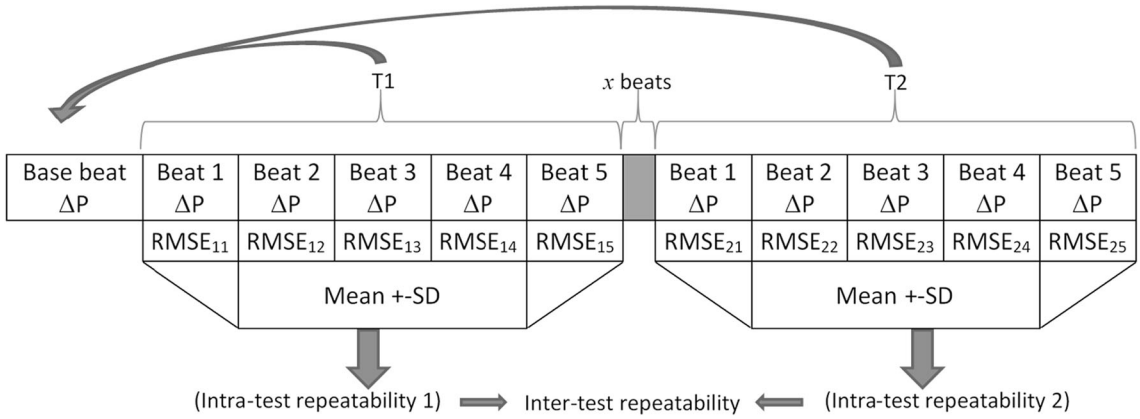

FIGURE 3. The concept used to evaluate repeatability of the CPD. *ΔP* differential pressure across PHV, *RMSE* root mean square error, *SD* standard deviation.

of a CPD's ability to produce physiological conditions but rather as a measure of a CPD's ability to reproduce a given complex setpoint over many cycles. As such, fidelity is not exclusively applicable to CPDs but can be applied to assess the performance of most controllers executing time-sensitive cyclic operations. For the case of CPDs, however, it was irrelevant to produce conditions that lie too far from the boundaries of physiology so the testing was limited to physiologically relevant conditions.

Since pressure was not controlled directly, there was no setpoint to which measurements could be compared. Consequently, certain features of the arterial pressure trace were chosen as reference: systolic (maximum), diastolic (minimum) and mean values. The systolic and diastolic pressures were used in conjunction with the theoretical time at which they should occur within a heartbeat. Together, these five measurements provided a good indication of arterial pressure conditions and morphology. The theoretical time, in terms of arterial pressure, where a maximum or minimum pressure should occur was estimated from the pump's piston speed (derived from the control waveform) and phased by using the beginning of systole as a reference.

The following equations were formulated to quantify CPD fidelity:

$$F_{P_{\text{syst}}} = \frac{\frac{\left|P_{\text{syst\_target}} - P_{\max}\right|}{P_{\text{syst\_target}}} + \frac{\left|Index_{P_{\text{syst\_target}}} - Index_{P_{\max}}\right|}{Index_{P_{\text{syst\_target}}}}}{2} \quad (1)$$

$$F_{P_{\text{diast}}} = \frac{\frac{\left|P_{\text{diast\_target}} - P_{\min}\right|}{P_{\text{diast\_target}}} + \frac{\left|Index_{P_{\text{diast\_target}}} - Index_{P_{\min}}\right|}{Index_{P_{\text{diast\_target}}}}}{2} \quad (2)$$

$$F_{P_{\text{MAP}}} = \frac{\left|P_{\text{MAP\_target}} - P_{\text{MAP}}\right|}{P_{\text{MAP\_target}}} \quad (3)$$

where: $F_{P_{\text{syst}}}$, $F_{P_{\text{diast}}}$, F_{MAP}—fidelity value for systolic, diastolic and mean pressures, respectively; $P_{\text{syst\_target}}$, $P_{\text{diast\_target}}$, MAP_{target}—target systolic, diastolic and mean pressures, respectively; $P_{\max}$, $P_{\min}$, MAP—measured systolic, diastolic and mean pressures, respectively; $Index_{P_{\text{syst\_target}}}$, $Index_{P_{\text{diast\_target}}}$—theoretical location within heartbeat when systolic and diastolic pressures, respectively, should occur (i.e., sample number).

To prevent negative values (which could bias the results towards zero when calculating the difference between the target and the measurement) the absolute value of the difference was used before normalising the result. This ensured that the error was centred on the target and negative values do not skew the result. Summing both terms ensured that if the target for one of the measurements was achieved but the other was not, an error would still be registered. Equations (1) and (2) contain two normalised terms so they were divided by two to give a range of one, where a value of one implies that the magnitude of each of the errors is as large as the target itself while a value of zero indicates perfect fidelity.

Equations (1)–(3) yield a fidelity value for each heartbeat. To express fidelity over time, the single heartbeat fidelity values for each type of pressure were accumulated in an array, resulting in three vectors. Using the ISO5840-3:2015 requirements for durability testing as a guide (requiring that a given differential pressure was achieved for at least 95% of the heartbeats),[13] the overall fidelity value for each type of pressure was then expressed as the 95th percentile. Finally, the average of the three percentiles yielded a single value expressing the overall fidelity of the CPD.

TABLE 2. Results for the tracking tests.

Operating point	HR = 70 bpm, SV = 71.4 mL			HR = 140 bpm, SV = 120 mL			HR = 189 bpm, SV = 128 mL			Range average		
Beat	RMSE, phased (mm)	Max abs (mm)	Lag (ms)	RMSE, phased (mm)	Max abs (mm)	Lag (ms)	RMSE, phased (mm)	Max abs (mm)	Lag (ms)	RMSE, phased (mm)	Max abs (mm)	Lag (ms)
Beat 1	0.016	*0.053*	13	0.064	*0.127*	10	0.044	*0.108*	9	–	–	11
Beat 2	0.016	*0.062*		0.063	*0.130*		0.048	*0.112*				
Beat 3	0.016	*0.049*		0.059	*0.158*		0.049	*0.120*				
Beat 4	0.018	*0.051*		0.069	*0.149*		0.049	*0.102*				
Beat 5	0.029	*0.057*		0.095	*0.144*		0.052	*0.111*				
Mean	0.019	*0.054*		0.070	*0.142*		0.048	*0.111*		**0.046**	***0.102***	
±SD	0.006	–		0.014	–		0.003	–		**0.008**	–	

RMSE root mean square error, *HR* heart rate, *SV* stroke volume, *SD* standard deviation; *Max abs* maximum absolute individual error (italicized values).

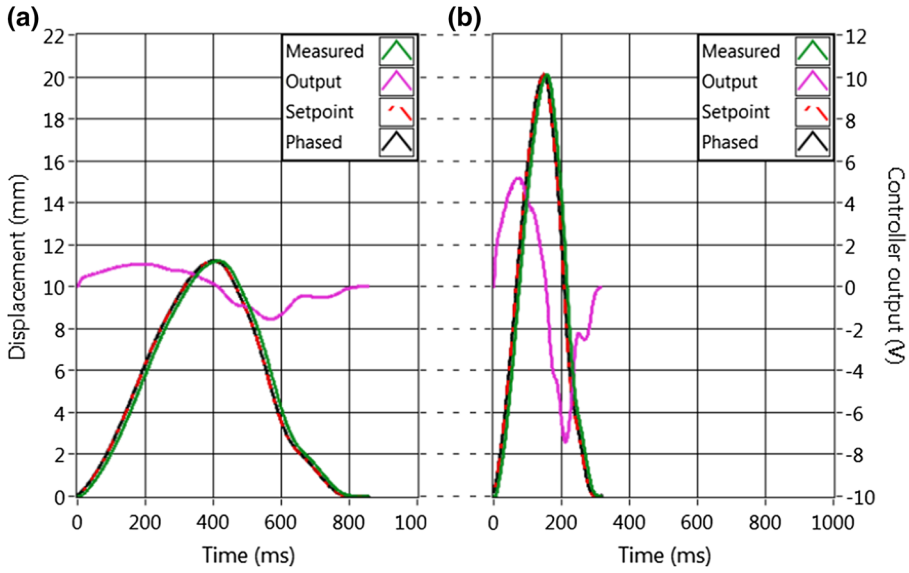

FIGURE 4. Position controller response for the cases of (a) rest (HR = 70 bpm, SV = 71.43 mL) and (b) maximal exercise (HR = 189 bpm, SV = 128 mL).

This method can be applied to any measurement (arterial pressure, ventricular pressure or flow rate) provided that target locations can be established for the measurement in question. To obtain a good visual representation of the data 100 consecutive heartbeats were recorded and analysed for the fidelity test.

RESULTS

Tracking Accuracy

Table 2 presents the results of the tracking tests with "RMSE, phased" indicating the effective tracking error. "Lag" is the amount of time by which the position feedback was shifted to obtain the phased RMSE and varies with cardiac output due to changes in the PID constants resulting from the action of the PID scheduling algorithm. For the most commonly used combination of heart rate and cardiac output (HR = 70 bpm and SV = 71.4 mL) the controller achieved a mean RMSE of 0.019 mm, (equivalent to 0.1 mL) with a lag of 13 ms. When running at the maximum designed cardiac output (HR = 189 bpm and SV = 128 mL), the mean RMSE was 0.048 mm (equivalent to 0.3 mL) and the lag was 9 ms. For each of these situations, the maximum individual error that was registered was 0.062 mm (0.364 mL) and 0.120 mm (0.763 mL), respectively. Figure 4 shows the controller's response to the vastly different operating conditions represented by the rest and maximal exercise cases (although the control waveform is morphologically identical for both cases).

TABLE 3. Hydrodynamic repeatability results.

	T1					T2				
	Beat 1	Beat 2	Beat 3	Beat 4	Beat 5	Beat 1	Beat 2	Beat 3	Beat 4	Beat 5
ΔP RMSE	3.4	1.6	1.3	2.2	1.1	2.8	2.0	3.1	1.8	2.5
Intra-test mean	1.9					2.4				
Intra-test ± SD	0.9					0.5				
Inter-test mean	2.2									
Inter-test ± SD	0.7									

All values are in mmHg.
ΔP RMSE root mean square error of the differential pressure across the PHV with respect to the baseline heartbeat, *SD* standard deviation.

Repeatability

Inter-test repeatability was 2.2 ± 0.7 mmHg. The two intra-test repeatability values were 1.9 ± 0.9 mmHg for the first test and 2.4 ± 0.5 mmHg for the second test. Full repeatability results are presented in Table 3, which follows the layout of Fig. 3 in order to help in visualising the flow of data leading to the overall (inter-test) repeatability value.

Fidelity

To analyse fidelity it helps to visualise the history of the entire process rather than concentrate on a single point of interest. Figure 5 depicts arterial and ventricular pressure for 100 heartbeats. The right panels make it clear how the location of a specific area of pressure (systolic or diastolic) changes in magnitude and phase from one heartbeat to the next. The combination graph in Fig. 6 shows only the variables of interest and provides more quantitative information. As per Table 4 (which supplements Fig. 6), given a target arterial pressure of 120/80 mmHg at 356/58 ms within the period of the control waveform, the mean values for the 100 recorded heartbeats were 120.3/82.9 mmHg and 367/57 ms respectively. Figure 7 presents pressures in a conventional fashion and the traces correspond to the first heartbeat of Fig. 5. This helps to visually contextualise the pressures with the scale and with each other.

Table 5 shows the individual fidelity values leading to the final statement of fidelity for the CPD's arterial pressure. These results indicate that the combination of pressure and its location (where applicable) is within 5.0% of the individual targets for at least 95% of the heartbeats. While the overall fidelity value is a good indicator of how closely a CPD replicates the intended test conditions, it is an average. Therefore, it is still important to state the individual fidelity values to provide an accurate description of the CPD's behaviour. In this case, the value and timing of the systolic pressure were within 3.0% of the targets for 95% of the heartbeats whereas for the diastolic phase, the timing and value of the pressure were within 10.3% of their targets for 95% of heartbeats. For the MAP, 90% of heartbeats achieved a value within 1.6% of the target.

DISCUSSION

Control Response

The tracking accuracy tests revealed that the control and actuation system for the ventricle pump was highly responsive and accurate, as indicated by the fact that the mean tracking RMSE remains below a theoretical 0.5 mL (0.070 mm at 140 bpm in Table 2). The control system's repeatability was also satisfactory, given the worst case scenario standard deviation of 0.014 mm (140 bpm) for the tracking RMSE, presented in Table 2. These results imply that, if given an appropriate control waveform, the contribution from the control and actuation system to any erratic behaviour observed in the pressure and flow measurements is negligible. This points to the characteristics of the hydraulic loop as the likely source of problems.

Mechanical Factors Affecting Hydrodynamics

It is also important to discuss mechanical design factors and their potential effect on CPD measurements, especially when dealing with aortic PHVs. The diameter, length and path, as well as the choice of materials for the hydraulic loop play an important role in shaping the pressure waves. Sugawara *et al.*[28] used a dog model to explain how fluid inertia affects ventricular pressure, especially at the end of the systolic period. Their hypothesis was that, due to its inertia, blood can continue moving forward for longer than the ventricle is in systole. Therefore, the ventricle must stop blood flow by going into diastole (before the aortic valve closes), rather than diastole starting after blood flow has decayed significantly. This implies that

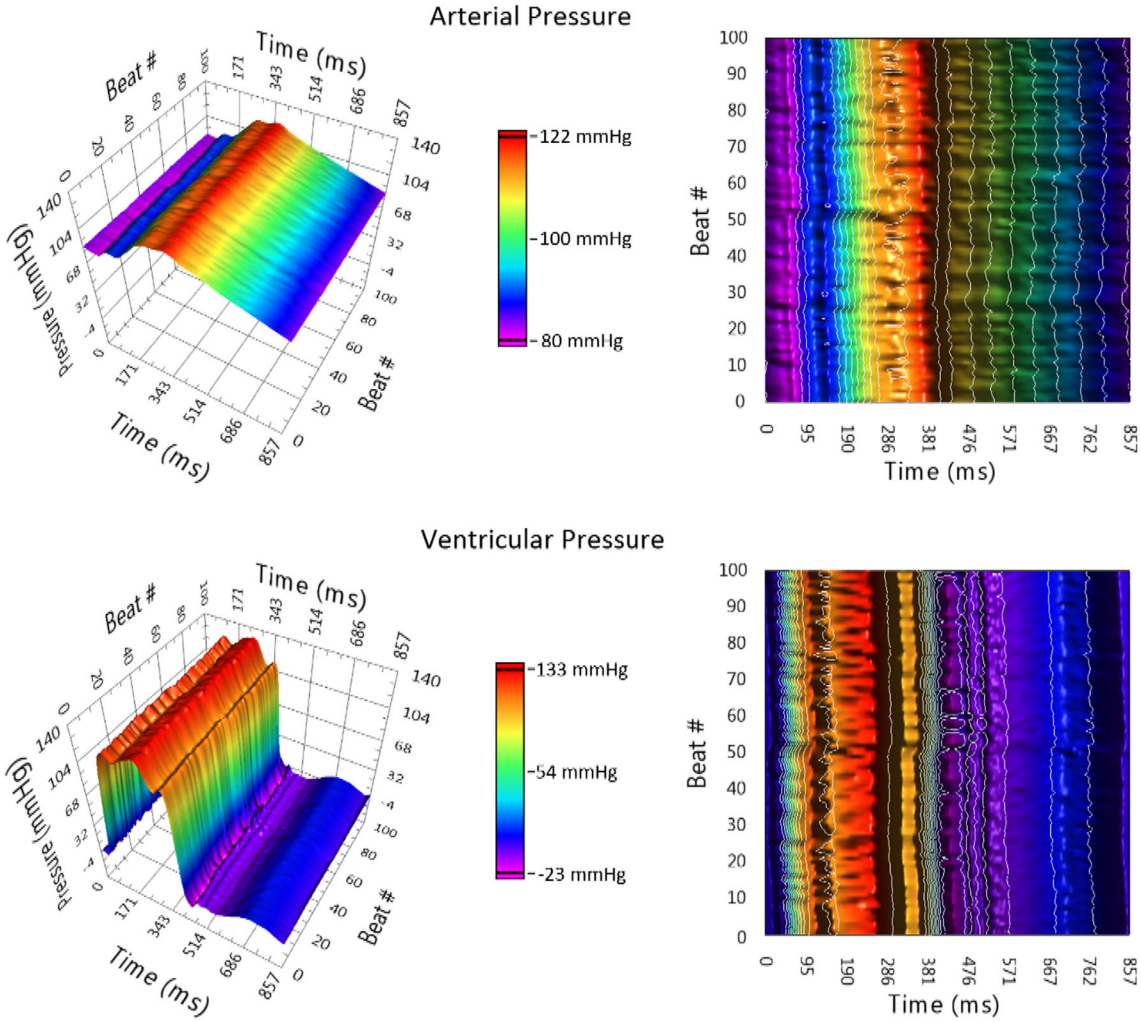

FIGURE 5. Left panels: Surface plot of (top) arterial and (bottom) ventricular pressure for 100 heartbeats. Right panels: XY plane view with contour lines of the surface plots, showing the locations of (top) arterial and (bottom) ventricular pressure. (HR = 70 bpm, SV = 71.43 mL).

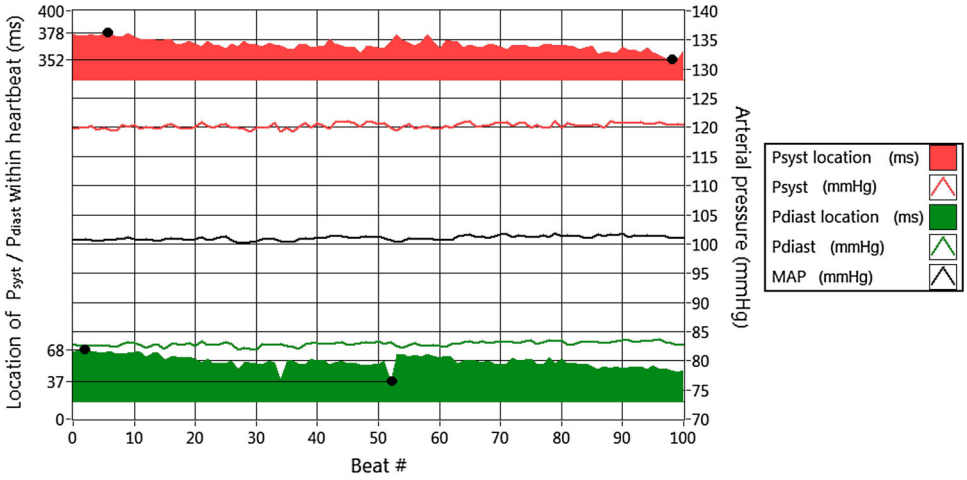

FIGURE 6. Graphical results for the variables of interest. *MAP* mean arterial pressure, P_{diast} diastolic pressure, P_{syst}: systolic pressure.

TABLE 4. Supplemental statistical results for Fig. 6.

	Systolic		Diastolic		
	Pressure (mmHg)	Location (ms)	Pressure (mmHg)	Location (ms)	MAP (mmHg)
Target	120.0	356	80.0	58	100.0
Max	121.1	378	83.7	68	101.8
Min	119.3	352	81.8	37	100.1
Mean	120.3	367	82.9	57	101.0
SD	0.5	5.5	0.4	5.7	0.5

MAP mean arterial pressure, *SD* standard deviation.

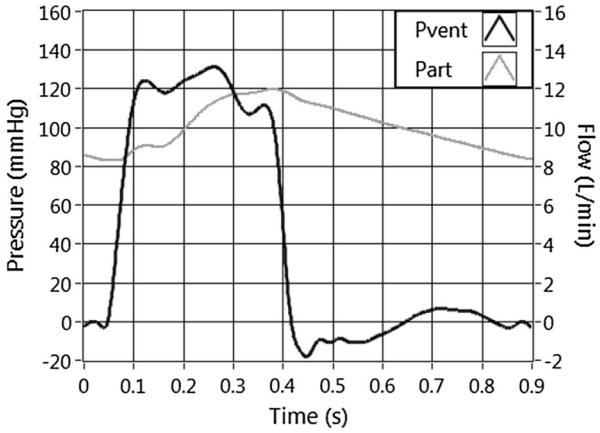

FIGURE 7. Pressure measurements for one heartbeat (HR = 70 bpm, SV = 71.43 mL). P_{vent} Ventricular pressure, P_{art} Arterial pressure.

TABLE 5. Fidelity description of the CPD.

	$F_{P_{syst}}$	$F_{P_{diast}}$	F_{MAP}	$F_{P_{arterial}}$
95th percentile	0.030	0.103	0.016	0.050

$F_{P_{syst}}$—fidelity value for systolic pressure, $F_{P_{diast}}$—fidelity value for diastolic pressure, F_{MAP}—fidelity value for mean arterial pressure, $F_{P_{arterial}}$—fidelity value for overall arterial pressure.

ventricular pressures are closely related to the volume of fluid subject to pulsatile flow, which defines the inertance property of the CPD. This property is by nature difficult to vary and as a result most CPDs do not include any means of inertance control. Thus, pressure features that are related to the inertance of the system remain constant for all PHV sizes, which proportionally changes their contribution to the overall expected pressure pulse for a corresponding PHV size. To achieve a reasonable inertance value, the CPD in this study used a test fluid with similar density as blood and the critical section of the hydraulic loop was designed to replicate the general dimensions of the human aorta (23 mm diameter and 40 cm from the aortic valve to the peripheral resistance element).

A critical component of the hydraulic loop is the aortic root, where the sinuses of Valsalva are found. D'Avenio *et al.*[7] noted that the same PHV produces different flow fields in different CPDs. Differences in the flow field have the potential to alter the perceived characteristic resistance of the PHV which would lead to differences in pressure values. These measurements are affected by the presence and geometry of the sinuses of Valsalva, with several studies having demonstrated the various ways in which the sinuses of Valsalva modify PHV behaviour and the resultant performance measurements.[5,21,23,24,29] Among the affected parameters are durability (higher leaflet stress), pressure drop across the PHV (and by extension energy losses), leaflet kinematics and flow field. The variables responsible for these effects include the sinus' size, shape and material (compliance) as well as the placement of the PHV within the sinus region. The fact that the size, material and configuration of the sinuses of Valsalva contribute significantly to the observed PHV performance (both *In vitro* and *in silico*) makes it clear that a "one size fits all" sinus is not a reasonable approach when deriving PHV performance indicators from CPD-based data. Due to project constraints, the CPD used in this study used pseudo-sinuses in the form of a 28° taper integrated on the aortic tube.

It is acknowledged that the reflected pressure wave contributes to the characteristic pressure pulse by combining with it and that the shape of the reflected pressure wave is influenced by the geometry of the arterial system.[1] The action of the reflected pressure wave on the systolic pressure wave is governed by the mechanical properties of the arterial system as stiffness controls pulse wave velocity and this affects the timing of the reflected pressure wave.[3,27,33] In turn, the effect of this timing upon the measured pressure pulse is dependent on the measurement location.[17] The design of the CPD in this study utilized the generally accepted distance of 40 cm between the aortic valve and the major reflection point of the pressure wave (the location of the peripheral resistance element).[20] However, in the present case and for most CPDs, the material of

the hydraulic loop between the aortic valve and the reflection point is acrylic and very stiff compared to the aorta, potentially affecting pressure measurements taken in the vicinity of the aortic valve. The effect of the reflected pressure wave can be seen in Fig. 7 starting from approximately 0.16 s and recurring every 0.1 s as the wave bounces between the ventricle and the aortic valve mount. Accommodating the flowmeter resulted in a tubular section of approximately 40 cm being added between the ventricle and the aortic valve and this is what gives rise to this oscillation. A small portion of this pressure oscillation is also perceivable on the arterial pressure trace but this trace also includes a contribution from the wave reflected at the peripheral resistance element. However, this contribution is much more subtle due to the action of the compliance chamber.

The results show that although the pressure variables are very accurate, their locations within the heartbeat oscillate about their target. This may be attributed to the design of the compliance chamber, where the height of fluid changes throughout the heartbeat due to the compression of air. The fluctuation occurs at a frequency which varies according to the height of fluid present in the chamber and the chosen compliance setting (the amount of air trapped above the fluid in the chamber). Such frequency does not correspond to the heart rate and results in pressure variations as it combines with or cancels out the primary pressure wave.

Fidelity

All these are design factors which vary from CPD to CPD influencing measurements and, by extension, a PHV's perceived performance. Nevertheless, the techniques discussed and used to calculate the fidelity value were conceived to isolate the performance of the CPD as much as possible from that of the PHV. These techniques involve the evaluation of historical data over a period much longer than required by the ISO5840-3:2015 standard[13] (which only calls for the hydrodynamic evaluation of ten cardiac cycles) and visualisation of these data in the form presented here provides an easy way to identify areas of unexpected behaviour, such as cycle-to-cycle pressure variations. While Fig. 5 provides a convenient way to display the whole dataset and is more effective at visually presenting overall results over time, Fig. 6 clearly highlights cycle-to-cycle variations for the variables of interest. Within the framework of PHV testing, fidelity serves various purposes:

- It is a useful tool to quantify CPD performance irrespective of design (enabling meaningful comparisons among CPDs and possibly the implementation of a performance factor to correct readings in certain areas).
- It contextualises PHV performance as it can point out why a certain PHV behaviour is observed in a given CPD (for example, larger effective stroke volumes or longer than expected flow times).
- It provides a more comprehensive indication of cycle-to-cycle repeatability.

The main consideration in making use of this technique is correctly establishing the reference location (within the heartbeat) of the features to be evaluated. To do this, the moment at which the pump begins the systolic phase should be synchronised with the moment at which ventricular pressure begins to rise. This eliminates all unknown behaviours between the pump and the test fluid if the pump does not directly drive the hydraulic loop, such as in the presence of ventricular compliance. Establishing the reference location of pressure values in relation to the pump's flow rate control signal is generally straight forward (systolic arterial pressure, for example, should occur at the end of the systolic dwell period just before the ventricle goes into diastole). For flow this can be more problematic since it is dependent on the characteristics of both the aortic and mitral valves. However, appropriate reference values can be derived from the pressure measurements given their usefulness in providing improved certainty.

Applications of Fidelity

Given the effects of CPDs' design variability, standardisation of the results by a given percentile is a sensible approach, where a standard could demand a specific percentile value for certain assessment criteria as shown in Table 5. A similar proposal was made by Vargas *et al.*[30] in relation to PHV flow performance where they suggested using the vortex ring formation number to quantify a PHV's flow performance. However, it has been shown both in this study and by D'Avenio *et al.*[7] that the CPD itself may modify this flow pattern. This and the demands imposed on test data by modern PHV development techniques (CFD and FSI among others) has created a growing need to ensure the accuracy and certainty of the measurements provided by CPDs. Therefore, establishing the performance characteristics of a CPD is more fundamental than determining the PHV's performance.

Extending beyond the applications of pressure and flow presented here, fidelity could be used for more complex measurements such as flow field analysis. As part of a protocol that could account for the assess-

ment of more advanced variables should be the use of a universal, simple and accessible reference valve employed to create a baseline on a reference CPD. A reference CPD would be a master device analogous to a National Institute of Standard and Technology (NIST) calibration source which would produce master datasets in line with the latest PHV standards. When testing the same reference valve, any deviations between a CPD and the master dataset can be corrected by a performance factor obtained through a method such as the fidelity analysis. If the fidelity value meets the minimum percentile requirement given by a CPD standardisation requirement, the CPD could be deemed reliable. This follows from the reasoning that while various types of instruments in a broad range of industrial settings are mandated to undergo regular NIST-traceable calibration, there is no equivalent requirement for CPDs (as systems), which are used for testing critical devices such as PHVs, to be calibrated against a master reference. Extending beyond PHV testing, the usefulness of an accurate and fully characterised CPD system lends itself as a test, validation and calibration platform for various other cardiovascular implant devices and medical equipment,[25] increasing the impact of the fidelity approach.

STUDY LIMITATIONS

The main limitation in this study was the flowmeter. It was not possible to remove the 0.1 s time constant and the internal signal filter. Further, the update rate of the flow signal was only 25 Hzwhich meant that at times critical portions of data were left out, resulting in cumulative discharge volume errors and problems in the detection of flow reversal. Hence, the data generated by the available flowmeter were not regarded as being of sufficient quality, resulting in no flow data being analysed in this study. The flow data for a single cycle is included in the supplementary information.

Due to constraints beyond the control of this study, it was not possible to include an anatomically correct sinus of Valsalva region in the CPD used for testing. To mitigate the effects of its absence, the aortic tube was oversized and a 28° taper was cut, blending from a root diameter of 33 mm to the final ascending aortic diameter of 23 mm.

While the pressure data presented is a fair approximation of hydrodynamic conditions in the presence of a PHV and is suitable for the purposes of this study, it does not reflect physiological conditions through the entire cardiac cycle. Specifically, the ventricular diastolic pressures (beginning and end) are acknowledged to be too low, possibly due to fluid interactions with the geometry of the test section between the ventricle and the aortic valve.

CONCLUSIONS

In this study we introduced the concept of fidelity as a tool to analyse various indicators of CPD performance. Fidelity is proposed as a metric to help determine the extent to which the performance of the CPD influences the performance of the PHV being tested by quantifying CPD performance, contextualising PHV performance and providing more comprehensive cycle-to-cycle measures of variability.

To demonstrate the application of fidelity as a CPD performance metric, a custom-built CPD was used to test a well-documented aortic PHV. The hydrodynamic data generated by the CPD were then analysed using the intra-test and inter-test fidelity techniques developed in this study.

It was shown that various aspects of CPD design have a measurable impact on the recorded variables, confirming the need for a measure of CPD fidelity. This study further proposes that in the future, the fidelity metric may help to overcome the effects of design differences on the flow field and the ramifications for the PHV test data generated by CPDs by enabling a more standardised system of evaluating CPD performance through the use of a reference CPD and PHV model.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (https://doi.org/10.1007/s13239-019-00416-3) contains supplementary material, which is available to authorized users.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Helmuth Weich and Prof Anton Doubell (Division of Cardiology, Tygerberg Hospital and Stellenbosch University, South Africa) for supplying the prosthetic heart valve used in this study.

CONFLICT OF INTEREST

RA Rodriguez and JH Muller declare that they have no conflict of interest. KH Dellimore is an employee of Philips Research, in Eindhoven, The Netherlands.

HUMAN STUDIES

No human studies were carried out by the authors for this article.

ANIMAL STUDIES

No animal studies were carried out by the authors for this article.

REFERENCES

[1]Baruch, M. C., K. Kalantari, D. W. Gerdt, and C. M. Adkins. Validation of the pulse decomposition analysis algorithm using central arterial blood pressure. *BioMed. Eng. Online* 13:96, 2014.

[2]Bazan, O., and J. P. Ortiz. Experimental validation of a cardiac simulator for in vitro evaluation of prosthetic heart valves. *Braz. J. Cardiovasc. Surg.* 31(2):151–157, 2016.

[3]Beulen, B. W. A. M. M., N. Bijnens, G. G. Koutsouridis, P. J. Brands, M. C. M. Rutten, and F. N. van de Vosse. Toward noninvasive blood pressure assessment in arteries by using ultrasound. *Ultrasound Med. Biol.* 37(5):788–797, 2011.

[4]Bjork, V. O., F. Intonti, and A. Meissl. A mechanical pulse duplicator for testing prosthetic mitral and aortic valves. *Thorax* 17:280–283, 1962.

[5]Bottio, T., E. Buratto, C. Dal Lin, A. Lika, G. Rizzoli, and G. Gerosa. Aortic valve hydrodynamics: Considerations on the absence of sinuses of Valsalva. *J. Heart Valve Dis.* 21(6):718–723, 2012.

[6]Bottio, T., V. Tarzia, G. Rizzoli, and G. Gerosa. The changing spectrum of bioprostheses hydrodynamic performance: Considerations on in vitro tests. *Interact Cardiovasc. Thorac. Surg.* 7(5):750–754, 2008.

[7]D'Avenio, G., M. Grigioni, C. Daniele, U. Morbiducci, and K. Hamilton. 3D velocity field characterization of prosthetic heart valve with two different valve testers by means of stereo-PIV. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2015:3327–3330, 2015.

[8]Davila, J., R. Trout, J. Sunner, and R. Glover. A simple mechanical pulse duplicator for cinematography of cardiac valves in action. *Ann. Surg.* 143(4):544–551, 1956.

[9]Duran, C. G., A. J. Gunning, and T. McMillan. A simple versatile pulse duplicator. *Thorax* 19:503–506, 1964.

[10]Goodale, F., and R. Shaw. Functional examination of the heart at autopsy. *N. Engl. J. Med.* 253:719–721, 1955.

[11]Hasler, D., A. Landlot, and D. Obrist. Tomographic PIV behind a prosthetic heart valve. *Exp. Fluids* 57:80, 2016.

[12]International Organization for Standardization. Cardiovascular Implants—Cardiac Valve Prostheses. ISO5840:2005. Geneva: ISO, 2005.

[13]International Organization for Standardization. Cardiovascular Implants—Cardiac Valve Prostheses—Part 3: Heart Valve Substitutes Implanted by Transcatheter Techniques. EN ISO5840-3:2013. Geneva: ISO, 2013.

[14]Kelley, R. R., F. Goodale, Jr, and B. Castleman. The dynamics of rheumatic and calcific aortic valve disease. *Circulation* 22:365–375, 1960.

[15]Kemp, I., K. Dellimore, R. Rodriguez, C. Scheffer, D. Blaine, H. Weich, and A. F. Doubell. Experimental validation of the fluid-structure interaction simulation of a bioprosthetic aortic heart valve. *Australas. Phys. Eng. Sci. Med.* 36(3):363–373, 2013.

[16]Laske, A., R. Jenni, M. Maloigne, G. Vassalli, O. Bertel, and M. Turina. Pressure gradients across bileaflet aortic valves by direct measurement and echocardiography. *Ann. Thorac. Surg.* 61:48–57, 1996.

[17]Latham, R. D., N. Westerhof, P. Sipkema, B. J. Rubal, P. Reuderink, and J. P. Murgo. Regional wave travel and reflections along the human aorta: A study with six simultaneous micromanometric pressures. *Circulation* 6(1257):69, 1985.

[18]Mao, W., K. Li, and W. Sun. Fluid-Structure Interaction Study of Transcatheter Aortic Valve Dynamics Using Smoothed Particle Hydrodynamics. *Cardiovasc. Eng. Technol.* 7(4):374–388, 2016.

[19]McMillan, I. K. R., R. Daley, and M. B. Matthews. The movement of aortic and pulmonary valves studied post mortem by colour cinematography. *Br. Heart J.* 14(1):42–46, 1952.

[20]Murgo, J. P., N. Westerhof, J. P. Giolma, and S. A. Altobelli. Aortic input impedance in normal man: Relationship to pressure wave forms. *Circulation* 62:105–116, 1980.

[21]Pisani, G., R. Scaffa, O. Ieropoli, E. M. Dell'Amico, D. Maselli, U. Morbiducci, and R. De Paulis. Role of the sinuses of Valsalva on the opening of the aortic valve. *J. Thorac. Cardiovasc. Surg.* 145:999–1003, 2013.

[22]Ramaswamy, S., M. Salinas, R. Carrol, K. Landaburo, X. Ryans, C. Crespo, A. Rivero, F. Al-Mousily, C. DeGroff, M. Bleiweis, and H. Yamaguchi. Protocol for relative hydrodynamic assessment of tri-leaflet polymer valves. *J. Vis. Exp.* 80:50335, 2013.

[23]Robicsek, F., and M. Thubrikar. Role of sinus wall compliance in aortic leaflet function. *Am. J. Cardiol.* 84(8):944–946, 1999.

[24]Salica, A., G. Pisani, U. Morbiducci, R. Scaffa, D. Massai, A. Audenino, L. Weltert, L. Guerrieri Wolf, and R. De Paulis. The combined role of sinuses of Valsalva and flow pulsatility improves energy loss of the aortic valve. *Eur. J. Cardiothorac. Surg.* 49:1222–1227, 2016.

[25]Segers, P., F. Dubois, D. De Wachter, and P. Verdonck. Role and relevancy of a cardiovascular simulator. *Cardiovasc. Eng.* 3(1):48–56, 1998.

[26]Segur, J. B., and H. E. Oberstar. Viscosity of glycerol and its aqueous solutions. *Ind. Eng. Chem.* 43:2117–2120, 1951.

[27]Steppan, J., V. Barodka, D. E. Berkowitz, and D. Nyhan. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. *Cardiol. Res. Pract.* 2011:263585, 2011.

[28]Sugawara, M., K. Uchida, Y. Kondoh, N. Magosaki, K. Niki, C. J. H. Jones, M. Sugimachi, and K. Sunagawa. Aortic blood momentum—the more the better for the ejecting heart in vivo? *Cardiovasc. Res.* 33(2):433–446, 1997.

[29]Toninato, R., J. Salmon, F. M. Susin, A. Ducci, and G. Burriesci. Physiological vortices in the sinuses of Valsalva: An in vitro approach for bio-prosthetic valves. *J Biomech* 49(13):2635–2643, 2016.

[30]Vargas, D. E., B. V. Weidner, G. C. D'Antonio, and O. Pierrakos. A novel flow performance metric for the assessment of prosthetic heart valves. *Proc. IEEE Syst. Inf. Eng. Des. Sympos. (SIEDS)*. 25(2014):255–259, 2014.

[31]Vinet, A., S. Nottin, A. M. Lecoq, and P. Obert. Cardiovascular responses to progressive cycle exercise in healthy

children and adults. *Int. J. Sports Med.* 23(4):242–246, 2002.
[32]Westerhof, N., N. Stergiopulos, and M. I. M. Noble. Viscosity. In: Snapshots of Hemodynamics: An Aid for Clinical Research and Graduate Education, edited by N. Westerhof, N. Stergiopulos, and M. I. M. Noble. Boston: Springer, 2005, pp. 3–7.
[33]Westerhof, B. E., J. P. van den Wijngaard, J. P. Murgo, and N. Westerhof. Location of a reflection site is elusive: Consequences for the calculation of aortic pulse wave velocity. *Hypertension* 52(478):83, 2008.
[34]Yokoyama, Y., O. Kawaguchi, T. Shinshi, U. Steinseifer, and S. Takatani. A new pulse duplicator with a passive fill ventricle for analysis of cardiac dynamics. *J. Artif. Organs* 13:189–196, 2010.