Violin plot data: A concerto of crucial information on valve thrombogenicity categorized in vitro by valve motion and inferred flow velocity

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Abstract:
Objectives
This in vitro study compares mechanical (MHV) and bioprosthetic (BHV) heart valves for high amplitude short duration regional flow velocities (RFV) near valve closure.

Background
We previously tested several clinical and prototype valves and observed RFV at levels which may be related to a dimensionless thrombogenic potential (TP).

Methods
A total of four valves were tested in aortic and mitral sites under pulsatile circulation in a pulse duplicator. Valves included both clinical models and experimental prototypes. An optical approach measuring projected dynamic valve area (PDVA) to gauge valve motion was implemented. Pulsatile pressures and flow rates were measured by conventional techniques and a quasi-steady flow tester was used to measure valve leakage. RFV was derived using time-dependent volumetric flow rate/PDVA. Since flow velocity and fluid shear force are related through flow velocity gradient, TPs for valves that achieve near closure during the forward flow deceleration phase were determined as RFVs relative to the control mechanical valve RFV value of -126 m/s.

Results
TP is dimensionless and ranged between -0.45 and +1.0. Negative TPs arise when transient rebound of valve occluders is accompanied by water-hammer phenomena. Positive TPs occur during the decelerating forward flow. Bioprostheses had lowest TP transient of 0.15 with exception of a mock-transcatheter aortic valve (mTAVI) that incorporated by design a trivial perivalvular leak (~1.35 ml/s). This device demonstrated a remarkably high transient TP of 0.95. The control mechanical valves had the highest TP of 1.0. The study implicates TP transients near mechanical valve closure, and not forward or non-flow phases, as primary to shear induced activation of the coagulation cascade.
Conclusions

Our data reveals distinct TP profile differences between valve models. If verifiable, the design of future valves may utilize currently available experimental tools to determine TPs resulting in advanced devices with significantly reduced TP.

I. Introduction and Background

Development of prosthetic heart valves is replete with innovative designs and materials intended to provide adequate hemodynamic performance and long term durability. Although early ball-in-cage valves from Starr, Harken and Smeloff partially met these requirements, an incidence of thrombotic and thromboembolic events stimulated investigation into novel geometries and new materials. Carpentier, Hancock, Ionescu and others devised bioprosthetic valves that mitigated the incidence of thromboembolic complications albeit at the expense of extended durability. Progressive modifications in mechanical valve geometry and enhancements of tissue preservation methodology have not yet resolved these longstanding shortcomings that vex prosthetic valve technology nearly 60 years later.

The earliest published data from investigation into sources of thrombogenicity in mechanical valves was the work of Davey [1] and Smeloff [2] in 1966, in which cyclic flow behavior was visualized by high-speed cinematography in a pulse duplicator with a transparent chamber and a sheet of light flow technique using aluminum flow tracer particles in transparent test fluids. Flow patterns adjacent to an early model Starr-Edwards valve ball occluder were identified and multiple retrograde impulses were observed at valve closure. Although the investigators speculated that these events were associated with high shear, equipment of that era was incapable of measuring the retrograde flow velocities associated with occluder rebound phenomena. More recently, computational methods employed to examine flow patterns, flow velocities, and pressures associated with contemporary mechanical and bioprosthetic valve function have generated extensive information on flow but as yet have not proposed a development pathway to eliminate thrombogenicity in the former and extend durability in the latter [e.g. 3-5].

In prior publications, [5-10] we hypothesized that mechanical valve occluder closing behavior was implicated in the thrombogenic discrepancy between mechanical and bioprosthetic valves. This work required innovative adaptations to our pulse duplicator to allow measurement of prosthetic valve dynamic area (PDVA). These adaptations provided crucial insight into the contribution of occluder oscillation, cavitation and occluder rebound that contribute in the complex genesis of valve thrombosis. Subsequent pulse duplicator adaptations in 2011 included a unique electro-optical subsystem that we referred to as Leonardo [6]. An unanticipated benefit of adding the Leonardo sub-system was that it facilitated determination of spatially averaged flow velocity in immediate proximity to a test valve. We found that transient RFVs occurred often near MHV closure and proposed it as a proxy for rapidly changing (transient) shear forces. Blood shear forces initiate multiple biochemical and functional reactions known to promote formation of micro-thrombi aggregates that may remain locally adherent or embolize [11-18]. Test results from this work provided stimulation to define geometry for a mechanical heart valve (MHV) with blood damage reduced to tissue valve levels and we subsequently extended this experimental methodology to study thrombogenic potential in transcatheter aortic valve replacement (TAVR) devices [8].
II. Methods

A) Test Apparatus

Since 2004, our valve testing has been conducted in an extensively cited commercial in vitro test flow system [6-10]. Typical simulation conditions included: pulse rate 70 beats/min; pressures ca.120/80 mmHg; and cardiac output 5 litres/min. Basic test methodology is depicted in Figure 1. The current photo sensor/amplifier in use was upgraded in 2011 yielding improved specifications in subsequent reports [7-10]. Valves were tested in pulsatile and quasi-steady pressure/flow systems and PDVA was obtained. Time-dependent RFV was derived by dividing the volumetric flow rate by the PDVA (volumetric flow rate/PDVA). A separate apparatus (model LT8991, ca. 2008) provided accurate measurement of small closed valve leakage rates under quasi-steady pressure/flow conditions. Such measures were used to estimate valve leakage area [8].

The Leonardo modified pulse duplicator originally adapted in 2011 has innovative features to measure PDVA from backlit valves. This unique electro-optical prototype remains in current use with improved spatial and temporal resolution capability (i.e., 0.001 cm² and 1 μs) compared with that originally reported in 2004 [6]. Test results from this prototype system were recently used to compare numerical simulations for contemporary porcine tissue and bovine pericardial bioprosthetic heart valves and with data from a similar independent pulse duplicator in which excellent agreement was noted [4].

A Visco-elastic Impedance Adapter (VIA model 7991, sn 44) was designed by Scotten in 1997 to model adjustable ventricle visco-elastic and isovolumetric functionality. Jennings et al. reported use of VIA in the Leeds valve tester for studying stentless porcine valves [19]. This physiological trait coincides with valve opening and closure, and influences ventricular pressure rates (dp/dt), the propensity for microbubbles, high intensity transient signals (HITS), cavitation, acoustic emissions, and possible vortex formation. The test fluid used was saline (viscosity 1 mPa·s; density 1.0 g/ml). Blood analog fluids such as saline-glycerin are problematic requiring temperature control to maintain stable optical and viscous properties. Other authors, testing a St. Jude Medical, (SJM) Regent™ valve, have shown that fluid viscosities ranging from 1.1 - 3.1 mPa·s have a negligible effect on valve-closing PDVA, but reduce the backflow rate by ca.14%.

Accurate measurement of closed valve leakage was obtained in a quasi-steady pressure/flow apparatus calibrated with known small orifice areas described previously [7-9]. Valve leakage areas assigned for pulsatile flow test data analysis were; 0.0178 cm² (SJM); 0.003 cm² (BV3D); and 0.012 cm² (control valve -Edwards pericardial).

B) Leonardo

Since only fleeting glimpses of prosthetic valve motion can be seen by the unaided eye, complex and costly high-speed imaging techniques are required to visualize quantitative details. Leonardo mitigates this problem through a simple solution that measures valve motion (see Figure 1). As an integral component of our model heart, a photo detector continuously measures the amount of light that transits the test valve (either aortic or mitral) during cyclic function. This approach provides important data about valve motion. An inherent advantage of monitoring valve motion (PDVA) with Leonardo is that all
signals are analog in close synchronization prior to acquisition with an analog to digital (A-D) converter [6].

C) Calibration

Two types of light sensors are useful for measuring high speed PDVA data from valve experiments. Data collected here and previously [6-10] utilized an analog-type light sensor (photodiode) calibrated with circular reference orifice areas placed temporarily in the aortic or mitral test site. Measured output voltages had exceptional linearity vs. geometric orifice areas. Specification section lists typical calibrations per linear regression equation fit. Alternate methods have employed either CMOS or CCD digital image chips where area-to-chip pixel scaling estimates can be made to calibrate PDVA vs. time data [4, 20].

![Diagram of optical approach gauging aortic or mitral valve function.]

Figure 1: Optical approach gauges aortic (or mitral) prosthetic heart valve function with occluder motion quantified as projected dynamic valve area (PDVA).

D) Specifications [7]

- Temporal resolution (based on voltage step waveform response, rise time from 10% to 90% amplitude) ≈ 1.04 μs;
- Bandwidth ≈ 0.35/risetime = 0.35/1.04μs = 337 KHz;
- Spatial area resolution (closed valve), 0.001 cm² (n=10 cycle average);
- Telecentric lens maintains constant magnification =0.16 x;
- Working distance =18 cm (AORTIC); ≈ 19 cm (MITRAL);
- Perspective error <0.3% (depth 15 mm);
- Spatial sensitivity variation <6%;
- Typical site dependent linear regression calibrations are:
  y=0.00128x, with R² =0.99988 (AORTIC);
y=0.00132x, with $R^2 =0.99959$ (MITRAL);
- LED back light source (diffuse red):
  - Wavelength 625±15 nm
  - Uniformity 99.24%
  - Luminance 5,780 cd/m²

E) Regional Flow Velocity and Shear Force

Regional flow velocity magnitude shown in Figure 3 can be considered a shear force surrogate associated with valve TP. Since flow velocity and fluid shear are related through flow velocity gradient, a proxy for valve thrombogenic potential may be inferred by flow velocity. Although TP cannot be assumed to increase linearly with flow velocity it is considered proportional to the inferred regional flow velocity (m/s) and independent of fabrication materials. The regional flow velocity determined by Leonardo must be appreciated as an estimated spatial average quantity (m/s) and not a site specific quantity. Since flow velocity gradients cannot be obtained with Leonardo, neither can shear force values (dyne/cm²) from measured RBVs (m/s).

F) Derivations and PDVA Synchronization Adjustment

Valve regional flow velocity (RFV) is equal to volumetric flow rate, divided by the PDVA (flow rate/PDVA) and is an estimate of the regional instantaneous spatial average.

Analog signal bandwidth differences between PDVA and transvalvular volumetric flow rate were 0-337 KHz vs. 0-100 Hz, respectively. As the PDVA signal preceded the other signals by -2.5 ms based on step signal response, a phase adjustment between the PDVA and the other signals was required. Accordingly, post experiment, we shifted the acquired PDVA signal 1 data acquisition interval of -3.4 ms [7].

G) Violin Plots with Relative Flow Velocity Scaling

Although “Violin” plots have not previously been utilized for presentation of in vitro valve test results, they attracted our attention as a powerful graphic technique to present voluminous quantitative or qualitative data. Sample Figure 2 depicts TP data density near valve closure and reveals different peaks, their position, and relative amplitudes. Here, split-violin plots benefit from superior spatial efficiency compared to full violin plots.
Figure 2: Sample split-violin plot depiction of inferred dimensionless valve thrombogenic potential (TP). Shaded margin $\Delta y$ represents probability of recurrence of an inferred TP (relative to an RFV of -126 m/s). All data points can be reduced to a split-violin shape with each configuration representing an independent data set and coverage of all data points. Single data points with minimum density depict baseline data values.

The broader split-violin region(s) convey greater recurrence of TP data values whereas narrower regions(s) contain fewer recurrences. TPs for valves during the forward flow deceleration phase on the verge of closure were determined as RFVs relative to a control mechanical valve RFV value of -126 m/s. RFV was derived using time-dependent volumetric flow rate/PDVA. Since flow velocity and fluid shear force are related through flow velocity gradient, TP of valves may be a useful surrogate for transfer of shear forces to blood cells and for coagulation activation potential.

I) Valve thrombogenic potential is consistent by multiple determinations

Since 2011, our investigations utilizing Leonardo have compared TP of test valves to controls. Over time, alternate metrics for assessing TP evolved (Table I). For example, a widely used clinical MHV (SJM) has consistently exhibited high TP compared with controls regardless of determination method [6-10]. Figure 3 shows that the inferred TP for the SJM aortic valve is high (1.0) for all the determination methods listed in Table I. All determinations utilized valve motion as a component metric for obtaining TP [6-10].

| Thrombogenic Potential (TP)                  | Quantity | References |
|---------------------------------------------|----------|------------|
| Peak Backflow Velocity, m/s                 | -235     | 6          |
| Thrombogenic Potential Index, TPI           | 3.9      | 10         |
| Split violin, maximum TP                    | 1.0      | (Present study) |
Figure 3: Inferred dimensionless TP of valves (based on near closure RFVs relative to -126 m/s). Illustrated valve BV3D shown in full open and closed positions. Negative data includes water hammer phenomena and occluder rebound RFVs except for valve BV3D. This early prototype valve is currently pending fabrication using refined prototype materials and geometry. Over the valve closing period (~495 ms, milliseconds), a total of 150 RFV data points for each of 10 consecutive cycles were acquired per experiment. Vioplot R software analyzed 10,500 data values to create full-violin plots. Subsequently, Visio software was used to trace, scale, and cut-in-half the full violin plots produced by Vioplot R to create the split-violin plots shown here.
Vioplot R* software package and Visio 2002 ** have been utilized to create the split-violin plots used in this study. Observers will appreciate that wider violin shape regions demonstrate show more probable flow velocities than those in the narrower zones.

*R Core Team (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

** Microsoft, Redmond, WA USA

III. Results and Discussion

Flow dynamics near valve closure cause rapidly changing PDVA and interrelated flow profiles to progressively constrain regurgitation (analogous to greater valve stenosis) before the complete motionless closed valve condition. This may stimulate cellular responses before that condition occurs. Over time our primary focus evolved into development of insights into thrombogenic factors specific to the valve closing phase. During brief crucial moments of valve closure, localized prothrombotic microenvironments may be relevant to generation of high velocity leakage jets, flow unsteadiness, valve flutter, cyclic variability of PDVA, turbulence, and excessive shear forces that may induce blood element damage [21-23]. The various influences mentioned previously may be relevant to multiple valve types for:

- conduction abnormalities
- reduced mobility of valve leaflets or occluders
- silent cerebral micro-infarction
- sub-clinical valve thrombosis
- potential for pannus formation
- acute and sub-acute embolic stroke and other adverse cerebrovascular events including TIA
- cavitation and high intensity trans-cranial signals (HITS) [6]

Closure dynamics therefore raise provocative questions about valve thrombogenic impact including:

1. Dynamics of valve closure that may mimic well studied pro-thrombotic aspects of forward valve flow (e.g., valve stenosis) and arterial flows (e.g., arterial sclerosis)
2. Valve closure dynamics may reflect combined biomechanical and biochemical responses sufficient to exacerbate risk for pathologic thrombus formation and propagation
3. Valve rebound and water-hammer -the SJM valve in the mitral position consistently manifested leaflet rebound observed as a momentary post closure partial re-opening driven by water-hammer power (transvalvular pressure × volumetric flow rate). This has been previously reported with magnified examples of high-resolution PDVA rebound data [7].

Figure 3 compares several contemporary and prototype cardiac valves near closure extending over the ~495 ms each cycle of 10 consecutive cycles gathered. One hundred fifty (150) RFV data points were collected for every cycle and 10 consecutive cycles were collected for each valve. The time increment was ~3.4 ms which was the interval used to collect data over the total cycle time of 867 ms (cycle rate =70 per minute). Inferred dimensionless TP of the test valves (X axis) is referenced to an RFV of -126 m/s, the peak observed for the SJM aortic MHV.
A) Study outcomes (previous and present reports) [7-9, 11]:

1. High amplitude RFVs and resultant supra-physiologic shear forces originating in small intra- and para-valvular leakage (PVL) gaps are mechanistic initiators of the clotting cascade.
2. Platelet activation is induced by high shear even with short exposure time [23, 24]
3. The disparity in closing dynamics between MHV vs. bioprosthetic valves is chronically overlooked as a primary indicator of valve TP.
4. Current MHVs have overt RFV transients at closure relating to occluder non-response to flow deceleration and residual PDVA.
5. A mock TAVR valve with trivial PVL generated high magnitude short duration RFVs.
6. An unintended consequence of reducing significant PVL to trivial PVL produces high RFVs and increased valve TP.
7. For a given volumetric backflow rate near valve closure, the smaller the total residual leakage area, the greater the magnitude of RFVs.
8. The highest recorded RFVs were generated by the SJM valve compared to the tissue control valves (Edwards pericardial).
9. Rapid prototype valve BV3D produced RFVs similar to the tissue control valves.
10. A spatial average of RFVs in immediate proximity to prototype valves may be a practical indicator in qualitative screening for valve TP.
11. Test data from valve BV3D strongly suggest that specific MHV leaflet geometries generate a closure force during forward flow deceleration and prior to flow reversal, a potentially beneficial “soft closure” response.
12. Since the motion of heart valves is too fast to see and too important to ignore, Leonardo provides a simple rapid means to pre-calibrate, record, and perform quantitative valve motion analysis.
13. Our technology enabled RFVs to be resolved and focused attention on overt RFVs previously overlooked and hidden due to brevity, small PVL gaps, and limited instrumentation resolution capability.
14. Our results infer shear damage to formed blood elements and a resultant continuous thrombogenic response constitute a mechanistic explanation for observed thrombogenic disparity in prosthetic valve types and designs now broadened to include observations of TAVI related thromboembolic events.
15. For MHVs, cyclic RFVs appear to be related to a prothrombotic state requiring chronic anticoagulation. This risk is much less recognized in bioprosthetic heart valves which appear not to generate a pro-thrombotic closing phase but TAVI prostheses with trivial PVL may generate pathologic RFVs similar to those observed in MHVs.
16. Promising prototype MHVs were designed and tested in vitro with dimensions optimized to provide minimum TP relative to BHV controls thereby attenuating potential of hemodynamic biomechanical forces and biochemical pathways known to initiate and amplify thrombus formation.

B) Caveats

While not a site specific quantity, we submit that RFVs are useful surrogates for flow induced blood cell damage potential. To infer valve TP directly from derived maximum flow velocities is an over simplification considering the complexity of blood coagulation factors recently reviewed by Rana and associates [26]. For example, the difference between laminar and turbulent flow and their respective
impact on blood component damage awaits experimental evidence to validate numerical simulations [27]. In contrast to laminar, turbulent fluid flow is characterized by chaotic flow/pressure fluctuations with sufficient shear forces to activate blood clotting mechanisms [28].

Development of advanced valves with clinical potential requires detailed and accurate prototypes with improved geometric leakage flow path area (GAP) control for final optimization and definitive laboratory testing prior to animal and durability testing.

IV. Conclusions

Importance – Promising MHVs have been designed and tested in vitro with dimensions optimized to provide minimum TP relative to BHV controls and thereby attenuating in vivo hemodynamic biomechanical forces and biochemical pathways known to initiate and amplify thrombus formation.

Current valve designs and manufacturing efforts focused on valve open phase performance largely exclude consideration of dynamic flow conditions during the closing phase. Although events close to valve closure involve multi-factorial influences, our prior work found that valve motion and flow velocity constituted a primary contribution to valve TP and that closure-related functional deficit is a common shortcoming of current MHVs [10].

In this study, dimensionless TP was used to rank valve thrombogenic potential based on in vitro measurements that determine spatially averaged regional flow velocities relative to a maximum (-126 m/s) obtained for the SJM mechanical valve (TP=1.0). TP ranged from -0.45 to 0 +1.0 with the clinical bioprosthetic control valve (Edwards Perimount™) having the least (TP = 0.17). These results are consistent with extensive qualitative clinical experience of thrombogenic disparity between these classes of valves. SJM recipients require life-long anticoagulants whereas bioprosthetic devices typically impose minimal increased thrombogenic risk.

Progress beyond the limitations of current prosthetic valves will require innovative MHV designs with substantially reduced TP confirmed by in vitro dynamic testing results indistinguishable from control tissue valves. This requires appreciation of valve closure as a crucial factor since very high flow short duration RFVs near valve closure result in transient or continual blood cell damage and initiation of the coagulation cascade [23].

Additionally, results suggest that designing a MHV with reduced TP comparable to clinically well established tissue valves is achievable with current technology. The objective is to produce a MHV that will not increase recipient thrombogenic risk. On a cautionary note, device manufacturers preoccupied with modifications of catheter delivered valves to minimize residual leak assume that reducing a major leak to a minor (trivial) one diminishes patient risk. However, we consistently observe smaller volume-metric paravalvular leaks (PVL) to associate with higher magnitude RFVs and counter-intuitively; that larger PVLs result in lower RFVs and shear forces. This is consistent with recently reported clinical experience where independent predictors of late leaflet thrombosis up to 3 years post implant were male sex and PVL less than mild [18].
In vitro, a tissue valve-like “soft” closing profile along with either complete sealing or optimized closed leakage area are important for minimizing water-hammer driven rebound and subsequent RFVs and may be an essential dynamic characteristic for low thrombogenic function. Bioprosthetic valves benefit from minimal volumetric backflow rates (VBRs) and a propensity to be fully competent when closed resulting in negligible RFVs.

Perhaps the most consequential outcome of our work is development of a practical method to screen valves for inferred thrombotic potential by determination of RFVs. In the case of MHVs, blood flow is disrupted predominantly by valve closure dynamics that produce elevated shear forces and stagnant low flows which trigger pro-thrombotic response.

Footnotes

Contributions: (I) Conception and design: LN Scotten; (II) Administrative support: LN Scotten; (III) Provision of study materials: LN Scotten; (IV) Collection and assembly of data: LN Scotten; (V) Data analysis and interpretation: LN Scotten, D Blundon; (VI) Manuscript writing: All authors; (VII) All authors have approved the final submitted version of the manuscript.

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V. References

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