TITLE:

Noninvasive Determination of Vortex Formation Time using Transesophageal Echocardiography During Cardiac Surgery

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Trans-mitral blood flow efficiency, vortex formation time, early left ventricular filling, fluid mechanics, diastolic function, intraventricular blood flow, continuity equation, transesophageal echocardiography

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SUMMARY:

We describe a protocol to measure vortex formation time, an index of left ventricular filling efficiency, using standard transesophageal echocardiography techniques in patients undergoing cardiac surgery. We apply this technique to analyze vortex formation time in several groups of patients with differing cardiac pathologies.

ABSTRACT:

Trans-mitral blood flow produces a three-dimensional rotational body of fluid, known as a vortex ring, that enhances the efficiency of left ventricular (LV) filling compared with a continuous linear jet. Vortex ring development is most often quantified with vortex formation time (VFT), a dimensionless parameter based on fluid ejection from a rigid tube. Our group is interested in factors that affect LV filling efficiency during cardiac surgery. In this report, we describe how to use standard two-dimensional (2D) and Doppler transesophageal echocardiography (TEE) to

45 noninvasively derive the variables needed to calculate VFT. We calculate atrial filling fraction (β)
46 from velocity-time integrals of trans-mitral early LV filling and atrial systole blood flow velocity
47 waveforms measured in the mid-esophageal four-chamber TEE view. Stroke volume (SV) is
48 calculated as the product of the diameter of the LV outflow track measured in the mid-
49 esophageal long axis TEE view and the velocity-time integral of blood flow through the outflow
50 track determined in the deep transgastric view using pulse-wave Doppler. Finally, mitral valve
51 diameter (D) is determined as the average of major and minor axis lengths measured in
52 orthogonal mid-esophageal bicommissural and long axis imaging planes, respectively. VFT is then
53 calculated as $4 \times (1-\beta) \times SV/(\pi D^3)$. We have used this technique to analyze VFT in several groups
54 of patients with differing cardiac abnormalities. We discuss our application of this technique and
55 its potential limitations and also review our results to date. Noninvasive measurement of VFT
56 using TEE is straightforward in anesthetized patients undergoing cardiac surgery. The technique
57 may allow cardiac anesthesiologists and surgeons to assess the impact of pathological conditions
58 and surgical interventions on LV filling efficiency in real time.
59
60 **INTRODUCTION**:
61 Fluid mechanics is a critical yet often underappreciated determinant of left ventricular (LV) filling.
62 A three-dimensional rotational body of fluid, known as a vortex ring, is generated whenever a
63 fluid traverses an orifice[1-3]. This vortex ring improves the efficiency of fluid transport compared
64 with a continuous linear jet[4]. Movement of blood through the mitral valve during early LV filling
65 causes a vortex ring to form[5-8] and facilitates its propagation into the chamber by preserving fluid
66 momentum and kinetic energy[9]. These actions enhance LV filling efficiency[4,10-13]. The ring not
67 only inhibits blood flow stasis in the LV apex[14-17] but also directs flow preferentially beneath the
68 anterior mitral leaflet[7,18], effects that decrease the risk of apical thrombus formation and
69 facilitate filling of the LV outflow track[19], respectively. Contrast echocardiography[17], Doppler
70 vector flow mapping[6,20,21], magnetic resonance imaging[7], and particle imaging velocimetry[9,22-24]
71 have been used to demonstrate the appearance and behavior of trans-mitral vortex rings under
72 normal and pathological conditions. The left atrial-LV pressure gradient, the degree of diastolic
73 mitral annular excursion, the minimum LV pressure achieved during diastole, and the rate and
74 extent of LV relaxation are the four major determinants of the duration, size, flow intensity, and
75 position of the trans-mitral ring[2,12,25-29].
76
77 Vortex ring development is most often quantified with a dimensionless parameter (vortex
78 formation time; VFT) based on fluid ejection from a rigid tube[3], where VFT is defined as the
79 product of the time-averaged fluid velocity and the duration of ejection divided by the orifice
80 diameter. The optimal size of a vortex ring is achieved when VFT is 4 *in vitro* because trailing jets
81 and energetic limitations prevent it from attaining a larger size[3,4]. Mitral valve VFT has been
82 approximated clinically using transthoracic echocardiography[8,30,31]. Based on analysis of trans-
83 mitral blood flow velocity and mitral valve diameter (D), it can be easily shown[8] that VFT = 4 × (1-
84 β) × EF × α^3, where β = atrial filling fraction, EF = LV ejection fraction, and α = $EDV^{1/3}/D$, where
85 EDV = end-diastolic volume. Ejection fraction is the ratio of stroke volume (SV) and EDV, allowing
86 this equation to be simplified to VFT = $4 \times (1-\beta) \times SV/(\pi D^3)$. Because VFT is dimensionless
87 (volume/volume), this index allows direct comparison between patients of varying size without
88 adjustment for weight or body surface area[8]. Optimal VFT ranges between 3.3 and 5.5 in healthy

89   subjects[8], and results are consistent with those obtained in fluid dynamics models[3,32]. VFT was
90   shown to be ≤ 2.0 in patients with depressed LV systolic function, findings that are also supported
91   by theoretical predictions[8]. Reductions in VFT independently predicted morbidity and mortality
92   in patients with heart failure[30]. Elevated LV afterload[33], Alzheimer's disease[34], abnormal diastolic
93   function[19], and replacement of the native mitral valve with a prosthesis[35] have also been shown
94   to decrease VFT. Measurement of VFT may also be useful to identify blood flow stasis or
95   thrombosis in patients with acute myocardial infarction[36,37].
96
97   Our group is interested in factors that affect LV filling efficiency during cardiac surgery[38-41]. We
98   use standard two-dimensional and Doppler transesophageal echocardiography (TEE) to
99   noninvasively derive the variables required to calculate VFT. In this report, we describe this
100   methodology in detail and review our findings to date.
101
102   **Protocol:**
103
104   The Institutional Review Board of the Clement J. Zablocki Veterans Affairs Medical Center
105   approved the protocols. Written informed consent was waived because invasive cardiac
106   monitoring and TEE are routinely used in all patients undergoing cardiac surgery in our
107   institution. Patients with relative or absolute contraindications for TEE, those undergoing repeat
108   median sternotomy or emergency surgery, and those with atrial or ventricular tachyarrhythmias
109   were excluded from participation.
110
111   **1. Anesthesia**
112
113   1.1. Provide each patient with intravenous midazolam (1 to 3 mg) and fentanyl (50 to 150 mcg)
114   for conscious sedation before surgery.
115
116   1.2. Use local anesthesia (subcutaneous 1% lidocaine) for insertion of intravenous and radial
117   artery catheters. Test the quality of the local anesthesia with a pinprick.
118
119   1.3. Ensure that the patient receives supplemental oxygen using a nasal cannula (2 to 4 L/min).
120
121   1.4. Place a central venous or pulmonary artery catheter using local anesthesia (subcutaneous
122   1% lidocaine) under sterile conditions through the right or left internal jugular vein with
123   ultrasound guidance based on appropriate clinical indications.
124
125   1.5. Induce anesthesia using intravenous fentanyl (5 mcg/kg), propofol (1 to 2 mg/kg), and
126   rocuronium (0.1 mg/kg). Maintain anesthesia using inhaled isoflurane (end-tidal concentration
127   of 1%) in an air-oxygen mixture, fentanyl (1 to 2 mcg/kg/h), and rocuronium (0.05 mg/kg) titrated
128   to effect using neuromuscular monitoring.
129
130   1.6. Suction the stomach using an oral-gastric tube.
131

132　1.7. Place ultrasound jelly in the patient's hypopharynx. Lift the jaw anteriorly and advance a TEE
133　probe into the esophagus with gentle pressure to overcome resistance of the hypopharygeus
134　muscle.
135
136　**2. Transesophageal echocardiography**
137
138　2.1. Perform a comprehensive TEE examination following American Society of
139　Echocardiography/Society of Cardiovascular Anesthesiologists guidelines[42] in each patient.
140
141　2.2. Place a pulse-wave Doppler sample volume between the tips of the mitral leaflets to record
142　trans-mitral blood flow velocity in the mid-esophageal four-chamber TEE imaging plane (**Figure**
143　**1**).
144
145　2.3. Identify the early LV filling and atrial systole blood flow waveforms of trans-mitral blood flow
146　velocity, and measure their corresponding peak velocities and velocity-time integrals (VTI_E and
147　VTI_A, respectively) using the echocardiography equipment's integrated software package (**Figure**
148　**1**).
149
150　2.4. Calculate the atrial filling fraction (β) as the ratio of atrial to total LV filling:
151

$$\beta = \frac{VTI_A}{VTI_E + VTI_A}$$

152

153
154　2.5. Measure the maximum diameter of the LV outflow tract immediately below the aortic valve
155　in the mid-esophageal aortic valve long axis TEE view during mid-systole (**Figure 2A**).
156
157　2.6. Calculate the area of the LV outflow tract assuming circular geometry as the product of $\pi/4$
158　and the square of the diameter (see step 2.5 above).
159
160　2.7. Obtain a deep transgastric long axis TEE view, and place a pulse-wave Doppler sample volume
161　in the distal LV outflow tract to record a blood flow velocity envelope (**Figure 2B**) at the same
162　level where the diameter was measured (see step 2.5 above); integrate the area of this waveform
163　using the echocardiography equipment's software package to obtain VTI.
164
165　2.8. Multiply the resulting velocity-time integral (VTI) of the LV outflow track blood flow velocity
166　waveform (**Figure 2B**) by the area of the outflow track (see step 2.6) to obtain stroke volume (SV).
167
168　2.9. Record video clips of the mid-esophageal bicommissural and LV long axis TEE imaging planes,
169　respectively[42]. Be sure to include several cardiac cycles in each recording.
170
171　2.10. Visually inspect slow-motion images of the video clips (see step 2.9 above) after the ECG T-
172　wave to choose the maximum opening of the mitral valve leaflets.
173

174 2.11. Measure the distance between the mitral leaflets (**Figures 3A** and **3B**) using the
175 echocardiography equipment's "caliper" function.
176
177 2.12. Calculate the mitral valve diameter (D) as the average of the major (transcommissural
178 anterior-lateral-posterior-medial) and minor (anterior-posterior) lengths.
179
180 2.13. Calculate VFT using the formula:

181
$$VFT = 4 \times (1 - \beta) \times \frac{SV}{\pi D^3}$$

182
183 2.14. Perform all quantitative echocardiographic measurements in triplicate at end-expiration.
184
185 **3. Experimental Design**
186
187 3.1. Determine VFT, indices of LV diastolic function, and hemodynamics during steady-state
188 conditions 30 minutes before and 15, 30, and 60 minutes after cardiopulmonary bypass (CPB) in
189 10 patients with normal preoperative LV ejection fraction under coronary artery surgery to test
190 the hypothesis that CPB transiently decreases VFT[39].
191
192 3.2. Test the hypothesis that LV pressure-overload hypertrophy produced by aortic valve stenosis
193 reduces VFT by examining (in one group of 8 patients undergoing aortic valve replacement) for
194 severe aortic stenosis and comparing observations to another group of 8 patients with normal LV
195 wall thickness undergoing coronary artery surgery[40]. Measure VFT, LV diastolic function,
196 hemodynamics, and end-diastolic posterior wall thickness during steady-state conditions 30
197 minutes before CPB.
198
199 3.3. Test the hypothesis that abnormal diastolic blood flow entering the LV affects trans-mitral
200 LV filling efficiency in 8 patients with aortic valve stenosis and moderate aortic insufficiency
201 versus 8 patients with aortic stenosis who do not have regurgitant valves[38]. Measure VFT and
202 other parameters as described above (step 3.2).
203
204 3.4. Test the hypothesis that advanced age is associated with a reduction in LV filling efficiency
205 quantified using VFT in 7 octogenarians (82 ± 2 years) compared to 7 younger patients (55 ± 6
206 years)[41] undergoing coronary artery surgery. Ensure that both groups have normal preoperative
207 LV ejection fraction. Measure VFT and other parameters as described above (step 3.2).
208
209 **4. Statistics**
210
211 4.1. Present the data as mean ± standard deviation.
212
213 4.2. Evaluate data using analysis of variance (ANOVA) followed by Bonferroni's modification of
214 Student's *t*-test.
215

216   4.3. Use linear regression analysis to determine the relationships between VFT and end-diastolic
217   posterior wall thickness and between VFT and age.
218
219   4.4. Reject the null hypothesis when $p < 0.05$.
220
221   **Representative Results:**
222   The current technique allowed us to reliably measure VFT during cardiac surgery under a variety
223   of clinical conditions by obtaining each determinant from blood flow and dimensional recordings
224   in standard TEE imaging planes. A pulse-wave Doppler sample volume was placed at the tips of
225   the mitral leaflets in the mid-esophageal four-chamber view to obtain the trans-mitral blood flow
226   velocity profile necessary to calculate atrial filling fraction (β; **Figure 1**). Stroke volume was
227   determined using the continuity equation (velocity-time integral of the LV outflow track blood
228   flow velocity waveform multiplied by the area of the outflow track) and LV outflow track diameter
229   was measured in the mid-esophageal LV long-axis view (**Figure 2A**), whereas blood flow through
230   the outflow tract was determined in the deep transgastric short axis imaging plane (**Figure 2B**).
231   Finally, average mitral valve diameter was calculated as the average of major and minor axis
232   diameters measured in the mid-esophageal bicommissural and LV long-axis planes (**Figures 3A**
233   and **3B**, respectively). Measurement of VFT was associated with intra- and interobserver
234   variability of 5% and 7%, respectively, similar to other indices of dimension and blood flow
235   measured using TEE (data not shown). Using this technique, we first showed that exposure to
236   CPB reduced VFT (5.3 ± 1.8 before *vs.* 4.0 ± 1.5 15 minutes after bypass, $p < 0.05$; **Figure 4**) in
237   patients undergoing coronary artery surgery. VFT recovered to baseline values within 60 minutes
238   after CPB. An increase in β (0.33 ± 0.04 before *vs.* 0.41 ± 0.07 15 minutes after CPB, $p < 0.05$)
239   consistent with greater atrial contribution to LV filling was primarily responsible for the decline
240   in VFT because SV and mitral valve diameter remained unchanged.
241
242   We also showed that a decrease in VFT occurs in patients with severe aortic valve stenosis and
243   LV pressure-overload hypertrophy compared with those with normal LV wall thickness (3.0 ± 0.6
244   *vs.* 4.3 ± 0.5, respectively; $p < 0.05$; **Figure 5**). Early LV filling was attenuated (*e.g.*, E/A, 0.77 ± 0.11
245   compared with 1.23 ± 0.13; β, 0.43 ± 0.09 compared with 0.35 ± 0.02; $p < 0.05$ for each), and SV
246   was reduced (72 ± 12 mL compared with 95 ± 10 mL; $p < 0.05$) in patients with *vs.* without LV
247   hypertrophy; however, mitral valve diameter was similar between groups. A significant inverse
248   correlation between VFT and posterior wall thickness (PWT) was shown with linear regression
249   analysis (VFT = -2.57 × PWT + 6.81; r = 0.408; $p = 0.017$). In addition, our results using this
250   technique demonstrated that the presence compared to absence of moderate aortic
251   insufficiency in patients with severe aortic valve stenosis increased VFT (5.7 ± 1.7 *vs.* 3.0 ± 0.6,
252   respectively; $p < 0.05$; **Figure 5**) concomitant with a decrease in mitral valve diameter (2.2 ± 0.2
253   *vs.* 2.6 ± 0.1 cm, respectively; $p < 0.05$), whereas indices of LV diastolic dysfunction and SV were
254   similar between groups. Finally, we were able to use our technique of measuring VFT to show
255   that VFT was lower in octogenarians compared with younger patients (3.0 ± 0.9 *vs.* 4.5 ± 1.2; p <
256   0.05) concomitant with an impaired relaxation pattern of LV diastolic dysfunction (*e.g.*, E/A of
257   0.81 ± 0.16 *vs.* 1.29 ± 0.19; β of 0.44 ± 0.05 *vs.* 0.35 ± 0.03, $p < 0.05$ for each). A significant inverse
258   correlation between VFT and age was also demonstrated (VFT = -0.0627 × age + 8.24; r = 0.639;
259    $p = 0.0139$; **Figure 6**).

260
261 **FIGURE LEGENDS:**
262 **Figure 1**: **Trans-mitral blood flow velocity waveforms.** Trans-mitral blood flow velocity
263 waveforms during early LV filling (E) and atrial systole (A) obtained in the mid-esophageal four-
264 chamber TEE view (left side of image); the area of each envelope was integrated using the
265 equipment's software to obtain velocity-time integrals (right side of image) and the atrial filling
266 fraction (β) was calculated. In this example, β = 4.28 cm/(4.28 cm + 6.73 cm) = 0.39 (see text).
267
268 **Figure 2: Measurement of LV outflow track diameter.** Measurement of LV outflow track
269 diameter during mid-systole in the aortic valve long axis TEE view (**A**) (diameter = 2.23 cm); (**B**)
270 blood flow velocity was measured in the in the distal LV outflow track using the deep transgastric
271 long axis TEE view and the area of the resulting envelope (left side of panel B) integrated using
272 the equipment's software to obtain a velocity-time integral (white arrow, right side of panel B).
273 In this example, stroke volume = $\pi/4 \times (2.23 \text{ cm})^2 \times 19.8 \text{ cm} = 77 \text{ mL}$ (see text).
274
275 **Figure 3: Average mitral valve diameter was calculated as the average of major and minor axis**
276 **diameters measured in the mid-esophageal bicommissural and LV long-axis planes.** Mid-
277 esophageal bicommissural (**A**) and LV outflow tract (**B**) TEE images were used to determine major
278 (transcommissural anterior-lateral-posterior-medial) and minor (anterior-posterior) axis
279 diameters, respectively. In this example, mitral valve diameter = (3.04 cm + 2.18 cm)/2 = 2.61 cm.
280 This figure is reproduced with permission from Elsevier[38].
281
282 **Figure 4: Temporal changes in VFT.** Temporal changes in VFT before and 15, 30, and 60 minutes
283 after cardiopulmonary bypass (CPB) in patients undergoing coronary artery surgery; *indicates
284 significant (p < 0.05) difference from the "before CPB" measurement.
285
286 **Figure 5: Effects of LV pressure-overload hypertrophy resulting from severe aortic valve**
287 **stenosis in the absence (-) or presence (+) of moderate aortic insufficiency (AI) in patients**
288 **undergoing aortic valve replacement**. Patients with normal LV wall thickness undergoing
289 coronary artery surgery served as controls (normal). *Significantly (p < 0.05) different from
290 normal; †Significantly (p < 0.05) different from both normal and hypertrophy-AI.
291
292 **Figure 6: Correlation between age and VFT in 14 patients undergoing coronary artery surgery**.
293 VFT = -0.0627 × age + 8.24; r = 0.639; p = 0.0139.
294
295 **DISCUSSION:**
296 The current results illustrate that VFT can be reliably measured during cardiac surgery using the
297 TEE techniques described here. Previous descriptions of VFT used transthoracic
298 echocardiography in conscious subjects, but this approach cannot be utilized when the chest is
299 open. We used intraoperative TEE to determine VFT in the anesthetized patients undergoing
300 cardiac surgery during which changes in LV filling dynamics are often encountered as a result of
301 ischemia-reperfusion injury or surgical interventions. Our findings indicate that VFT
302 measurements reflect changes in LV filling efficiency produced by transient CPB-induced
303 impaired relaxation pattern diastolic dysfunction, aortic valve disease, and aging. The current

304 technique for calculating VFT during cardiac surgery requires high-quality TEE images and video
305 clips during steady-state hemodynamic conditions to assure precise measurements of mitral
306 valve and LV outflow tract dimension and blood flow (**Figures 1, 2,** and **3**). Not all patients will
307 have optimal imaging windows because of off-axis rotation of the heart or pathological changes
308 in cardiac geometry. Despite these potential limitations, experienced intraoperative
309 echocardiographers should be able to easily obtain the necessary mid-esophageal four-chamber,
310 mid-esophageal bicommissural, mid-esophageal LV long axis, and deep transgastric long axis
311 views during the comprehensive TEE examination[42]. The technique may also be unreliable when
312 rapidly changing hemodynamic conditions are present. It does not provide direct visualization of
313 blood flow movement within the LV associated with the vortex, as previously characterized using
314 Doppler vector flow mapping[6,20,21] or particle imaging velocimetry[9,22-24]. Accurate measurement
315 of LV outflow track diameter using two-dimensional echocardiography is especially important
316 because this variable is squared in the calculation of area and errors are magnified as a result.
317 Similarly, accurate measurements of mitral valve minor and major axis length are essential
318 because the cube of the average of these two dimensions appears in the denominator of the VFT
319 formula. Two-dimensional echocardiography consistently underestimates aortic and mitral valve
320 areas compared with three-dimensional reconstruction techniques[43, 44]. The impact of these
321 differences between two- and three-dimensional TEE on VFT is an area of current research by
322 our group.
323
324 Additionally, isoflurane was used for maintenance of anesthesia in our studies. This volatile
325 anesthetic is a vasodilating negative inotrope that reduces LV preload and afterload, decreases
326 myocardial contractility, and affects LV diastolic function in a dose-related manner[45,46]. These
327 cardiovascular changes may have influenced atrial filling fraction and stroke volume in our
328 studies. Nevertheless, the values of VFT obtained in anesthetized patients with normal
329 preoperative LV ejection fraction undergoing coronary artery surgery before CPB were similar to
330 those described in healthy conscious subjects[8]. These data suggest that baseline anesthesia does
331 not substantially alter LV filling efficiency, but we are currently examining this hypothesis. VFT
332 has been previously shown to be an independent predictor of mortality in patients with
333 congestive heart failure[30], but it is unknown whether intraoperative changes in VFT are predictive
334 of perioperative morbidity or mortality in cardiac surgery patients. This topic is also an area of
335 interest that we are actively pursuing.
336
337 We first used this technique of noninvasively calculating VFT in a study examining the impact of
338 CPB on VFT in isoflurane-fentanyl-anesthetized patients with normal preoperative LV ejection
339 fraction undergoing coronary artery surgery[39]. LV diastolic dysfunction occurs after
340 cardiopulmonary bypass as a result of global ischemia-reperfusion injury and a profound systemic
341 inflammatory response[47-49]. This diastolic dysfunction eventually recovers within minutes to
342 hours based on the efficacy of myocardial protection during and the duration of CPB[50]. Indeed,
343 our findings confirmed that LV diastolic dysfunction occurs after CPB. This effect was
344 accompanied by transient reductions in VFT that recovered within one hour after separation from
345 CPB. The declines in VFT resulted from an increase in β and a modest decrease in SV because
346 mitral valve diameter was unchanged. The recoveries of VFT, β, E/A, and SV after CPB were
347 similar. Notably, VFT observed here did not fall below the normal range of VFT (3.3 to 5.5) in

348 healthy individuals. Our patients had normal preoperative LV systolic and diastolic function, were
349 exposed to relatively short CPB times (93 ± 27 min), and were treated with regular doses of
350 antegrade and retrograde cardioplegia. These factors probably combined to reduce ischemia-
351 reperfusion injury during aortic cross-clamp application[39]. CPB has also been shown to cause
352 transient declines in trans-mitral blood flow propagation velocity (V_p) consistent with attenuated
353 early LV filling in patients undergoing coronary artery surgery[49] as a result of decreases in LV
354 compliance[51] and reductions in early diastolic intraventricular pressure gradients[52]. A
355 relationship between vortex ring formation and V_p was previously demonstrated[53], and our
356 findings supported those of other investigators[49] in similar patient populations.
357
358 We subsequently examined the effects of pressure-overload LV hypertrophy produced by severe
359 calcific degenerative aortic valve stenosis in patients with preserved LV systolic function
360 undergoing aortic valve replacement[40]. A second group of patients with normal LV wall thickness
361 undergoing coronary artery surgery served as controls. Chronically elevated LV end-systolic wall
362 stress causes LV pressure-overload hypertrophy as a compensatory response in the presence of
363 aortic valve stenosis[54]. LV wall thickening without dilatation occurs as a consequence of an
364 increase in the diameter of individual myocytes. This LV remodeling is associated with interstitial
365 fibrosis[55,56]. Delays in apical recoil[57,58] also occur that further attenuate early LV filling[58,59], which
366 causes LV diastolic dysfunction by delaying LV relaxation and reducing LV compliance[55,60]. Thus,
367 VFT is reduced in the presence of delayed relaxation in patients with LV pressure-overload
368 hypertrophy *vs.* those with normal LV wall thickness. Our findings were attributed to an increase
369 in β and decline in SV at similar filling pressures consistent with a decrease in LV compliance. A
370 significant correlation between decreases in VFT and the severity of hypertrophy was shown
371 using linear regression analysis. This observation suggests that the degree of pressure-overload
372 hypertrophy is inversely related to LV filling efficiency quantified using vortex formation time.
373
374 Valvular insufficiency often occurs in conjunction with severe calcific degenerative aortic valve
375 stenosis because prominent leaflet calcification prevents complete coaptation. We conducted
376 another investigation to ascertain whether regurgitant blood flow into the LV through an
377 incompetent aortic valve affects LV filling efficiency by interfering with trans-mitral blood flow[38].
378 We compared patients with severe aortic valve stenosis undergoing valve replacement who had
379 moderate centrally-directed aortic insufficiency with a second group of patients who did not have
380 regurgitation. We quantified aortic insufficiency using the regurgitant jet width LV outflow track
381 diameter ratio measure with color Doppler M-mode echocardiography[61]. Our results showed
382 that moderate aortic insufficiency increases VFT in patients with aortic valve stenosis. However,
383 this increase in VFT does not suggest an improvement in LV filling efficiency has occurred because
384 of abnormal regurgitant flow into the LV through the aortic valve. LV diastolic pressure rapidly
385 increases in moderate to severe aortic insufficiency[62], attenuating trans-mitral LV filling and
386 reducing mitral valve area[63-65]. The results indicate that mitral valve diameter and area were
387 reduced in patients with moderate aortic insufficiency *versus* those without regurgitation. These
388 observations were most likely due to a decrease in minor axis length, resulting from attenuated
389 anterior mitral leaflet opening caused by aortic regurgitant during LV filling, thereby, falsely
390 elevated VFT. Indeed, VFT reported in our study (5.7 ± 1.7) was greater than the upper limit of
391 normal VFT (5.5) in healthy conscious individuals[8] and patients with normal LV geometry during

392 anesthesia (4.3 ± 0.5)[40]. Therefore, it is highly likely that abnormal diastolic flow into the LV
393 invalidates VFT as an index of LV filling efficiency.
394
395 We recently studied the influence of advanced age on VTF in elderly patients undergoing
396 coronary artery surgery[41]. Progressive LV diastolic stiffening[66], decreased intraventricular
397 diastolic kinetic energy[67], and attenuated diastolic suction[68] cause LV diastolic function in the
398 elderly[69-72]. Octogenarians with normal preoperative LV ejection were compared with a younger
399 cohort of patients (≤ 62 years of age). We found that VFT was lower in octogenarians compared
400 with younger patients. These observations were expected and occurred in conjunction with an
401 impaired relaxation pattern of LV diastolic dysfunction and a modest reduction in SV at similar LV
402 filling pressures. Mitral valve diameter was similar in octogenarians *versus* younger patients and
403 did not contribute to the differences in VFT between groups. It is noteworthy that VFT was similar
404 in octogenarians compared with patients with severe aortic valve stenosis that we previously
405 reported[38,40]. Indeed, aortic stenosis is another condition characterized by impaired relaxation
406 LV diastolic dysfunction and reductions in LV compliance. A significant inverse correlation
407 between VFT and age was also demonstrated despite the small sample size (n = 7 per group;
408 **Figure 6**). The decline in VFT that occurs with age that may eventually become indistinguishable
409 from heart failure produced by pathological processes such as restrictive diastolic dysfunction[19]
410 or dilated cardiomyopathy[8]. Our results were consistent with reductions in early peak diastolic
411 intraventricular kinetic energy in elderly subjects with depressed LV function[67].
412
413 In summary, noninvasive measurement of VFT using standard two-dimensional and Doppler TEE
414 is straightforward in anesthetized patients undergoing cardiac surgery. This technique may allow
415 cardiac anesthesiologists and surgeons to assess the impact of pathological conditions and
416 surgical interventions on LV filling efficiency in real time.
417

425

426 **References**
427 1. Collier, E., Hertzberg, J., Shandas, R. Regression analysis for vortex ring characteristics during
428 left ventricular filling. *Biomedical Sciences Instrumentation*. **38** (2), 307-311 (2002).
429 2. Kheradvar, A., Gharib, M. Influence of ventricular pressure drop on mitral annulus dynamics
430 through the process of vortex ring formation. *Annals of Biomedical Engineering*. **35** (12), 2050-
431 2064 (2007).
432 3. Gharib, M., Rambod, E., Shariff, K. A universal time scale for vortex ring formation. *Journal of
433 Fluid Mechanics*. **360** (1), 121-140 (1998).
434 4. Krueger, P. S., Gharib, M. The significance of vortex ring formation to the impulse and thrust
435 of a starting jet. *Physics of Fluids*. **15** (5), 1271-1281 (2003).

436 5. Reul, H., Talukder, N., Muller, W. Fluid mechanics of the natural mitral valve. *Journal of*
437 *Biomechanics*. **14** (5), 361-372 (1981).

438 6. Kim, W. Y., et al. Two-dimensional mitral flow velocity profiles in pig models using epicardial
439 Doppler echocardiography. *Journal of the American College of Cardiology*. **24** (2), 532-545 (1994).

440 7. Kilner, P. J., et al. Asymmetic redirection of flow through the heart. *Nature*. **404** (6779), 759-
441 761 (2000).

442 8. Gharib, M., Rambod, E., Kheradvar, A., Sahn, D. J., Dabiri, J. O. Optimal vortex formation as an
443 index of cardiac health. *Proceedings of the National Academy of Sciences USA.* **103** (16), 6305-
444 6308 (2006).

445 9. Rodriguez Munoz, D., et al. Intracardiac flow visualization: current status and future directions.
446 *European Heart Journal Cardiovascular Imaging*. **14** (11), 1029-1038 (2013).

447 10. Martinez-Legazpi, P., et al. Contribution of the diastolic vortex ring to left ventricular filling.
448 *Journal of the American College of Cardiology.* **64** (16), 1711-1721 (2014).

449 11. Dabiri, J. O., Gharib, M. The role of optimal vortex formation in biological fluid transport.
450 *Proceedings of the Royal Society B.* **272** (1572), 1557-1560 (2003).

451 12. Kheradvar, A., Gharib, M. On mitral valve dynamics and its connection to early diastolic flow.
452 *Annals of Biomedical Engineering.* **37** (1), 1-13 (2009).

453 13. Linden, P. F., Turner, J. S. The formation of "optimal" vortex rings, and the efficiency of
454 propulsion devices. *Journal of Fluid Mechanics.* **427** (1), 61-72 (2001).

455 14. Domenichini, F., Pedrizzetti, G., Baccani, B. Three-dimensional filling flow into a model left
456 ventricle. *Journal of Fluid Mechanics.* **539** (1), 179-198 (2005).

457 15. Sengupta, P. P., et al. Left ventricular isovolumic flow sequence during sinus and paced
458 rhythms: new insights from use of high-resolution Doppler and ultrasonic digital particle imaging
459 velocimetry. *Journal of the American College of Cardiology.* **49** (8), 899-908 (2007).

460 16. Rodriguez Munoz, D., et al. Flow mapping inside a left ventricular aneurysm: a potential tool
461 to demonstrate thrombogenicity. *Echocardiography.* **31** (1), E10-E12 (2014).

462 17. Son, J. W., et al. Abnormal left ventricular vortex flow patterns in association with left
463 ventricular apical thrombus formation in patients with anterior myocardial infarction: a
464 quantitative analysis by contrast echocardiography. *Circulation Journal.* **76** (11), 2640-2646
465 (2012).

466 18. Kheradvar, A., Falahatpisheh, A. The effects of dynamic saddle annulus and leaflet length on
467 trans-mitral flow pattern and leaflet stress of a bileaflet bioprosthetic mitral valve. *The Journal of*
468 *Heart Valve Disease.* **21** (2), 225-233 (2012).

469 19. Kheradvar, A., Assadi, R., Falahatpisheh, A., Sengupta, P. P. Assessment of trans-mitral vortex
470 formation in patients with diastolic dysfunction. *Journal of the American Society of*
471 *Echocardiography.* **25** (2), 220-227 (2012).

472 20. Chen, R., et al. Assessment of left ventricular hemodynamics and function of patients with
473 uremia by vortex formation using vector flow mapping. *Echocardiography.* **29** (9), 1081-1090
474 (2012).

475 21. Hendabadi, S., et al. Topology of blood transport in the human left ventricle by novel
476 processing of Doppler echocardiography. *Annals of Biomedical Engineering.* **41** (12), 2603-2616
477 (2013).

478   22. Sengupta, P. P., Pedrizetti, G., Narula, J. Multiplaner visualization of blood flow using
479   echocardiographic particle imaging velocimetry. *Journal of the American College of Cardiology*
480   *Cardiovascular Imaging*. **5** (5), 566-569 (2012).
481   23. Sengupta, P. P., et al. Emerging trends in CV flow visualization. *Journal of the American College*
482   *of Cardiology Cardiovascular Imaging*. **5** (3), 305-316 (2012).
483   24. Hong, G. R., Kim, M., Pedrizzetti, G., Vannan, M. A. Current clinical application of intracardiac
484   flow analysis using echocardiography. *Journal of Cardiovascular Ultrasound.* **21** (4), 155-162
485   (2013).
486   25. Kheradvar, A., Milano, M., Gharib, M. Correlation between vortex ring formation and mitral
487   annulus dynamics during ventricular rapid filling. *American Society for Artificial Internal Organs*
488   *Journal.* **53** (1), 8-16 (2007).
489   26. Hong, G. R., et al. Characterization and quantification of vortex flow in the human left
490   ventricle by contrast echocardiography using vector particle image velocimetry. *Journal of the*
491   *American College of Cardiology Cardiovascular Imaging.* **1** (6), 705-717 (2008).
492   27. Zhang, H., et al. The evolution of intraventricular vortex during ejection studied by using
493   vector flow mapping. *Echocardiography.* **30** (1), 27-36 (2013).
494   28. Nogami, Y., et al. Abnormal early diastolic intraventricular flow 'kinetic energy index' assessed
495   by vector flow mapping in patients with elevated filling pressure. *European Heart Journal*
496   *Cardiovascular Imaging.* **14** (3), 253-260 (2013).
497   29. Zhang, H., et al. The left ventricular intracavity vortex during the isovolumic contraction
498   period as detected by vector flow mapping. *Echocardiography.* **29** (5), 579-587 (2012).
499   30. Poh, K. K., et al. Left ventricular filling dynamics in heart failure: echocardiographic
500   measurement and utilities of vortex formation time. *European Heart Journal Cardiovascular*
501   *Imaging*. **13** (5), 385-393 (2012).
502   31. Belohlavek, M. Vortex formation time: an emerging echocardiographic index of left
503   ventricular filling efficiency? *European Heart Journal Cardiovascular Imaging.* **13** (5), 367-369
504   (2012).
505   32. Dabiri, J. O., Gharib, M. Starting flow through nozzles with temporally variable exit diameter.
506   *Journal of Fluid Mechanics.* **538** (1), 111-136 (2005).
507   33. Jiamsripong, P., et al. Impact of acute moderate elevation in left ventricular afterload on
508   diastolic trans-mitral flow efficiency: analysis by vortex formation time. *Journal of the American*
509   *Society of Echocardiography*. **22** (4), 427-431 (2009).
510   34. Belohlavek, M., et al. Patients with Alzheimer disease have altered trans-mitral flow:
511   echocardiographic analysis of the vortex formation time. *Journal of Ultrasound in Medicine.* **28**
512   (11), 1493-1500 (2009).
513   35. Pedrizzetti, G., Domenichini, F., Tonti, G. On the left ventricular vortex reversal after mitral
514   valve replacement. *Annals of Biomedical Engineering*. **38** (3), 769-773 (2010).
515   36. Martinez-Legazpi, P., et al. Stasis mapping using ultrasound: a prospective study in acute
516   myocardial infarction. *Journal of the American College of Cardiology Cardiovascular Imaging*. **11**
517   (3), 514-515 (2018).
518   37. Harfi, T. T., et al. The E-wave propagation index (EPI): a novel echocardiographic parameter
519   for prediction of left ventricular thrombus. Derivation from computational fluid dynamic
520   modeling and validation on human subjects. *International Journal of Cardiology.* **227** (1), 662-667
521   (2017).

522 38. Pagel, P. S., Boettcher, B. T., De Vry, D. J., Freed, J. K., Iqbal, Z. Moderate aortic valvular
523 insufficiency invalidates vortex formation time as an index of left ventricular filling efficiency in
524 patients with severe degenerative calcific aortic stenosis undergoing aortic valve replacement.
525 *Journal of Cardiothoracic and Vascular Anesthesia.* **30** (5), 1260-1265 (2016).
526 39. Pagel, P. S., Gandhi, S. D., Iqbal, Z., Hudetz, J. A. Cardiopulmonary bypass transiently inhibits
527 intraventricular vortex ring formation in patients undergoing coronary artery bypass graft
528 surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* **26** (3), 376-380 (2012).
529 40. Pagel, P. S., Hudetz, J. A. Chronic pressure-overload hypertrophy attenuates vortex formation
530 time in patients with severe aortic stenosis and preserved left ventricular systolic function
531 undergoing aortic valve replacement. *Journal of Cardiothoracic and Vascular Anesthesia.* **27** (4),
532 660-664 (2013).
533 41. Pagel, P. S., Dye III, L., Boettcher, B. T., Freed, J. K. Advanced age attenuates left ventricular
534 filling efficiency quantified using vortex formation time: a study of octogenarians with normal left
535 ventricular systolic function undergoing coronary artery surgery. *Journal of Cardiothoracic and
536 Vascular Anesthesia*. **32** (4), 1775-1779 (2018).
537 42. Shanewise, J. S., et al. ASE/SCA guidelines for performing a comprehensive intraoperative
538 multiplane transesophageal echocardiography examination: recommendations of the American
539 Society of Echocardiography Council for Intraoperative Echocardiography and the Society of
540 Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal
541 Echocardiography. *Journal of the American Society of Echocardiography.* **12** (10), 884-900 (1999).
542 43. Gaspar, T., et al. Three-dimensional imaging of the left ventricular outflow tract: impact on
543 aortic valve area estimation by the continuity equation. *Journal of the American Society of
544 Echocardiography.* **25** (7), 749-757 (2012).
545 44. Karamnov, S., Burbano-Vera, N., Huang, C. C., Fox, J. A., Shernan, S. A. Echocardiographic
546 assessment of mitral stenosis orifice area: a comparison of a novel three-dimensional method
547 *versus* conventional techniques. *Anesthesia and Analgesia.* **125** (3), 774-780 (2017).
548 45. Pagel, P. S., Kampine, J. P., Schmeling, W. T., Warltier, D. C. Comparison of end-systolic
549 pressure-length relations and preload recruitable stroke work as indices of myocardial
550 contractility in the conscious and anesthetized, chronically instrumented dog. *Anesthesiology.* **73**
551 (2), 278-290 (1990).
552 46. Pagel, P. S., Kampine, J. P., Schmeling, W. T., Warltier, D. C. Alteration of left ventricular
553 diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog
554 with autonomic nervous system blockade. *Anesthesiology.* **74** (6), 1103-1114 (1991).
555 47. De Hert, S. G., Rodrigus, I. E., Haenen, L. R., De Mulder, P. A., Gillebert, T. C. Recovery of
556 systolic and diastolic left ventricular function early after cardiopulmonary bypass.
557 *Anesthesiology.* **85** (5), 1063-1075 (1996).
558 48. Gorcsan III, J., Diana, P., Lee, J., Katz, W. E., Hattler, B. G. Reversible diastolic dysfunction after
559 successful coronary artery bypass surgery. Assessment by transesophageal Doppler
560 echocardiography. *Chest*. **106** (5), 1364-1369 (1994).
561 49. Djaiani, G. N., et al. Mitral flow propagation velocity identifies patients with abnormal
562 diastolic function during coronary artery bypass graft surgery. *Anesthesia and Analgesia.* **95** (3),
563 524-530 (2002).

564 50. Casthely, P. A., et al. Left ventricular diastolic function after coronary artery bypass grafting:
565 a correlative study with three different myocardial protection techniques. *Journal of Thoracic and*
566 *Cardiovascular Surgery.* **114** (2), 254-260 (1997).
567 51. Tulner, S. A., et al. Perioperative assessment of left ventricular function by pressure-volume
568 loops using the conductance catheter method. *Anesthesia and Analgesia*. **97** (4), 950-957 (2003).
569 52. Firstenberg, M. S., et al. Relationship between early diastolic intraventricular pressure
570 gradients, an index of elastic recoil, and improvements in systolic and diastolic function.
571 *Circulation.* **104** (12 Suppl 1), I330-I335 (2001).
572 53. Cooke, J., Hertzberg, J., Boardman, M., Shandas, R. Characterizing vortex ring behavior during
573 ventricular filling with Doppler echocardiography: an *in vitro* study. *Annals of Biomedical*
574 *Engineering.* **32** (2), 245-256 (2004).
575 54. Grossman, W., Jones, D., McLaurin, L. P. Wall stress and patterns of hypertrophy in the human
576 left ventricle. *Journal of Clinical Investigation.* **56** (1), 56-64 (1975).
577 55. Hess, O. M., et al. Diastolic function and myocardial structure in patients with myocardial
578 hypertrophy. Special reference to normalized viscoelastic data. *Circulation.* **63** (2), 360-371
579 (1981).
580 56. Hess, O. M., et al. Diastolic stiffness and myocardial structure in aortic valve disease before
581 and after valve replacement. *Circulation*. **69** (5), 855-865 (1984).
582 57. Sandstede, J. J. W., et al. Cardiac systolic rotation and contraction before and after valve
583 replacement for aortic stenosis: a myocardial tagging study using MR imaging. *American Journal*
584 *of Roentgenology.* **178** (4), 953-958 (2002).
585 58. Stuber, M., et al. Alterations in the local myocardial motion pattern in patients suffering from
586 pressure overload due to aortic stenosis. *Circulation.* **100** (4), 361-368 (1999).
587 59. Nagel, E., et al. Cardiac rotation and relaxation in patients with aortic valve stenosis. *European*
588 *Heart Journal.* **21** (7), 582-589 (2000).
589 60. Rakowski, H., et al. Canadian consensus recommendations for the measurement and
590 reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on
591 Diastolic Dysfunction by Echocardiography. *Journal of the American Society of Echocardiography*.
592 **9** (5), 736-760 (1996).
593 61. von Homeyer, P., Oxorn, D. C. Aortic regurgitation: echocardiographic diagnosis*. Anesthesia*
594 *and Analgesia.* **122** (1), 37-42 (2016).
595 62. Landzberg, J. S., et al. Etiology of the Austin Flint murmur. *Journal of the American College of*
596 *Cardiology.* **20** (2), 408-413 (1992).
597 63. Flint, A. On cardiac murmurs. *American Journal of Medical Sciences.* **91** (1), 27 (1886).
598 64. Botvinick, E. H., Schiller, N. B., Wickramasekaran, R., Klausner, S. C., Gertz, E.
599 Echocardiographic demonstration of early mitral valve closure in severe aortic insufficiency. Its
600 clinical implications. *Circulation.* **51** (5), 836-847 (1975).
601 65. Mann, T., McLaurin, L., Grossman, W., Craige, E. Assessing the hemodynamic severity of acute
602 aortic regurgitation due to infective endocarditis. *New England Journal of Medicine*. **293** (3), 108-
603 113 (1975).
604 66. Borlaug, B. A., et al. Longitudinal changes in left ventricular stiffness: a community-based
605 study. *Circulation Heart Failure.* **6** (5), 944-952 (2013).

606 67. Wong, J., et al. Age-related changes in intraventricular kinetic energy: a physiological or
607 pathological adaptation? *American Journal of Physiology Heart Circulatory Physiology.* **310** (6),
608 H747-H755 (2016).
609 68. Carrick-Ranson, G., et al. Effect of healthy aging on left ventricular relaxation and diastolic
610 suction. *American Journal of Physiology Heart Circulatory Physiology.* **303** (3), H315-H322 (2012).
611 69. Iskandrian, A. S., Hakki, A. H. Age-related changes in left ventricular diastolic performance.
612 *American Heart Journal.* **112** (1), 75-78 (1986).
613 70. Schulman, S. P., et al. Age-related decline in left ventricular filling at rest and exercise.
614 *American Journal of Physiology.* **263** (6 Pt 2), H1932-H1938 (1992).
615 71. Stork, M., et al. Age-related hemodynamic changes during diastole: a combined M-mode and
616 Doppler echo study. *Internal Journal of Cardiovascular Imaging.* **6** (1), 23-30 (1991).
617 72. Sanders, D., Dudley, M., Groban, L. Diastolic dysfunction, cardiovascular aging, and the
618 anesthesiologist. *Anesthesiology Clinics.* **27** (3), 497-517 (2009).
619
620