ISSN 1936-8798/10/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.12.014

Stunning and Cumulative Left Ventricular Dysfunction Occurs Late After Coronary Balloon Occlusion in Humans

Insights From Simultaneous Coronary and Left Ventricular Hemodynamic Assessment

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Objectives We aimed to investigate whether left ventricular (LV) stunning could be detected late after coronary occlusion when coronary flow has normalized.

Background Stunning and cumulative LV dysfunction after ischemia reperfusion has been clearly demonstrated in animal models but has been refuted in several angioplasty models in humans. However, these studies have assessed LV function early, during the reactive hyperemic phase, which might have augmented LV function.

Methods We recruited 20 male subjects with single-vessel, type A coronary disease, and normal ventricular function. We simultaneously measured LV function with a conductance catheter and coronary flow velocity with a Combowire (Volcano Therapeutics, Inc., Rancho Cordova, California) at baseline (BL), for 30 s after a low-pressure coronary balloon occlusion for 1 min and again after 30 min, before a second balloon occlusion.

Results Stunning was detected at 30 min after a 1-min balloon occlusion: stroke volume (ml) BL1: 88.4 (22.8) versus BL2: 79.4 (24.0), $p = 0.04$; τ (ms) BL1: 49.8 (9.0) versus BL2: 52.5 (8.9), $p = 0.02$, despite full recovery of coronary average peak velocity ($p = 0.62$). A second balloon occlusion caused cumulative LV dysfunction: stroke volume (ml) BO1: 77.3 (34.6) versus BO2 64.9 (22.9), $p = 0.01$. Reactive hyperemia significantly augmented early recovery systolic function: dP/dt max 30 s: +5.8% versus 30 min − 5.4%, $p = 0.0009$.

Conclusions Coronary occlusion for 1-min results in late stunning and cumulative LV dysfunction after 30 min. Reactive hyperemia augments stunned LV systolic function in early recovery. (J Am Coll Cardiol Intv 2010;3:412–8) © 2010 by the American College of Cardiology Foundation

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Manuscript received October 1, 2009; revised manuscript received December 15, 2009, accepted December 23, 2009.

Myocardial stunning is post-ischemic myocardial dysfunction in the absence of infarction, despite restoration of normal flow, and is completely reversible (1,2). Stunning has been described in animal models of supply ischemia–reperfusion and is proportional to the degree and duration of ischemic insult (3,4). Repeat episodes of ischemia–reperfusion have also been shown to lead to more prolonged and severe left ventricular (LV) dysfunction that remains reversible—a phenomenon termed cumulative stunning (5). Similarly, cumulative stunning has been described during repeat episodes of demand ischemia in animals and humans (6–9). However, stunning caused by supply ischemia in humans has not been clearly demonstrated, and cumulative stunning and LV dysfunction are thought not to occur after serial 1-min coronary balloon occlusions (10–12). However, assessment of LV function in these studies was made early in recovery during the reactive hyperemic phase of reperfusion. It is possible that a hyperemia-induced inotropic effect might have confounded the detection of stunning.

We hypothesized that late assessment of LV function at 30 min after balloon occlusion, when coronary flow is normal, would detect stunning and that repeating a 1-min coronary occlusion in late recovery would induce cumulative LV dysfunction. We simultaneously assessed coronary and LV hemodynamic status with a pressure-flow velocity guidewire and intracavity conductance catheter, respectively, to assess late stunning in humans during elective coronary angioplasty.

Methods

Subjects and study design. Twenty consecutive male patients (mean age 58 years [range 38 to 80]; with left anterior descending [n = 17], left circumflex [n = 2], and right coronary artery [n = 1] coronary disease) awaiting elective percutaneous coronary intervention (PCI) to a single vessel with a proximal American College of Cardiology/American Heart Association type-A stenosis and normal LV function assessed by angiography were recruited. Patients underwent simultaneous conductance catheter assessment of LV function and Combowire (Volcano Therapeutics, Inc., Rancho Cordova, California) assessment of coronary flow velocity during a 1-min low-pressure (<4 atms) coronary occlusion with a compliant balloon. These measurements were repeated after a 30-min interval, during a second 1-min balloon occlusion. Left ventricular pressure-volume loops and intracoronary instantaneous peak velocity were recorded at baseline, during the 1-min low-pressure coronary occlusion, and at 10-s intervals after coronary balloon deflation.

Patients were excluded if they had diabetes mellitus, suffered a myocardial infarction in the preceding 3 months, and were not in sinus rhythm. All patients gave written informed consent before study inclusion. The study was approved by the Local Research Ethics Committee (LREC 06/Q0106/52) and conformed to the Declaration of Helsinki. The trial number was ISRCTN42864201.

Pre-study protocol. Variables that could alter coronary physiology were minimized. Patients were asked to abstain from caffeine, alcohol, nicotine, and oral/sublingual nitrates and nicorandil for a 24-h period before their procedure. All subjects fasted for 6 h and received aspirin 300 mg, clopidogrel 300 mg, and diazepam 5 mg at least 6 h before PCI. The catheter laboratory was maintained at a constant ambient temperature (21°C ± 0.5°C), and noise was kept to a minimum.

Study protocol. CARDIAC CATHETERIZATION. Bilateral femoral arterial (7-F and 8-F) and venous (6-F) sheaths were inserted. A PCI was performed with 6-F or 7-F guiding catheters. All patients were anti-coagulated with a heparin bolus (70 to 100 U/kg) after arterial sheath insertion to achieve an activated coagulation time >250 s. No hemodynamic altering medication was administered during the procedure.

Angiographic stenosis severity was assessed before each low-pressure balloon occlusion by quantitative coronary angiography (Cardiac Viewer CV-1000, version 2.1.0, Liverpool, New York).

LV HEMODYNAMIC CALIBRATION. The conductance catheter technique has previously been described in detail by Baan et al. (13) to determine LV pressure-volume relations. A 7-F, 8-electrode conductance catheter with an integrated micromanometer tip (Millar Instruments, Houston, Texas) was advanced via a femoral sheath into the LV apex. It was placed along the longitudinal axis of the ventricle to minimize motion during the cardiac cycle.

Abbreviations and Acronyms

APV = average peak velocity
BL1 = measurements at baseline 1
BO1 = measurements at balloon occlusion 1
BL2 = measurements after 30 min at baseline 2
BO2 = measurements at balloon occlusion 2
LV = left ventricular
PCI = percutaneous coronary intervention

The catheter was connected to a signal conditioning and processing unit (CD Leycom, Zoetermeer, the Netherlands), and signals were acquired with custom software at 250 Hz. A 20-kHz, 30-pA current was applied to the distal and proximal electrodes, and the remaining 6 electrodes were used to measure a time-varying ventricular conductance, G(t), as the sum of the intervening 5 segments. The relationship between the time-varying volume, V(t), and the time-varying conductance, G(t), is given by the formula: $V(t) = 1/\alpha \times L^2 \times r[G(t) - G(p)]$; α is the ratio of the conductance-derived volume to true ventricular volume, L is the inter-electrode distance, r is the resistivity of blood in Ω/cm, and G(p) is the parallel conductance due to the conductance of structures outside the ventricular blood pool. Volume correction for G(p) was calculated from the formula: $Vc = 1/\alpha \times L^2 \times r(Gp)$ estimated by the hypertonic saline injection technique described by Baan et al (13). The slope coefficient, α, calculated

to correct for inhomogeneity of the electric field, was determined by an average Fick cardiac output, measured 3 times.

LV HEMODYNAMIC MEASUREMENTS. Conductance catheter data were analyzed offline with PVAN software (Millar Instruments). Five cardiac cycles at baseline, after 1-min balloon occlusion (just before balloon deflation) and at 10-s intervals in recovery were recorded (Fig. 1). Mean index of diastolic function (maximum rate of pressure decline: LV dP/dt_{min} and

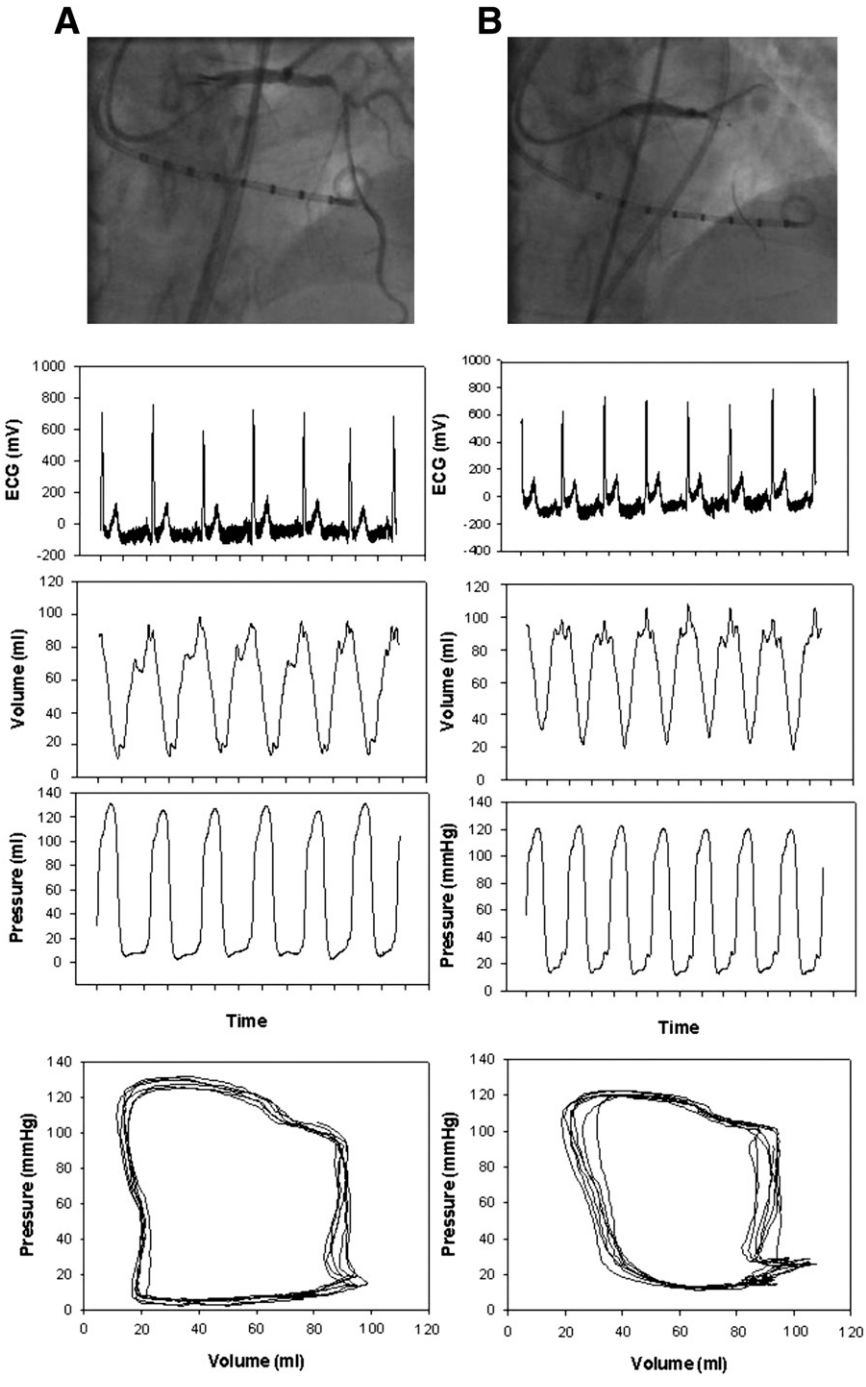

Figure 1. Conductance Catheter in LV Cavity and Doppler Wire in LAD

Cranial right anterior oblique fluoroscopic views of a Millar conductance catheter in the left ventricular (LV) cavity, and Volcano Doppler flow velocity wire tip in the mid left anterior descending coronary artery (LAD) at baseline **(A)** and during low-pressure balloon occlusion of a proximal LAD stenosis **(B)**. The pressure–volume relations at baseline and during balloon occlusion are plotted. ECG = electrocardiogram.

time constant of LV isovolumic relaxation: LV τ); systolic function (maximum rate of pressure generation: LV dP/dt_{max}); and LV end-diastolic pressure and volume, stroke volume, and ejection fraction were calculated at these time points.

The time constant of pressure relaxation (P_t), measured from the time of peak rate of pressure decline to 5 mm Hg above end-diastolic pressure is derived (14) and used to calculate LV τ (τ): $P_t = K e^{-t/\tau}$; τ is the slope of the log P_t versus t relation ($\tau = -1/\text{slope}$, assuming $P_\infty = 0$).

CORONARY HEMODYNAMIC MEASUREMENTS. A ComboWire XT 9500 (Volcano Therapeutics, Inc.) 0.014-inch guidewire with a Doppler flow velocity sensor at the tip was used. The measurements were recorded digitally onto a ComboMap (Volcano Therapeutics, Inc.) console for offline analysis.

The tip of the wire was positioned 3 to 5 cm beyond the stenosis, in a segment of vessel that was straight and free from side-branches. Rotation of the wire, to ensure that the tip was in the center of the vessel, optimized the velocity signals. The wire tip position was fluoroscopically stored to ensure that successive measurements were made with the wire tip in the same vessel location.

Measurement of intracoronary flow velocity was acquired at baseline (BL1), during a low-pressure balloon occlusion at <4 atms for 1-min duration (BO1) and at 10-s intervals in early recovery. Coronary occlusion was confirmed by contrast injection during balloon inflation. After 30 min, measurements were repeated at baseline (BL2) and during a second low-pressure balloon occlusion for 1-min (BO2). An average of 5 beats was used to calculate average peak velocity (APV), at baseline, just before balloon deflation and in early recovery.

Post-study protocol. Once the study measurements were complete, lesions were treated by high-pressure balloon angioplasty and coronary stenting. Angiographic success was defined as a residual stenosis of <15% and Thrombolysis In Myocardial Infarction flow grade 3 in the target vessel. Cardiac troponin-I was analyzed at 12 to 24 h after procedure (Bayer ADVIA IMS Troponin-I Ultra method, Leverkusen, Germany).

Statistical analysis. Data are expressed as mean ± SD unless otherwise stated. Left ventricular hemodynamic data after balloon occlusion were converted to a percentage change from baseline values to facilitate data comparison. Comparisons between data were made with the paired Student *t* test. No adjustments for multiple comparisons were made. A probability level of $p < 0.05$ was considered significant. All calculations were done with SPSS for Windows, version 14 (SPSS, Inc., Chicago, Illinois).

Results

Patient demographic data are summarized in Table 1. All patients recruited had stable angina (Canadian Cardiovascular Society score ≥2) with evidence of ischemia on functional testing. Serial low-pressure balloon inflations did not alter the coronary stenosis severity measured by quantitative coronary angiography (82.9% vs. 81.8%, p = 0.63), and this was confirmed by a constant APV at each baseline reading (15.5 vs. 15.4 cm/s, p = 0.62).

Table 1. Patient Demographic Data and Baseline Hemodynamic Status

Body mass index, kg/m^2	29.3 (3.9)
Treated hypertension	8 (40)
LDLc, mmol/l	1.9 (0.6)
Current smoker	2 (10)
Medications	
Aspirin	20 (100)
Clopidogrel	20 (100)
Statin	20 (100)
Beta-blocker	17 (85)
ACE inhibitor or ARB	14 (70)
Nitrates	9 (45)
Hemodynamic status	
Systolic blood pressure, mm Hg	121 (18)
Diastolic blood pressure, mm Hg	66 (11)
Heart rate, beats/min	60 (11)
Stenosis severity, %	82.1 (11.3)

Values are n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDLc = low-density lipoprotein cholesterol.

Analysis of serial baseline measurements of LV function (Fig. 2, Table 2) demonstrate that 30 min after a 1-min coronary balloon occlusion the ventricle had not recovered, despite normalization of coronary flow velocity. This is consistent with LV stunning. A second coronary balloon occlusion for 1 min resulted in a further deterioration in LV function − cumulative LV dysfunction.

Comparison of LV function during early recovery (30 s after balloon deflation) with late recovery (30 min after balloon deflation) demonstrated persistent LV diastolic dysfunction (delta τ: early +5.0% vs. late +6.0%, p = 0.66). However, systolic function reached supra-baseline levels at 30 s into recovery that subsequently deteriorated at 30 min (delta dP/dt max: early +5.8% vs. late −5.4%, p = 0.0009). Simultaneous analysis of coronary APV confirmed that during early recovery there was reactive hyperemia (APV [cm/s]: early: 31.1 [3.9] vs. late 15.4 [1.1], p = 0.0002) (Fig. 3). When the coronary flow velocity had returned to baseline values at 30 min after balloon deflation, ventricular stunning was observed.

Discussion

In this study of simultaneous LV and coronary hemodynamic assessment during coronary occlusion in humans, we have demonstrated that stunning is apparent late after a 1-min coronary occlusion, when the hyperemic phase has

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 4, 2010
APRIL 2010:412–8

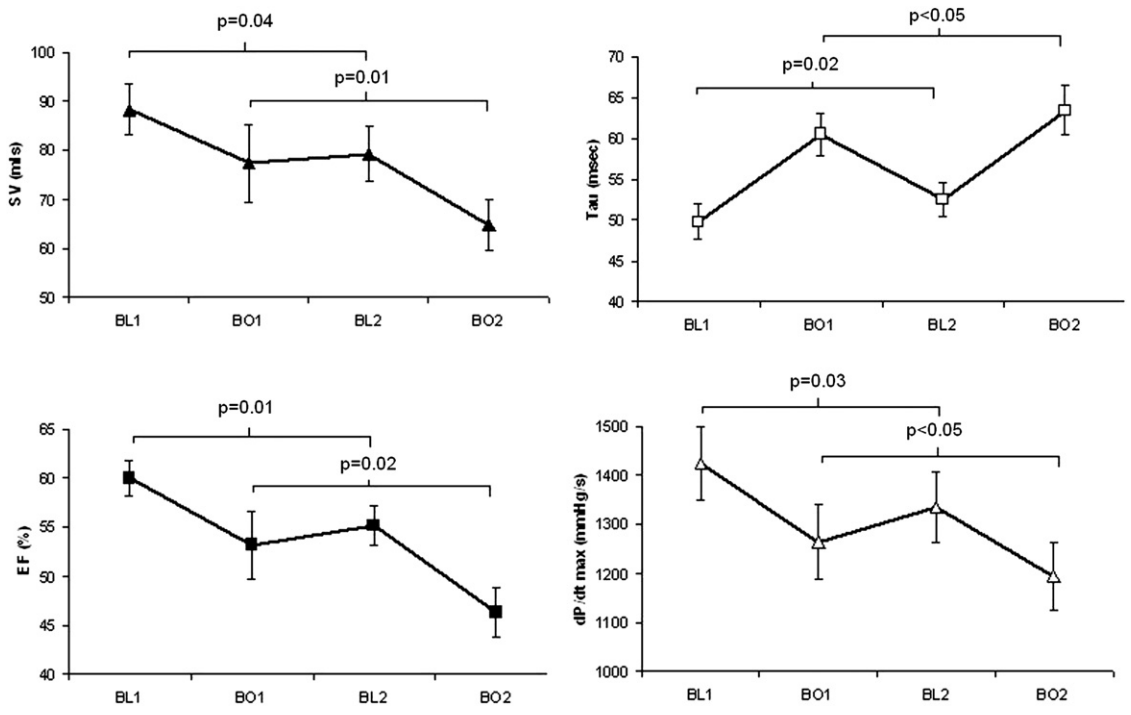

Figure 2. Serial Measurements at Baselines and Balloon Occlusions

Serial measurements at baseline 1 (BL1) and balloon occlusion 1 (BO1) and 30 min later at baseline 2 (BL2) and balloon occlusion 2 (BO2) for stroke volume (SV), ejection fraction (EF), time constant of isovolumic relaxation (τ), and maximal rate of pressure increase (dP/dt max) (mean [SEM]).

subsided. Cumulative LV dysfunction occurs after a second coronary occlusion, 30 min after the first. These observations provide compelling evidence of stunning in humans and give insight into the interplay between coronary and ventricular hemodynamic status.

Acute myocardial ischemia impairs contractile function. The dysfunction can persist for several hours after a transient nonlethal ischemic insult but will completely recover (3). This is termed myocardial stunning: contractile dysfunction with normal flow in the absence of infarction,

Table 2. Comparison of Left Ventricular and Coronary Hemodynamic Measurements

	Baseline 1	Baseline 2	p Value	BO1	BO2	p Value
Heart rate, beats/min	57.3 (8.2)	55.6 (7.6)	0.07	60.3 (5.3)	62.2 (5.3)	0.52
MAP, mm Hg	89.3 (14.5)	88.7 (12.7)	0.53	88.4 (14.3)	87.3 (15.1)	0.80
LVEDP, mm Hg	14.1 (4.2)	14.3 (4.4)	0.76	18.6 (5.3)	18.1 (5.5)	0.47
LVEDV, ml	147.7 (37.0)	143.0 (36.3)	0.09	142.5 (37.0)	139.1 (35.5)	0.17
LVESV, ml	59.1 (15.8)	63.6 (20.6)	0.17	63.6 (20.5)	74.2 (22.7)	0.03
SV, ml	88.4 (22.8)	79.4 (24.0)	0.04	77.3 (34.6)	64.9 (22.9)	0.01
CO, l/min	4.99 (1.06)	4.76 (2.31)	0.61	4.68 (2.28)	4.49 (2.95)	0.76
EF, %	60.1 (4.4)	55.0 (8.9)	0.01	54.0 (15.1)	46.3 (11.1)	0.02
LV dP/dt_{max}, mm Hg/s^{-1}	1,424 (329)	1,335 (317)	0.03	1,265 (328)	1,194 (304)	<0.05
LV dP/dt_{min}, mm Hg/s^{-1}	−1,878 (460)	−1,868 (408)	0.83	−1,560 (449)	−1,490 (416)	0.20
LV τ, ms	49.8 (9.0)	52.5 (8.9)	0.02	60.5 (11.1)	63.4 (13.1)	<0.05
APV, cm/s^{-1}	15.2 (5.2)	15.3 (5.3)	0.62	5.9 (2.9)	6.0 (3.4)	0.96

Comparison of left ventricular (LV) and coronary hemodynamic measurements recorded at baseline 1 and 30 min later (after balloon occlusion 1) at baseline 2. Serial balloon occlusions 1 (BO1) and 2 (BO2) are also compared (mean [SD]).

APV = average peak velocity; CO = cardiac output; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MAP = mean arterial pressure; SV = stroke volume.

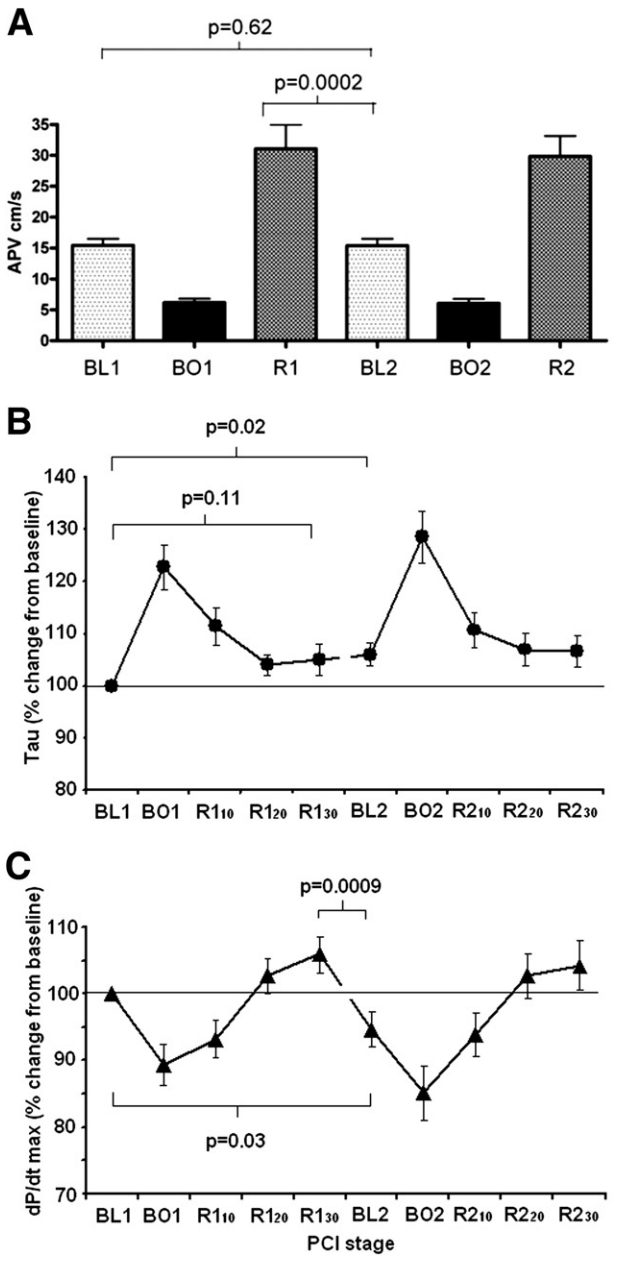

Figure 3. Comparison of APV, τ, and dP/dt Max

Comparison of coronary average peak velocity (APV) **(A)**, diastolic function (time constant of isovolumic relaxation − τ) **(B)**, and systolic function (maximal rate of pressure increase − dP/dt max) **(C)**, at baseline (BL), during balloon occlusion (BO), and in early recovery (R) at 10-s intervals for 30 s. Repeated measurements at baseline, during balloon occlusion, and recovery were performed 30 min after the first (mean [SEM]). Abbreviations as in Figure 2.

which is completely reversible (1). The degree of stunning is proportional to duration and severity of the ischemic insult. In patients with coronary artery disease, repeated episodes of demand ischemia (failure to adequately augment flow during stress) can lead to cumulative stunning that might be the substrate for chronic ischemic LV dysfunction (hibernation) (8,15). However, the effect of stunning and cumulative dysfunction has not been observed in a supply ischemia (reduction of flow) model in humans.

Several studies have assessed LV function during 30- to 60-s coronary balloon occlusions in humans and observed that ventricular function rapidly returned to baseline values (10–12). In addition, cumulative LV dysfunction after serial balloon inflations performed in early reperfusion was not observed. Authors have surmised that coronary balloon occlusion for 60 s is an insufficient ischemic insult to induce stunning or cumulative LV dysfunction. However, in another study, prolonged LV diastolic dysfunction after angioplasty in humans was observed (16).

An important limitation of several of these studies was that coronary blood flow was not assessed, and neither was the effect of coronary flow on LV function accounted for. Immediately after coronary balloon release, reactive hyperemia occurs to repay the oxygen debt (3). An increase in microvascular volume opens stretch-activated channels, resulting in calcium influx and calcium-sensitive augmentation of cardiac myocyte contractility. This is known as the Gregg or "garden-hose" effect (17). Stunned myocardium retains the ability to mount a hyperemic inotropic response (18). This might mask early stunning within the first few minutes of reperfusion.

In this published study we have clearly demonstrated that stunning is observed after a single 1-min coronary balloon occlusion, when assessed in late recovery, 30 min after balloon occlusion, when coronary blood flow has normalized. In addition, a second balloon occlusion during this period results in cumulative LV dysfunction. Ventricular systolic contractility was augmented to above baseline values in early recovery, during the hyperemic phase, possibly due to the Gregg effect. However, we did not observe a similar increase in lusitropy to above baseline values during the hyperemic phase in early recovery. The Salisbury or "scaffold" effect of the coronary arteries, whereby the external coronary turgor increases ventricular stiffness (19,20), might have influenced LV diastolic recovery.

Clinical significance. The late ventricular stunning we have observed is clinically important, particularly because many PCI procedures involve balloon occlusion for substantially longer than 60 s. During left main or proximal left anterior descending PCI, large volumes of myocardium might be stunned. This could precipitate clinically discernable periprocedural heart failure in patients with already-impaired LV function and low contractile reserve and might mandate additional hemodynamic support with intra-aortic balloon pump in these patients.

Study limitations. We were unable to confirm that LV function returned to baseline after the second balloon occlusion with the conductance catheter, due to time and

safety limitations. Full and complete reversibility is the hallmark of stunning. In addition, we cannot confirm that lethal myocardial injury was absent after each low-pressure balloon occlusion in all patients. Ten patients had PCI-induced myocardial injury (myocardial infarction 4a) (21) when troponin was measured at 12 to 24 h. However, we believe the majority of procedure-related embolic injury occurred during stent implantation (22). This assumption is confirmed by observing that the coronary flow velocity returned back to baseline after the first 1-min low-pressure occlusion.

Conclusions

Coronary occlusion for 1 min results in late stunning and cumulative LV dysfunction during a second coronary occlusion when performed after 30 min. Reactive hyperemia augments stunned LV systolic function in early recovery and prevents initial detection immediately after PCI.

Acknowledgments
The authors acknowledge the assistance of all the catheter laboratory staff at Papworth Hospital and thank our patients for participating in this study.

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Key Words: coronary balloon occlusion ■ coronary disease ■ cumulative ischemic LV dysfunction ■ human ■ stunning.