The Linear External-Work Pressure-Time Integral Relationship Ties the Frank and Starling Phenomena Together and Elucidates the Regulatory Roles of the Preload and Afterload

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Background: The mechanisms underlying the Frank Starling Law (FSL) of the heart are elusive and the prevalent concept suggests that the FSL is afterload independent. Isolated fiber studies suggest that the afterload determines cardiac function by modulating cross-bridge cycling and through established cross-bridge dependent cooperativity mechanisms. The study unveils the role of the afterload at the whole heart level. **Methods and Results:** The LV was exposed by left-thoracotomy in adult sheep (69.1±9.6Kg, n=8). Different afterloads were imposed by partial aortic occlusions. Transient inferior vena-cava occlusions (tIVCOs) were preformed at each steady afterload. External work (EW) and pressure time integral (PTI) were measured for each beat during the tIVCOs. A highly linear EW-PTI relationship (WPTiR) was found for each afterload (R^2=0.98±0.02) during the tIVCOs (n=54). Interestingly, the slope of the WPTiR was determined by the afterload. The slope was 34±2.8 mJ/mmHg/sec at baselines and decreased by 0.91±0.53 mJ/mmHg/sec per 1 mmHg·min/L increase in the peripheral resistance. The preload has a proportional effect on the EW and PTI. The afterload has opposing effects on the PTI and EW. Furthermore, a unique WPTiR was obtained during both occlusion and release phases of each tIVCO, while two distinct EW-preload relationships were observed, implying that the linear WPTiR is not a result of the FSL but relates directly to the underlying mechanism. **Conclusions:** A novel linear and afterload dependant WPTiR was described. This consistent WPTiR represents a basic feature of cardiac control of contraction that ties the Frank (pressure-preload) and Starling (EW-preload) phenomena together.

Sarcomere Lengthening Decreases the Rate of Cross-Bridge Cycling; Implications for the Ischemic Myocardium.

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The effects of stretch, encountered in ischemic myocardium, on force development and energy consumption, are not well understood. Prevalent theories suggest that stretch increases the force per cross-bridge (XB) but decreases the number of strong XBs (N_{XB}). We hypothesize that XB kinetics is determined by the filament sliding velocity. XB transition-rate from strong to weak state increases during shortening and decreases during stretch. Consequently, the stretch increases the force by increasing N_{XB}. The study investigates these opposing predictions under stretch conditions. **Methods:** Trabeculae were isolated from rat right ventricles. Sarcomere length was measured by laser diffraction and controlled by a fast servomotor. The number of strong XB (N_{XB}) was evaluated by fast and small oscillations. Stretches at different velocities (0-2.4μm/s) and instants were imposed on isometric twitches. **Results:** Faster stretches yielded larger forces. A tight linear correlation between force and N_{XB} was obtained, implying that the force increased due to the increase in N_{XB}. The phenomenon can not be attributed to the Force-length relationship since fast stretches (>1.6μm/sec) increased N_{XB} by >100% with only small (7.8%) sarcomere lengthening. Identical increase in force and N_{XB} was observed when similar stretches were imposed at different instants, suggesting that the phenomenon is activation level independent. **Conclusions:** stretch increases the number of strong XBs but decrease XB cycling rate and energy consumption. This yields a protective effect in the stretch ischemic myocardium by reducing energy consumption. The post-systolic shortening may results from the energy stored in the XBs that were recruited during the stretch.

Routine Upstream Use of GP IIb/IIIa Inhibitor (Eptifibatide) Preceding Primary PCI in STEMI

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Background: TIMI-3 flow rates pre primary-PCI (PPCI) for STEMI preceded by conventional therapy (aspirin and heparin) are reported in only 10-15% of patients. Adjunctive therapy with IIb/IIIa inhibitors before PPCI might increase these rates.

Methods: 144 patients (age 59 ± 13 yrs) with STEMI <12 h who underwent successful PPCI were pre-treated by protocol, with eptifibatide (in the CCU or ER) before emergency catheterization over the last 4 years (2004-2007). The primary end-point was TIMI-3 flow in the infarct-related artery on the first diagnostic angiogram pre PPCI.

Results:

Pain to Balloon (hr)	N	TIMI -0	TIMI -3	Eptifibatide to balloon (min)
<3	65	25 (38%)	25 (38%)	56 ± 22
3-6	51	17 (33%)	16 (31%)	85 ± 43
>6	28	16 (57%)	6 (13%)	100 ± 92
All	144	58 (40%)	47 (33%)	70 ± 56

The average time from pain onset to eptifibatide therapy was 100 min in pts with TIMI-3 flow, and 150 min in all other pts. TIMI 2-3 flow was more frequently observed in pts who received eptifibatide <180 min from pain onset than in those who received it >180 min from pain onset (53% vs. 30%, respectively, $p<0.01$). The average duration of eptifibatide therapy before PPCI was 70 min (range 10-270 min).

Conclusions: Routine adjunctive upstream use of eptifibatide in the ER or CCU in patients with STEMI before PPCI is associated with a 33% TIMI-3 flow in the infarct-related artery prior to intervention. This rate seems to be inversely correlated with the time from pain onset to eptifibatide therapy.

Stent Thrombosis Clinical Manifestation: Drug Eluting vs. Bare Metal Stents

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Background: Stent thrombosis has been the focus of intense interest because of high associated morbidity and mortality.

Objectives- We investigated the differences in angiographic definite stent thrombosis (ST), according to ARC definition, in patients with drug eluting stents (DES) vs. bare metal stents (BMS) implanted at out institution.

Methods: We evaluated all consecutive ST events during the period from 8/2000 and 7/2007, and recorded in details their clinical characteristics, median time to the ST event and outcomed in term of mortality at 30 days and 6 month.

Results: During the last seven years we identify 52 patients (55 vessels) who developed ST in the BMS group and 17 patients (19 vessels) that had ST in DES. Patients' demographics are described in the following **Table**.

Stent Thrombosis	**BMS**	**DES**	**P value**
Patients No	**N=52**	**N=17**	
Age (yr)	63±12	61±11	
Male	81%	71%	0.4
HTN	55%	53%	0.7
Dyslipidemia	55%	71%	0.4
Smoker	35%	18%	0.04
NIDDM	33%	29%	0.8
Previous CABG	2%	29%	0.04
renal failure	12%	24%	0.3
2/3 VD	54%	82%	0.08

The median time to stent thrombosis was 6 days (range 3 to 60d) in the BMS versus 100 days (range 14 to 450) in the DES group (p=0.03). ST in BMS was associated with mortality at 30 days of 7.7% as compare to 5.9% in the DES group (p=0.8). Following 6 month, the mortality rate in the BMS group was 19% vs. 12% in the DES group (p=NS). Recurrent ST were encountered in 4 patients in each group, with one (25%) mortality event in the BMS group, no mortality in the DES group and the need for revascularization (PCI, CABG) was 50% in both groups.

Conclusions: ST remains a severe complication for both BMS and DES although the average time interval from implantation to event is different (i.e. longer for DES vs. BMS). There was no difference in terms of mortality in both groups after six month but we noticed a worse prognosis among patients with ecurrent episodes of ST.

Prevalence and Prognostic Significance of Persistent Anemia after Acute Myocardial Infarction

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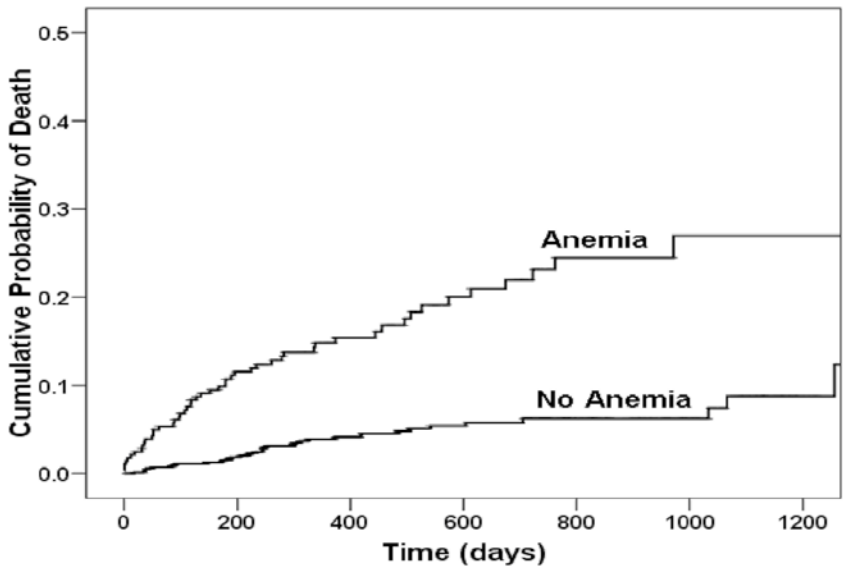
Background: Recent studies have shown that anemia occurring during an acute myocardial infarction (AMI) is an independent indicator of mortality. Anemia may be viewed as a transient phenomenon, secondary to antithrombotic agents and invasive procedures. However, anaemia might worsen or fail to improve after hospital discharge .

Methods: We studied 1110 pts with AMI who survived the acute event. Hemoglobin (Hb) levels were obtained at hospital discharge and >3 weeks after discharge (median 5.2 months). The relationship between post-discharge Hb and the primary endpoints of all-cause mortality were evaluated using Cox models, adjusting for age, gender, creatinine, previous infarction, diabetes, hypertension, smoking, anterior infarction, coronary revascularization during hospital stay, Killip class at admission, presence of known malignancy, pre-discharge Hb and pre-discharge ejection fraction .

Results: Using the WHO definition (Hb < 13 g/dL in men and < 12 g/dL in women), anemia was present in 392 pts at hospital discharge (35.3%). At follow up, anemia was present in 218 (55.6%) and 64 (8.9%) pts with and without anemia at hospital discharge, respectively. During a median follow up of 13 months after the post-discharge Hb measurements, 89 patients died (8.0%). The Kaplan-Meier curves of pts with and without anemia after hospital discharge are shown in the Figure. In a multivariable Cox regression model, the adjusted HR was 1.3 for each 1 gr/dL decrease in post discharge Hb (95% CI 1.1-1.4, P = 0.0004). In a similar model, the HR for mortality in pts with anemia after hospital discharge was 2.0 (95% CI 1.2-3.4, P = 0.008) compared with pts with increasing Hb level.

Conclusion: Pts after AMI who are discharged with anemia frequently fail to increase their Hb levels, and some Pts develop anemia after hospital discharge. Persistent or worsening anemia after AMI is associated with markedly increased risk for mortality .

Figure: Mortality of patients with and without post-discharge anemia



Relationship between Activated Clotting Time (ACT) and Ischemic and/or Hemorrhagic Complications Following Primary PCI in STEMI pts Treated with Heparin Combined with Eptifibatide

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BACKGROUND: Unfractionated heparin (UFH) is the most widely used anti-thrombin medication during percutaneous coronary intervention (PCI). Uncertainty remains about the optimal activated clotting time (ACT) for prevention of ischemic or hemorrhagic complications especially when combined with GP-IIb/IIIa receptor inhibitors.
AIM: We tested the relationship between ACT and cardiac or bleeding complications in STEMI pts undergoing primary PCI and treated using UFH in conjunction with GP-IIb/IIIa receptor inhibitors (eptifibatide [Ept] as a bolus plus infusion for 8-18 h).
METHODS: We evaluated the outcome at 30 days of 527 consecutive patients who underwent primary PCI. Patients were divided into 25-s intervals of ACTs.

RESULTS: The main results are shown in the **Table** as follow**:**

	<216 sec N=128	216-244 sec N=134	245-280 sec N=133	>280 sec N=132	P-value
Age (year)	58±12	59±11	58±12	60±12	0.5
Male	90%	87%	85%	78%	0.05
DM	22%	31%	16%	19%	0.02
Ant MI	48%	47%	43%	48%	0.9
2/3 VD	56%	65%	51%	57%	0.1
BMI (Kg/m^2)	27.5±4.2	26.9±4.3	27.3±3.6	27.6±4.2	0.6
Hemoglobin drop{mg%}	0.6±1.0	0.7±1.0	0.9±1.3	1.0±1.2	0.02
30 d Death	2.3%	2.2%	0%	0%	0.1
30 d ST	2.3%	3%	1.5%	0%	0.1
30 d Re-MI	3.1%	2.2%	1.5%	0.8%	0.5
Groin Hematoma	3.9%	1.5%	5.3%	4.6%	0.4
MACE	6.3%	7.5%	3.8%	3.8%	0.4
Hemorrhagic CVA	0%	0%	0%	0%	1.0

CONCLUSIONS: In STEMI patients undergoing primary PCI and treated using UFH+Ept, an ACT higher than >245s tended to be associated with better suppression of ischemic events but at hazards of higher hemoglobin drop due to hemorrhagic complications during the course of hospitalization.

The Significance of ST Elevation in Right Precordial Leads in Acute Anterior Myocardial Infarction

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Background: The clinical implications of ST-segment elevation in the right precordial leads in the circumstances of anterior acute myocardial infarction (AMI) are unknown.
Objectives: To asses the clinical utility of ST-segment elevation in leads V_3R and V_4R in anterior AMI.
Methods: This study comprised 120 consecutive patients admitted within 12 hours of symptom onset of anterior ST elevation AMI. All had 18-lead electrocardiograms with right precordial leads. Patients were stratified into two groups based on whether they had ST elevation $\geq$1 mV in V_3R and V_4R (group A) or not (group B).
Results: Group A included 39 patients (age mean±SD 59±11 years, males 82%) and group B included 81 patients (age 58±14 years, males 84%). Group A patients were more likely to experience primary ventricular fibrillation (VF) and comprised more patients who suffered from heart failure (HF) during hospitalization, compared with group B [for VF 8/39 (20%) vs. 2/81(2%), p=.0019, for HF 15/39 (38%) vs. 14/81(17%), p=.021]. Patients in group A compared with group B had a trend towards less spontaneous reperfusion (14% vs. 32%, p=.063), and had a higher incidence of multivessel coronary artery disease [median (interquartile range) of 2 (1-3) vs. 1 (1-2), p=.097 respectively]. There was no significant difference in the size of the infarct analyzed by peak CPK, or sum of ST-segment elevations.
Conclusions: In anterior ST-segment elevation AMI, right precordial leads could predict primary VF and HF during hospitalization, and if confirmed in large cohorts should be a routine part of the initial electrocardiogram.

Results of Drug Eluting Stents in Diabetic Versus Non-Diabetic Patients for Diffuse In-Stent Restenosis

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Background: Drug-eluting stents (DESs) are often used for the treatment of in-stent restenosis (ISR). The clinical outcome following implantation of DES for the treatment of diffuse ISR is less well defined among patients with Diabetes mellitus (DM).

Objective*:* We sought to compare the clinical outcomes using DES treatment for ISR in DM versus non DM patients.

Methods: we studied 110 patients who were treated for diffuse ISR [Mehran class >1] using DES. We identified 52 DM patients with ISR receiving DES, and compared them to 58 non DM pts treated for ISR with DES. We compared the procedural and angiographic results and clinical outcome at 6-months.

Results*:* Clinical characteristic, long-term outcome are summarized:

	No DM (N=58)	**DM (N=52)**	**P-value**
Age (years)	63±12	66±10	0.2
Males (%)	81	58	*0.007*
GFR (<60 mL/min/1.73 m^2) (%)	14%	12%	0.7
Chronic total occlusion (%)	16%	19%	0.6
Small vessel size (<2.5mm)	2.6±0.6	2.6±0.7	0.9
Mean stents length	27±7	27±7	0.99
6 months outcome			
Death (%)	3.5	1.9	0.6
Re-AMI	0	5.8	0.06
Stent thrombosis	0	7.8	*0.03*
Target vessel revascularization (%)	3.5	17.3	*0.02*
CABG	1.7	1.9	0.9
MACE$^+$	6.9	22	*0.03*

$^+$MACE= Death, re-AMI, TVR

Conclusions*:* DES implantation for diffuse ISR is associated with increase risk for stent thrombosis, re-infarction and/or need for repeat revascularization in diabetic patients compared to non-diabetic counterparts. Thus, diffuse ISR may be associated with more 'malignant' clinical course in diabetic patients.

Perfect Stent Positioning in Bifurcations: To Kiss or not to Kiss

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Background: Kissing balloons (KB) are considered essential to prevent stent distortion when treating side branches even with provisional bifurcation stenting. Current stent deployment techniques disregard the precise deployment position of the stent and its cells in relation to the sidebranch (SB) ostium. We postulated that stent deployment with precise orientation (both longitudinally and radially) followed by SB inflation would result in a patent SB in the absence of stent distortion.

Methods: Five bifurcations were treated in 3 juvenile pigs. Using a novel fixed wire based bifurcation system, stents were advanced to the bifurcation. Based on the marker system the rotational and longitudinal orientation and positioning of the stent was confirmed with relation to the main vessel and SB. The stents were deployed and in three cases the SB was dilated with balloons on the initial side branch wire. OCT was performed in two cases.

Under fluoroscopic control in a human cath lab stents were deployed silicone phantoms with a bifurcation set at 60 degrees. The stents was advanced in the main branch (MB) and deployed with the SB access cell in the proximal or distal portion of the ostium, with perfect rotational alignment. The SB was initially inflated and then followed by kissing balloon procedure, or kissing balloon (KB) was performed immediately. Phantoms were imaged with microCT and 3D reconstructions were performed at each stage of the study.

Results: In all cases the stents could be oriented as predetermined. Angiographic results were excellent with no stenoses of side branches. OCT demonstrated an unimpeded SB ostium with no stent distortion. In the phantoms, when the stent was deployed without SB post dilation stent achitecture was undistorted wih excellent patency to the SB. With proximal positioning of the SB access cell, SB inflation resulted in reflection of stents struts back into the lumen. This was only partially corrected by KB. In the same position KB immediately post stent rendered a perfect result. However with distal positioning of the SB access cell, SB inflation alone provided a perfect result. When pefect radial aligment was used therewas no stent distortion on the wall opposing the SB. Ex vivo CT analysis of the stented pig coronary confirmed these findings.

Conclusion: Using current stent techniques KB must be the next step following MB stenting. When perfect stent positioning is used the SB can be dilated with no MB stent distortion.

Impact of Final Minimal Luminal Diameter of the Stent on Long-term Results Following Sirolimus-eluting Stent Implantation for Diffuse in-stent Restenosis

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OBJECTIVES: We assessed the predictive value of minimal luminal diameter (MLD) for long-term patency of sirolimus-eluting stents (SES) implantation for diffuse in-stent restenosis .

BACKGROUND: By IVUS studies minimum stent area is a consistent predictor of in-stent restenosis. The value of angiographic MLD as a predictive value for SES failure still limited.

METHODS: From the RMC-ISR database, 110 patients were treated for diffuse ISR [Mehran class>1] using SES {Cypher}. Baseline angiography including pre- and post stenting QCA measurement were analyzed. Post-procedure MLD [<2.5mm] were correlated with 12 months target lesion revascularization [TLR].

RESULTS: Mean age 64±11 years with 70% male, 47% with DM and 16% with recurrent ISR. At baseline, 83% of the lesions were diffuse and proliferative and 16% total occlusions. The SES implantation was successful in all patients except one. Anti GP 2b/3a was used 45% of patients. The mean balloon pressure for stent deployment was 19±4 atmosphere. The mean stents length was 27±7mm. At 12-month follow-up, the total MACE rate was 12.7% (death 4.5%, MI .2.7%, CABG 3.6%, stent thrombosis 0.9%, TVR 12%, TLR 12%). Final MLD<2.5mm was positively correlated to 12 months TLR.

In a multivariate analysis adjustment to DM, time to restenosis, MLD<2.5mm [OR=4.2, 95% CI=1.1-16, P=0.03] was significant independent predictors of 12 months TLR. DM was borderline **[**[OR=3.12, 95% CI=0.8-12, P=0.08

CONCLUSIONS: In this study, reduced restenosis in the malignant type if in stent restenosis. MLD<2.5mm is a significant angiographic predictor of 12 months TVR