EuroIntervention

The effect of repeated ischaemic periods on left ventricular dynamics during percutaneous coronary intervention

Maurice Remmelink, MD, PhD; Robbert J. de Winter, MD, PhD; José P.S. Henriques, MD, PhD; Karel T. Koch, MD, PhD; René J. van der Schaaf, MD; Marije M. Vis, MD; Jan G.P. Tijssen, PhD; Jan J. Piek; MD, PhD; Jan Baan Jr.*, MD, PhD

Department of Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

The authors have no conflicts to declare.

KEYWORDS
Angioplasty, contractility, ischaemia, pressure-volume relations, stunning

Abstract

Aims: To study online left ventricular (LV) dynamic effects of transmural ischaemia and reperfusion during consecutive balloon coronary occlusions in the setting of percutaneous coronary intervention (PCI).

Methods and results: In 10 consecutive unselected patients with stable angina (seven males, mean age 62±3 years) who underwent elective PCI, LV dynamics were continuously recorded using a pressure-conductance catheter to simultaneously measure pressure and volume (PV-loop). The effects of a prolonged balloon coronary occlusion (148±19 s) and a second occlusion on various LV function parameters were studied, as well as recovery of these parameters after reperfusion. Ischaemia caused an immediate (<5 s) decrease in diastolic function, followed by a decrease in contractile function, indicated by a rightward shift of the PV-loop, and a decreased dP/dt_{max} and ejection fraction. All parameters recovered within two minutes after reperfusion. The second occlusion caused a more rapid and more pronounced decrease in systolic and global LV function, while the 12-lead ECG showed less ST-segment deviation.

Conclusions: Online LV pressure-volume measurements during elective PCI show that prolonged balloon coronary occlusion causes a phased ischaemic response of diastolic dysfunction, and then systolic dysfunction with more pronounced deterioration during a consecutive ischaemic period, paradoxical to the ischaemic electrocardiographic signs.

** Corresponding author: Department of Cardiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands*

E-mail: j.baan@amc.uva.nl

Introduction

Ischaemia caused by occlusion of a coronary artery leads to a cascade of left ventricular (LV) dynamic effects.[1] Repeated or long coronary occlusions during percutaneous coronary intervention (PCI) may possibly induce myocardial stunning[2], but may also protect the myocardium against subsequent ischaemic periods.[3]

Data on ischaemia-induced effects on LV function are available from experimental studies in animals[4] as well as from studies during angioplasty in humans.[5-7] However, usually relatively short ischaemic bouts were studied and not continuously and directly measured.[5-7] Hence, the magnitude and timing of acute ischaemia-induced effects in humans is poorly documented. Furthermore, limited information is available on LV function responses to repeated prolonged ischaemic bouts. Experimental studies have shown that ischaemic contractile dysfunction develops more rapidly and pronounced when preceded by one ischaemic bout.[8] However, this phenomenon has never been confirmed in humans. In humans, pulmonary artery pressure together with cardiac vein flow and lactate production was assessed[9], as well as LV pressure[10], while most studies were focused on ST-segment deviations[11] and wall motions scores.[12]

Therefore, the main objective of this study was to evaluate acute responses of LV dynamic parameters to ischaemia and reperfusion throughout elective PCI procedures by direct and continuous assessment of LV pressure and volume (PV-loop), enabled by a pressure-conductance catheter.[13,14] This allowed us to study 1) the immediate and continuous responses to a prolonged balloon coronary occlusion until occurrence of transmural ischaemia, and to subsequent reperfusion, and 2) the responses to a second prolonged balloon coronary occlusion.

Methods

Patients

The study population consisted of 10 consecutive unselected patients with stable angina and single vessel disease, who underwent an elective PCI of the left anterior descending coronary artery (LAD) and of the right coronary artery (RCA). Exclusion criteria were previous myocardial infarction, impaired LV systolic and diastolic function, valvular disease and LV thrombus. The study complied with the Declaration of Helsinki and was approved by the institutional research and ethics committee. All patients gave written informed consent.

Study protocol

Patients were pre-treated with aspirin (100 mg) and clopidogrel (300 mg) and received a bolus of heparin (5000 IU IV) before PCI. After placement of the 6 Fr guiding catheter, the 7 Fr pigtail equipped combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was placed in the LV via the femoral artery. The Swan-Ganz catheter was placed in the pulmonary artery via the femoral vein. A 5 mL blood sample was used to measure rho, blood resistivity. Cardiac output was determined by thermodilution and parallel conductance by hypertonic saline injections in order to calibrate the volume signals of the conductance catheter.[13] Patients were subjected to prolonged balloon predilatation (first balloon inflation) of the stenosis until transmural ischaemia (as >2 mm ST-segment elevation in two contiguous leads) and chest pain occurred. The subsequent balloon inflation for stent placement (second balloon inflation) followed the same protocol. A five minute period between the coronary occlusions was pursued to allow LV dynamic indices to return to baseline values. Intracoronary drugs such as nitroglycerin were not administered prior to completion of the measurements.

LV dynamic measurements and analysis

LV dynamics were recorded continuously during the PCI and were analysed offline. Balloon occlusion duration, time until chest pain and ECG changes were assessed. Maximal ischaemia-induced effects were assessed just before balloon deflation and compared to pre-balloon inflation baseline. Per-beat averages of the recorded variables were calculated as the mean of all beats during a steady state of at least eight seconds and covering two respiratory cycles. The following indices were obtained: heart rate (HR), cardiac output (CO), ejection fraction (EF), stroke volume (SV), stroke work as the area of the PV-loop (SW), end-systolic and end-diastolic volume (ESV, EDV), end-systolic and end-diastolic pressure (ESP, EDP), maximal rate of pressure change (dP/dt_{max}), and the relaxation time constant Tau, defined as that time required for the cavity pressure at dP/dt_{min} to be reduced by half.[15] Effective arterial elastance (E_A), an index of LV afterload, was calculated by ESP/SV. End-systolic elastance (E_{ES}) was estimated by ESP/ESV[16], and end-diastolic stiffness (E_{ED}) by EDP/EDV. Subsequently, the ventricular-arterial coupling ratio was calculated by E_{ES}/E_A, which describes the interaction between LV performance and the systemic arterial system.[17] Regional cycle efficiency (RCE) was calculated for the most basal and apical volume segment by $SW/(\Delta P_{LV} \cdot \Delta V_{LV})$, as previously described.[18] Lastly, the half-time value, a 50% change of maximal effect was used to calculate the rate of change of the LV function indices.

Statistical analysis

Data are expressed as mean ±SEM or n(%). All changes were tested with Student's paired *t*-test.

Results

Patient characteristics

The baseline characteristics of the 10 patients are shown in Table 1. All patients were in sinus rhythm.

First balloon inflation

The left panel of Table 2 shows changes in LV dynamics during the first coronary balloon occlusion (148±19 s). First, diastolic function decreased (started<5 s): as indicated by an increased Tau, EDP and EDV. Second, contractile function decreased, as indicated by a rightward shift of the PV-loop during all LAD occlusions and three out of five RCA occlusions, an increased ESV and a decreased EF, and dP/dt_{max}. Global LV function decreased indicated by the changed SV, E_A and E_{ES}/E_A ratio. Regional LV function decreased

Table 1. Baseline characteristics (n=10).

Age, y	62±3
Male	7(70)
Coronary risk factors	
Diabetes	0(0)
Hypertension	3(30)
Hypercholesterolaemia	4(40)
Family history of CAD	6(60)
Current smoking	4(40)
Medication	
ß-blockers	9(90)
Nitrates	5(50)
Calcium antagonists	2(20)
ACE inhibitors	2(20)
Statins	8(80)
Aspirin	10(100)
Canadian Cardiovascular Society	
class II	2
class III	8
Physiologic parameters	
Heart rate, bpm	64±2
Mean systolic blood pressure, mm Hg	141±4
Mean diastolic blood pressure, mm Hg	76±2
Left Ventricular Ejection Fraction,%	60±1
Target lesion	
LAD	5(50)
RCA	5(50)
proximal segment	1(10)
mid segment	9(90)
%DS per offline QCA	72±4 (53-99)

Values are n(%) or mean ±SEM (range). CAD, coronary artery disease; LAD, left anterior artery; RCA, right coronary artery;%DS, percentage diameter stenosis; QCA, quantitative coronary angiography.

indicated by the decreased apical RCE. All indices showed some degree of stabilisation shortly after their initial rapid deterioration. LV dynamics including RCE showed no differences in response to ischaemia between the LAD and RCA patients. The mean time to maximal ST-segment deviation was 96±32 s and the mean time to chest pain 105±26 s. Figure 1A illustrates a typical patient with a rightward shift of the PV-loop. The two patients without a PV-loop shift had a subtotal RCA stenosis and angiographic collateral flow (Rentrop class II and III). Their coronary occlusion was terminated at 180 seconds, without ECG changes or angina.

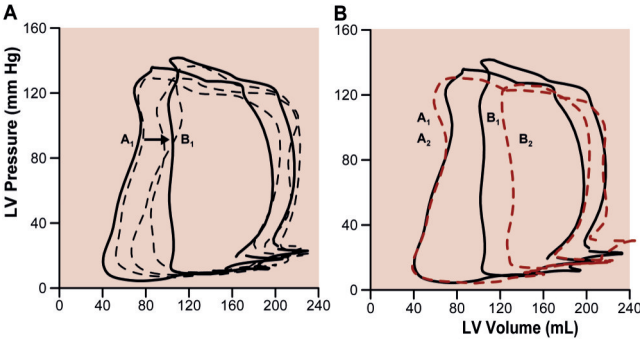

Figure 1. Typical PV-loops during PCI of the LAD. Panel A illustrates a 60 s coronary occlusion (baseline, solid line A_1), at 6, 15 and 30 s occlusion (dashed lines) and just before balloon deflation (solid line B_1). Panel B illustrates, in the same patient, a more pronounced response to the second (62 s) occlusion (dashed line B_2) relative to its baseline (dashed line A_2). Note the smaller area of the PV-loop (stroke work) during the second occlusion.

After balloon deflation, all ischaemia-induced dynamic changes returned to baseline: Tau (12±2 s), dP/dt_{max} (19±6 s) and SW (18±1 s) rapidly returned to baseline, whereas EDV (34±7 s), ESV (47±14 s) and EDP (57±18 s) slowly returned to baseline. There was a transient overshoot of SW above pre-ischaemic baseline of 19±9% (p=0.04) up to 12.39±1.18 mm Hg·L (time after deflation 45±13 s, lasting for 84±39 s) and of dP/dt_{max} 15±6% (p=0.07) up to 1877±73 mm Hg/s (time after deflation 35±7 s, lasting for 91±35 s). Total ST-segment resolution occurred within 50 seconds.

Second balloon inflation

The right panel of Table 2 shows changes in LV dynamics during the second coronary balloon occlusion (90±14 s). Changes occurred in a similar order as during the first occlusion. There was a rightward shift of the PV-loop in all patients. Changes of mainly global (i.e. SV, SW and E_A) and systolic (i.e. ESV, EF and E_{ES}) LV parameters were more pronounced during the second occlusion. The more pronounced response of LV dynamics including RCE to the second ischaemic period was not different between the LAD and RCA group. Apical RCE after predilatation (Figure 2), was nearly significantly increased compared to before this first balloon inflation (71±3 vs. 63±4%, p=0.05). Figure 1B illustrates a typical patient with a more pronounced shift of the PV-loop, including a smaller SW.

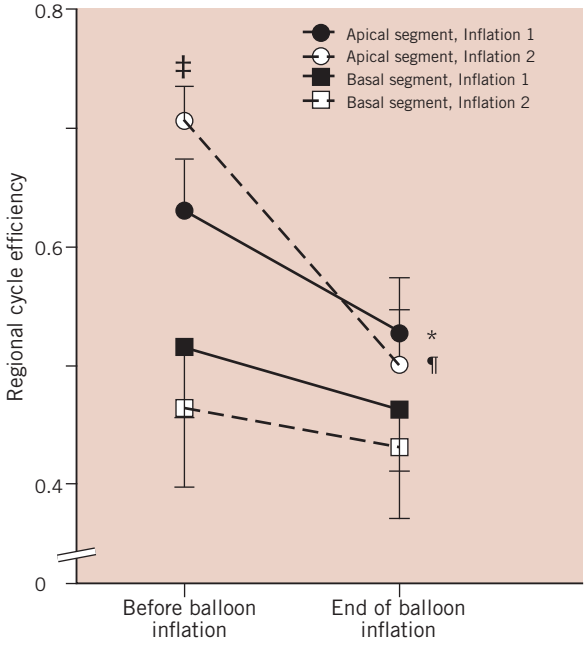

*Figure 2. Regional cycle efficiency of the LV, before and during balloon coronary occlusion. Cycle efficiency was higher in the apical segments compared to the basal segments. Apical cycle efficiency showed a 17±4% (*p<0.001) decrease during the first occlusion, and a 29±6% (¶p=0.002) decrease during the second occlusion. Basal cycle efficiency showed no change. Note that apical cycle efficiency before the second occlusion (i.e., after predilatation of the stenosis) was higher than before the first occlusion, 71±3% versus 63±4% (‡p=0.05).*

Table 2. Changes in LV dynamics relative to pre-balloon occlusion of two consecutive coronary balloon occlusions in 10 patients.

Change in LV dynamics	Baseline 1st inflation	% change 1st inflation	Baseline 2nd inflation	% change 2nd inflation	*P*-value
Global function					
HR, bpm	60±3	6±4	60±3	8±3*	0.6
SV, mL	90±7	−8±3*	91±8	−21±4†	0.002
CO, L/min	5.4±0.5	−3±4	5.4±0.5	−15±4*	0.04
SW, mm Hg·L	10.31±0.67	−4±3	10.25±0.69	−18±5*	0.003
E_A, mm Hg/mL	1.67±0.22	22±10*	1.56±0.19	39±8†	0.07
E_{ES}/E_A	1.70±0.23	−28±8*	1.89±0.37	−48±6*	0.001
Systolic function					
ESV, mL	62±9	38±12*	60±10	66±16†	0.02
EF,%	58±3	−14±3†	60±4	−26±4†	0.001
ESP, mm Hg	137±8	10±5	130±6	8±3*	0.8
EES, mm Hg/mL	2.79±0.52	−16±7	2.88±0.56	−31±5*	0.001
dP/dt_{max}, mm Hg/s	1569±83	−8±3*	1519±82	−9±2*	0.7
Diastolic function					
EDV, mL	158±13	7±3*	150±13	10±4*	0.2
EDP, mm Hg	14±1	47±22*	11±2	105±39†	0.2
E_{ED}, mm Hg/mL	0.098±0.013	35±21	0.073±0.008	78±30*	0.2
Tau, ms	35±2	17±5*	35±1	20±7*	0.5
Regional function					
RCE of basal segment,%	52±6	−8±8	46±7	−6±8	0.9
RCE of apical segment,%	63±4	−17±4†	71±3	−29±6†	0.2

Values are mean±SEM; P-value in the last column relates to the difference between the % changes of first versus second inflation; *p<0.05 and †p<0.005, the % change relative to pre-balloon occlusion; HR, heart rate; SV, stroke volume; CO, cardiac output; SW, stroke work; E_A, effective arterial elastance; E_{ES}/E_A, ventricular-arterial coupling ratio; ESV, end-systolic volume; EF, ejection fraction; ESP, end-systolic pressure; E_{ES}, end-systolic elastance; dP/dt_{max}, maximal rate of left ventricular pressure change; EDV, end-diastolic volume; EDP, end-diastolic pressure; E_{ED}, end-diastolic stiffness; Tau, relaxation time constant; RCE, regional cycle efficiency.

An increased rate of change of LV parameters during the second occlusion is illustrated in Figure 3. On the 12-lead ECG, the summed ST-segment deviation (measured 80 ms after the J-point), was less during the second ischaemic period (10.1±2.1 vs. 6.0±2.0 mm, p=0.02). ECGs were obtained at maximal chest pain (87±13 s).

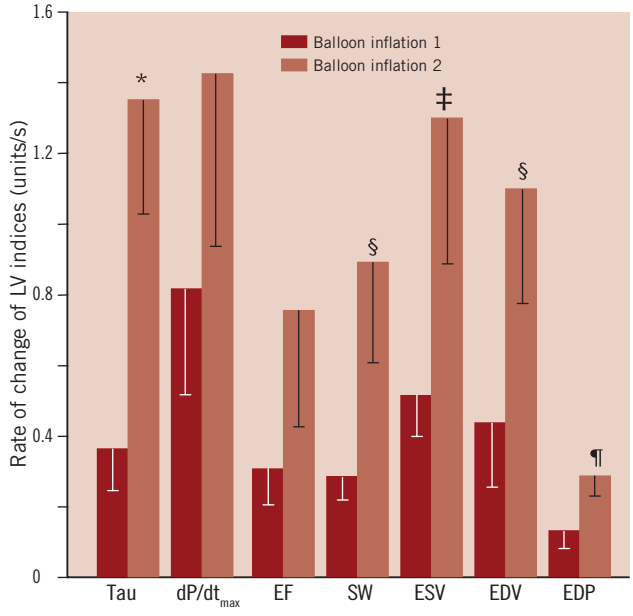

*Figure 3. Illustration of the rate of change during ischaemia until the index reaches its half-time value, a 50% change of the maximal effect. Tau (ms); dP/dt_{max} (0.1·mm Hg/s); EF (–); SW (10·mm Hg·L); ESV (mL); EDV (mL), and EDP (mm Hg). A factor 0.1 was applied to dP/dt_{max}, and a factor 10 to SW for illustrative purposes. Note that all indices show a higher rate of change during the second balloon inflation compared to the first inflation. *p=0.006, ¶p=0.03, ‡p=0.05, §p<0.08.*

The Rentrop class II patient, showed a marked ischaemic response with a rightward shift of the PV-loop, as indicated by the increased ESV (by 36 mL) and EDV (by 20 mL). This time, the particular patient experienced angina requiring balloon deflation after 32 seconds.

The time between balloon inflations (460±68 s, range 207-825 s) did not influence the more pronounced LV responses to the second inflation, when we compared the responses between patients with either a short or a long interval between inflations (data not shown). The range of time in between balloon inflations was mainly PCI-procedure-related. After balloon deflation, LV dynamic parameters fully returned to baseline and followed similar patterns as after the first inflation. Figure 4 illustrates the time course of several LV dynamic indices in a patient during two consecutive LAD occlusions followed by reperfusion.

Discussion

This is the first study in humans to evaluate acute and continuous LV dynamic responses to consecutive coronary balloon occlusions in an elective PCI population with stable angina, by direct online LV pressure and volume measurements. A second coronary occlusion following an initial prolonged occlusion caused a more pronounced negative inotropic response.

Phased response to a prolonged coronary occlusion

We studied the magnitude and timing of LV dynamics in response to prolonged ischaemic bouts. In contrast to previous studies[5-7], we chose prolonged balloon occlusions (>90 s) to allow LV indices to

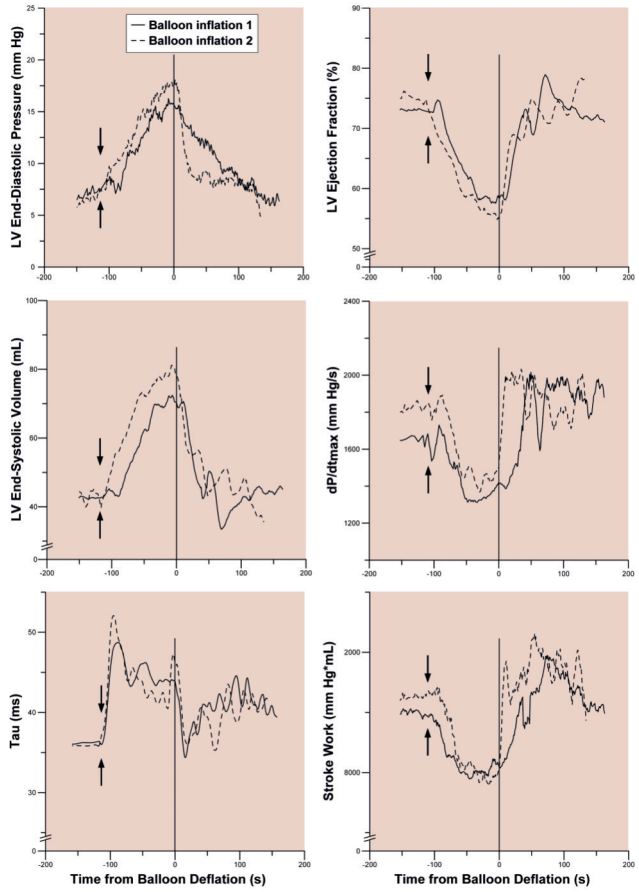

Figure 4. LV dynamic changes during consecutive LAD occlusions for PCI in a typical patient. Note the immediate changes after the onset (arrows) of the first balloon inflation (solid line), and the more pronounced ischaemic response during the second balloon inflation (dashed line). Also note the immediate recovery after deflation (at 0 s on the x-axis).

stabilise, and continuous assessment of combined LV pressure and conductance-derived volume, instead of LV dimensions at several time points obtained by LV angiograms to provide us detailed information on LV dynamics throughout elective PCI.

Our data show that ischaemia causes an instantaneous decrease in diastolic function as indicated by a prolonged LV relaxation, and suggests a decrease in passive diastolic function as indicated by an increased diastolic stiffness (E_{ED}). The increase in E_{ED} was mainly driven by the large increase in EDP. Yet, EDV also showed a small increase, which suggests that there was an up and rightward shift of the PV-loop following its nonlinear end-diastolic pressure-volume relation, in line with previous results.[5]

Contractility decreased during ischaemia as indicated by a decrease in EF, dP/dt_{max} and E_{ES}. Moreover, the increase in ESV could be interpreted as a rightward shift of the end-systolic pressure-volume point[19], since ESP remained practically unchanged. Therefore, the rightward shift of the end-systolic pressure-volume relation indicated a decrease in contractility as well.[20,21] Furthermore, we demonstrated that the ventricle loses its optimal interaction with the arterial system, as indicated by the decrease of the ventricular-arterial coupling ratio (E_{ES}/E_A) below the critical value of 1.0. The latter has been used as a threshold value for systolic dysfunction.[22] The decrease in contractility (E_{ES}) in combination with a maintained peripheral resistance provides an excessive arterial load (i.e. afterload) on the LV, as indicated by the increase in effective arterial elastance (E_A).

Coronary occlusion led to a more pronounced decrease in RCE of the apical segment compared to the basal segment, representing a larger decrease in contractile function, which may be attributed to the obstructed perfusion of the LV apex. Assessment of RCE, as a relatively novel parameter of LV contractility, has been applied to identify optimal pacemaker lead positioning for resynchronisation therapy[18], but has not been investigated previously during ischaemia. In line with optimal resynchronisation therapy, our findings of ischaemic effects on RCE may be applied to assess LV segmental function recovery after revascularisation therapy for e.g. acute myocardial infarction.

The present study showed that following balloon deflation, the initial recovery phase was a hyperactivity phase, during which there was an increased dP/dt_{max} and SW, indicating an increased oxygen demand in response to the period of oxygen deprivation by the coronary occlusion. This overshoot phenomenon has been observed in animals[23], but to our knowledge, this is the first report in humans.

Repeated ischaemia

The main observation in our study is that the LV shows a more rapid and more pronounced negative inotropic response during repeated ischaemia, which has never been shown in humans, but is in line with experimental studies.[8] Our findings may not have been observed during previous clinical studies, because PV-loops were not assessed continuously, and the ischaemic bouts may have been too short.[5-7] Moreover, our observations are not in conflict with observations from animal[24] and human[10,12] studies of LV function measured by other methods, which showed no preserved contractility during repeated ischaemia.

Previous clinical studies showed that brief ischaemic episodes resulted in a reduced ST-segment deviation during repeated ischaemia.[11,12] In line with these studies, our study shows a deterioration of LV function during subsequent balloon coronary occlusion notwithstanding less ST-segment shift.

Theoretically, several physiologic mechanisms may be responsible for our findings.

First, the initial coronary occlusion reversibly impairs the LV on cellular level[25] and decreases contractile reserve due to energy depletion in analogy to some experimental studies[26], and to our findings of a smaller stroke work, i.e. oxygen consumption[27], during the second occlusion. Our findings may therefore in fact provide an explanation for the preconditioning phenomenon by limiting energy utilisation. Furthermore, some of the ventricles may already have adapted to less oxygen supply due to coronary artery disease resulting in a hibernating state without alteration of LV contraction, but with an altered contractile reserve during periods of increased demand.

Second, the initial balloon inflation used as predilatation for the stenosis causes de-recruitment of collateral vessels[5,28,29] – as observed in one of our RCA patients with Rentrop class II – due to improved coronary perfusion pressure by the dissolved pressure

gradient.[30] Thus, the myocardium supplied by the previously stenotic but now un-stenotic coronary artery is more subject to ischaemia by a second coronary occlusion.

Limitations

We realise that the term preconditioning was ultimately meant for a reduction of infarct size after repeated ischaemia[3], which obviously is not possible to investigate in humans. Nevertheless, we did meet the prerequisite for myocardial preconditioning by using prolonged coronary artery occlusions (90 to 180 s) as used in previous studies.[9-11] The explanation of our observation remains to be elucidated, for instance by measuring coronary blood flow and obtaining coronary sinus metabolic samples.

Clinical implications

The present study confirms and extends previous studies by providing further knowledge on ischaemia-induced changes in LV dynamics during repeated coronary balloon occlusion during performance of a PCI, by assessment of online arithmetical and load-independent data from PV-loops. Limiting energy utilisation during repeated ischaemia may be responsible for the preconditioning phenomenon.

Conclusion

In this study, we demonstrated acute LV dynamic responses to prolonged coronary balloon occlusion, with an immediate depression of first diastolic and second systolic function. We found a faster and stronger negative inotropic response to a subsequent ischaemic bout with a concomitant decrease in energy utilisation and a paradoxically decreased ST-segment shift.

Acknowledgements

The authors acknowledge our nursing staff of the cardiac catheterisation laboratory for their skilled assistance with special thanks to W.J. Rohling, RN.

References

1. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol* 1987;59:23C-30C.

2. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146-1149.

3. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74:1124-1136.

4. Bolli R, Zhu WX, Thornby JI, O'Neill PG, Roberts R. Time course and determinants of recovery of function after reversible ischemia in conscious dogs. *Am J Physiol* 1988;254:H102-H114.

5. Kass DA, Midei M, Brinker J, Maughan WL. Influence of coronary occlusion during PTCA on end-systolic and end-diastolic pressure-volume relations in humans. *Circulation* 1990;81:447-460.

6. Serruys PW, Wijns W, van den Brand M, Meij S, Slager C, Schuurbiers JC, Hugenholtz PG, Brower RW. Left ventricular performance, regional blood flow, wall motion, and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:25-36.

7. Wijns W, Serruys PW, Slager CJ, Grimm J, Krayenbuehl HP, Hugenholtz PG, Hess OM. Effect of coronary occlusion during percutaneous transluminal angioplasty in humans on left ventricular chamber stiffness and regional diastolic pressure-radius relations. *J Am Coll Cardiol* 1986;7:455-463.

8. Kolocassides KG, Galinanes M, Hearse DJ. Dichotomy of ischemic preconditioning: improved postischemic contractile function despite intensification of ischemic contracture. *Circulation* 1996;939:1725-1733.

9. Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW, Jr., Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty. Clinical, hemodynamic, and metabolic features. *Circulation* 1990;82:2044-2051.

10. Dupouy P, Geschwind H, Pelle G, Aptecar E, Hittinger L, El GA, Dubois-Rande JL. Repeated coronary artery occlusions during routine balloon angioplasty do not induce myocardial preconditioning in humans. *J Am Coll Cardiol* 1996;27:1374-1380.

11. Tomai F, Crea F, Gaspardone A, Versaci F, Esposito C, Chiariello L, Gioffre PA. Mechanisms of cardiac pain during coronary angioplasty. *J Am Coll Cardiol* 1993;22:1892-1896.

12. Sakata Y, Kodama K, Kitakaze M, Masuyama T, Hirayama A, Lim YJ, Ishikura F, Sakai A, Adachi T, Hori M. Different mechanisms of ischemic adaptation to repeated coronary occlusion in patients with and without recruitable collateral circulation. *J Am Coll Cardiol* 1997;30:1679-1686.

13. Baan J, van der Velde ET, de Bruin HG, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984;70:812-823.

14. Baan J, Jr., Steendijk P, Mikuniya A, Baan J. Systolic coronary flow reduction in the canine heart in situ: effects of left ventricular pressure and elastance. *Basic Res Cardiol* 1996;91:468-478.

15. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation* 1984;69:836-841.

16. Steendijk P, Tulner SA, Bax JJ, Oemrawsingh PV, Bleeker GB, van Erven L, Putter H, Verwey HF, van der Wall EE, Schalij MJ. Hemodynamic effects of long-term cardiac resynchronization therapy: analysis by pressure-volume loops. *Circulation* 2006;113:1295-1304.

17. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983;245:H773-H780.

18. Lieberman R, Padeletti L, Schreuder J, Jackson K, Michelucci A, Colella A, Eastman W, Valsecchi S, Hettrick DA. Ventricular pacing lead location alters systemic hemodynamics and left ventricular function in patients with and without reduced ejection fraction. *J Am Coll Cardiol* 2006;48:1634-1641.

19. Schreuder JJ, van der Veen FH, van der Velde ET, Delahaye F, Alfieri O, Jegaden O, Lorusso R, Jansen JR, van Ommen V, Finet G, Wellens HJ. Beat-to-beat analysis of left ventricular pressure-volume relation and stroke volume by conductance catheter and aortic Modelflow in cardiomyoplasty patients. *Circulation* 1995;91:2010-2017.

20. Schreuder JJ, Biervliet JD, van der Velde ET, ten Have K, van Dijk AD, Meyne NG, Baan J. Systolic and diastolic pressure-volume relationships during cardiac surgery. *J Cardiothorac Vasc Anesth* 1991;5:539-545.

21. Steendijk P, Baan J, Jr., van der Velde ET, Baan J. Effects of critical coronary stenosis on global systolic left ventricular function quantified by pressure-volume relations during dobutamine stress in the canine heart. *J Am Coll Cardiol* 1998;32:816-826.

22. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J* 1993;125:1659-1666.

23. Pagani M, Vatner SF, Baig H, Braunwald E. Initial myocardial adjustments to brief periods of ischemia and reperfusion in the conscious dog. *Circ Res* 1978;43:83-92.

24. Ovize M, Przyklenk K, Hale SL, Kloner RA. Preconditioning does not attenuate myocardial stunning. *Circulation* 1992;85:2247-2254.

25. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003;83:1113-1151.

26. Kolocassides KG, Galinanes M, Hearse DJ. Preconditioning accelerates contracture and ATP depletion in blood-perfused rat hearts. *Am J Physiol* 1995;269:H1415-H1420.

27. Suga H. Global cardiac function: mechano-energetico-informatics. *J Biomech* 2003;36:713-720.

28. Piek JJ, Koolen JJ, Hoedemaker G, David GK, Visser CA, Dunning AJ. Severity of single-vessel coronary arterial stenosis and duration of angina as determinants of recruitable collateral vessels during balloon angioplasty occlusion. *Am J Cardiol* 1991;67:13-17.

29. Werner GS, Emig U, Mutschke O, Schwarz G, Bahrmann P, Figulla HR. Regression of collateral function after recanalization of chronic total coronary occlusions: a serial assessment by intracoronary pressure and Doppler recordings. *Circulation* 2003;108:2877-2882.

30. Verhoeff BJ, Siebes M, Meuwissen M, Atasever B, Voskuil M, de Winter RJ, Koch KT, Tijssen JG, Spaan JA, Piek JJ. Influence of percutaneous coronary intervention on coronary microvascular resistance index. *Circulation* 2005;111:76-82.