Effects of 1:1, 1:2 or 1:3 intra-aortic balloon counterpulsation/heart support on coronary haemodynamics and cardiac contractile efficiency in an animal model of myocardial ischaemia/reperfusion†

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Abstract

OBJECTIVES: The effects of operational modes of intra-aortic balloon pumping (IABP) on coronary haemodynamics and oxygen delivery/demand ratio are unknown and were investigated in an experimental model of myocardial ischaemia reperfusion.

METHODS: Healthy swine (n = 24) underwent 120-minute ligation of the left anterior descending coronary artery followed by 24 h of reperfusion and were randomly assigned to have IABP 1:1 (n = 6), IABP 1:2 (n = 6), IABP 1:3 (n = 6) in the descending aorta or to no IABP implantation (n = 6) 5 min after the onset of reperfusion. Systolic (CBFSys) and diastolic (CBFDia) coronary blood flow, systolic (CRSys) and diastolic (CRDia) coronary resistances and endocardial viability ratio (EVR), as an expression of the oxygen delivery/demand ratio, were measured at 30 min, 1, 6, 12 and 24 h after coronary reperfusion, respectively.

RESULTS: IABP at the 1:1 operational mode significantly increased CBFDia and EVR, and reduced CRDia throughout the experiment. Contrarily, IABP at 1:3 mode resulted in a significant reduction in CBFDia, in a steady increase in CRDia, in a steady reduction in O2 delivery and a constant increase in O2 demand over time. IABP at the 1:2 mode had no overall effect on assessed parameters.

CONCLUSIONS: IABP at the 1:1 mode enhanced coronary haemodynamics and cardiac contractile efficiency in an acute animal model of coronary ischaemia/reperfusion. On the contrary, IABP support set at the 1:2 or 1:3 modes failed to provide benefit. Progressive reduction in balloon inflation with a 1:1 mode instead of decreasing the heart/IABP operational ratio might represent a better IABP withdrawal protocol and is currently under investigation.

Keywords: Intra-aortic balloon pump • Myocardial ischaemia • Reperfusion injury

INTRODUCTION

Intra-aortic balloon pumping (IABP) is a common and effective method of cardiocirculatory support with established benefits for acute failing hearts, ongoing coronary ischaemia or refractory ventricular arrhythmias. Besides coronary flow augmentation directly linked to diastolic balloon inflation, a reduction in left ventricular work load achieved by afterload reduction been also has shown [1, 2]. Additionally, IABP improves survival in patients with acute myocardial infarction and cardiogenic shock [3] and it has been shown to reduce the extent of post-reperfusion ‘no-reflow’ phenomenon and to improve clinical outcomes in patients with large acute infarcts [4, 5].

In the daily practice, the balloon is programmed to assist depending upon the underlying haemodynamic status, and an IABP-to-R wave trigger ratio of 1:1 or a lower frequency ratio may be chosen. However, when initiating the withdrawal from IABP support, a progressive frequency reduction from full assistance of 1:1 to partial assistance (1:2, 1:3) is commonly employed. Nonetheless, little is known about the actual consequences on coronary haemodynamics, when the support ratio of IABP is reduced. Therefore, the main aim of this study was to assess changes in coronary blood flow, coronary resistances (CRs) and myocardial delivery/demand ratio in an animal model of ischaemia reperfusion at different frequencies of IABP assistance.

METHODS

The study was approved by the Institutional Ethics Committee and animals were managed according to the principles of the Guide for
the Care and Use of Laboratory Animals and according to the Italian national guide for the care and use of laboratory animals (DL 116/1992) and in compliance with the recommendations of the European Economic Community (86/609/CEE) for the care and use of laboratory animals and with the good laboratory practice.

Twenty-four healthy swine, (mean weight 60 ± 8.6 kg) had pre-operative intramuscular 15 mg/kg ketamine (Parke Davis-Pfizer, Karlsruhe, DE) and 5 mg/kg diazepam (Roche, Fontenay-sous-Bois, France). General anaesthesia was induced with intravenous ketamine (2 mg/kg) and animals were mechanically ventilated with oxygen supplemented by NO2 (50%) and sevoren (1–2%). 0.1 mg/kg pancuromium bromide (N/V Organon, OSS, NL) was given to achieve muscle relaxation. Tidal volume, respiratory rate and per cent inspired oxygen were adjusted to maintain an arterial pH between 7.35 and 7.45, pCO2 between 35 and 45 mmHg and pO2 >100 mmHg. Basic monitoring consisted of ECG (DII) and SpO2. The right internal jugular vein was cannulated with a three-lumen catheter for the measurement of central venous pressure (CVP). The right femoral artery was cannulated with a standard 18-gauge catheter and connected with Most-Care™ monitor (Release 1.0 A, Vytech Healthcare, Padova, Italy) for haemodynamic measurements, which was powered by the pressure recording analytical method (PRAM). The pressure signals were acquired at 1000 Hz by mean of an analog-digital multifunction card (DAQ Card-700, National Instruments Corporation, Austin, TX, USA) working on the tension signals with 12 bits from −2.5 to 2.5 v. All signals were recorded on a personal computer (Acer Travelmate C 110, Acer Taipei Hsien, Taiwan, ROC). The PRAM method technique is based on the analysis of the peripheral artery waveform morphology. The PRAM is based on a software (Mostcare, Vytek, Padua, Italy) that analyses the pressure signal obtained via the analogic card by means of a routine that identifies the characteristic points of the pressure wave during each beat. The morphologic analysis of the beat allows the determination of the stroke volume that, multiplied by cardiac frequency, provides the cardiac output value. The resulting signal was processed for determination of the beat-to-beat stroke volume and cardiac output (stroke volume × heart rate) analysis. Stroke volume determination was validated according to established clinical method [6].

A median sternotomy was performed and the pericardium was longitudinally opened. The left anterior descending (LAD) coronary artery was dissected just below the second diagonal branch and surrounded by a tourniquet. Coronary flow was measured by a transit time ultrasound flow-meter (Perivascular flow-meter TS 420, Transonic System, Inc., Ithaca, NY, USA) through a flow probe (2-mm PSB flow probe, Transonic System, Inc., Ithaca, NY, USA) positioned around the coronary artery and distal to the ligature. Animals were randomly assigned to one of the following four groups, each of six animals: No IABP, IABP 1:1, IABP 1:2 and IABP 1:3. In animal assigned to an IABP group, a 40-ml intra-aortic balloon was placed in the descending aorta via the right femoral artery under transoesophageal echocardiographic guidance and activated just after coronary reperfusion. The animals belonging to the no-IABP group did not undergo balloon implant. The IABP was connected to a DataScope 98 XT console (Datascope 98 XT, MAQUET/Datascope Corp., Fairfield, NJ, USA) and was synchronized to the ECG to provide diastolic aortic augmentation. The balloon was set at 1:1, 1:2 and 1:3, in the three IABP groups, respectively.

After baseline measurements (B), animals underwent 120-min occlusion of the LAD coronary artery, which was followed by release of the tourniquet and subsequent reperfusion. Measurements and calculations were then carried out 30 min (t80, 1), 1 (ts), 6 (t6), 12 (t12), 24 h (t24) after the onset of reperfusion. Animals were maintained under sedation during the experiment and then they were euthanized by intracardiac KCl injection.

**Measurements**

Systolic coronary blood flow (CBFsys) was measured between the onset of aortic pressure augmentation by cardiac contraction and aortic valve closure, marked as the onset of the dicrotic notch on the aortic pressure tracing, while diastolic coronary flow (CBFDao) was measured during the remainder of the cardiac cycle. CRs were calculated in systole (CRsys) and diastole (CRdia) according to the Hagen–Poiseuille equation: CR = (P2−P1)/CBF, where P2 is the systolic or diastolic arterial pressure, respectively (in mmHg), P1 is the CVP (in mmHg) and CBF is the systolic or diastolic coronary flow, respectively (in ml/min).

The tension time index (TTI) was calculated as the area under the left ventricular systolic pressure curve (an estimate of myocardial oxygen demand), diastolic pressure time index (DPTI) as the area under the diastolic arterial pressure curve (an estimate of myocardial oxygen supply) the and endocardial viability ratio (EVR) as DPTI/TTI, a comprehensive index of the relationship between myocardium oxygen supply and demand [7, 8].

Values for each parameter were obtained by averaging measurements from five consecutive cardiac-assisted beats in case of IABP assistance [9] and from five consecutive cardiac beats in animals without IABP assistance at the same time settings.

**Statistical analysis**

Randomization was carried out by Stats Direct for Windows (release2.3.8, Stats Direct Ltd., Cheshire, UK) employing the Mersenne Twister algorithm of Matsumoto and Nishimura [10], which has a resolution of 32 bits and a period of 239,397. The allocation sequence was generated by F.L., and R.C. blindly assigned participants to the groups. The power analysis was determined by Graph Pad StatMate software (release 2.00; GraphPad Prism Software, Inc., San Diego, CA, USA) on the basis of the following assumptions: Type I error of 0.05 (two-sided) and difference in CBFDao of 1 ml/min. The calculated statistical power was 0.85. Continuous data were expressed as mean ± SD. Data were checked for normality with the Kolmogorov–Smirnov test. Normally distributed variables were compared with Student’s t-test, whereas the Mann–Whitney U test was used in case of not normally distributed variables. Multiple comparisons were carried out by the analysis of variance (ANOVA) for repeated measures, with Tukey’s or Dunn’s post hoc testing, where appropriate. Significance was assumed when the P-value was ≤0.05. SPSS (v.12.0; SPSS, Chicago, IL, USA) was used for these calculations.

**RESULTS**

**Global LV-related haemodynamics**

Prolonged LAD occlusion, as expected, significantly impaired LV function. Such a condition generated an increase in the heart
rate in all animals. Significant declines in systemic blood pressure values as well as in cardiac output and stroke volume were observed in the group without IABP. In contrast, IABP animals had increased CO and SV when compared with controls, particularly in 1:1 supported animals, which showed a greater IABP support to LV volume ejection up to 24 h from reperfusion, whereas 1:2 and 1:3 animals had a progressively reduced benefit of IABP from 6 h on, although with a still better LV haemodynamics than control ones (Table 1).

Coronary blood flow

Coronary blood flows were not significantly different among groups at baseline (Table 2). After myocardial ischaemia, CBF-related values changed significantly in all time settings only in the 1:1 IABP group (Fig. 1). In particular, when IABP was set at 1:1, CBFDia increased significantly from the baseline value ($P < 0.001$) with a maximum increase at $t_{1:1}$. Contrastingly, CBFDia values without IABP showed a significant reduction either from the baseline or from IABP assistance. With IABP set at 1:2, there were no relevant changes from the baseline. Interestingly, CBFDia was significantly lower with IABP at 1:3.

CBF Sys decreased slightly, although significantly, without IABP, whereas IABP at 1:2 or at 1:3 did not induce relevant changes. However, when IABP 1:1 was considered, CBF Sys increased significantly with a maximum benefit at $t_{1:1}$. Finally, CBF Mean over time mirrored CBF Sys. It is noteworthy that, beneficial 1:1 IABP support was maintained until 24 h from reperfusion (Table 2).

Coronary resistances

Mean CRs measured at baseline in diastole were $3.3 \pm 0.5$ mmHg/ml/min, whereas in systole $12 \pm 0.9$ mmHg/ml/min (Fig. 2). When IABP 1:1 was considered, $C_{R_{Dia}}$ significantly decreased from the baseline at $t_{0.5}$ ($P = 0.004$), $t_{1:1}$ ($P = 0.006$), $t_{6.6}$ ($P < 0.001$), $t_{1:1:2}$ ($P < 0.001$) and $t_{2:4}$ ($P < 0.002$). In contrast, with IABP 1:3, $C_{R_{Dia}}$ increased at $t_{1:1}$ ($P = 0.002$), $t_{6.6}$ ($P = 0.002$), $t_{1:1:2}$ ($P < 0.001$), $t_{2:4}$ ($P < 0.002$). On the other hand, $C_{R_{Dia}}$ did not change significantly from the baseline without IABP or when the balloon was set at 1:2.

On the other hand, $C_{R_{Sys}}$ reduced significantly from the baseline with an IABP 1:1 at $t_{0.5}$ ($P < 0.001$) and $t_{1:1}$ ($P = 0.003$) and then increased progressively but never reaching preoperative values. On the other hand, $C_{R_{Sys}}$ remained constant throughout the experiment with IABP 1:2, 1:3 or without IABP.

Oxygen delivery/demand ratio

Oxygen delivery, expressed as the DPTI increased significantly with IABP 1:1 at $t_{0:5}$ ($P = 0.01$) and at the following experimental steps (all, $P = 0.03$). In contrast, the DPTI reduced at any step with IABP 1:3 (all, $P = 0.006$), whereas it remained comparable with the baseline value with IABP 1:2 or without IABP (Table 3).

On the other hand, oxygen demand, expressed as TTI, reduced significantly with IABP 1:1 (all, $P = 0.002$), but increased with an IABP 1:3 (all, $P = 0.01$), and no significant changes in TTI were noticed with an IABP 1:2 or without balloon (Table 3).

### Table 1: Haemodynamic parameters

<table>
<thead>
<tr>
<th>Time</th>
<th>HR 1:1</th>
<th>SAP 1:1</th>
<th>DAP 1:1</th>
<th>MAP 1:1</th>
<th>CO 1:1</th>
<th>SV 1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>96.0 ± 13.8</td>
<td>111.9 ± 19.0</td>
<td>88.7 ± 9.8</td>
<td>95.3 ± 11.2</td>
<td>5.8 ± 0.6</td>
<td>59.2 ± 8.0</td>
</tr>
<tr>
<td>IABP 1:1</td>
<td>87.2 ± 11.0</td>
<td>109.5 ± 14.5</td>
<td>78.3 ± 10.3</td>
<td>92.1 ± 11.5</td>
<td>6.0 ± 0.4</td>
<td>68.0 ± 19.0</td>
</tr>
<tr>
<td>IABP 1:2</td>
<td>88.0 ± 13.7</td>
<td>108.4 ± 17.8</td>
<td>84.0 ± 13.7</td>
<td>93.4 ± 15.9</td>
<td>5.8 ± 0.5</td>
<td>65.2 ± 17.8</td>
</tr>
<tr>
<td>IABP 1:3</td>
<td>90.0 ± 12.2</td>
<td>108.7 ± 18.0</td>
<td>87.2 ± 13.3</td>
<td>93.0 ± 15.8</td>
<td>5.7 ± 0.6</td>
<td>62.8 ± 15.3</td>
</tr>
<tr>
<td>$t_{0.5}$</td>
<td>No IABP 100.8 ± 24.1</td>
<td>93.1 ± 33.5*</td>
<td>58.1 ± 6.1*</td>
<td>73.8 ± 13.9*</td>
<td>4.3 ± 1.4*</td>
<td>45.2 ± 22.4*</td>
</tr>
<tr>
<td>$t_{1:1}$</td>
<td>IABP 101.1 ± 26.1</td>
<td>101.5 ± 28.1</td>
<td>47.7 ± 5.5*</td>
<td>66.3 ± 12.3*</td>
<td>5.7 ± 1.1*</td>
<td>50.7 ± 18.0*</td>
</tr>
<tr>
<td>$t_{1:2}$</td>
<td>IABP 102.2 ± 24.6</td>
<td>106.0 ± 28.2</td>
<td>53.4 ± 4.5*</td>
<td>73.1 ± 12.8*</td>
<td>6.1 ± 1.2*</td>
<td>58.3 ± 21.0*</td>
</tr>
<tr>
<td>$t_{1:3}$</td>
<td>IABP 102.4 ± 23.4</td>
<td>106.3 ± 28.4</td>
<td>54.6 ± 5.8*</td>
<td>73.2 ± 11.7*</td>
<td>5.6 ± 1.6*</td>
<td>54.8 ± 26.0*</td>
</tr>
<tr>
<td>$t_{1:6}$</td>
<td>No IABP 100.3 ± 19.0</td>
<td>94.8 ± 29.5*</td>
<td>59.6 ± 5.3*</td>
<td>70.6 ± 11.8*</td>
<td>4.5 ± 1.2*</td>
<td>47.4 ± 21.0*</td>
</tr>
<tr>
<td>IABP 1:1</td>
<td>99.6 ± 18.1</td>
<td>98.7 ± 25.9</td>
<td>45.3 ± 6.0*</td>
<td>64.6 ± 12.1*</td>
<td>5.6 ± 1.3*</td>
<td>61.0 ± 15.0</td>
</tr>
<tr>
<td>$t_{1:12}$</td>
<td>No IABP 109.8 ± 24.1</td>
<td>96.0 ± 18.0</td>
<td>46.6 ± 10.0*</td>
<td>64.1 ± 11.7*</td>
<td>5.4 ± 1.6*</td>
<td>60.8 ± 16.0</td>
</tr>
<tr>
<td>$t_{1:24}$</td>
<td>No IABP 100.5 ± 18.1</td>
<td>95.1 ± 17.7*</td>
<td>46.3 ± 9.2*</td>
<td>63.7 ± 12.4*</td>
<td>5.2 ± 1.4*</td>
<td>53.3 ± 21.0*</td>
</tr>
</tbody>
</table>

HR: heart rate (beats/min); SAP: systolic arterial pressure (mmHg); DAP: diastolic arterial pressure (mmHg); MAP: mean arterial pressure (mmHg); CO: cardiac output (/min); SV: stroke volume (ml); $t_{0:5}$: 30 min after reperfusion; $t_{1:1}$: 1 h after reperfusion; $t_{6:6}$: 6 h after reperfusion; $t_{1:1:2}$: 12 h after reperfusion; $t_{2:4}$: 24 h after reperfusion. *$P < 0.05$ vs. baseline. Tukey’s or Dunn’s post hoc testing: **$P < 0.05$ no IABP vs. 1:1, 1:2 and 1:3, respectively. †$P < 0.05$ 1:1 vs. 1:2 and 1:3, respectively.
Finally, EVR was significantly higher than baseline with an IABP 1:1, whereas it was constantly lower with an IABP 1:3 (Fig. 3).

**DISCUSSION**

The main findings of our study can be summarized as follows: (i) IABP set 1:1 significantly increased CBFSys, CBFSys and CBFSys, whereas IABP set at 1:2 or 1:3 was associated with a significant reduction in both CBFSys and CBFSys; (ii) CRs in diastole were markedly reduced by IABP at 1:1 while, when set at 1:3, CRDia increased steadily over time. (iii) The oxygen delivery/demand ratio increased significantly with IABP at 1:1, whereas it was reduced when the IABP was set at 1:3.

In normal hearts, the CBF control is mainly regulated by the balance between oxygen supply and oxygen consumption [11]. Thus, the decrease in afterload and O2 demand during IABP was expected to be associated with a decrease in CBF. Instead, CBF was increased by IABP during reperfusion, and this might be explained by the inability of the reperfused myocardium to auto-regulate its blood flow and by its marked dependence on the level of diastolic aortic pressure [12].

We employed a long (2 h) ischaemic period and observations were carried out over 24 h, for two main reasons: (i) even though in the clinical practice IABP-dwelling time is at least 24 h, most studies in the literature share the limitation of evaluating short-time IABP effects [11, 13], whereas the few reports with prolonged use of IABP suggest that the haemodynamic effects of IABP are more long lasting [14]; (ii) there is considerable evidence to indicate that reperfusion injury occurs as a result of a post-ischaemic inflammatory reaction and the respective durations of ischaemia and reperfusion, in particular a short-reperfusion time, can influence the extent of reperfusion injury and the efficacy of compounds administered to reduce it [15]. Based on these premises, the paramount importance of appropriate periods of both ischaemia and reperfusion to allow full development of the post-ischaemic response is self-explanatory when designing experimental models of compounds aimed to be effective against reperfusion injury.

In our study, the IABP enhanced CBFSys in parallel with a reduction in CRDias, which is attributable to an enhancement in diastolic aortic pressure [16] rather than to vasodilatation. Indeed it has been shown that maximum vasodilatation is impaired in the acute infarcted zone during reperfusion [17, 18] and it contributes to increasing the "no-reflow" phenomenon [4, 15, 16, 19].

The decrease in systolic blood pressure by the IABP leads to a temporary raise in CBFSys rather than to vasodilatation. Conversely, we observed a transient reduction in CRDias paralleled by an increment in CBFSys during the first hour of reperfusion in IABP 1:1. This might be presumably related to a mechanical effect of IABP as this temporary raise in CBFSys was not observed when the balloon was set at 1:3 or 1:2.

Our findings related to the mean CBF and the CBFSys are in accordance with the data of Pierrokos et al. [20], who showed a peak increase in the mean CBF of 320% at 5 min from reperfusion with 1:1 IABP support, and with the data of Bonios et al. [16], who showed a peak increase in the mean CBF of 301% at 2 min from reperfusion and a peak increase in the CBFSys of 375% at 2 min from reperfusion, respectively. In our experiment, however, the highest mean CBF (maximum increase in 245%...
from the baseline) and the highest CBFSys (maximum increase of 381% from the baseline) were observed at 6 h from reperfusion, respectively. These differences in peak-related timing, most likely, might be ascribed to the different coronary occlusion time and related myocardial ischaemia (1 vs. 2 h in our study), and by the IABP activation timing (10 min before reperfusion vs. 10 min after reperfusion in our study) with likely impact on coronary circulation and myocardial tissue conditions/response. Furthermore, in Pierrikos and Bonios experiments, IABP off and on data were obtained from the same animals, and, therefore, the activation of IABP support before coronary opening might have influenced subsequent coronary haemodynamics also in unsupported beats [16, 20].

Clinical considerations

Our experimental evidence of a better myocardial and coronary support with IABP at 1:1 compared with other modalities of IABP assistance or no IABP may also be relevant for the clinical practice. Usually, patients are weaned from IABP once haemodynamic stability is enhanced or recovered. Two IABP weaning methods are routinely employed: balloon volume reduction with fixed operational mode vs. frequency ratio reduction. The volume weaning method consists of reducing balloon volume in 20% increments [21]. This method is an alternative to frequency ratio weaning in patients who may be severely compromised by small changes in the haemodynamic status [21]. Because of the increased risk of thrombus formation in the balloon’s surface folds, the most frequent method is the frequency ratio weaning,
from full assistance to partial assistance (1:2, 1:3 or further), although no evidences are available to confirm the thrombotic risk theoretically linked to progressive reduction in balloon inflation. However, the effectiveness of frequency reduction weaning in the gradual withdrawal of IABP is questionable and there are no relevant experimental studies addressing this issue specifically. It is certain that reduction in frequency exposes the heart to large variations in afterload on a beat-to-beat basis. As a result, this variation has an impact on the amount of work the myocardium is expected to perform [21]. Fuchs et al. [22] compared the effects of IABP on regional myocardial blood flow in patients with unstable angina. Great cardiac vein flow measurements were used as an indicator of the ability of IABP to augment the diastolic perfusion of arteries fed by post-stenotic portions of the LAD coronary artery. Authors found that IABP increased great cardiac vein flow at a frequency of 1:1. They also demonstrated that a frequency of 1:1 provided an increase in great cardiac vein flow regardless of the intermediate catheter volume. Assist ratios of less than 1:1, however, led to no increase in great cardiac vein flow despite full catheter volume. Furthermore, great cardiac vein flow does not significantly differ whether the assist frequency is set to 1:4 or if the pump is turned off [21]. In addition, Bolooki [23] concluded that a frequency ratio of 1:3 should be considered as balloon ‘off’, after studying the haemodynamic data from 12 post-cardiotomy patients. Interestingly, Cheung et al. have shown, in a limited series of patients submitted to cardiac surgery followed by postoperative IABP assistance, that the 1:1 IABP/heart ratio decreased the LV end-diastolic cross-sectional area, whereas there was no effect at either 1:2, 1:4 modes or without IABP support [24]. Furthermore, in that study, the 1:1 operational mode has shown to reduce the LV preload burden, whereas 1:2 or 1:4 have not produced beat-to-beat changes in LV preload based on the changes in pulmonary artery pressures, central venous pressures or LV end-diastolic short-axis dimensions.

Our data seem to indicate that reduced frequency ratios may not represent intermediate IABP assistance, but, rather, the haemodynamic equivalent of complete IABP withdrawal. A reduction in IABP frequency will provide little—if any—support and, more importantly, it may not provide any advantage during reperfusion after prolonged ischaemia.

Even though there is no direct evidence to suggest that either frequency weaning or volume weaning exhibits a clear advantage and both are offered as legitimate options for the withdrawal of IABP support, our findings indicate that frequency reduction certainly results in greater haemodynamic suppression and thus, we believe, it should be carefully employed. Accordingly, volume weaning should be seen as a more physiological approach. Indeed, the reduction in intra-aortic balloon catheter volume will gradually increase cardiac workload and it has also been demonstrated that larger catheter inflation volumes may further augment cardiac output [25]. However, the renewed popularity and the increase of use of IABP as temporary mechanical circulatory support encourages further larger experimental and clinical studies that are necessary to determine the most effective manner of weaning intra-aortic balloon counterpulsation.

### Limitations of the study

One of the main limitations of the study is the use of young pigs with normal peripheral arteries and this condition is different from cardiopathic patients undergoing IABP implantation, who normally have atherosclerotic vessels and higher afterload.

Secondly, we did not analyse the venous blood from the coronary sinus. Indeed, the coronary venous oxygen tension would have given more precise information about the balance between oxygen delivery and consumption. However, the cardiac EVR (the ratio of area under the diastolic portion of the arterial pulse

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Table 3: Oxygen delivery/demand

<table>
<thead>
<tr>
<th></th>
<th>DPTI</th>
<th>TTI</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>No IABP</td>
<td>33.4 ± 8.1</td>
</tr>
<tr>
<td></td>
<td>IABP 1:1</td>
<td>34.1 ± 7.9</td>
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<tr>
<td></td>
<td>IABP 1:2</td>
<td>33.8 ± 8.7</td>
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<tr>
<td></td>
<td>IABP 1:3</td>
<td>33.7 ± 8.5</td>
</tr>
<tr>
<td>f_{R0.5} No IABP</td>
<td>33.7 ± 6.3</td>
<td>27.2 ± 7.3</td>
</tr>
<tr>
<td></td>
<td>IABP 1:1</td>
<td>38.4 ± 11.9</td>
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<td></td>
<td>IABP 1:2</td>
<td>33.3 ± 8.0</td>
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<tr>
<td></td>
<td>IABP 1:3</td>
<td>28.1 ± 6.9</td>
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<tr>
<td>f_{R1} No IABP</td>
<td>33.3 ± 7.5</td>
<td>27.4 ± 5.3</td>
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<tr>
<td></td>
<td>IABP 1:1</td>
<td>36.5 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>IABP 1:2</td>
<td>32.7 ± 8.1</td>
</tr>
<tr>
<td></td>
<td>IABP 1:3</td>
<td>28.1 ± 6.0</td>
</tr>
<tr>
<td>f_{R24} No IABP</td>
<td>33.3 ± 7.7</td>
<td>27.4 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>IABP 1:1</td>
<td>36.5 ± 8.0</td>
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<tr>
<td></td>
<td>IABP 1:2</td>
<td>32.6 ± 8.8</td>
</tr>
<tr>
<td></td>
<td>IABP 1:3</td>
<td>28.1 ± 6.0</td>
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</tbody>
</table>

DPTI: diastolic pressure time index (mmHg × s/min × 100); TTI: tension time index (mmHg × s/min × 100). *P < 0.05 vs. baseline. **P < 0.05 vs. 1:1, 1:2 and 1:3, respectively. †§ P < 0.05 no IABP vs. 1:1, 1:2 and 1:3, respectively. ¶# P < 0.05 1:1 vs. 1:2 and 1:3, respectively.
pressure trace, corresponding to DPTI, to the area under the systolic component of the arterial pulse pressure trace, corresponding to TTI) has been shown to accurately assess the relationship of the myocardial blood supply to the oxygen demand [7, 8].

Moreover, myocardial specimens were not taken for histological examination, thus we do not information whether, while improving the oxygen delivery/demand ratio by raising oxygen supply, IABP protects cellular integrity and effectively reduces the ischaemic or necrotic areas. However, the study was specifically designed to record haemodynamic and coronary flow-based parameter assessment through a continuous on-line and flow-probe monitoring. On the other hand, the potential correlation between biochemical markers of myocardial damage, histological patterns of ischaemia/reperfusion injury and different patterns of IABP assistance might further unveil the role of IABP as a heart support device and might also suggest a mechanism that would result in a measurable clinically relevant marker. Accordingly, histological and biochemical analyses are part of the design of a current study and therefore the eventual effects of IABP at cellular level are still under investigation.

One other limitation of the study is the lack of echocardiographic details. However, due to the peculiar experimental model (24 h of continuous recording), it was possible to perform echocardiographic evaluation only at the beginning of the experiment in each animal, to assess the correct position of the IABP at implantation, just after the relief of 2-h ischaemia.

No comparisons were made between a declining IABP/heart ratio vs. IABP balloon volume reduction as far as the IABP weaning process is concerned and, hence, the potential advantage of the latter method is only speculative and currently under investigation, as clearly mentioned.

CONCLUSIONS

To our best knowledge, this is the first study assessing the variations in coronary circulation comparing different magnitudes of IABP assistance. In our study, the 1:1 IABP/heart ratio significantly enhanced coronary diastolic flow, reduced diastolic resistances and increased the oxygen delivery/demand ratio. On the contrary, the 1:2 or 1:3 operational mode failed to provide benefit in our experimental model of myocardial ischaemia. These findings suggest that progressive reduction in balloon inflation with a 1:1 mode instead of a decreasing heart/IABP operational ratio might represent a better IABP withdrawal protocol, but ad hoc investigations are warranted and currently in progress at our laboratory.

REFERENCES


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Conflict of interest: The authors thank Maquet/Datascope Italy for having provided the IABP balloons and console.
APPENDIX. CONFERENCE DISCUSSION

**Dr. D. Fullerton** (Denver, CO, USA): The intra-aortic balloon pump, of course, has been around a long time, and I actually thought we knew everything there was to know about it, but I have learned a great deal from your study. In particular, I found it very interesting that although any of the settings, 1:1, 1:2, 1:3, would increase the cardiac output and increase the stroke volume (the two parameters that we use at the bedside), paradoxically there was a very nice increase in coronary blood flow at 1:1, but as you showed, a significant decrease in coronary blood flow at 1:3, despite the fact that it was helping the heart work better. Do you have any idea why that should be?

**Dr. Gelsomino**: We do not have an answer to this; we can only postulate what happens. This topic is discussed amongst researchers, and we can say that in this situation, in an ischaemic situation, it has been proved that there is no local regulation of blood flow, first of all. Blood flow is strongly dependent on the diastolic pressure. So we can explain with the improvement in diastolic pressure, the improvement in blood flow in the diastolic phase, of course, and at the same time to justify the reduction with the lesser improvement in diastolic pressure in the 1:3 and 1:2 set.

The question is most tricky I think for systolic. We were surprised with the systolic improvement, and it is interesting to follow this. It is not constant; it is just transitory. And we can say that it could be, it might be, related to just the mechanical action of the counterpulsation and not to vasodilatation because there is vasoparalysis during reperfusion. So just the dilatation. Then when the reperfusion damage occurs, I think it is stronger than the action of the intra-balloon pump, and the systolic flows go down again. It is just what we think.

**Dr. Fullerton**: That is very interesting. My last question is in regard to the EVR, where you nicely demonstrate that at 1:3, the supply is insufficient for the demand, so your EVR goes down. So back to the bedside. Is there any way, when we are trying to wean someone off the balloon pump, that we might be able to recognize clinically subtle signs that this is in fact the case? Have you thought about that at all?

**Dr. Gelsomino**: No. We wanted to study the difference between the two methods of weaning because it is really interesting. There is no indication for the ideal weaning from IBP, and we are collecting data for a new study with this as the object. We are just collecting data, but at the moment we have no data about this difference between volume and the frequency of weaning.

**Dr. B. Walpoth** (Geneva, Switzerland): I have two comments. Firstly, we performed a similar study more than ten years ago in patients with coronary bypass grafts, and we saw a similar trend in our patients, but could not demonstrate the 100% improvement that you describe. Secondly, I would like to comment on the fact that you show us the results of flow measurements without relating this to the general haemodynamics of the pig heart during flow measurements. One is depending on the other. So unless you have stable reproducible hemodynamics during 1:1, 1:2, 1:3 counterpulsation, you cannot comment only on the coronary flow. So you have to be very careful about this.

**Dr. Gelsomino**: Would like to start from the last question. We had the problem of splitting up our results into two different papers because of length requirements. But I can say that they are very similar results in terms of their correlation with haemodynamics. Of course, this may be a good suggestion to correlate the flow with the haemodynamics. Regarding your first question, this is not a new finding because there is another paper published reporting more than 100% increase; we have 150% improvement. The problem, I think, of the new finding of this paper is that we have, first of all, the longest ischaemic time, two hours, and the longest observation time.

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