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Citation for published version (APA):

Schampaert, S., van Nunen, L., Pijls, N., Rutten, M., van Tuijl, S., van de Vosse, F., & van 't Veer, M. (2015). Intra-aortic balloon pump support in the isolated beating porcine heart in nonischemic and ischemic pump failure. *Artificial Organs*, 39(11), 931-938. <https://doi.org/10.1111/aor.12470>

Document license:
TAVERNE

DOI:
[10.1111/aor.12470](https://doi.org/10.1111/aor.12470)

Document status and date:
Published: 01/11/2015

Document Version:
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Intra-Aortic Balloon Pump Support in the Isolated Beating Porcine Heart in Nonischemic and Ischemic Pump Failure

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Abstract The blood pressure changes induced by the intra-aortic balloon pump (IABP) are expected to create clinical improvement in terms of coronary perfusion and myocardial oxygen consumption. However, the measured effects reported in literature are inconsistent. The aim of this study was to investigate the influence of ischemia on IABP efficacy in healthy hearts and in shock. Twelve slaughterhouse porcine hearts (hearts 1–12) were connected to an external circulatory system, while physiologic cardiac performance was restored. Different clinical scenarios, ranging from healthy to cardiogenic shock, were simulated by step-wise administration of negative inotropic drugs. In hearts 7–12, severe global myocardial ischemia superimposed upon the decreased contractile states was created. IABP support was applied in all hearts under all conditions. Without ischemia, the IABP induced a mild increase in coronary blood flow and cardiac output. These effects were strongly augmented

in the presence of persisting ischemia, where coronary blood flow increased by $49 \pm 24\%$ ($P < 0.01$) and cardiac output by $17 \pm 6\%$ ($P < 0.01$) in case of severe pump failure. As expected, myocardial oxygen consumption increased in case of ischemia ($21 \pm 17\%$; $P < 0.01$), while it slightly decreased without ($-3 \pm 6\%$; $P < 0.01$). In case of progressive pump failure due to persistent myocardial ischemia, the IABP increased hyperemic coronary blood flow and cardiac output significantly, and reversed the progressive hemodynamic deterioration within minutes. This suggests that IABP therapy in acute myocardial infarction is most effective in patients with viable myocardium, suffering from persistent myocardial ischemia, despite adequate epicardial reperfusion. **Key Words:** Intra-aortic balloon pump—Isolated beating porcine heart—Persistent ischemia.

The blood pressure changes induced by the intra-aortic balloon pump (IABP) are expected to create clinical improvement in terms of coronary perfusion and myocardial oxygen consumption (1–3). However, the measured effects reported in literature are inconsistent and ambiguous in human and experimental studies (3–16). Furthermore, recent randomized clinical trials all failed to reach their primary efficacy end points (17–19) as was clearly depicted by Rognoni et al. (20).

It has been suggested that the variable degree of IABP efficacy depends on the patient's baseline hemodynamics (2,21,22). Both Zehetgruber et al. (21) and Kern et al. (22) measured the change in coronary blood flow velocity in patients undergoing IABP therapy, and showed that the increase in coronary blood flow velocity was considerably larger in patients with a compromised hemodynamic status compared to those with normal baseline hemodynamics. In addition, an animal study of Powell et al. (2) showed a decrease in myocardial oxygen consumption during support when myocardial performance and coronary blood flow were normal, while an increase was observed in case of severely impaired myocardial performance.

The findings mentioned above might be attributed to the presence of coronary autoregulation in healthy

doi:10.1111/aor.12470

Received August 2014; revised November 2014.

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situations, and its absence in pathologic states. It is illusionary to presume that the augmented diastolic pressure translates into increased coronary blood flow as long as autoregulation is intact (23). Only when coronary autoregulation is absent, is blood flow directly related to the diastolic perfusion pressure, allowing the IABP to be effective. One of the common clinical conditions where coronary autoregulation is exhausted is large myocardial infarction with successful epicardial stenting, but persistent microvascular obstruction, that is, no-reflow. Furthermore, in a case of (persistent) myocardial ischemia with still viable myocardium, myocardial oxygen consumption will naturally increase when more blood is offered to the ischemic tissue, in contrast to the consumption of oxygen in myocardial tissue that is already adequately perfused.

Consequently, the aim of this study was to investigate the effects of IABP support in different clinical scenarios, ranging from normal contractile state to cardiogenic shock, whether or not accompanied by global myocardial ischemia. These scenarios were simulated in the isolated beating porcine heart model (24), a platform in which the hemodynamic conditions can be controlled very accurately and proved to be capable of generating flow patterns and pressure curves that closely mimicked aortic and coronary *in vivo* flow and pressure (24). As the isolated beating porcine heart is in a permanent state of exhausted autoregulation (25), it allows evaluation of the IABP without the confounding effect of autoregulatory responses in different states of pump failure, whether or not complicated by superimposed ischemia.

MATERIALS AND METHODS

Twelve hearts ($n = 2 \times 6$) were obtained from Dutch Landrace hybrid pigs that were slaughtered for human consumption. Following regular slaughter protocols, the thorax of the pigs was opened to isolate the heart (heart weight 520 ± 55 g). The isolated heart was immediately cooled and cannulated for administration of 1 L of cold cardioplegic solution (4°C modified St. Thomas 2 added with 5000 IU of heparin) to the coronary arteries, such that warm ischemic time never exceeded 5 min. Preparation of the hearts was carried out in the laboratory under cold and cardioplegic conditions (25). After preparation, the isolated porcine heart was mounted to an external circulatory system (extracorporeal circulation) (LifeTec Group, Eindhoven, The Netherlands) (24). The systemic circulation was divided into an upper and a lower part by extending the aorta by a proximal side branch mounting into a standard four-

element Windkessel model. The preload model controlled the left atrial filling pressure (set between 10 and 15 mm Hg) by means of a Starling resistance overflow from the preload model back into a venous reservoir. Through coronary reperfusion and controlled cardiac loading, physiological cardiac performance was achieved (25). Heart rate was fixed by means of ventricular pacing. Based upon our own clinical experience, a 50 cc polyurethane balloon with a 7Fr catheter (Maquet Getinge Group) was positioned in the aorta and connected to a CS300 IABP system (Maquet Getinge Group, Rastatt, Germany). Arterial and venous blood gas values, temperature, and electrolytes were measured using a CDI 500 blood parameter monitoring system (Terumo Cardiovascular Systems Corporation, Tokyo, Japan), which was calibrated using a VetScan i-STAT 1 (Abaxis, Union City, CA, USA). The model of Kelman (26) was subsequently used to transform the measured blood gas values into actual saturation levels. Coronary blood flow was measured with an ultrasound flow probe (LifeTec Group) around the pulmonary artery line, as the right ventricle was only subjected to a volume loading, resulting from ventricular filling with coronary venous blood. Hemodynamic parameters were continuously monitored and after performing the hemodynamic interventions, the heart was arrested with a potassium chloride injection into the aortic cannula after cross clamping the aorta.

In summary, in this beating heart model (24), afterload, preload, and contractility can be varied independently as well as heart rate and myocardial oxygen supply. All these parameters can be measured continuously and in addition total coronary blood flow, cardiac output, and myocardial oxygen consumption are monitored continuously.

Hemodynamic interventions

In this model (24), different clinical scenarios, ranging from normal contractile state to cardiogenic shock, were defined (Fig. 1). A healthy state was defined as a nonischemic cardiac output larger than 4.75 L/min and a mean aortic pressure larger than 77.5 mm Hg, preshock as a cardiac output between 3.75 and 4.75 L/min and a mean aortic pressure between 67.5 and 77.5 mm Hg, and cardiogenic shock as a cardiac output of less than 3.75 L/min and a mean aortic pressure of less than 67.5 mm Hg. When neglecting venous pressure, these clinical scenarios were all associated with a fixed systemic vascular resistance (ratio of mean aortic pressure and cardiac output), which increases in case of more impaired hemodynamic conditions. With the heart beating in

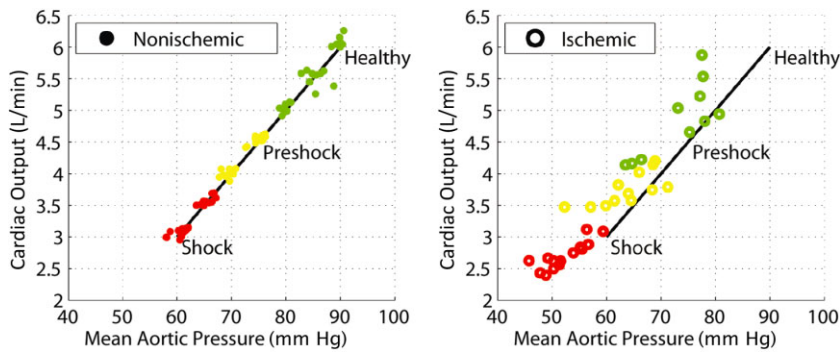


FIG. 1. Clinical scenarios at baseline, ranging from healthy (green) to preshock (yellow) to shock (red). On the left side (solid dots), no ischemia is present. On the right side (open dots), extensive myocardial ischemia is superimposed upon the different (hypo) contractile states.

periodic continuous working left heart mode, systemic vascular resistance was adapted in order to achieve the best clinical scenario feasible, given the specific contractility of the heart. Subsequently, the transition between the different hemodynamic states was accomplished by step-wise administration of negative inotropic agents (1 mg metoprolol or 10 mg esmolol per step), while systemic vascular resistance was adapted accordingly. Next, in the second series of six hearts (hearts 7–12), the clinical scenario of a large myocardial infarction in conjunction with the pump failure was mimicked. Because occlusion of a large coronary artery in the porcine heart could induce severe arrhythmias and even ventricular fibrillation, we chose to create global severe ischemia by decreasing the arterial oxygen supply in the extracorporeal circulation. In all simulated scenarios, measurements were performed with and without IABP support. The support capabilities of the pump were evaluated in terms of coronary blood flow, cardiac output, and myocardial oxygen consumption, as the mutual relation between these three parameters determines the efficacy of the IABP. To test reproducibility of the observations, the sequence of all measurements was repeated without and with IABP support, leaving all other parameters unchanged.

RESULTS

Clinical scenarios of pump failure and ischemia

The isolated beating porcine heart (24) was capable of generating flow patterns and pressure curves that closely mimicked aortic and coronary in vivo flow and pressure, which was already confirmed by De Hart et al. (24). In all hearts, heart rate could be fixed within a physiologic range (94–125 beats/min) (Table 1).

Step-wise administration of negative inotropic drugs enabled the transition towards clinical states of progressively impaired pump failure precisely (Fig. 1;

Table 1). Deterioration of myocardial performance was reflected by a decrease in the maximum rate of left ventricular pressure change (dp/dt_{max}) from 1093 ± 162 mm Hg/s in healthy state to 818 ± 212 mm Hg/s in cardiogenic shock without ischemia. The corresponding decreased aortic pressure, which functioned as driving pressure for coronary perfusion, resulted in a proportional decrease in coronary blood flow and oxygen consumption of the heart, as the external mechanical work the heart had to perform also decreased. In the end, the simulated clinical scenarios, whether or not superimposed with myocardial ischemia, covered the complete range from healthy to pathologic (Fig. 1).

In the nonischemic hearts (hearts 1–12), myocardial perfusion was considered to be adequate. Beating in a healthy scenario (Fig. 1, Table 1), hyperemic coronary blood flow amounted to 1.2 ± 0.2 L/min, myocardial oxygen consumption, corrected for the heart's weight, was found to be in the same range as the oxygen consumption of an in vivo human heart at rest (5.5 ± 1.7 mL/min/100 g), and the blood oxygen saturation level reduced from $97 \pm 1\%$ (arterial) to $84 \pm 6\%$ (venous) on passing through the cardiac tissue. In the hearts where myocardial ischemia was introduced (hearts 7–12) (Fig. 1; Table 1), however, the lowered arterial oxygen saturation ($56 \pm 22\%$), despite similar coronary blood flow levels (1.2 ± 0.4 L/min), induced a (sub)critical oxygen insufficiency. Venous oxygen saturation was depressed accordingly ($43 \pm 17\%$) and went along with a progressive hemodynamic deterioration over time (Fig. 2). At the same time, dp/dt_{max} further decreased and preload, as reflected by left atrial pressure, further increased (Table 1).

IABP support

A representative example of the effects of IABP support is shown in Fig. 2. When switching on IABP support, the catheter-mounted polyurethane balloon induced a diastolic blood pressure augmentation as

TABLE 1. Heart specific baseline hemodynamic parameters (mean \pm SD and range of values) recorded with the hearts beating in the different clinical scenarios (ranging from healthy to shock). In hearts 7–12, global severe myocardial ischemia was superimposed upon the initially tuned nonischemic reference state

Parameter	Unit	Nonischemic (hearts 1–12)			Ischemic (hearts 7–12)		
		Healthy	Preshock	Shock	Healthy	Preshock	Shock
HR	Beats/min	1.2 \pm 0.2 (0.9, 1.8)	107 \pm 10 (100, 124)				
Q_{cor}	L/min	1.0 \pm 0.2 (0.7, 1.8)	1.0 \pm 0.2 (0.7, 1.8)	0.8 \pm 0.2 (0.5, 1.4)	1.2 \pm 0.4 (0.7, 1.8)	107 \pm 9 (94, 125)	0.7 \pm 0.4 (0.4, 1.1)
CO	L/min	5.5 \pm 0.4 (4.9, 6.2)	4.3 \pm 0.3 (3.9, 4.6)	3.3 \pm 0.3 (3.0, 3.7)	4.9 \pm 0.6 (4.1, 5.9)	1.0 \pm 0.3 (0.6, 1.6)	2.7 \pm 0.2 (2.4, 3.1)
$M\dot{V}O_2$	mL/min/100 g	5.5 \pm 1.7 (0.9, 7.2)	4.2 \pm 1.7 (1.0, 6.2)	3.7 \pm 1.6 (0.7, 5.5)	4.2 \pm 1.4 (2.2, 5.9)	3.7 \pm 0.3 (3.5, 4.2)	3.9 \pm 1.4 (2.0, 6.1)
p_{ao}	mm Hg	84 \pm 4 (79, 90)	72 \pm 3 (68, 76)	63 \pm 3 (58, 67)	73 \pm 6 (64, 81)	64 \pm 6 (52, 71)	52 \pm 4 (46, 59)
p_{la}	mm Hg	14 \pm 3 (9, 22)	14 \pm 2 (8, 18)	14 \pm 2 (9, 18)	29 \pm 4 (23, 35)	26 \pm 3 (21, 30)	26 \pm 5 (20, 31)
dp/dt_{max}	mm Hg/s	1093 \pm 62 (737, 1341)	1077 \pm 367 (601, 1911)	818 \pm 212 (445, 1262)	1017 \pm 182 (737, 1341)	947 \pm 373 (601, 1911)	668 \pm 156 (445, 952)
SVR	dyn·s/cm ⁵	1234 \pm 44 (1168, 1319)	1356 \pm 37 (1304, 1434)	1532 \pm 58 (1447, 1638)	1214 \pm 83 (1055, 1307)	1360 \pm 82 (1205, 1503)	1547 \pm 66 (1356, 1632)

HR, heart rate; Q_{cor} , coronary flow; CO, cardiac output; $M\dot{V}O_2$, myocardial oxygen consumption; p_{ao} , aortic pressure; p_{la} , left atrial pressure; dp/dt_{max} , maximum rate of left ventricular pressure change; SVR, systemic vascular resistance.

well as a systolic reduction in afterload. Without ischemia, these blood pressure changes resulted in a significant (but mild) increase in coronary blood flow and cardiac output, with increases of $10 \pm 6\%$ ($P < 0.01$) and $3 \pm 2\%$ ($P < 0.01$), respectively in cardiogenic shock (Fig. 3A,B, solid bars; Table 2). Furthermore, the IABP induced a limited decrease in myocardial oxygen consumption when the (nonischemic) heart was perfused adequately ($-3 \pm 6\%$; $P < 0.01$) (Fig. 3C, solid bars; Table 2). With superimposed ischemia, however, the increase in coronary blood flow and cardiac output (and decrease of left atrial pressure) became largely augmented and the more with increasing degree of pump failure. In case of severe heart failure with superimposed ischemia, coronary blood flow and cardiac output were able to increase by $49 \pm 24\%$ ($P < 0.01$) and $17 \pm 6\%$ ($P < 0.01$), respectively (Fig. 3A,B, hatched bars; Table 2), while left atrial pressure decreased by $42 \pm 14\%$ ($P < 0.01$). As expected, myocardial oxygen consumption increased ($23 \pm 10\%$; $P < 0.01$) when more blood was offered to ischemic tissue (Fig. 3C, hatched bars; Table 2). All these effects occurred within several minutes and were very reproducible (Fig. 2).

DISCUSSION

In this study, we studied the effects of IABP support on both cardiac and coronary hemodynamics in the isolated beating porcine heart (24) under controllable physiologic and pathologic conditions. Although the magnitude of induced effects slightly varied between the individual hearts, these were generally limited with pump failure alone, but largely augmented with increasing myocardial ischemia. In case of severe pump failure with superimposed myocardial ischemia, the IABP was capable of effectively supporting the circulation by increasing hyperemic coronary blood flow, blood pressure, and cardiac output by $49 \pm 24\%$, $13 \pm 5\%$, and $17 \pm 6\%$, respectively. At the same time, left atrial pressure decreased by $42 \pm 14\%$ and myocardial oxygen consumption increased by $23 \pm 10\%$, reflecting that not only more oxygen was delivered to the ischemic heart but also utilized.

In contrast to former studies on the pathophysiologic mechanism of IABP support, which are often difficult to interpret (27), our results were very consistent and reproducible. Those earlier studies reported a wide divergence of changes, for example, changes in coronary blood flow range from a 100% increase (21), to no change (13) or even a 10% decrease (14). We were able to reduce the variability within the same clinical conditions considerably by

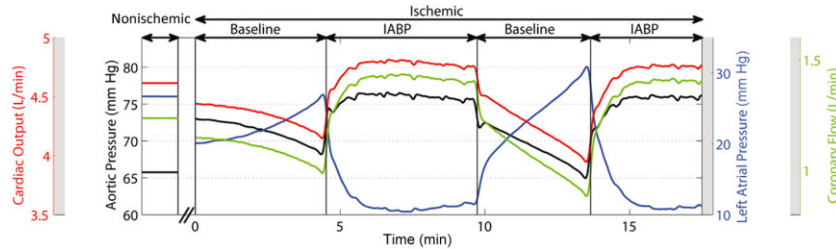


FIG. 2. Example of the effect of IABP on hemodynamic parameters in one of the hearts, starting in the preshock mode. Without ischemia (left part of the figure), cardiac output equals 4.6 L/min (red line), blood pressure equals 76 mm Hg (black line), left atrial pressure equals 16 mm Hg (blue line), and coronary blood flow equals 1.2 L/min (green line). Next, additional global ischemia is slowly created by decreasing arterial oxygen saturation in the extracorporeal circulation. This is accompanied by a slow decrease in cardiac output, coronary blood flow, and blood pressure and an increase in left atrial pressure. At a particular point in time (called $t = 0$ min), the downward spiral is accelerated and progressive deterioration occurs. Next, without any change in external oxygen supply or any of the other controllable parameters, the IABP is switched on ($t \approx 5$ min) and within 2 min, a significant improvement of cardiac output, coronary blood flow, and blood pressure occurs, while left atrial pressure decreases dramatically. All parameters stabilize within a few minutes. At $t \approx 10$ min, the IABP is switched off again without any change in any of the controllable parameters, whereafter the heart rapidly deteriorates and enters the negative vicious circle again. By switching on the IABP ($t \approx 15$ min), significant improvement and stabilization occurs again.

better classifying the different clinical scenarios, based on their hemodynamic characteristics of pump failure and the presence or absence of myocardial ischemia. This allowed us to evaluate more accurately the hemodynamic state dependency of IABP support.

Former studies in this field consistently overlooked the effect of coronary autoregulation, which counteracts any increase of coronary blood flow by increased

diastolic aortic pressure in nonischemic pump failure (23). Neither did they sufficiently recognize the difference between pump failure due to irreversible damage of myocytes (necrosis), as encountered in many clinical conditions of (pre)shock, and pump failure as a result of temporarily depressed function of still viable myocytes caused by severe ischemia due to no-reflow after acute myocardial infarction or cardiac surgery.

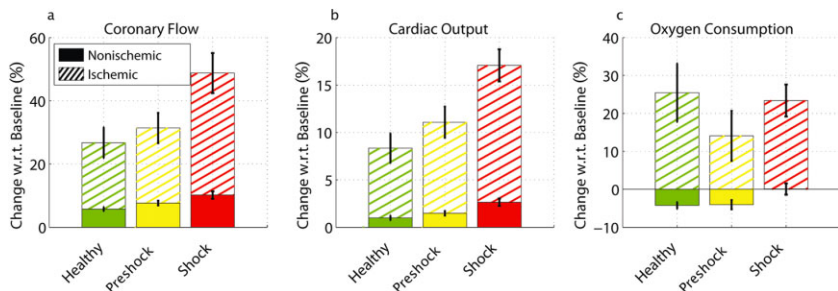


FIG. 3. Change (mean \pm SEM) by IABP support compared with the status without IABP of coronary blood flow (left), cardiac output (center), and myocardial oxygen consumption (right) for different clinical scenarios, ranging from healthy to cardiogenic shock, whether (hatched) or not (solid) in the presence of global myocardial ischemia.

TABLE 2. Percent changes of hemodynamic parameters (mean \pm SD and range of values) after starting IABP support (compared to the status without IABP) in the different hemodynamic scenarios, whether or not with superimposed persisting myocardial ischemia (hearts 1–12: without ischemia; hearts 7–12: with ischemia)

Parameter	Unit	Nonischemic (hearts 1–12)			Ischemic (hearts 7–12)		
		Healthy	Preshock	Shock	Healthy	Preshock	Shock
Q_{cor}	% Δ	$6 \pm 3^*$ (0, 12)	$8 \pm 4^*$ (0, 14)	$10 \pm 6^*$ (-2, 22)	$27 \pm 15^*$ (6, 53)	$31 \pm 17^*$ (4, 56)	$49 \pm 24^*$ (26, 105)
CO	% Δ	$1 \pm 1^*$ (-2, 3)	$1 \pm 2^*$ (-1, 4)	$3 \pm 2^*$ (0, 9)	$8 \pm 5^*$ (1, 16)	$11 \pm 6^*$ (3, 19)	$17 \pm 6^*$ (10, 32)
$M\dot{V}O_2$	% Δ	$-4 \pm 5^*$ (-15, 4)	$-4 \pm 6^*$ (-16, 6)	0 ± 7 (-12, 14)	$25 \pm 22^*$ (-5, 66)	14 ± 16 (-1, 38)	$23 \pm 10^*$ (13, 40)
p_{ao}	% Δ	$1 \pm 2^*$ (-2, 10)	$1 \pm 2^*$ (-2, 4)	$2 \pm 2^*$ (-2, 7)	$6 \pm 5^*$ (-1, 11)	$8 \pm 6^*$ (-2, 17)	$13 \pm 5^*$ (5, 26)
p_{la}	% Δ	$-14 \pm 12^*$ (-33, 6)	$-14 \pm 12^*$ (-36, 5)	$-15 \pm 10^*$ (-36, -1)	$-30 \pm 17^*$ (-52, -1)	$-39 \pm 14^*$ (-62, -16)	$-42 \pm 14^*$ (-64, -21)
dp/dt_{max}	% Δ	11 ± 19 (-18, 43)	3 ± 16 (-21, 43)	$16 \pm 24^*$ (-18, 68)	13 ± 19 (-18, 43)	9 ± 17 (-18, 43)	$26 \pm 23^*$ (-4, 68)
SVR	% Δ	0 ± 1 (-2, 6)	0 ± 1 (-5, 3)	-1 ± 2 (-5, 2)	$-2 \pm 2^*$ (-5, 0)	$-3 \pm 2^*$ (-6, -1)	$-3 \pm 2^*$ (-7, 2)

*Paired t -test: $P < 0.05$ versus baseline.

Q_{cor} , coronary flow; CO , cardiac output; $M\dot{V}O_2$, myocardial oxygen consumption; p_{ao} , aortic pressure; p_{la} , left atrial pressure; dp/dt_{max} , maximum rate of left ventricular pressure change; SVR , systemic vascular resistance.

From the data obtained in this study, one can conclude that in case of pump failure alone without myocardial ischemia, the IABP induces only small effects. That is in congruence with earlier negative studies to the effects of the IABP in shock without concomitant ischemia (17–19). With intact autoregulation (which is the case with isolated pump failure outside the setting of acute myocardial infarction or cardiac surgery), it cannot be expected that coronary blood flow will increase and the only effect to be expected is the change of cardiac output by afterload reduction, which is limited as shown in this study. In contrast, in case of pump failure with viable ischemic myocardium and exhausted autoregulation, a direct relation between coronary blood flow and diastolic aortic pressure is present and higher diastolic pressure is linearly related to higher coronary blood flow, as we have shown before (25). In such situations, improved perfusion of the ischemic myocardium will in turn relieve ischemia of the myocytes, enhance oxygen utilization, and restore contractile function and cardiac output, thereby further improving coronary perfusion and reversing a negative spiral. A corresponding clinical condition where autoregulation is exhausted exists inside the patient with a large myocardial infarction and successful epicardial reperfusion by stenting, but so-called no-reflow and persistent ischemia of still viable myocardium (28). A recent retrospective analysis of Van Nunen et al. (29) showed that the outcome in these patients is favorable and mandates further prospective studies. Another clinical scenario resembling these conditions exists inside the patient after coronary bypass surgery with good bypasses but transient myocardial stunning due to prolonged extracorporeal circulation (30,31). In response to this hypothesis, a sub-analysis of the Counterpulsation Reduces Infarct Size Percutaneous coronary intervention Acute Myocardial Infarction (CRISP-AMI) study (18) was performed, in which IABP support in patients with large anterior wall myocardial infarction complicated by persistent ischemia after primary percutaneous coronary intervention was investigated (32).

It has been hypothesized that during IABP support myocardial oxygen consumption should decrease because of the extended work by the IABP due to afterload reduction. In the nonischemic states, we indeed found a limited decrease in myocardial oxygen consumption despite a small increase of cardiac output, suggesting that external energy was delivered to the circulation indeed, in agreement with findings of Powell et al. (2). However, in the ischemic states, myocardial oxygen consumption increased, which can be explained by the fact that the

increased coronary blood flow in this situation effectively increased myocardial oxygen supply, leading to utilization of oxygen by the ischemic myocytes, reduction of myocardial ischemia, and increase of cardiac output, and migration of the no-reflow phenomenon, as confirmed by Pierrakos et al. (33). This improvement of left ventricular contractility was in congruence with a recent study of the effects of the IABP in a setting of acute ischemic heart failure (34).

Based upon the findings of this study, one can also hypothesize that in case of pump failure without ischemia, left ventricular assist devices and transvalvular assist devices, like Impella (Abiomed Cardiovascular Inc., Danvers, MA, USA), are more effective than IABP because the action of these devices is based upon direct increase of cardiac output without interacting primarily with coronary blood flow or myocardial oxygen utilization. In contrast, when pump failure is due to reversible ischemia of the myocardium, the IABP is effective by relieving ischemia, supporting temporarily depressed contractile function, salvage of myocardium, and therefore beneficial in the long run.

Strengths and limitations of this study

Although the isolated beating porcine heart was capable of generating flow patterns and pressure curves that closely mimicked in vivo flow and pressure (24), ex vivo testing is not the equivalent of in vivo testing. Not all physiologic feedback mechanisms are still intact in the isolated heart as proven earlier: coronary autoregulation is absent (25) (an advantage in this particular ex vivo model to investigate IABP effects), heart rate was fixed within a physiologic range by means of pacing (assuring no interference with the required time for complete inflation and deflation of the balloon), and systemic vascular resistance was only tuned initially to render the prescribed clinical scenarios and not changed thereafter. Furthermore, the effects of IABP support would probably be even more pronounced when the preload reduction following institution of IABP support would be compensated by increased filling as would have been the case in vivo. The reduced preload by the IABP in this model lowered the end diastolic left ventricular filling pressure and volume, and consequently ventricular contractility (Frank-Starling mechanism). So, in the in vivo situation where the preload reduction by the IABP would have been compensated, the increase in cardiac output would most likely have been even more pronounced than in our ex vivo model.

Because occlusion of a large coronary artery in the porcine heart could induce severe arrhythmias and

even ventricular fibrillation, we had to create global severe ischemia by step-wise decreasing the arterial oxygen supply in the extracorporeal circulation, thereby simulating the scenario of a large myocardial infarction with viable myocardium. Another limitation of this method was that the accuracy of measuring blood gasses of the CDI 500 blood parameter monitoring system (Terumo Cardiovascular Systems) is reduced when blood oxygen levels are low.

One of the strengths of this model is that a larger number of interacting physiologic parameters involved in vivo are excluded in this isolated beating porcine heart model (24), allowing good control of the hemodynamic condition. Measurements can be performed far more accurately than in vivo. Another specific strength is that the isolated beating porcine hearts are not live animal experiments as these organs are slaughterhouse by-products. This ex vivo testing is therefore time and cost efficient, while ethical objections are reduced, because sacrificing large animals for experimental research is avoided. Therefore, the isolated beating porcine heart forms an accessible platform to investigate the heart and the coronary circulation in its truly morphologic and physiologic way, including studying changes in cardiac output, coronary blood flow, and oxygen metabolism in response to IABP support.

CONCLUSION

In this ex vivo beating heart study, the intra-aortic balloon pump significantly improved coronary blood flow, blood pressure, and cardiac output, enhanced oxygen utilization, and within minutes reversed the progressive hemodynamic deterioration in case of severe pump failure with superimposed myocardial ischemia. Consequently, in clinical practice, IABP support can be expected to be most effective in patients with viable myocardium, suffering from persistent myocardial ischemia, despite adequate epicardial reperfusion. This is the case in acute myocardial infarction patients after successful stenting but accompanied by no-reflow or after bypass surgery with stunning and ischemic but viable myocardium. Large randomized clinical trials are mandatory to support these views.

Acknowledgments: The research is funded by the Dutch Technology Foundation STW (Stichting Toegepaste Wetenschappen) under project number 11052. The authors are grateful to LifeTec Group (Eindhoven, The Netherlands) for giving access to their isolated beating porcine heart platform.

Author contributions: Stéphanie Schampaert designed the study, performed the experiments, analyzed data and wrote the article. Nico H.J. Pijls, Marcel van 't Veer, and Lokien X. van Nunen conceived the idea of the measurements, contributed in writing, and were, together with Marcel C.M. Rutten, involved in study design, data collection, and data analysis. Sjoerd van Tuijl prepared and performed the experiments and collected data. Frans N. van de Vosse and Nico H.J. Pijls supervised the project. All authors discussed the results and commented on the manuscript.

Conflict of Interest: Nothing to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Isolated beating porcine heart beating in periodic continuous working left heart mode.