

Automated control of Impella maintains optimal left ventricular unloading during periods of unstable hemodynamics and prevents myocardial damage in acute myocardial infarction



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ABSTRACT

Background: Left ventricular (LV) unloading by Impella, an intravascular microaxial pump, has been shown to exert dramatic cardioprotective effects in acute clinical settings of cardiovascular diseases. Total Impella support (no native LV ejection) is far more efficient in reducing LV energetic demand than partial Impella support, but the manual control of pump speed to maintain stable LV unloading is difficult and impractical. We aimed to develop an Automatic IMPella Optimal Unloading System (AIMOUS), which controls Impella pump speed to maintain LV unloading degree using closed-feedback control. We validated the AIMOUS performance in an animal model.

Methods: In dogs, we identified the transfer function from pump speed to LV systolic pressure (LVSP) under total support conditions ($n = 5$). Using the transfer function, we designed the feedback controller of AIMOUS to keep LVSP at 40 mmHg and examined its performance by volume perturbations ($n = 9$). Lastly, AIMOUS was applied in the acute phase of ischemia-reperfusion in dogs. Four weeks after ischemia-reperfusion, we assessed LV function and infarct size ($n = 10$).

Results: AIMOUS maintained constant LVSP, thereby ensuring a stable LV unloading condition regardless of volume withdrawal or infusion ($\pm 8 \text{ ml/kg}$ from baseline). AIMOUS in the acute phase of ischemia-reperfusion markedly improved LV function and reduced infarct size (No Impella support: 13.9 ± 1.3 vs. AIMOUS: $5.7 \pm 1.9\%$, $P < 0.05$).

Conclusions: AIMOUS is capable of maintaining optimal LV unloading during periods of unstable hemodynamics. Automated control of Impella pump speed in the acute phase of ischemia-reperfusion significantly reduced infarct size and prevented subsequent worsening of LV function.

Abbreviations: AF, atrial fibrillation; AIMOUS, automated Impella optimal unloading system; AMI, acute myocardial infarction; AP, arterial pressure; ECMO, extracorporeal membrane oxygenation; ECPELLA, the combination therapy of extracorporeal membrane oxygenation and Impella; Ees, end-systolic elastance; EW, external work; LAP, left atrial pressure; LV, left ventricle; LVAD, left ventricular assist device; LVEDP, left ventricular end-diastolic pressure; LVP, left ventricular pressure; LVSP, left ventricular systolic pressure; LVV, left ventricular volume; MVO₂, myocardial oxygen consumption; PE, potential energy; PI, proportional integral; PVA, pressure-volume area; PVC, premature ventricular contraction; RAP, right atrial pressure; RV, right ventricle.

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1. Introduction

The recent development of the percutaneous left ventricular assist device (LVAD), Impella (Abiomed, Inc., Danvers, MA) [1], has been revolutionizing therapeutic intervention in acute clinical settings of cardiovascular diseases such as acute coronary syndrome and acute heart failure. The percutaneous LVAD not only provides powerful circulatory support but also unloads the left ventricle (LV) [2–5].

The pressure-volume relationship of the LV determines LV energetics. Suga et al. reported [6] that the pressure-volume area (PVA), which is the sum of LV external work (EW) and potential energy (PE), correlates linearly with myocardial oxygen consumption (MVO_2). Mechanical unloading, such as with Impella, decreases LV pressure (LVP) and volume (LVV), and thereby PVA.

The optimal degree of LV unloading varies depending upon the nature of the pathophysiology. In myocardial infarction, the degree of LV unloading in the acute phase is inversely correlated with infarct size. Acute unloading therapy reduces infarct size and prevents the development of subsequent heart failure [2]. Furthermore, LV unloading before coronary reperfusion in a swine model reduces ischemia-reperfusion injury [3,7]. However, device-related adverse events undermine these beneficial effects of unloading because rapid pump speed can cause suction in the LV or hemolysis due to excessive shear stress, resulting in myocardial injury, arrhythmias, insufficient LV support, and acute kidney injury [8–10]. In the recovery phase, careful monitoring of LV function and hemodynamics is essential for successful pump withdrawal.

In partial support, the LV continues to eject blood through the aortic valve. Although Impella withdraws blood from the LV and reduces preload (i.e., end-diastolic volume), the increased net cardiac output (i.e., native LV output + Impella flow) elevates arterial pressure and arterial afterload. As a result of these opposing effects of Impella support on the LV, the net effect of partial support on the reduction of PVA is limited [5]. Therefore, partial support achieves only partial unloading and a limited reduction of MVO_2 . In contrast, the LV no longer ejects in total support, and systemic flow depends entirely on Impella. Thus, total Impella support markedly reduces PVA and MVO_2 [5,11], and exerts powerful cardioprotective effects. However, a subtle alteration of pump speed, LV function, and/or LV loading conditions can dramatically change the LVP leading to device suction in the LV and labile hemodynamics. As a result, total support is inherently unstable and requires meticulous manual Impella flow regulation. Such a critical requirement for manual control of Impella speed makes its clinical utilization impractical.

On the basis of these considerations, we aimed to develop an automated pump control system enabling optimal and stable LV unloading in the acute phase of cardiovascular diseases. We used Impella CP and developed an Automated IMpella Optimal Unloading System (AIMOUS). The performance of AIMOUS was validated in a dog model of impaired LV function. We demonstrated that AIMOUS could establish total support and reduce infarct size in a dog model of ischemia-reperfusion in the chronic phase.

2. Methods

2.1. Automated Impella optimal unloading system (AIMOUS)

The Impella device pumps blood from the LV to the aorta. We previously reported that increases in Impella flow linearly decrease PVA [11]. In the setting of total Impella support, where the LV is no longer ejecting through the aortic valve, a small rise in Impella flow markedly decreases LVP and LVV and results in potentially harmful suction. This pump speed-supersensitivity of total Impella support makes the manual control of pump-speed impractical. To overcome this limitation, AIMOUS was developed to maintain stable total Impella support. The term “optimal unloading” is used because the controller was designed to

stably and totally unload the LV. We used LV systolic pressure (LVSP) as an indicator of the degree of unloading. Fig. 1 shows the system block diagram of AIMOUS. First, we determined a target LVSP value. Then, we derived the error signal as the difference between the target LVSP and measured LVSP. The error signal drives the feedback controller, and the controller changes the pump speed until the error signal becomes zero, which implies that the measured LVSP matches the target value. Specific details of AIMOUS operation are described in the supplemental material online, *Method S1*.

2.2. Animals, anesthesia, and preparation

The Committee on Ethics of Animal Experiments at Kyushu University Graduate School of Medical Sciences and the Animal Subjects Committee at the National Cerebral and Cardiovascular Center reviewed and approved the protocols. We used a total of 24 adult mongrel dogs weighing 14.5 to 17.5 kg. We induced anesthesia by intravenous pentobarbital (25 mg/kg) and vecuronium bromide (0.08 ml/kg). Dogs were intubated and artificially ventilated with room air. An appropriate anesthesia level was maintained with 1–2% isoflurane and body temperature was kept constant at approximately 38 °C. In all experiments, a 5F catheter was placed in the left femoral vein for administering fluids. Another 5F catheter was inserted in the right femoral artery for measuring aortic pressure (AP). After a median sternotomy, we inserted fluid-filled catheters to the left and right atria. We measured AP, left atrial pressure (LAP), and right atrial pressure (RAP) by using pressure transducers (model DX-360; Nihonkohden, Tokyo, Japan). The simultaneous LVP and LVV measurements for PV loop analysis were also conducted in each protocol (see supplemental material online, *Method S2*). In protocols 1 and 2, myocardial infarction was induced to cause LV failure, and only in protocol 3 was the ischemia-reperfusion study. After a left thoracotomy at the fifth intercostal space, the left anterior descending coronary artery and the major diagonal branches were ligated with 3–0 nylon sutures to create the impaired LV condition. In protocol 3, we ligated the same coronary arteries for three hours and then reperfused with or without AIMOUS. The control group was not supported by Impella. We closed the chest and allowed the animals to recover. Four weeks after acute myocardial infarction (AMI) with reperfusion, we reanesthetized animals and evaluated LV function and infarct size.

Impella CP (Abiomed Inc., Danvers, MA) was used for mechanical support in all protocols. After left thoracotomy at the second intercostal space, we inserted an Impella CP catheter into the LV via the left subclavian artery because the femoral approach was difficult in dogs. We carefully positioned the Impella CP in the LV under fluoroscopic guidance.

2.2.1. Protocol 1: Static and dynamic impact of Impella CP on hemodynamics

In protocol 1, in five dogs, we identified the dynamic characteristics of the plant to be controlled. The input to the plant is the command

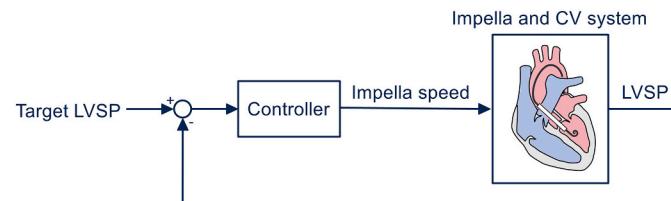


Fig. 1. The functional diagram of the automated Impella optimal unloading system (AIMOUS). AIMOUS consists of a closed-feedback system. The difference between the target left ventricular systolic pressure (Target LVSP) and measured LVSP is processed in the controller, and the resultant controller output regulates the Impella speed to achieve the stable total Impella support (no LV ejection in systole) and profound LV unloading.

speed to Impella CP, and the output is LVSP under total Impella support. We increased the Impella CP speed to the point where LVSP becomes about 50% of AP. This Impella CP speed ensured total Impella support and served as the predetermined reference speed. We then estimated the dynamic characteristics of the plant. We switched the Impella pump speed with a minimum interval of 2 s between ± 2000 rpm around the reference speed according to a binary random sequence. Data were recorded for 10 min. The resultant dynamic characteristics of the plant were used to design the AIMOUS controller.

2.2.2. Protocol 2: AIMOUS performance study

The performance of AIMOUS was demonstrated under volume perturbation in nine dogs before and after the creation of the impaired LV. We changed the target LVSP to examine if the AIMOUS can achieve the target LVSP under the total Impella support. We then set the target LVSP at 40 mmHg, and imposed the volume perturbation stepwise with a manual syringe connected to the femoral vein from the baseline to ± 8 ml/kg. In each step, we completed the infusion or withdrawal in <10 s and waited for at least 100 s to allow hemodynamics to reach a steady state. We then examined the stability of LVSP. We compared the LVSPs controlled with and without AIMOUS (i.e., constant Impella flow).

2.2.3. Protocol 3: AIMOUS for AMI and its longterm effects

The impact of AIMOUS on infarct size and cardiac function was investigated four weeks after ischemia-reperfusion. We ligated the coronary arteries to induce ischemia and reperfused 180 min after the ligation. We randomly allocated 10 dogs into the AIMOUS group ($n = 6$) and no Impella support group ($n = 4$). In the AIMOUS group, we activated AIMOUS 60 min after ischemia with the target LVSP of 40 mmHg and terminated AIMOUS 60 min after the reperfusion (a total time of 180 min on AIMOUS). Subsequently, the chest was closed, and animals were allowed to recover. Four weeks after ischemia-reperfusion, LV function and infarct size in each dog were evaluated.

2.3. Data analysis

We digitized all time-series data at 200 Hz using a 16-bit analog to digital converter (PowerLab 16/35; ADInstruments, NSW, Australia) and stored in a dedicated laboratory computer system.

For the assessment of dynamic function, after identifying LVSP every beat and holding the same LVSP between the beats, we resampled LVSP and the Impella speed at 10 Hz with an anti-aliasing filter and segmented the data into 10 sets of half overlapping bins of 1024 points each. After detrending, the data were windowed with a 4-term Blackman-Harris window and were then Fourier transformed. The power spectra of Impella speed [$|Imp(f)|^2$] and LVSP [$|LVSP(f)|^2$] and their cross-spectra [$LVSP(f) \bullet Imp^*(f)$] were calculated in each bin and then ensembled over the 10 segments, where * implies complex conjugate. The transfer function of Impella speed to LVSP ($H(f)$) is derived as,

$$H(f) = \frac{LVSP(f) \bullet Imp^*(f)}{|Imp(f)|^2}$$

We also calculated the magnitude squared coherence [$Coh^2(f)$], which indicates the linear dependence of Impella speed and LVSP by the following equation:

$$Coh^2(f) = \frac{|LVSP(f) \bullet Imp^*(f)|^2}{|Imp(f)|^2 \bullet |LVSP(f)|^2}$$

2.4. Statistical analysis

We expressed data as mean \pm SD. In protocol 2, we used paired *t*-test to compare hemodynamics between no AIMOUS (i.e., constant Impella flow) and AIMOUS of the same perturbation. In protocol 3, we used Student's *t*-test to compare the data between the AIMOUS group and no

Impella support group in the dogs with ischemia-reperfusion. Differences were considered significant at $P < 0.05$. We performed the statistical analysis using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Protocol 1: Static and dynamic response of Impella

Fig. 2A-C represents the static impact of changes in Impella speed on hemodynamics. As the Impella speed increases, arterial pulse pressure decreases, while LVSP remains relatively unchanged. Once the pump speed exceeds a critical level, arterial pulse pressure nearly disappears, and LVSP suddenly falls (**Fig. 2A**). The pressure-volume loops (**Fig. 2B**) reproduce the sudden reduction of LV volume and LVSP. **Fig. 2C** (top panel) illustrates the LVSP-pump speed relationship. The steep portion is under total Impella support and indicates the super-sensitivity of LVSP against changes in pump speed. The basic characteristics did not differ between control and impaired LV conditions. Although PVA also parallels LVSP, it is not as sensitive as LVSP to pump speed (**Fig. 2C**, bottom).

Fig. 2D shows the representative time-series data of the dynamic response of LVSP to changes in Impella speed. Changes in Impella speed alter AP and LVSP out of phase. The transfer function of Impella speed to LVSP is shown in **Fig. 2E** (top 3 panels). The transfer function resembles the first-order lowpass filter with a corner frequency of 0.03 Hz. The numerically derived step response from the transfer function via inverse Fourier transform reached a steady-state in approximately 10 s (**Fig. 2E**, bottom). Based on these observations, we determined the PI controller parameters of AIMOUS as $K_p = 1$ (unitless) and $K_i = 25/s$ to attain robust controllability without sacrificing stability (Matlab R2018b, Mathworks, Natick, MA).

3.2. Protocol 2: AIMOUS performance study

Fig. 3A shows the representative time-series data under AIMOUS control. Changing the target LVSP from 40 to 70 and back to 40 mmHg altered LVSP asymptotically toward the command LVSP levels. The performance of AIMOUS in response to volume perturbation is shown in **Fig. 3B**. Although the volume load significantly increased LVSP and volume loss decreased LVSP in the constant Impella speed group, AIMOUS kept LVSP at 40 mmHg reasonably well regardless of volume perturbation.

Overall, the volume load markedly changed the Impella speed to stabilize LVSP (**Fig. 3C**), reflecting the feedback regulation of AIMOUS. In the constant pump speed group, a volume loss decreased LVSP to 3.8 ± 10.7 mmHg, and a volume addition increased LVSP to 82.3 ± 10.0 mmHg (**Fig. 3D**). In contrast, by automatically modulating pump speed, AIMOUS kept LVSP at 40 mmHg regardless of alterations in volume load. Changes in LVSP were translated into those of PVA (**Fig. 3E**). In the setting of constant speed, the volume load markedly increased PVA, which led to incomplete unloading. In contrast, the volume load hardly affected the PVA controlled by AIMOUS, thus ensuring stable, energetic unloading.

3.3. Protocol 3: AIMOUS for AMI and its longterm effects

Fig. 4A shows the representative time-series data of the effects of AIMOUS on an acute ischemia-reperfusion experiment. AIMOUS was introduced 60 min after the onset of ischemia and terminated 60 min after reperfusion. Although premature ventricular contractions (PVC) increased after reperfusion, AIMOUS controlled LVSP at 40 mmHg during support. **Fig. 4B** illustrates the impact of AIMOUS on LV function and infarct size four weeks after the acute ischemia-reperfusion. AIMOUS significantly increased E_{es} (9.5 ± 7.5 vs. 19.5 ± 5.0 mmHg/ml, $P < 0.01$), lowered LV end-diastolic pressure (LVEDP) (11.4 ± 0.7

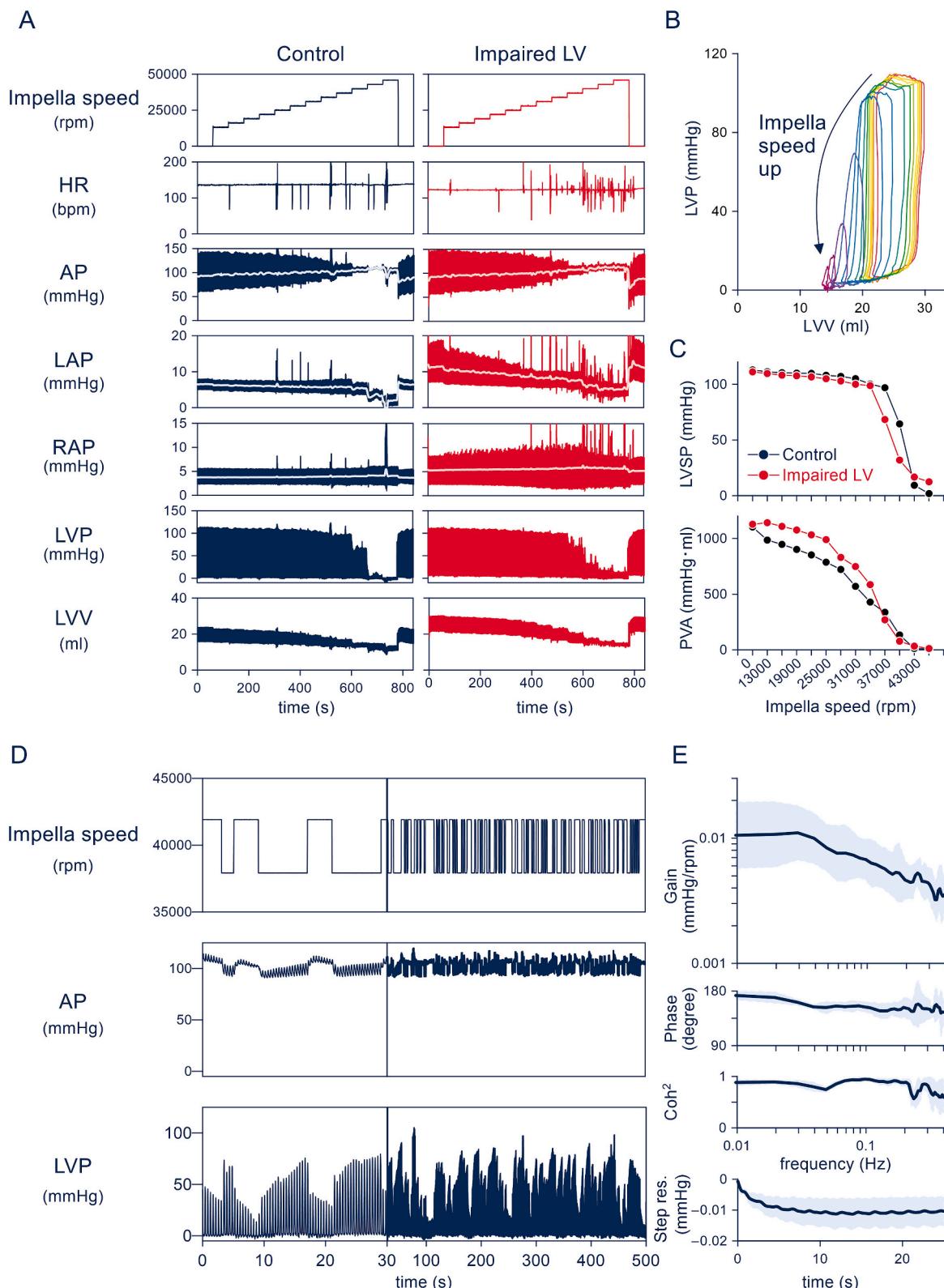


Fig. 2. The static and dynamic impact of Impella support on hemodynamics. A) Increases in Impella speed lower pulse pressure regardless of LV function. B) The impact of changes in Impella speed on LV pressure-volume loops. Impella decreases left ventricular systolic pressure (LVSP) and pressure-volume area (PVA). C) The LVSP-Impella speed relationship (top). LVSP remains relatively constant until Impella speed reaches a threshold. At the Impella speed of 34,000 rpm in an impaired LV and 37,000 rpm in control, LVSP begins to fall steeply. Nearly one-half of PVA decreases before Impella speed reaches the threshold speed (bottom). D) Time series of Impella speed, arterial pressure (AP), and left ventricular pressure (LVP). We set the average Impella speed at 40,000 rpm (reference speed) so that LV does not eject. We changed the Impella speed ± 2000 rpm around the reference speed. E) Transfer function from Impella speed to LVSP and the corresponding step response. The gain of the transfer function shows the characteristics of a first-order lowpass filter with a corner frequency of 0.03 Hz. The step response reaches a steady-state in 10 s. HR indicates heart rate; LAP, left atrial pressure; LVV, left ventricle volume; and RAP, right atrial pressure.

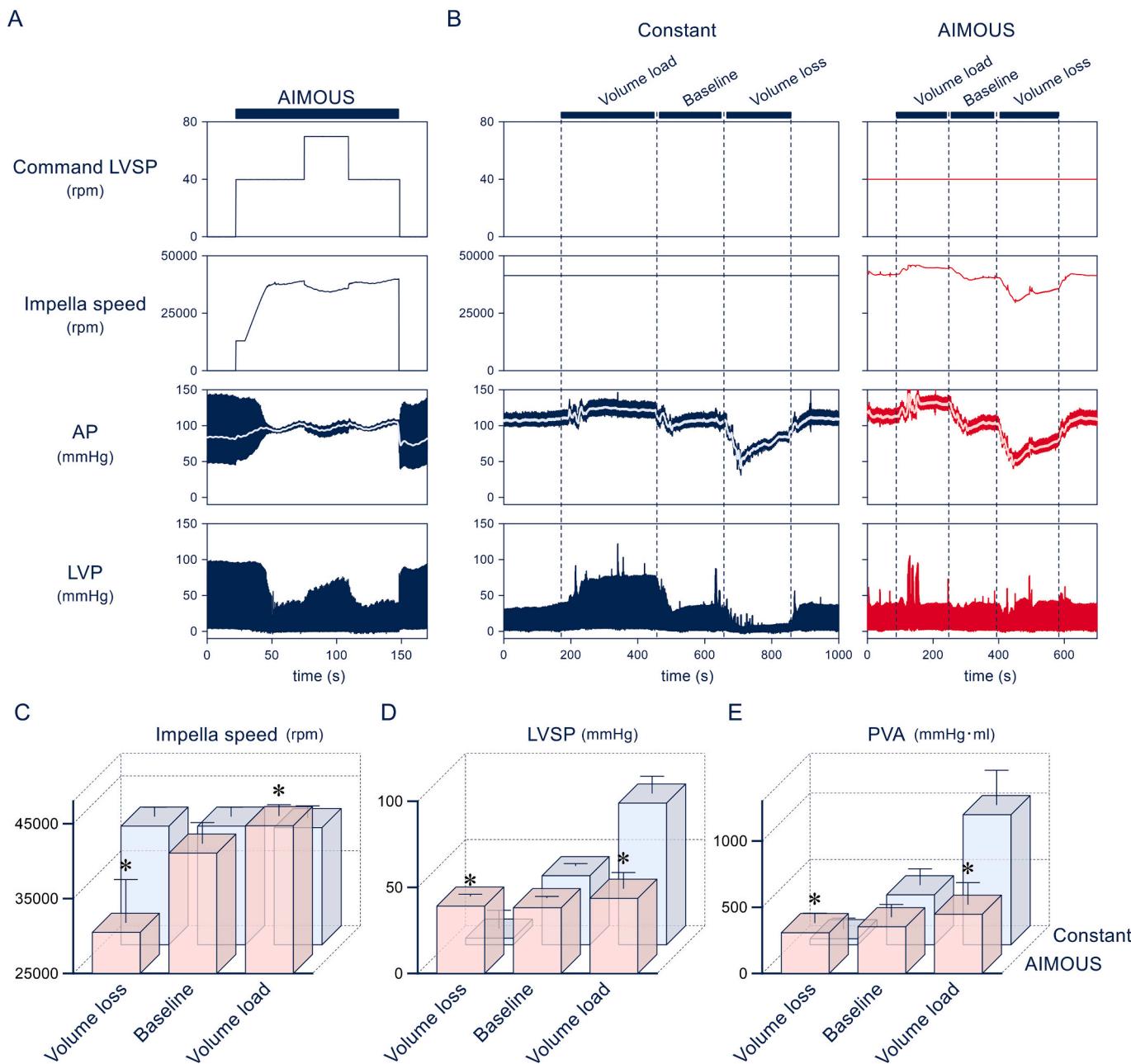


Fig. 3. Experimental validation of the performance of AIMOUS. A) AIMOUS is capable of realizing target LVSP. B) Effects of volume perturbation on LVSP with and without AIMOUS. LVSP varies widely with volume perturbation when Impella speed is constant (40,000 rpm). In contrast, activation of AIMOUS stabilizes LVSP at 40 mmHg in the presence of volume perturbations.

Pooled data on the impact of volume perturbation on Impella speed, LVSP, and PVA with AIMOUS and without AIMOUS (C-E). C) The volume perturbation dynamically changes Impella speed to keep LVSP at a constant value. D) The volume perturbation markedly changes LVSP from 80 to nearly 0 mmHg without AIMOUS. However, the activation of AIMOUS stabilizes LVSP, regardless of volume loading. E) AIMOUS maintained a constant PVA in the presence of volume perturbation. In contrast, PVA markedly changed with volume perturbation without AIMOUS. * $P < 0.05$.

vs. 5.7 ± 2.1 mmHg, $P < 0.05$), and reduced the infarct size (13.9 ± 1.3 vs. $5.7 \pm 1.9\%$, $P < 0.01$) compared with no Impella support group. AP remained unaltered. These results indicate that LV unloading by AIMOUS in the acute phase of ischemia can markedly improve LV function and reduce the infarct size in the chronic phase.

4. Discussions

In this study, we developed an Automated IMpella Optimal Unloading System (AIMOUS). The AIMOUS controller algorithm was

designed based on the dynamic characteristics of the Impella speed-LVSP relationship. In the AIMOUS performance study, AIMOUS achieved stable LV unloading and reduced PVA irrespective of volume perturbation, while a fixed speed Impella showed striking volume dependence of LVSP and PVA, thereby insufficient and unstable LV unloading. AIMOUS during the acute phase of ischemia-reperfusion significantly reduced the infarct size and prevented subsequent worsening of LV function as we previously showed in total Impella support [5].

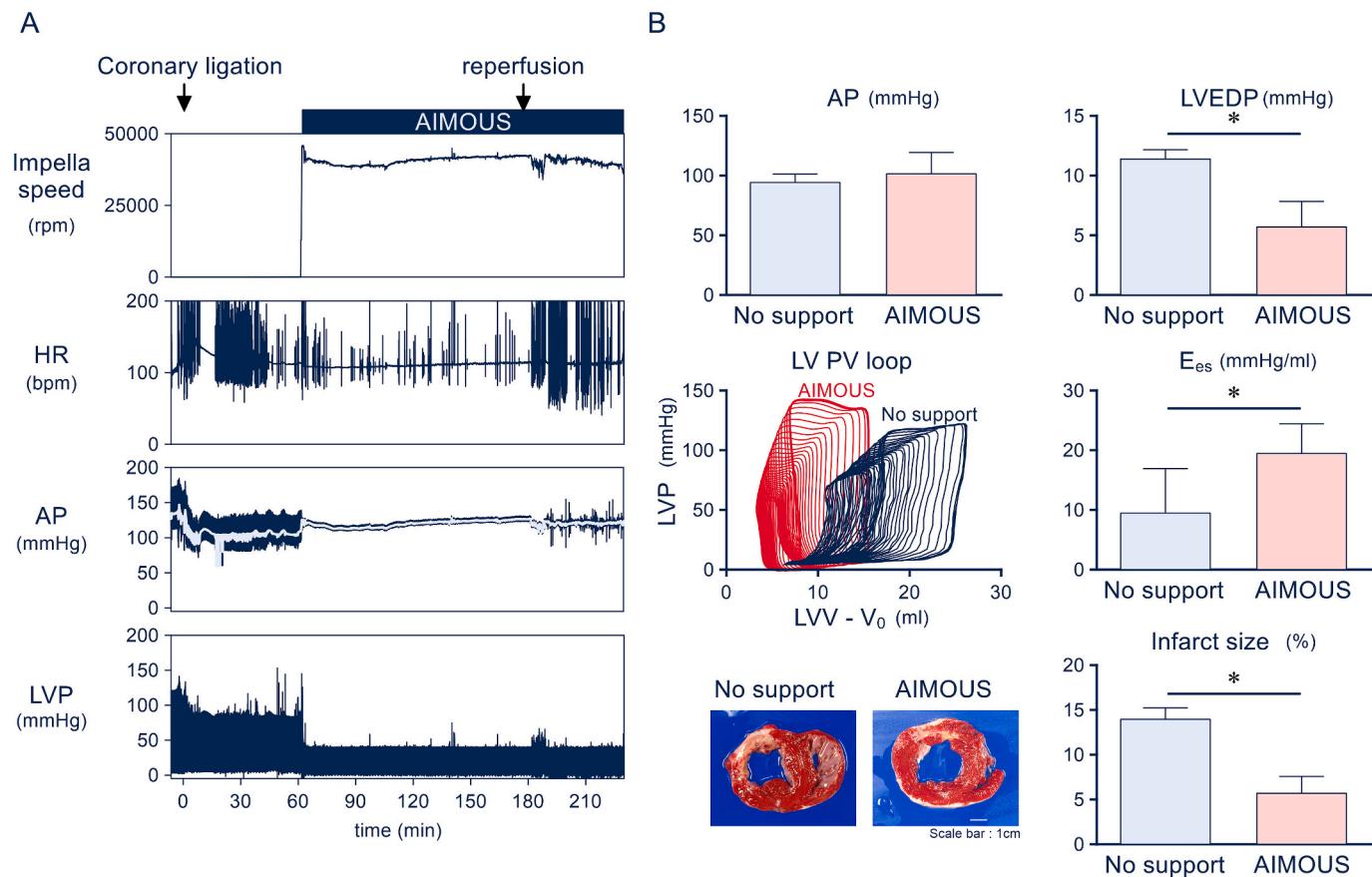


Fig. 4. The impact of AIMOUS in the setting of acute myocardial infarction. A) Representative time-series data of AIMOUS on an acute ischemia-reperfusion model. We ligated major coronary arteries and created ischemia for three hours, and reperfused. We started AIMOUS 60 min after the onset of ischemia and continued the support 60 min after reperfusion. B) LV function, hemodynamics, and infarct size one month after the ischemia-reperfusion injury in the AIMOUS group and no Impella support group. AP does not change. LV end-diastolic pressure (LVEDP) falls with AIMOUS. The pressure-volume loops shifted upper-leftward with AIMOUS support. The end-systolic elastance (E_{es}) is significantly higher with AIMOUS. The AIMOUS support in the acute phase of ischemia-reperfusion more than halved the infarct size. * $P < 0.05$. LVV indicates left ventricular volume; PV, pressure-volume; and V_0 , volume axis intercept of the end-systolic pressure-volume relationship derived from the multiple pressure-volume loops.

4.1. Development of AIMOUS for stable LV unloading

Since the cardioprotective effect parallels the degree of LV unloading [5,11], especially in acute myocardial infarction, a stable pump control system is a prerequisite to realize the full benefit of LV unloading in clinical settings. As addressed in the introduction, a small change in pump speed or instability of LV function under total Impella support could make LVSP labile and vulnerable to LV suction. In this study, we chose LVSP as the control target, considering it an indicator of both LV unloading and suction. By keeping LVSP lower than mean AP, total Impella support can be maintained. Moreover, the present study demonstrated that a slight change in Impella speed markedly decreased LVSP (Fig. 2C), indicating the potential to cause LV suction. This finding suggests that maintaining an appropriate LVSP level could serve as an indicator to prevent LV suction. The LVSP under total Impella support is determined by the cardiovascular properties, Impella pump characteristics, and their interactions. This is the first report to evaluate the dynamic characteristics between Impella speed and in-vivo hemodynamic responses using the transfer function under the total Impella support condition. The transfer function resembles the first-order lowpass filter with a corner frequency of 0.03 Hz. Based on this transfer function, we designed a conventional PI controller with $K_p = 1$ (unitless) and $K_i = 25/s$. The developed controller can accommodate a 400% change in gain and keep LVSP remarkably constant irrespective of volume perturbation. We consider this dynamic range of gain sufficient to establish the stable operation of AIMOUS in various pathophysiological conditions.

To stabilize total Impella support, the LVSP was set at 40 mmHg, where the LV is totally supported but not totally unloaded. Suga et al. reported that the reduction of PVA correlates linearly with MVO_2 , and that even when PVA is zero, indicating total unloading, MVO_2 remains at approximately 50% [6]. Considering the impracticality of achieving total unloading in vivo and the limited effectiveness of such interventions, we assumed that LVSP of 40 mmHg would be a realistic and achievable goal of optimal LV unloading by AIMOUS.

As summarized in Figs. 3, AIMOUS is capable of maintaining LVSP remarkably well in the presence of volume perturbation. We imposed the volume perturbation of $\pm 8 \text{ ml/kg}$. The activation of AIMOUS almost totally abolished preload dependent changes in LVSP. These results suggest that AIMOUS can maintain stable LV unloading and effectively respond to various hemodynamic fluctuations that may occur in clinical settings, such as changes in preload and afterload. Particularly in situations prone to suction events, such as Impella with concomitant right ventricular (RV) dysfunction/failure or the combination of Impella and VA-ECMO, AIMOUS is expected to contribute to stable circulatory support.

AIMOUS operation requires the continuous, precise, and stable measurement of LVP as an input to derive LVSP. Therefore, in this study, we used a dedicated LVP sensor catheter that satisfies this requirement. However, the requirement for high-quality LVP becomes a significant impediment to introducing AIMOUS to clinical settings. Recently, Abiomed Inc. has developed and released SmartAssist™, which measures AP by an optical sensor on the pump outlet and estimates the LVP

waveform from the motor current of Impella and AP [12]. SmartAssist™ makes AIMOUS technically feasible without a dedicated LVP transducer and provides a great opportunity for AIMOUS clinical applications. The accuracy of LVP estimated by SmartAssist™ remains uncertain for use in AIMOUS, necessitating further validation to confirm its reliability and utility.

4.2. AIMOUS for AMI

Acute myocardial infarction is one of the suitable cardiovascular diseases to which AIMOUS can contribute to the treatment. We previously reported that LV unloading in the acute phase of ischemia reduced infarct size paralleled the degree of LV unloading [5,11]. As shown in Fig. 4, AIMOUS was capable of achieving total Impella support (no LV ejection) during ischemia-reperfusion in dog hearts and strikingly reduced the infarct size (60%) and ameliorated the worsening of LV function and subsequent heart failure. These results were consistent with previous Impella experiments from other investigators [2,3].

4.3. AIMOUS and total hemodynamic management

Since AIMOUS at this stage targets stable LV unloading with total Impella support, total blood flow perfusion and AP may be inadequate in clinical cases. Particularly in the setting of RV dysfunction/failure, reduced LV preload may exacerbate Impella suction and compromise systemic perfusion. Because the Impella alone cannot address systemic flow perfusion inadequacy due to RV dysfunction/failure, additional interventions are required. Inotropes may improve RV function and volume loading may increase LV return. If LV preload remains inadequate, additional mechanical circulatory support such as VA-ECMO or Impella RP may be required.

Furthermore, the use of LVADs, including extracorporeal LVADs, has increased not only as a bridge to heart transplantation but also as a bridge to recovery [13,14]. LVADs, which can provide higher flow rates than the Impella, are expected to achieve robust and stable LV unloading when adapted to the AIMOUS algorithm, expanding its clinical applicability.

4.4. Limitations

There are some limitations to this study. First, the Impella CP with AIMOUS may not achieve total Impella support in most human cases. Total Impella support has been maintained with Impella CP (maximum flow rate 3.7 l/min) in mongrel dogs weighing <20 kg. However, in the clinical setting, there may be a case where Impella cannot achieve total Impella support even when we have attached AIMOUS for Impella 5.5 (maximum flow rate 5.5 l/min). In such cases, we must consider a comprehensive hemodynamic management strategy to achieve total Impella support, such as combination with VA-ECMO (AIMOUS mounted ECPELLA). In addition, it is also clear that maintenance of total support is not the only correct answer for treating AMI and managing Impella. Since developing a control system to guarantee total support was a significant challenge in the design of AIMOUS, this study focused on the operation and utility of AIMOUS for maintaining LVSP at 40 mmHg in animal models. However, in clinical practice, alternative targets such as partial support aimed at a 50% reduction in aortic pulse pressure may be required. Second, our system calculates LVSP and provides feedback on a beat-by-beat basis, making it susceptible to variations in LVSP caused by atrial fibrillation (AF) and frequent premature ventricular contractions (PVCs). To minimize the impact of noise caused by these arrhythmias, we have implemented a slow-response control system. As a result, we were able to attenuate the effect of isolated premature ventricular contractions on LVSP control in this experiment (Protocol 3). Although we could not validate in our experiment, a slow-response control system of AIMOUS may have the potential to control the average LVSP in the presence of AF. Since the

multiple patterns of AF and PVCs are possible to occur during the acute phase of AMI, further development of AIMOUS algorithm that can achieve stable LV unloading and Impella control during each arrhythmia will be necessary for clinical application. Third, AIMOUS cannot stabilize LVP and hemodynamics in a condition where LVSP is lower than the target LVSP when LV function and/or stressed blood volume is excessively low. This hemodynamic condition is beyond the AIMOUS controllable range and requires more intensive therapeutic interventions. Fourth, we determined the AIMOUS controller's parameters by the transfer function obtained from the animal study with Impella CP. In clinical applications, Impella CP may not provide total Impella support. Higher flow Impella such as Impella 5.5 is required in certain patients and pathologies. Therefore, we need to re-establish the controller's parameter values that give stable LV unloading in humans. Fifth, because AIMOUS is designed to achieve stable total Impella support, there is a risk of thrombosis due to blood stasis in the aortic root and aortic insufficiency. Further studies are needed to evaluate the optimal duration of AIMOUS to achieve stable total Impella support. Sixth, this study lacks an assessment of LV remodelling due to the relatively short observation period of a month after ischemia-reperfusion. Future studies with longer follow-up periods are warranted to investigate the potential impact of AIMOUS on the progression of LV remodelling after AMI. Seventh, the sample size of this study is small. As the goal of the present study is to prove the principle of automated operation of AIMOUS and is the first step to develop the automated pump control system, the limited sample size does not overshadow the value of this study. In contrast, a larger number of experiments may be needed to examine the feasibility of AIMOUS application in the clinical setting. Finally, we compared infarct size in the AIMOUS group with that in the no Impella support group. Therefore, we could not show the isolated beneficial effect of automated Impella control on infarct size reduction. To address this issue, we need a study that compares the effect of AIMOUS in dogs with AMI to a manually controlled Impella group.

5. Conclusions

AIMOUS was capable of controlling Impella speed to establish sufficient LV unloading in an unstable hemodynamic condition. In the setting of AMI, hemodynamic unloading with AIMOUS reduced the infarct size and lessened cardiac dysfunction in a dog model of ischemia-reperfusion. The automated pump control system may maximize the clinical benefit of Impella in the management of acute ischemia.

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Disclosure

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CRediT authorship contribution statement

Takuya Nishikawa: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kazuhiro Kamada:** Methodology, Investigation, Data curation. **Hidetaka Morita:** Data curation. **Shohei Yokota:** Supervision, Investigation. **Kei Sato:** Supervision, Investigation. **Takashi Unoki:** Supervision, Investigation. **Hiroyuki Tsutsui:** Supervision, Investigation. **Kenji Sunagawa:** Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Keita Saku:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2024.132244>.

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