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Letters

TO THE EDITOR

Methodological Issues and Their Impact on Conclusions

The study by Weil et al. (1) used pressure-volume (PV) analysis to compare hemodynamic effects of 2 different percutaneous mechanical circulatory support (MCS) strategies: a transvalvular pump (Impella CP ICP]) and a left atrial-to-femoral artery bypass pump (TandemHeart [TH]) in an animal model of post-myocardial infarction left ventricular (LV) dysfunction. We have written extensively on the theories of this topic, which are supported by both preclinical studies and previously described simulation of the cardiovascular system (2). Weil and colleagues identify apparent discrepancies between their experimental findings and theoretical predictions. In an accompanying editorial, Kern and Seto (3) encourage efforts directed at resolving those discrepancies. We noted several methodological issues not addressed during the review of the paper that may invalidate several of the findings. Only the most overt issues can be discussed in this brief letter, though a more thorough critique has been shared with the authors.

The shapes of the PV loops recorded by Weil et al. (1) during ICP support are not consistent with either theoretical or prior experimental data. The latter indicate that PV loops during transvalvular MCS assume more of a triangular shape due to the continuous pumping of blood from the LV throughout the cardiac cycle. The loops chosen by Weil et al. to depict the typical response to ICP support remained rectangular and were strikingly similar to their pre-support counterpart (both reproduced here in **Figure 1A**). We digitized these loops (**Figure 1B**) and observed that after applying a simple scaling factor to the volume signal, the ICP-supported loops are essentially identical to the pre-support loops (**Figure 1C**). This indicates that the example chosen by Weil et al. (1) may reflect a simple scaling error rather than any true effects of an ICP. Second, Figure 4 of Weil et al. (1) illustrates a response to ICP activation that is in opposition to those in Figure 1. The authors graciously provided additional original PV loops (personal communication, November 21, 2016), which are reproduced here in **Figure 1D**. Compared with the pre-support loops (blue), the loops during ICP support (red) shift slightly rightward indicating ventricle loading (not unloading) by ICP support. The characteristics of the loops between Weil et al.'s (1) Figures 1 and 4 are dramatically different so that those of Figure 1 cannot be claimed to be representative.

We then noticed in the representative fluoroscopic image (reproduced here in **Figure 1E**) that the pigtail tip of the ICP is inappropriately curled in the LV apex and its outflow port (located just distal to the motor) is inappropriately located within the LV. With both inflow and outflow ports inside the LV, no net flow out of the LV is expected. Although comments by the authors that no aortic regurgitation was noted with both the ICP and admittance volume catheters sitting across the valve, other changes in the PV loop exhibited in **Figure 1D** suggest that aortic regurgitation could have overshadowed the effects of ICP.

There are limited published data concerning PV loops during ICP support. Existing and emerging experimental data are consistent with theory in showing flow-dependent left-shifted triangular-shaped PV loops during LV→arterial MCS, be it provided by ICP as illustrated in **Figures 1F** (preclinical data) and **Figure 1G** (a patient supported during high-risk percutaneous coronary intervention and administered nitroglycerin), by an extracorporeal LV→arterial pump (**Figure 1H**) or from a durable LV assist device (**Figure 1I**).

Weil et al. (1) and Kern and Seto (3) also noted apparent discrepancies between theory predications and measured effects of TH. However, we noted remarkable concordance when we simulated the actual hemodynamics of the examples given. Kern and Seto (3) hypothesized that some discrepancies could be because Weil et al. (1) did not establish a cardiogenic shock state in their model. Note that the stroke volume in the post-myocardial infarction state in their Figure 2C (1) is ~120 ml (with cardiac output of ~7.2 l/min at a heart rate of ~60 beats/min). If we simulate a state of cardiogenic shock by decreasing the ejection fraction to ~20%, we observe a qualitatively different hemodynamic response to TH support that is similar to our prior reports (2). The nature of the response to any form of MCS depends on the conditions (contractility, afterload, pre-load, heart rate) in which they are applied (2).

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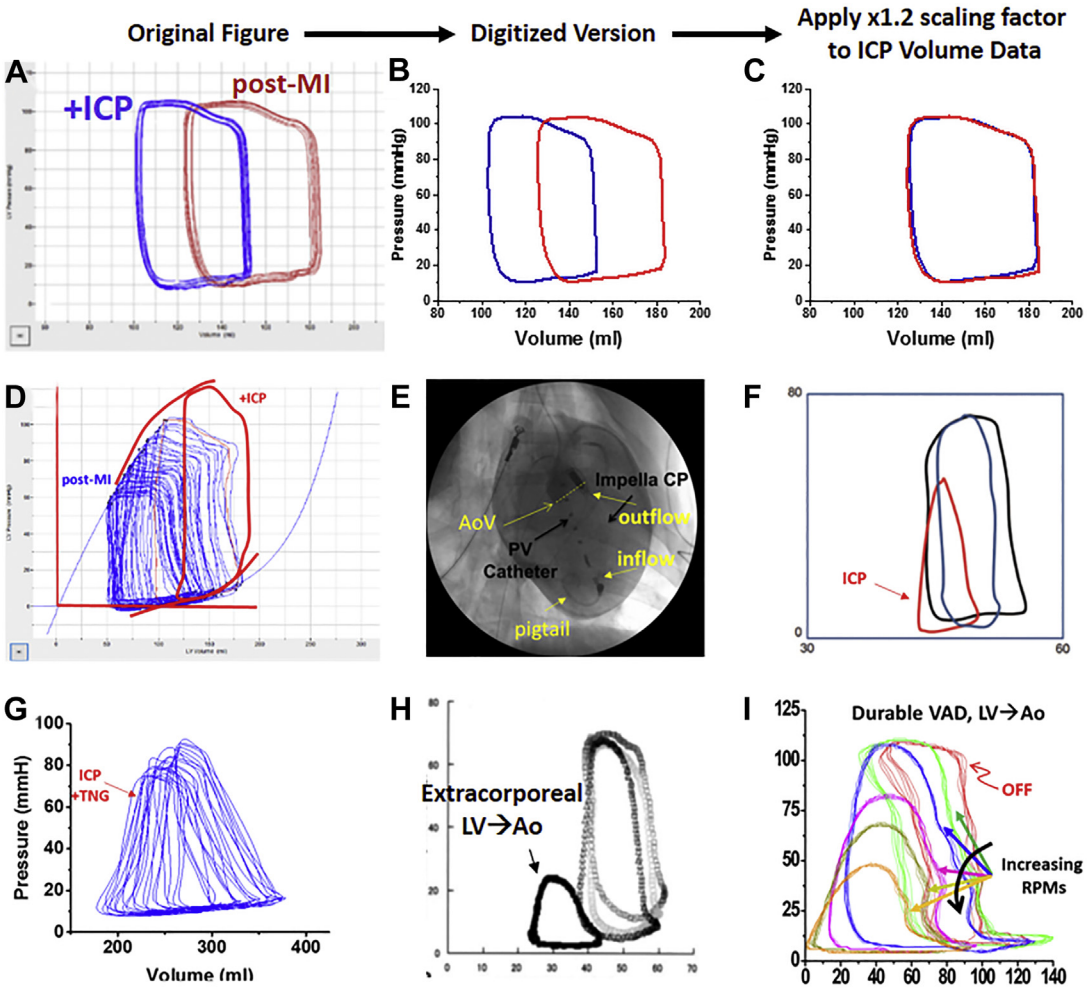
FIGURE 1 Analysis and Comparison Of Results to Other Studies



Original post-myocardial infarction (post-MI) and Impella (ICP)-supported pressure-volume (PV) loops from Weil et al. (1) **(A)** were digitized **(B)** and a scaling factor of 1.2 applied to the volume signal of ICP loop **(C)** to reveal that those loops were simply scaled versions of each other. ICP-supported loops from another case **(D, red)** were superimposed on PV loops from vena caval occlusion **(blue)** showing in this case that ICP increased the load on the heart. Fluoroscopic image from Weil et al. (1) **(E)** showing Impella outflow port positioned below the aortic valve (AoV), inside the left ventricle (LV). Results from other sources **(F and G)** reveal that during ICP support, PV loops are left-shifted (ventricular unloading) and become triangular in shape, reflecting loss of isovolumic phases due to continuous pumping of blood throughout the cardiac cycle. Such shape is present with all forms of LV-to-aorta (LV→Ao) support, including extracorporeal pumps **(H)** and durable ventricular assist devices (VAD) **(I)**. The latter loops show that the greater the VAD speed, the more triangular and left-shifted the loops become. Further details and references are provided in the text. RPM = revolutions per minute; TNG = trinitroglycerin.

There are additional methodological issues. There is no mention about whether and how often the admittance volume signal was calibrated. In our experience, the gain and offset of a conductance or admittance volume signal require calibration at several points during the course of a prolonged experiment. The authors display nonlinear end-systolic PV relationships on the graphs, but report values for a linear slope (Ees). There is no reporting of values of the volume axis intercept of the end-systolic pressure-volume relationship, which are required for complete characterization of changes in contractility. The authors report a value for β (a diastolic stiffness constant), but do not define what it is or how it is calculated. It is unclear why LV stiffness would decrease during circulatory support as indicated by results in the authors' Table 1; the end-diastolic PV relationships in the authors' examples do not appear to change during any form of MCS.

We believe these and other issues that have been raised speak to the need for additional educational resources and efforts for individuals interested in using and evaluating hemodynamic effects in the PV domain. On the basis of information provided in the paper, additional information that has been graciously shared by the authors, and the methodological concerns summarized in the preceding text, the experimental data presented by Weil et al. (1) concerning ICP are not compelling and we believe are not valid.

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Ventricular Unloading in Porcine Models

We read with great interest the paper by Weil et al. (1) addressing left ventricular unloading in a porcine model of acute ischemic left ventricular dysfunction. The study addresses a highly relevant problem of unloading an acutely failing left ventricle and the need of understanding and choosing the optimal percutaneous mechanical support system. Pressure-volume (PV) analysis was used to compare the left ventricular hemodynamic effects of 2 available percutaneous mechanical circulatory support systems: the Impella CP and the TandemHeart. The study suggested a more effective unloading using TandemHeart compared with the Impella CP.

However, the shapes of the PV loops presented by Weil et al. (1) during Impella support raise serious concerns of whether the Impella device was used correctly in their study. Looking at Figure 3 in the paper, PV loops during Impella support are rectangular. However, when you have devices continuously pumping blood out of the left ventricle throughout the cardiac cycle, the PV loops should be triangular. In the same figure, a fluoroscopic image shows the Impella device apparently with both the outlet and inlet port located within the ventricular cavity. With such a deep and inappropriate placement of the device, no flow will be delivered by the device into the aorta. With only 7 animals in their study, even 1 improper placement of the device could have great impact on their results.

The authors concluded that the TandemHeart reduced the native cardiac output more than the Impella CP although it is not mentioned how they calculated the native cardiac output. Total cardiac output derived from a pulmonary artery catheter (right ventricular output) was similar between the devices, and only minor differences in device flow were reported (Impella CP 3.3 ± 0.1 l/min vs. 3.6 ± 0.1 l/min). We assume the authors calculated native cardiac output using the PV catheter-derived volumes in the left ventricle, and this further raises concerns about the placement of the Impella device and the integrity of the PV loop recordings. We believe the authors need to explain this in greater detail because the presented data raise serious concerns and thus we question the validity of their study.

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REFERENCE

1. Weil BR, Konecny F, Suzuki G, Iyer Y, Canty JM Jr. Comparative hemodynamic effects of contemporary percutaneous mechanical circulatory support devices in a porcine model of acute myocardial infarction. J Am Coll Cardiol Intv 2016;9:2292-303.