INFOLETTER 4

21 April 2022

IMPRESS trial: Long-term mortality in MI patients treated with Impella or IABP is comparable

Management of a severe cardiogenic shock (CS) with mechanical circulatory support (MCS) is becoming increasingly common. A multicentre, randomized IMPRESS trial provided a direct comparison of a percutaneous MCS using an Impella device with an intra-aortic balloon pump (IABP) in the setting of severe CS after myocardial infarction with ST-segment elevations (STEMI). Long-term 5-year data were recently published. A total of 48 patients took part in the trial. There was no statistically significant difference regarding the primary endpoint, 5-year all-cause mortality (50% in Impella group vs. 63% in IABP; relative risk [RR] 0.87, 95% confidence interval [CI] 0.47–1.59, P = 0.65). Major adverse cardiac and cerebrovascular events (MACCE), consisting of death, myocardial re-infarction, repeat percutaneous coronary intervention, coronary artery bypass grafting, and stroke occurred in a 50% vs 79% of the subjects (P = 0.07), which was a non-significant difference. Although the mortality rate was high, the survivors tended to have good outcomes. All except one were in New York Heart Association Class I/II and none had residual angina, with no in-between group difference in left ventricular ejection fraction (LVEF).

The trial confirmed that the mortality of CS patients is mostly determined in the acute phase, with only an additional absolute mortality increase of ~6% at 5 years compared with 30-day outcomes. Although there wasn't any formal power analysis conducted regarding MACCE, a numerically higher occurrence of the events was observed in the IABP group. However, the trial didn't change the fact that no randomized data showed the superiority of any support device over the other to date. Nevertheless, the authors speculate that devices offering more hemodynamic support may be beneficial in this population. The limitations of the study were the small sample size and the fact that it was not formally powered to show a long-term difference in mortality. Further studies are therefore needed.

Karami, M., Eriksen, E., Ouweneel, D. M., Claessen, B. E., Vis, M. M., Baan, J., Beijk, M., Packer, E. J., Sjauw, K. D., Engstrom, A., Vlaar, A., Lagrand, W. K., & Henriques, J. P. (2021).

Long-term 5-year outcome of the randomized impress in severe shock trial: Percutaneous mechanical circulatory support vs. intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *European Heart Journal. Acute Cardiovascular Care*, *10*(9), 1009–1015. https://doi.org/10.1093/ehjacc/zuab060

EUROMACS-RHF risk score has limited predictive power in the setting of an LVAD implantation

Right heart failure (RHF) causes significant morbidity and mortality, its prediction in the setting of a left ventricular assist device (LVAD) implantation remains challenging. The present study provided the first external validation of the EUROMACS right-sided heart failure risk score (EUROMACS-RHF). The authors analyzed the data from 662 patients with a newly implanted continuous LVAD. RHF, defined as a need for right-sided circulatory support, continuous ionotropic support for at least 14 days, or nitric oxide for more than 48 hours post-operatively, occurred in 32% of the patients. Those with RHF had higher creatinine, bilirubin, right atrial pressure, and lower INTERMACS class ($P < 0.05$) and also the length of stay and in-hospital mortality were higher. The area under the ROC curve for RHF prediction of the EUROMACS-RHF score was 0.64, which is under the desirable 0.7 (95% CI 0.60–0.68). Patients in the high-risk category had significantly higher in-hospital and 2-year mortality (HR 1.64 (95% CI 1.16–2.32) $P = 0.005$).

The authors concluded that the EUROMACS-RHF score, which was derived in one of the largest cohorts to date and was internally validated, showed limited discrimination in RHF prediction. However, the discrimination was better than for previously published scores and the best results were seen when applied on top of them. Investigators also argued that the score was less accurate in the low-risk patients, but in a high-risk group with five or more points its positive predictive value increased to almost 50%. In those patients, going directly to biventricular mechanical support or transplant if candidates might be beneficial, trials are however needed to confirm that.

Rivas-Lasarte, M., Kumar, S., Derbala, M. H., Ferrall, J., Cefalu, M., Rashid, S. M., Joseph, D. T., Goldstein, D. J., Jorde, U. P., Guha, A., Bhimaraj, A., Suarez, E. E., Smith, S. A., & Sims, D. B. (2021). Prediction of right heart failure after left ventricular assist implantation: External validation of the EUROMACS right-sided heart failure risk score. *European Heart Journal. Acute Cardiovascular Care*, *10*(7), 723–732. https://doi.org/10.1093/ehjacc/zuab029

Predictors of poor prognosis differ between OHCA and IHCA treated with ECPR

Extracorporeal cardiopulmonary resuscitation (ECPR) is becoming more available. The retrospective study analyzed data from a total of 413 patients (78% male, median age 57) with

in-hospital (IHCA, n=163) and out-of-hospital cardiac arrest (OHCA), treated in five European ECPR centers. Unfavorable neurological outcome was defined as a cerebral performance category score (CPC) of 3–4 or death. The median time from collapse to ECMO was 63 [45–82] minutes. An unfavorable outcome after 3 months was seen in 81% of the overall group, 90% in OHCA, and 66% in IHCA. In OHCA, unfavourable outcome was associated with prolonged time from collapse to ECMO initiation (odds ratio [OR] 1.02, $p < 0.01$) and higher ECMO blood flow (OR 1.99, $p = 0.01$), conversely protective factors included initial shockable rhythm (OR 0.04, $p < 0.01$), previous heart disease (OR 0.20, $p < 0.01$) and pre-hospital use of hypothermia (OR 0.08, $p < 0.01$). Analogically, in the IHCA group, prolonged time from arrest to ECMO implantation (OR 1.02, $p = 0.03$), high lactate level on admission (OR 1.15, $p < 0.01$), and higher body weight (OR 1.03, $p < 0.01$) were independently associated with unfavorable outcome.

Therefore the location of the arrest might influence the selection criteria for ECPR, such as. initial rhythm, pre-implantation low-flow duration, and pre-cannulation lactate level. Notably, the authors discussed that the counter-intuitive association of higher ECMO blood flow with unfavorable outcomes in OHCA may be attributable to the more severe cardiovascular impairment. This is supported by the fact that IHCA patients required lower mean ECMO blood flow without a similar prognostic association. Whether higher ECMO blood flow might itself worsen the outcome remains to be studied. In IHCA patients, prolonged low-flow time was associated with poor prognosis, which warrants rapid decision making to ECMO implementation.

Halenarova, K., Belliato, M., Lunz, D., Peluso, L., Broman, L. M., Malfertheiner, M. V., Pappalardo, F., & Taccone, F. S. (2022). Predictors of poor outcome after extra-corporeal membrane oxygenation for refractory cardiac arrest (ECPR): A post hoc analysis of a multicenter database. *Resuscitation*, *170*, 71–78. https://doi.org/10.1016/j.resuscitation.2021.11.015

Low cerebral near- infrared spectroscopy (NIRS) might predict futile cannulations during ECPR

Another study examining the predictors for an ECPR outcome was conducted by a German group from Regensburg. They investigated retrospectively whether cranial near-infrared spectroscopy (cNIRS) can be used to identify patients with poor prognosis and, therefore, avoid futile cannulations. Data were gathered from 97 patients requiring ECPR due to a cardiac arrest with a cNIRS measurement performed before cannulation immediately after the ECPR team arrived on the scene. Although the mortality was high (72.1%), the vast majority of survivors (88.9%) had a favorable neurological outcome of CPC 1 or 2 and an initial regional cerebral

oxygen saturation (rSO2) was not associated with neurological outcome in this group. The lowest possible rSO2 of 15 was seen in 11 patients, all non-survivors.

During the CPR, increasing rSO2 is associated with survival, whereas persistently low rSO2 predicts poor outcomes. The present study however examined rSO2 measurements before ECPR initiation. The value of 15% did not result in any survivors irrespective of the initial rhythm and might be, therefore, a tool to identify potential futile cannulations. Conversely, though, high rSO2 was not associated with a favorable prognosis and overall there wasn't any correlation between initial rSO2 and outcome in the survivors group. The main limitations of the study were the small sample size and concerns about using a single cNIRS measurement as the sole predictive marker for deciding on whether to implement a potentially life-saving therapy.

Wiest, C., Philipp, A., Foltan, M., Lunz, D., Merten, C., Blecha, S., Seyfried, T., Geismann, F., Schneckenpointner, R., Müller, T., & Lubnow, M. (2021). Does cerebral near- infrared spectroscopy (NIRS) help to predict futile cannulation in extracorporeal cardiopulmonary resuscitation (ECPR)? *Resuscitation*, *168*, 186–190. https://doi.org/10.1016/j.resuscitation.2021.08.008

VA-ECMO and IABP after cardiac arrest provide better neurologic outcomes than VA-ECMO alone, especially after ACS

The data for an MCS machine selection after a CPR with the return of spontaneous circulation (ROSC) are limited. In a recent Japanese study venoarterial extracorporeal membrane oxygenation (VA-ECMO) and IABP combined (n = 762) were retrospectively compared with VA-ECMO only (n = 173). The primary endpoint was a 30-day favorable neurological outcome, which was significantly higher in the combined group (35% vs. 25%; $P < 0.001$). This effect was even more pronounced in patients with an acute coronary syndrome (ACS) as a cause of the initial cardiac arrest (34% vs. 18%; $P < 0.001$), while in the non-ACS group the difference was non-significant (38% vs. 32%; $P = 0.11$). The results persisted after a propensity score matching analysis.

According to previous literature, the patients with ECMO + IABP had a 20% increase in coronary blood flow and brain blood flow than with ECMO alone. The authors, therefore, argued that the combined usage of IABP and ECMO could result in lesser multiorgan dysfunction and brain dysfunction. Moreover, IABP can mitigate the negative hemodynamic effects of VA-ECMO with left ventricular unloading. According to the authors, both methods can in theory have distinct benefits - VA-ECMO helps maintain perfusion of the vital organs and IABP provides ground for a myocardial recovery with a more efficient coronary blood flow. To confirm the clinical benefit, prospective randomized trials are needed.

Kuroki, N., Nagao, K., Otsuka, T., Kuwabara, M., Nakata, J., Takayama, T., Hosokawa, Y., Ashida, T., Suzuki, K., Yamamoto, T., & Takayama, M. (2021). Combined use of venoarterial extracorporeal membrane oxygenation and intra-aortic balloon pump after cardiac arrest. *Resuscitation*, *167*, 345–354. https://doi.org/10.1016/j.resuscitation.2021.07.019

The SynCor Trial: ECG-synchronized pulsatile ECMO seems feasible

Although ECMO is a potentially life-saving method, adverse effects are common, some of them caused by unnatural continuous flow generated by the machine. Therefore, innovative tools with a pulsatile flow are developed, such as the ECG-synchronized cardiac assist device i-cor. The machine, which is based on a VA-ECMO concept, was clinically evaluated in the SynCor trial in the patients with a cardiogenic shock (CS, n=13) and during a high-risk percutaneous coronary intervention (HRPCI, n=34). Device implantation and initiation of ECG-synchronized mode were successful in all patients, no technical failure was observed. The intervention was finished and weaning was accomplished in 97.1% of the HRPCI group, 30-day survival in those patients reached 94.1%. In the CS group, 30-day survival was 69.2%. Main complications included bleeding events (14.7% HRPCI, 23.1% CS) and critical limb ischemia (2.9% HRPCI, 38.5% CS).

The authors concluded that the results are consistent with those observed in previous literature and the device seems like a feasible option. They also argued that the animal model trials provided promising results regarding hemodynamics in the setting of a pulsatile extracorporeal circulatory support, as it provides more hemodynamic energy and improves systemic microcirculation. More prospective data are needed for an evaluation in humans and a comparison with already available technology.

Voigt, I., Spangenberg, T., Ibrahim, T., Bradaric, C., Viertel, A., Tallone, E. M., Skurk, C., Abel, P., Graf, J., Rinne, T., Böhm, J., Ghanem, A., & Liebetrau, C. (2021). Efficacy and safety of ecg- synchronized pulsatile Extracorporeal Membrane Oxygenation in the clinical setting: The syncor trial. *Artificial Organs*, *46*(3), 387–397. https://doi.org/10.1111/aor.14147

Left ventricular unloading during ECPR might be beneficial

VA-ECMO therapy is associated with increased afterload, which might be treated with left ventricular unloading. In the present German study from the University of Cologne, the investigators retrospectively evaluated the addition of a transfemoral micro-axial blood pump Impella during ECPR on top of a VA-ECMO in both OHCA and IHCA patients. A total of 18 patients with Impella and VA-ECMO were compared with 90 subjects treated with VA-ECMO only. In the combined group, all-cause mortality was lower (82% vs. 56%, P = 0.01), low-flow time was shorter (60 min vs. 55 min, P = 0.01) and weaning was successful more often (72%

vs. 32%, P = 0.01), but the patients more frequently experienced acute kidney injury with the need for dialysis (72% vs. 18%, P ≤ 0.01). Conversely, the time of circulatory support was shorter in the ECMO-only cohort (2.0 ± 1.73 vs. 4.76 ± 2.88 p = 0.05).

There is no universally recommended unloading strategy to date. As the authors mentioned, randomized trials are necessary to confirm the reduction in mortality going along with LV-unloading. The present study had several limitations, especially the small size of the Impella treated group. Also, selection bias was possibly present, as those with additional unloading might have been more clinically and hemodynamically stable, allowing for the Impella device implantation.

Gaisendrees, C., Djordjevic, I., Sabashnikov, A., Adler, C., Eghbalzadeh, K., Ivanov, B., Walter, S., Schlachtenberger, G., Merkle- Storms, J., Gerfer, S., Carstens, H., Deppe, A. C., Kuhn, E., & Wahlers, T. (2021). Impact of left ventricular unloading using a peripheral Impella®- pump in ECPR patients. *Artificial Organs*, *46*(3), 451–459. https://doi.org/10.1111/aor.14067

MRI study: Subclinical cerebral lesions are common in ECMO patients

ECMO patients frequently suffer from neurologic complications, the full extent of which is unknown. The group from Johns Hopkins University retrospectively evaluated a group of 78 ECMO patients, out of which 26 survived. Among survivors, only 8 patients had MRI performed. The median ECMO support time was 8 days and the median time from decannulation to MRI was 12 days. Of those 8 patients, 63% had ischemic infarcts, 50% cerebral microhemorrhage, 25% intracranial hemorrhage, and 13% thoracic cord ischemic infarct on their MRI scans. None of the group had a normal MRI. All patients also underwent transcranial Doppler (TCD), which showed the presence of microemboli in 50%. All ischemic infarcts had a diffuse pattern of punctate to small lesions, microhemorrhages were lobar, deep, or both.

Although the study included only 8 patients, it is the largest MRI series in adult survivors after ECMO to date. The vascular lesions were present in all survivors with MRI imaging available, highlighting the need for neuromonitoring protocols for both diagnostic purposes and prognostication. The most common findings were diffuse punctuate ischemic infarcts, possibly as a result of hemodynamic instabilities, hypoxia, and changes in cerebral blood flow. The lesions might have been secondary to ECMO treatment, the underlying condition, or reperfusion injury and were often subclinical. Additional studies with cognitive assessment will be necessary for the adult ECMO population to determine accurate long-term functional and cognitive outcomes. Besides the small sample size, potential selection bias is a major limitation of the study.

Ong, B. A., Geocadin, R., Choi, C. W., Whitman, G., & Cho, S.-M. (2020). Brain Magnetic Resonance Imaging in adult survivors of Extracorporeal Membrane Oxygenation. *Perfusion*, *36*(8), 814–824. https://doi.org/10.1177/0267659120968026