Interactive CardioVascular and Thoracic Surgery 20 (2015) 365–371
doi:10.1093/icvts/ivu421 Advance Access publication 21 December 2014

Inverted-Takotsubo cardiomyopathy: severe refractory heart failure in poly-trauma patients saved by emergency extracorporeal life support

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Received 28 July 2014; received in revised form 14 November 2014; accepted 18 November 2014

Abstract

OBJECTIVES: The sequelae of severe poly-trauma may include myocardial dysfunction followed by acute heart failure and death. Inverted-Takotsubo cardiomyopathy (ITC) is a variant of stress cardiomyopathy, characterized by a contractile abnormality with extensive left ventricular circumferential dyskinesia or akinesia with a hyperkinetic apex. We report our experience with refractory cardiogenic shock and/or cardiac arrest, treated with extracorporeal life support.

METHODS: From June 2008 to December 2011, we treated 4 adult poly-trauma patients (3 men, 1 woman, mean age: 27.7 ± 13.5 years, mean ISS score 53.2 ± 15.9) with veno-arterial (V-A) extracorporeal life support for cardiopulmonary failure/cardiac arrest refractory to conventional treatment, due to inverted-Takotsubo cardiomyopathy. We used a miniaturized extracorporeal life support (ECLS) device.

RESULTS: ITC myocardial dysfunction appeared 15.4 ± 11.6 h after intensive care unit admission and rapidly evolved to refractory cardiopulmonary failure and cardiac arrest (within 4.8 ± 2.5 h of the onset). At ECLS, initiation median pH was 7.12 ± 0.14 (6.91–7.25), median lactate was 6.7 ± 2.8 (4–10) mmol/l and median vasoactive-inotropic score was 192.1 ± 50.6 μg/kg/min. Tissue perfusion improved significantly within 4 h on ECLS. Cardiac function improved gradually but consistently. Initial median ejection fraction was 14.2 ± 4.7% and median global longitudinal strain test was −7.4 ± 4.7. At complete cardiac recovery, they were 62.73 ± 7.8 and −18.43 ± 2.4%, respectively. After that, 2 patients survived and were sent to neurological rehabilitation before hospital discharge. In the other 2 cases, post-traumatic cerebral death occurred and they underwent organ explantation.

CONCLUSIONS: Rapid heparin-free ECLS may improve outcome in the most severe cases of poly-traumatized patients demonstrating refractory inverted-Takotsubo cardiomyopathy.

Keywords: Trauma • Emergency • Cardiomyopathy • Heart failure • Myocardial recovery • Circulatory assistance

INTRODUCTION

Poly-trauma is a leading cause of death worldwide, often involving young victims. Stress cardiomyopathy is a rare but potentially lethal complication in this setting, featuring transient myocardial contractile dysfunction. Takotsubo cardiomyopathy is a variation, first described by Dote *et al*. [1]. It was so-named because of an unusual shape of the left ventricle that is similar to that of a Japanese octopus trap, 'Takotsubo', when observed on left ventriculography in the systolic phase. The inverted-type is more common in young people and when associated with specific clinical conditions [2], including trauma [3]. It is characterized by akinesia or dyskinesia of the basal left ventricular segments and hypercontractility of the apex. Endogenous and exogenous catecholamine surges are believed to be the mediators [4, 5]. The interindividual difference in myocardium adrenergic receptors distribution is the factor that determines typical Takotsubo rather than the Inverted-type [6, 7]. Although inverted-Takotsubo cardiomyopathy (ITC) is a rare complication, it occurs more frequently in poly-trauma patients. Moreover, it is characterized by left ventricular wall motion abnormalities in the mediobasal segments and always by normal coronary arteries [8].

Extracorporeal life support (ECLS) in veno-arterial (V-A) configuration is an advanced treatment that can provide full haemodynamic support in cases of post-traumatic refractory cardiovascular shock and refractory cardiac arrest. The need for anticoagulation to prevent clot formation in the ECLS circuit has prevented the use of this technique extensively in poly-trauma patients due to risk of bleeding.

Nowadays, technological progress has made available miniaturized circuits with 'tip-to-tip' heparin coating, thus delaying heparin administration for 48-72 h [9, 10].

We report our experience in initiating ECLS as a rescue therapy in poly-trauma patients with severe cardiogenic shock. The rationale for this therapeutic approach is to provide adequate

systemic perfusion, avoiding multiple organ failure and allowing organ recovery [11].

MATERIALS AND METHODS

Our ECLS team was established in 2006 and is composed of a cardiac surgeon, an anaesthesiologist, a cardiologist and a perfusionist. ECLS treatment was performed every time standard therapy failed. From June 2008 to December 2011, we treated 4 adult polytrauma patients (3 men and 1 woman, mean age 27.7 ± 13.5 years, mean ISS score 53.2 ± 15.9), who experienced cardiopulmonary failure and cardiac arrest due to ITC, with V-A ECLS because they did not respond to conventional treatment.

Three patients had been involved in road accidents resulting in multiple injuries—cranial and parenchymal contusions with extradural haemorrhage, chest trauma with multiple rib fractures and bilateral pulmonary contusions, abdominal trauma with splenetic lesions, multiple fractures of the limbs. The fourth one had fallen from a height and had received head injuries with subarachnoid haemorrhage and parenchymal contusion, multiple rib fractures and pulmonary contusions to the chest (Table 1).

The onset of the cardiomyopathy, proved by compliance with the echocardiographic criteria and typical strain and strain rate (SR) features, occurred after 15.4 ± 11.6 h and resulted in the rapid cardiac function deterioration, leading to cardiac failure and cardiac arrest after 4.8 ± 2.5 h. In 3 of 4 patients, advanced cardiopulmonary resuscitation (advanced cardiac life support) was required. Depending on the decline in patients' cardiocirculatory conditions, we undertook ECLS in the emergency department (n = 1) and in the intensive care unit (n = 3).

All patients presented severe bleedings and 2 of 4 patients developed haemorrhagic shock and thus received fluid resuscitation, massive blood transfusions (packed red blood cell) and blood components (platelets and fresh-frozen plasma). In all cases, activated recombinant factor VII (rfVIIa) was administrated to control refractory bleedings (Table 2).

Clinical and instrumental assessment of patients

All patients underwent transthoracic and transoesophageal echocardiography. We measured the dimension of the left atrium and left ventricle—in accordance with the indications of the American Society for Echocardiography (ASE), the left ventricular mass using the Devereux formula and the ventricle mass index based on body surface. The relative wall thickness was calculated as (ventricular septum in diastole × 2)/left ventricle end-diastolic diameter. The ejection fraction (EF) of the left ventricle was calculated by the Simpson method and the diastolic function was estimated by analysis of the trans-mitral flow. Valve disease was defined by the degree of severity in accordance with ASE recommendations.

Strain (S) and SR analyses were performed on cine-loop cardiac cycles acquired by 2D echocardiography. This technique allowed us to assess accurately and quantitatively the function and contractility of the myocardium and to define exactly the pathological myocardial segment [9, 10]. The systolic S correlates directly to the EF whereas the SR at the systolic peak is closely associated with myocardial contractility [11].

The left ventricle in four-chamber apical view was divided into six segments (two basal, two medium, two apical), the segmental S/SR and the global strains were calculated for each of them by 'EchoPac Dimension 06 – GE Healthcare'. A re-evaluation was performed every 24 h or if clinical evidence of patient haemodynamic conditions changed.

Extracorporeal life support circuit

We used the PLS-System, (Maquet Cardiopulmonary AG, Hechingen, Germany), consisting of a Rotaflow Maquet Centrifugal Pump (MAQUET GmbH & Co KG, Rastatt, Germany) and a hollow fibre polymethylpentene membrane oxygenator (Quadrox-D Oxygenator, MAQUET GmbH & Co KG). The system is entirely 'tip-to-tip' heparin-coated. The circuit includes a special intake stopcock for large-volume administration, particularly effective in poly-traumatized patients who require high-speed fluid resuscitation. Depending on

Table 1: Dynamics of the accident, mode of rescue and injuries suffered by victims

Patient	Age/ gender	Accident type	Mode for emergency transport	Lesions diagnosed in emergency department	ISS/haemorrhagic shock
1	16/M	Road accident (motorbike)	Helicopter rescue	Severe head trauma with fractures, chest trauma with pulmonary contusion, aspiration pneumonia	38/No
2	30/M	Road accident (motorbike)	Helicopter rescue	Brain trauma, chest trauma with multiple rib fractures, bilateral pneumothorax and left pulmonary contusion, spleen rupture with splenectomy, multiple vertebral fractures	41/No
3	19/F	Road accident (car)	Helicopter rescue	Head trauma with bilateral otorrhagia, rhinorrhagia with maxillofacial trauma, extensive wound of right forehead, contusive trauma of chest, abdominal trauma with haemoperitoneum by rupture of the spleen and colon laceration	66/Yes
4	46/M	Fall from height	Helicopter rescue	Head trauma with post-traumatic SAH, skull base fracture, facial trauma, chest trauma with pulmonary contusion, multiple rib fractures	68/Yes
	27.7 ± 13.5				53.2 ± 15.9

ISS: injury severity score; SAH: sub arachnoid hemorrhage.

Table 2: Pre-ECLS patient treatment

Patient	Transfused units/rfVIIa administration	Refractory CS/CA	ACLS (min)	Time to ECLS (h)	ECLS apply location	Outcome
1	PRBC: 17 FFP: 25 rfVIIa	CA	30	144	ICU	Survived
2	PRBC: 27 FFP: 4 PLT: 5 rfVIIa	CA	60	168	ICU	Survived
3	PRBC: 20 FFP: 8 rfVIIa	CS	–	3	ED	Organ donation
4	PRBC: 24 FFP: 19 PLT: 22 rfVIIa	CA	2 × 15	48	ICU	Organ donation
			30 ± 21.2			

ECLS: extracorporeal life support; PRBC: packed red blood cells; FFP: fresh-frozen plasma; rfVIIa: recombinant activated factor VII; CS: cardiogenic shock; CA: cardiac arrest; ACLS: advanced cardiac life support; ICU: intensive care unit; ED: emergency department.

the patient, we used a 21F or 23F arterial cannula and a 25F, 27F, or 29F venous cannula (PLS femoral cannula, MAQUET GmbH & Co KG). A heat-exchanger device was integrated in the ECLS circuit to control the patient's temperature. The PLS-System has received the CE certification for continuous use up to 30 days.

Extracorporeal life support initiating, management and weaning

In all cases, a percutaneous cannulation procedure was carried out by using the Seldinger technique without any skin incision, thus preventing future cannula site bleeding. Transthoracic/transoesophageal echocardiography was performed to position the cannulae.

To prevent leg ischaemia, we adopted the femoro-femoral configuration, by inserting a small shunt cannula (8–10 F) in the femoral artery distal to the ECLS cannula.

In all cases, because of actual or potential bleeding risk, we initially performed heparin-free ECLS until bleeding stopped and normalization of patient coagulative status was achieved (mean delay 16.7 ± 9 h; range 2.4–72 h).

No clotting formation in the circuit was observed during support period. If cardiopulmonary resuscitation was performed before ECLS or brain injury was suspected, hypothermia was rapidly induced and maintained for 48 h at a temperature between 32 and 34°C. Transoesophageal echocardiography was performed every 24 h (or if clinical evidence of patient haemodynamic conditions changed) to evaluate cardiac function and cardiac recovery.

Lung-protective ventilation was adopted and daily thoracic echography was performed to evaluate pulmonary status. Heparin administration was delayed in case of bleeding and it was started only when the absence of active bleeding was verified, after 16.7 ± 9 h (range, 2.4–72 h) from ECLS initiation. It was adjusted according to bedside measurements of activated partial thromboplastin time (APTT; target value, 40–50 s) and activated clotting time (ACT; target value, 160–180 s) which were controlled every 2 h. An intra-aortic balloon pump was inserted in 2 patients with CA and profound myocardial dysfunction, thus reducing cardiac afterload and promoting myocardial recovery. During ECLS treatment, additional specific modules were added to the ECLS circuit when needed for renal function (continuous VV haemofiltration,

Table 3: ECLS application and on-course characteristics, techniques, modalities, procedures and complications

Extracorporeal life support techniques, modalities and procedures
ECLS modality
Veno-arterial (V-A), *n* = 4 (100%)
Cannulation technique
Percutaneous Seldinger technique, *n* = 4 (100%)
Femoro-femoral cannulation, *n* = 4 (100%)
ECLS procedure location
ICU, *n* = 3 (75%)
ED, *n* = 1 (25%)
Coagulation management
Initially heparin-free ECLS, *n* = 4 (100%)
Heparin administration delay from ECLS start (h)
16.7 ± 9 (2.4–72)
ECLS flow (l/min)
4.4 ± 1.2 (4–6)
ECLS-FiO_2 (%)
100%
Protective hypothermia at 32–34°C (h)
48–72, *n* = 4 (100%)
Procedures during ECLS
CVVH, *n* = 4 (100%)
Endotoxin removal cartridge, *n* = 2 (50%)
Damage control surgery, *n* = 1 (25%)
IABP, *n* = 4 (100%)
ECLS-related complications
Leg ischaemia, *n* = 1 (25%)

ECLS: extracorporeal life support; ICU: intensive care unit; ED: emergency department; FiO_2: fraction of inspired oxygen; CVVH: continuous veno-venous haemofiltration; IABP: intra-aortic balloon pump.

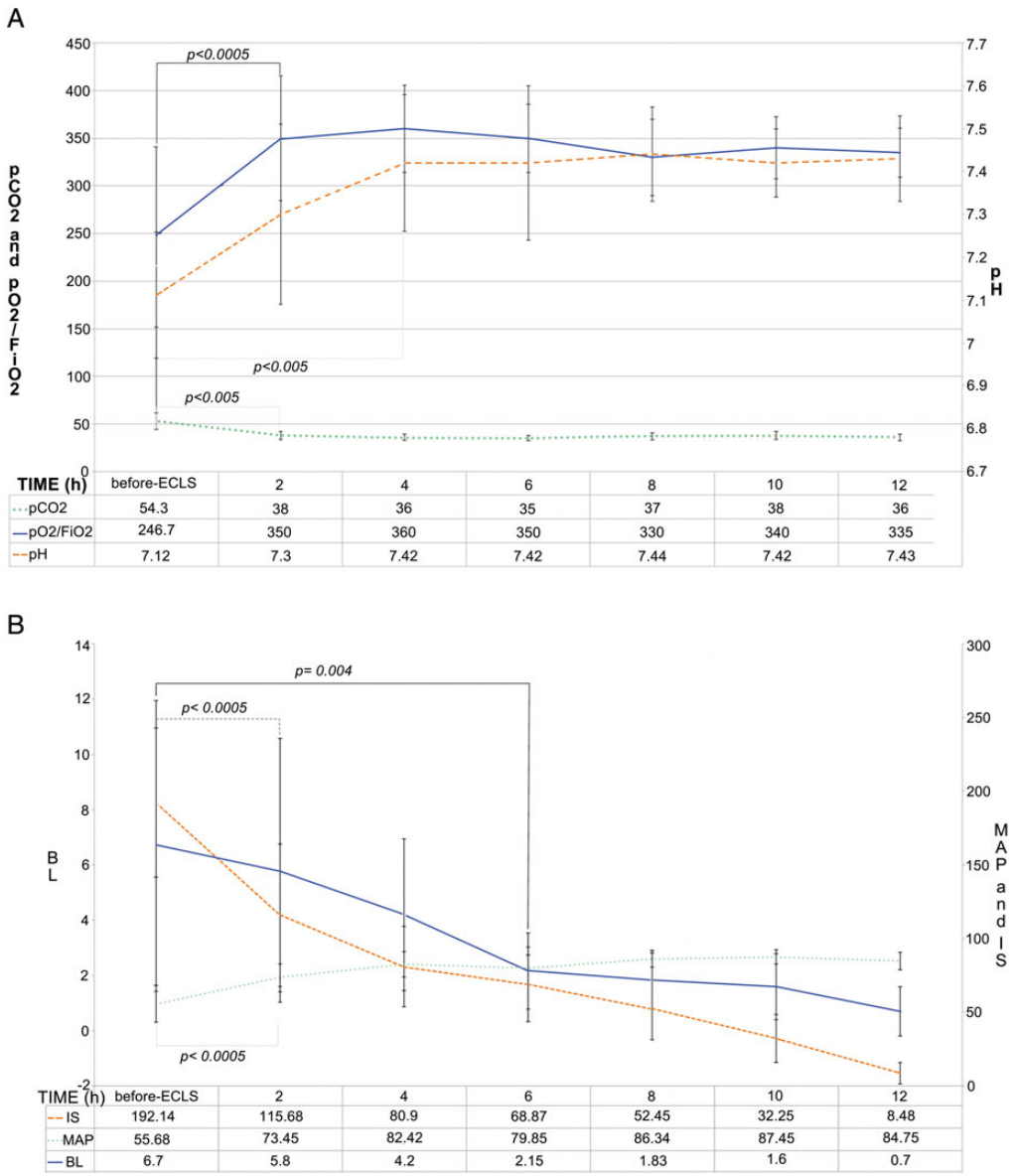

Figure 1: Vital parameters and their rapid improvement a few hours after ECLS initiation. (**A**) Variations in paO_2 and $PaCO_2$. (**B**) Variations in blood lactate; inotropic score and mean arterial pressure. $PaCO_2$: arterial carbon dioxide tension (mmHg); PaO_2: arterial oxygen tension (mmHg); FiO_2: fraction of inspired oxygen (%); IS: inotropic score (μg/kg/min): dosage of dopamine + dobutamine (μg/kg/min) + [dosages of epinephrine + norepinephrine + isoproterenol (μg/kg/min)] × 100 + dosage of milrinone (μg/kg/min) × 15; MAP: mean arterial pressure (mmHg); BL: blood lactate (mmol/l).

n = 4) or in case of sepsis (endotoxin removal cartridge, *n* = 2). The modalities and the procedures performed during ECLS are summarized in Table 3.

RESULTS

V-A ECLS was implanted in 4 patients according to patients' clinical status (particularly their haemodynamic and respiratory instability) in the presence of a lack of response to maximum standard therapy and a refractory but potentially reversible clinical setting.

Few hours after ECLS initiation, there was a general improvement of the clinical parameters (Fig. 1A and B). No patient showed bleeding related to the procedure and the only complication was the appearance, in the first patient, of distal right lower limb ischaemia despite selective perfusion of the distal femoral artery. It subsided spontaneously once we decreased doses of inotropic drugs leaving no permanent injury. All measured data (mean ± SD) before ECLS, after weaning and at discharge are presented in Table 4. As it is evident, the mean values of these parameters prior to ECLS and after are statistically significant, thus indicating a considerable recovery of cardiac function.

The Doppler ultrasound highlighted the emergence of functional mitral regurgitation from moderate to severe in all patients, with mean value of 3.4 (range of severity 0–4). The severity of the functional mitral regurgitation was performed according to the recommendations of the European Society of Cardiology. The valvular disorder was classified as functional, characterized by a morphologically intact valve structure in the presence of concomitant ventricular dysfunction. This was confirmed by the evidence that mitral regurgitation gradually improved along with the

Table 4: Left and right cardiac function (measured using standard Doppler echocardiography) at various stages of treatment demonstrating considerable recovery post-ECLS treatment

	Pre-ECLS	Pre-ECLS explantation	At discharge	*P*-value (before-ECLS versus before-ECLS explant)
LAD (mm)	35.8 ± 7.4	25.3 ± 7.8	21.3 ± 6.7	0.014
TDD LV (mm)	56.48 ± 5.8	48.24 ± 6.8	48.3 ± 7.6	0.045
TSD LV (mm)	54.6 ± 6.3	36.8 ± 5.32	25.8 ± 4.29	0.0384
IVS d (mm)	9.67 ± 2.41	11.28 ± 3.04	10.32 ± 3.24	0.049
RW d (mm)	9.33 ± 2.37	10.56 ± 2.78	10.26 ± 3.23	0.048
LVM (g)	192.6 ± 65.5	188 ± 76.4	189.3 ± 64.2	ns
LVMI (g/m^2)	90. 8 ± 24	86.2 ± 32.7	89.6 ± 32.5	ns
RWT	0.33 ± 0.11	0.44 ± 0.13	0.42 ± 0.17	0.002
EF (%)	14.2 ± 4.7	46. 9 ± 9.5	62.73 ± 7.8	0.042
MAPSE (cm)	2.1 ± 3.6	14.2 ± 4.5	16.7 ± 3.3	0.0034
TAPSE (cm)	3.5 ± 4.55	18.4 ± 4.5	24.7 ± 6.5	0.0012
MRS (0–4)	3.4 ± 0.55	0.6 ± 0.35	0.45 ± 0.37	0.0001
E (m/s)	2.96 ± 0.14	1.21 ± 0.23	1.14 ± 0.19	0.002
A (m/s)	0.81 ± 0.19	0.85 ± 0.14	0.79 ± 0.17	0.032
E/A	3.65 ± 0.73	1.42 ± 0.31	1.45 ± 0.36	0.002
E decT (ms)	107.5 ± 41.7	198.3 ± 76.7	188.6 ± 84.7	0.026

LAD: left atrium diameter; TDD LV: telediastolic diameter of the left ventricle; TSD LV: telesystolic diameter of the left ventricle; IVS d: interventricular septum in diastole; RW d: rear wall in diastole; LVM: left ventricle mass; LVMI: left ventricular mass index; RWT: relative wall thickness; EF: ejection fraction; MAPSE: mitral annular plane systolic excursion; TAPSE: tricuspid annular plane systolic excursion. MRS: mitral regurgitation severity; E: E-wave peak velocity; A: A-wave peak velocity; E/A: E/A ratio; E decT: E-wave deceleration time.

Table 5: Septal longitudinal S/SR of the septal and lateral portion of the left ventricle wall

Segment	Pre-ECLS	Pre-ECLS explantation	At discharge	*P*-value (before-ECLS versus before-ECLS explant)
Septal				
Basal	2.7 ± 1.7	−17.4 ± 3.46	−18.9 ± 2.7	0.0125
	0.14 ± 0.11	−1.17 ± 0.41	−1.2 ± 0.21	0.0473
Mid	−5.8 ± 2.3	−16.9 ± 2.7	−19.6 ± 4.4	0.014
	−0.12 ± 0.2	−1.14 ± 0.35	−1.22 ± 0.11	0.0441
Apical	−17.8 ± 2.3	−19.8 ± 4.3	−18.9 ± 4.9	ns
	−0.93 ± 0.25	−1.32 ± 0.42	−1.33 ± 0.36	ns
Lateral				
Basal	−1.3 ± 3.4	−16.6 ± 4.8	−18.6 ± 5.1	0.001
	−0.23 ± 0.8	−1.5 ± 0.4	−1.7 ± 0.63	0.015
Mid	−8.3 ± 5.6	−15.7 ± 4.5	−16.7 ± 6.1	0.048
	−0.57 ± 0.94	−1.23 ± 0.42	−1.46 ± 0.64	0.0396
Apical	−16.1 ± 3.7	−16.6 ± 6.3	−16.4 ± 6.2	ns
	−1.43 ± 0.71	−1.25 ± 0.58	−1.33 ± 0.57	ns

Positive values correspond to dyskinetic movement of the segment.

recovery of normal ventricular contractility. Mitral regurgitation at the time of weaning from the circuit was almost completely resolved (Table 4). The analysis of trans-mitral flow allowed us to document the presence, prior to ECLS, of severe global impairment of diastolic function. Initially, the values of the E-wave velocity, the E/A ratio and the mean time of E-wave deceleration time (E decT) were severely impaired due to the presence of poor diastolic relaxation and increased filling pressures. These values during the ECLS had gradually normalized, indicating a recovery of normal ventricular diastolic function (Table 4).

The 2D strain analysis demonstrated in all patients an alteration of the longitudinal, radial and circumferential S, in particular for the first. Longitudinal S and SR are more sensitive and reproducible, and they were characterized by mean values much lower than normal, indicating the presence of a reduced longitudinal systolic function. The analysis of the segmental S of the left ventricle showed values of longitudinal S and SR severely depressed at the basal and mid segments in the septal and lateral portions of the wall while, in the apical segments, they were essentially preserved (Table 5). The transverse and circumferential S showed the same spatial characteristics, although this was less relevant (Table 6).

The trend of segmental S was to increase from the basal segments to the apical portions of the lateral and septal wall. Similarly, the values of segmental SR showed a gradual increase from the base to the apex of the ventricle, only in the septal wall.

We noted a gradual recovery of cardiac contractile function, with recovery in the most affected segments (basal and mid segments). At the time of weaning from the extracorporeal circuit, the cardiac contractility was reserved in all patients at substantial values of normality. In Fig. 2, we report the electrocardiography findings.

The mean duration of ECLS in our patients was 78 ± 63 h (maximum 168 h), after which 2 patients survived, while the other 2 suffered brain death. In the success group (Patients 1 and 2), we had complete recovery of cardiac function, EF passed, respectively, from 10.4 and 12.4 to 55%, after 58.9 h, and 59%, after 72.4 h. These patients were discharged from the ICU and sent to neurological rehabilitation, respectively, after 18 and 22 days from admission (final neurological status of the patients corresponded, respectively, to Category 1 and 2 of cerebral performance). In the other 2 patients (Patients 3 and 4), ECLS was used to allow time for

Table 6: Four-chamber global strain

	Pre-ECLS	Pre-ECLS explantation	At discharge	*P*-value (before-ECLS versus before-ECLS explant)
Global radial strain	20.72 ± 8.7	34.27 ± 17.51	40.71 ± 16.82	0.013
Global circumferential strain	−6.84 ± 3.4	−11.91 ± 2.52	−13.43 ± 3.25	0.003
Global longitudinal strain	−7.4 ± 4.7	−17.6 ± 3.1	−18.43 ± 2.4	0.0021

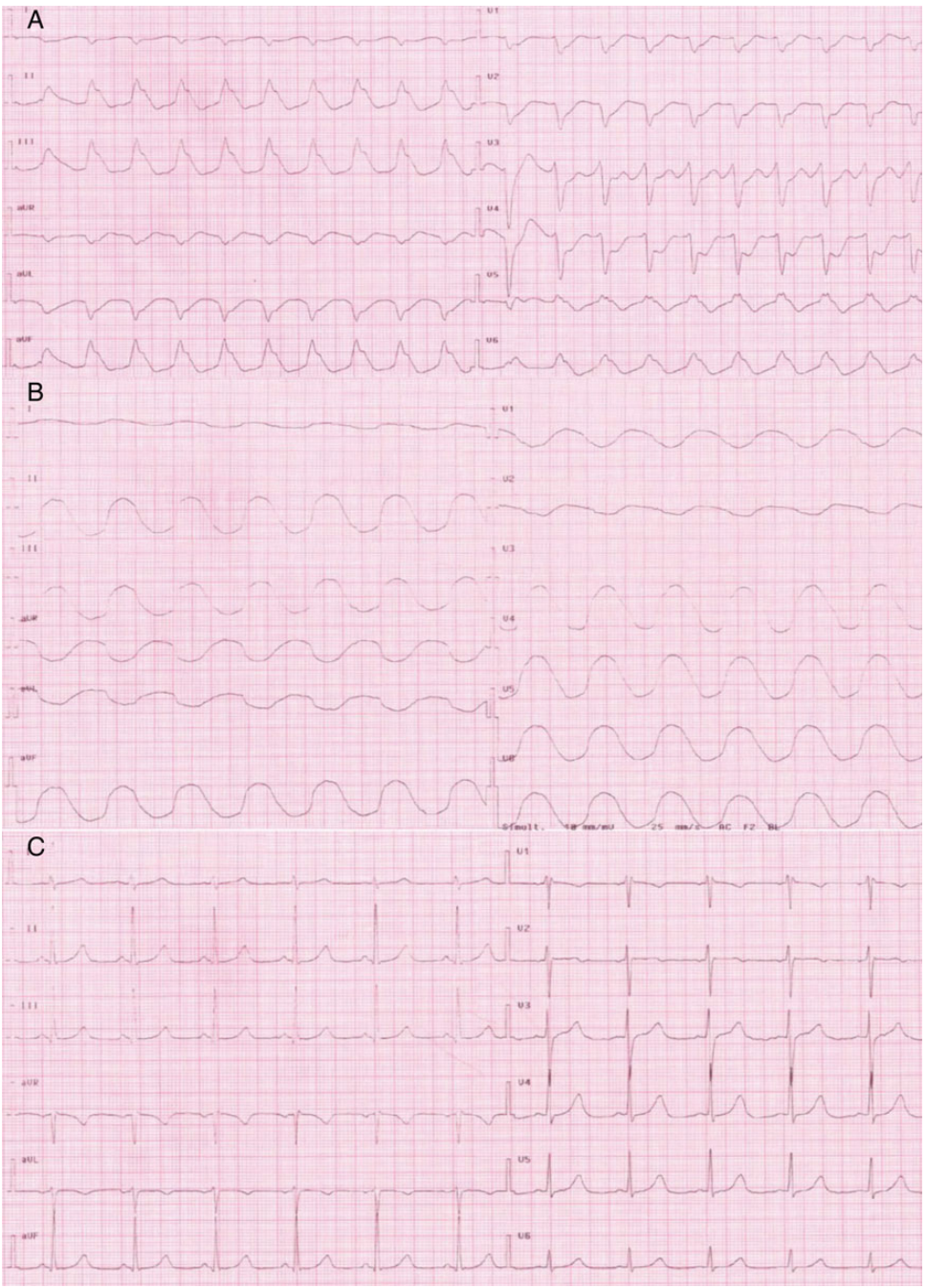

Figure 2: Electrocardiography findings dynamics in the first patient: (**A**) at onset of cardiac dysfunction and cardiac arrest; (**B**) during the first 76 h on-ECLS; (**C**) at ECLS weaning. ECLS: extracorporeal life support.

post-traumatic brain death assessment and continued to support organ vitality as long as necessary to start the surgical procedure for organ donation (bridge to organ donation). Both patients underwent successful removal of liver and kidneys for donation.

DISCUSSION

Inverted-Takotsubo is an unusual variation of stress cardiomyopathy and is rare but fatal, causing complications in severely poly-traumatized patients. ECLS in these patients is therefore the ideal technique when all other therapies of choice have failed.

The first experience of ECLS in a poly-traumatized patient by Donald Hill dates back to 1971 [12]. Since this paper, many advances in technology, materials and knowledge have occurred [13, 14].

Nowadays, the use of ECLS in cardiogenic shock from different causes has been accepted and a new group of indications is being considered. Moreover, as stated in the current study and in others already published [9, 15], anticoagulation can be safely delayed for 48–72 h due to improved biocompatibility. Anticoagulation can be maintained at low level, as confirmed in our previous study [15], and studies by Saczkowski *et al.* [16] and Sobieski *et al.* [17].

Furthermore, ECLS has proved to be effective in expanding the donor pool and allowing time for brain death assessment as presented by Hsieh *et al.* and Magliocca *et al.* [11, 18], and confirmed by our paper. Currently, there are neither identified nor reported predictors of ECLS success based on the patient's clinical status before implantation. The identification of predictors for ECLS unsuitability and failure could result in better identification of patients.

CONCLUSIONS

ECLS has become the reference therapy in many clinical conditions—post-cardiotomic refractory cardiogenic shock, post-acute myocardial infarct or myocarditis and respiratory failure by acute respiratory distress syndrome. Recently, ECLS has emerged as an effective therapeutic resource in the treatment of poly-trauma, demonstrating safety and efficacy, despite the critical condition of these patients and risks associated with the procedure, when it is promptly initiated by a specialized team. Our experience was focused on a subset of poly-trauma patients affected by ITC. The results have undoubtedly been positive and encouraging, allowing mortality to be halved and the number of candidates for organ donation to be increased. In particular, the choice of initial treatment without anticoagulation has allowed the cessation of bleeding without significantly increasing the haemorrhagic risk. The artificial inotropic support provided by ECLS promotes a faster weaning from pharmacological inotropes and a more rapid recovery of cardiac contractility.

As it does not impede conventional therapies, ECLS can be instituted early, not only to give the patient the maximal chance of survival but also as a new way of expanding the donor pool for organ transplantation. Future improvements in materials and techniques are expected to make ECLS even easier and safer to manage, leading to a further extension of its uses and indications.

Conflict of interest: none declared.

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