Reversible Myocardial Dysfunction in Survivors of Out-of-Hospital Cardiac Arrest

Ivan Laurent, MD,* Mehran Monchi, MD,* Jean-Daniel Chiche, MD,* Luc-Marie Joly, MD,*
Christian Spaulding, MD,‡ Bénédicte Bourgeois, MD,† Alain Cariou, MD,* Alain Rozenberg, MD,†
Pierre Carli, MD,† Simon Weber, MD,‡ Jean-François Dhainaut, MD, PhD*

Paris, France

OBJECTIVES	The aim of the study was to assess the hemodynamic status of survivors of out-of-hospital cardiac arrest (OHCA).
BACKGROUND	The global prognosis after successfully resuscitated patients with OHCA remains poor. Clinical studies describing the hemodynamic status of survivors of OHCA and its impact on prognosis are lacking.
METHODS	Among 165 consecutive patients admitted after successful resuscitation from OHCA, 73 required invasive monitoring because of hemodynamic instability, defined as hypotension requiring vasoactive drugs, during the first 72 h. Clinical features and data from invasive monitoring were analyzed.
RESULTS	Hemodynamic instability occurred at a median time of 6.8 h (range 4.3 to 7.3) after OHCA. The initial cardiac index (CI) and filling pressures were low. Then, the CI rapidly increased 24 h after the onset of OHCA, independent of filling pressures and inotropic agents (2.05 [1.43 to 2.90] 8 h vs. 3.19 l/min per m^2 [2.67 to 4.20] 24 h after OHCA; p < 0.001). Despite a significant improvement in CI at 24 h, a superimposed vasodilation delayed the discontinuation of vasoactive drugs. No improvement in CI at 24 h was noted in 14 patients who subsequently died of multiorgan failure. Hemodynamic status was not predictive of the neurologic outcome.
CONCLUSIONS	In survivors of OHCA, hemodynamic instability requiring administration of vasoactive drugs is frequent and appears several hours after hospital admission. It is characterized by a low CI that is reversible in most cases within 24 h, suggesting post-resuscitation myocardial dysfunction. Early death by multiorgan failure is associated with a persistent low CI at 24 h. (J Am Coll Cardiol 2002;40:2110–6) © 2002 by the American College of Cardiology Foundation

Despite community-based interventions, survival after out-of-hospital cardiac arrest (OHCA) remains low. Less than 30% of cardiopulmonary resuscitation (CPR) attempts started out of hospitals lead to restoration of spontaneous circulation and to hospital admission (1). In-hospital treatment of comatose survivors of cardiac arrest is usually supportive, and hospital mortality is as high as 70% (2,3). Late mortality and morbidity are due to post-anoxic neurologic consequences, with 10% to 40% of survivors sustaining significant permanent brain damage (1–4). In contrast, early death is often due to persistent hemodynamic instability leading to multiple organ failure (1). Animal studies support the concept that post-resuscitation hemodynamic instability is related to acute myocardial dysfunction. In animal models, post-resuscitation myocardial dysfunction is characterized by impaired contractile function, decreased work capacity, and variable diastolic dysfunction that reverses several hours or days after resuscitation (5–7).

Few studies have investigated post-resuscitation hemodynamic instability and myocardial dysfunction in humans

(8,9). To address this issue, hemodynamic data during the first 72 h after arrest were prospectively gathered in a consecutive series of 165 patients included in a study on the value of immediate coronary angiography followed, if necessary, by angioplasty after successful resuscitation from OHCA (10). The prevalence, risk factors, and evolution of post-resuscitation hemodynamic instability and myocardial dysfunction, as well as their influence on survival with or without neurologic damage, were assessed.

METHODS

Patient selection. In Paris, management of OHCA involves emergency units equipped with ambulances that are always staffed by one or two physicians trained in emergency medicine. In cases of sudden OHCA, CPR was initiated according to standard procedures. Successfully resuscitated patients were included in a prospective study on the value of immediate coronary angiography followed, if necessary, by coronary angioplasty, if they were between 30 and 75 years old, if sudden cardiac arrest occurred within 6 h of the onset of symptoms in patients who were previously leading a normal life, and if there was no obvious noncardiac cause of cardiac arrest.

Patients who met the criteria were brought directly to the cardiac catheterization laboratory of our hospital, and immediate coronary and left ventricular angiography was

performed according to standard techniques. If a recent coronary artery occlusion was found, coronary angioplasty was attempted, unless the infarct-related vessel was too small or the operator considered the procedure to be technically impossible. Standard resuscitation and stabilization procedures were continued during the procedure. The patients were then transported to the medical intensive care unit for supportive treatment, including mechanical ventilation. Hypotension, defined as a mean arterial blood pressure <75 mm Hg, was treated according to the following protocol: 1) volume expansion was determined by the left ventricular end-diastolic pressure (LVEDP) measured before left ventricular angiography: volume expansion consisted of 1,000 ml of crystalloids if LVEDP was <18 mm Hg or 500 ml if LVEDP was between 18 and 25 mm Hg; the administration was repeated twice if there was no evidence of pulmonary congestion; and 2) vasoactive drug infusion was initiated if hypotension was unresponsive to volume challenge or when there was no previous volume expansion if LVEDP was >25 mm Hg and/or if clinical or radiologic signs of pulmonary edema were noted. Hemodynamic instability was defined as the need for vasoactive drugs, leading to invasive monitoring by an arterial pressure and pulmonary artery catheter that was performed as soon as possible after the onset of vasoactive drug therapy. Shock was defined by the association between hypotension unresponsive to vasoactive drug infusion and evidence of inadequate organ perfusion revealed by elevated plasma lactate concentrations, metabolic acidosis, or oliguria (<50 ml/h).

Invasive monitoring. A 7F pulmonary artery catheter (Baxter-Edwards, Irvine, California) was inserted through the central port of an introducer in a central vein (internal jugular or subclavian vein) and guided by pressure waveforms into a branch of a pulmonary artery. The right position in West's third zone was systematically controlled by standard chest radiography. An arterial pressure catheter (Vygon SA, Ecouen, France) was inserted through a radial or femoral artery to continuously monitor blood pressure. Pressure waveforms were recorded on a Hewlett-Packard monitor (Merlin, Hewlett-Packard, Palo Alto, California). Cardiac output was determined by thermodilution after injection of 10 ml of cold isotonic glucose. The cardiac output values represented the average of three measurements within 20% of each other. Cardiac index (CI) was obtained by dividing cardiac output by body surface area.

Data collection. The clinical data collected during resuscitation and hospitalization were prospectively entered in a computer database described previously (10). Coronary angiograms underwent final qualitative and quantitative review. Left ventricular ejection fraction was estimated by the biplane area–length method, as described by Dodge et al. (11). The time of the lowest mean arterial pressure unresponsive to volume expansion, measured by noninvasive methods, was entered as time 0.

Hemodynamic data provided by invasive monitoring were reviewed. Measurements performed immediately after insertion of the pulmonary artery catheter (time 1) were entered in the data base, as well as measurements obtained 4 (time 2) and 12 h (time 3) after insertion. Finally, a fourth set of measurements performed 72 h after the onset of OHCA was included (time 4). If death occurred during the first 72 h, the final measurements were entered as time 4.

The final neurologic status at hospital discharge was assessed using the five-point Pittsburgh modification of the Glasgow outcome categories (1). Cerebral performance categories (CPCs) are defined as follows: CPC-1 = good cerebral performance; CPC-2 = moderate cerebral disability; CPC-3 = severe cerebral disability; CPC-4 = persistent vegetative state; and CPC-5 = brain death or clinical death.

The study protocol was reviewed and approved by the Ethics Committee of Cochin Hospital. Because informed consent was impossible to obtain immediately from the patients, the next of kin provided consent for management, according to the protocol described previously, and for the use of data gathered before admission and during the hospital stay for scientific purposes. Survivors also provided consent as soon as possible.

Statistical analysis. Because of asymmetric distribution, continuous variables are reported as median values and interquartile ranges (25th and 75th percentiles). Discrete variables are expressed as percentages. Univariate analysis was performed using the chi-square tests for categorical variables and the Mann-Whitney *U* test for numeric data. Hemodynamic parameter variations were tested using nonparametric analysis of variance (Kruskall-Wallis test). Posthoc comparisons between points in time were performed using the Wilcoxon matched-pairs, signed, rank-sum test. Parameters found to be significantly associated with hemodynamic instability on univariate analysis were subsequently included in a multivariate logistic regression model to test their independent association. A two-tailed p value <0.05 was considered to indicate statistical significance. All statistical analyses were done on a personal computer using STATA version 7.0 software (Stata Corp., College Station, Texas).

RESULTS

Study population. From January 1994 to March 1998, four emergency units in Paris responded to 2,555 cases of suspected OHCA. In 1,232 patients, CPR was not attempted because of the medical team's late arrival or because the patient had a severe preexisting disease. Resuscitation was attempted in the remaining 1,323 patients (52%), and a

Table 1. Patient Characteristics

Characteristics	Group A: Hemodynamic Instability (n = 73)	Group B: No Hemodynamic Instability (n = 75)	p Value
Age (years)	57 (49–65)	56 (43–64)	0.31
Male gender	57 (78%)	67 (89%)	0.09
History of CAD	17 (23%)	16 (21%)	0.76
Intervals			
Onset of arrest to initial CPR (min)	5 (1–10)	5 (2–9)	0.59
Onset of arrest to ROSC (min)	25 (14–38)	15 (7–30)	< 0.01
VF recorded as initial cardiac rhythm	51 (70%)	50 (66%)	0.75
Number of countershocks	3 (1–6)	2 (1–3)	< 0.01
Total dose of epinephrine during CPR (mg)	10 (3–15)	2 (0–10)	< 0.01
Perfusion of epinephrine required			
Maximal perfusion rate during first day (mg/h)	2 (0–3)	0	< 0.01
Duration of treatment (days)	2 (1–4)	0	< 0.01
Angiographic data			
Heart rate (beats/min)	105 (75–143)	85 (48–118)	< 0.05
MAP (mm Hg)	95 (85–105)	98 (91–110)	0.85
LVEDP (mm Hg)	18.5 (10–32)	12.1 (5–25)	< 0.01
LVEF (%)	32 (25–40)	43 (35–50)	< 0.01
Significant CAD	54 (74%)	53 (71%)	0.98
Single-vessel disease	26 (48%)	26 (49%)	
Two- or three-vessel disease	28 (52%)	27 (51%)	
Recent coronary artery occlusion	37 (50.7%)	28 (37.3%)	0.06
Angioplasty attempted	31 (83.7%)	25 (89.2%)	0.45
Angioplasty successful	23 (74.1%)	19 (76%)	0.29

Data are presented as the median value (interquartile range) or number (%) of patients.
CAD = coronary artery disease; CPR = cardiopulmonary resuscitation; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PTCA = percutaneous transluminal coronary angioplasty; ROSC = return of spontaneous circulation; VF = ventricular fibrillation.

stable hemodynamic state was obtained in 458 (18%). Fatal recurrent cardiac arrest occurred during transportation in 182 patients: the terminal rhythm was asystole in 164 and electromechanical dissociation in 18. So, 276 patients (11%) were successfully transported. A total of 111 patients were excluded from the study either because they had an obvious noncardiac cause of cardiac arrest (n = 66) or because they were outside of the age range for the study. Therefore, 165 patients (6.5%) were included. Immediate coronary angiography was attempted in all patients; it was impossible to perform in one because of extensive peripheral artery disease. Follow-up was then performed in the intensive care unit. Hemodynamic instability requiring vasoactive drugs occurred in 90 patients (54.5%) during the first 72 h after resuscitation. Invasive monitoring was considered to be futile for 17 moribund patients. Therefore, 73 patients were effectively monitored invasively for hemodynamic instability (group A), and 75 patients did not develop hemodynamic instability during follow-up (group B).

Risk factors for hemodynamic instability after resuscitation. Patient characteristics are summarized in Table 1. The interval between the onset of arrest and the return of spontaneous circulation was significantly longer in group A patients (25 [14 to 38] vs. 15 min [7 to 30], p < 0.01). The dose of epinephrine received during CPR was higher in patients with hemodynamic instability (10 [3 to 15] vs. 2.0 mg [0 to 10], p < 0.01). Similarly, there were more countershocks in group A patients than in group B patients

(3 [1 to 6] vs. 2 [1 to 3], p < 0.01). Hemodynamic data gathered during the angiographic procedure showed significant differences between the groups: the left ventricular ejection fraction was decreased in both groups, but significantly lower in group A (32% [25 to 40%] vs. 43% [35 to 50%] in group B, p < 0.01), and LVEDP was higher in group A (18.5 [10 to 32] vs. 12.1 [5 to 25] mm Hg in group B, p < 0.01). A trend toward a higher incidence of post-resuscitation hemodynamic instability was noted if acute coronary occlusion was the cause of OHCA (50.7% vs. 37.3%, p = 0.06). On multivariate analysis, the dose of epinephrine received during CPR was the only predictive factor of hemodynamic instability (odds ratio 1.05 per mg of epinephrine received during CPR, 95% confidence interval 1.01 to 1.11; p = 0.035).

Hemodynamic profile and renal and hepatic variables in patients with hemodynamic instability. Hemodynamic data are summarized in Table 2. The onset of hemodynamic instability was most often delayed after admission to the intensive care unit. A significant decrease in mean arterial pressure unresponsive to volume expansion was noted 6.8 h (range 4.3 to 7.3) after OHCA (time 0) and led to infusion of vasoactive drugs and invasive monitoring by a pulmonary artery catheter 8 h (range 7 to 9) (time 1) after cardiac arrest (mean arterial pressure at admission in intensive care unit: 87 [75 to 103] vs. 62 [46 to 71] mm Hg at time 0; p < 0.01). Hemodynamic data recorded at time 1 revealed a low CI (2.05 l/min per m² [range 1.43 to 2.90]), which

Table 2. Hemodynamic Data During the First 72 Hours

Hemodynamic Parameters	ICU Admission: 3.0 (2.0–3.6)	Time 0: 6.8 (4.3–7.3)	Interval From Onset of Cardiac Arrest to Measurement (h)				p Value§
			Time 1: 8.0 (7.0–9.0)	Time 2: 12.0 (11.0–13.5)	Time 3: 24.0 (23.0–25.7)	Time 4: 67.0 (52.0–72.0)	
Temperature (°C)	36.0 (35.4–36.7)	—	36.6* (35.8–37.5)	37.3† (36.7–38.1)	37.6† (37.0–38.2)	37.8† (37.3–38.3)	< 0.001
Epinephrine perfusion (mg/h)	0	0	1.0‡ (0–2.2)	1.3‡ (0–2.0)	1.5‡ (0–2.7)	0.4‡ (0–1.6)	0.042
HR (beats/min)	110 (89–123)	111 (91–124)	108 (97–125)	111 (98–128)	112 (101–125)	101* (94–120)	0.215
MAP (mm Hg)	87 (75–103)	62† (46–71)	79† (69–102)	76† (69–87)	80 (71–89)	80 (73–88)	0.04
MPAP (mm Hg)	—	—	28 (22–32)	24† (20–28)	24† (20–27)	28 (24–32)	0.005
RAP (mm Hg)	—	—	11 (8–15)	10 (8–13)	11 (8–13)	12 (9–15)	0.189
POAP (mm Hg)	—	—	14 (11–18)	12‡ (10–15)	13 (10–16)	14 (10–18)	0.248
CI (l/min per m^2)	—	—	2.05 (1.43–2.90)	2.61‡ (1.90–3.46)	3.19‡ (2.67–4.20)	3.69* (2.92–4.49)	< 0.001
SVRI (dynes/cm$^5\cdot$m^2)	—	—	2,908 (1,946–4,658)	1,936‡ (1,493–2,951)	1,672† (1,300–2,034)	1,518† (1,153–1,852)	< 0.001
PVRI (dynes/cm$^5\cdot$m^2)	—	—	438 (339–593)	363† (221–488)	261† (183–346)	274* (206–371)	< 0.001
SI (ml/m^2)	—	—	20.0 (15.0–23.8)	22.5† (18.4–32.1)	29.3† (24.8–37.4)	35.3‡ (28.5–42.1)	< 0.001
LVSW (g·m/m^2)	—	—	23.8 (19.3–31.0)	24.5 (19.8–34.9)	33.3† (25.0–43.1)	41.1‡ (31.4–50.0)	< 0.001

*p <0.05, †p <0.01, ‡p <0.001 for all tests performed versus baseline. Baseline values were at intensive care unit (ICU) admission for temperature, epinephrine infusion, and heart rate; time 0 for mean arterial pressure (MAP); and time 1 for the other values. Mean arterial pressure at admission and time 0 was determined by noninvasive methods, and MAP at times 1, 2, 3, and 4 by invasive monitoring. §The p value in the last column refers to nonparametric analysis of variance (Kruskall-Wallis test). Data are presented as the median value (interquartile range).

CI = cardiac index; HR = heart rate; LVSW = left ventricular stroke work; MPAP = mean pulmonary artery pressure; POAP = pulmonary occlusion arterial pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SI = stroke index; SVRI = systemic vascular resistance index.

improved linearly through time (Kruskall-Wallis test: p < 0.001). An alteration of CI was associated with normal or low filling pressures that required a median of 8,000 ml (range 7,500 to 9,000) of volume expansion to keep the patient stable during the first 72 h. After a further decrease in mean arterial pressure, despite initiation of dobutamine or epinephrine, systemic hypotension began to improve progressively, allowing, in most cases, discontinuation of vasopressor treatment within 72 h.

Renal and hepatic variables recorded at 24 h are summarized in Table 3. Significant increases in plasma creatinine and diuresis and a decrease in the International Normalized Ratio were noted in group A.

Fourteen patients from group A (19.2%) died of shock during the early phase. Their hemodynamic status differed markedly from that of the other patients (Table 4). Invasive monitoring showed a low CI, which did not improve significantly (Kruskall-Wallis test: p = 0.40), despite increased doses of epinephrine. This difference appears at time 2 and becomes significant at time 3.

In-hospital mortality and neurologic outcome. Of the 73 patients who required hemodynamic monitoring, 28 had a favorable in-hospital outcome, as hemodynamic instability was reversible and neurologic sequelae were absent or minimal (i.e., CPC-1 or CPC-2 at hospital discharge). Fourteen patients died of shock, and 31 developed transient hemodynamic instability but had major post-anoxic brain damage: 4 had severe cerebral disability (CPC-3), 21 remained in a persistent vegetative state (CPC-4), and 6 had brain death. There was no difference in the neurologic outcome between patients with hemodynamic instability and the other patients (42.4% in group A vs. 44% in group B with severe brain damage, p = 0.54).

DISCUSSION

After successful resuscitation from cardiac arrest, patients admitted to intensive care units often develop multiorgan failure leading to death during the first three days (2,3). In contrast, late mortality is directly related to neurologic damage, with >50% of patients remaining in a vegetative state (4). The present report is the first clinical study to elucidate the hemodynamic status of survivors of CPR: hemodynamic instability requiring the administration of vasoactive agents was noted in more than half of survivors after successful CPR. The onset of hemodynamic instability onset was delayed 4 to 7 h after admission, and full recovery was seen in survivors by 72 h. Early death by multiorgan failure was associated with a persistent low CI at 24 h. Hemodynamic status was not predictive of the neurologic outcome.

Risk factors for hemodynamic instability after cardiac arrest. On multivariate analysis, the amount of epinephrine used during CPR predicted the occurrence of hemodynamic instability. Our results confirm experimental data that suggest that epinephrine potentiates myocardial dysfunction

Table 3. Renal and Hepatic Variables at 24 Hours

Characteristics	Group A: Hemodynamic Instability	Group B: No Hemodynamic Instability	p Value
Plasma urea (mmol/l)	8.3 (6.7–11.3)	7.6 (6.2–8.8)	0.03
Plasma creatinine (μmol/l)	153 (121–184)	111 (98–128)	0.0001
Diuresis (l/24 h)	1.0 (0.3–1.9)	1.5 (1.1–2.4)	0.001
Plasma total bilirubin (μmol/l)	11 (8–14)	10 (7–13)	0.28
INR	1.3 (1.0–1.8)	1.0 (0.9–1.4)	0.001

Data are presented as the median value (interquartile range).
INR = International Normalized Ratio.

after resuscitation (12). Previous clinical studies suggest that high doses of epinephrine given during resuscitation may alter the CI after return of spontaneous circulation and could be an independent predictor of mortality (9,13).

In contrast, the duration of CPR predicted the occurrence of hemodynamic instability by univariate, but not multivariate, analysis. According to our resuscitation procedures, the amount of epinephrine used increased with the CPR duration. This factor may have influenced our multivariate analysis, which was performed in a relatively small number of patients. Therefore, a relationship between CPR duration and hemodynamic instability cannot be excluded.

A trend toward a higher rate of post-resuscitation hemodynamic instability was noted if acute coronary occlusion was the cause of OHCA (50.7% vs. 37.3%, p = 0.06). Global post-resuscitation myocardial stunning may prevent acute compensatory mechanisms during OHCA due to myocardial infarction, such as hyperkinesia of noninfarcted left ventricular segments, thereby potentiating refractory shock and multiorgan failure. In our study, successful angioplasty was always performed within 3 h after the onset of cardiac arrest. Angioplasty failure occurred in eight patients; 5 died of refractory shock. In contrast, a 13.5% mortality rate from refractory shock was noted after successful angioplasty, which compares favorably to the 19.1% mortality rate from refractory shock in patients without

acute myocardial infarction. Therefore, a favorable hemodynamic effect of successful angioplasty cannot be excluded. In contrast, no relationship was found between the extent of coronary disease and the occurrence of shock. The amount of ischemic damage occurring during cardiac arrest and resuscitation may therefore be so substantial that even the myocardium fed by normal coronary arteries is severely affected. Severe myocardial dysfunction can therefore occur after cardiac arrest, independent of severe underlying coronary disease.

Evidence for post–cardiac arrest myocardial stunning. Our data suggest that myocardial stunning is an important cause of post-resuscitation shock. The left ventricular ejection fraction was severely depressed at hospital admission. The time course of post-resuscitation shock in our study showed marked depression of the CI at 8 h after arrest and a return to normal values within 24 h, with discontinuation of inotropic support at 72 h after the onset of cardiac arrest in survivors. Other common causes of acute myocardial dysfunction, such as hypoxia and hypercapnia, were ruled out by monitoring oxygen transport during the post-resuscitation period. Furthermore, immediate coronary angiography was performed in all patients at admission, and severe but transient myocardial dysfunction was observed in 36 group A patients (49.3%) with no acute coronary occlusion. The characteristics of the myocardial dysfunction

Table 4. Evolution of Cardiac Index, Mean Arterial Pressure, and Epinephrine Requirements Through Time According to Prognosis

	Admission	Time 1	Time 2	Time 3	Time 4
Hemodynamic instability, good neurologic outcome (n = 28)					
CI (l/min per m^2)	—	2.13 (1.40–2.81)	3.01 (2.22–3.64)	3.35 (3.12–4.33)	3.86 (2.92–4.31)
MAP (mm Hg)	83 (69–104)	75 (67–89)	75 (69–83)	80 (74–86)	82 (74–95)
Epinephrine perfusion (mg/h)	0	0.5 (0–2.0)	0.75 (0–2.0)	1 (0–2.0)	0 (0–1.0)
C[a−v̄]O$_2$ (ml/dl)	—	6.5 (4.59–8.84)	4.71 (3.48–5.90)	3.81 (3.23–5.04)	3.43 (2.71–4.70)
Hemodynamic instability, poor neurologic outcome (n = 31)					
CI (l/min per m^2)	—	2.04 (1.41–2.89)	2.44 (1.86–3.17)	3.10 (2.70–4.25)	3.76 (3.26–4.79)
MAP (mm Hg)	86 (77–103)	89 (77–110)	81 (70–90)	78 (70–91)	80 (74–87)
Epinephrine infusion (mg/h)	0	1.0 (0–3.0)	1.0 (0–2.0)	1.0 (0–2.7)	0.5 (0–1.5)
C[a−v̄]O$_2$ (ml/dl)	—	5.80 (4.45–7.37)	5.16 (3.38–6.39)	3.89 (3.44–4.47)	4.00 (3.27–4.56)
Shock leading to death (n = 14)					
CI (l/min per m^2)	—	2.37 (1.26–3.83)	2.39 (1.88–2.80)	2.56 (2.27–2.98)†	2.90 (2.15–3.57)*
MAP (mm Hg)	89 (77–108)	85 (62–103)	74 (66–91)	76 (65–84)	73 (68–75)*
Epinephrine perfusion (mg/h)	0	2.0 (0–3.1)	2.0 (0.5–8.0)	3.0 (1.2–8.2)*	2.0 (1.0–8.0)†
C[a−v̄]O$_2$ (ml/dl)	—	5.23 (2.92–8.22)	5.44 (4.08–7.25)	4.66 (4.32–5.69)†	4.71 (3.88–5.54)*

*p < 0.05, †p < 0.01, ‡p < 0.001 for all tests performed versus baseline. Data are presented as the median value (interquartile range).
C[a−v̄]O$_2$ = oxygen content difference between arterial and mixed venous blood; CI = cardiac index; MAP = mean arterial pressure.

observed in our patients are similar to those in previously published experimental reports (5,6). Gazmuri et al. (5) reported post-resuscitation myocardial dysfunction by using a model of ventricular fibrillation in pigs. Progressive impairment in contractile function with ventricular dilation was detected early after resuscitation and was maximal at 6 h. Kern et al. (6) studied, using both invasive and noninvasive measurements of left ventricular function, 23 domestic swine successfully resuscitated after 10 or 15 min of untreated cardiac arrest. Severe myocardial systolic and diastolic left ventricular dysfunction was documented and peaked at 2 to 5 h after resuscitation, despite the return of myocardial blood flow to normal levels. Full recovery of this post-resuscitation myocardial dysfunction was seen after 48 h.

Superimposed vasodilation. Despite rapid improvement in CI in our patients, hemodynamic instability worsened (mean arterial pressure: 79 mm Hg [69 to 102] at 8 h and 76 mm Hg [69 to 87] at 12 h, $p < 0.01$; epinephrine perfusion: 1.0 mg/h [0 to 2.2] at 8 h and 1.3 mg/h [0 to 2.0] at 12 h, $p < 0.05$). Discontinuation of vasopressor drugs was therefore delayed despite improvement of CI. A large volume expansion was initially required (cumulative crystalloid volume infused: 5,000 [3,500 to 6,500] ml at 24 h; 8,000 ml [7,500 to 9,500] at time 4) to maintain filling pressures >12 mm Hg and resulted in hemodilution at day 3 (hemoglobin: 9.8 g/100 ml at day 3 [9.0 to 11.5] vs. 14.6 g/100 ml [13.4 to 15.8] at admission; $p < 0.001$). Therefore, our data suggest that vasodilation occurred during the first two days after CPR. Further studies are needed to confirm these preliminary results and to characterize the role of each component of post-resuscitation hemodynamic instability. Of particular interest, post-CPR vasodilation has not been clearly identified in animal studies.

Hemodynamic status and neurologic outcome. In contrast to previous experimental data, no relationship between the occurrence and pattern of post-resuscitation hemodynamic instability and neurologic outcome was noted (7). We suggest that aggressive treatment of hemodynamic instability in selected cases is justified during the first days after cardiac arrest, until reliable assessment of the neurologic prognosis can be performed.

Study limitations. Vasoactive drugs and hemodynamic monitoring were started in survivors of OHCA with hemodynamic instability, defined by a mean arterial pressure <75 mm Hg and unresponsiveness to volume expansion. Patients were treated with vasoactive drugs before the occurrence of clinical signs of shock, such as cool extremities, tachycardia, or a decreased urine output. Precise definitions of hemodynamic instability or shock in this setting are lacking; however, close monitoring of blood pressure and administration of vasoactive drugs are recommended (14). Furthermore, variations of renal and hepatic variables were noted at 24 h in patients with hemodynamic instability, thereby suggesting extensive systemic hypoperfusion.

Hemodynamic monitoring was only performed in pa-

tients who developed hemodynamic instability after cardiac arrest. A severe alteration in left ventricular ejection fraction was also observed initially in group B (43.0% [35% to 50%]), suggesting that transient myocardial dysfunction was present in all patients, but clinically relevant in selected cases. Serial studies of left ventricular function using non-invasive techniques, such as echocardiography, in all survivors of OHCA would allow a more accurate evaluation of post-resuscitation myocardial dysfunction.

Patients with a noncardiac cause of arrest were excluded from the study; therefore, the conclusions of our study cannot be applied to all survivors of OHCA.

Conclusions. In survivors of OHCA, hemodynamic instability leading to the administration of vasoactive drugs is frequent and appears 4 to 7 h after hospital admission. It is associated with the use of high doses of epinephrine during CPR. Post-resuscitation hemodynamic instability is characterized by a low CI and normal or low filling pressures. The CI rapidly increases 24 h after the onset of OHCA, independent of filling pressures and vasoactive agents. A superimposed vasodilation requires a large initial volume expansion and delays the discontinuation of vasopressor drugs. Recovery is most often obtained within three days. This unique hemodynamic profile is suggestive of post-resuscitation myocardial stunning associated with vasodilation. Hemodynamic status did not predict the final neurologic outcome. Aggressive management of post-resuscitation hemodynamic instability therefore seems justified until accurate prediction of the neurologic outcome is feasible.

Reprint requests and correspondence: Dr. Christian Spaulding, Cardiology Department, Cochin Hospital, René Descartes University, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: christian.spaulding@cch.ap-hop-paris.fr.

REFERENCES

1. Safar P. Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. Crit Care Med 1988;16:923–41.
2. The Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 1986;314:397–403.
3. Gueugniaud PY, Mols P, Goldstein P, et al. Comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. N Engl J Med 1998;339:1595–601.
4. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. Lancet 1994;343:1055–9.
5. Gazmuri RJ, Weil MH, Bisera J, Tang W, Fukui M, McKee D. Myocardial dysfunction after successful resuscitation from cardiac arrest. Crit Care Med 1996;24:992–1000.
6. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol 1996;28:232–40.
7. Cerchiari EL, Safar P, Klein E, Cantadore R, Pinsky M. Cardiovascular function and neurologic outcome after cardiac arrest in dogs: the cardiovascular post-resuscitation syndrome. Resuscitation 1993;25:9–33.

8. Deantonio HJ, Kaul S, Lerman BB. Reversible myocardial depression in survivors of cardiac arrest. Pacing Clin Electrophysiol 1990;13:982–5.
9. Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. Chest 1994;106:1499–507.
10. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336:1629–33.
11. Dodge HT, Sandler H, Ballew DW, Lord JD Jr. The use of biplane angiocardiography for the measurement of left ventricular volume in man. Am Heart J 1960;60:762–76.
12. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation 1995;10:3089–93.
13. Behringer W, Kittler H, Sterz F, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. Ann Intern Med 1998;15:450–6.
14. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Agents to Optimize Cardiac Output and Blood Pressure. Circulation 2000;102 Suppl I:I129–35.