



Right and left heart failure in severe H1N1 influenza A infection

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ABSTRACT: Influenza infection can affect cardiac function. The recent pandemic of H1N1 influenza A provided an opportunity to study echocardiographic findings in critically ill infected patients.

We hypothesised that critically ill patients with H1N1 infection would have a higher incidence of right and left heart failure than is seen in unselected populations of patients with septic shock and/or acute respiratory distress syndrome (ARDS).

We retrospectively studied all patients admitted to four intensive care units at three hospitals in Salt Lake County, UT, USA, with laboratory-confirmed H1N1 infection in whom a clinical echocardiogram was available.

23 out of 48 patients had qualifying echocardiograms. Right ventricular (RV) dilatation (50–80%) and at least moderate systolic impairment (23%) were common, higher than the range described in general populations with ARDS. Left ventricular systolic dysfunction was present in 17% of patients. No single echocardiographic parameter was associated with 28-day mortality or ventilator-free days to 28 days.

Critically ill patients with H1N1 infection frequently exhibit right heart dilatation and failure. RV basal dilatation was extremely common. These patients have less left heart failure than expected on the basis of prior descriptions of influenza myopericarditis or of general populations of septic patients.

KEYWORDS: Acute respiratory distress syndrome, echocardiography, heart failure, influenza A virus, pulmonary heart disease

A pandemic of novel H1N1 influenza A virus (H1N1) recently affected most countries of the world [1–6]. In spring and summer 2009, Salt Lake County, UT, USA, experienced a dramatic surge in intensive care unit (ICU) admissions for acute cardiopulmonary failure resulting from H1N1 infection [7]. An evolving literature in critical care has begun to describe patterns of cardiac dysfunction in patients with undifferentiated acute respiratory distress syndrome (ARDS) and septic shock. Most of these studies have emphasised relative diastolic dysfunction of both ventricles in patients with septic shock, with a significant minority of patients also demonstrating left ventricular (LV) systolic dysfunction [8–14]. Studies in ARDS have suggested right ventricular (RV) systolic dysfunction and dilatation in a significant minority of patients [15, 16]. In distinction to this critical care literature, the large majority of studies on cardiac dysfunction during influenza infection emphasise myopericarditis. Despite the relative wealth of data on myopericarditis in acute influenza [17–27], there are no published studies in English of RV findings

in life-threatening influenza infection. We reviewed clinical echocardiographic results in our patients to characterise the incidence and extent of right and left heart failure in patients with life-threatening H1N1 infection.

METHODS

Study patients were admitted to any of four ICUs in three academic hospitals in Salt Lake County. Any patients presenting with symptoms typical of influenza-like illness during the outbreak period (May–June 2009) to participating ICUs were considered to have suspected H1N1. Suspect cases were then confirmed using PCR results of respiratory tract samples, with specific confirmation of the pandemic H1N1 strain at the Utah State laboratory (Salt Lake City, UT, USA) and/or the Centers for Disease Control and Prevention (Atlanta, GA, USA) [28]. Of patients with confirmed H1N1, we included those who underwent echocardiography for clinical indications. We excluded patients with known pre-existing cardiomyopathy or current pregnancy.

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ARDS and acute lung injury (ALI) were defined according to consensus criteria [29], as was septic shock [30]. Mortality was defined as in-hospital mortality. Secondary end-points included ventilator-free and ICU-free days at 28 days after admission [31]. Levels of mechanical ventilatory support at the time the echocardiogram was performed were determined from the electronic medical record, which is prospectively updated by respiratory therapists. We also measured receipt of vasopressor and/or inotropic therapy, body mass index (BMI), age, sex, serum troponin I levels nearest in time to the echocardiogram, and admission Acute Physiology and Chronic Health Evaluation (APACHE) II scores [32]. Elevation of troponin I ($\geq 0.4 \text{ ng}\cdot\text{mL}^{-1}$) was defined according to the assay employed at study hospitals.

Echocardiographic studies were obtained at the discretion of the clinical teams caring for the patients. Images were obtained using either a Philips SONOS 5500 or iE-33 (Philips Medical Systems, Bothell, WA, USA) bedside transthoracic echocardiographic imaging system and digitally stored as per routine. Images were reviewed by a research sonographer (K.D. Horton), with subsequent review by the senior author (C.K. Grissom), a Testamur of the National Board of Echocardiography and Level-II critical care echocardiographer. At the time of review, these two authors were blinded to clinical status and patient outcome.

RV fractional area change (RVFAC) was measured in the apical four-chamber view, as per consensus guidelines [33]. The tricuspid annular plane systolic excursion (TAPSE), another validated measure of RV systolic function, was also defined as per consensus guidelines and measured using M-mode through the anterior tricuspid annulus in the apical four-chamber view [34–36]. When an M-mode tracing was unavailable, TAPSE was

measured from two-dimensional images. LV-ejection fraction (LVEF) was defined using Simpson's method of stacked disks [37]. The ratio of RV to LV areas, a standard measure of relative RV dilatation, and the RV basal and mid-chamber diameters were measured as per consensus guidelines [37]. LV diastolic function was defined on the basis of pulse-wave Doppler of the mitral inflow (in patients in sinus rhythm and without mitral stenosis) and tissue Doppler of the medial (septal) mitral annulus according to consensus guidelines, which stratify diastolic filling into normal, impaired relaxation, pseudonormal, or restrictive [38]. Pulmonary venous inflow into the left atrium was measured using pulse-wave Doppler generally at the right superior pulmonary vein in the apical four-chamber view, and was classified as systolic (normal in most adults by middle age), diastolic, or codominant [38].

Statistical methods

Descriptive statistics and CIs are provided in tables 1 and 2. Percentages and Fisher exact 95% CIs are reported for binary measures; means and normal 95% CIs for normally distributed continuous measures; and medians and bootstrap 95% CIs are provided for non-normally distributed continuous measures. Normality was determined by examination and using the Shapiro–Wilk test. To evaluate correlation between continuous variables, we fitted linear regression models. To compare mortality for different measures of RV failure, we employed univariate logistic regression models. A two-tailed $p < 0.05$ was considered statistically significant. All analyses were performed with the R statistical package, version 2.10.1 [39].

The Institutional Review Boards at Intermountain Healthcare and the University of Utah approved this study with waiver of the requirement for informed consent.

TABLE 1 Clinical characteristics of patient cohort

Characteristic	Entire cohort [#]	Patients with ARDS [†]	Patients without echocardiogram [‡]
Age yrs	41 (36–47)	42 (36–48)	30 (24–36)
Female sex %	70 (49–90)	68 (45–91)	48 (26–70)
BMI $\text{kg}\cdot\text{m}^{-2}$	39 (34–44)	39 (35–43)	34 (30–38)
ALI or ARDS %	91 (79–100)	NA	65 (44–86)
ARDS %	83 (66–99)	NA	48 (26–70)
Required mechanical ventilation %	87 (72–100)	95 (84–100)	35 (14–56)
Maximum PEEP cmH_2O	21 (17–24)	21 (17–24)	16 (8–24)
Minimum $P_{a,O_2}:F_{i,O_2}$ ratio	59 (50–98)	58 (50–72)	146 (73–240)
Ventilator days	7.3 (2.8–13)	7.8 (3.4–16)	11 (3–19)
Septic shock %	61 (39–82)	74 (52–95)	17 (1–34)
Minimum Sc_{v,O_2} %	62 (55–70)	63 (54–68)	51 (24–78)
APACHE II	26 (22–30)	26 (22–36)	16 (12–20)
ICU length-of-stay days	6.4 (3.1–13)	10 (6.5–14)	5 (2–8)
Troponin I nearest in time to echocardiogram $\text{ng}\cdot\text{mL}^{-1}$	0.03 (0.01–0.2)	0.08 (0.02–0.26)	NA
Elevated troponin %	8.7 (0–21)	11 (0–26)	0
In-patient mortality %	30 (10–51)	37 (13–61)	4 (0–13)

Data are presented as point estimate (95% CI); point estimate is mean for normally distributed data, median otherwise. BMI: body mass index; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; P_{a,O_2} : arterial oxygen pressure; F_{i,O_2} : inspired oxygen fraction; Sc_{v,O_2} : oxygen saturation in superior vena cava; APACHE II: Acute Physiology and Chronic Health Evaluation score; ICU: intensive care unit; NA: not applicable. [#]: n=23; [†]: n=19; [‡]: n=23.

TABLE 2 Echocardiographic characteristics

Characteristic	Entire cohort: point estimate (95% CI)	n for parameter	ARDS: point estimate (95% CI)	n for parameter
Depressed LVEF %	17 (5–37)	23	21 (1–41)	19
Mitral E velocity $\text{cm}\cdot\text{s}^{-1}$	88 (76–99)	19	87 (76–99)	17
E:A ratio	1.3 (1.0–1.5)	16	1.3 (1.1–1.5)	15
Low TAPSE %	36 (28–42)	22	34 (27–40)	18
Low RVFAC %	43 (20–66)	21	47 (21–74)	17
RA area cm^2	14 (11–16)	17	14 (12–17)	14
Em velocity $\text{cm}\cdot\text{s}^{-1}$	9.5 (7.1–12)	15	10 (7–13)	12
E:Em ratio	9.2 (7.4–12)	13	8.7 (7.3–13)	12
Abnormal PVI %	69 (40–98)	13	64 (30–98)	11
High RV:LV ratio %	83 (66–100)	23	90 (74–100)	19
Dilated RV–base %	90 (77–100)	21	90 (74–100)	17
Dilated RV–mid %	32 (11–53)	22	33 (9–57)	18
Septal bowing %	39 (18–61)	23	37 (13–61)	19
Dilated RV + septal bowing %	30 (10–51)	23	32 (9–55)	19
High RV area %	19 (1–37)	21	18 (0–38)	17
TR gradient mmHg	28 (22–34)	13	29 (22–36)	11

Point estimate is mean for normally distributed data, median otherwise. ARDS: acute respiratory distress syndrome; LVEF: left ventricular-ejection fraction; E: early diastolic mitral inflow; A: atrial mitral inflow; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change; RA: right atrium; Em: early diastolic septal annular velocity; PVI: pulmonary venous inflow; RV:LV ratio: ratio of right ventricular to left ventricular end-diastolic area; RV: right ventricle; TR: tricuspid regurgitation.

RESULTS

25 out of 48 patients treated in participating ICUs with H1N1 had echocardiograms available within 48 h of ICU admission. One patient had premorbid cardiomyopathy and was excluded from analysis, as was the single pregnant patient. Of the remainder, all 23 were of sufficient quality to analyse most if not all parameters of RV and LV function. Clinical characteristics of the 23 patients are presented in table 1. Almost all patients (91%) met criteria for ALI (83% met criteria for ARDS) with a mean nadir ratio of arterial oxygen pressure to fraction of inspired oxygen ($P_{a,O_2}:F_{i,O_2}$) of 88 (median 59) requiring a mean positive end-expiratory pressure (PEEP) among those ventilated of 21 (median 24) cmH_2O . Nearly two-thirds were in shock, with a mean nadir oxygen saturation in the superior vena cava of 62%. Mean APACHE II score was 26. Seven (30%) of the 23 patients died. Patients who underwent echocardiography were more severely ill than patients who did not undergo echocardiography: mean APACHE II score was 16 in patients who did not undergo echocardiography ($p<0.01$ for comparison), and mean PEEP was 16 in patients who did not undergo echocardiography ($p=0.2$ for comparison), while shock was present in 17% of patients who did not undergo echocardiography ($p<0.01$ for comparison). Venous thrombosis was rare (three patients had thrombosis in a leg vein), while pulmonary embolism was not observed. 10 patients were screened by ultrasound, one by computed tomography. No patients with thrombosis died. Three patients had bacterial superinfection, one of whom had shock. Among those superinfected, only the patient with shock died.

Echocardiographic parameters are presented in table 2. The most common finding was dilatation of the RV, whether

measured by the basal RV diameter, mid-RV diameter or RV diastolic area. Using the published range for normals, 90% of patients had an RV basal diameter consistent with dilatation, while 32% met criteria for dilatation on measurement at mid-chamber, and 19% met criteria for at least moderate RV dilatation by diastolic area. Using the proposed ratio of RV to LV end-diastolic areas (>0.6) employed in the critical care echocardiography literature [40], 83% of patients had RV dilatation. Septal flattening was a less common finding, although 30% of patients had both RV dilatation and septal flattening. Mean RV basal diameter was 4.2 cm, mean RV diastolic area was 23 cm^2 , and the mean ratio of RV end diastolic area to LV end diastolic area was 0.72, where <0.6 is considered normal. Density distributions of measures of RV dilatation are presented in figure 1.

The two main measures of RV systolic function, TAPSE and RVFAC, demonstrated a similarly high rate of RV dysfunction, as demonstrated in figure 2.

TAPSE was ≤ 1.5 cm in 36% of patients, while RVFAC was below normal ($<32\%$) in 43% of patients. (Mean RVFAC was 35%; mean TAPSE was 1.6 cm.) These two measures of RV systolic dysfunction were concordant in 16 patients and discordant in four. If the presence of either finding was considered evidence of RV failure, then 48% of patients exhibited RV systolic failure. In those patients ($n=13$) who had a tricuspid regurgitation jet velocity measured, the mean tricuspid pressure gradient was 28 mmHg. Restricting the analysis to the 19 patients with ARDS did not significantly alter these findings.

LV diastolic function was generally evaluable: mitral inflow was fused or indeterminate in only four out of 23 patients.

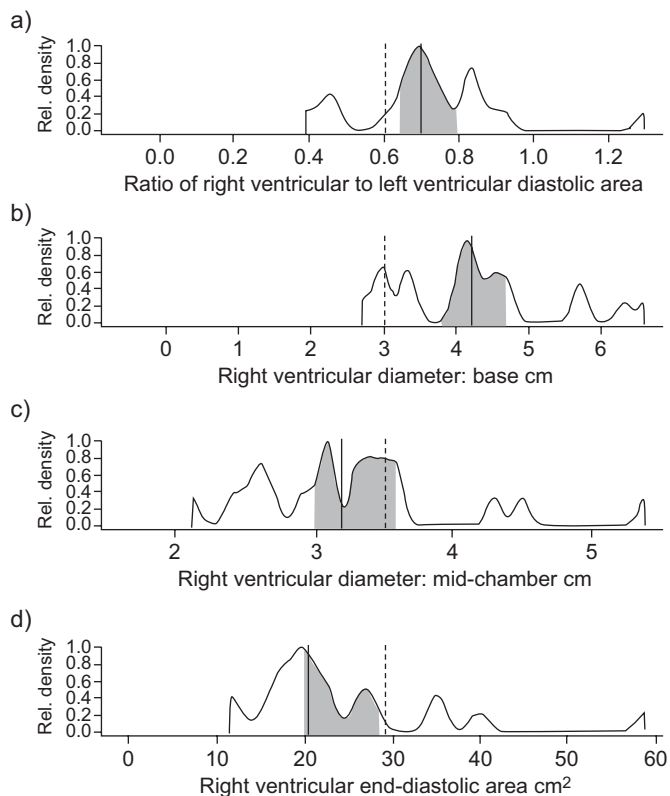


FIGURE 1. Measures of right ventricular dilatation. Observed density distributions of measures of systolic function. Median value is indicated by vertical solid line, with shading indicating 95% bootstrap CI. The vertical dotted line indicates the upper limit of normal from consensus documents and normal populations. a) $n=23$; normal <0.6 ; median=0.70. b) $n=21$; normal <3.0 ; median=4.2. c) $n=22$; normal <3.5 ; median=3.20. d) $n=21$; normal <29.0 ; median=20.30. Rel: relative.

A normal pattern of mitral inflow was documented in nine patients (39%). Mean early diastolic mitral inflow (E) velocity was $88 \text{ cm}\cdot\text{s}^{-1}$, mean atrial mitral inflow (A) velocity was $69 \text{ cm}\cdot\text{s}^{-1}$, and the mean E:A ratio was 1.25. Mitral septal tissue Doppler velocities were obtained in 15 patients, with mean early velocity (Em) of $9.5 \text{ cm}\cdot\text{s}^{-1}$ and a median E:Em ratio of 9.2. In the 13 patients in whom reliable pulmonary venous inflows could be determined, 69% were diastolic or codominant.

Pericardial effusion was an uncommon finding, two patients had a trivial effusion, while one other patient had a small effusion. None had evidence of tamponade physiology. Troponin I was elevated in two (9%) patients, neither of whom had evidence of depressed LV systolic function. Four patients (17%) had depressed LV systolic function, one of whom had a borderline elevation of troponin I ($0.38 \text{ ng}\cdot\text{mL}^{-1}$); mean LVEF for the entire cohort was 57%, while for patients with depressed LV systolic function, mean LVEF was 33%. Depressed LV systolic function was only observed in patients with shock, affecting four (29%) out of 14 patients with septic shock. In patients who survived, LV systolic dysfunction resolved on follow-up echocardiograms.

In this group of critically ill patients, no association between echocardiographic parameters and fatal outcome reached statistical significance on univariate logistic regression. Linear

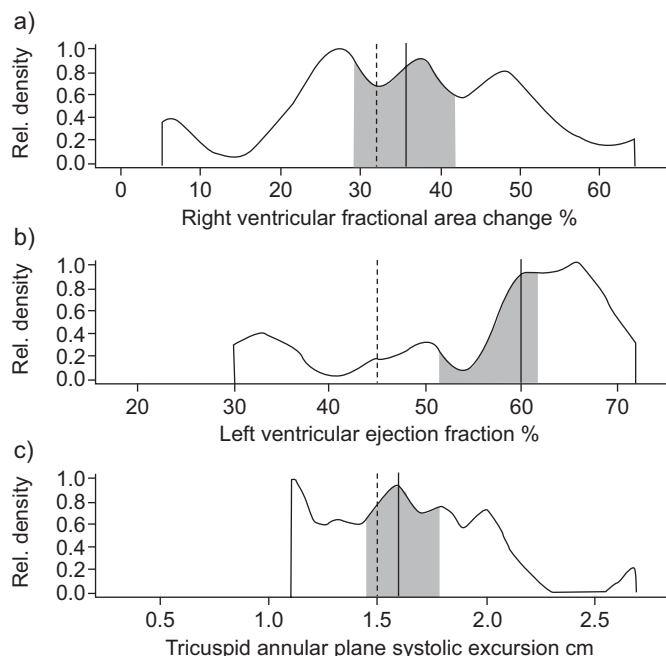


FIGURE 2. Measures of ventricular systolic function. Observed density distributions of measures of systolic function. Median value is indicated by vertical solid line, with shading indicating 95% bootstrap CI. The vertical dotted line indicates the lower limit of normal from consensus documents and normal populations. a) $n=21$; normal ≥ 32.0 ; median=35.78. b) $n=23$; normal ≥ 45 ; median=60.0. c) $n=22$; normal ≥ 1.5 ; median=1.60. Rel: relative.

regressions of echocardiographic parameters and ventilator-free days also failed to achieve statistical significance.

Although there was no strong linear correlation between BMI and various measures of RV dilatation, obese patients (BMI ≥ 30) had a higher RV diastolic area (25.5 versus 16 cm^2 ; $p<0.01$) and mid-chamber diameter (3.4 versus 2.6 cm ; $p<0.01$) than non-obese patients (no non-obese patients met criteria for RV dilatation by diastolic area or mid-chamber diameter). Measures of RV systolic function did not correlate with obesity. End-expiratory, peak, or plateau pressures on the mechanical ventilator at the time of echocardiography were not significantly associated with RV dilatation or systolic dysfunction. The ratio of $P_{a,O_2}:F_{I,O_2}$ was also not significantly associated with RV dilatation or systolic dysfunction.

DISCUSSION

Severe H1N1 infection, in this retrospective cohort of 23 critically ill patients, is frequently associated with RV dilatation and systolic dysfunction, at rates that somewhat exceed those in unselected populations of patients with ARDS. Moderate or severe RV dilatation and/or systolic dysfunction was present in more than half of 23 patients with H1N1 requiring ICU admission for whom echocardiograms were available. This degree of acute pulmonary heart failure (also called acute *cor pulmonale*) complicating H1N1 appears higher than prior estimates (10–25%) of the prevalence of pulmonary heart disease in a general population of patients with ARDS [15, 41]. Our sample appears similar, however, to patients with sepsis. In one cohort of 67 patients with septic shock, the mean

RVFAC was 35% [14] essentially identical to the mean (31%) in patients with septic shock in our cohort.

The prevalence of LV systolic dysfunction in patients with septic shock in our cohort (29%) is somewhat lower than prior estimates (38%) for septic shock [14]. LV systolic dysfunction occurred exclusively in patients with septic shock, suggesting that influenza-specific myopericarditis was not a major factor in the cardiac insufficiency associated with life-threatening H1N1. Compatible with our findings, recent studies in ambulatory patients with influenza suggest that prior estimates of 10% incidence of myopericarditis are significant overestimates [42–44]. Contrary to older reports about the nature of heart failure in life-threatening influenza, the cardiac insufficiency in this group of patients with H1N1 appears to be largely related to lung injury and mechanical ventilation with secondary *cor pulmonale* and/or septic cardiomyopathy rather than influenza-associated myopericarditis. The recent study by To *et al.* [45] describing findings in a similar-sized cohort of H1N1-infected patients with ARDS in Hong Kong reported a higher incidence (22%) of myopericarditis than in our cohort, though their definition of myopericarditis was not explicit and did not clearly distinguish influenza-specific phenomena from the general effects of sepsis. Whether low-grade influenza myopericarditis occurs, our study suggests that such myopericarditis does not play a major role clinically.

ARDS is a reasonably well-characterised cause of acute *cor pulmonale*, with evidence for microvascular disruption in the pulmonary circulation, high intrathoracic pressure gradients, and endothelial cell oedema all playing an important role [46–48]. Whether H1N1 induces disproportionate pulmonary vascular disease is not known, though preliminary autopsy results may be compatible with this finding [49].

The thin-walled right heart is particularly susceptible to ischaemia and failure in the face of acute increases in afterload. Right heart dysfunction has direct effects on LV diastolic and systolic function [50, 51]. Mechanical ventilation increases the afterload on the RV and impairs ventricular preload. The patients in our cohort had high PEEP levels (mean 21 cmH₂O) but were uniformly ventilated using low tidal volumes [52]; patients ventilated with higher tidal volumes would likely exhibit more RV dilatation and failure [41].

The degree of right heart dilatation in this cohort may be related to the high prevalence of obesity, the mean BMI in this cohort was 39 kg·m⁻², and at least four of our patients suffered from premonitory obstructive sleep apnoea. Whether these patients had RV dilatation before onset of H1N1 is not certain, although there was not a clear linear relationship between BMI and RV dilatation.

An important limitation of our study is its retrospective nature. The fact that echocardiograms were ordered for clinical purposes means that our results describe the most severely ill patients with H1N1 infection. Our observations may not apply to patients with less severe cardiopulmonary dysfunction during H1N1 infection. Patients not requiring mechanical ventilation may have different echocardiographic findings.

Some authors have suggested, extrapolating from the use of echocardiography during and immediately after surgery, that

certain echocardiographic findings should influence ventilation strategies, use of inotropes and vasopressors, and the determination of optimal fluid loading conditions in patients with respiratory and/or circulatory failure [53–57]. In this cohort, indices of RV impairment were not significantly associated with mortality or ventilator-free days. While a variety of techniques to unload the RV have been tested in ARDS without clear benefit, and some authors have used extracorporeal membrane oxygenation for ARDS caused by H1N1 [5, 49], these techniques are not yet well validated. The fact that findings of RV impairment were not clearly associated with in-patient mortality in this cohort may reflect small sample size.

The variability of classification of RV dilatation and impaired systolic function in this population is also an important finding. Different measures of impairment yield different estimates of the prevalence of *cor pulmonale* in this patient cohort: no single measure is obviously superior to others. Cutoffs for classification of chamber dimensions and function are generally drawn from healthy volunteers and may not be as useful in critically ill patients with acute *cor pulmonale*. Larger cohorts in general ARDS and septic shock populations should strive to define which parameters at which thresholds most usefully identify clinically relevant distinctions.

This report highlights the high prevalence of RV dilatation and dysfunction in patients with ARDS and septic shock complicating H1N1 infection and the comparatively low incidence of LV systolic dysfunction. Further research should investigate the reproducibility and therapeutic implications of these findings.

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STATEMENT OF INTEREST

None declared.

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