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Clinical paper

NT-proBNP in patients with out-of-hospital cardiac arrest: Results from the FINNRESUSCI Study☆

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ABSTRACT

Aim: To assess whether the established cardiovascular biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) provides prognostic information in patients with out-of-hospital cardiac arrest due to ventricular tachycardia or fibrillation (OHCA-VT/VF).
Methods: We measured NT-proBNP levels in 155 patients with OHCA-VT/VF enrolled into a prospective multicenter observational study in 21 ICUs in Finland. Blood samples were drawn <6 h of OHCA-VT/VF and later after 24 h, 48 h, and 96 h. The end-points were mortality and neurological outcome classified according to Cerebral Performance Category (CPC) after one year. NT-proBNP levels were compared to high-sensitivity troponin T (hs-TnT) levels and established risk scores.
Results: NT-proBNP levels were higher in non-survivors compared to survivors on study inclusion (median 1003 [quartile (Q) 1–3 502–2457] vs. 527 [179–1284] ng/L, $p = 0.001$) and after 24 h (1913 [1012–4573] vs. 1080 [519–2210] ng/L, $p < 0.001$). NT-proBNP levels increased from baseline to 96 h after ICU admission ($p < 0.001$). NT-proBNP levels were significantly correlated to hs-TnT levels after 24 h (rho = 0.27, $p = 0.001$), but not to hs-TnT levels on study inclusion (rho = 0.05, $p = 0.67$). NT-proBNP levels at all time points were associated with clinical outcome, but only NT-proBNP levels after 24 h predicted mortality and poor neurological outcome, defined as CPC 3–5, in models that adjusted for SAPS II and SOFA scores. hs-TnT levels did not add prognostic information to NT-proBNP measurements alone.
Conclusion: NT-proBNP levels at 24 h improved risk assessment for poor outcome after one year on top of established risk indices, while hs-TnT measurements did not further add to risk prediction.

Introduction

Sudden cardiac death accounts for >50% of the total cardiovascular mortality and 15–20% of all deaths.[1,2] Despite extensive research, the overall survival rate after out-of-hospital cardiac arrest (OHCA) has not improved during the last decades.[3] A recent study showed 30-day survival of 10.5% with bystander-initiated cardiopulmonary resuscitation (CPR), and only 4% in patients not receiving bystander-initiated CPR.[4] Post-cardiac arrest myocardial dysfunction occurs in a large proportion of patients after successful return of spontaneous circulation (ROSC) and may influence

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outcome via refractory shock (post-cardiac arrest shock), multi-organ failure, hypoxic-ischemic brain injury, and recurrent cardiac arrests.[5–8] Scoring systems for risk prediction after cardiac arrest are calculated after 24 h, but cardiac biomarkers are currently not included into the models.[9,10]

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by cardiomyocytes in response to myocardial stretch or pressure overload.[11] NT-proBNP is known to predict mortality in conditions characterized by myocardial dysfunction, including chronic heart failure,[11] acute coronary syndromes,[12] severe sepsis,[13] and acute respiratory failure.[14] Elevated NT-proBNP levels have also been found independently associated with increased risk of ventricular arrhythmias.[15] Some reports on the B-type natriuretic peptides (BNP and NT-proBNP) in cardiac arrest are published, but the results have been diverging. Earlier work reported that BNP could provide important information for prognosis after cardiac arrest,[16,17] while a more recent study failed to demonstrate incremental prognostic information by NT-proBNP to the information available on ICU admission.[18] However, a limitation of the latter study was that only 59% of the patients had ventricular arrhythmia-induced cardiac arrest, which could influence the results as patients presenting with non-shockable rhythm have a worse prognosis.[19] Hence, limited data are available regarding the value of measuring NT-proBNP levels in patients with OHCA due to ventricular tachycardia or fibrillation (OHCA-VT/VF). Moreover, it is not known whether the combination of NT-proBNP and high-sensitivity troponin T (hs-TnT), which could provide complementary information on acute myocardial infarction[20] and prognosis,[21] may further improve risk prediction in OHCA-VT/VF. Accordingly, in this study we hypothesized that NT-proBNP improves risk assessment for 1-year mortality and poor neurological outcome in patients with OHCA-VT/VF, and that the addition of hs-TnT may further improve risk assessment for these endpoints.

Methods

Study design

This was a substudy of FINNRESUSCI, a large, nationwide, multicenter, prospective observational study that included all patients >18 y admitted to the ICU after OHCA with successful resuscitation ($n = 548$). Only the patients with shockable rhythm ($n = 311$, 97% VF) and consent from the patient or a next of kin to draw blood samples were included into this biomarker substudy ($n = 155$, 50%) (Fig. 1). The local Ethics Committee required written informed consent from the patients or a next of kin before blood sampling could take place for the FINNRESUSCI Laboratory Study; i.e. within 6 h (latest time point for first blood sampling), and logistic issues related to obtaining consent were the main causes for lack of blood sampling. Of note, the patients that were included into the FINNRESUSCI Laboratory Study were comparable to the patients in the main FINNRESUSCI cohort related to most demographic and clinical variables and clinical outcomes.[22] A subgroup of patients underwent serial blood sampling at 24 h: $n = 150$ (97%), 48 h: $n = 138$ (89%) and 96 h: $n = 107$ (69%).

Seventeen hospitals treating OHCA, all part of the Finnish Intensive Care Consortium, included patient to this laboratory substudy.[23] Data were collected from March 1, 2010 to February 28, 2011 into a standardized, internet-based, case report form comprising age, gender, body mass index (BMI), and previous medical history. Pre-hospital data were collected by paramedics, and this included whether the cardiac arrest was witnessed, time from call to dispatch center to ROSC, and the use of adrenaline (epinephrine) or other administration of life support according to Utstein guidelines. Information from the ICU such as treatment, complications, severity scoring (Simplified Acute Physiology Score [SAPS II] and Sequential Organ Failure Assessment [SOFA]), and hospital mortality were recorded electronically. Attending physicians decided whether coronary angiography was indicated based on the clinical setting. Analogous to previous FINNRESUSCI studies,[22–28] the co-primary endpoint of the study was all-cause mortality and neurological outcome after one year. Data regarding survival status were obtained from Statistics Finland. A specialist in neurology (MT), who was blinded to ICU care and laboratory results, assessed the neurologic status using the Pittsburgh Cerebral Performance category (CPC).[29] We further dichotomized the neurological outcome into good (CPC 1 or 2: absent, mild or moderate neurological disability) or poor (CPC 3–5: severe neurological disability, persistent vegetative state or death) as previously reported.[22,23,25–28] The Local Ethics Committees approved the study before study commencement.

Biochemical analysis

Serum samples were drawn at study inclusion (<6 h after cardiac arrest) and after 24 h, 48 h, and 96 h. The samples were left at room temperature to coagulate and subsequently centrifuged at $\sim 1500 \times g$ for 15 min, and the supernatant was transferred to acid-handled plastic tubes and stored at minimum −20 °C. Samples were later sent to Kuopio University Hospital and stored at −80 °C. We measured NT-proBNP levels by a commercially available immunometric assay (proBNP II, Roche Diagnostics, Mannheim, Germany), and hs-TnT was measured as previously reported.[22]

Statistical analysis

The data are presented as medians (quartile [Q] 1–3) or as absolute numbers and percentages. We assessed normal distribution

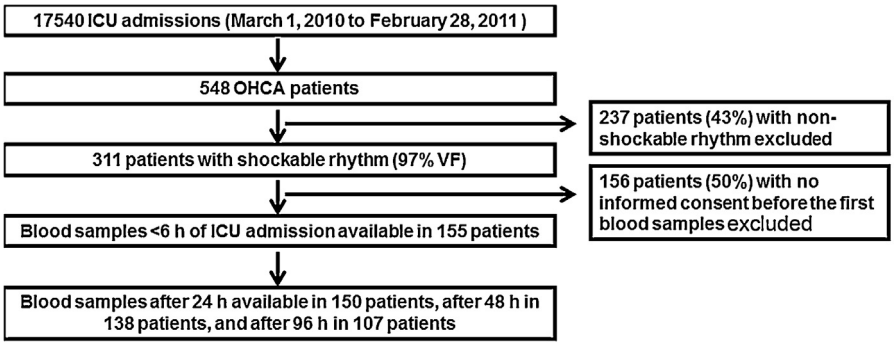

Fig. 1. Flow chart of the study (OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation).

Table 1
Characteristics and laboratory values of patients after out-of-hospital cardiac arrest with ventricular arrhythmias according to 1-year mortality.

	All patients (n = 155)	Survivors (n = 96)	Non-survivors (n = 59)	p
Age, y	63 (56–72)	61 (53–67)	69 (61–75)	0.002
Male sex	132 (85%)	79 (82%)	53 (89%)	0.74
Body mass index, kg/m^2	26 (24–29)	26 (24–29)	26 (24–29)	0.89
Creatinine clearance, mL/min	94 (72–126)	100 (80–132)	77 (64–117)	0.002
History of				
Coronary artery disease	50 (32%)	23 (24%)	27 (46%)	0.004
Diabetes mellitus	33 (21%)	18 (19%)	15 (25%)	0.02
Hypertension	70 (45%)	42 (44%)	28 (48%)	0.34
Heart failure	23 (15%)	9 (9%)	14 (24%)	0.008
Witnessed cardiac arrest	143 (92%)	92 (96%)	51 (86%)	0.10
Bystander CPR	105 (68%)	66 (69%)	39 (66%)	0.86
Initial rhythm VF	153 (99%)			
Time to ROSC, min	20 (14–29)	17 (11–23)	27 (21–32)	<0.001
Therapeutic hypothermia	134 (87%)	82 (85%)	52 (88%)	0.64
Coronary angiography	34 (22%)	28 (29%)	6 (10%)	0.01
PCI	15 (10%)	14 (15%)	1 (2%)	0.05
Pneumonia	64 (41%)	40 (42%)	24 (41%)	0.84
Sepsis	9 (6%)	5 (5%)	4 (7%)	0.77
Mechanical ventilation, h	50 (40–79)	46 (39–66)	65 (48–92)	0.04
ICU LOS, days	3.2 (2.2–5.0)	3 (2–6)	3 (2–4)	0.10
SAPS II score	58 (40–69)	50 (34–63)	66 (55–72)	<0.001
SOFA score	9 (7–11)	8 (6–10)	10 (8–11)	<0.001
NT-proBNP on admission, ng/L	706 (213–1624)	527 (179–1284)	1003 (502–2457)	0.001
NT-proBNP 24 h, ng/L[a]	1360 (609–2570)	1080 (519–2210)	1913 (1012–4573)	<0.001
NT-proBNP 48 h, ng/L[b]	1446 (554–2536)	1318 (510–2329)	1930 (808–4786)	0.02
NT-proBNP 96 h, ng/L[c]	2265 (1088–5143)	1870 (842–4131)	3256 (1352–9928)	0.03
hs-TnT on admission, ng/L	415 (199–916)	345 (188–733)	747 (201–1132)	0.03
hs-TnT 24 h, ng/L[a]	342 (111–1448)	200 (91–1195)	515 (202–1791)	0.01
hs-TnT 48 h, ng/L[b]	283 (94–1007)	162 (74–879)	479 (192–1419)	0.004
hs-TnT 96 h, ng/L[c]	331 (46–1269)	213 (43–935)	473 (78–1542)	0.13

Data presented as numbers (%) or median (interquartile range).
[a] n = 150 (97%).
[b] n = 138 (89%).
[c] n = 107 (69%).
Abbreviations: CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; PCI, percutaneous coronary intervention; LOS, length of stay; SAPS II, simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; NT-proBNP, N-terminal pro-B-type natriuretic peptide and hs-TnT, high-sensitivity troponin T.

of continuous variables by the Kolmogorov–Smirnov one sample test. Continuous variables were compared with the Student's t-test or the Mann–Whitney U test for non-parametric data. Paired data were analyzed by the Wilcoxon's Signed Rank Test. Categorical data were compared by the Chi-square test or the Fisher exact test, as appropriate. Correlations were calculated by Spearman rank correlation. We transformed NT-proBNP and hs-TnT levels by the natural logarithm prior to regression analysis due to a right-skewed distribution. We explored variables available on ICU admission to predict mortality and neurological outcome after one year by univariate and multivariate logistic regression analysis. The odds ratios (ORs) are presented with 95 confidence intervals (CIs). Variables that were tested in the univariate models comprised age, gender, BMI, previous CVD, diabetes mellitus, information on the cardiac arrest, indicators of acute coronary occlusion, creatinine clearance, SAPS II score, SOFA score, and NT-proBNP and hs-TnT levels. We included univariate predictors of the endpoints in the multivariate models using a forward selection strategy. The same variables were analyzed by linear regression analysis also to assess variables that were associated with higher NT-proBNP levels on admission. Prognostic accuracy was calculated from the area under the receiver-operating characteristics (ROC) curve (AUC) with 95% confidence intervals (CI). The AUCs are from nested models and presented as recently recommended.[30] p values <0.05 were considered significant for all analysis. Statistical analyses were performed with IBM® SPSS® Statistics Version 22 for Windows and MedCalc Statistical Software version 14.10.2 (MedCalc for Windows (Mariakerke, Belgium)).

Results

Baseline characteristics

The baseline characteristics of the patients stratified according to 1-year mortality are presented in Table 1. The majority of the OHCA-VT/VF events were witnessed (n = 143, 92%). VF was the dominant initial rhythm (n = 153, 99%). In total, 105 patients (68%) received bystander CPR and the median time to ROSC was 20 (Q1–Q3 14–29) min. In total, 134 patients (87%) received therapeutic hypothermia. Compared to one year survivors, non-survivors were older, had more comorbidities, worse kidney function, and a longer time to ROSC (Table 1).

NT-proBNP levels in patients with OHCA-VT/VF

Median NT-proBNP concentration on inclusion in the study was 706 (Q1–Q3 213–1624) ng/L with the maximum NT-proBNP concentration of 17,553 ng/L. Patients with NT-proBNP levels above the median on study inclusion were older, had worse kidney function, and higher prevalence of coronary artery disease and heart failure compared to the patients below the median value (Supplementary Table 1). The prevalence of bystander CPR was lower in patients with supramedian NT-proBNP concentrations. These patients had also higher SAPS II score after 24 h compared to the patients with NT-proBNP levels below the median. The median NT-proBNP level after 24 h was 1360 (Q1–Q3 609–2570) ng/L, after 48 h 1446 (554–2536) ng/L, and after 96 h 2265 (1088–5143) ng/L (Table 1),

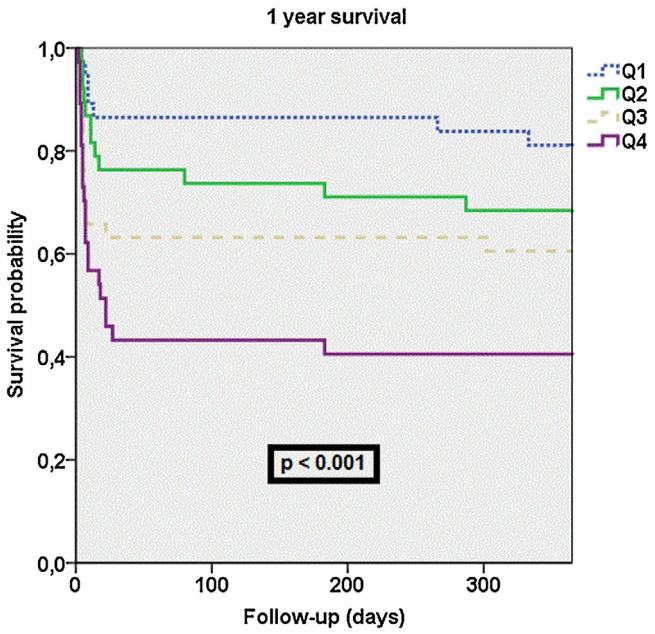

Fig. 2. Survival curves according to 1-year survival in OHCA-VF/VT stratified by NT-proBNP quartiles measured 24 h after ICU admission $n = 150$ (OHCA-VF/VT, out-of-hospital cardiac arrest – ventricular fibrillation/ventricular tachycardia).

$p < 0.001$ for trend. Older patients and those with higher creatinine levels had higher NT-proBNP levels at all time points, while patients with high hs-TnT levels on ICU admission and longer time to ROSC had higher NT-proBNP levels only at 24 h (Supplementary Table 2). Determinants of NT-proBNP levels on all time points are presented in the Supplementary Table 3.

NT-proBNP levels and 1-year neurological outcome and mortality

In total, 59 patients (38%) were dead after one year and 65 patients (42%) were categorized as having a poor neurological outcome or had died (CPC score 3–5, which includes death [CPC 5]). NT-proBNP levels at all time points were higher in patients with unfavorable vs. good neurological outcome, and in non-survivors compared to survivors (Table 1). NT-proBNP quartiles also separated survivors and non-survivors after 1 year (Fig. 2, $p < 0.001$ by the log-rank test). Analogously, and as the combined endpoint of poor neurological function and mortality after 1 year (CPC 3–5) was driven mainly by deaths (91% of the events [59/65]), survival curves with NT-proBNP separated into quartiles were almost identical for this endpoint (Supplementary Fig. 1). NT-proBNP values on all the time points were also associated with mortality and poor neurological outcome after one year by univariate logistic regression (Table 3A). However, only NT-proBNP concentrations after 24 h were associated with mortality (OR 1.56 [95% CI 1.03–2.36, $p = 0.04$]) and poor neurological outcome (OR 1.69 [1.12–2.55], $p = 0.01$) in multivariate models, also when including SOFA and SAPS II scores (Table 3B). The change in NT-proBNP levels from study inclusion to 24 h was 49 (Q1–Q3 1–139) ng/L and increasing NT-proBNP levels were also independently associated with mortality (OR 2.73 [95% CI 1.58–4.73], $p < 0.001$) and poor neurological outcome (OR 2.22 [1.39–3.55], $p = 0.001$) in the same multivariable models (Supplementary Table 4). hs-TnT levels measured on study inclusion, after 48 h, and after 96 h did not provide independent prognostic information. Of note, through the different time points there were an increasing unfavorable prognostic value among patients with history of coronary artery disease, with the highest OR for mortality after 96 h: 6.13 (95% CI 2.06–18.20), $p < 0.001$. Moreover, there was no positive effect on assessment of mortality or poor neurological outcome after 1 year by the combination of NT-proBNP and hs-TnT levels over NT-proBNP measurements alone (Table 3A).

Table 2
Prognostic value of NT-proBNP at different time points as assessed by receiver operating characteristics curve analysis, presented as area under the curve with 95% confidence intervals.

	1-year mortality	CPC 3–5 after 1 year
Admission	0.68 (0.56–0.80)	0.66 (0.55–0.77)
24 h	0.68 (0.56–0.81)	0.68 (0.56–0.79)
48 h	0.65 (0.52–0.78)	0.68 (0.56–0.80)
96 h	0.63 (0.50–0.76)	0.66 (0.54–0.78)

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; CPC, cerebral performance categories.

The AUC of NT-proBNP after 24 h to predict mortality after 1 year was 0.68 (95% CI 0.56–0.81) and the AUC to predict poor neurological status after 1 year was 0.68 (0.56–0.79), while AUCs for NT-proBNP measurements at other time points demonstrated lower AUCs (Table 2).

Discussion

The principal result of this study was that NT-proBNP levels were higher in one-year non-survivors and patients with poor neurological outcome compared to patients with a favorable outcome in OHCA-VT/VF. NT-proBNP levels after 24 h also provided additional prognostic information to established risk indices, while the addition of hs-TnT measurements to NT-proBNP levels did not improve prediction of mortality or poor neurological outcome after 1 year over NT-proBNP measurements alone.

NT-proBNP and hs-TnT are the two cardiovascular biomarkers in clinical use with primary utility to diagnose heart failure and acute myocardial infarction, respectively. The rationale for testing cardiovascular biomarkers in OHCA-VT/VF is the substantial morbidity and mortality attributed to post-resuscitation cardiac shock. However, currently limited information is available whether NT-proBNP separately, or in combination with hs-TnT, may improve risk assessment after OHCA-VT/VF. Hence, for this study we found it important to include only patients with VF or VT as the initial rhythm as these patients have higher occurrence of cardiac etiology as the cause for the cardiac arrest.[31] These patients also clearly have a different prognosis compared to patients presenting with a non-shockable rhythm.[19,31]

The main finding of this study was the incremental prognostic information on outcome from NT-proBNP measurements after 24 h. Our data support that measurements of NT-proBNP after 24 h could further improve risk assessment adjusted for SAPS II[9] and SOFA.[10] The dynamics of NT-proBNP were also assessed in this study and the change (delta) was calculated to evaluate potential relevance. The majority of patients ($n = 111$, 74%) had increasing values between study inclusion and measurement after 24 h and patients with rising NT-proBNP concentrations also had increased risk of mortality and poor neurological outcome after 1 year, including in analysis that adjusted for established risk models. Of note, separating patients according to rising or stable/declining NT-proBNP levels is analogous to the strategy previously reported by Smit et al.[18] on 250 patients with cardiac arrest. In contrast to our results, they found no independent associations between NT-proBNP and mortality after 28 days, including for delta NT-proBNP levels. However, only 59% of the patients in that study had OHCA-VT/VF, and, thus, these studies are not comparable. The inclusion of patients with non-shockable rhythm in their study is also reflected in worse outcome for these patients (mortality 46%) compared to our patients with OHCA-VT/VF (mortality 33%).[18]

Table 3A
1-Year mortality and poor neurological outcome (CPC 3–5) in patients after out-of-hospital cardiac arrest with ventricular arrhythmia. A univariate model.

Univariate analysis	1-Year mortality			CPC 3–5 after 1 year		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age, per 1 y increase	1.05	1.02–1.08	0.002	1.05	1.02–1.08	0.001
Male gender	1.90	0.70–5.13	0.21	1.79	0.70–4.64	0.23
Body mass index, per 1 kg/m^2 increase	1.00	0.94–1.08	0.91	0.99	0.93–1.07	0.87
History of						
Coronary artery disease	2.68	1.34–5.36	0.005	2.65	1.33–5.28	0.006
Diabetes mellitus	1.48	0.68–3.22	0.33	1.20	0.55–2.60	0.64
Hypertension	1.16	0.61–2.23	0.65	1.07	0.56–2.03	0.83
Heart failure	3.01	1.20–7.48	0.02	3.08	1.22–7.77	0.02
Witnessed cardiac arrest	0.28	0.08–0.97	0.04	0.22	0.06–0.83	0.03
Bystander CPR	0.89	0.44–1.77	0.73	0.89	0.44–1.77	0.73
Time to ROSC, per 1 min increase	1.09	1.05–1.13	<0.001	1.09	1.05–1.13	<0.001
Therapeutic hypothermia	1.27	0.48–3.35	0.63	1.20	0.47–3.10	0.70
Coronary angiography	0.28	0.11–0.71	0.008	0.28	0.11–0.70	0.006
PCI	0.10	0.01–0.79	0.03	0.09	0.01–0.66	0.02
Estimated creatinine clearance <6 h, per mL/min	0.99	0.98–1.00	0.05	0.99	0.98–1.00	0.06
NT-proBNP <6 h, per 1 ng/L increase	1.52	1.16–2.00	0.002	1.50	1.15–1.95	0.003
hs-TnT <6 h, per 1 ng/L increase	1.26	0.97–1.63	0.09	1.26	0.97–1.63	0.08
hs-TnT and NT-proBNP above median, <6 h	3.21	1.50–6.86	0.003	3.47	1.60–7.52	0.002
NT-proBNP at 24 h, per 1 ng/L increase	1.93	1.37–2.72	<0.001	1.94	1.38–2.73	<0.001
hs-TnT at 24 h, per 1 ng/L increase	1.28	1.04–1.57	0.02	1.26	1.04–1.54	0.02
hs-TnT and NT-proBNP at 24 h above median	3.23	1.57–6.52	<0.001	2.82	1.40–5.66	0.004
SOFA score at 24 h, per 1 point increase	1.38	1.19–1.60	<0.001	1.37	1.18–1.60	<0.001
SAPS II score at 24 h, per 1 point increase	1.07	1.04–1.09	<0.001	1.08	1.05–1.10	<0.001
NT-proBNP 48 h, per 1 ng/L increase	1.52	1.10–2.11	0.01	1.60	1.15–2.22	0.005
NT-proBNP 96 h, per 1 ng/L increase	1.54	1.04–2.30	0.03	1.63	1.11–2.40	0.01

NT-proBNP and hs-TnT levels were transformed by the natural logarithm before analysis.
Abbreviations: CPC, cerebral performance categories; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; PCI, percutaneous coronary intervention; SAPS II, simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and hs-TnT, high-sensitivity troponin T.

Although we found significant associations between NT-proBNP levels after 24 h and clinical outcomes, the ROC-AUCs were of only moderate strength. One plausible explanation may be that in addition to myocardial dysfunction, brain injury and other organ dysfunction contribute to outcome after OHCA-VT/VF. Hence, it is not likely that a single biomarker may accurately reflect all the different pathophysiology related to outcome in OHCA-VT/VF. In addition, factors associated with the arrest itself, such as whether the arrest was witnessed, the initiation and the quality of bystander CPR,[4,32,33] the duration of the VF,[34] and the duration of resuscitation[35] will also influence outcome. Still, as we found NT-proBNP measurements to provide additional prognostic

Table 3B
1-Year mortality and poor neurological outcome (CPC 3–5) in patients after out-of-hospital cardiac arrest with ventricular arrhythmia. Predictive factors in multivariate models. All variables significantly associated to outcome in the univariate model (Table 3A) were included in the models. Multivariate analysis on admission: final model.

	1-Year mortality			CPC 3–5 after 1 year		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Admission						
Age, per 1 y increase	1.06	1.02–1.10	0.003	1.06	1.02–1.10	0.002
Time to ROSC, per 1 min increase	1.10	1.05–1.14	<0.001	1.10	1.06–1.15	<0.001
After 24 h						
Time to ROSC, per 1 min increase	1.10	1.05–1.15	<0.001	1.10	1.05–1.15	<0.001
Age, per 1 y increase	1.05	1.00–1.10	0.02	1.05	1.01–1.10	0.01
NT-proBNP at 24 h, per 1 ng/L increase	1.52	1.02–2.24	0.04	1.52	1.02–2.25	0.04
After 24 h (with SAPS II and SOFA)						
Time to ROSC, per 1 min increase	1.07	1.03–1.12	0.001	1.07	1.02–1.11	0.003
History of coronary artery disease	2.58	1.09–6.12	0.03	n.s.		
Coronary angiography	n.s.			0.31	0.11–0.91	0.03
SAPS II score at 24 h, per 1 point increase	1.04	1.02–1.07	0.002	1.06	1.03–1.09	<0.001
NT-proBNP at 24 h, per 1 ng/L increase	1.56	1.03–2.36	0.04	1.69	1.12–2.55	0.01
After 48 h						
Time to ROSC, per 1 min increase	1.10	1.05–1.15	<0.001	1.12	1.06–1.18	<0.001
Age, per 1 y increase	1.05	1.01–1.10	0.02	n.s.		
History of heart failure	n.s.			4.57	1.19–17.49	0.03
After 96 h						
History of coronary artery disease	6.13	2.06–18.20	0.001	4.27	1.46–12.52	0.008
Time to ROSC, per 1 min increase	1.08	1.02–1.14	0.004	1.08	1.03–1.14	0.002

NT-proBNP was transformed by the natural logarithm before analysis.
Abbreviations: CPC, cerebral performance categories; ROSC, return of spontaneous circulation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAPS II, simplified acute physiology score II and SOFA, Sequential Organ Failure Assessment.

information to these variables, NT-proBNP could improve outcome prediction after ventricular arrhythmia-induced cardiac arrest by reflecting myocardial dysfunction.

The pathophysiology behind elevated NT-proBNP levels in patients with OHCA-VT/VF is not clear and we explored this by linear regression analyses. One could possibly speculate that cardiac stress related to the CPR/resuscitation could be a major contributor to elevated NT-proBNP levels in OHCA-VT/VF, but our results do not support this hypothesis. First, NT-proBNP levels did not normalize after ROSC, but rather increased throughout the four time points for blood sampling, which is different from dynamics of hs-TnT levels that previously have been found associated with acute coronary artery occlusion and time to ROSC in the FINNRESUSCI Study.[22] Linear regression analyses also did not identify time to ROSC or bystander-initiated life support as associated with high NT-proBNP levels. In contrast, variables previously associated with elevated NT-proBNP levels in other conditions, like history of heart failure, coronary artery disease and high age,[11] were associated with increasing NT-proBNP levels also in patients with OHCA-VT/VF. Analogously, inverse associations between NT-proBNP and BMI and creatinine clearance have previously been reported[11] and these variables were also inversely associated with NT-proBNP levels in OHCA-VT/VF. In addition to these associations, we believe the dynamics of NT-proBNP may have potential to identify the development of myocardial dysfunction in our patients. To identify this pathophysiology early is of great interest as it occurs in as many as 68% of OHCA patients and post-cardiac arrest shock thus is considered an important contributor to a poor outcome in patients with cardiac arrest.[6] Of note, previous studies have also found the intermediate post-arrest phase (between 6–12 h and 72 h) of the post-cardiac arrest syndrome to be the time point where injury pathways are most active and aggressive treatment can be initiated.[36] NT-proBNP levels were most prognostic after 24 h, which supports our model of NT-proBNP as a marker of post-cardiac arrest shock. However, future studies with more extensive imaging on inclusion and follow-up are needed to assess this important issue more closely. On the later time points (48 h and 96 h) there were no associations between NT-proBNP measurements and mortality or poor neurological outcome after adjusting for demographics, comorbidities, other biomarkers and parameters related to cardiac arrest. In contrast, we found a strong independent association to outcome from patients with history of coronary artery disease after 96 h (OR for mortality 6.13 [95% CI 2.06–18.20], $p < 0.001$). This finding will need validation in independent cohorts, but could suggest that a strategy of delayed angiography may be helpful in the subjects that survive the first days in the ICU after OHCA-VT/VF and have a history of coronary artery disease.

Our study has several strengths and limitations. A strength is that the patients in the FINNRESUSCI laboratory substudy were comparable to the patients in the large nationwide Finnish epidemiological FINNRESUSCI Study.[22] Thus, our patients were representative of real-world OHCA-VT/VF patients. The majority of our patients were also treated with targeted temperature management according to the current guidelines. Blood sampling was also done at several time points, which allowed us to assess information from serial biomarker measurements. Our study also has some limitations. First, we did not record echocardiographic data or invasive measurements concerning cardiac function and volume status. Second, we lack detailed information on given fluids which may increase the expression of NT-proBNP as a result of increased myocardial stretch. Third, we have no detailed data on the causes of death. Fourth, we lack blood samples from a proportion of patients that were included into the epidemiological FINNRESUSCI Study. The reason for missing blood samples was due to logistics and the need to obtain written informed consent from the patients or a next in kin within 6 h. As the patients in the FINNRESUSCI Laboratory Study were comparable to the patients in the main FINNRESUSCI cohort for most demographic and clinical variables and clinical outcomes,[22] we do not consider this to be a major limitation to our study.

Conclusion

NT-proBNP levels after 24 h provided incremental information to clinical data for the prediction of 1-year mortality and neurological outcome in patients with OHCA-VT/VF, while hs-TnT measurements did not further improve outcome prediction.

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Conflict of interest statement

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Appendix.

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.04.007.

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