Review Article

The role of B-type natriuretic peptide in the diagnosis and treatment of decompensated heart failure

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Abstract
Heart failure (HF) is a common disease associated with increasing age. B-type natriuretic peptide (BNP), is a cardiac neurohormone, and is released as proBNP and then enzymatically cleaved to the N-terminal-proBNP (NT-proBNP) and BNP upon ventricular myocyte stretch. Blood measurements of BNP have been used to identify patients with HF. The BNP assay is currently used as a diagnostic and prognostic aid in HF. In general, a BNP level below 100 pg/mL excludes acutely decompensated HF and levels > 500 pg/mL indicate decompensation. Recombinant human BNP (hBNP, nesiritide) is an approved intravenous treatment for acute, decompensated HF. Nesiritide given in supraphysiologic doses causes vasodilation, natriuresis, diuresis, and improved symptoms over the course of a 48-hour infusion. This paper will sort out the literature concerning the use of this peptide both as a diagnostic test and as an intravenous therapy. (J Geriatr Cardiol 2004;1:21-28.)

Introduction
Heart failure is a common condition in the elderly and has considerable age-dependent all-cause mortality (Fig. 1).1 Heart failure is the leading cause of hospitalization for elderly Americans, accounting for at least 900,000 hospitalizations and 250,000 deaths each year in ≥65 years individuals. Nearly 50% of patients discharged with a diagnosis of heart failure (HF) are readmitted within 6 months, and the one-year mortality rate is 20% after an initial diagnosis is established. We are in the midst of a chronic HF epidemic.1 The number of discharges for HF rose from 377,000 in 1979 to 999,000 in 2000, an increase of 165 percent, with direct costs of care exceeding 24 billion U.S. dollars annually.2,4 Accordingly, much effort has been directed towards understanding the pathophysiology of heart failure, as well as improving the diagnostic and cost-effective therapeutic strategies available. The recognition of B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) as markers for the diagnosis, prognosis and severity of HF is a major breakthrough for the clinician and patient faced with this disorder. This article will focus on the latest advances in the role of natriuretic peptides in the diagnosis and management of decompensated heart failure.

B-type natriuretic peptides
There are three major natriuretic peptides, all sharing a common 17-amino-acid ring structure; atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP). B-type natriuretic peptide is synthesized and stored in the ventricular myocardium as a precursor prohormone. Cleavage of the 32 amino acid sequence from the C-terminal end of ProBNP results in human BNP and the N-terminal portion of proBNP (NT-proBNP). B-type natriuretic peptide is secreted into the circulation in a pulsatile fashion through the coronary sinususes in response to left ventricular wall stretch and multiple neurohumoral factors (Fig. 2), and is metabolized by neutral endopeptidase (~30%) and receptor-mediated endocytosis (~70%) which occurs predominantly in the kidney. Its half-life is 22 minutes, in comparison with the much longer (120 minutes) half-life of its inactive counterpart, NT-proBNP. Plasma BNP levels reflect the decompensated state of circulatory congestion, with modest correlations between BNP level and left ventricular end diastolic pressure and pulmonary capillary wedge pressure. Infusions of BNP reduce sympathetic outflow, promote vascular relaxation, and reduce the plasma concentration of renin and aldosterone. Together, these effects lead to natriuresis, diuresis, vasorelaxation and reduction in blood pressure most apparent in states of volume overload. Because BNP reflects volume status and has a short half-life, levels reflect dynamic changes in volume attributed to diuresis, making the assay an attractive marker to guide heart failure therapy.5,9
Mechanical factors
- wall tension
- volume expansion
- sodium intake

Endothelium-derived factors
- endothelin-1
- nitric oxide

Osmolality

Neurohumoral factors
- adrenaline
- noradrenaline
- acetylcholine
- angiotensin II
- vasopressin

Hypoxia
Heart rate

BNP Synthesis and Secretion

Fig. 2. Multiple factors that stimulate the release of BNP

Natriuretic peptides as a diagnostic tool in decompensated heart failure

Measuring BNP levels can facilitate proper diagnosis of patients with heart failure. Because BNP levels correlate with end-diastolic pressure and left ventricular wall tension, it follows that BNP levels correlate well with congestive heart failure (CHF) functional classification. In the Breathing Not Properly (acronym BNP) Multinational Study of 1586 patients who presented to the emergency department with acute dyspnea, Maisel et al., demonstrated that a BNP level of 100 pg/ml or more had a sensitivity of 90% and a specificity of 76% in differentiating between dyspnea due to heart failure and dyspnea related to other causes. In determining the correct diagnosis, adding BNP to clinical judgment would have increased the diagnostic accuracy from 74% to 81%. The diagnostic power of BNP was superior to both National Health and Nutrition Examination Survey (NHANES) and Framingham criteria, the two most commonly used criteria to diagnose HF. Further analysis of the BNP Multinational database sought to determine any correlation between estimated glomerular filtration rate (eGFR) and BNP level in patients with CHF. BNP levels were found to correlate weakly with eGFR owing to the increased left ventricular wall tension in patients with diminished creatinine clearance. BNP was, however, found to be independently associated with CHF after taking renal function into consideration, although chronic kidney disease did raise the optimum cut-point for diagnosing CHF from 100 to 200 pg/ml for patients with eGFR less than 60 ml/min.

Because BNP is a reflection of left ventricular wall tension, it follows that BNP levels would identify patients with dyspnea related to heart failure with preserved ejection fraction, or non-systolic heart failure, or diastolic heart failure. Lubien et al. reported their analysis of BNP levels in 294 patients referred for echocardiography to evaluate ventricular function with careful classification of diastolic filling patterns. Transmitral pulsed Doppler velocity recordings were used to derive the deceleration time. Short deceleration times are known to be highly associated with left ventricular end-diastolic pressures > 25 mmHg. In this analysis, BNP levels were higher in patients with deceleration times < 160 ms (249 ± 43 pg/ml), in comparison to the near normal BNP levels (70 ± 13 pg/ml) in patients with normal deceleration times. Similarly, in a post hoc analysis of the BNP Multinational Study, Maisel et al. reported the median BNP of patients with diastolic HF was 413 pg/ml, in comparison to 34 pg/ml in patients with dyspnea not due to heart failure. B-type natriuretic peptide levels did not separate patients with systolic HF from those with diastolic HF, although levels trended higher in patients with systolic heart failure (821 pg/ml), likely related to this cohort’s higher NYHA functional classification status.

B-type natriuretic peptide and prognosis

Risk stratification and prognosis in heart failure is complicated by the complex interplay of neurohumoral, mechanical, electrical and multi-organ derangements. In determining prognosis, clinicians use several clinical and laboratory markers to guide their assessment of the severity of HF. Measurement of BNP provides useful information regarding volume status, hormonal derangements and compensatory responses, making this an attractive prognostic indicator in heart failure. Koglin et al. evaluated the prognostic power of BNP in 78 patients referred to their heart failure clinic. Levels of BNP were significantly correlated with the heart failure survival score, and patients with high levels of BNP were much
more likely to develop clinical deterioration or die over a median 398-day follow-up period.\textsuperscript{15} Harrison et al., followed 6-month outcomes in 325 patients presented to the emergency department with dyspnea. They reported a 51\% six-month cumulative probability of death, hospital (cardiac) readmission and repeat emergency department visits for CHF in patients with an initial BNP value of 480 pg/ml or more. Furthermore, the relative risk of CHF death was 24.1 in patients with initial BNP levels exceeding 230 pg/ml.\textsuperscript{16} As nearly half of the heart failure mortality in these and other trials is felt to represent sudden cardiac death, Berger et al. investigated the association of BNP with future cardiac death in 452 patients with left ventricular ejection fraction (LVEF) < 35\%. Forty-four (10\%) of the patients developed sudden death over a period of 592 days, with equal distribution between ischemic and non-ischemic heart failure etiology. Among 16 clinical and laboratory variables reported, log BNP was the only independent predictor of sudden death. They reported an 81\% sudden-death free survival rate among patients with high BNP levels (defined as log BNP > 130 pg/ml), compared with 99\% sudden-death free survival rates for patients with low BNP levels.\textsuperscript{17}

The prognostic power of a multi-marker approach, incorporating B-type natriuretic peptide in combination with other markers, has also been studied in HF patients. As outlined, high levels of BNP appear to identify a subgroup of patients with left ventricular dysfunction who are at increased risk of sudden death. This predictive power may be related to electrical instability and mechanical dysfunction seen in these patients. Authors have proposed that QTc interval prolongation may be a risk factor for arrhythmia and death in HF patients, however, data on the predictive power of QTc interval and heart failure mortality are few and inconsistent. Based upon the ability of high BNP levels to select patients at increased risk of cardiac death, Vrotec et al. investigated the prognostic ability of prolongation of the QTc interval in combination with an elevated BNP level. They analyzed the QTc interval in 241 patients with heart failure and BNP levels exceeding 400 pg/ml. Exclusion criteria included NYHA class I to II symptoms, patients with defibrillators and those taking type III antiarrhythmic drugs. In this select group of patients with natriuretic peptide evidence of circulatory congestion and myocardial stretch, prolonged QTc was an independent predictor of all cause death, cardiac death, and pump failure death. Other multi-marker approaches have recently been reported. Horwich et al. studied the combination of BNP and cardiac Troponin I (cTnI) levels upon initial heart transplantation evaluation in 98 patients with ischemic and non-ischemic cardiomyopathy. Independently, detectable levels of cTnI were associated with a two-fold increased mortality risk, and the combination of detectable cTnI and high BNP levels ( > 485 pg/mL) portended a 12-fold relative risk of death.\textsuperscript{19} These studies support the notion that a multi-marker approach may provide incremental prognostic information in patients with advanced HF.

The role of natriuretic peptides in predicting treatment outcomes and guiding the management of heart failure patients

B-type natriuretic peptide, and numerous other biochemical markers, have demonstrated the ability to predict adverse outcomes in the patient with chronic HF (Fig. 3). The ability of these markers to assess and guide therapeutic responses to pharmacologic management, however, is less well established. Several recent trials support the usefulness of changes in BNP levels, as well as predischarge BNP levels, as important markers to optimize the care of patients hospitalized with HF. Bettencourt et al. investigated the ability of changes in BNP levels during hospitalization to track clinical outcomes in 50 consecutive patients hospitalized with decompensated HF. BNP levels decreased in most patients, but to a significantly greater degree in those who remained free of readmission for cardiovascular causes and death. Of the seven patients with increases in BNP levels during hospitalization, only one patient was event free at 6 months. Within the subgroup of patients with declining BNP levels during hospitalization, the degree of change in BNP tracked 6 month outcomes. In patients without 6-month hospital readmission or death, BNP levels fell from 619 ± 491 pg/ml to 328 ± 314 pg/ml (P < 0.0001). In comparison, changes in BNP levels were less pronounced in those who suffered events, with BNP levels decreasing from 779 ± 608 pg/ml to 643 ± 465 pg/ml (P = 0.08) in this group.\textsuperscript{20} Similar results were reported by Cheng et al. in their analysis of 72 patients admitted with decompensated NYHA Class III-IV HF. Of the 72 patients admitted with HF, 22 patients developed 30-day rehospitalization or death. The BNP levels increased by 233 pg/ml in these patients, in comparison to a 215 pg/ml decrease in those who remained free of 30-day adverse events.\textsuperscript{21} These small, single center studies were validated in a recent analysis of the Valsartan in Heart Failure Trial (Val-HeFT). The Val-HeFT trial evaluated the role of valsartan in moderate to severe HF, and represents the largest collection of neurohumoral data in heart failure patients. BNP was measured in all patients at randomization, with
follow-up values measured at 4, 12, and 24 months thereafter. Patients with a BNP level above the median had a relative risk of 2.1 for mortality, and 2.2 for first morbid events, in comparison to those with BNP levels below the median. Furthermore, there was an incremental increase in relative risk of mortality and morbidity throughout each quartile of BNP levels. There are several important inferences from this analysis (Fig. 3); 1) approximately half of well-treated HF patients had BNP levels < 100 pg/ml when measured as outpatients; 2) the lowest quartile of BNP (< 50 pg/ml) had the lowest all-cause mortality; 3) the highest quartile (> 238 pg/ml) had the highest mortality of ~ 32% at 30 months. Importantly, change from baseline and the percent change of BNP level over a 4 and 12 month period were also evaluated (Fig. 4). This analysis demonstrated a direct relationship between percent change from baseline BNP levels and 4 month mortality. Highest mortality was seen in patients with the largest percent increase in BNP, while the lowest mortality was observed in those with the largest percent decrease in BNP (Fig. 4). 

These compelling data raise the argument that neurohormonal levels, in particular BNP levels, may be useful in guiding and monitoring treatment of patients with HF. This argument is supported by the recent findings from Mueller et al. These authors randomized 452 patients who presented to the emergency department with acute dyspnea, to a diagnostic strategy including a single measurement of BNP level versus the use of a standard diagnostic strategy without the aid of BNP level. Serial measurements of BNP were not performed in either group. The measurement of BNP level in the emergency department resulted in reduced time to discharge (8.0 vs 11.0 days, \( P = 0.001 \)), reduced rate of hospitalization (75% vs 85%, \( P = 0.008 \)), less frequent admission to the intensive care unit (15% vs 24%, \( P = 0.01 \)), and improved total cost of treatment (\$5,410 vs \$7,264, \( P = 0.006 \)). These data suggest that a single measurement of BNP level improves the care of patients with dyspnea. Although there are no large, randomized studies of neurohormonal guided management of HF, a well conducted prospective clinical trial of 69 patients with symptomatic HF (NYHA class II-IV; left ventricular ejection fraction < 40%) provides support for BNP guided titration of therapy. Patients hospitalized with decompensated HF, or referred from cardiology clinics, were randomized between N-BNP guided treatment (BNP group) and standardized clinically guided (clinical group) treatment. The treatment target in the BNP group was an N-BNP level < 200 pmol/L, and the target for the clinical group was based upon an objective standardized heart failure scoring system. If patients did not meet target, pharmacotherapy (ACE inhibitors, diuretics, digoxin and vasodilators) was up-titrated in a prespecified protocol, with repeat assessment in two weeks. In the BNP group, BNP levels fell by an average of 79 pmol/L from baseline, in comparison to a 3 pmol/L rise in the clinical group. More importantly, after a 9.5-month follow-up there were more events (cardiovascular death, hospital admission for any cardiovascular event, and outpatient decompensated heart failure) in the clinical group than the BNP group (54 vs 19 events, respectively, \( P = 0.02 \)). The improvement in outcome seen in the BNP group was attributed to a statistically significant increase in dosage of ACE-inhibitors, diuretics, and additional spironolactone use.

These important studies suggest that there may be a role for a neurohormonal guided approach to titration of heart failure pharmacotherapy and management of patients with HF.
Intravenous infusions of natriuretic peptide as therapy in heart failure

Congestive heart failure is associated with activation of the renin-angiotensin-aldosterone system (RAAS), and elevated levels of vasopressin, norepinephrine, and sympathetic nervous system (SNS) activity. These neurohumoral derangements result in adverse cardiac, vascular and renal effects. With increasing severity of left atrial and left ventricular overload, the natriuretic peptides are released in a compensatory fashion. These counter-regulatory hormones oppose the vasoconstrictive and sodium retentive hormonal systems associated with HF. These protective mechanisms are ultimately overwhelmed, however, with greater degrees of left ventricular dysfunction. The pharmacologic management of patients with decompensated HF targets these mechanisms with the use of diuretic, inotropic and vasodilating agents. The newest intravenous vasodilator for the management of decompensated heart failure, human BNP (nesiritide), was approved by the U.S. Food and Drug Administration for use in decompensated HF in October 2001.

The effects of intravenous infusions of BNP

The neurohumoral, physiologic and hemodynamic effects of exogenous intravenous (IV) human BNP (hBNP, nesiritide) are well established. Human BNP leads to neurohumoral suppression as evidenced by a reduction in angiotensin, norepinephrine, aldosterone and endothelin-1 levels. Favorable hemodynamic effects are seen through a decrease in filling pressures, including dose dependent decreases in pulmonary capillary wedge pressure and right atrial pressure, and increases in cardiac index.25 Nesiritide is able to suppress the sodium retentive and renal vasoconstrictive activation observed in HF through significantly increased urine volume and urine sodium excretory effects26,27 and may increase glomerular filtration rate and filtration fraction. Administration of hBNP also produces beneficial vasodilatory effects as evidenced by reductions in pulmonary capillary wedge pressure and systemic vascular resistance (Fig. 5). Favorable reductions in systemic blood pressure are seen in patients with elevated baseline blood pressure; conversely, there is a low incidence of symptomatic hypotension, indicating that the vasodilatory effects of nesiritide may be self-regulatory.28 Nesiritide mediated vasodilation is also observed in coronary arteries at doses typically used for the management of patients with decompensated HF. In contrast to that observed with the inotropic agent dobutamine, this coronary vasodilation is accompanied by a decrease in myocardial oxygen uptake without significant change in cardiac output or heart rate.29 It is felt that these favorable hemodynamic and vascular effects of hBNP are mediated by the membrane-bound guanylyl cyclase-A (GC-A) receptor located on the surface of vascular smooth muscle cells. Of note, the BNP level measured in blood during an hBNP infusion elevate out of the measureable range, however, when the infusion is stopped, the endogenous BNP level has a relative drop indicating improvement in left ventricular wall tension (Fig. 6).

Fig. 5. Hemodynamic effects of nesiritide compared to placebo in 16 patients who underwent invasive hemodynamic monitoring (data adapted from Abraham WT et al. J Cardiac Failure 1998;4:37-44). HR = heart rate, RAP = right atrial pressure, PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular resistance, CI = cardiac index, SVI = stroke volume index

Fig. 6. Relative changes in endogenous BNP levels after nesiritide infusion. Data adapted from Maisel AS et al. Heart Failure Society of America Annual Meeting; September 22-25, 2002; Boca Raton, FL.

Nesiritide in decompensated heart failure: clinical trials

Nesiritide consistently and rapidly lowers elevated filling pressures and increases cardiac index in a dose dependent manner. In contrast to other commonly used agents for management of heart failure, hBNP achieves these favorable effects without significant inotropic, chronotropic, or arrhythmogenic effects. Accordingly, several clinical trials have compared the safety, clinical effectiveness, and cost-effectiveness of nesiritide with dobutamine in hospitalized patients with decompensated
HF. The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide (PRECEDENT) study randomized 255 patients with decompensated HF to intravenous nesiritide or dobutamine, and stratified the patients based upon history of ventricular tachycardia. Dobutamine was associated with a significant increase in all measures of ventricular ectopy (number of ventricular tachycardia events, repetitive ventricular beats per hour, and premature ventricular beats) as well as an increased heart rate. Nesiritide infusion, conversely, resulted in no ectopy and had no effect on baseline heart rate.30 Similar results were reported by Burger et al in their randomized investigation of 305 patients with decompensated HF requiring intravenous therapy. Sustained ventricular tachycardia was seen in 4 patients (7%) treated with dobutamine, in comparison with 2 patients (1%) treated with nesiritide. Additionally, three patients (5%) suffered from a cardiac arrest in the dobutamine group, in comparison with no patients in the nesiritide group.31

Although dobutamine is widely accepted as a standard inotropic therapy in CHF, its use is limited by these and other safety concerns. This, together with the shorter treatment course and reduced rehospitalization rate seen in some studies of patients treated with nesiritide,32,33 have persuaded many clinicians to consider nesiritide as a first line agent in patients (particularly those with predilection for ventricular ectopy) with decompensated HF.

Based on the positive results of multiple efficacy and comparator trials, a large randomized clinical trial was recently conducted to determine the efficacy and safety of intravenous nesiritide as an adjunct to standard care for decompensated heart failure. In a randomized, double-blind trial of 489 inpatients with decompensated CHF (dyspnea at rest, estimated or measured elevation of pulmonary capillary wedge pressure), intravenous nesiritide, intravenous nitroglycerin, or placebo, was added to existing medications (diuretics, inotropic agents, beta blockers, ACE inhibition, digoxin, hydralazine, and nitrates). Nesiritide treated patients had a significantly greater reduction in PCWP at three hours (mean change from baseline, - 5.8 mmHg) than patients treated with nitroglycerin (3.8 mmHg) or placebo (2.0 mmHg). The findings among patients with systolic and diastolic heart failure were similar (Scios Inc., data on file.). Hemodynamic effects of nesiritide were statistically significant within 15 minutes of initiating therapy. At three hours, nesiritide also led to a significant improvement in dyspnea compared with placebo, and no difference in dyspnea score in comparison with nitroglycerin treated patients. In patients with renal insufficiency, nesiritide was safe and improved hemodynamics and dyspnea to an extent similar to that in nesiritide-treated patients with serum creatinine less than 2.0 mg/dL.34,35 There was no significant difference in the frequency of adverse cardiovascular events associated with treatment, with an 8% incidence of asymptomatic hypotension in both vasodilator groups, and similar rates of symptomatic hypotension between the nitroglycerin (5%) and nesiritide (4%) treated patients. The duration of the hypotension was longer, however, in the nesiritide treated group.36,37

Management of patients with chronically decompensated heart failure

Based on the hypothesis that chronic neurohumoral suppression with nesiritide may improve outcomes by reducing left ventricular remodeling and maintaining renal function over time, a study using serial outpatient infusions of nesiritide was recently conducted (Follow Up Serial Infusions of Nesiritide, FUSION Trial). In this open-label pilot study, 210 patients with advanced CHF (NYHA class III-IV symptoms who had more than two acutely decompensated heart failure events requiring intravenous therapy in the past 12 months) were randomized to standard care (which could include inotropes at the investigator’s discretion) or weekly nesiritide infusion (bolus as high as 2 mcg/kg followed by infusion of 0.005 or 0.01 mcg/kg/min over 6 hours). All patients were required to visit the clinic weekly, and the frequency of nesiritide infusions could be adjusted based upon symptomatology. Results demonstrated that outpatient infusion was well tolerated. Compared to standard care, there was a trend toward fewer hospitalizations, reduced mortality, reduced aldosterone and endothelin levels, improved ejection fraction, and an improvement in clinical status as assessed by the physician. The patients deemed to be “high risk” (based upon prognostic factors) appeared to have the greatest benefit from nesiritide, with a reduced incidence of worsening heart failure, less hypotension, fewer adverse renal events, and a trend towards reduced mortality. These results suggest that there may be a role for long-term intermittent treatment with nesiritide in patients with advanced CHF and repeated rehospitalizations.38

Conclusions

B-type natriuretic peptide levels correlate with left ventricular pressure and accurately reflect the decompensated state of circulatory congestion found in patients with heart failure. The natriuretic peptides help defend against volume overload by suppression of the sodium retentive and renal vasoconstrictive activation seen in heart failure, as well as promotion of vascular relaxation resulting in favorable hemodynamic effects.
BNP levels can facilitate the proper diagnosis of patients with heart failure, and add valuable information to the physician faced with the assessment of patients with and without known heart failure. BNP levels identify a subgroup of patients with left ventricular dysfunction who are at increased risk of sudden death, and show promise as a useful marker to guide the therapeutic response to heart failure management. Administration of the human brain-type natriuretic peptide, nesiritide, helps to suppress the neurohumoral activation associated with heart failure, and leads to improved hemodynamics through diuretic and natriuretic effects. It is likely that future algorithms incorporating BNP levels and other markers, as well as acute and chronic administration of nesiritide, will guide physicians in the management of patients with heart failure.

References


20. This study explored the prognostic implications of BNP and cardiac troponin I (cTnl) levels in patients with advanced heart failure (50% NYHA Class IV). The combination of elevated cTnl and BNP identified patients with a markedly
increased risk of death.


• Changes in BNP and plasma norepinephrine levels were associated with morbidity and mortality in this large prospective evaluation of patients with heart failure. These data support a role for serial biomarkers in the management of patients with heart failure.


• Small prospective evaluation of the effects of intravenous nesiritide on coronary hemodynamics and myocardial oxygen uptake as determined by doppler-tipped coronary guidewires. This is the first study to evaluate these effects in human coronary vasculature.


• First large, multicenter, randomized trial to evaluate the clinical effects of intravenous nesiritide added to standard treatment for decompensated congestive heart failure. Nesiritide reduced pulmonary capillary wedge pressure (out to 24 hrs) more effectively than nitroglycerin, with a similar adverse effect profile.


38. Yancy C. Management of patients with congestive heart failure after hospitalization; Results from the Follow Up Serial Infusions of Nesiritide (FUSION) trial. *J Card Fail* 2003;9;S11; # 034.