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Biomarker Changes During Acute Heart Failure Treatment

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Abstract

Introduction—Biomarker changes may provide physicians with objective evidence of treatment efficacy in patients with acute decompensated heart failure (ADHF), and facilitate early hospital discharge. We hypothesize that MR-proADM, CT-pro-ET-1 and MR-proANP change during the first 24 hours of ADHF therapy.

Methods—Eligible subjects had an ED diagnosis of ADHF and fulfilled modified Framingham Criteria. Clinical data, serum, and plasma were collected at enrollment, 2–4 hours, and 12–24 hours after treatment. We calculated changes in biomarker concentrations from baseline to 2–4 hours, baseline to 12–24 hours, and 2–4 to 12–24 hours. Fisher's exact and Kruskal-Wallis tests were used for comparisons.

Results—Forty-eight subjects were included. Median age was 62 years (range 40–88), 54% were male and 50% were white. More subjects had changes in MR-pro-ANP levels in the first 2–4 hours after ADHF therapy compared to MR-proADM or CT-pro-ET-1 (36% vs. 16% and 24%). However, 12–24 hours after therapy similar proportions of patients had changes in MR-proANP, MR-proADM, and CT-proET-1 levels (47%, 41% and 49%).

Conclusion—In this preliminary study patients with ADHF had measurable changes in MR-proANP, MR-proADM and CT-pro-ET-1 24 hours after initial therapy. A study of association with clinical course and outcomes to determine the role of these markers in risk-stratification is warranted.

Keywords

adrenomedullin; atrial natriuretic peptide; cardiovascular biomarkers; endothelin; acute heart failure; biomarkers

INTRODUCTION

The high incidence of adverse events in patients with acute decompensated heart failure (ADHF) has not changed in decades. In-hospital mortality is 4–7%, 60-day mortality rates are about 10% and recidivism rates are about 25%. The unpredictability of the natural course of ADHF results in over 80% of emergency department (ED) presentations for ADHF being admitted to the hospital, and the majority of admitted patients have prolonged hospital length of stay (LOS).[1–7]

Current ADHF guidelines for ED and hospital disposition are based on limited empirical evidence and there is a lack of objective measures indicating when sufficient therapy has been provided to safely discharge the patient.[4, 8–11] It has been postulated up to 50% of all ADHF patients could be safely discharged after initial therapy either directly from the ED or after a brief inpatient stay.[2, 12–14] Providing physicians with objective evidence of the effectiveness of ADHF therapy in an individual patient may facilitate early, safe ED and hospital discharge. Measuring how biomarkers change with therapy might provide this information, and thus augment physician decision making.

Previous investigations of biomarker-guided therapy have had variable results, and have been focused primarily on b-type natriuretic peptide (BNP). Several novel biomarkers have been identified that are attractive candidates for serial measurements, including C-terminal-Pro-Endothelin-1 (CT-pro-ET-1), Mid-regional-Pro-Adrenomedullin (MR-proADM), and Mid-regional-Pro-Atrial Natriuretic peptide (MR-proANP).[15–19] Similar to C-peptide and Insulin, these inactive peptides represent cleavage products of prohormones. The active products of these compounds have vasoactive and/or natriuretic properties that have been implicated in the pathological vascular and/or cardiac structural changes associated with ADHF. [20–22] These prohormone fragments have increased stability and half-life *in vivo* compared to their transient, active cleavage partners, endothelin-1, atrial natriuretic peptide (ANP), and adrenomedullin, yet undergo changes which are rapid enough to be followed in the acute setting. The prohormone fragments are elevated in patients with heart failure and have been associated with poor outcomes in patients with ADHF and stable heart failure.[20, 23, 24]

In sum, the previous findings suggest these 3 markers are mechanistically linked to the pathology of ADHF and have half-lives small enough to make them candidate biomarkers for characterizing response to acute therapy. However, the extent to which these biomarkers change during the first 24 hours of care has yet to be investigated. Quantifying these changes is a necessary first step in determining whether the differences observed in the markers have prognostic utility as objective endpoints of ADHF therapy. Our hypothesis was that MR-proADM, CT-pro-ET-1 and MR-proANP would change during the course of the first 24 hours of ADHF therapy.

METHODS

This study is an analysis of data and specimens collected from a prospective observational cohort study of ED patients presenting with suspicion of ADHF *that were being studied as possible candidates for ED observation*. The initial study and this secondary use of data were approved by the local Institutional Review Board.

Study Population and Setting

Patients were recruited by clinical study assistants at three EDs: a large urban academic hospital, an urban community hospital, and a suburban community hospital. Screening occurred between 0800 and midnight. Patients were eligible if they fulfilled modified

Framingham Criteria (Table 1). Patients were excluded if it had been more than two hours since initial ED treatment with diuretics or vasodilators, if they had ischemic ECG changes or positive cardiac biomarkers of *infarction*, if they were on inotropes or vasopressors, or they had *new onset* heart failure. For the purposes of this analysis, patients were included if they had a primary diagnosis of ADHF at ED disposition as determined by the treating ED physician, if biomarker measurements were available for at least two time points, and if their baseline BNP level was greater than 100 pg/mL. At the time of disposition, the ED physician had history, physical examination, chest radiography and laboratory testing, including BNP, available if ordered as part of routine care.

Study Protocol and Data Collection

Clinical data, serum and plasma were collected prospectively at the time of enrollment, as well as at 2–4 hour and 12–24 hour time points following treatment. The data included demographics, medical history, and physical examination results as documented by the ED physician. Laboratory data, chest radiography findings as documented by a board-certified radiologist, and prior and current measures of ejection fraction were recorded from the medical record. BNP was also measured at baseline as well as at 2–4 hours and 12–24 hours after therapy using both the *Biosite Triage Profiler Shortness of Breath Panel* and the *Bayer Centaur*. Cardiac troponin was measured using the *Bayer Centaur* and *Biosite Triage Profiler Shortness of Breath Panel*. The number of doses of nitroglycerin and furosemide given prior to ED arrival and in the first 24 hours were also recorded. Serum and plasma were processed and stored for further analysis. The serum tube was allowed to clot for 30 minutes and the tubes were then centrifuged at 2000g for 10 minutes. The serum and plasma were transferred to cryovials and stored at -70°C .

Measurements of biomarkers

Biomarkers were measured in stored serum and plasma. After retrieval and thawing at room temperature, the samples were vortex mixed and centrifuged to remove debris. CT-pro-ET-1, MR-proANP, and MR-proADM levels were measured in samples collected at baseline (i.e. time of ED physician evaluation) and at 2–4 and 12–24 hours after baseline. Samples were assayed using a fully automated bench top random-access sandwich immunoassay system (BRAHMS KRYPTOR Compact, Hennigsdorf/Berlin, Germany). Using fluorescent detection, biomarker concentration was calculated using pre-test calibration curve standards. Two levels of quality control material for each analyte were run daily, in duplicate, before samples were tested. The manual assays that were combined into the automated assay system have been described thoroughly in previous studies.[25–27]

Quality control data from 17 total runs at two different concentrations were used to calculate inter-assay coefficients of variation for each biomarker; the coefficients of variation were 7.1%, 3.5% and 8.2% for MR-proADM, MR-proANP and CT-proET-1, respectively. The assay analytical detection limits are 0.4 pmol/L for CT-proET-1, 6.0 pmol/L for MR-proANP, and 0.08 nmol/L for MR-proADM. [25–27] Specimens were run in duplicate and values were never >10% between replicates; the mean of the two replicates was used for statistical analysis.

Statistical analysis

The primary goal of this study was to determine whether biomarkers changed from baseline through 12–24 hours. Secondary analyses considered the association between biomarker changes and clinical characteristics such as heart failure signs and symptoms and diagnostic testing variables, including BNP.

The percentage changes in biomarker concentrations during three intervals were calculated: 1) baseline to 2–4 hours; 2) baseline to 12–24 hours; and 3) 2–4 to 12–24 hours. Patients were grouped by whether the specific biomarker increased, decreased, or remained stable; changes less than twice the inter-assay coefficients of variation were considered stable. Clinical and treatment data were compared between patients whose biomarker increased, decreased or remained stable. Chi-square or Fisher's exact test was used to compare categorical variables between groups and the Kruskal-Wallis test was used to compare continuous data between groups. All analyses used SPSS v 18.0 (SPSS Inc., Chicago, IL). While this analytic approach resulted in the conduct of many statistical tests, the largely exploratory nature combined with the relatively small sample size suggests that use of a correction for multiple comparisons would be overly conservative.

RESULTS

Patient Characteristics

There were 48 patients included in the study. The median age was 62 years (range 40 – 88), 54% were male, and 50% were white. Most patients (75%) had BNP concentrations greater than 500 pg/mL and 56% had an ejection fraction below 55% (Table 2). All but one patient received at least one dose of furosemide, and 68% received nitroglycerin, most often via the topical or sublingual route.

Biomarker Changes

Biomarker levels were detectable in all samples. In the first 2–4 hours after ADHF therapy, a greater proportion of patients experienced changes in MR-pro-ANP levels compared to MR-proADM or CT-pro-ET-1 (36% vs. 16% and 24%). However, 12–24 hours after baseline treatment all three groups had similar proportions of patients with changes from baseline (47%, 41% and 49% for MR-pro-ANP, MR-proADM and CT-pro-ET-1, respectively) (Table 3).

Biomarker Changes and their Association with Clinical Characteristics

In this preliminary investigation, many clinical variables appeared to be associated with biomarkers changes (Table 4).

CT-pro-ET-1—Changes in CT-pro-ET-1 2–4 hours after baseline were associated with changes in sodium and BUN values. Decreasing CT-pro-ET-1 was associated with decreasing sodium while increasing CT-pro-ET-1 was associated with increasing sodium. BUN values were higher for patients with a decrease in CT-pro-ET-1 than those with an increase in CT-pro-ET-1. Changes in CT-pro-ET-1 between 2–4 hours and 12–24 hours showed associations with ejection fraction, heart rate, and BNP. Abnormal ejection fractions (<55%) were noted more frequently in patients with a decrease or no change in CT-pro-ET-1 than those with an increase. Heart rate was lowest among those with stable CT-pro-ET-1. Decreasing CT-pro-ET-1 was associated with decreasing BNP while increasing CT-pro-ET-1 was associated with increasing BNP.

MR-proADM—MR-proADM changes between baseline and 2–4 hours suggested associations with jugular venous distension. No patients with a decrease in MR-proADM presented with jugular venous distension, 10/14 (71.4%) of patients with no change in MR-proADM presented with jugular venous distension, and 4/14 (28.6%) with an increase in MR-proADM presented with jugular venous distension ($p = 0.069$). The interval between 2–4 hours and 12–24 was notable for changes in several clinical variables including peripheral edema, respiratory rate, oxygen saturation, sodium and BUN level.

MR-proANP—The change profile for MR-proANP from baseline to 2–4 hours showed associations with paroxysmal nocturnal dyspnea. Decreasing MR-proANP was associated with a greater likelihood of paroxysmal nocturnal dyspnea. The interval between 2–4 hours and 12–24 hours was most associated with heart failure therapy; increased doses of nitroglycerin were associated with decreasing biomarker levels.

DISCUSSION

Our preliminary study suggests changes in these three novel biomarkers can be seen early after therapy for ADHF. While we have seen analytical changes in biomarkers in a large proportion of patients, a larger cohort with an increased number of clinical events is needed to determine whether these changes aid in clinical decision making. Furthermore, whether these changes provide independent or complementary information to that provided by BNP also needs to be delineated. Objective biomarker changes that are temporally associated with clinical events in patients with ADHF would be particularly useful if they add risk-stratification information to that provided by BNP. While our small sample size limits conclusions about prognosis that can be drawn about the clinical impact of the biomarker changes, there were some noteworthy physiologic patterns that should be investigated.

Decreases in CT-pro-ET-1 over 2–4 hours post-therapy were associated with decreases in sodium concentration compared to those with increases in CT-pro-ET-1, who had elevations in sodium. Endothelin-1 has a known role in decreasing sodium excretion, thus decreases in its C-terminal peptide may reflect improved renal perfusion and sodium excretion.[28]

Adrenomedullin is a protein found to be elevated in fluid overloaded patients who have elevated filling pressures, and it has vasodilatory, natriuretic, and inotropic properties.[29] In this study, patients whose MR-proADM levels tended to increase during acute therapy had findings associated with persistent congestion. This marker may identify a subset of patients who have more severe ADHF who are less responsive to therapy. In the first 2–4 hours, patients with elevations of MR-proADM exhibited JVD and then later in the 12–24 hour time period had increased peripheral edema and respiratory rates and relatively worse hyponatremia. Similarly, patients who had decreases in MR-proADM levels over 12–24 hours showed decreases in their respiratory rate and improvement in pulse oximetry. *These patients also had decreases in BNP and increases in serum sodium, suggesting decreases in MR-proADM may be associated with decreased congestion.* Persistent congestion and hyponatremia during hospitalization have been associated with increased morbidity and mortality.[30–32]

Atrial natriuretic peptide is a vasodilator that is released in response to increasing atrial filling pressures. Patients that exhibited decreases in MR-proANP over the first 12–24 hours were more likely to have received a greater number of nitrate doses during initial therapy. Nitroglycerin's preload reduction may have decreased release of MR-proANP due to reduced filling pressures and shear stress on the atrial myocytes. Similar findings have also been seen with BNP.[33] However, with a shorter half-life than BNP, MR-proANP may be even more sensitive to changes in cardiac filling pressures. [34]

Limitations

Our data suggest that there are measurable changes in biomarkers that might be associated with characteristics of ADHF. However, there are several limitations. First, this study included only a small convenience sample of patients with relatively mild ADHF. *As a result of the conservative inclusion criteria, there were no deaths or cardiac arrests and only 4 events at 30 days. This limits the ability of the authors to make any solid comparisons about changes in biomarkers and their association with adverse events.* Further, due to the

small sample size, some physiological patterns that were described failed to meet statistical significance despite there being plausible effects. A larger prospectively designed study may be useful in best characterizing the associations *with physiological patterns as well as adverse events*. It is also noted that blood was only available at three time points during the first 24 hours following initiation of therapy, and in some instances, blood was not attained during specified time intervals. Marker changes of greater magnitude might be expected over longer periods of time, and better characterization of changes over time by more frequent sampling would provide more information. Finally, the determination of ADHF was made by the ED physician in this study. *This reflects real world clinical management, and could be considered a relative strength of the investigation. The treating physician's clinical impression combined with a BNP > 100 pg/ml formed the foundation of our criterion standard. Other studies choose to use a cardiologist's chart review as the criterion standard, which could be considered to be a limitation of our study.* While an ED diagnosis of ADHF has been shown to be approximately 85% accurate, there is a possibility of misdiagnosis.[35] By including patients with a minimum baseline BNP of 100 pg/ml, we reduced the chances of misdiagnosis.

Conclusion

The results of this preliminary study suggest that MR-proANP, MR-proADM and CT-pro-ET-1 all undergo changes during the 24 hours after initial therapy in patients with ADHF. Since measurable changes occur, a study of association with clinical course and outcomes to determine the role of these markers in risk-stratification before and after ADHF therapy is warranted.

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List of Abbreviations

ADHF	acute decompensated heart failure
ED	emergency department
LOS	length of stay
BNP	b-type natriuretic peptide
CT-pro-ET-1	C-terminal-Pro-Endothelin-1
MR-proADM	Mid-regional-Pro-Adrenomedullin
MR-proANP	Mid-regional-Pro-Atrial Natriuretic peptide
ANP	atrial natriuretic peptide
TRACE	Time Resolved Amplified Cryptate Emission
BUN	blood urea nitrogen

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Table 1

Modified Framingham Criteria used to identify participants eligible for study participation.

Two from the left column OR one from the left column plus two from the right column	
• Paroxysmal nocturnal dyspnea	• Extremity edema
• Neck vein distention	• Night cough
• Pulmonary edema on chest radiograph	• Dyspnea on exertion
• Rales	• Hepatomegaly
• Cardiomegaly on chest radiograph	• Pleural effusion
• S ₃ gallop	• Tachycardia (≥ 130 beats/min)
• Jugular venous distension	
• Positive hepatojugular reflex	

Table 2

Baseline demographics, medical history, presenting signs and symptoms and laboratory values. Data are shown as counts and percentages unless otherwise indicated.

Demographics		
Age (median, range)	61.0	40–88
Male	26	54.2
Female	22	45.8
Non-White	25	52.1
White	23	47.9
Medical History		
Congestive heart failure	34	70.8
Coronary artery disease	25	54.3
Hypertension	44	93.6
Valvular heart disease	12	26.1
Cardiomyopathy	19	40.4
ICD/Pacemaker	7	14.9
Symptom onset >48 hours prior	27	56.3
Initial Examination Findings		
Systolic blood pressure, mm Hg (median, range)	146.5	95–218
Pulse rate, beats/min (median, range)	83	52–136
Respiratory Rate, breaths/min (median, range)	20	11–32
Oxygen saturation, % (median, range)	96	83–100
Jugular venous distention	16	34.8
Peripheral edema	33	68.8
Dyspnea	44	93.6
Paroxysmal nocturnal dyspnea	19	41.3
S3	4	8.5
Rales	27	57.4
Baseline Laboratory Findings		
BNP 100–499 (pg/mL)	12	25.0
BNP ≥ 500 (pg/mL)	36	75.0
BUN (mg/dL)	23	8–118
Creatinine ≥ 2 (mg/dL)	11	22.9
Ejection Fractions		
<55% at previous visit	13	46.4
<55% at current visit	17	56.7
Chest X-Ray Findings		
Pathological Findings	46	95.6
Cardiomegaly	40	83.3
Pulmonary congestion	33	68.8

BNP= b-type natriuretic peptide; BUN= blood urea nitrogen

Table 3

Count and proportion values of patients with designated change profiles for each time interval along with median biomarker starting values at earlier of the two time points and absolute median change of biomarker levels.

CT-pro-ET-1 (pmol/L)	N	%	Median Starting Value	Median Change	Median Percent Change
Decrease	5	11.9	143.30	-33.80	-23.6
No change	32	76.2	163.60	-3.10	-1.9
Increase	5	11.9	92.80	63.20	68.1
2-4 Hours to 12-24 Hours					
Decrease	10	30.3	148.60	-49.25	-33.1
No change	21	63.6	180.60	-1.80	-1.0
Increase	2	6.1	94.00	21.67	23.1
Baseline to 12-24 Hours					
Decrease	12	34.3	149.40	-47.57	-31.8
No change	18	51.4	199.90	-5.85	-2.9
Increase	5	14.3	65.30	62.30	95.4
MR-ProADM (nmol/L)					
Decrease	2	4.7	1.18	-0.43	-36.4
No change	36	83.7	1.91	-0.02	-1.0
Increase	5	11.6	0.88	0.56	63.9
2-4 Hours to 12-24 Hours					
Decrease	5	14.7	2.07	-0.42	-20.3
No change	23	67.6	1.80	0.02	1.1
Increase	6	17.6	1.39	0.27	19.4
Baseline to 12-24 Hours					
Decrease	6	17.6	1.73	-0.50	-28.9
No change	20	58.8	1.88	0.02	1.1
Increase	8	23.5	1.24	0.49	39.6
MR-proANP (pmol/L)					
Decrease	10	23.8	344.90	-54.05	-15.7
No change	27	64.3	375.10	-3.20	-0.9
Increase	5	11.9	355.20	45.10	12.7
2-4 Hours to 12-24 Hours					
Decrease	13	38.2	346.00	-46.40	-13.4

CT-pro-ET-1 (pmol/L)	N	%	Median Starting Value	Median Change	Median Percent Change
No change	12	35.3	563.70	-4.40	-0.8
Increase	9	26.5	259.60	53.90	20.8
Decrease	12	35.3	369.30	-56.65	-15.3
Baseline to 12-24 Hours	18	52.9	430.90	8.05	1.9
Increase	4	11.8	269.20	90.15	33.5

Table 4

Association between clinical characteristics and changes in biomarker levels

CT-pro-ET-1	Decrease		No change		Increase		P Value
Baseline-2-4 Hours							
Paroxysmal nocturnal dyspnea	5	29.4%	9	52.9%	3	17.6%	0.007
Sodium change (mEq/L)	-1.5	-5-0	0.0	-8-4	3.0	0-6	0.068
BUN value (mg/dL) (baseline)	32.0	10-38	23.0	10-118	12.0	8-19	0.029
2-4 Hours to 12-24 Hours							
Congestive heart failure	6	26.1%	17	73.9%	0	0.0%	0.065
Current ejection fraction<55%	7	46.7%	7	46.7%	1	6.7%	0.043
Heart rate (2-4 hours)	92.5	68-120	70.0	54-110	83.5	57-110	0.050
Respiration rate (12-24 hours)	18.0	17-20	20.0	14-24	24.0	22-26	0.025
Respiration rate change	-2.0	-6-4	0.0	-4-8	6.0	-	0.056
BNP change (pg/mL)	-368.0	-921-80	-142.5	-355-1912	-76.0	-85- -67	0.065
Sodium value (2-4 hours) (mEq/L)	141.0	140-143	140.0	137-142	137.5	137-138	0.054
Baseline-12-24 Hours							
Current ejection fraction <55%	9	60.0%	4	26.7%	2	13.3%	0.003
BUN value (mg/dL) (baseline)	18.5	8-98	32.0	12-118	18.0	9	0.071
Creatinine value: 12-24 hours (mg/dL)	1.2	0.6-5.5	1.6	0.7-5.7	1.3	1.0-2.1	0.052
Furosemide doses	2.0	1-4	3.0	1-5	1.0	1-5	0.019
MR-proADM	Decrease		No change		Increase		P Value
Baseline-2-4 Hours							
Jugular venous distention	0	0.0%	10	71.4%	4	28.6%	0.069
Rales	2	8.0%	22	88.0%	1	4.0%	0.075
Sodium value (2-4 hours) (mEq/L)	137.0	--	140.0	137-143	139.5	137-142	0.092
Glucose value (baseline) (mg/dL)	93.5	90-97	115.0	62-324	99.0	84-123	0.066
2-4 Hours to 12-24 Hours							
Valvular heart disease	3	33.3%	6	66.7%	0	0.0%	0.025
Cardiomyopathy	3	23.1%	9	69.2%	1	7.7%	0.094

CT-pro-ET-1	Decrease		No change		Increase		P Value
Peripheral edema	2	8.7%	15	65.2%	6	26.1%	0.077
Respiration rate (12–24 hours)	18.0	17–20	20.0	14–26	20.0	18–24	0.098
Respiration rate change	–3.0	–6–0	0.0	–4–6	2.0	–3–8	0.096
Oxygen saturation (2–4 hours)	94.5	93–96	97.0	94–100	97.0	93–99	0.083
Oxygen saturation change	1.0	–1–3	–2.0	–4–3	–1.0	–5–2	0.098
BNP value (12–24 hours) (pg/mL)	398.5	309–859	929.5	119–5288	374.5	196–637	0.095
Sodium value (12–24 hours) (mEq/L)	140.0	129–144	140.0	134–144	137.0	135–139	0.057
BUN change (mg/dL)	–2.0	–2– –20	1.0	–3–6	5.0	0–9	0.100
Baseline-12–24 Hours							
Valvular heart disease	4	44.4%	4	44.4%	1	11.1%	0.075
Jugular venous distention	3	25.0	3	25.0	6	50.0	0.002
Creatinine change (mg/dL)	–0.2	–1.9–0.1	0.0	–0.3–0.4	0.2	0.0–1.0	0.006
MR-proANP	Decrease		No change		Increase		P Value
Baseline-2–4 Hours							
Coronary artery disease	7	35.0%	9	45.0%	4	20.0%	0.004
Paroxysmal nocturnal dyspnea	6	35.3%	11	64.7%	0	0.0%	0.055
Heart rate (2–4 hours)	76.0	57–94	90.0	54–125	72.0	67–84	0.058
Sodium value (mEq/L)(baseline)	140.5	136–145	139.0	127–142	138.0	132–141	0.100
2–4 Hours to 12–24 Hours							
Prior ejection fraction < 55%	1	10.0%	6	60.0%	3	30.0%	0.055
Nitro doses	2.0	1–3	2.0	1–3	1.0	-	0.014
Baseline-12–24 Hours							
Prior ejection fraction < 55%	1	10.0%	9	90.0%	0	0.0%	0.054
Sodium change (mEq/L)	–0.5	–4–2	0.0	–2–3	3.0	0–7	0.059
Furosemide doses	2.0	1–3	3.0	1–5	4.0	2–5	0.025
Nitro doses	3.0	1–3	1.0	1–3	1.0	1–2	0.017