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Effect of Laser-Cut Slow-Flow Nipples on Preterm Feeding Performance

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EFFECT OF LASER-CUT SLOW-FLOW NIPPLES ON PRETERM FEEDING PERFORMANCE

BY

Katlyn Elizabeth McGrattan

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the
College of Health Professions
Department of Health Sciences and Research

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Abstract of Dissertation Presented to the Doctor of Philosophy Program in Health and Rehabilitation Science
Medical University of South Carolina
In Partial Fulfillment of the Requirements of the Degree of Doctor of Philosophy

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Background: Dysphagia of prematurity is a highly prevalent condition that carries negative developmental, social, and financial implications. Although the modification of bottle nipple properties is a widely used treatment for dysphagia of prematurity, there have been a paucity of investigations examining the effect of this intervention on refined measures of feeding performance. **Methods**: Healthy preterm infants were evaluated for measures of milk ingestion and respiratory performance during oral intake on a laser-cut slow-flow and standard-flow nipple. Time to achieve hospital discharge milestones was recorded. **Results**: Few differences were observed in feeding performance between slow-flow and standard-flow nipples. Characteristics of respiration during oral intake and at rest were correlated with time to hospital discharge. **Conclusions**: Slow-flow nipples may reduce the need for skilled feeders that are able to adapt feeding method based on infant feeding performance; when broadly applied to all infants by skilled feeders the clinical benefits are in question.

Acknowledgements

This dissertation reports findings of a clinical investigation that formally marks the completion of my doctoral study. The true significance of this document, however, spans far beyond a solitary investigation or the formal provision of a degree. This dissertation represents a series of lessons, some taught subtly through example, and others taught abruptly through trial and error. The individuals who taught me these lessons are the ones who truly deserve acknowledgement on the cover of this work. It is through these individuals and God's grace that I was granted the opportunity to learn lessons that have built on one another to make the following work possible.

To my mentor, Dr. Martin-Harris, whose captivating demonstration of knowledge in the fall of 2008 served as the catalyst and ongoing inspiration that fueled for my doctoral pursuit. Thank you, Dr. Martin-Harris, for teaching me to question the accepted, to excel above mediocrity, and above all, to maintain a focus on bettering the lives of patients.

To Luke McCurry, a little boy who with the slightest of grins can bring light to my darkest day. It is through your continuous embodiment of happiness and strength in the face of adversity that I draw strength. Thank you, Luke, for teaching me these lessons of thankfulness, perseverance, faith, and for opening my eyes to the social and emotional consequences of dysphagia that span far beyond the presenting impairments addressed in the clinic.

And to my parents, Barb and Ed McGrattan, who were never too busy to conduct a goodnight rendition of "knees up mother brown," provide a post-game review of the three D's of defense, or to sit at the dinner table over a home-cooked meal to inquire about my day. You used these seemingly mundane life events as a classroom to teach me lessons through example that laid the foundation for this work. Thank you, Mom and Dad, for teaching me that anything is possible through hard work, that sharing love with others is the most powerful thing to share, and that laughter is the remedy for all ailments.

> *"What we do for ourselves dies with us. What we do for others and the world remains and is immortal."*
>
> *-Albert Pine*

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ABBREVIATIONS

BPD	Bronchopulmonary Dysplasia
bpm	Breaths per Minute
C-SW-C	Respiratory Cessation-Swallow- Respiratory Cessation
CN	Cranial Nerve
	CN V Trigeminal Nerve
	CN VII Facial Nerve
	CN X Vagus Nerve
	CN XI Accessory Nerve
	CN XII Hypoglossal Nerve
CP	Cricopharyngeous
CPG	Central Program Generator
dB	Decibel
E-SW-E	Expiration-Swallow-Expiration
F	French
FIR	Finite Impulse Response
GA	Gestational Age
GER	Gastroesophageal Reflux
GMH	Germinal Matrix Hemorrhage
Hz	Hertz
IIR	Infinite Impulse Response
I-SW-E	Inspiration-Swallow-Expiration
IVH	Intraventricular Hemorrhage

L	Liters
mL	Milliliters
mmHg	Millimeters Mercury
ms	Milliseconds
µV	Microvolt
NNS	Non-Nutritive Sucking
NOMAS	Neonatal Oral-Motor Assessment Scale
NS	Nutritive Sucking
OFS	Oral Feeding Skills
PES	Pharyngoesophageal Segment
PMA	Postmenstrual Age
PRO	Proficiency
PVH	Periventricular Hemorrhage
PVL	Periventricular Leukomalacia
RDS	Respiratory Distress Syndrome
RIP	Respiratory Inductance Plethsmography
RT	Rate of Transfer
SB	Suck-Burst
SBB	Suck-Burst Break
V	Vol

CHAPTER I: PROJECT SUMMARY

Successful bottle-feeding requires an effortless transition between the physiologic processes of sucking, swallowing, and respiration.(Delaney & Arvedson, 2008) Despite the unique physiology and function within each of these processes, their interrelationships during bottle-feeding demonstrate functional interdependence. Of great importance in the establishment of this interdependence is the infant's ability to fluently interpose respiration between sequential swallows. Adequate systemic oxygenation requires respiration to continue throughout a feed, yet the shared function of the aerodigestive tract necessitates the inhibition of respiration during swallowing.(Ardran, Kemp, & Lind, 1958; Hooker, 1954; Koenig, Davies, & Thach, 1990; Logan & Bosma, 1967) The ability to meet respiratory demands during feeding requires neuromotor

control between the mechanisms of sucking, swallowing, and respiration.(S. Barlow, 2009; S. Barlow M., 2009) Specifically, full-term infants must alter sucking and respiratory mechanics to maximize ventilation during sucking while minimizing respiratory inhibition during the pharyngeal swallow.

The neurologic immaturity of the preterm infant has been shown to negatively influence the coordinative processes of sucking, swallowing, and respiration.(Amaizu, Schanler, & Lau, 2008; Amaizu et al., 2008; Bamford, Taciak, & Gewolb, 1992; Bu'Lock, Woolridge, & Baum, 1990; I. Gewolb, Vice, Schweitzer-Kenney, Taciak, & Bosma, 2001;

I. Gewolb et al., 2001; Howe, Sheu, & Holzman, 2007; Lau, Alagugurusamy, Schanler, Smith, & Shulman, 2000; Lau, Smith, & Schanler, 2003; Medoff-Cooper, McGrath, & Shultz, 2002; Mizuno & Ueda, 2003; Mizuno & Ueda, 2003) Preterm infants have a reduced ability to interpose respiration within sequential swallows, contributing to decreased systemic oxygenation(I. H. Gewolb & Vice, 2006; O. P. Mathew, 1988; Mizuno & Ueda, 2003; Shivpuri, Martin, Waldemar, & Fanaroff, 1983) and volume of milk transfer(Amaizu et al., 2008; Lau et al., 2003b; Lau & Smith, 2011; Lau, Sheena, Shulman, & Schanler, 1997) during bottle feeding. Past investigations have revealed that reductions in milk flow rate facilitate improved preterm feeding performance(Al-Sayed, Schrank, & Thach, 1994; Fucile, Gisel, Schanler, & Lau, 2009; Lau & Schanler, 2000; Fadavi, Punwani, Jain, & Vidyasagar, 1997; O. Mathew, 1991; O. P. Mathew & Cowen, 1988; Scheel, Schanler, & Lau, 2005) yet none have examined the effectiveness of clinically available methods of milk flow rate reduction on feeding performance in preterm infants.

The goal of this project is to examine the effectiveness of laser-cut slow-flow nipples in the improvement of preterm feeding performance when compared to a standard-flow nipple. This will be accomplished through measurements of respiratory function and milk ingestion during bottle-feedings using slow-flow and standard-flow nipples. This investigation is a critical first step in the achievement of the principal investigator's long term goal of developing a clinically practical, valid, and reliable objective measure of bedside dysphagia assessment that enables the identification of physiologic impairment and the facilitates the provision of targeted treatment.

Research Question 1: What is the difference in inspiratory time (ms), respiratory period (ms) respiratory cycle rhythmicity (SD), respiratory rate (bpm), tidal volume (% SS), and minute volume (% SS) between slow-flow and standard-flow nipples during bottle-feeding in preterm infants?

Research Question 2: What is the difference in rate of transfer (mL/min) and proficiency (%) of oral intake between slow-flow and standard-flow nipples in the preterm infant?

Research Question 3: What is the association between inspiratory time (ms), respiratory period (ms) respiratory cycle rhythmicity (SD), respiratory rate (bpm), tidal volume (% SS), and minute volume (% SS) on the slow-flow and standard-flow nipple and time to discharge?

CHAPTER 2: REVIEW OF THE LITERATURE

SECTION I

NORMAL FEEDING PHYSIOLOGY: SUCKING, SWALLOWING, AND RESPIRATION

Coordinative Dynamics Between Sucking and Swallowing

Sucking Physiology

Sucking and swallowing are time-linked processes that engage interdependent structural movements of the upper aerodigestive tract. The interdependence between sucking and swallowing is believed to maximize the efficiency of both processes while also maximizing the temporal-kinematic coordination of oropharyngeal structural movements required for airway protection and bolus clearance.(Bu'Lock et al., 1990) Primitive rooting and sucking reflexes aid in the initiation of this movement pattern by facilitating reflexive rooting and sucking with perioral stimulation.(Marshall, 2012; Papousek, 1959) When perioral stimulation occurs in the presence of an expressible bolus from a nipple, the resulting physiologic pattern is termed, nutritive sucking (NS).(Wolff, 1968)

Nutritive sucking is the result of the infant's alternation between the generation of negative pressure within the oral cavity and positive pressure within the bottle's nipple.(Colley & Creamer, 1958)

The negative pressure in the oral cavity during sucking is termed suction, and the positive pressure in the nipple is termed compression/expression.(Ardran et al., 1958; Balint,1948; Colley & Creamer, 1958; Darwin, 1971; Lau & Schanler, 1996; Sameroff, 1968) It is by these complementary forces of suction and compression/expression that peak bolus flow is achieved through generation of a pressure gradient differential within the oral cavity and nipple. (Lau et al., 2000) These two functions are achieved by the contraction of 21 pairs of facial, lingual, and palatal muscles that are supplied by the trigeminal (V), facial (VII), vagus (X), accessory (XI), and hypoglossal (XIII) nerves. *Table 2.1 Orofacial Muscles of Suction and Compression/Expression* provides a full listing of muscular and neural structures responsible for normal sucking movement patterns.(Arvedson, 1996; Arvedson & Lefton-Greif, 1996; Bosma, Hepburn, Josell, & Baker, 1990; Seikel, King, & Drumright, 2005)

Table 2.1. Orofacial Muscles of Suction and Compression/Expression

Suction				
Sucking Component	**Component**	**Musculature**	**Muscular Movement**	**Innervation**
Closed System	Anterior Seal	Orbicularis Oris	Constrict Oral Opening	VII
	Anterior Seal	Mentalis	Chin Elevation	VII
	Lateral Seal	Buccinater	Cheek Constriction	VII
	Lateral Seal	Depressor Anguli Oris	Compression of Upper Lip Inferiorly	VII
	Lateral Seal	Genioglossus	Lingual Depression	XII
	Lateral Seal	Superior Longitudinal	Lingual Elevation	XII
	Lateral Seal	Transverse Intrinsic	Tongue Narrowing	XII
	Posterior Seal	Palatoglossus	Elevates Tongue Depresses Soft Palate	XI X
	Posterior Seal	Styloglossus	Retraction Tongue Elevates Tongue	XII
	Posterior Seal	Palatopharyngeous	Lowers Soft Palate	XI X
Anterior-Inferior Mandibular Trajectory	Anterior Movement	Lateral Pterygoid	Mandibular Protrusion	V
	Inferior Movement	Digastric	Mandibular Depression	V
	Inferior Movement	Geniohyoid	Mandibular Depression	XII
	Inferior Movement	Mylohyoid	Mandibular Depression	V
	Inferior Movement	Platysma	Mandibular Depression	VII

Table 2.1. Continued

Compression/Expression				
Sucking Component	**Component**	**Musculature**	**Muscular Movement**	**Innervation**
Superior-Posterior Mandibular Trajectory	Superior Movement	Masseter	Mandibular Elevation	V
	Superior Movement	Medial Pterygoid	Mandibular Elevation	V
	Superior Movement	Temporalis	Mandibular Elevation	V
	Posterior Movement	Temporalis	Mandibular Retraction	V
Lingual Trajectory	Inferior Movement	Vertical Internal	Lingual Depression	XII
	Inferior Movement	Inferior longitudinal	Lingual Tip Depression	XII
	Inferior Movement	Genioglossus	Lingual Depression	XII
	Inferior Movement	Chondroglossus	Lingual Depression	XII
	Superior Movement	Superior Longitudinal	Lingual Tip Elevation	XII
	Superior Movement	Styloglossus	Lingual Elevation	XII
	Superior Movement	Palatoglossus	Lingual Elevation	XI X
	Posterior Movement	Inferior longitudinal	Lingual Retraction	XII
	Posterior Movement	Genioglossus	Lingual Retraction	XII
	Posterior Movement	Superior Longitudinal	Lingual Retraction	XII
	Posterior Movement	Styloglossus	Lingual Retraction	XII

Arvedson, J. C. (1996). Dysphagia in pediatric patients with neurologic damage. *Seminars in Neurology, 16*(4), 371-86. **Arvedson, J. C., & Lefton-Greif, M. A. (1996).** Anatomy, physiology, and development of feeding. *Seminars in Speech & Language, 17*(4), 261-8. **Bosma, J., Hepburn, L., Josell, S., & Baker, K. (1990).** Ultrasound demonstration of tongue motions during suckle feeding. *Developmental Medicine & Child Neurology, 32*, 223-229. **Seikel, J., King, D., & Drumright, D. (2005).** *Anatomy and physiology for speech, language, and hearing.* 2005: Thomson Delmar Learning.

Negative pressure required for oral suction is generated by the infant's establishment of a closed space within the oral cavity that is then enlarged in area by lingual and mandibular movement. The closed space is accomplished by the infant's generation of an anterior labial nipple seal, lateral lingual nipple seal, and posterior lingual-to-palatal seal.(Ardran et al., 1958; Kramer, 1985; Seikel et al., 2005) Once the closed space has been established, its expansion causes a generation of negative pressure. Expansion of the oral cavity occurs in both horizontal and lateral planes as the mandibular-lingual complex moves in an anterior-inferior trajectory. The result is a pressure gradient differential between the bottle nipple and the oral cavity that produces bolus flow. (Ardran et al., 1958; Seikel et al., 2005)

These same movement patterns that are used to generate negative oral pressure for suction are also complementary to those movement patterns that generate positive nipple pressure for compression/expression. Return of the mandible from its anterior-inferior trajectory provides one component of nipple compression as the mandible stabilizes itself along the inferior base of the nipple.(Ardran et al., 1958; Seikel et al., 2005) Of greater contribution to bolus flow, however, is the subsequent nipple compression that is facilitated by the movement of the mandible's muscular attachments. Contraction of the internal and external lingual musculature exerts positive pressure along the inferior nipple edge that serves to eject milk from the nipple through an anterior-posterior lingual wave *(Figure 2.1 Sucking and Swallowing Movement Patterns)*.(Ardran et al., 1958; Balint, 1948; Bosma et al., 1990; Bu'Lock et al., 1990; Goldfield et al., 2010; J. Miller L. & Kang, 2007; Sameroff, 1968; Weber, Woolridge, & Baum, 1986)

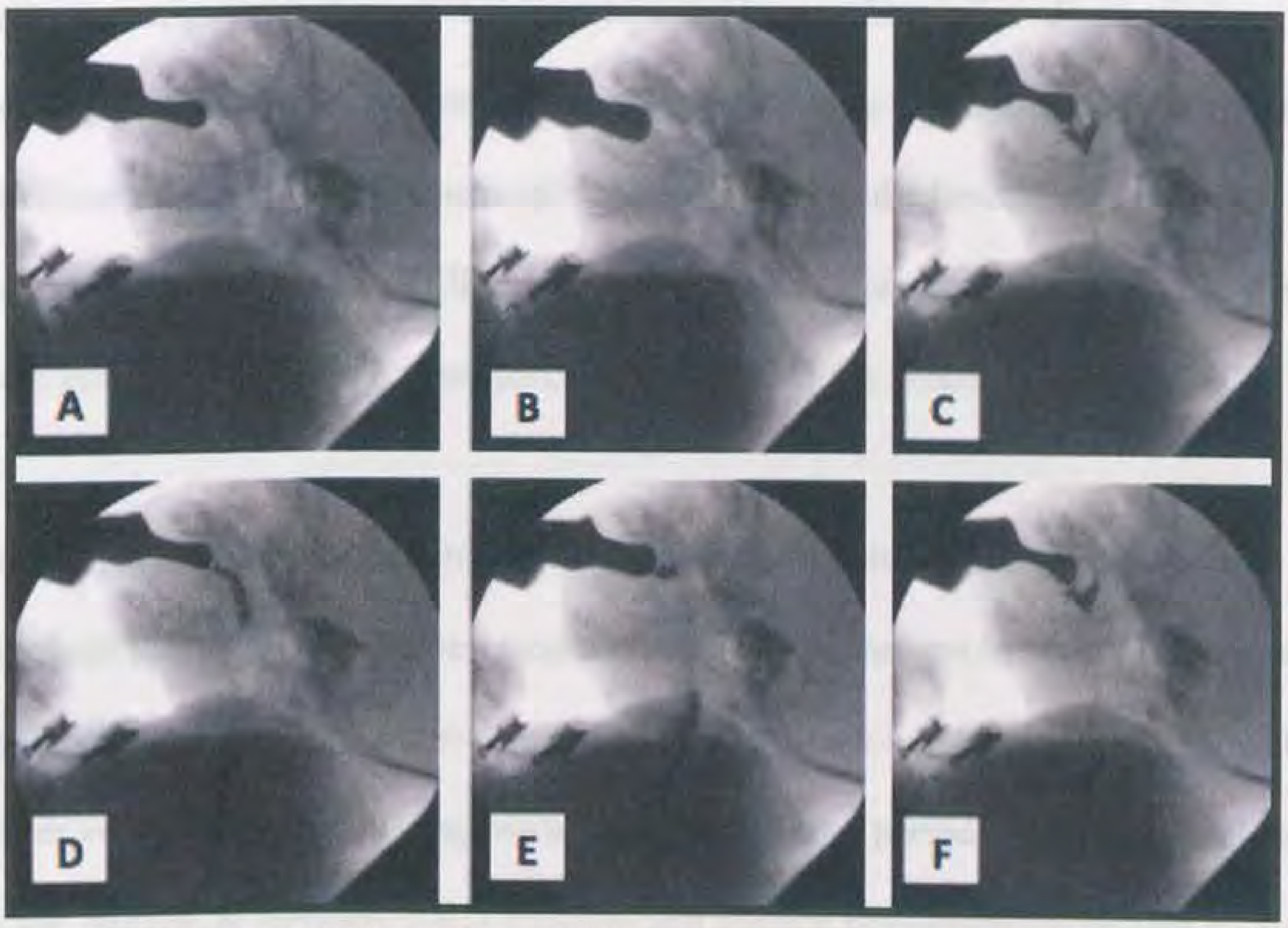


Figure 2.1. Sucking and Swallowing Movement Patterns **A.** Resting Position: No tongue base to soft palate contact; **B.** Initiation of Suction: Soft palate depression, tongue base retraction, anterior-inferior mandibular movement; **C.** Nipple Compression: Mandibular stabilization on nipple base with posterior stripping of nipple edge; **D.** Bolus Propulsion: Continuation of the superior-posterior lingual trajectory to transport the bolus past the ramus to initiate the swallow; **E.** Positive Pressure Generation: Continuation of tongue base retraction and soft palate elevation to create positive pressure on the tail of the bolus; **F.** Transverse of Midline for Next Compression: Tongue and mandible pass through midline to generate the next suck-sequence.

Full-term infants combine a series of suction and compression/expression movement patterns during bottle-feeding that adapt to respiratory demands, maturational capacities, and environmental factors. Two hypothesized adaptations to sucking pattern that facilitate the infant's obtainment of respiratory demands over a prolonged period of diminished respiratory allowance are the segmentation of the continuous suck-swallow series by suck-burst breaks, and the alteration of sucking rate and force. Suck-burst breaks are characterized by a brief pause in the infant's chain of suck-swallow sequences (suck-bursts) during which only respiration occurs. This brief cessation in sucking and swallowing enables the infant to increase ventilation through the re-initiation of a rhythmic respiratory pattern that is uninterrupted by swallow-induced period of respiratory cessation. Respiration is also optimized during sucking-bursts through the infant's reduction in the rate and amplitude of sucking as the feed progresses and respiratory reserve is reduced.(Bamford et al., 1992; Koenig et al., 1990; W. Lang et al., 2010; Pollitt, Consolazio, & Goodkin, 1981; Wolff, 1968; Wolff, 1968)

Sucking patterns have also been found to demonstrate maturational changes that contribute to a more efficient oral intake system. These changes include a faster rate of swallowing and a higher frequency of sucks within a suck burst that cumulatively allow a greater volume of milk consumption to occur in a shorter period of time.(Qureshi, Vice, Taciak, Bosma, & Gewolb, 2002) External and internal environmental factors such as light, sound, taste, temperature, and infant level of alertness are other variables that influence infant sucking pattern.(Crook & Lipsitt, 1976; Eisele & Berry, 1975; Peck, 1970; Wolff, 1968) The majority of investigations that have examined infant sucking response to these factors have focused on non-nutritive sucking response. These investigations have found that auditory, visual, and gustatory stimuli contribute to alteration in sucking rate and pattern.(Desor, Maller, & Turner, 1973) Future investigations are necessary to determine the mechanisms that underlie internal and externally imposed alterations in nutritive sucking physiology, and their relevance to optimal feeding performance.

Swallowing Physiology

Just as suction and compression/expression are complementary to one another in the ejection of milk from the nipple, these movement patterns are also complementary to the passage of the milk through the pharynx during the synergistic process of swallowing.(Bu'Lock et al., 1990; Martin-Harris, Michel, & Castell, 2005) Ultrasonographic investigations of infant sucking dynamics have revealed the continuation of the lingual stripping used to express the bolus from the nipple also serves to transport the bolus from the oral cavity to the oropharynx for the initiation of the pharyngeal swallow.(Bu'Lock et al., 1990) Transport of the bolus without resistance requires concurrent elevation of the soft palate by means of the levator veli palatine muscle. Together, these movement patterns, and those associated with contraction of the superior pharyngeal constrictors, facilitate a pneumatic shift from a system centered on negative oral pressure for suction to one centered on positive pharyngeal pressure for bolus propulsion during the swallow. (Ardran et al., 1958; Gullung, Hill, Wahlquist, & Martin-Harris, 2013)

The cascade of events that follows this pneumatic shift is the result of afferent stimulation of the facial (VII), glossopharyngeal (IX), and vagus nerves (X). These nerves are dispersed throughout the mucosa of the oral cavity, pharynx, and larynx.(Arvedson & Lefton-Greif, 1996; Dodds, 1989; Dodds, Stewart, & Logemann, 1990; Larson, 1985; A. J. Miller, 1986) As the bolus is transported into the oropharynx prior to the swallow, stimulation of the internal branch of the vagus nerve (X) and the pharyngeal branch of the glossopharyngeal nerve (IX) generate an ascending response to central neurons housed within the nucleus tractus solitarious (NTS) and ventral medial reticular formation.(Arvedson & Lefton-Greif, 1996; Dodds, 1989; Dodds et al., 1990; Larson, 1985; Matsuo & Palmer, 2008; A. J. Miller, 1982; A. J. Miller, 1986) This grouping of interneurons, commonly referred to as the swallowing central pattern generator (CPG), function as a relay system that acquire afferent signals from the ascending pathways and translate them to an appropriate descending efferent response through the trigeminal (V), facial (VII), glossopharyngeal, (IX), vagus (X), and hypoglossal nerves (XII).(Arvedson & Lefton-Greif, 1996) In the adult mechanism these efferent responses are further governed by cortical networks that adapt swallowing physiology to changing internal and external conditions. (Dziewas et al., 2003; Michou & Hamdy, 2009; Mosier & Bereznaya, 2001) The role of the cortex in neonatal swallowing is less understood. Neonates and the adults do, however, share similar swallowing responses to the excitation of afferent neural pathways. The swallowing response is composed of a synergy of motor movements that are finessed in spatiotemporal organization yet are able to rapidly adapt to unique bolus properties.(Martin-Harris et al., 2005)

Two integrated functions that are achieved by the muscular response of the swallowing central program generator are laryngeal closure and bolus clearance.(Dodds, Stewart, & Logemann, 1990) Laryngeal closure results from the contraction of the suprahyoid musculature, including the mylohyoid, geniohyoid, digastric, and the stylohyoid, as well as through contraction of the longitudinal pharyngeal musculature including the stylopharyngeus, salpingopharyngeus, and palatopharyngeus.(Ludlow, 2005) Traction placed on the larynx with the contraction of these muscles pulls the hyolaryngeal complex in a superior-anterior trajectory which in turn, inverts the epiglottis.(Bu'Lock et al., 1990; Dodds, 1989; Dodds et al., 1990; Kramer, 1985; Pearson, Hindson, Langmore, & Zumwalt, 2013; Pearson, Langmore, & Zumwalt, 2011; Pearson, Langmore, Yu, & Zumwalt, 2012) In the adult mechanism, this movement prevents bolus entry into the laryngeal vestibule by displacing the orifice of the larynx under the mandibular complex. The higher, more anterior resting laryngeal posture in the neonate, in conjunction with the larger size of the neonatal arytenoid cartilages, may lessen the distance that the infant laryngeal complex must travel to obtain closure.(Arvedson, 1996; Kramer, 1985; Sapienza, Ruddy, & Baker, 2004) Supplemental airway protection is also established through the approximation and forward displacement of the arytenoid cartilages, as well as the approximation of the true vocal folds. (Shaker, Dodds, Dantas, Hogan, & Arndorfer, 1990; Shaker et al., 2002) Contraction of the transverse arytenoid, oblique cricoarytenoid, lateral cricoarytenoids, and thyroarytenoids move the vocal folds from an abducted respiratory posture to an adducted swallowing posture.(B. J. W. Martin & Robbins, 1995; Seikel et al., 2005; Shaker et al., 1990; Shaker et al., 2002) These movements contribute to airway protection by establishing a supraglottic barrier that prevents bolus entry into the trachea during the swallow.(B. J. W. Martin & Robbins, 1995; Shaker, Dodds, Dantas, Hogan, & Arndorfer, 1990b)

The second primary function of the pharyngeal swallow, bolus clearance, is dependent on the infant's ability to achieve both anterior hyolaryngeal movement and positive pressure on the tail of the bolus.(I. J. Cook et al., 1989; Matsuo & Palmer, 2008) In the adult mechanism, bolus passage from the pharynx into the esophagus requires relaxation of the cricopharyngeal muscle and distention of the lowermost segment of the pharyngeal constrictors. These two muscles comprise the pharyngoesophageal segment (PES). Tonic contraction of the cricopharyngeal (CP) muscle and apposition of the cricoid cartilage to the posterior pharyngeal wall create a high pressure zone.(I. Cook et al., 1989; I. M. Lang, Dantas, Cook, & Dodds, 1991; I. M. Lang & Shaker, 1997) Relaxation of the CP muscle must occur to facilitate bolus flow during the swallow.(Asoh & Goyal, 1978; I. M. Lang, Sarna, & Dodds, 1993; I. M. Lang et al., 1991) Esophageal bolus passage also requires PES distention through external muscular contraction that is in part achieved through superior-anterior hyolaryngeal movement.(I. Cook et al., 1989; I. M. Lang & Shaker, 1997; Matsuo & Palmer, 2008) Muscular attachment of the PES to the cricoid cartilage by the oblique pars oblique and horizontal pars fundiformis results in anterior traction of the cricoid cartilage and PES during hyolaryngeal displacement. Functionally this action serves to pull the cricoid cartilage away from the cervical spine and open the PES.(I. Cook et al., 1989; Dodds, 1989; Dodds et al., 1990; I. M. Lang & Shaker, 1997; Matsuo & Palmer, 2008)

Establishment of positive pressure on the tail of the bolus is also required for bolus passage through the PES. This is first achieved through composite pressure generated by retraction of the tongue base, elevation and retraction of the soft palate, and pharyngeal constriction as the bolus is transferred from the oral cavity to the oropharynx. Progression of the swallow movement pattern yields a continuation of tongue base and pharyngeal constrictor contraction that moves from the superior pharynx to the inferior pharynx. The result of these synchronous, superior-inferior muscular contractions is a compact, fast moving bolus that facilitates PES distention through provision of a circumferential bolus force.(I. Cook et al., 1989; Dantas et al., 1990; Pearson et al., 2012) As the tail of the bolus passes through the PES the completion of the muscular contractions constituting the pharyngeal swallow cause the hyolaryngeal complex to descend while resumption of vagal stimulation causes the CP to resume tone. (I. M. Lang et al., 1993; I. M. Lang et al., 1991) In the adult this is accompanied by concurrent return of the oral, pharyngeal, and laryngeal musculature to resting position. The repetitive chain of suck-swallow movements observed in bottle-fed infants, however, results in a bypassing of resting position by the mandibular-lingual complex to begin the next anterior-inferior sucking trajectory *(Figure 2.1 Sucking and Swallowing Movement Patterns).*

Coordinative Control Between Respiration and Swallowing

Equally important as the movement patterns that facilitate laryngeal closure and bolus clearance are the temporal relationships of these patterns within the respiratory cycle. The shared functions of the upper aerodigestive tract as a conduit for both respiration and swallowing require the bottle-fed infant to encompass a time-linked alternation between respiration and swallowing. Respiration must promptly cease once the bolus is transported to the pharynx, and swallowing must conclude rapidly to allow safe resumption of respiratory efforts.(Ardran et al., 1958; S. Barlow, 2009; Cichero, 2006; Kelly, Huckabee, Jones, & Frampton, 2007; Koenig et al., 1990; Logan & Bosma, 1967; Weber et al., 1986; Wilson, Thach, Brouillette, & Abu-Osba, 1981) The high rates of exchange between respiration and swallowing during bottle-feeding necessitate refined neurologic control in which respiration is adapted to accommodate bolus flow without sacrificing oxygenation requirements.(Al-Sayed et al., 1994; Bamford et al., 1992; S. Barlow M., 2009; Cichero, 2006; O. Mathew, Clark, Pronske, Luna-Solarzano, & Peterson, 1985; Mizuno & Ueda, 2003) Similar to the neuroregulation of swallowing, the adaptability of the respiratory system around bolus flow is the result of an ascending-descending neuromuscular feedback loop termed the respiratory control system.(Darnall, Ariagno, & Kinney, 2006)

Neuro-Structural Control of Respiration During Bottle-Feeding

The respiratory control system is composed of cortical (forebrain and hypothalamus), subcortical (pons and medulla oblongata), and peripheral (arterial chemoreceptors, neuromuscular stretch receptors, and corresponding muscular innervations) structures that together, facilitate two primary functions: 1) the maintenance of continuous, rhythmic respiration; and 2) the facilitation of respiratory aberration based on metabolic demand.(Darnall et al., 2006; G. Davis & Bureau, 1987) Continuous, rhythmic ventilation is the combined result of pontomedullary neural networks that drive respiratory musculature, and mechanical recoil forces that perpetuate the respiratory cycle.(Darnall et al., 2006) Rhythmic activation of the medullary pre-botzinger complex initiates and maintains the continuous respiratory cycle by stimulating the muscles of inspiration. These include the diaphragm, external intercostal musculature, accessory musculature, and upper airway musculature.(G. Davis & Bureau, 1987; Funk & Feldman, 1995) Despite the corollaries in respiratory function that can be drawn between the adult and infant respiratory system, the respiratory mechanics that facilitate ventilation in the infant vary greatly from the adult due to differences in cardiopulmonary anatomy.

As in the adult respiratory system, the infant's primary generator of thoracic expansion and resulting inspiratory airflow is the diaphragm.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) Diaphragmatic contraction causes inferior diaphragm displacement that directly elevates thoracic volume through enlargement of the thorax in the inferior plane.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) While this expansion is supplemented in the adult respiratory system by concurrent chest wall expansion in the superior and anterior plane, the compliancy of the infant's chest wall limits their ability to generate these planes of expansion.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) Compliancy of the infant ribcage, instead, causes an inward ribcage distortion during diaphragmatic contraction as a result of the inward forces exerted by the shared pleural membranes. As a result, rather than the intercostal musculature facilitating anterior-superior expansion, it functions primarily as a ribcage stabilizer against counteracting inward ribcage distortion.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) These kinematic behaviors contribute to inspirations that are of lesser lung volume due to decreased ribcage expansion. They also contribute to inspirations that are at increased susceptibility to paradoxical movement during periods of increased respiratory effort or decreased muscular activation.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) Elevated reliance on the diaphragm for inspiration poses additional barriers to the infant respiratory system due to the lower proportion of type I, fatigue resistant, diaphragmatic muscle fibers. Past investigators have hypothesized that the lower proportion of type I fibers places infants at increased risk for diaphragmatic fatigue during periods of increased respiratory effort.(G. M. Davis & Bureau, 1987; Muller et al., 1979)

The transition from inspiration to expiration is the combined result of mechanical recoil forces of the lung and ribcage and central and peripheral stretch receptor reflex arcs that are also unique to the infant's respiratory system.(Darnall et al., 2006; G. M. Davis & Bureau, 1987) Just as the infant's chest wall compliancy limits anterior-superior ribcage expansion, it also inhibits their ability to generate the mechanically induced inspiratory-expiratory shift utilized by the adult respiratory system.(Stocks, 1999) Instead, the infant respiratory system relies on central and peripheral stretch receptors to initiate the inspiratory-expiratory shift in respiratory muscle recruitment by means of the Hering-Breuer reflex. This reflex triggers the transition from inspiratory muscle activation to expiratory muscle activation through the stimulation of vagal stretch receptors within the smooth muscles of the airways. (Cross, Klaus, Tooley, & et al., 1960; Darnall et al., 2006; G. M. Davis & Bureau, 1987) The shift from inspiration to expiration is characterized by a reduction in inspiratory muscle force which enables a gradual reduction in negative thoracic pressure for a controlled expiratory airflow.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979) The maintenance of inspiratory muscle force during expiration is especially critical in the infant with a compliant chest wall, as it maintains chest wall stability through elevation of end expiratory lung volume.(G. M. Davis & Bureau, 1987; Gaultier, 1995; Muller et al., 1979)

These mechanically imposed reductions in lung volume and structurally imposed reductions in systemic oxygenation that are unique to the infant's respiratory system make the second function of the respiratory system, facilitation of respiratory aberration based on metabolic demand, critical to the infant's well-being. Despite the infant's compensation for reduced efficiency of ventilation through elevation in respiratory rate, the continued presence of reduced lung volumes provide the infant little respiratory reserve during periods of respiratory perturbation.(James & Adamsons, 1964) Consequently, during these periods of perturbation and increased metabolic demand, the infant must rapidly adapt respiratory rate, amplitude, and muscular recruitment to obtain adequate systemic oxygenation using an aberrant respiratory pattern. Chemoreceptors located in the carotid artery, aortic artery, and medulla signal the need for aberration in respiratory pattern based on oxygen and carbon dioxide concentrations in the blood and extracellular cortical fluid.(G. M. Davis & Bureau, 1987) These signals, paired with those signals from solute-sensitive pharyngeal and laryngeal chemoreceptors and environmentally influenced cortical structures, follow ascending afferent pathways to pontomedullary structures for the generation of the appropriate neuromotor respiratory response.(Darnall et al., 2006)

It is the neuro-structural integrity within these two functions of the respiratory system that enable the healthy, term infant to adapt respiratory pattern during bottle-feeding in a way that accommodates both bolus flow and systemic oxygenation requirements. Just as at rest, the pre-botzinger complex is critical to the infant's continued respiratory efforts during the bottle-feeding process. The rhythmic respiratory efforts that are fulfilled by this signal, however, are perturbed during bottle-feeding by the over-riding respiratory inhibition governed by the swallow. (Bamford et al., 1992; Cichero, 2006; Koenig et al., 1990; Lau, Smith, & Schanler, 2003; O. Mathew, 1991; O. P. Mathew, 1988; Shivpuri et al., 1983) In order for the infant to continue to meet metabolic demands during this period of respiratory restriction they must rapidly adapt their respiratory pattern to optimize ventilation around changing rates of bolus flow. Reduced respiratory allowance between swallows necessitates the infant's imposition of a mechanical adaptation to respiratory pattern that reduces respiratory volume and rate.(Bamford et al., 1992; Shivpuri et al., 1983) In the same manner, the infant must capitalize on periods of unrestricted respiratory allowance during suck-burst breaks by resuming resting respiratory volume and rate.(Bamford et al., 1992; Shivpuri et al., 1983) The ability of the infant to make these mechanical adaptations to respiratory pattern are critical not only to their ability to meet oxygenation requirements during bottle-feeding, but also to their ability to maximize efficiency in respiratory-swallow coordination for the obtainment of nutritional needs.

Respiratory-Swallow Phase Patterning

Coordinative control of the manner in which respiration and swallowing interact is also believed to be of importance to the fulfillment of nutritional and respiratory requirements. This control is termed respiratory-swallow phase patterning. The adult respiratory-swallow phase pattern is characterized by a highly stable expiration, swallow, expiration (E-SW-E) pattern that occurs at mid-to-low lung volume.(Charbonneau, Lund, & McFarland, 2005; Hirst, Ford, Gibson, & Wilson, 2002; Hiss, Treole, & Stuart, 2001; Hiss, Strauss, Treole, Stuart, & Boutilier, 2003; Jobin et al., 2007; Kijima, Isono, & Nishino, 1999; B. J. Martin, Logemann, Shaker, & Dodds, 1994; B. J. W. Martin, 1991; Martin-Harris, Brodsky, Price, Michel, & Walters, 2003; Martin-Harris et al., 2005; Martin-Harris et al., 2005; McFarland & Lund, 1993; McFarland & Lund, 1995; Nishino, Yonezawa, & Honda, 1985; Nixon, Charbonneau, Kermack, Brouillette, & McFarland, 2008; J. B. Palmer & Hiiemae, 2003; Paydarfar, Gilbert, Poppel, & Nassab, 1995a; Perlman, He, Barkmeier, & Van Leer, 2005; Preiksaitis, Mayrand, Robins, & Diamant, 1992; Preiksaitis & Mills, 1996; Smith, Wolkove, Colacone, & Kreisman, 1989) This pattern has been linked to important mechanical advantages that enhance airway protection and bolus clearance.(B. J. Martin et al., 1994; B. J. W. Martin, 1991a; McFarland, Lund, & Gagner, 1994) One mechanical advantage of the E-SW-E pattern is the elimination of diaphragmatic contraction. In the adult, the downward traction placed on the larynx and esophagus during inspiration and the early periods of expiration(Andrew, 1955; Mitchinson & Yoffey, 1947) is believed to interfere with the opposing superior laryngeal and esophageal movements required for laryngeal closure, PES opening, and esophageal clearance.(Edmundowicz & Clouse, 1991; McFarland et al., 1994; Winans, 1972) Swallowing when the diaphragm is relaxed at mid to late expiration(Agostoni & Mead, 1964) eliminates inferior laryngeal and esophageal traction, thereby facilitating superior laryngeal displacement with the least amount of resistance.(McFarland et al., 1994) A second advantage of the E-SW-E pattern is its provision of airway protection by means of glottic closure.(B. J. Martin et al., 1994; B. J. W. Martin, 1991) In contrast to the adducted inspiratory vocal fold posture, the expiratory paramedian vocal fold posture minimizes the amount of movement required to obtain complete adduction during the swallow.(B. J. W. Martin, 1991; B. J. W. Martin et al., 1994; Murakami & Kircherner, 1972; Murakami & Kirchner, 1972)

Dominance of the mechanically advantageous E-SW-E respiratory-swallow phase relationship that has been observed in the adult mechanism has not been found to translate to the infant. (Bamford et al., 1992; I. H. Gewolb & Vice, 2006; Kelly et al., 2007; Koenig et al., 1990; Lau et al., 2003; Selley, Ellis, Flack, & Brooks, 1990) Past investigations of infant respiratory-phase relationships have indicated the phase of respiration that infants swallow is highly variable, with no clear dominant pattern. This body of literature suggest that although infants swallow with variability in the phase of respiration preceding the swallow, the phase of respiration following the swallow is less variable, and is instead characterized by a post-swallow expiration (SW-E) that increases in predominance with increasing postmenstrual age (PMA). Unfortunately, agreement on the other commonly observed respiratory-swallow phase relationships is much less consistent across investigations, leading many to question the validity of these findings due to the presence of methodological limitations, and the heterogeneity in population characteristics and methods across investigations.

One methodological limitation in previous investigations of respiratory-swallow coordination is the use of poorly validated measures of respiration and swallowing. Extraneous noise within signals obtained by hyoid drum, laryngeal microphone, and submental electromyography contribute to poor validity within these assessment methods for swallow detection.(Wilson, Thach, Brouillette, & Abu-Osba, 1981) Similar limitations exist in the previously utilized methods of respiratory assessment. Isolated measure of nasal airflow for respiratory-phase detection also have poor validity due to the susceptibility to airflow artifact created from oropharyngeal muscular contraction during the swallow(Brodsky, McFarland, Michel, Orr, & Martin-Harris, 2012; Feroah, Forster, & Fuentes, 2002; Hirst et al., 2002; B. J. Martin, Logemann, Shaker, & Dodds, 1994; B. J. W. Martin, 1991a; Martin-Harris et al., 2003; Martin-Harris et al., 2005; McConnel et al., 1998; Paydarfar, Gilbert, Poppel, & Nassab, 1995; Perlman, Ettema, & Barkmeier, 2000; Sokol, Heitmann, Wolf, & Cohen, 1966) and the inability to assess true respiratory effort. Previously utilized methods of respiratory effort also have their limitations. The isolated assessment of respiratory effort without synchronized measure of nasal airflow does not detect obstructed breaths in which no airflow occurs despite thoracic movement. Although the combined use of these respiratory measures eliminates this obstacle, the failure of past investigations to measure both planes of respiratory mechanics (ribcage expansion and abdominal distention) has impeded their ability to validly differentiate central cessation of respiratory effort from mechanically imposed reductions in respiratory mechanics resulting from neonatal ribcage compliancy.

The presence of uncontrolled extraneous variables that are known to impact infant feeding performance may be another source of the appreciated inconsistency within and across investigations. Rapid maturation of neonatal cardiopulmonary, oropharyngeal, and neurologic structures and networks likely contribute to alterations in respiratory-swallow phase relationships throughout the first days, weeks, and months of life. The potential impact of structural development on respiratory-swallow phase relationships is supported by findings of increased stability of respiratory-swallow phase patterns that occur during major developmental changes such as hyolaryngeal descent at 9 months of age. (Kelly et al., 2007; Lieberman, McCarthy, Hiiemae, & Palmer, 2001) As a result of these changes, the comparison of respiratory-swallow phase relationships across infants of differing PMA may contribute to variability in observations of respiratory-swallow phase relationships that are a reflection of varying levels of systemic development instead of true variability innate to the task. Additional sources of heterogeneity within and across study designs include the lack of uniformity within other variables that are influential to feeding performance such as milk flow rate and body position. Further discussion of how these variables influence feeding performance is discussed in *Section II: Interventions to Enhance Preterm Feeding Deficits*.

Lastly, differing methods of signal analysis may also contribute to the inconsistency in findings across investigations. Thresholds used for categorization of respiratory cessation across investigations range between .15 seconds and 2 seconds, and thresholds for inspiratory/expiratory breath detection have rarely been identified. The ability to compare study results is further complicated by differences in the duration and sequencing of signal analysis due to the known changes in respiration, sucking, and swallowing rates throughout a feed. Future, controlled investigations using validated measures of respiratory assessment and analysis are needed to truly understand the respiratory-swallow coupling within the bottle-fed infant. *Table 2.2* provides a detailed description of the methodological features of respiratory-swallow phase relationship studies and their associated findings.

Table 2.2. Characteristics of Investigations within Infant Respiratory-Swallow Phase Relationships

Author	Year	Subject Age	Respiration Measure	Swallow Measure	Feeding System	Feeding Position	Segment Analyzed	Respiratory Thresholds	Pattern
Gewolb	2006	1-4 days; 1 month	•Chest Strain Gauge	Pharyngeal Pressure Transducer	Standard Bottle	Not Indicated	Up to 20 Minutes	Inspiraiton/Expiration •Not Indicated Respiratory Cessation •≥ 2 seconds	•I-SW-E 39% •E-SW-I 32% •E-SW-E 17% •I-SW-I 11% •% I-SW-E increased and % E-SW-I decreased over time.
Selley	1990	8 hrs-6 days	•Nasal Anemometer •Pressure Transducer	Laryngeal Microphone	Zero Hydrostatic Pressure	Not Indicated	First 20mL of intake	Inspiraiton/Expiration •Not Indicated Respiratory Cessation •Not Indicated	•I-SW-E 79% •E-SW-E 15% •E-SW-I 5% **Percent babies with "predominate" pattern* •SW-E 83%
								Inspiraiton/Expiration •≥ 20% of resting	•I-SW-E 24% •E-SW-I 18% •C-SW-C 15% •E-SW-E 14% **Percent Swallows* •I-SW 36% •E-SW 39% •SW-I 26% •SW-E 43%
Bamford	1992	14 hrs-40 hrs	•Mercury-in-Rubber Chest Strain Gauge •Nasal Thermistor	Pharyngeal Pressure Transducer	Not Indicated	Not Indicated	Not Indicated	Respiratory Cessation •≥.15 seconds	•No correlation with age

***Table 2.2.** Continued*

Kelly	2007	48hrs Week 1, 2, 3 Month 1, 2, 3, 6, 9, 12	•Nasal Airflowmeter	Submental EMG Laryngeal Microphone	Bottle and Breastfed	Supine if possible; stated at 9 months not as successful to maintain	Not Inidcated	Inspiraiton/Expiration •Not Indicated Respiratory Cessation •≥ 2 seconds	•I-SW-E 35% •E-SW-I 16% •C-SW-C 6% •E-SW-E 30% •I-SW-I 13% •SW-E 65% •Primary change was E-SW-E dominance at 48 hrs to I-SW-E at 12 mths •% I-SW-E increased between 9-12 mths •% E-SW-E decreased between 48hrs and 1 week •No difference between bottle and breast resp-swallow phase
Lau	2003	0-1 weeks; 2-4 weeks	•Drum at Thoracic-Abdominal Junction	•Hyoid Drum	Caregiver Determined Nipple; Zero Hydrostatic Pressure Bottle	Not Stated	Average of 2 sucking bursts during the first and last 2 minuts of the feed	Inspiraiton/Expiration •Not Indicated Respiratory Cessation •≥ 2 seconds	•C-SW-C 37% •E-SW-I 36% •I-SW-E 14% •I-SW-I 9% •E-SW-E 4% •Over time decrease in C-SW-C (13%) and increase in I-SW-E (27%) and I-SW-I (19%)

SECTION II

FEEDING DEFICITS IN THE PRETERM INFANT: IMPAIRMENT IN STRUCTURE AND FUNCTION

Neuro-Structural Deficits within the Preterm Feeding Systems

Neurogenesis of the Feeding Systems

Premature birth is defined as delivery prior to 37 weeks gestation.(Behrman & Butler, 2007) Although neuro-structural development enables viability as early as 23 weeks gestational age (GA),(Breborowicz, 2001) the underdevelopment of these networks and structures precludes successful oral intake. Correlates of oral feeding impairment in the preterm infant are multifaceted. Underdevelopment of the systems controlling the coordination of sucking, swallowing, and respiration, as well as those controlling self-regulation and arousal serve as barriers to the obtainment of oral intake milestones.(Als, Butlet, Kosta, & McAnulty, 2005; M. A. Hassan, Lund, Howard, & Sacker, 2007; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Liang, Co, Zhang, Pineda, & Chen, 1998; Mirmiran, Maas, & Ariagno, 2003; Mouradian, Als, & Coster, 2000) Acquired pulmonary, gastrointestinal, and neurologic pathologies that stem from preterm entry into the ex-utero environment further inhibit the achievement of this seemingly basic function.(Bancalari, Claure, & Sosenko, 2003; Verma, 1995; Volpe, 1998) The culmination of these pathologies causes feeding impairments that are marked by reductions in the quality and quantity of milk transfer.(Bu'Lock et al., 1990; Colley & Creamer, 1958; I. Gewolb et al., 2001; I. H. Gewolb & Vice, 2006; Lau et al., 2000; Lau & Schanler, 2000; Lau et al., 2003; Lau et al., 1997; Lau & Kusnierczyk, 2001; Mizuno & Ueda, 2003)

Neurogenesis is the process by which the fetal brain is populated with functioning neurons through the division of precursor cells.(Bessa, Almeida, & Sousa, 2010) Neurogenesis of the structures critical for bottle-feeding initiates 3 weeks after fertilization with the generation of the embryologic neural tube.(F. H. Gilles, Leviton, & Dooling, 1983; Joseph, 2000; Sidman & Rakic, 1982) Differentiation of this tube into the primary cortical and subcortical structures follows a caudal-rostral developmental pattern in which the brain structures required for primitive vital functions, including the brainstem and cerebellum, are first developed, with subsequent development of those cerebral structures for accessory functions of limbic and cognitive control. (Darnall et al., 2006; Debakan, 1970; Joseph, 2000; Kinney, Brody, Kloman, & et al., 1988) The resulting early development of the medulla and the pons is critical to swallowing function, as these structures are the neurologic origins for both respiration and swallowing. The medulla is the first of these structures to develop and occurs at the most rapid rate.(Joseph, 2000) By 13 weeks gestation primary medullary structures have been established, and pontine development has initiated.(Darnall et al., 2006) Early generation of these brainstem structures is linked to early presentation of respiratory, sucking, and swallowing patterns between 10-13 weeks gestation. (Bu'Lock et al., 1990; Derkay & Schechter, 1998; deVries, Visser, & Prechtl, 1985; Joseph, 2000; Nijhuis, 2003) These early movement patterns are not representative of the mature patterns necessary for successful bottle-feeding and serve no role in fetal nutrition or oxygenation. They do, however, serve critical roles in the regulation of amniotic fluid levels, recirculation of amniotic solutes, and the maturation of the gastrointestinal tract.(Bu'Lock et al., 1990;

Delaney & Arvedson, 2008) Fetal respiratory and swallow movement patterns have also been identified to serve as a possible source of respiratory muscular strengthening, organ development, and neurologic development.(Jansen & Chernick, 1991)

At the time of viability the primary cerebral structures necessary for bottle-feeding have been formed yet they lack the differentiation and myelination required for normal function.(F. Gilles, 2011) The development of these cerebral structures over the remaining 17 weeks of development is critical to the fluency of the oral intake system. Fetal brainstem proliferation contributes to significant growth in brainstem length and volume that is accompanied by equally rapid growth of the cerebral cortex.(Darnall et al., 2006) Between 14 and 27 weeks gestation the fetal cortex increases 4-fold in volume and 2-fold in area.(Zhan et al., 2013) This growth is largely attributed to the maturation of the corpus callosum that results in frontal and parietal lobe expansion, as well as significant sulcation, gyration, and myelination.(Zhan et al., 2013; Clouchoux et al., 2012; F. Gilles, 2011) Development of these structures follows a nonlinear trajectory where an interplay of generation and degeneration of neural networks occurs as the cortical and subcortical structures become a refined, integrated system.(Darnall et al., 2006) Recent literature suggests, however, that early introduction to the ex-utero environment may stifle both of these processes, causing deficits in gross neurologic control.(Haldipur et al., 2011; Limperopoulos et al., 1999; Volpe, 2009; Forslund & Bjerre, 1983; P. G. Palmer, Dubowitz, Verghote, & Dubowitz, 1982; Pineda et al., 2013) Evidence of this alteration includes reductions in size and function of the preterm cerebral structures at term gestation.(Haldipur et al., 2011; Limperopoulos et al., 1999; Volpe, 2009; Forslund &

Bjerre, 1983; P. G. Palmer et al., 1982; Pineda et al., 2013) As a result, although ex-utero neurogenesis in the preterm infant follows a similar neurodevelopmental trajectory to that of the infant in-utero, it is a trajectory of significantly reduced rate and precision. (Haldipur et al., 2011; Limperopoulos et al., 1999; Volpe, 2009; Forslund & Bjerre, 1983; P. G. Palmer et al., 1982; Pineda et al., 2013)

Manifestation of Preterm Neurologic and Structural Underdevelopment

Incomplete neurogenesis upon entry of the preterm infant into the ex-utero environment, as well as the associated acquired cerebral injury that often ensues both contribute to impairment in the preterm infant's neuroregulation of autonomic functions that are critical for bottle-feeding success.(Als et al., 2005; B. B. Hassan et al., 2002; Holditch-Davis et al., 2004; Mouradian et al., 2000; Pineda et al., 2013; Volpe, 1998) One manifestation of autonomic dysfunction in the preterm infant is impairment in self-regulatory function. Self-regulatory deficits inhibit the preterm infant's ability to selectively attend to environmental stimuli; causing cardiopulmonary instability that is characterized by abrupt fluctuations in heart rate, respiratory rate, blood pressure, and oxygen saturation in the presence of subtle auditory, visual, and tactile stimulation. (Bowden, Greenber, & Donaldson, 2000; Bremmer, Byers, & Kiehl, 2003; Philbin & Klass, 2000) Impairment in self-regulation not only delays the initiation of oral intake due to baseline instability, but it also may add an increasing level of complexity to bottle-feeding once it is initiated by dividing the limited neuromotor resources between the co-occurring demands of self-regulatory control and suck, swallow breath coordination. Fluctuations in cardiopulmonary stability also originate from deficits in preterm level of arousal.(Holditch-Davis et al., 2004; Stefanski et al., 1984) The preterm infant exhibits elevated periods of active sleep and reduced periods of alertness.(Holditch-Davis et al., 2004; Mouradian et al., 2000; P. G. Palmer et al., 1982) Past investigations have found these states to correspond to reductions in cardiovascular, respiratory, and gastrointestinal function that can both interfere with feeding performance and the availability of alert periods during which oral intake must occur.(Holditch-Davis et al., 2004; McCain, 1997; McGrath & Medoff-Cooper, 2002; Mouradian et al., 2000; P. G. Palmer et al., 1982; Pickler, Best, Reyna, Wetzel, & Gutcher, 2005; Stefanski et al., 1984)

Of particular detriment to successful oral intake in the preterm infant are the deficits in respiratory performance that stem from altered neuroregulation of the respiratory control system. Blunting of pulmonary stretch receptors, upper airway neuromotor feedback loops, and arterial and cerebral chemoreceptors all give way to impairment in respiratory rhythmicity and adaptability. These deficits are exacerbated by immaturity of the surrounding respiratory structures. The preterm respiratory system is one of pulmonary hyperperfusion, elevated ribcage compliance, reduced lung alveoli, reduced type I diaphragmatic muscle fibers, and reduced levels of oxygen retaining surfactant.(Burri, 1984; Gaultier, 1995; Strang, 1977; Verma, 1995) These characteristics not only inhibit optimal respiratory mechanics, but they also inhibit pulmonary gas exchange by predisposing the preterm lung to air-space collapse and pulmonary fibrosis. (Bancalari et al., 2003b; Gaultier, 1995). (See *Table 2.3 Pathogenesis of Preterm Acquired Cerebral and Pulmonary Pathology*.) Manifestations of these impairments include periodic episodes of respiratory cessation, paradoxical respiratory movement, and changes in lung volume and respiratory rate during resting respiration.(Verma, 1995) Deficits in the neuro-structural control of respiration pose even greater barriers to the preterm infant's ability to execute respiration under the increasingly complex demands of bottle-feeding: demands that require the rapid initiation of brief, forceful respiratory movements that enable maximal gas exchange around periods of obligate respiratory inhibition. Disconnect between preterm respiratory capacities and bottle-feeding physiology is widened by elevated rates of preterm respiration that necessitate greater refinement in respiratory-swallow control. The cumulative impairment resulting from immaturity within the preterm infant's neurologic and respiratory systems contributes to a characteristic feeding impairment unique to the preterm infant.

Table 2.3. Pathogenesis of Preterm Acquired Cerebral and Pulmonary Pathology

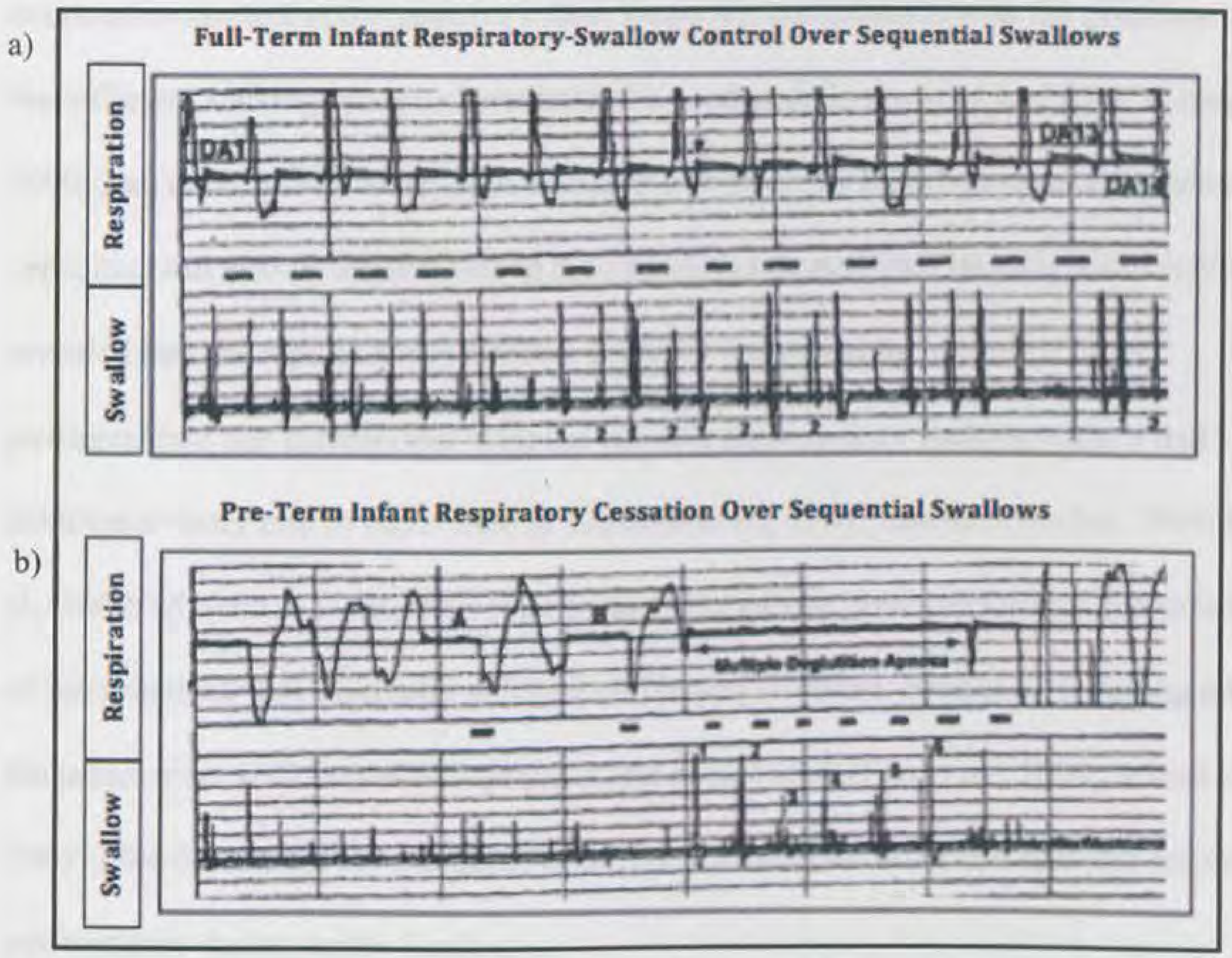
Acquired Pulmonary Injury			
Type	Pathogenesis	Pathology	Presentation
Respiratory distress syndrome (RDS) (Verma, 1995)	Birth prior to 37 weeks GA requires the infant to breathe using an immature respiratory system characterized by reduced central respiratory control, pulmonary hyperperfusion, high chest wall compliance, reduced amounts of surfactant, and less alveolar surface area. Respiration using this immature system causes changes in anatomy of the respiratory structures.	Anatomic changes within the respiratory system including alveolar atelectasis, alveolar distention, pulmonary edema, disrupted or engorged pulmonary capillaries, edematous lymphatic and interstitial spaces, and hyaline membrane fibrosis.	Respiratory distress and cyanosis at birth characterized by tachypnea, retractions, expiratory grunting. Progression of this disease during the postnatal period varies. Mild cases may regain full respiratory function with development, while more severe cases result in prolonged mechanical respiratory support or death as a result of respiratory failure.
Bronchopulmonary dysplasia (BPD) (Bancalari, Claure, & Sosenko, 2003a; Coalson, 2006)	Birth prior to 32 weeks GA results in a disruption in saccular stage alveolar growth due to: ▪ Respiration using the immature respiratory system *(see above)* ▪ Respiratory interventions required for preterm survival (oxygen and mechanical ventilation) ▪ Prenatal and postnatal infection	Disruption in the growth of preterm alveoli resulting in epithelial lesions, smooth muscle hyperplasia, alveolar over-inflation and atelectasis, fibrosis, large simplified air spaces with reduced alveoli, and dysmorphic capillary configuration.	Respiratory distress characterized by tachypnea, retraction, and expiratory grunting persisting beyond the early postnatal period. Mild: Requirement of supplemental oxygen for ≥ 28 postnatal days but < 36 weeks PMA Moderate: Requirement of supplemental oxygen for ≥ 28 postnatal days and the requirement of ≤30% oxygen at ≥36 weeks PMA Severe: Requirement of supplemental oxygen for ≥ 28 postnatal days and the requirement of >30% oxygen/ventilation at ≥36 weeks PMA

Table 2.3. *Continued*

Acquired Cerebral Injury			
Type	Pathogenesis	Pathology	Presentation
Germinal Matrix/ Intraventricular/ Periventricular Hemorrhage (GMH/IVH/PVH-IVH)(Papile, Burstein, Burstein, & Koffler, 1978; Volpe, 1998b)	Prior to 30 weeks GA the germinal matrix is of heightened vascularization due to the high rates of neural proliferation. These vessels are thin-walled, and susceptible to rupture with sudden changes in perfusion pressures associated with preterm hemodynamic instability.	Venous rupture within the germinal matrix with or without subsequent rupture and infarction within the lateral ventricles, terminal, and medullary veins respectively. Grade I: Hemorrhage confined to germinal matrix Grade II: Extension to ventricles without dilation Grade III: Extension to ventricles with dilation Grade IV/PVH-IVH: Extension to ventricles with rupture and hemorrhage of surrounding white matter	Variable neurologic presentation depending on severity of hemorrhage. Low grade GMH/IVH may be asymptomatic whereas high-grade lesions may contribute to profound neurologic impairment including spastic hemiparesis and intellectual deficits.
Periventricular Leukomalacia (PVL)(Volpe, 1998b)	Birth prior to 32 weeks GA causes infant susceptibility to impairments that contribute to PVL. Incomplete periventricular vascularization leads to watershed areas highly susceptible to ischemia caused by preterm hemodynamic instability and IVH. Consequences are exacerbated by the higher proportion of early differentiating oligodendrocytes, which are of increased susceptibility to cell death, within the preterm infant's white matter.	Necrosis of cerebral white matter dorsal and lateral to the external angles of the lateral ventricles	Often associated with long-term neuromotor impairment that varies by the extent of the damage. Mild cases may be isolated in impairment to spastic dysplasia of the lower extremities, while more severe cases contribute to diffuse cognitive and physical impairment.
Verma, R. (1995). *Respiratory distress syndrome of the newborn infant. Obstetrical & Gynecological Survey, 50(7), 542-555.* ***Bancalari, E., Claure, N., & Sosenko, I. (2003).*** *Bronchopulmonary dysplasia: Changes in pathogenesis, epidemiology, and definition. Seminars in Neonatology, 8, 63-71.* ***Coalson, J. J. (2006).*** *Pathology of bronchopulmonary dysplasia. Seminars in Perinatology, 30, 179-184.* ***Papile, L. A., Burstein, J., Burstein, R., & Koffler, H. (1978).*** *Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with* birthweights less than 1500 g. *J Pediatr, 92,* 529-534.			

Characteristics of Impairment in Preterm Feeding Performance

Preterm feeding impairment stemming from the aforementioned neuro-structural immaturity is characterized by a primary deficit in respiratory-swallow coordination that likely induces subsequent deficits in sucking physiology, cardiopulmonary stability, feeding endurance, and the obtainment of nutritional needs.(Hanlon et al., 1997; Lau & Schanler, 1996; Lau & Schanler, 2000; Lau et al., 1997; O. Mathew, 1991; O. P. Mathew, 1988) Past investigations have revealed that neuro-structural immaturity of the preterm respiratory system contributes to a reduced ability to rapidly resume respiratory efforts upon completion of the pharyngeal swallow. Hanlon et al. (1997) found preterm infants to have significantly longer periods of respiratory inhibition in single swallows (760ms) when compared to term infants (672 ms).(Hanlon et al., 1997) As the sequential swallow pattern of bottle-feeding requires the infant to interpose respiration in the brief period of time between swallows, the prolongation of respiratory inhibition following the swallow may reduce the infant's ability to obtain adequate lung volume prior to initiating the next episode of respiratory inhibition for the subsequent swallow. The result is a sequence of swallows that are both preceded and followed by respiratory cessation (C-SW-C) (see *Figure 2.2 Comparison of Term and Preterm Respiratory-Swallow Control*)(I. Gewolb et al., 2001; Hanlon et al., 1997; Lau & Schanler, 1996; Lau et al., 2000; Lau et al., 1997; O. Mathew, 1991; O. P. Mathew, 1988) Preterm infants exhibit a greater proportion and longer duration of swallows preceded and followed by respiratory cessation than full-term infants. As such, their feeding respiratory-swallow pattern is characterized by suck-bursts with arrhythmic, low volume respirations that are followed by infant or caregiver imposed suck-burst breaks. It is during the suck-burst breaks that the infant meets its primary metabolic demands through the use of elevated respiratory rates and lung volumes to compensate for the drastic reduction in ventilation that occurred during the suck-burst.(Law-Morstatt, Judd, Snyder, Baier, & Dhanireddy, 2003)



a) Full-Term Infant Respiratory-Swallow Control Over Sequential Swallows

b) Pre-Term Infant Respiratory Cessation Over Sequential Swallows

Figure 2.2. Comparison of Term and Preterm Respiratory-Swallow Control **a)** full-term respiratory-swallow coordination; **b)** pre-term respiratory swallow coordination. Top channel representing respiration and the bottom channel representing swallows. Hanlon, M. B., Tripp, J. H., Ellis, R. E., Flack, F. C., Selley, W. G., & Shoesmith, H. J. (1997). Deglutition apnoea as indicator of maturation of suckle feeding in bottle-fed preterm infants. *Developmental Medicine & Child Neurology, 39*, 534-542.

The reduced capacity of the preterm infant to rapidly shift between respiration and swallowing is reflected in what is hypothesized to be a compensatory alteration in sucking physiology. As discussed in *Section I,* the healthy term infant utilizes a highly efficient sucking pattern composed of rhythmic alterations in oral suction and nipple compression to obtain maximum rates of bolus flow.(Ardran et al., 1958; Balint, 1948;

Colley & Creamer, 1958; Darwin, 1971; Lau & Schanler, 1996; Sameroff, 1968) This necessitates refined neuromotor control to accommodate the corresponding elevation in rate that the infant must shift between respiration and swallowing. Absence of this neuromotor control in the preterm infant, however, corresponds with the presence of a less efficient sucking pattern characterized by reduced rhythmicity and force.(Lau et al., 2000; Lau et al., 1997) Adaptation of sucking physiology based on respiratory-swallow capacities can also be appreciated in the opposing manner. Past investigations have revealed that the enhanced neuromotor integrity possessed by infants of higher postmenstrual age corresponds with the use of a more mature sucking pattern that achieves a faster rate of bolus flow.(I. Gewolb et al., 2001; Lau & Schanler, 1996; Lau et al., 2000; Mizuno & Ueda, 2003)The same effect can be obtained through the provision of interventions that externally enhance respiratory-swallow control by reducing rate that the infant must shift between respiration and swallowing.(Lau et al., 2000; Scheel et al., 2005).(See *Section III* for a detailed description of interventions that enhance respiratory performance during bottle-feeding.)

Despite the preterm infant's ability to adapt their sucking physiology to reduce the rate of milk flow, they are unable to do so with enough precision to obtain a milk flow rate that enables adequate ventilation between swallows. This contributes to significant reductions in tidal volume, minute volume, respiratory rate, oxygen saturation, and heart rate.(I. Gewolb et al., 2001; Hanlon et al., 1997; Lau & Schanler, 1996; Lau & Schanler, 2000; Lau et al., 1997; O. Mathew, 1991; Shivpuri et al., 1983). Cardiopulmonary instability, however, is not solely attributed to decreased ventilation stemming from prolonged periods of respiratory cessation. Respiratory-swallow discoordination may also contribute to a reduction in spatiotemporal precision between respiratory inhibition, laryngeal closure, and bolus transport that further predisposes the infant to cardiopulmonary instability as a result of laryngeal penetration and tracheal aspiration. (S. Barlow, 2009) This is both detrimental to the infant's developing pulmonary structures and to their cardiopulmonary stability as it can elicit a heightened preterm chemoreflex characterized by prolonged respiratory cessation, laryngeal constriction, hypertension, and bradycardia.(Davies, Koenig, & Thach, 1988; Thach, 2001)

Alterations to the preterm infant's sucking physiology and cardiopulmonary stability that stem from their impairment in respiratory-swallow coordination appear to also contribute to a common functional limitation in the preterm infant's ability to meet nutritional needs by mouth. The reduction in bolus flow that is achieved by the infant's alterations in sucking physiology causes a reduced rate of milk transfer that may be inadequate for consumption of the necessary volume of milk during the preterm infant's brief periods of sustained arousal.(Lau et al., 2000; Lau et al., 1997) Similar outcomes may exist as a result of the infant's abrupt alternations in periods of heightened cardiopulmonary demand followed by periods of cardiopulmonary recovery. In contrast to the controlled level of hypoventilation that can be sustained throughout a feed by the term infant, the abrupt fluctuations in ventilation observed within the preterm infant may be unsustainable throughout an entire feed, contributing to a rapid decline in arousal as the feed progresses.

Acknowledging these two etiologies that contribute to the preterm infant's inability to meet nutritional needs by mouth, Lau and Smith (2011) established a clinical tool titled the Oral Feeding Skills (OFS) to objectively identify the source of the preterm infant's primary feeding impairment.(Lau & Smith, 2011) Through simple measurements of proficiency (volume consumed during the first 5 minutes of the feed/total volume prescribed) and rate of milk transfer (total milk consumed/total duration of oral feeding), the OFS separates deficits into those of efficiency of milk transfer, potentially caused by immature sucking kinematics, from deficits in endurance for sustained feeding performance, potentially caused by elevated cardiopulmonary demands.(Lau & Smith, 2011). (See *Figure 2.3 Oral Feeding Skills* for a schematic of the OFS scale.) Despite its validation as a method for categorizing and tracking the nature of impairment against objective measures of sucking physiology and feeding outcomes, the OFS has never been validated as a measure of respiratory-swallow performance.(Lau & Schanler, 2000; Lau & Smith, 2011) Future studies directly investigating the correlation between efficiency and proficiency of milk transfer, sucking physiology, and respiratory-swallow function are needed to better define the true interdependence between these physiologic processes and functional measures.

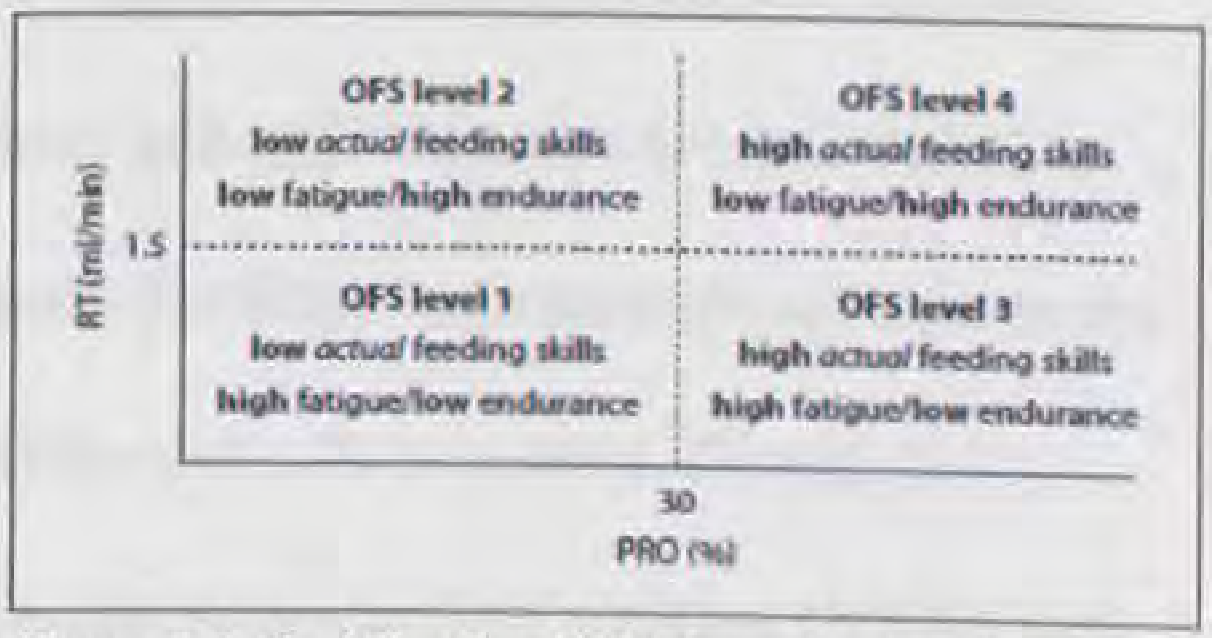


Figure 2.3. Oral Feeding Skills Lau, C., & Smith, E. (2011). A novel approach to assess oral feeding skills of preterm infants. *Neonatology*. 64-64-70.

SECTION III

INTERVENTIONS TO IMPROVE PRETERM FEEDING DEFICITS

Preterm feeding performance can be improved by interventions that target neuromotor development and by those that compensate for the presenting physiologic deficit. Theoretical foundation for interventions that target neuromotor development lies in their ability to stimulate extrauterine neurogenesis. The compensatory approach to the treatment of preterm feeding deficits emphasizes the reduction of bottle-feeding demands to meet the infant's current physiologic capacities. Combined use of these techniques in clinical practice facilitates maximum short-term yield through physiologic compensation while gradually gaining functional independence via neuromotor enhancement.

Treatments to Expedite Neuromotor Development

Interventions that expedite neuromotor development can be categorized into those that indirectly or directly improve respiratory-swallow coordination. Indirect interventions facilitate neurogenesis within the cortical structures and pathways that are influential to bottle-feeding success. In contrast, direct treatments facilitate neurogenesis specific to the cortical pathways and structures governing respiratory-swallow control. Direct interventions including skin-to-skin contact, massage, non-nutritive sucking (NNS), and auditory/visual stimulation, have been found to be successful in expediting the rate of extrauterine maturation in the preterm infant.(S. Barlow, Finan, Lee, & Chu, 2008; Bernbaum, Gilberto, Pereira, Pckham, & Peckham, 1983; Case-Smith, 1988; De Curtis, McIntosh, Ventura, & Brooke, 1986; Dodd, 2005; Field et al., 1982; Fucile, Gisel, McFarland, & Lau, 2011; Gaebler & Hanzlik, 1996; Hill, 2005; Mendes & Procianoy, 2008; Sehgal, Prakash, Gupta, Mohan, & Anand, 1990; Standley, 2003; R. White-Traut et al., 2002; R. C. White-Traut et al., 2004) Functional outcomes of extrauterine maturation include improvement in self-regulation and arousal, which are through to facilitate subsequent improvements in sucking stage, feeding efficiency, and time to achieve oral intake milestones.(S. Barlow et al., 2008; Bernbaum et al., 1983; Case-Smith, 1988; Dodd, 2005; Fucile et al., 2011; Gaebler & Hanzlik, 1996; Hill, 2005; Mendes & Procianoy, 2008; Standley, 2003; R. White-Traut et al., 2002; R. C. White-Traut et al., 2004)

Less is known about the effectiveness of indirect interventions. Indirect interventions aim to simultaneously enhance strength, flexibility, and sensitivity of the oral motor structures. The primary type of indirect intervention, termed oral motor stimulation, includes the provision of gentle pressure and stretching of the lips, tongue, and cheeks.(J. Arvedson, Clark, Lazarus, Schooling, & Frymark, 2010; Case-Smith, 1988; Fucile et al., 2011; Gaebler & Hanzlik, 1996) While this approach has been shown to be beneficial when paired with non-nutritive sucking in the enhancement of gross neurologic maturation, (Fucile et al., 2011; Rocha, Moreira, Pimenta, Ramos, & Lucena, 2007) the evidence to support the effectiveness of this practice in isolation has been limited by the inability to obtain reproducible results across investigations.(Case-Smith, 1988; Gaebler & Hanzlik, 1996)

Interventions that directly target neurogenesis of the respiratory-swallow pathways have achieved greater efficacy and consistency of results. Early introduction of oral intake is the most effective method of improving preterm feeding performance due to the hypothesized elevation in respiratory-swallow training opportunities for which it provides. (Lau & Smith, 2012; Simpson, Schanler, & Lau, 2002) Although bottle-feeding has historically served as the primary method of this exposure,(Simpson et al., 2002) recent work by Lau et al. (2012) has identified the ability to achieve similar benefit by using a syringe to provide a single bolus to the infant's oral cavity. (Lau & Smith, 2012) The physiologic simplicity of this task in relation to bottle-feeding not only enables it to be initiated at an earlier postmenstrual age, but it also prevents cardiopulmonary compromise commonly appreciated during early bottle-feeding attempts. Early introduction of oral intake, whether by bottle or syringe, has been shown to provide greater enhancement to physiologic maturation and the obtainment of oral intake milestones than other intervention approaches.

Compensation for Neuro-Structural Insufficiency

Alteration to Caregiver Feeding Method: Effect of Infant Pacing and Positional Adaptations

A second approach used to improve preterm feeding performance is the use of compensatory feeding techniques that reduce bottle-feeding demands. Alteration to caregiver feeding technique through pacing and positioning are two ways in which this is achieved. Pacing is a method of facilitating cardiopulmonary stability during bottle-feeding through the periodic, external cessation of milk provision.(Law-Morstatt et al., 2003; J. B. Palmer, Kuhlemeier, Tippett, & Lynch, 1993) This serves to both reduce the duration of respiratory inhibition associated with sucking bursts, while simultaneously increasing the duration of respiratory recovery that is associated with sucking burst breaks.(Law-Morstatt et al., 2003; J. B. Palmer et al., 1993) Clinically this is achieved by systematically removing the nipple from the oral cavity to facilitate controlled periods of suck-bursts and suck-burst breaks that are each 3-5 seconds in duration. (Law-Morstatt et al., 2003; J. B. Palmer et al., 1993) Immediate benefits of this intervention to cardiopulmonary stability include the reduction in episodes of bradycardia and apnea. (Law-Morstatt et al., 2003; J. B. Palmer et al., 1993) Although pacing is a compensatory treatment approach, Law-Mostatt (2003) found that infants who received paced feeding had significantly higher NOMAS sucking stage scores at discharge than the infants who did not receive paced feeding during their hospital stay.(Law-Morstatt et al., 2003) These findings suggest that this compensatory intervention may also facilitate neurodevelopmental gains. Future investigations utilizing objective methods of assessing functional measures of feeding performance and associated physiologic correlates are necessary to further elucidate the specific mechanism by which feeding performance is improved.

Adaptation to infant feeding position is another compensatory method for the enhancement of respiratory-swallow coordination. There is currently limited literature examining the effectiveness of postural modifications on respiratory-swallow coordination, however there is an abundance of literature demonstrating the effectiveness of postural modification on resting respiratory and gastrointestinal function. Investigations of postural influence on resting respiratory function have identified the ability to enhance preterm respiratory function through the provision of head elevation and postural pronation.(Dimitriou et al., 2002; Heimler, Langlois, Hodel, Nelin, & Sasidharan, 1992; Kravitz, Elegant, & Block, 1958; R. J. Martin, Hernell, & Rubin, 1979; Wolfson, Greenspan, & Deoras, 1992). When compared to infants in the horizontal supine position, preterm in the elevated supine or prone horizontal position obtain greater lung compliance, tidal volume, respiratory rate, and thoracoabdominal synchrony, as well as reductions in energy expenditure and arterial oxygen tension.(Dimitriou et al., 2002; Heimler et al., 1992; Kravitz et al., 1958; R. J. Martin et al., 1979; Wolfson et al., 1992). These improvements in respiratory function are hypothesized to be the result of abdominal content displacement that facilitates improved respiratory mechanics. Specifically, the superior and anterior abdominal shift resulting from pronation and elevation is thought to stabilize the preterm infant's compliant chest wall during inspiration while also enabling the posterior, more efficient portion of the diaphragm to distend without opposition.(Dimitriou et al., 2002)

In addition to enhancing the mechanics of respiration, postural adaptations may also improve respiratory function through their effects on the gastrointestinal system. (Corvaglia et al., 2007) Gastroesophageal reflux (GER) and delayed gastric emptying are thought by some to stimulate episodes of apnea and recurrent desaturation in the preterm infant.(Dimitriou et al., 2002; North American Society for Pediatric Gastroenterology and Nutrition, 2001; Wilkinson & Yu, 1974) Modification of infant position is a commonly used intervention to facilitate gastrointestinal function. Preterm infants placed in left lateral position have fewer episodes of GER due to the gravitational displacement of gastric contents away from the esophagogastric junction.(Corvaglia et al., 2007; Ewer, Durbin, Morgan, & Booth, 1996; Omari et al., 2004; Tobin, McCloud, & Cameron, 1997) However, this posture also slows gastric emptying by simultaneously shifting gastric contents away from the pyloric inlet. Placement of the infant in right lateral position has the opposite effect in the reduction of GER, but serves to enhance rates of gastric emptying. (Cohen, Mandel, Mimouni, Solovkin, & Dollberg, 2004; Corvaglia et al., 2007) As the clinical presentation of delayed gastric emptying and GER are thought to cause equally significant impairment to the preterm respiratory system, neither left nor right lateral positions fully eliminate the symptoms that appear to inhibit feeding performance.(Ewer et al., 1996; Omari et al., 2004; Van den Plas & Sacre-Smiths, 1985)

The contribution of positioning to gastrointestinal function is not limited to the lateral plane. Studies show that head elevation and pronation may offer additional benefits to gastrointestinal function that lateral postures do not. Both pronation and head elevation of the preterm infant serve to enhance gastric emptying(Cohen et al., 2004; Dellagrammaticas, Kapetanakis, Papadimitriou, & Jourakis, 1991; Yu, 1975) and reduce GER(Corvaglia et al., 2007; Tobin et al., 1997) by displacing the gastric contents over the pyloric inlet while simultaneously maintaining gastric contents below the level of the esophagogastric junction.

To the author's knowledge there have only been two studies that have examined the effects of postural modifications on feeding performance.(Clark, Kennedy, Pring, & Hird, 2007; Lau & Smith, 2012) The results of these investigations have been mixed. Clark et al. (2007) observed a trend towards improved cardiopulmonary stability during the middle 3 minutes of a feed completed in elevated lateral position when compared to feeds completed in the elevated supine position. The observed trends did not reach statistical significance.(Clark et al., 2007) In contrast, work by Lau et al. (2012) did not support functional advantages of altered positions. No significant differences in measures of sucking maturation or obtainment of oral intake milestones were found between infants fed in the lateral, elevated supine, and upright postures.(Lau & Smith, 2012) The ability to interpret the effect of feeding position from these studies is limited by their failure to control for postural-induced changes in hydrostatic pressure that can independently alter preterm feeding performance.(Al-Sayed et al., 1994; Jain, Sivieri, Abassi, & Bhutani, 1987) Future studies examining both physiologic and functional bottle-feeding outcomes are necessary to determine the manner in which postural induced respiratory and gastrointestinal modifications benefit preterm feeding performance.

Alteration to Milk Flow Rate

Reduction in milk flow rate is one of the most widely used interventions to improve preterm feeding performance. In contrast to infant pacing, which maintains cardiopulmonary stability by allocating time for respiration following a chain of swallows, reduction in milk flow rate enhances the infant's ability to rhythmically coordinate respiration between each swallow by reducing the rate of swallowing. Although it has been shown that both term and preterm infants adapt sucking physiology to increase or decrease milk flow rate based on their respiratory-swallow capacities,(Al-Sayed et al., 1994; Colley & Creamer, 1958; Fadavi et al., 1997; Fucile et al., 2009; Lau & Schanler, 2000; Scheel et al., 2005; Schrank, Al-Sayed, Beahm, & Thach, 1998) the fluid dynamics of conventional bottle systems paired with the neurologic immaturity of the preterm infant inhibit the preterm infant from achieving adequate milk flow rate reductions. External modifications of the milk chamber(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) and nipple(Fadavi et al., 1997; O. Mathew, 1991; O. P. Mathew & Cowen, 1988; Scheel et al., 2005) within conventional bottle systems can reduce the rate of milk flow to a greater extent than what can be achieved by sucking adaptations alone. Reduced milk flow rates achieved by these methods results in improved sucking physiology, higher respiratory rate, elevated minute ventilation, shorter feeding times, more full oral feeds, and a higher rate of milk transfer.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000;Fadavi et al., 1997; O. Mathew, 1991; O. P. Mathew & Cowen, 1988; Scheel et al., 2005) The efficacy of this modification appears to be greatest in those infants with greatest impairment in respiratory-swallow coordination, including preterm infants during their early oral intake experiences and those infants born at very-low birth weights.(Scheel et al.,2005).

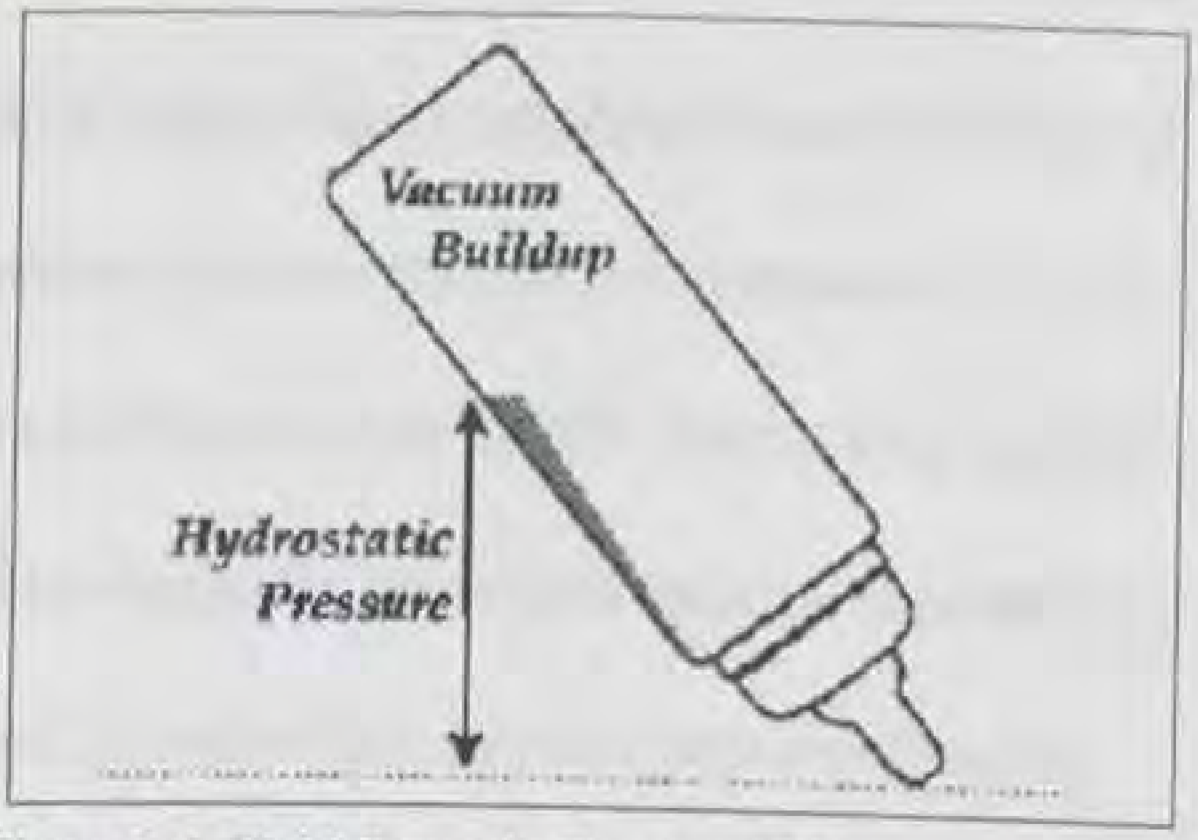


Figure 2.4. Fluid Dynamic Forces within Conventional Bottle Systems Lau, C., & Schanler, R. J. (2000). Oral feeding in premature infants: Advantages of a self-paced milk flow. *Acta Paediatr., 89*, 453-459.

One method of reducing the rate of milk flow is the modification of the bottle chamber. The goal of this modification is to establish a self-regulated rate of milk flow that is uninhibited by external forces.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) Milk flow rate in conventional bottle systems is largely influenced by both hydrostatic pressure and air pressure (see *Figure 2.4 Fluid Dynamic Forces within*

Conventional Bottle Systems).(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) Hydrostatic pressure producing milk flow is a result of the gravitational force acting on the liquid above the height of the nipple.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) The amount of hydrostatic pressure is directly related to liquid depth and density, and is therefore greatly influenced by milk volume and angle of bottle inversion. In a conventional bottle system, hydrostatic pressure results in a continuous milk flow in the absence of sucking as well as an elevated volume of milk flow in the presence of sucking.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) As liquid is drawn out of conventional bottle systems, the resulting negative air pressure within the bottle chamber opposes the action of hydrostatic pressure.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) Suck-swallow sequences without the release of the lingual/labial nipple seal contributes to a build-up of negative pressure within the closed bottle-chamber that can exceed the pressures generated by oral suction of the preterm infant.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) Counteracting this vacuum requires increased energy expenditure to achieve bolus flow and has been hypothesized to contribute to poor preterm feeding endurance.(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) Eliminating the effects of both hydrostatic pressure and negative air pressure allows for a "self-paced"(Al-Sayed et al., 1994; Fucile et al., 2009; Lau & Schanler, 2000) milk flow rate that is solely dependent on the force and frequency at which an infant sucks. Unfortunately, despite the widespread benefits achieved by the self-paced bottle system in the research arena, the failure to translate its prototype into a commercially available system has limited its clinical application.

Modification of the bottle nipple is another method of reducing milk flow. In contrast to the self-paced milk flow that is achieved by modifying the bottle chamber, the purpose of nipple modification is to externally reduce the rate of milk flow by adapting nipple properties. This is achieved by adjusting the nipple shape, pliability, and orifice size.(O. P. Mathew & Cowen, 1988; Scheel et al., 2005) Adjustments to these nipple parameters reduce both the volume of milk that can be expressed per suck and the rate of continuous milk flow that occurs as a result of hydrostatic pressure.

The ability to improve preterm feeding performance through adaptations to nipple orifice, the most widespread clinical method of milk flow rate reduction, is largely dependent on the method of modification. Mechanical drilling methods that have historically been used to create commercially available nipple orifices contribute to a highly variable milk flow rate within and across nipples.(O. P. Mathew & Cowen, 1988)This has limited the ability of previously investigated nipple units to consistently provide the desired rate of milk flow needed to enhance preterm feeding performance across feeds.(Fadavi et al., 1997; O. Mathew, 1991; P. Mathew, Belan, & Thoppil, 1992; Scheel et al., 2005) Demonstrated effectiveness of adaptations to the nipple orifice in the treatment of preterm feeding impairment has also been limited by previously available nipple orifice sizes. Early investigators viewed deficits in preterm sucking efficiency and bolus transfer to stem from weakness within the preterm orofacial structures that inhibited their ability to express sufficient milk from the nipple. As a result, the majority of past investigations have tested the ability to enhance preterm feeding performance through elevated milk flow rates provided with commercially available moderate-flow and previous labeled preterm fast-flow nipples.(Fadavi et al., 1997; O. Mathew, 1991; P. Mathew, Belan, & Thoppil, 1992; Scheel et al., 2005) While the fallacy of this theory is now well established (in large part due to findings from these investigations), these investigations served an integral role in initiating a shift toward what is now a widespread clinical method of enhancing preterm feeding performance: laser-cut slow-flow nipples. Custom made laser-cut slow-flow nipples have been found to be an effective and reliable method of consistently enhancing preterm respiratory function during bottle-feeding in the research arena,(O. Mathew, 1991) however the ability to achieve these outcomes in clinically available nipple units with varying orifice sizes has not been investigated. Likewise, there has been a paucity of investigations examining the impact of reduced milk flow rate on other critical functions of preterm feeding performance such as efficiency, proficiency, and overall transfer. Understanding the effect of laser-cut slow-flow nipples on preterm respiratory performance and proficiency of milk transfer is critical to optimizing the rehabilitation of feeding deficits within the preterm infant

CHAPTER 3: SIGNIFICANCE

Dysphagia in the Preterm Infant: Importance and Need for Treatments with Clinical Utility

Preterm births account for 1 in every 10 live births, affecting over 15 million infants each year. (Behrman & Butler, 2007; March of Dimes Perinatal Data Center, 2003) Advances in medical care have improved survival rates, yet equal advances have not occurred in the rehabilitation techniques needed to facilitate the safe and timely achievement of critical developmental milestones. Of these milestones, the preterm infant's inability to meet nutritional needs through the refined coordination between the processes of sucking, swallowing, and respiration, poses the greatest barrier to timely hospital discharge.(Lau et al., 2000; Simpson et al., 2002) Past investigations have identified the ability to improve this coordination through the provision of reduced milk flow rates in the laboratory setting,(Al-Sayed et al., 1994; Fadavi et al., 1997; Fucile et al., 2009; Lau & Schanler, 2000; O. Mathew, 1991; O. P. Mathew & Cowen, 1988; Scheel et al., 2005) yet none have examined the ability to achieve these outcomes using clinically available methods of milk flow rate reduction. The current investigation fills this gap in evidence by measuring the effect of slow-flow nipples on preterm feeding performance in the clinical setting.

Refinement of Respiratory Assessment: Enabling Differentiation of Central and Peripheral Origins of Respiratory Cessation

While the primary aim of this study is of high clinical relevance, it is not particularly novel. The innovative nature of this project is the opportunity it afforded the principal investigator to detail and validate respiratory signals that occur during feeding and remain understudied and poorly understood. A primary characteristic of preterm feeding impairment is the presence of prolonged periods of respiratory cessation during sequential swallows.(I. Gewolb et al., 2001; Hanlon et al., 1997; Lau & Schanler, 1996; Lau et al., 2000; Lau et al., 1997; O. Mathew, 1991; O. P. Mathew, 1988) Past investigations suggest that the preterm infant's failure to interject respiration between sequential swallows is related to disruption in the neurologic control of respiration. Methodological limitations used in past investigations, however, have hindered the ability to differentiate respiratory deficits of central origin from those attributable to peripheral airway obstruction or mechanical decoupling. Through the advanced physiologic analysis of simultaneous respiratory kinematics and airflow measures that were developed by our research team, we were able to explore and distinguish the underlying mechanisms of respiratory cessation, and quantify the effects of milk flow rate adjustments. An understanding of these underlying deficits is critical to the development of effective feeding interventions that will normalize respiratory-swallow patterns in the preterm infant.

CHAPTER 4: RESEARCH DESIGN AND METHODS

PARTICIPANTS

A convenience sample of 15 preterm infants from the Medical University of South Carolina Children's Hospital was recruited. The study was approved by the Institutional Review Board for Human Subjects. Informed consent was obtained for all study participants meeting inclusion and exclusion criteria.

Inclusion Criteria: Preterm infants were included in study participation if they 1) were born between 26 and 33 weeks gestation as determined by obstetrical ultrasound and clinical exam; 2) were appropriate size for gestational age at birth.

Exclusion Criteria: Preterm infants were excluded from study participation if they presented with 1) congenital anomalies including those specific to craniofacial or cardiac regions; 2) chronic medical conditions including but not limited to grade III or IV intraventricular hemorrhages, severe bronchopulmonary dysplasia, periventricular leukomalacia, or necrotizing enterocolitis; 3) prenatal drug exposure; or 4) supplemental oxygen requirements. Infants who were diagnosed with any of these excluding conditions, or those that required temporary cessation of enteral feeds for greater than 7 consecutive days following recruitment were removed from study participation and their data was not analyzed as part of the sample.

RECRUITMENT

All caregivers of patients meeting eligibility requirements (see *Participants*) were approached regarding their interest in study participation. All procedures, risks, and benefits of the proposed study were presented. Those caregivers expressing interest in study participation were consented as is consistent with the Institutional Review Board for Human Research at MUSC. To ensure feasibility of recruiting 15 subjects for the proposed study, our team conducted a site-specific descriptive analysis of infants meeting inclusion/exclusion criteria during pilot testing between January 2013 and February 2013. During this time, a total of 18 patients meeting eligibility criteria were identified within our neonatal nurseries. Caregivers of 8 eligible infants were approached regarding participation in pilot testing, of which 7 caregivers provided consent for participation. Given the ease of subject recruitment during pilot testing, the minimally invasive nature of this investigation, and the personal and global benefits to study participation, we did not anticipate, nor encounter difficulties in recruitment.

DATA COLLECTION

Consented infants underwent assessment of two oral feeds completed within 48 hours of each other. Feeding assessments initiated within 48 hours of the infant consuming 4 consecutive feeds of $\geq$15mL. One feed was completed with the Enfamil® standard-flow nipple (.014 inch orifice size), and one feed was completed with the Enfamil® slow-flow nipple (.011 inch orifice size). Although carry-over effect of nipple choice was not anticipated, the order of slow-flow and standard-flow nipple presentations was randomized across the feeds. All nipples for each infant were placed in the same nipple ring with only the unit administrative assistant privy to the blinding key. Feedings were completed by one of MUSC's level II neonatal nurses. A consistent nurse was maintained across each infant's data collection series to reduce changes in infant feeding performance induced by differences in nurse feeding techniques. Years of level II neonatal experience were recorded for all feeding nurses.

Oral feeds were provided based on physician feeding orders and nursing assessment of infant's appropriateness for feeding based on level of arousal. All milk was provided in the Similac Volu-Feeder® and was warmed to room temperature. Milk type was determined by physician order based on clinical indication, and remained constant for each infant within each feeding period to eliminate changes in feeding performance resulting from changes in milk attributes. Prior to initiating all feeding assessments the principal investigator collected demographic information including race, ethnicity, gender, date of birth, gestational age, birth weight, weight at time of data collection, Apgar scores, oral intake history, and respiratory history. Bottle weight and bib weight were recorded. Once all background information was collected the principal investigator calibrated and place all appropriate data collection equipment on the infant.

All electronic signals were be recorded at 1000Hz and stored as a synchronized data file using the Biopac AcqKnowledge® 4 Acquisition and Analysis System. Sucking pressures were acquired using the Millar Mikro-cath® 3.5F pressure transducer calibrated to 0 and 25 mmHg and were inserted laterally into a pre-assembled silastic sheath thread laterally along the nipple edge. Abdominal (ABD) and ribcage (RIB) excursion were measured using Ambulatory Monitoring, Inc. Respiratory Inductance Plethsmography (RIP) Inductobands placed around the infant's umbilicus and axillae. RIP signals were acquired with a unity gain of 10. Nasal airflow (Nasal) was collected using a neonatal nasal cannula secured in place with allergen-free adhesive tape and connected to the Hans Rudolph Heated Linear Pneumotach measuring airflow rates of 0-10L/minute. Nasal airflow signals were acquired with a gain of 5,000 and 10Hz low pass filter.

Upon calibration and placement of all instrumentation, five minutes of pre-feeding respiratory signals were collected. During this time the infant was positioned in the posture that the nurse was going to conduct the feeding based on nurse preference. Nurses were instructed to feed the baby exactly as they would during clinical care while maintaining this posture to the best of their ability. Immediately prior to nipple provision the PI recorded infant sleep/wakefulness state. When all pre-feeding data had been collected, the feeder insert the test nipple into the infant's oral cavity with the pressure transducer positioned downward along the lingual surface. Five minutes after the infant established a latch on the nipple the bottle and bib were removed from the infant's oral cavity to be weighed. A new pre-weighed bib and the previously weighed bottle were then returned to the infant for resumption of oral intake efforts until the feed was completed. Bottle and bib weights were once again recorded, and the nurse then placed the infant back in the basinet. (See *Figures 4.1-4.3* for a schematic of the levels and attributes of data collection.)

Infants were followed throughout their hospital course to determine the date that 1) all required discharge developmental milestones except for oral feeding were met; 2) when full oral feeds were achieved; and 3) date of hospital discharge. Achievement of required discharge milestones was determined as the date the infants was able to maintain body temperature in an open crib, exhibit continued weight gain, and maintain cardiopulmonary stability without oxygen support for 48 hours. Obtainment of full oral feeds was identified by the date the infant demonstrated the ability to orally consume the prescribed daily volume of milk for 48 hours.

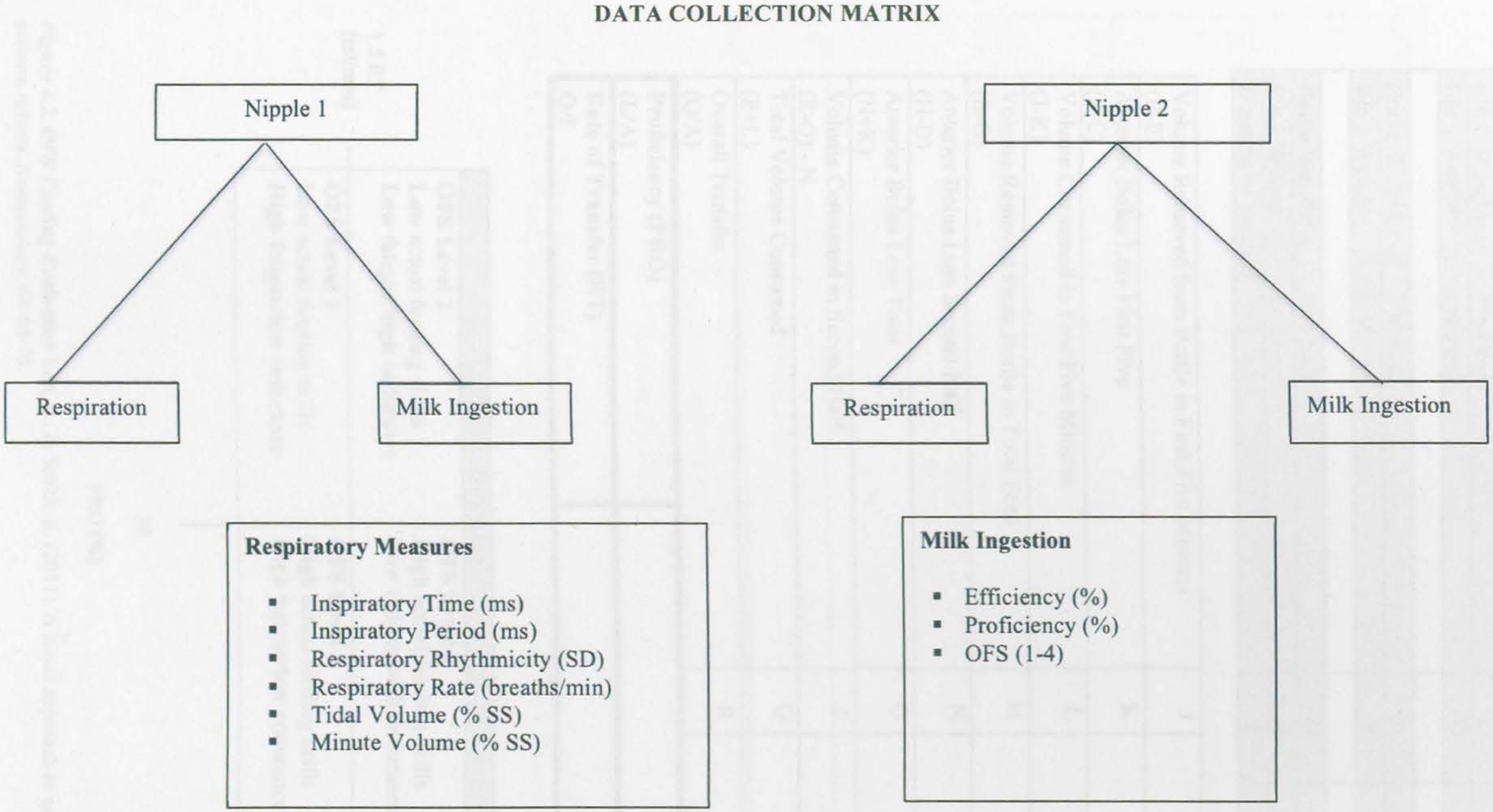
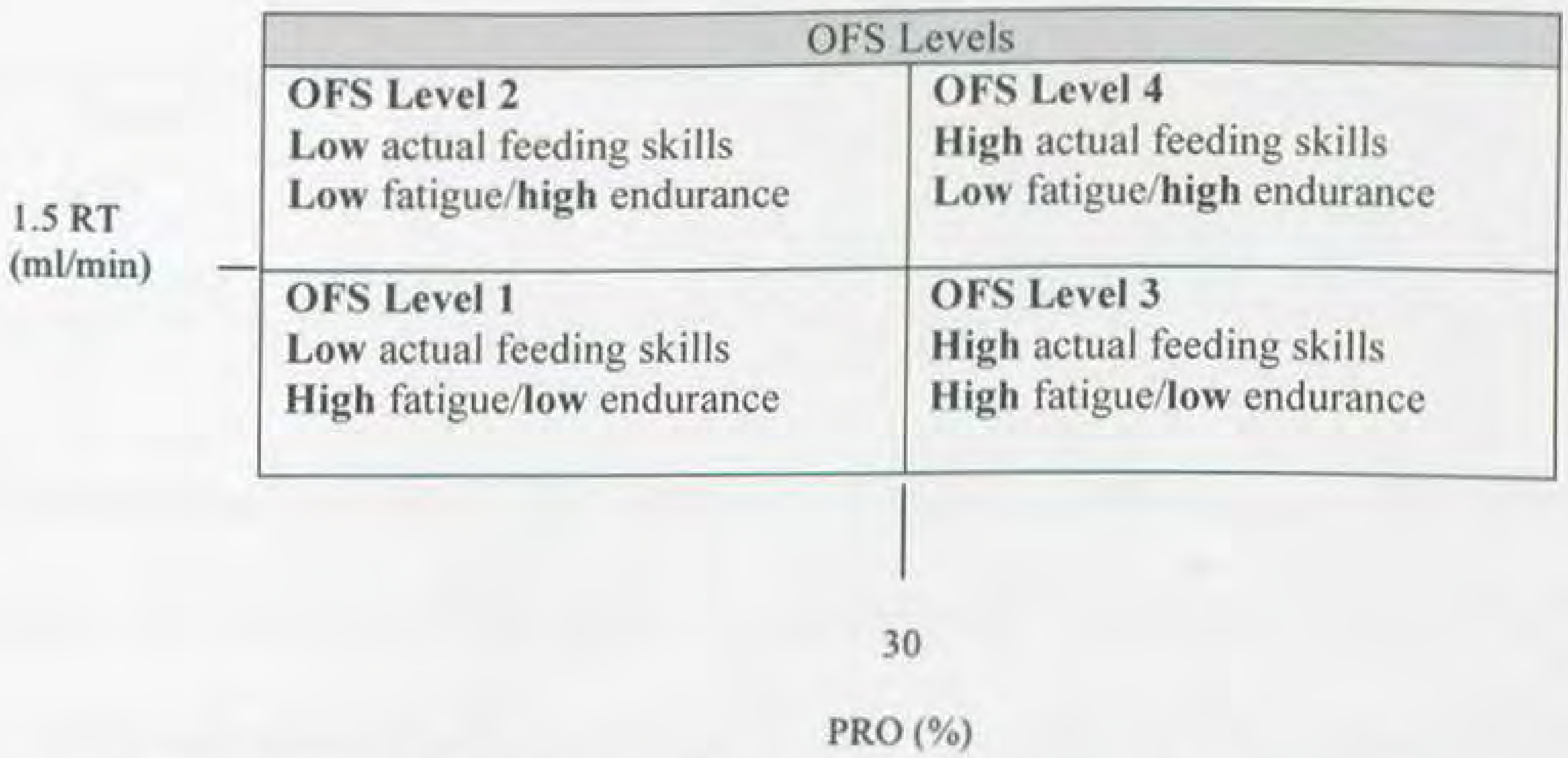


Figure 4.1. Data Collection Matrix Nipple 1 and 2 will be randomized to slow-flow and standard-flow nipples across infants.

Volume Prescribed		A	mL
Bottle Weight:	Pre Feed	B	Grams
Bib 1 Weight:	Pre-Feed	C	Grams
Bib 2 Weight:	Pre-Feed	D	Grams
Bottle Weight:	5 Minute	E	Grams
Bib 1 Weight:	5 Minute	F	Grams
Bottle Weight:	End Feed	G	Grams
Bib 2 Weight:	End Feed	H	Grams
Duration of Feeding		I	Min.

Volume Removed from Bottle in First Five Minutes (B-E)	J	mL
Anterior Bolus Loss First Five (F-C)	K	mL
Volume Consumed in First Five Minutes (J-K)	L	mL
Volume Removed From Bottle in Total Feed (B-G)	M	mL
Anterior Bolus Loss Second Half (H-D)	N	mL
Anterior Bolus Loss Total (N+K)	O	mL
Volume Consumed in Second Half (E-G) - N	P	mL
Total Volume Consumed (P+L)	Q	mL
Overall Transfer (Q/A)	R	%

Proficiency (PRO) **(L/A)**	**%**
Rate of Transfer (RT) **Q/I**	**mL/minute**



OFS Levels	
OFS Level 2 **Low** actual feeding skills **Low** fatigue/**high** endurance	**OFS Level 4** **High** actual feeding skills **Low** fatigue/**high** endurance
OFS Level 1 **Low** actual feeding skills **High** fatigue/**low** endurance	**OFS Level 3** **High** actual feeding skills **High** fatigue/**low** endurance

Figure 4.2. OFS Feeding Evaluation Lau, C., & Smith, E. (2011). A novel approach to assess oral feeding skills of preterm infants. *Neonatology*, 64-64-70.

Table 4.1. Sleep Wakefulness State

State	Description
I	▪ Eyes closed ▪ Flaccid appearance ▪ Body movement limited to startles with immediate return to flaccid ▪ Rhythmic jaw jerking for 1-2 sec.
II	▪ Eyes closed ▪ Body movement with slow intermittent writhing movements, startles, small extremity movement, frown, smile, chewing, sucking grimaces, grunts whimpers
III	▪ Rapid eye movement ▪ May have occasional eye opening, remain closed, or briefly half open ▪ Body movements from state I or II
IV	▪ Eyes open or closed ▪ Non-reflexive movement of limbs with prolonged startles and stretching ▪ Intermittent motionless but alert ▪ No crying ▪ Facial activity usually present
V	▪ Crying ▪ Those of IV
VI	▪ Recovery after crying ▪ Deep rapid respiration ▪ Little extremity movement ▪ Eyes usually closed

Stefanski, M., Schulze, K., Bateman, D., Kairam, R., Pedley, T., Masterson, J., et al. (1984). A scoring system for states of sleep and wakefulness in term and preterm infants. *Pediatric Research, 18*(1), 58-62.

DATA SET CONSTRUCTION

Collected data was saved by subject ID and feed number to maintain blinding of the principal investigator to the nipple type during analysis. All historical and milk ingestion data were input into REDCap database. Respiratory signals were processed in AcqKnowledge® 4. Once signal processing was complete, all respiratory, historical, and milk ingestion data were exported to Statistical Package for Social Sciences® (SPSS) for statistical analysis.

Signal Filtering

Given the paucity of literature identifying appropriate methods of processing preterm feeding signals, signal-processing methods were developed in pilot testing by visually comparing various filter domains for those that provided the best-fit. Minimum cut-off frequencies were identified within each of the channels based on each signal's Nyquist rate. (See *Table 4.2* for Nasal, RIP, and Sucking Nyquist frequencies.)

Table 4.2. Signal Nyquist Rate Chart

Signal	Maximum Frequency	Nyquist Rate
Nasal	2.2	4.4
RIP	2.2	4.4
Sucking	0.7	1.4

Finite impulse response (FIR) filters were determined the optimal filter response for all signals due to their inherent ability to maintain linear phase characteristics that are critical for multi-channel comparisons (*Figure 4.3*). Likewise, the Blackman -61dB filter was determined the optimal filter type for all signals due to the filter's ability to provide a steep transition region without causing phase shift or pass/stop-band ripple effect that would interfere with breath demarcation.

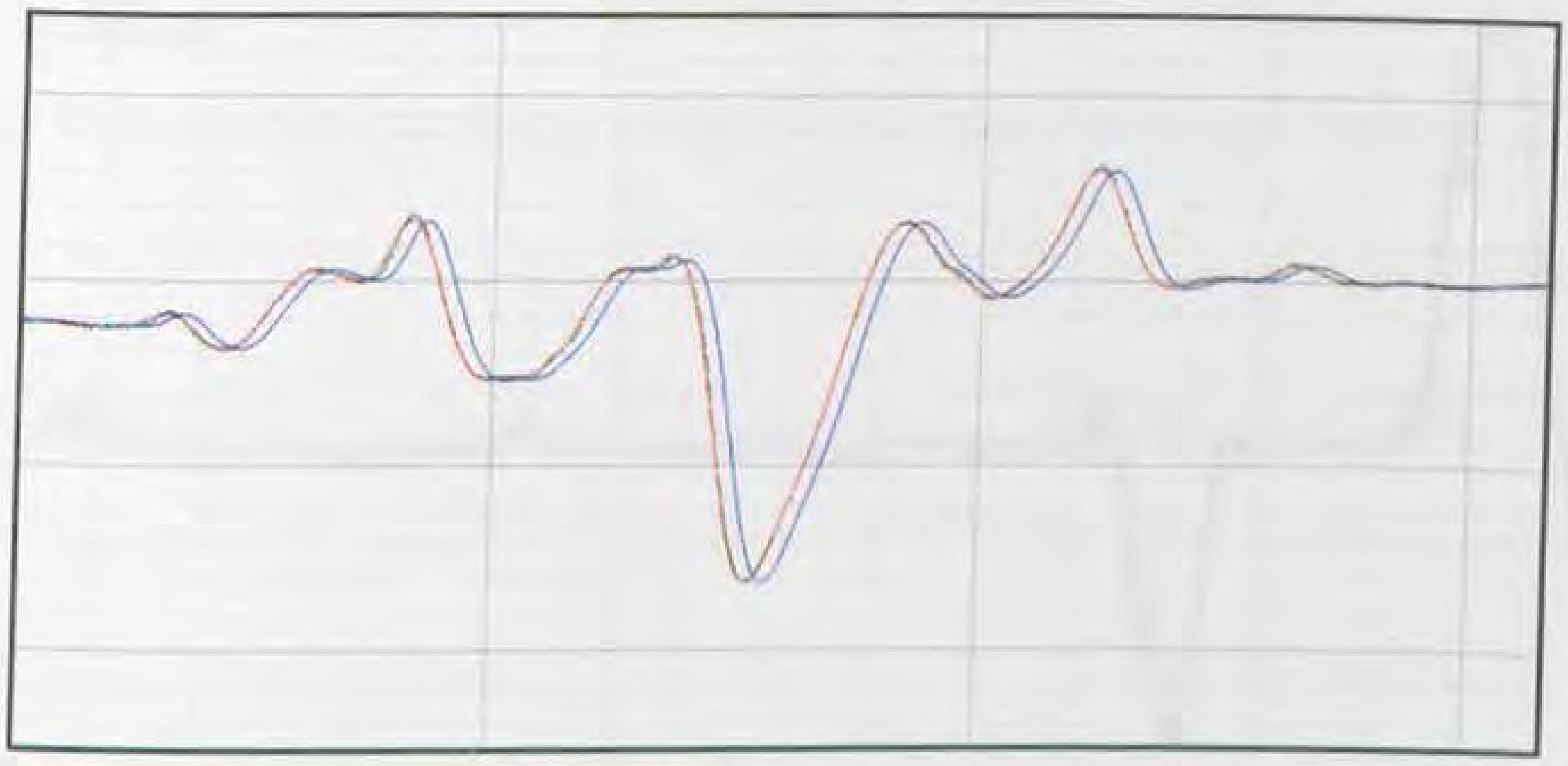


Figure 4.3. Nasal Airflow FIR vs IIR Red indicating raw nasal airflow signal, blue indicating 15Hz low pass IIR filter, green indicating 15Hz FIR filter.

Nasal Airflow

Nasal airflow signals were filtered with a 15Hz low pass, FIR, Blackman -61dB filter. The cut-off frequency was determined by identifying highest frequency above the Nyquist rate that enabled sufficient high frequency noise extraction necessary for accurate signal demarcation without moving potentially relevant high frequency physiologic signal attributes. (See *Figure 4.4* for comparison of two tested cut-off frequencies.) Fluctuations in end expiratory volume that contribute to baseline shift in the nasal airflow signal were compensated for by zeroing the baseline in 15 seconds increments in the filtered Nasal signal throughout the duration of the feed.

Figure 4.4. Nasal Airflow Cut-off Frequency Comparison Red indicating raw nasal airflow signal, blue indicating filtered signal at 6Hz (top channel) and 15Hz (bottom channel). 6Hz filter resulting in signal distortion which is absent with the 15Hz filter.

Respiratory Inductance Plethsmography (RIP)

The initial stage of breath demarcation occurred on a differential RIP signal. Filtered RIP signals were determined to be unfit for the initial stage of breath demarcation due to the resulting signal distortion at the occurrence of transient events resulting from the application of high pass, drift removing filters. Points of inspiratory initiation and cessation identified on the differential signal were transposed to the RIP signal for measurements of interest. Raw RIP signals were duplicated and smoothed using 15 sample mean value smoothing to enable accurate inspiratory initiation and cessation breath demarcation once the signal was differentiated. The derivative of the smoothed signal was filtered with a 5Hz low pass FIR, Blackman -61dB filter. This cut-off frequency was determined by identifying the highest frequency above the Nyquist rate that resulted in the minimum number of non-respiratory zero crossings in the derivative channel without 1) failing to detection true respiratory movements; and 2) contributing to significant signal phase shift. Zero crossings indicative of a valid breath that remained after the application of this filter were further refined using pre-determined breath criteria. (See *Breath Detection Criteria* for RIP respiratory movement thresholds and *Figure 4.5* for a schematic of the RIP phase response to filtering.)

Figure 4.5. 5Hz vs. 15Hz Low Pass RIP Filter **A.** Nasal signal; **B.** 5Hz Low Pass RIP Signal; **C.** 15Hz Low Pass RIP Signal. Circles indicating non-respiratory movements identified on 15Hz signal but not on the 5Hz signal. Dashed line illustrates the presence of minimal phase shift between filters.

Sucking

Sucking demarcation occurred on a differential sucking signal due to the presence of a pass-band and stop-band ripple generated by the application of low-pass, drift removing filters. (See *Suck Burst Identification* for full description of sucking demarcation methods.) Raw sucking signals were duplicated and differentiated using a 15Hz low pass, FIR, Blackman -61dB filter. The cut-off frequency was determined by identifying the highest frequency above the Nyquist frequency that extracted sufficient signal noise to enable accurate differential signal demarcation without removing potentially relevant high frequency physiologic signal attributes. (See *Figures 4.6-4.7* for schematics of changes to signal attributes and signal phase across cut-off frequencies.)

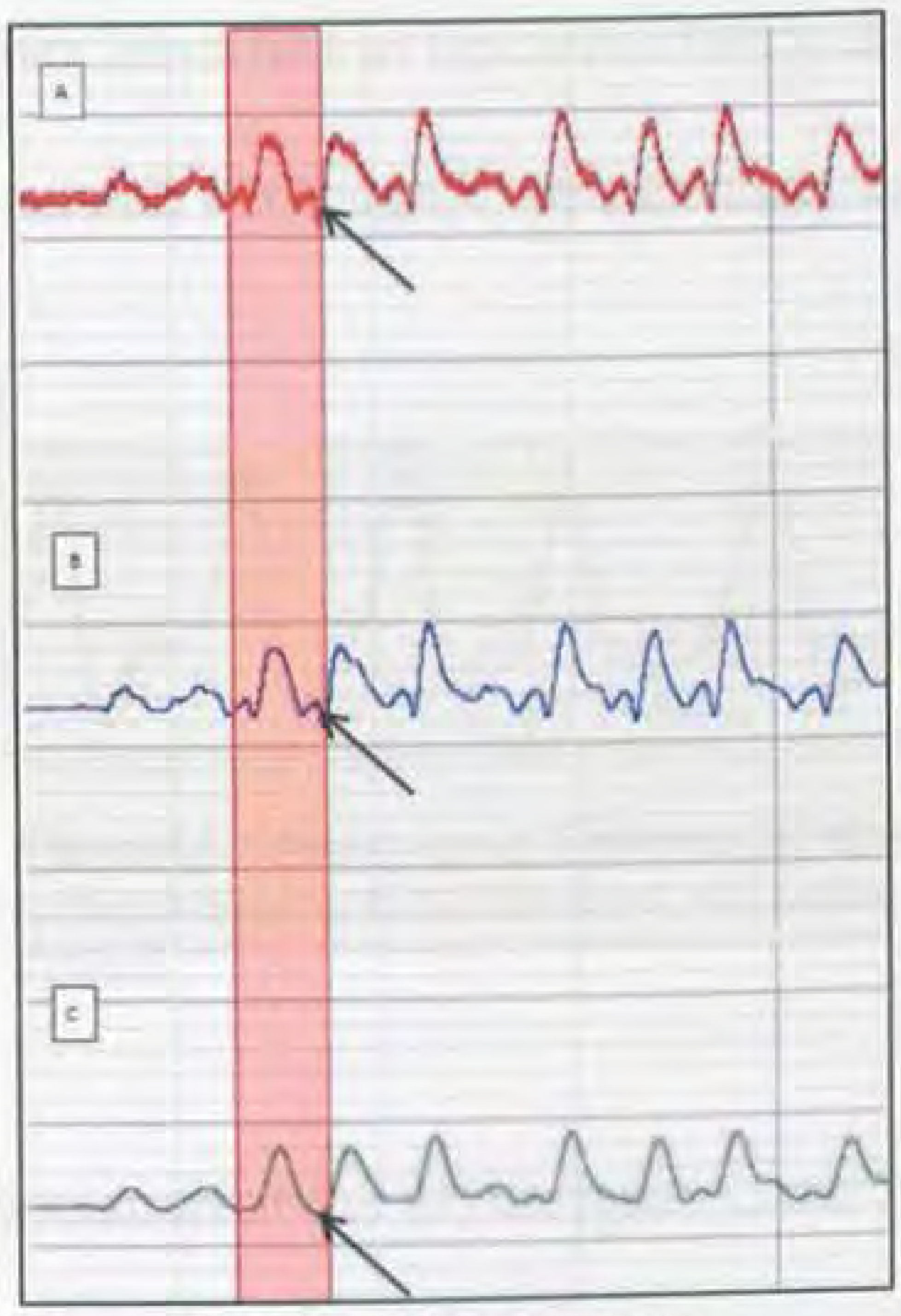


Figure 4.6. 3Hz vs. 15Hz Low Pass Sucking Filter Signal Attributes **A.** Raw sucking signal; **B.** 15Hz low pass sucking signal; **C.** 3 Hz low pass sucking signal. Arrows indicate relevant signal attributes lost with the application of a 3Hz cut-off frequency.

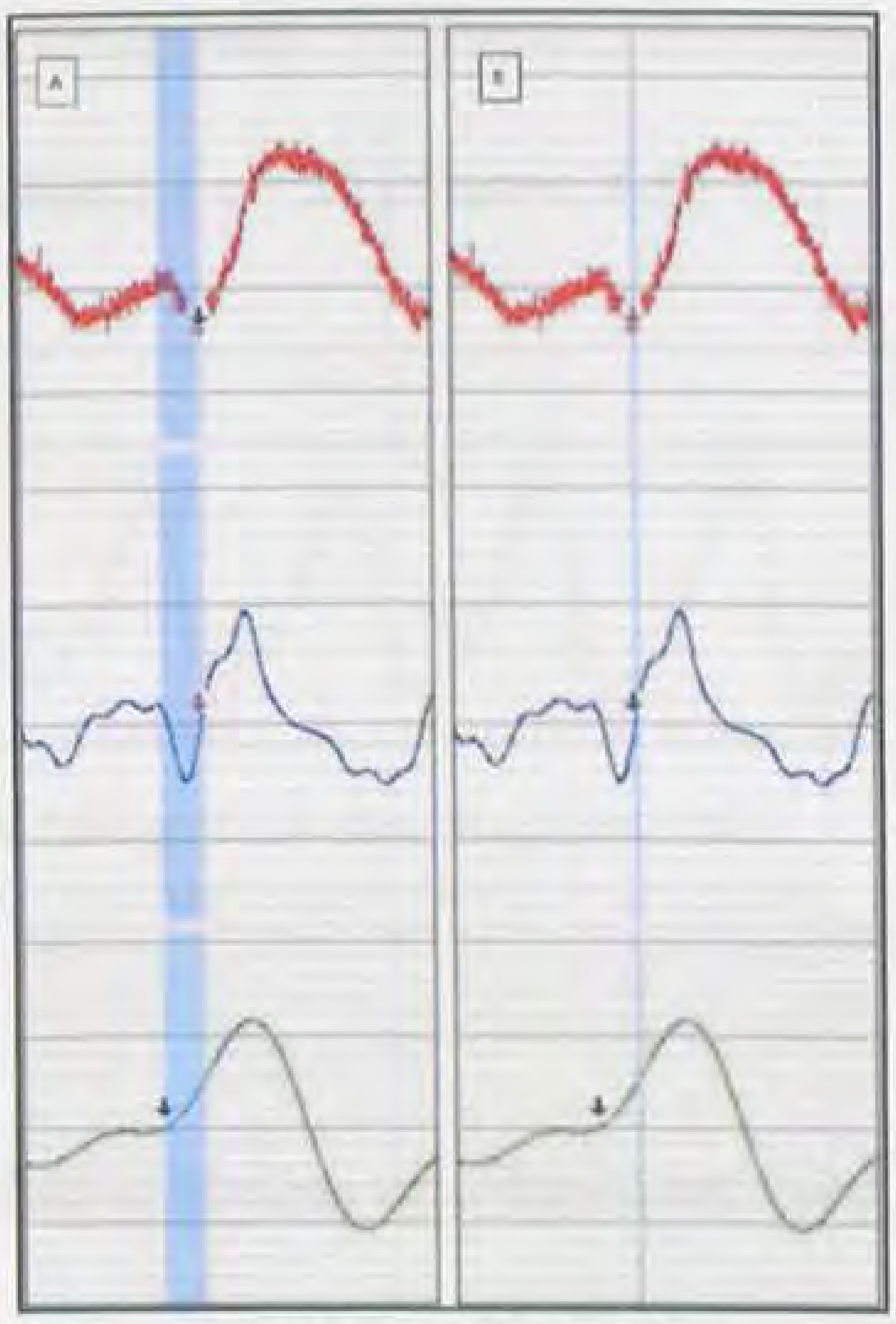


Figure 4.7. 2Hz vs. 15Hz Low Pass Sucking Filter Phase Shift **A.** Blue region highlighting the 92 ms phase shift in initiation of inspiration with the 3Hz low pass filter that is reduced to **B.** 4ms with the 15z low pass filter.

Breath Detection, Demarcation, and Quantification

Lung Volume Calibration Testing

Given the paucity of literature validating the use of the calibrated SUM (ABD+RIB) RIP signal for measures of infant lung volume during feeding, we performed RIP calibration testing. Calibration used an infant-derived calibration quotient based on steady-state respiration. Infant-derived calibration quotients were generated by differentiating the cleaned RIB and ABD signals, inverting the cleaned nasal signal to maintain inspiratory/expiratory relationships across signals, and conducting linear modeling using the equation Param(0)*RIB+Param(1)*ABD. The SUM signal was then plotted by creating an expression that multiplied RIB and ABD by the param(0) and param(1) values identified in linear modeling above. During steady-state respiration, the SUM signal and PNT signal were strongly correlated (Subject 1 r =.96)(*Figure 4.8*)

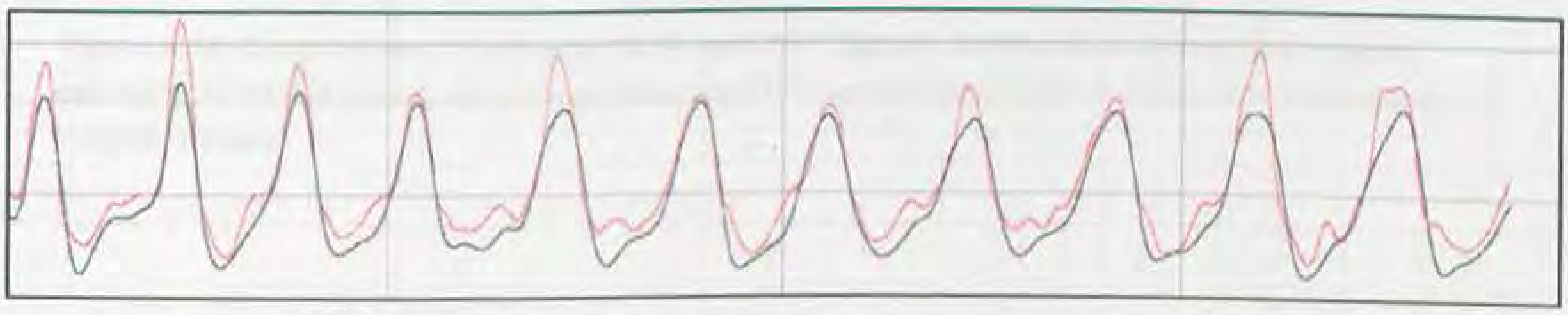


Figure 4.8. Comparison of Calibrated SUM and PNT Signals During Steady-State Respiration Black tracing indicating SUM RIP signal, red tracing indicating PNT signal. Both signals similar in timing and volume.

Correlation of the SUM signal to the PNT signal during feeding was then completed. Feeding SUM and PNT signals were found to have poor correlation (Subject 1 r =.06). Visual inspection revealed best signal correlation during suck-burst breaks, and worst during suck-bursts (*Figure 4.9-4.10*). Based on these findings it was determined the PNT signal would be used for all volume measures.

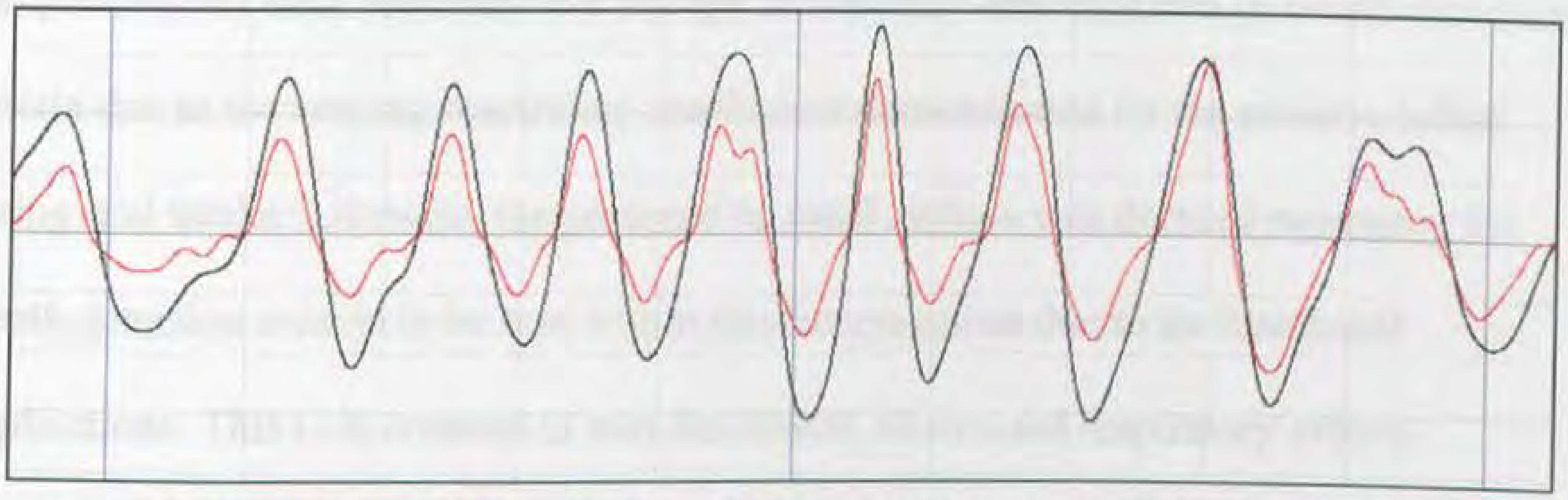


Figure 4.9. Comparison of Calibrated SUM and PNT Signals During Suck-Burst Breaks Black tracing indicating SUM RIP signal, red tracing indicating PNT signal. Signals are similar in temporal features of inspiration and expiration but exhibit greater differences in volume.

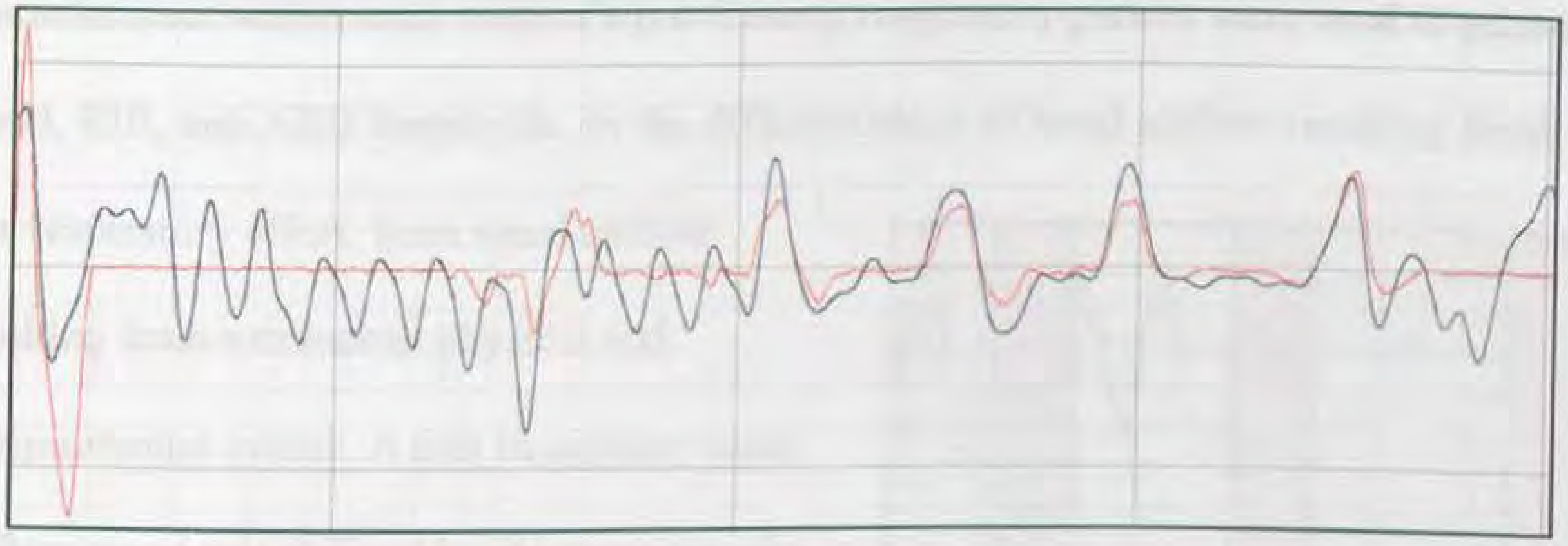


Figure 4.10. Comparison of Calibrated SUM and PNT Signals During Suck Bursts Black tracing indicating SUM RIP signal, red tracing indicating PNT signal. Signal exhibit differences in temporal and volume features.

Breath Detection Criteria

Respiratory performance was analyzed separately for periods of respiration occurring during suck-bursts, and respiration occurring during suck-burst breaks between slow-flow and standard-flow nipples. Measures were expressed as percent change from each subject's unique pre-feeding, steady-state, respiratory pattern. Characteristics of steady-state respiratory pattern were used to establish subject-specific nasal airflow and inductance thresholds for use in the breath detection algorithm. Breaths were generally defined as the presence of nasal airflow resulting from abdomen or ribcage movement.

The presence of both abdomen and ribcage movement were included in breath detection criteria due to the varying respiratory mechanics demonstrated by the preterm infant during oral intake. Likewise, the presence of nasal airflow was deemed necessary for breath detection criteria to be met within this investigation due to its functional implications. This is in contrast to non-functional, obstructed respiratory efforts characterized by ribcage or abdomen movement in the absence of nasal airflow. (See *Figure 4.11* for a schematic of respiratory mechanics and resulting nasal airflow.) Signal characteristics within each subject's pre-feeding respiratory pattern were used to generate Nasal, RIB, and ABD thresholds for the differentiation of nasal airflow resulting from true respiratory effort, from nasal airflow resulting from extraneous physical and environmental events. A true inspiratory nasal airflow event was defined by the presence of a negative inflection in the nasal airflow signal that had a volume of ≥15% of pre-feeding steady-state inspiratory volume that occurred in conjunction with RIB or ABD inflection with a slope and delta ≥15% of pre-feeding steady-state values (*Figure 4.12-4.13*).

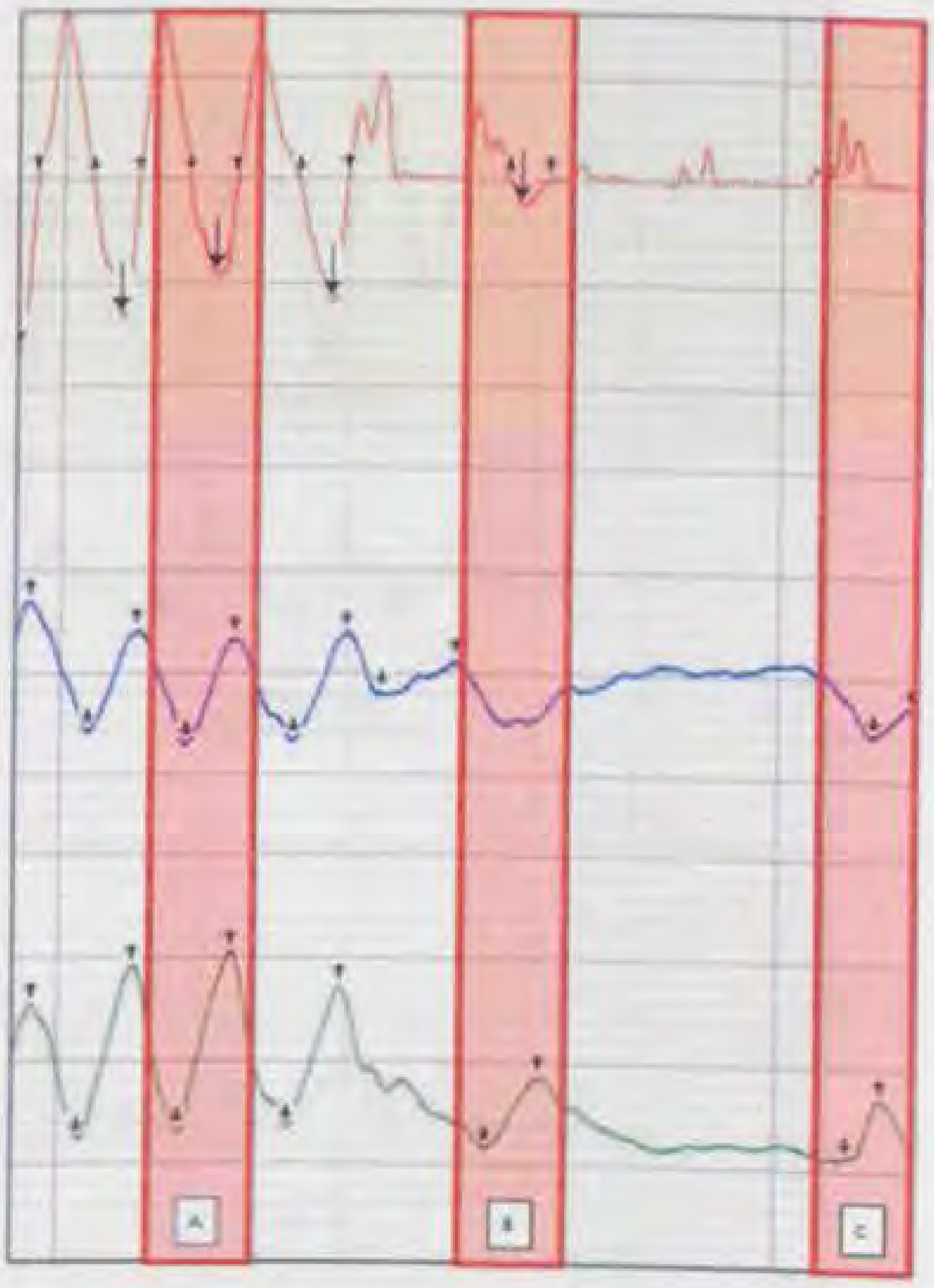


Figure 4.11. Respiratory Patterns Downward arrow indicating start of inspiration, upward arrow indicating end of inspiration in the nasal (red) RIB (blue) and ABD (green) signals. **A.** ABD and RIB movement resulting in nasal airflow; **B.** ABD movement with RIB paradoxical movement contributing to reduced nasal airflow; **C.** ABD and RIB without nasal airflow (obstruction).

ABD and RIB thresholds were derived by identifying the minimal signal deviation that consistently occurred in conjunction with a deviation in the Nasal signal. Likewise, the minimal nasal airflow inspiratory volume threshold was derived by identifying the minimum inspiratory volume that occurred in the presence of ABD or RIB movement.

$$\text{Breath} = (\text{Nasal}^{\geq 15\%\ \textit{Steady State volume}})\ \text{AND}\ ((\text{Ribcage}^{\geq 15\%\ \textit{Steady State Slope}\ \text{AND Delta}})\ \text{or}\ (\text{ABD}^{\geq 15\%\ \textit{Steady State Slope AND Delta}}))$$

Figure 4.12. Breath Detection Algorithm

Figure 4.13. Breath Detection Thresholds Column 1 indicating a valid breath meeting RIP and Nasal criteria; column 2 indicating an invalid breath not meeting RIP or Nasal thresholds.

Steady-State Breath Demarcation

A sequence of 10 breaths simultaneously observed in the Nasal, RIB, and ABD channels were identified from the baseline data-collection period for quantification of steady-state characteristics. The entire five minute baseline data-collection period was not used for threshold generation due to intermittent periods of infant agitation that contributed to highly variable respiratory patterns. The 10 breath steady-state sequence was identified by selecting a sequence of 10 breaths that had 1) uniform period and amplitude upon visual inspection; and 2) was preceded and followed by a sequence of at least five breaths with similar respiratory characteristics to eliminate recovery respiration following periods of apnea.

Nasal Airflow: the minimum nasal airflow differential for each inspiration was identified with the cycle detector programmed to detect negative peaks. Identified peaks were marked using predetermined peak events (short arrow). Differential inspiratory peak events (short arrow) were used as a point of reference for identification of the initiation and cessation of inspiratory airflow. The cycle detector, programmed to select approximately +/-.4 seconds preceding and following unmatched differential inspiratory peak events, was used to insert a minimum and maximum event marker at the point of 0 Nasal signal crossing. The selection window varied by approximately +/- .1 seconds based on each infant's unique respiratory profile. All event markers were visually inspected for validity. (See *Figure 4.14* for a schematic of the steps for the delineation of the inspiratory nasal airflow signal.)

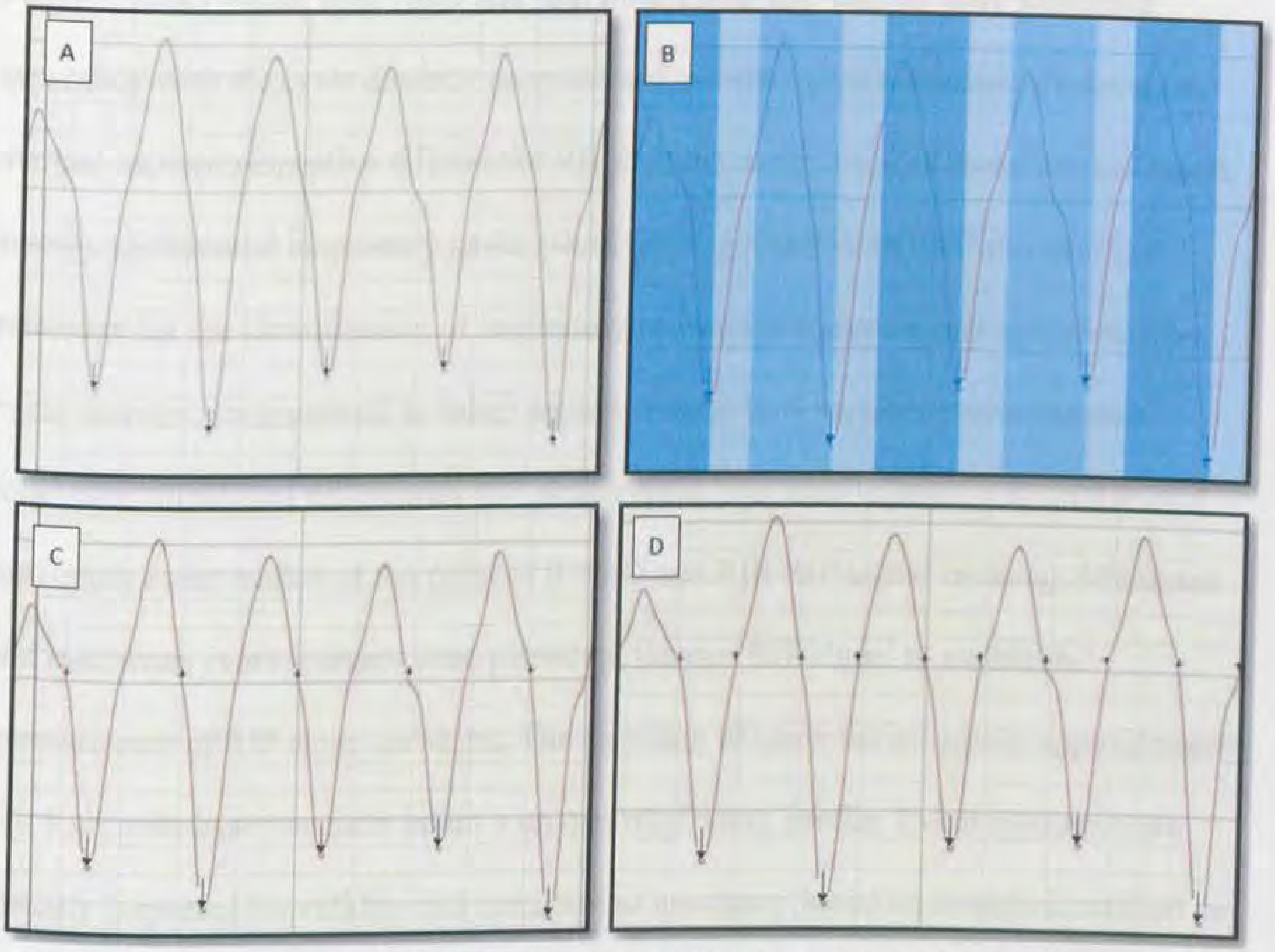


Figure 4.14. Nasal Airflow Steady-State Inspiratory Cycle Delineation **A**. Nasal airflow signal with inspiratory differential peaks marked with short arrow events; **B.** Selection of .4 seconds preceding peak inspiratory differential event (dark shading) for location of 0 signal threshold crossing **C.** Inspiratory start markers placed on the point of 0 crossing; **D.** Final marked nasal airflow signal with event markings: short arrow indicating differential peak, and min/max representing inspiratory initiation/cessation.

<u>*Respiratory Inductance Plethsmography (Abdominal and Ribcage)*</u>*:* Raw respiratory inductance plethsmography (RIP) signals were duplicated to create a RIP signal in its raw form, and a RIP signal for differential transformation. The differential RIP signal was used in the generation of breath-detection thresholds, as well as in the identification of points of inspiratory movement initiation and cessation. The Raw differential signal was obtained by completing 15-sample mean value smoothing followed by a transformation of the signal to its derivative using a 5Hz low pass finite impulse response Blackman filter.

Positive peaks within both ABD and RIB differential RIP signals were identified separately with the cycle detector programmed to detect positive peaks. Peaks were marked on their respective differential RIP channel using the peak event marker (short arrow). Differential inspiratory peaks (short arrow events) were used as a point of reference for the identification of inspiratory movement initiation and cessation. The cycle detector, programmed to select approximately +/-.4 seconds preceding and following unmatched differential RIP peak events, was used to insert a minimum and maximum event marker at the point of 0 ABD and RIB RIP signal crossing. Minimum and maximum event markers were placed on the raw RIP signal to enable the measurement of RIP slope and delta. The selection window varied within approximately +/- .1 seconds based on each infant's unique respiratory profile. Event markers were visually inspected for validity and corrected as necessary based on breaths identified on the Nasal signal. (See *Figure 4.15* for a schematic of steps in the delineation of inspiration in the ABD differential signal and *Figure 4.16* for final the fully-delineated steady state tracings.)

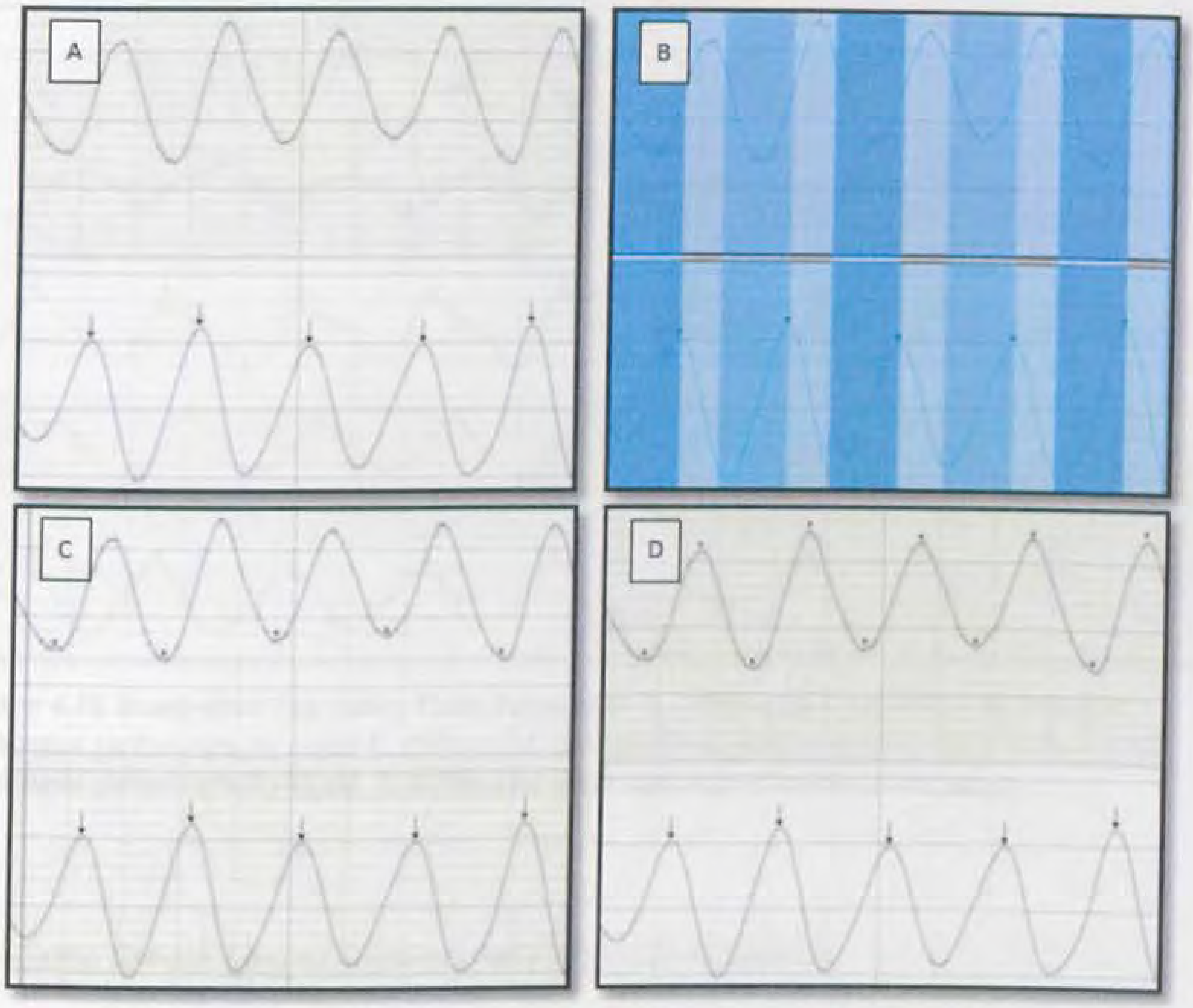


Figure 4.15. Abdominal Respiratory Inductance Plethsmography Steady-State Inspiratory Cycle Delineation ABD RIP Raw in top channel and ABD RIP Differential in bottom channel. **A**. Inspiratory differential peaks marked with short arrow events on ABD RIP differential signal; **B.** Selection of .4 seconds preceding peak inspiratory differential event (dark shading) for location of 0 signal threshold crossing **C.** Inspiratory start markers placed on the raw ABD RIP signal at the point of 0 differential RIP signal crossing; **D.** Final marked ABD RIP Signal with event markings (larger downward arrows on bottom tracing indicate differential peaks, and short downward/upward arrows on upper signal indicate inspiratory initiation/cessation respectively.

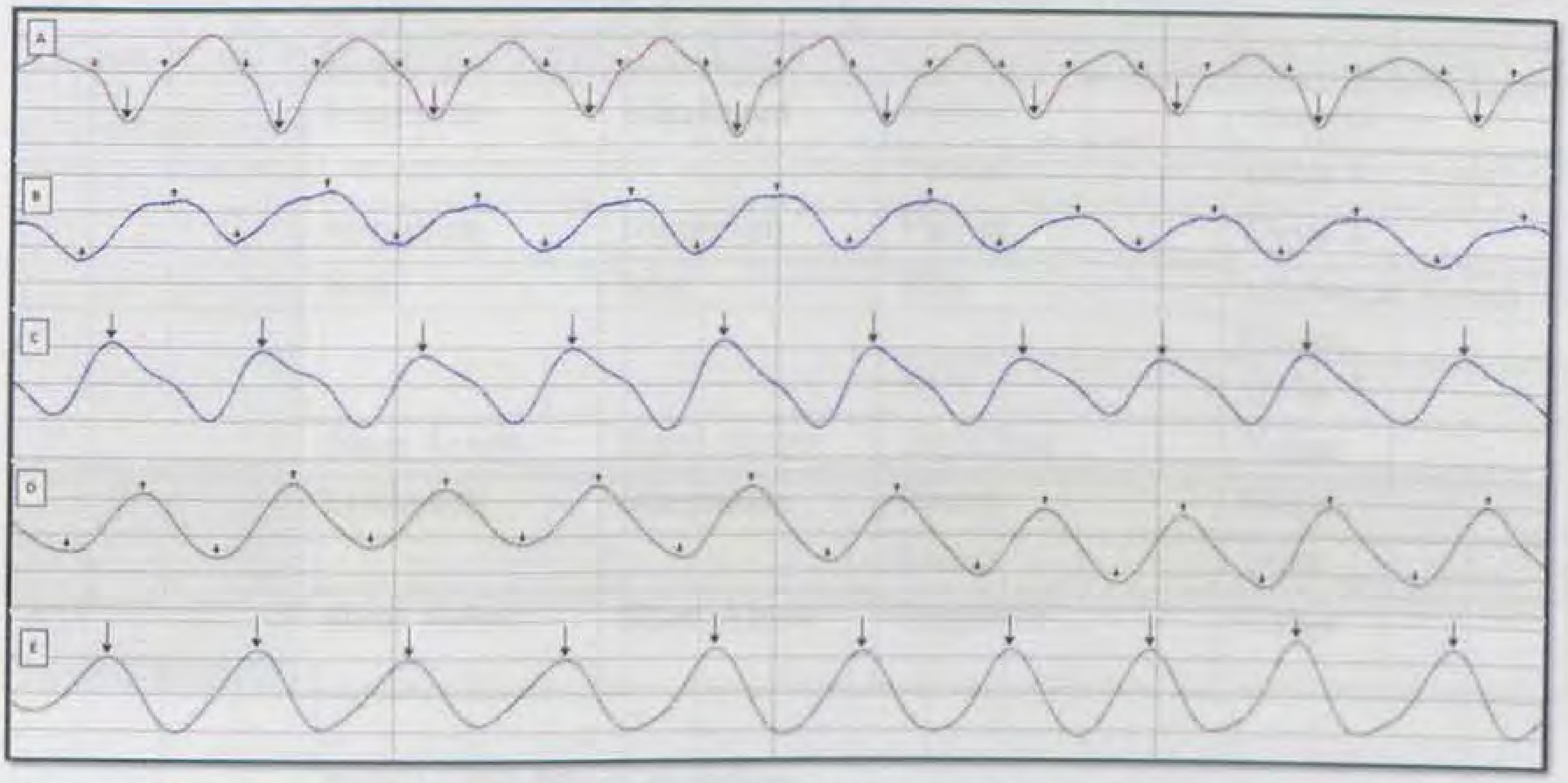


Figure 4.16. Steady-State Inspiratory Cycle Delineation **A**. Differential nasal airflow **B.** Raw RIB inductance plethsmography signal **C.** Differential RIB inductance plethsmography signal **D.** Raw ABD inductance plethsmography signal; **E.** Differential ABD inductance plethsmography signal.

Steady-State Breath Quantification and Offset Identification

Extraction of values quantifying steady-state respiration was completed by selecting the desired channel of measurement (Nasal, ABD, or RIB), selecting the appropriate measurement for the selected channel, and running the cycle detector to output derived measurements into an SPSS® spreadsheet for the event(s) identified. These measurements were then copied and saved into a composite data collection spreadsheet. (See Tables 4.3-4.4 for channel, event, pairing, and measurement selection criteria for the quantification of all steady-state and offset values.)

Table 4.3 Steady-State Breath Quantification

Channel	Starting Event	Ending Event	Paired/Unpaired	Measurement
Nasal	Minimum	Maximum	Paired	Integral
			Paired	Delta T
	Minimum	Minimum	Paired	Delta T
	N/A	N/A	N/A	Minimum Event Count
			N/A	Delta T
	Short Arrow	Short Arrow	Unpaired	Value
RIP	Minimum	Maximum	Paired	Slope
			Paired	Delta
RIP Differential	Short Arrow	Short Arrow	Unpaired	Value

Table 4.4 RIP Offset Calculations

Event	Channel 1	Channel 2	Measurement
Minimum	ABD	Nasal	Delta T
Minimum	RIB	Nasal	Delta T

Composite summary scores for outcome variables with multiple data points were generated, and calculations for rhythmicity, minute volume, and respiratory rate were conducted. Measures that were used for future breath detection including thresholds (nasal airflow peak inspiratory differential, nasal airflow inspiratory volume, as well as the RIB and ABD RIP peak inspiratory differentials, deltas, and slopes), were multiplied by .15 to determine the 15% minimum threshold for future use in breath demarcation during feeding.

Suck-Burst and Suck-Burst Break Identification

Suck-Bursts were defined by the presence of ≥2 sucks occurring within 2 seconds of each other on a nipple with an expressible bolus. Sucks that occurred in the absence of an expressible bolus, such as those generated during the provision of external pacing resulting in the visually identified displacement of milk from the nipple tip, were excluded. The initiation of the suck-burst was identified as the point that the sucking force was first initiated. Completion of the suck-burst was identified as 760 ms following the cessation of the last sucking force. This time offset was determined based on findings from Hanlon et al. (1997) which indicate the preterm infant swallow occurs over 760 ms. (Hanlon et al., 1997; Lau & Schanler, 1996; Lau & Schanler, 2000; Lau et al., 1997; O. Mathew, 1991; O. P. Mathew, 1988) Individual sucks were identified using a combined threshold and video assessment approach. A combined approach was necessary due to the inability to reliability differentiate nutritive sucking from other movements that cause similar inflections such as sucking during the provision of external pacing, feeder manipulation of the nipple within the infant's oral cavity, and infant nipple manipulation.

Suck Identification: Preliminary signal analysis of signal features characteristic of a suck revealed the majority of sucks to be composed of two peaks that varied in amplitude and temporal relation within and across infants. Comparison of sucking peaks to periods of respiratory cessation in infants with good ventilation during suck-bursts revealed respiratory cessation to immediately follow the second peak. Although sucks regularly were composed of two peaks, some sucks were composed of one. Those sucks with only one peak were not immediately followed by respiratory cessation. Consequently, the initial peak was hypothesized to be lingual stripping of the nipple, and the second peak was hypothesized to be caused by anterior-posterior bolus transport prior to the swallow. (See Appendix 4.1 for full report of signal characteristics and their observed relationship to nasal airflow.) Due to the variability in nutritive sucking attributes that warrants further validation using supplemental imaging techniques, sucks were identified in the current investigation by the presence of a positive inflection in the sucking signal that was confirmed by synchronized video analysis.

Video recordings were first synchronized with the sucking signal by determining the time-offset between the registered pressure signals resulting from nipple placement in the infant's oral cavity with video verification of nipple placement in the oral cavity. Once the video signal and sucking signal were synchronized, sucking signals were cleaned as indicated in the *Cleaning Signals* section. The filtered sucking signal was then duplicated and transformed to obtain its derivative. Sucks were identified by identifying a threshold indicative of a suck within the differential sucking pressure signal. Infant-dependent sucking thresholds were determined by identifying the approximate median value of maximum peak differential pressures generated during infant sucking. Once the threshold was identified, the differential sucking channel was selected, and the cycle detector was used to identify positive peaks within the differential pressure signal that surpassed the identified threshold. Short arrow event markers were then placed on the differential sucking channel to identify peak differential pressures that met this threshold criterion. As stated above, this threshold was not used as the sole source of suck identification due to the above stated variables. This threshold was instead used as an efficient and precise method of identifying and marking the point of maximal pressure generation in the majority of sucks that was then verified and modified by event removal and addition when necessary against the synchronized video recording. This method was found to be the most accurate method of initial suck-detection when compared to attempted percent threshold techniques used during breath demarcation. In addition to using video recordings for suck verification, video recordings were also used to mark periods of extraneous infant movement caused by things such as burping, for exclusion from respiratory analysis.

Suck-Burst Identification: Suck-bursts were marked by placing selection begin and selection end events at suck-burst initiation and cessation respectively. A series of sucks that met suck-burst criteria (≥ 2 sucks occurring within ≤ 2 seconds of each other) was identified by generating an expression channel that displayed a 1 when sucks were separated by ≤ 2 seconds, and a 0 when sucks were separated by > 2 seconds. To generate this expression, the differential sucking channel was selected and its associated measurement channel was programmed to measure Delta T. The cycle detector was then used to select matched pairs of short arrow differential sucking events with the corresponding measurement values output to a new Delta T channel. Delta T channel values were used to generate the binary expression channel: LESS(-2,$\text{CH}^{\text{SUCK DELTA T}}$).(See *Figure 4.17* for a schematic of suck-burst differentiation using the expression channel.)

Figure 4.17. Suck-Burst Delineation Expression Channel **A**. Filtered sucking signal; **B.** Differential sucking signal with short arrow sucking events; **C.** Delta T between short arrow suck-events; **D.** LESS(-2, CH$^{\text{SUCK DELTA T}}$) channel with 1 indicating sucks with Delta T ≤ 2 seconds, and 0 indicating sucks with Delta T >2 seconds.

Selection begin events were placed using the "I" tool to select approximately 1 second preceding the initial suck of the suck-burst, as defined in the expression channel. The cycle detector was programmed to mark the right edge of positive-to-negative (+) 0 threshold crossings between unmatched short arrow events within the selected differential sucking channel area. This process was repeated at each initial suck of the suck-burst indicated on the LESS(-2,CH$^{\text{SUCK DELTA T}}$) expression channel throughout the feed. Placement of selection end event markers demarcating the end of the suck-burst followed a similar method, with adjustments made to select the 1 second following the last suck of the suck-burst defined on the expression channel. The cycle detector was programed to mark the left edge of the positive-to-negative (+) 0 threshold crossing between unmatched short arrow events within the selected differential sucking channel area. This point was demarcated through the placement of a minimum event marker. Visual inspection of all selection begin and minimum event markers was completed to ensure accuracy of placement. Markers were refined in placement in the occurrence of aberrant sucking patterns. This process was repeated at each final suck of suck-bursts indicated on the LESS(-2,CH$^{\text{SUCK DELTA T}}$) channel. After all minimum event markers had been placed to mark the end of sucking within the suck-burst, the end of the suck-burst was marked with a selection end event marker. This was completed by selecting the differential sucking channel and programming the cycle detector to place a right edge selection end event marker 760 ms following each unmatched minimum event marker. (See *Figure 4.18* for a schematic of steps in suck-burst delineation.)

Figure 4.18. Suck-Burst Event Placement A. Initial suck selection; **B.** Delineation with selection begin event; **C.** Final suck selection; **D.** Delineation with minimum event; **E.** .76sec. swallow selection; **F.** Delineation with selection end event.

Suck-Burst Break Identification: Suck-burst breaks were defined as the 15 seconds following sucking cessation. This period of time was chosen due to the occasional presence of extended suck-burst breaks during which rapid return to baseline respiratory pattern would impede the ability to identify potential changes in respiration between milk-flow rates. Consequently, although periods of sucking cessation were delineated during the demarcation of suck-bursts stated above (opposing area between selection end and selection begin event marks), those suck-burst breaks lasting >15 seconds required revision of the suck-burst break end event. Suck-burst breaks lasting >15 seconds were identified by generating an expression that yielded a 0 when the suck-burst break was >15 seconds, and a 1 for SBB ≤ 15 seconds. To establish this expression the differential sucking channel was selected with the associated measurement channel set to measure Delta T. The cycle detector was programmed to select matched pairs of selection end to selection begin differential sucking events with measurement values output to a new Delta T channel. Once the Delta T channel was generated, an expression channel LESS(-15,$\mathrm{CH}^{\mathrm{SUCK\ DELTA\ T}}$) was created using previously established Delta T values. Suck-burst breaks lasting >15 seconds as indicated by a 0 on the LESS(-15,$\mathrm{CH}^{\mathrm{SUCK\ DELTA\ T}}$) expression channel were segmented to include the first 15 seconds by placing a suck-burst break end Star event. This was completed by using the "I" tool to select approximately 20 seconds following the last suck of the preceding suck-burst, and running the cycle detector to output a star event mark on the right edge of the 15 second suck-burst break period following the selection end event marker on the differential sucking channel (*Figures 4.19-4.20*).

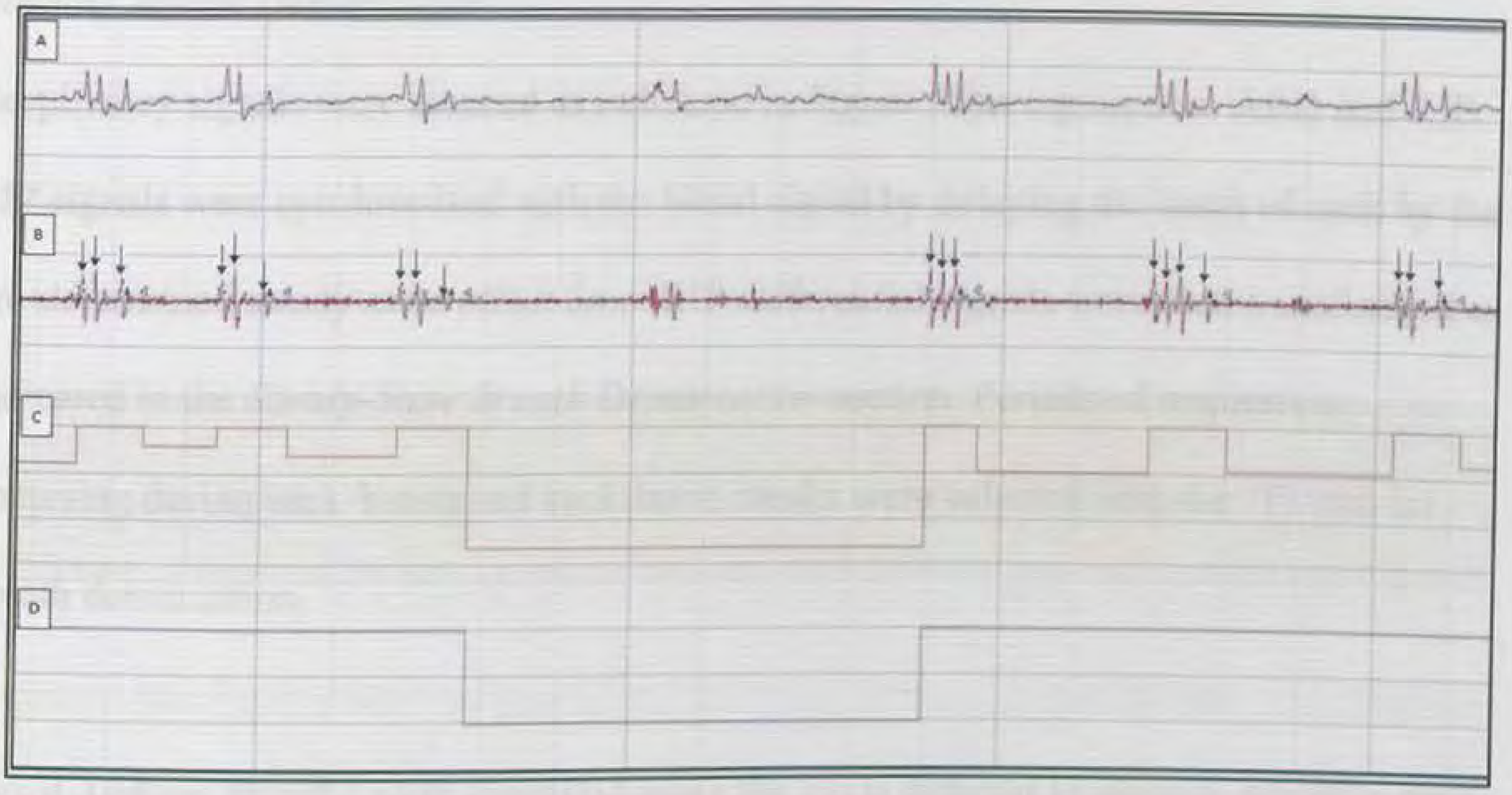


Figure 4.19. Suck-Burst Break Expression Channel **A.** Filtered sucking signal; **B.** Differential sucking signal with suck-burst events; **C.** Delta T between selection end and selection begin events; **D.** LESS(-15, $CH^{SUCK\ DELTA\ T}$) channel with 1 indicating suck-burst breaks with Delta T ≤ 15 seconds and 0 indicating suck-burst-breaks with Delta T >15 seconds.

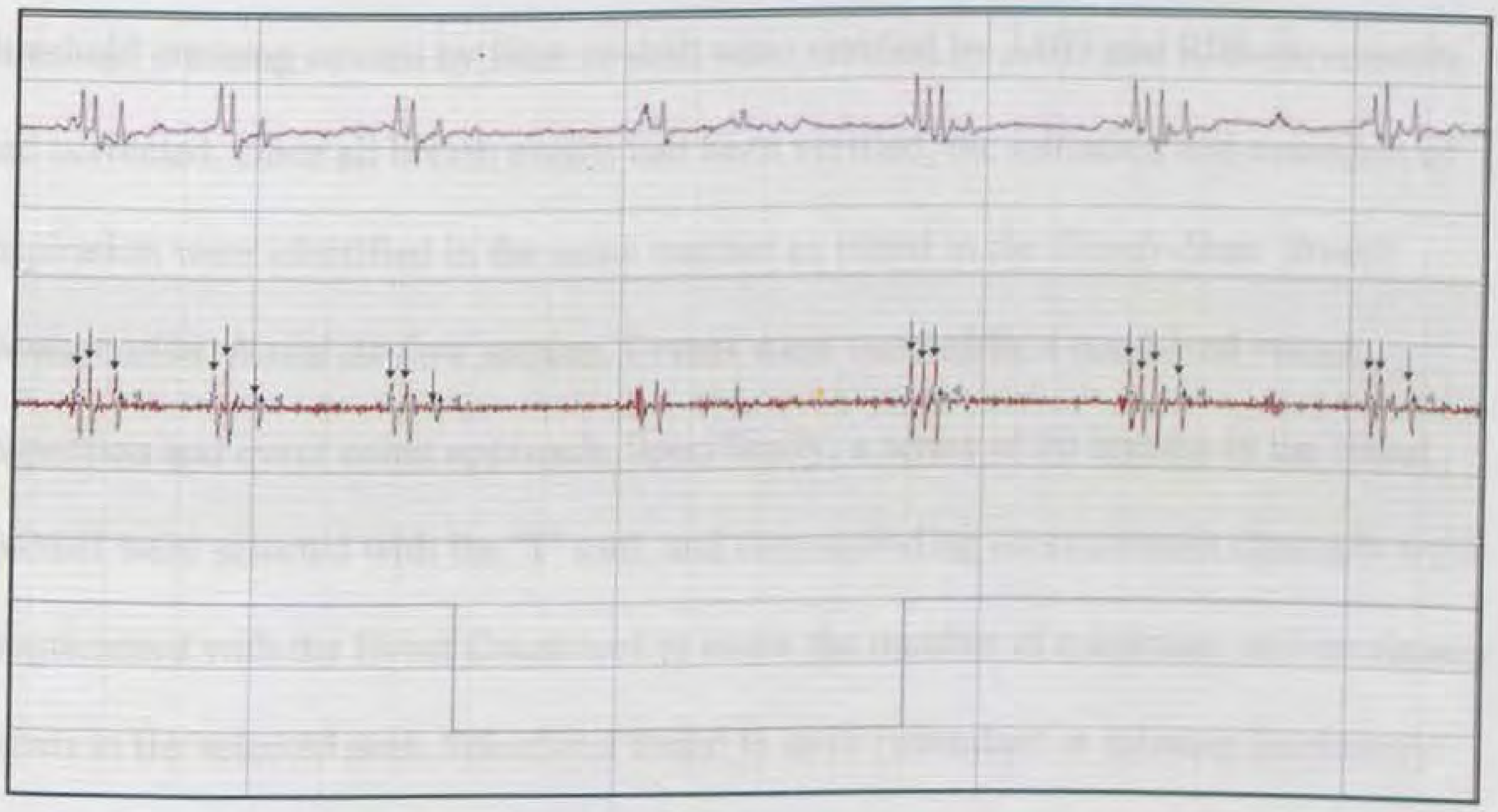


Figure 4.20. Suck-Burst Break End Event Placement Star event inserted on the sucking differential channel 15 seconds following the end of the preceding suck-burst.

Feeding Breath Demarcation

Respiratory signals were cleaned as indicated in *Signal Filtering* section. ABD and RIB RIP signals were synchronized with the Nasal signal by delaying the onset of each by the pre-determined steady-state offset time. RIP differential signals were then transformed as indicated in the *Steady-State Breath Demarcation* section. Periods of respiration occurring during suck-bursts and suck-burst breaks were selected with the "I" tool for breath demarcation.

Nasal Airflow: Breaths were identified using the cycle detector to identify negative peaks in the differential nasal signal meeting the 15% steady-state peak differential threshold. Identified peaks were marked using the short arrow event marker as indicated in the *Steady-State Breath Demarcation: Nasal Airflow* section. All marked Nasal signals were visually inspected for accuracy. Breaths marked with more than one event due to double threshold crossing caused by jitter or drift were verified by ABD and RIB movements and corrected. Once all breath events had been verified, the initiation and cessation of inspiration were identified in the same manner as stated in the *Steady-State Breath Demarcation: Nasal Airflow* section. Events were verified by a combined visual inspection and event count approach. Specifically, a series of 10 breaths in the Nasal channel were selected with the "I" tool, and corresponding measurement channels were programmed with the Event Count tool to count the number of minimum and maximum events in the selected area. Selections found to have redundant or missing inspiratory demarcations as evident by visual inspection or event count inequalities were corrected.

Once all breath delineations were verified, an expression was generated to determine those breaths that met previously established 15% steady-state integral criteria. Breaths meeting criteria were identified by generating an expression channel that indicated a 1 when the breath integral was $\geq X^{15\%\ \text{Steady-State Integral}}$, and a 0 when the breath integral was $<X^{15\%\ \text{Steady-State Integral}}$. This was established by selecting the Nasal channel, setting the associated measurement channel to calculate integral, and running the cycle detector to measure and output the integral between matched pairs of minimum and maximum event marks on the Nasal channel to a new Nasal Integral channel. Volumes in the established integral channel meeting 15% criteria were then identified by generating a new channel depicting the previously identified binary categorization from the expression $\mathrm{OR}(\mathrm{NOT}(\mathrm{CH}^{\mathrm{INTEGRAL}}),\mathrm{LESS}(X^{\mathrm{INTEGRAL\ THRESHOLD}},\mathrm{CH}^{\mathrm{INTEGRAL}}))$.(See *Figure 4.21* for a schematic of methods in the identification of signals meeting Nasal criteria.)

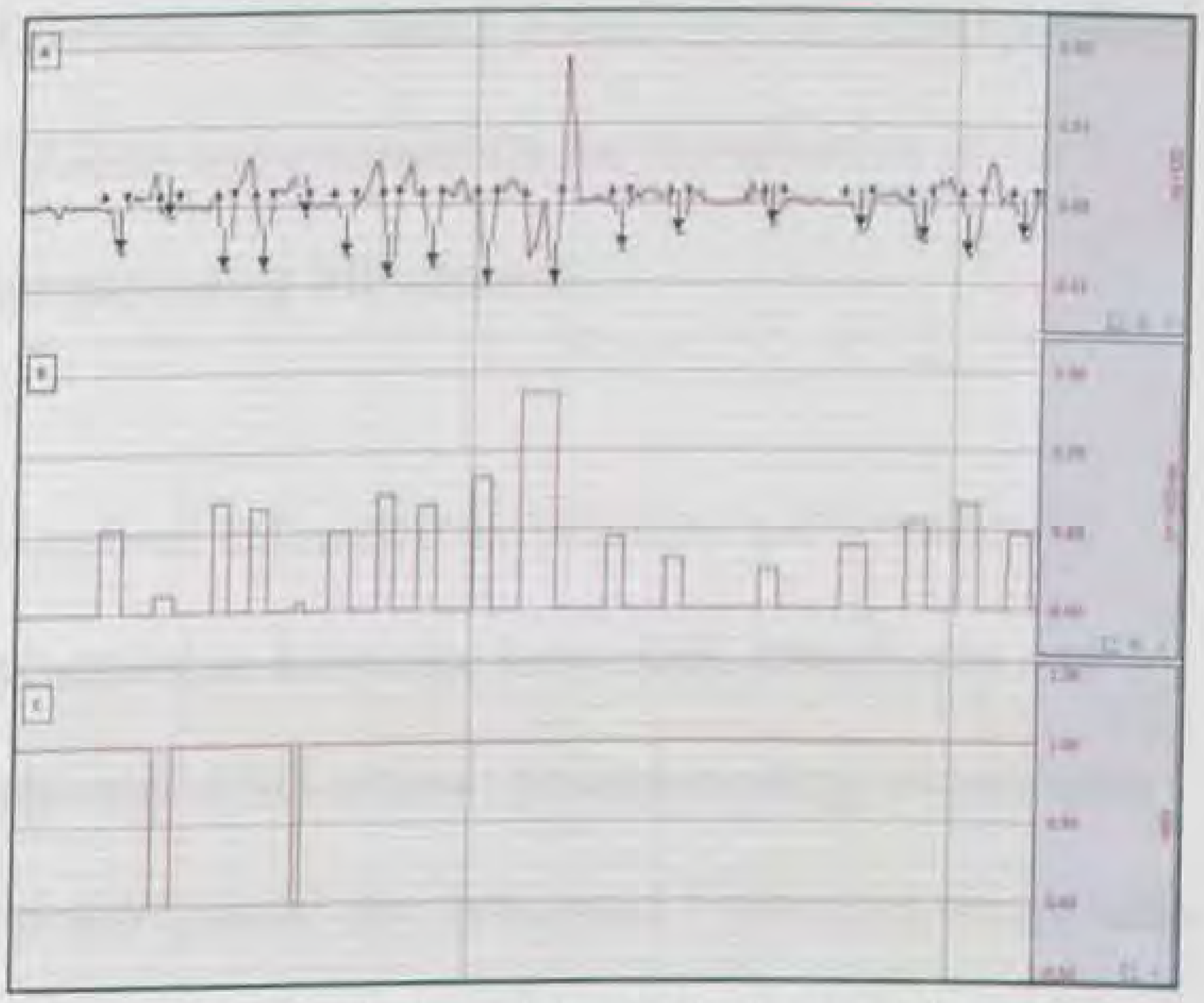


Figure 4.21. Identification of Signals Meeting Nasal Criteria **A.** Cleaned and marked Nasal signal; **B.** Nasal integral; **C.** $\mathrm{OR}(\mathrm{NOT}(\mathrm{CH}^{\mathrm{INTEGRAL}}),\mathrm{LESS}(X^{\mathrm{INTEGRAL\ THRESHOLD}},\mathrm{CH}^{\mathrm{INTEGRAL}}))$ indicating 0 when marked nasal airflow breath does not meet breath criteria.

<u>*Respiratory Inductance Plethsmography (Abdominal and Ribcage):*</u> Respiratory movements in the ABD and RIB RIP channels were identified separately by using the cycle detector to identify positive peaks in their corresponding differential signals that met previously established 15% steady-state peak differential thresholds. Identified peaks were marked using the

Once all breath delineations were verified, an expression was generated to determine those breaths that met previously established 15% steady-state integral criteria. Breaths meeting criteria were identified by generating an expression channel that indicated a 1 when the breath integral was $\geq X^{15\%\ \text{Steady-State Integral}}$, and a 0 when the breath integral was $<X^{15\%\ \text{Steady-State Integral}}$. This was established by selecting the Nasal channel, setting the associated measurement channel to calculate integral, and running the cycle detector to measure and output the integral between matched pairs of minimum and maximum event marks on the Nasal channel to a new Nasal Integral channel. Volumes in the established integral channel meeting 15% criteria were then identified by generating a new channel depicting the previously identified binary categorization from the expression $\text{OR(NOT(CH}^{\text{INTEGRAL}}\text{),LESS(X}^{\text{INTEGRAL THRESHOLD}}\text{,CH}^{\text{INTEGRAL}}\text{))}$.(See *Figure 4.21* for a schematic of methods in the identification of signals meeting Nasal criteria.)

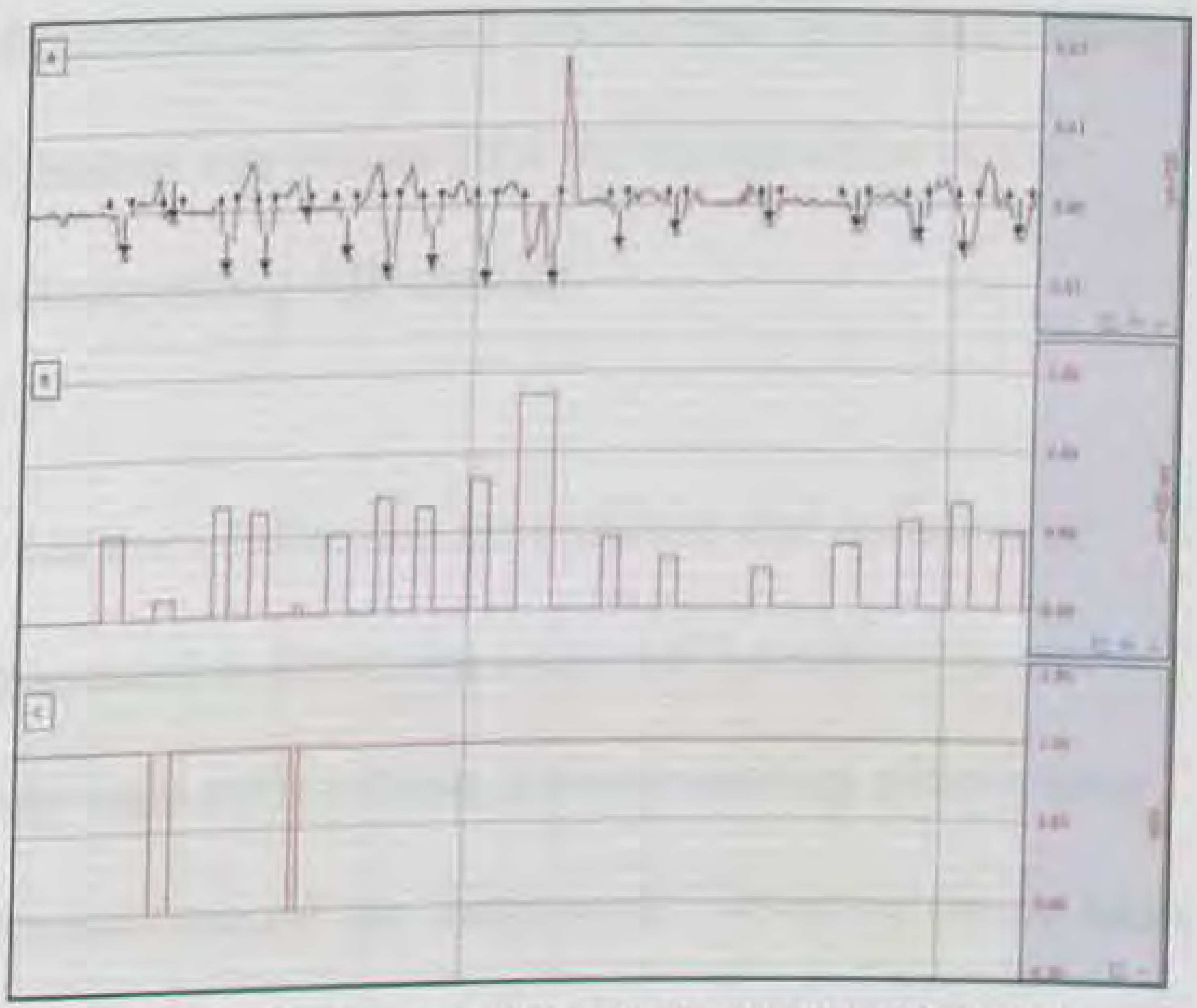


Figure 4.21. Identification of Signals Meeting Nasal Criteria **A.** Cleaned and marked Nasal signal; **B.** Nasal integral; **C.** $\text{OR(NOT(CH}^{\text{INTEGRAL}}\text{),LESS(X}^{\text{INTEGRAL THRESHOLD}}\text{,CH}^{\text{INTEGRAL}}\text{))}$ indicating 0 when marked nasal airflow breath does not meet breath criteria.

Respiratory Inductance Plethsmography (Abdominal and Ribcage): Respiratory movements in the ABD and RIB RIP channels were identified separately by using the cycle detector to identify positive peaks in their corresponding differential signals that met previously established 15% steady-state peak differential thresholds. Identified peaks were marked using the short arrow event marker as indicated in the *Baseline Steady-State Inspiratory Cycle Delineation: Respiratory Inductance Plethsmography* section. Once identified, all marked RIP signals were visually inspected for accuracy. Respiratory movements marked with more than one event mark due to double threshold crossing were deleted. Once all breath events were verified, the initiation and cessation of inspiration was identified in largely the same manner as stated in the *Steady-State Breath Demarcation: Respiratory Inductance Plethsmography* section, however instead of placing marks on the respective filtered RIP channel, events were placed on the corresponding RIP differential channel. Events were verified by a combined visual inspection and event count approach as described in the *Feeding Breath Demarcation: Nasal Airflow* section. Verified events were then transposed onto the filtered RIP signal by running the cycle detector to output unmatched pairs of minimum differential RIP channel events onto the corresponding filtered RIP channel. The same process was repeated for the transposition of the maximum event marks on the corresponding RIP channel.

Once all ABD and RIB breaths had been delineated for initiation and cessation of inspiration, an expression was generated to determine those ABD breaths that met previously established 15% steady-state ABD criteria. Breaths meeting criteria were identified by generating an expression channel that indicated a 1 when the breath had a slope and delta $\geq X^{\text{15\% Steady-State slope and delta}}$, and a 0 when the slope or delta were $< X^{\text{15\% Steady-State slope and delta}}$. Expression channels were established by selecting the filtered ABD channel, setting two associated measurement channels to calculate slope and delta, and running the cycle detector to measure and output the slope and delta values between matched pairs of minimum and maximum ABD events to new slope and delta measurement channels. Breaths with slope and delta values that met predetermined 15% thresholds were indicated through the generation of a new channel depicting the previously identified binary categorization from the expression AND(OR(NOT(CH$^{\text{SLOPE}}$),LESS(X$^{\text{SLOPE THRESHOLD}}$,CH$^{\text{SLOPE}}$)), OR(NOT(CH$^{\text{DELTA}}$), LESS(X$^{\text{DELTA THRESHOLD}}$,CH$^{\text{DELTA}}$))). The same process was then completed for the RIB RIP channel, using respective RIB steady-state thresholds (See *Figure 4.22* for a schematic of methods in the identification of signals meeting RIP criteria).

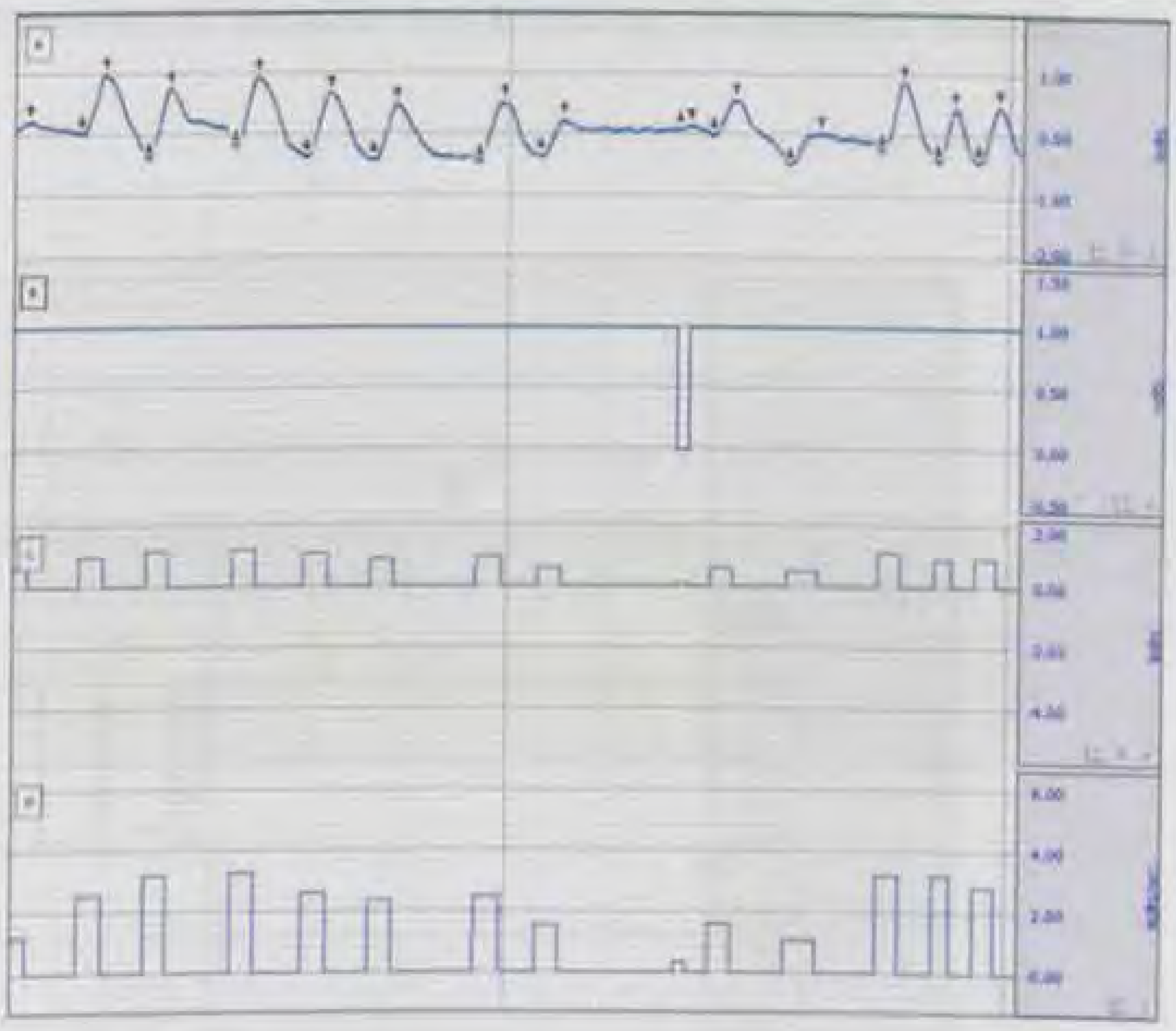


Figure 4.22. Identification of Signals meeting RIB Criteria **A.** Offset filtered RIP signal with markings **B.** Expression channel indicating demarcated breath not meeting threshold criteria by a 0; **C and D.** Measurement channels for slope and delta of filtered RIP signal.

A composite binary breath criteria expression was created using the previously generated Nasal, ABD, and RIB binary expression channels to indicate a 0 when composite breath criteria were not met: a.) Nasal integral is <15% steady state threshold; **or** b.) Both RIB and ABD have delta and slope values <15% steady state thresholds. The composite breath criteria channel was generated with the expression AND(LESS(.5,CH$^{\text{PNT INTEGRAL}}$),OR(LESS(.5,CH$^{\text{RIB COMBINED SLOPE/DELTA EXPRESSION}}$),LESS(.5,CH$^{\text{ABD COMBINED SLOPE/DELTA EXPRESSION}}$))).

Events delineating breaths not meeting composite breath criteria were removed from the nasal channel. Remaining breaths were marked on RIB and ABD delta measurement channels using the cycle detector programmed to export unmatched pairs of short arrow events, for visual confirmation that all breaths marked on the Nasal channel occurred during ABD or RIB movement. (See *Figure 4.23* and *Figure 4.24* for a schematic of methods in the identification and correction of breaths not meeting composite breath criteria.)

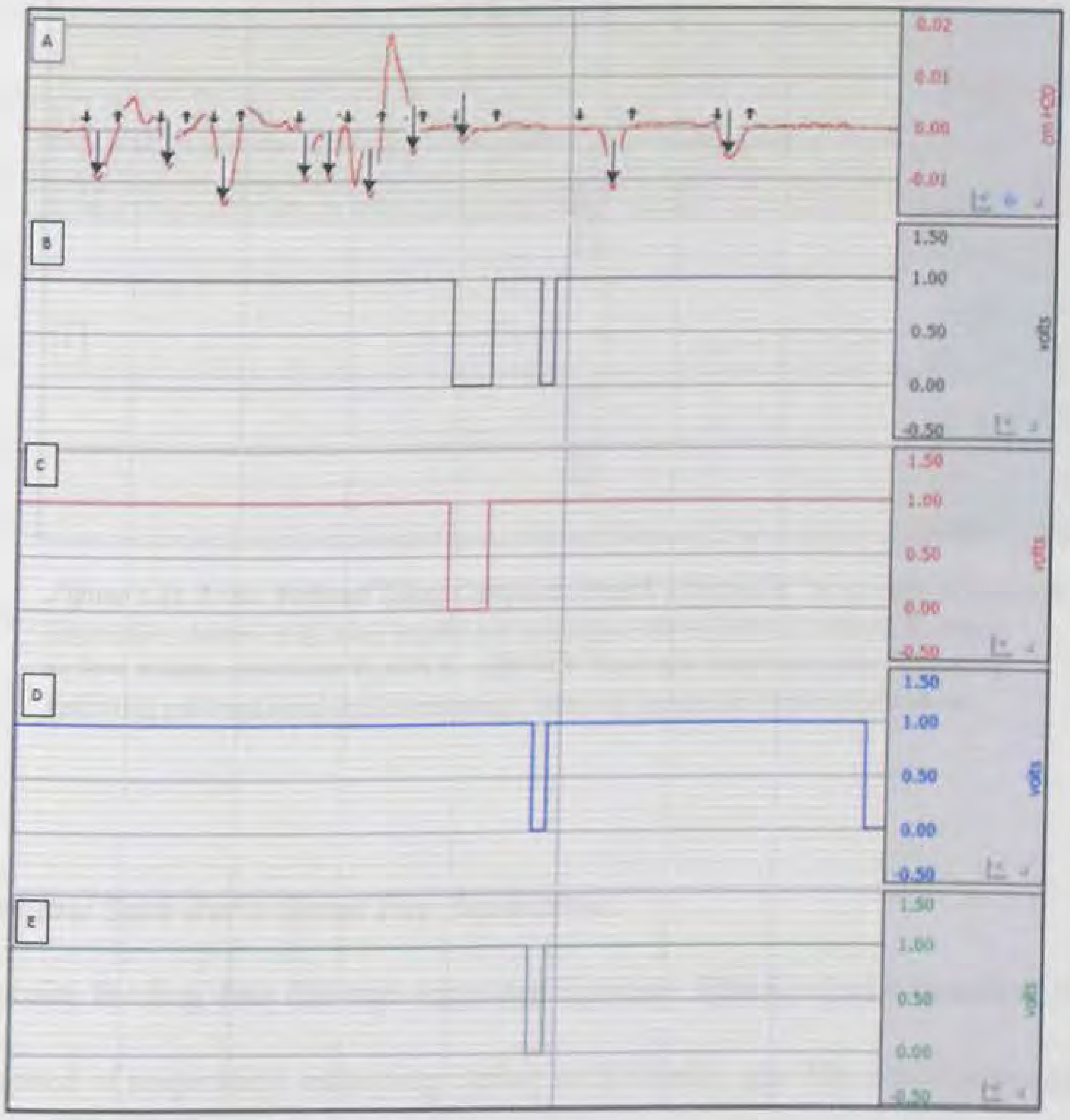


Figure 4.23. Identification of Signals meeting Composite Breath Criteria **A.** Nasal airflow signal; **B.** Expression channel indicating breaths not meeting composite breath criteria; **C.** Nasal airflow volume expression **D.** RIB **E.** ABD RIP slope and delta expression.

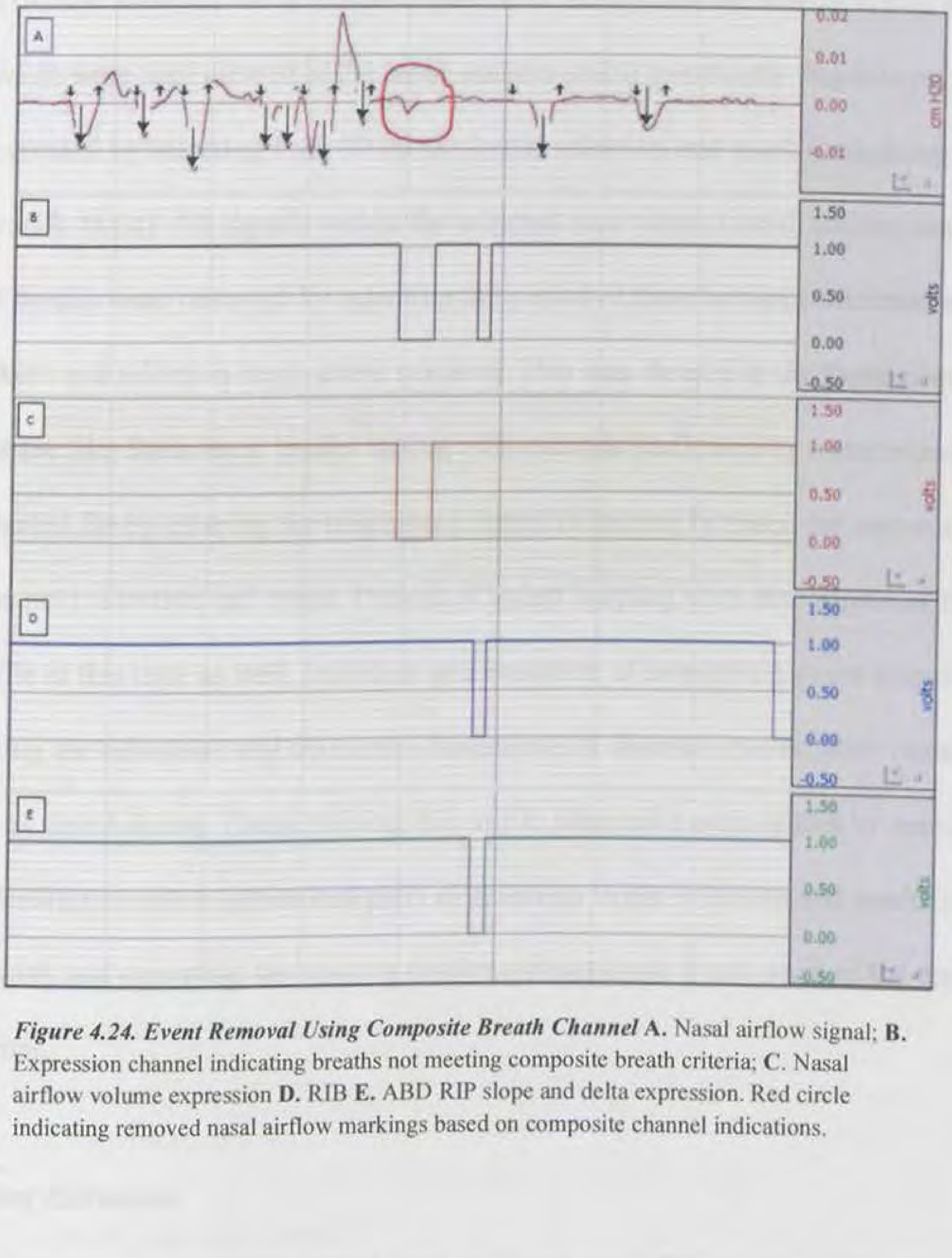


Figure 4.24. Event Removal Using Composite Breath Channel **A.** Nasal airflow signal; **B.** Expression channel indicating breaths not meeting composite breath criteria; **C.** Nasal airflow volume expression **D.** RIB **E.** ABD RIP slope and delta expression. Red circle indicating removed nasal airflow markings based on composite channel indications.

Suck-Burst and Suck-Burst-Break File Separation

The composite feeding data file was separated into two files for data extraction. One file was composed of respiration occurring during suck-bursts, one file was composed of respiration occurring during suck-burst-breaks. Suck-Burst files were created by selecting time 00:00- the initial selection begin mark (indicating the first suck burst). All signals within the selected area were cleared. Subsequent suck-bursts were removed by selecting the period of time between the selection begin event marker and the selection end event marker, which were then cleared in the same manner stated previously. Suck-burst break files were created by selecting time 00:00-the initial selection end mark (indicating the end of the suck-burst). All signals within the selected area were cleared. Subsequent suck-burst breaks were removed by selecting the period of time between selection end event markers and selection begin event markers. This was cleared in the same manner throughout the file. Suck-burst breaks lasting >15 seconds (indicated by a star event) were accounted for by clearing the respiratory signal occurring between the star event through the next selection end event. Periods of infant burping were also removed from the video file at this time as well. Initiation and cessation of inspiration event marks were verified using the minimum and maximum measurement channels paired with visual inspection as stated above. Those missing due to file separation were added by running the cycle detector to select unmatched pairs of selection begin/selection end marks in the sucking signal, and exporting the missing minimum/maximum event mark to the nasal airflow signal.

Measurement Extraction

Inspiratory time (ms), inspiratory period (ms), tidal volume (μV), number of breaths, and total signal duration time (sec) were extracted from the respective suck-burst and suck-burst-break files using the methods stated in *Extraction of Inspiratory Cycle Values: Nasal Airflow* section. Period measures reflecting time between suck-bursts/suck-burst breaks were removed by placing the measurement channel to time, and programming the cycle detector to identify and export times of unmatched pairs of selection begin markers. The same process was also completed on the sucking channel to identify timing of star events. Values preceding the exported event times were removed, as those were the times reflecting periods across suck-burst or suck-burst break boundaries and were not truly representative of inspiratory period. Respiratory rate was calculated by dividing the number of breaths by time and multiplying by 60 (bpm). Minute volume was then calculated by multiplying tidal volumes by respiratory rate. Measures of tidal volume and minute volume were then converted into percent steady-state volume by dividing by the infant's steady-state values (*Table 4.5, Figure 4.25-4.27*).

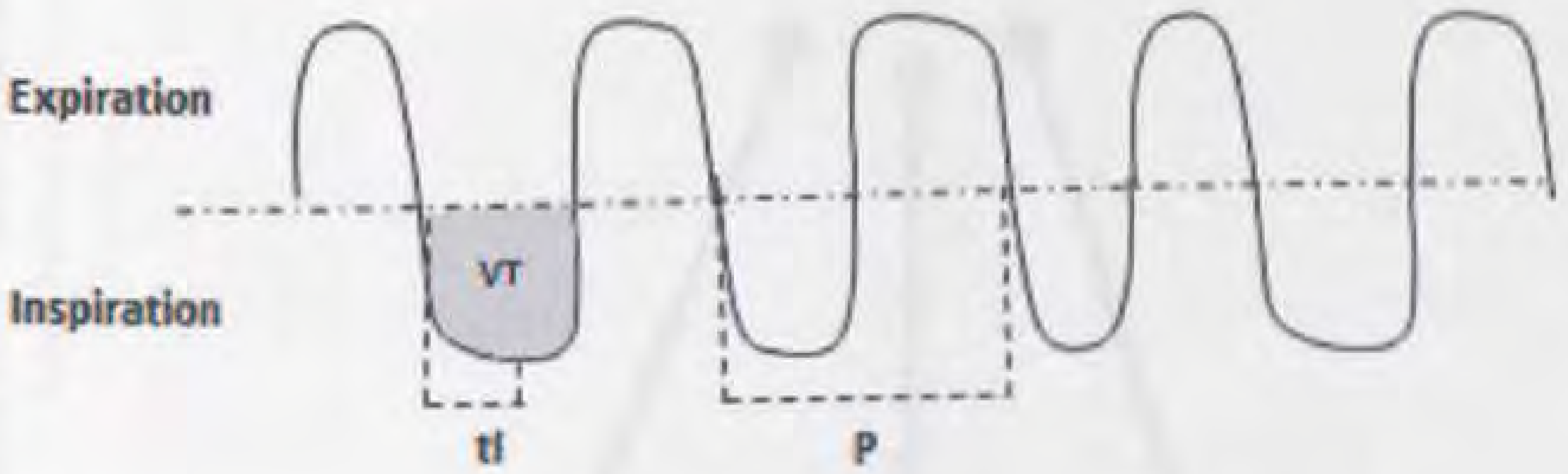


Figure 4.25. **Lung Volume Plot** Lung volume measures plotted from PNT over a sequence of 4 breathing cycles. Cycles above midline indicate expiration, cycles below midline indicate inspiration **tI:** Inspiratory Time; **V_T:** Tidal Volume **P:** Period. Bates, J., Schmalisch, G., Filbrun, D., & Stocks, J. (2000). Tidal breath analysis for infant pulmonary function testing. *Eur Respir J. 16*, 1180-1192.

Table 4.5. Respiratory Measure Calculations

Respiratory Measure	**Calculation**
Respiratory Rate (RR)	(Breath Count/Time)*60
Respiratory Rhythmicity	σ of P
Minute Volume (Raw)	V_T*RR

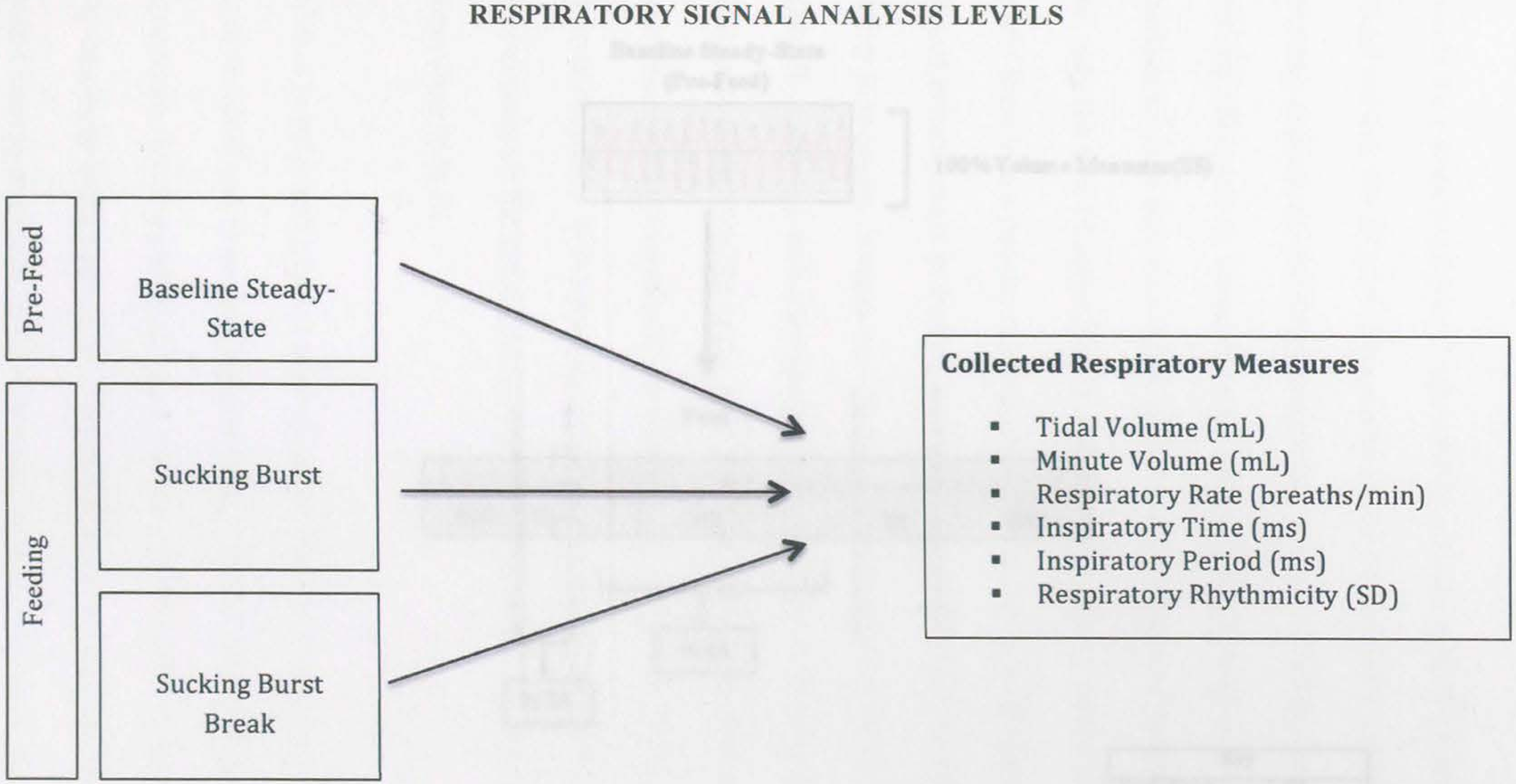


Figure 4.26. Levels of Signal Analysis

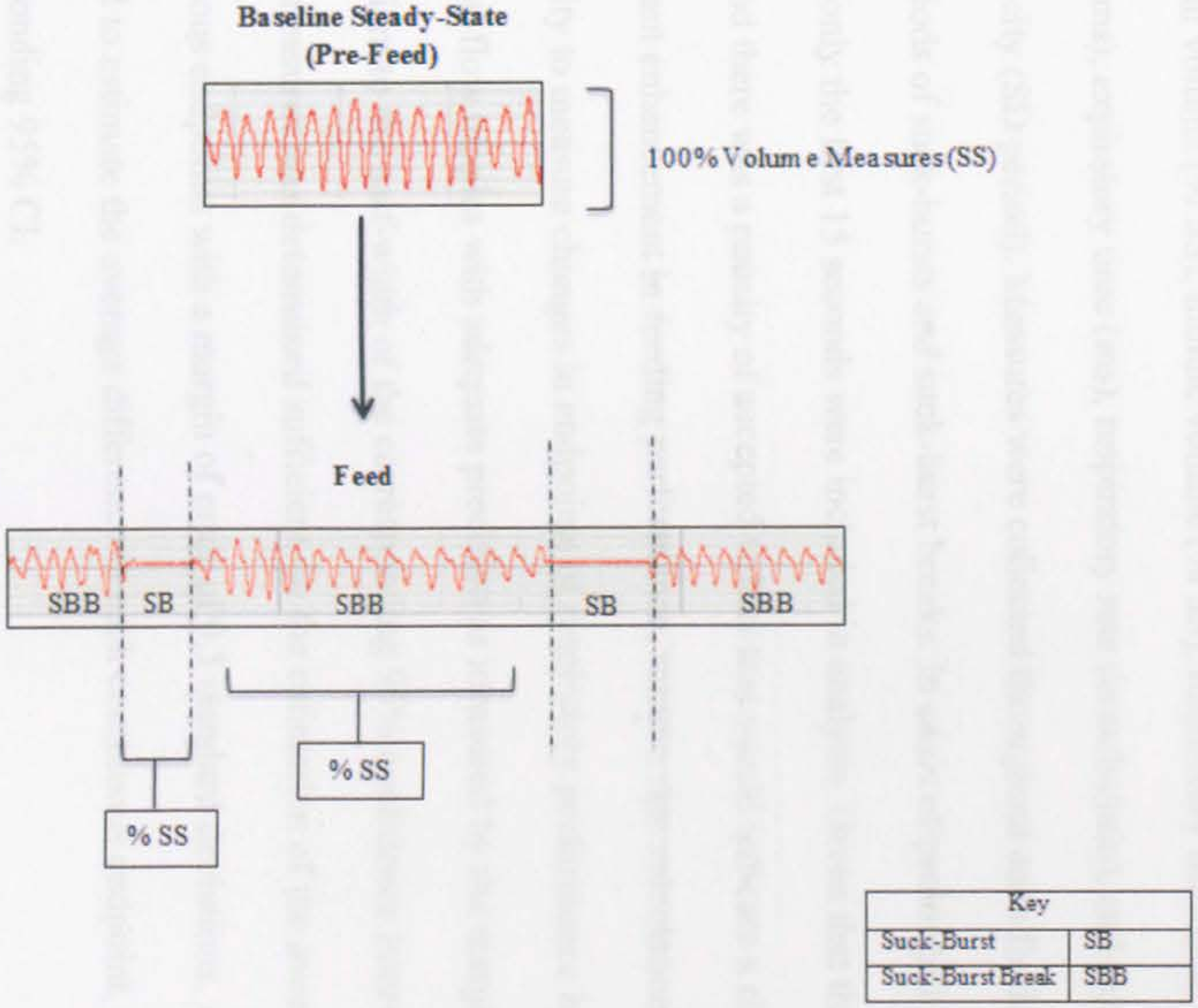


Figure 4.27. Respiratory Analysis

Statistical Analysis Plan

Endpoints for research question 1 are continuous measures of percent baseline steady-state tidal volume (% SS), minute volume (% SS), inspiratory time (ms), inspiratory period (ms), expiratory time (ms), respiratory rate (breaths/min), and respiratory rhythmicity (SD period). Measures were collected throughout each feed, and segmented into periods of suck-bursts and suck-burst breaks. In cases of prolonged suck-burst breaks, only the first 15 seconds were included in analysis. Given that this was a pilot study and there was a paucity of accepted values that would indicate a clinically significant enhancement in feeding performance, sample size calculations were based on the ability to measure changes in endpoints of respiratory performance between standard and slow-flow nipples with adequate precision as measured by the margin of error (equivalent to the half-width of the corresponding 95% confidence interval). Fifteen paired measures was determined sufficient for the estimation of the average difference in continuous endpoints with a margin of error of 0.5 standard deviations. Accordingly, we planned to estimate the average difference in each continuous endpoint, and construct the corresponding 95% CI.

In addition to point and interval estimation, we planned to compare continuous endpoints between standard and slow-flow nipples using paired t-tests or Wilcoxon signed-rank test as appropriate. We planned to compare the association between feeding performance and time to discharge using Spearman's Correlation with feeding performance as a fixed effect and time to discharge as the dependent variable. Standard analysis approaches for time-to-event data such as Cox proportional hazards regression or competing risks analysis were determined appropriate for the analysis of time to discharge if the data were subject to censoring (i.e. certain patients are not discharged by the end of the study) or if another event prevented discharge from occurring (e.g. death). In statistical analysis planning, we noted that this was a small pilot study designed to estimate average changes in endpoints with good precision, and was not powered to detect pre-specified clinical effects. Therefore, it was appreciated we would need to be cautious in our interpretation of findings.

CHAPTER 5: RESULTS

PARTICIPANT CHARACTERISTICS

Twenty-four subjects meeting eligibility criteria (see *Participants*) were recruited from the Medical University of South Carolina's Children's Hospital between October and December 2013. Six of these subjects did not undergo data collection for reasons including hospital transfer (n=2), identification of a comorbid condition excluding the patient from eligibility (n=3), and passing of the data collection window before data collection could occur (n=1). Five of the remaining subjects underwent data collection but were not included in analysis for reasons including failure to obtain a sufficient latch to the bottle nipple during data collection (n=3), and poor signal quality (n=2). A total of thirteen subjects were included in the final analysis.(See *Table 5.1* for subject demographics.) Subjects ranged in gestational age from 29 weeks 6 days to 33 weeks 5 days and included 7 infants born very low birth weight (VLBW <1500g), 5 infants born low birth weight (1500g-2500g), and 1 infant born normal birth weight (>2500g). *Table 5.2* provides a full description of sample health characteristics including 1 and 5 minute APGAR scores, as well as the number of infants requiring commonly used cardiopulmonary interventions during their hospital course.

Table 5.1. Demographics

Demographic Category	Number	Percent
Sex		
Male	5	39%
Female	8	61%
Race		
African American	8	61%
Caucasian	5	39%
Ethnicity		
Hispanic/Latino	0	0%
Not Hispanic/Latino	13	100%

Ten Registered Nurses fed the subjects during data collection. Infant PMA at time of data collection ranged from 32 weeks 5 days to 35 weeks 4 days (median 34 weeks 1 day). Nurses had between 3 months and 20 years of neonatal nursing experience (median 5 years).

Table 5.2. Sample Health Characteristics

Characteristics	Study Sample (n=13)
Gestational Age (wks.)	31.4 (29.6-33.5)[a]
Birth Weight (g)	1425 (1230-2680)[a]
APGAR 1 min.	7 (2-9)[a]
APGAR 5 min.	8 (6-9)[a]
Intubation (Y/N)	1 (8%)[b]
CPAP (Y/N)	10 (77%)[b]
Surfactant (Y/N)	3 (23%)[b]
Caffeine (Y/N)	8 (62%)[b]

[a] *Values shown as median (range)*

[b] *Values shown as number of infants with intervention (%)*

Ninety-two percent (n=12) of infants were fed by their assigned nurse for data collection feeds. One infant was not fed by their assigned nurse, and was instead fed by the lead unit nurse due to scheduling constraints. Each nurse independently chose the feeding position they would feed the infant in during data collection feeds. This was maintained throughout all feeds for each infant, and ranged from upright, right side lying, and left side lying positions across the sample. The most common feeding schedule at the time of data collection was BID with cues (54%), although feeding schedule was variable across the sample. (See *Table 5.3* for subject feeding characteristics at the time of

Table 5.3. Sample Feeding Characteristics

Characteristics	Study Sample (n=13)
PMA at PO Initiation (wks.)	33.3 (31.5-35.0)[a]
PMA at Data Collection (wks.)	34.1 (32.5-35.4)[a]
Weight at Data Collection (g)	1924.5 ± 322.5[a]
Feeding Position at Collection	
Upright	3 (23%)[b]
R Side Lying	1 (7%)[b]
L Side Lying	9 (69%)[b]
PO Feeding Schedule at Collection	
BID	1 (7%)[b]
BID with Cues	8 (62%)[b]
Cues	1 (8%)[b]
Every Other	1 (8%)[b]
Ad Lib	2 (15%)[b]

[a] *Values shown as mean ± s.d.*

[b] *Values shown as number of infants (%)*

data collection.)

Infant state of arousal was consistently rated as a IV upon initiation of both standard-flow and slow-flow oral feedings in 11/13 infants (85%). This was characterized by eyes open or closed, non-reflexive movements of limbs, intermittent motionless but alert, and facial activity without crying. Pre-feeding state of arousal was different between slow-flow and standard-flow oral feeds in 2/13 infants (15%). Both of these infants were rated as a level IV prior to the standard-flow presentation and a state of III, characterized by rapid eye movement, occasional eye opening, and small grunts or extremity movement, prior to the provision of the slow-flow nipple. (See *Table 4.2* for a full description of state of arousal categories.)

CHARACTERISTICS OF STEADY-STATE RESPIRATION

Individual and composite group data reflecting respiratory measures were reviewed in their raw form prior to statistical analysis to determine sample dispersion. Data were viewed separately during the initial suck-burst, the subsequent suck-burst, and the suck-burst break. All measures were found to be negatively skewed during at least one of these time points, with the majority skewed left during all three. Median was determined to be the best summary composite measure of all outcome variables to maintain consistency in the reporting of results. Tidal and minute volumes were converted to their respective percent steady-state values for analysis and subsequent reporting. The Wilcoxon signed rank test was used for comparison of all data. Respiratory performance was directly compared between slow-flow and standard-flow nipples during the initial 30 seconds of sucking, the subsequent sucking period, and the suck-burst break.) Respiratory performance between slow-flow and standard-flow nipples was also indirectly compared for consistency in associations with steady-state respiration and temporal feeding patterns. All outcomes were reported as difference in paired median composite measures (*Appendices 5.1-5.9* provide individual and composite histograms for each outcome variable.)

Parameters of baseline, steady-state, respiration varied greatly across subjects and are reported in *Table 5.4*. Varying respiratory mechanics, characterized by differing amounts of RIB to ABD displacement during steady-state respiration were found. Approximately half of the subjects demonstrated greater ABD than RIB expansion (n=7, 54%) (ratio <1), while the other half demonstrated greater RIB than ABD expansion (n=6, 46%) (ratio > 1). RIB:ABD ratio was negatively correlated with respiratory rate (r = -.56, p = .04), where infants with greater ABD than RIB contribution (ratio<1) exhibited a higher respiratory rate than those with greater RIB than ABD contribution (ratio>1) (*Figure 5.1*).

Table 5.4. Steady-State Respiration

Respiratory Measure	Median	Minimum	Maximum
Inspiratory Time (ms)	340	200	450
Period (ms)	750	430	1220
Rhythmicity (SD)	0.1	0.0	0.2
Respiratory Rate (bpm)	76	43	133
RIB:ABD Ratio	0.8	0.1	2.3

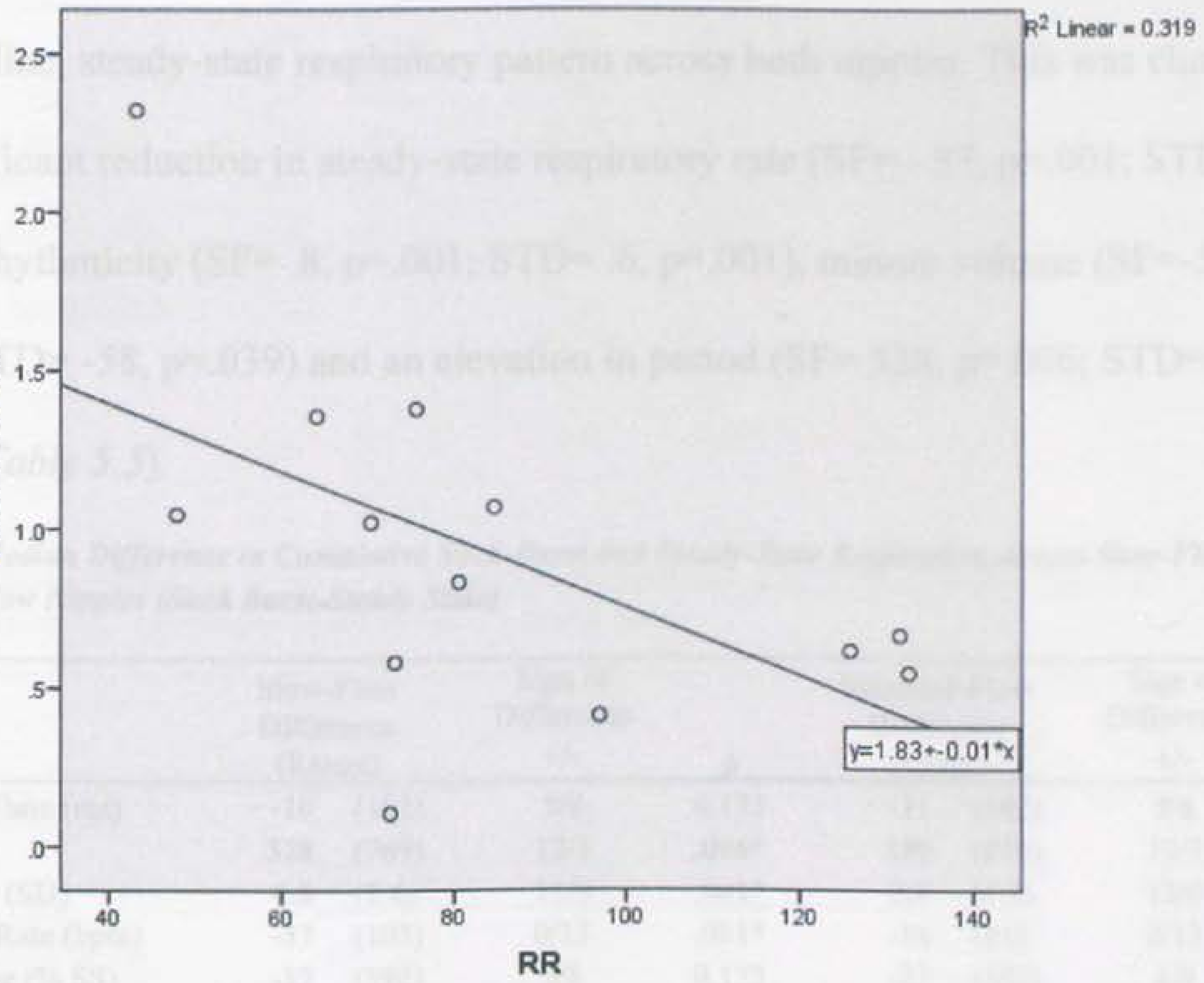


Figure 5.1. Relationship between RIB:ABD Ratio and Respiratory Rate Increasing RIB contribution correlated with decreasing RR.

RESEARCH QUESTION 1

What is the difference in inspiratory time (ms), respiratory period (ms) respiratory cycle rhythmicity (SD), respiratory rate (bpm), tidal volume (% SS), and minute volume (% SS) between slow-flow and standard-flow nipples during bottle-feeding in preterm infants?

All subjects exhibited periods of suck-bursts and suck-burst breaks once the bottle was introduced to the oral cavity. Respiration during suck-bursts was significantly diminished from baseline, steady-state respiratory pattern across both nipples. This was characterized by a significant reduction in steady-state respiratory rate (SF= - 37, p=.001; STD= -34, p=.001), rhythmicity (SF= .8, p=.001; STD= .6, p=.001), minute volume (SF=-53, p=.023; STD= -58, p=.039) and an elevation in period (SF= 328, p=.006; STD= 359, p=.007) (*Table 5.5*).

Table 5.5. Median Difference in Cumulative Suck-Burst and Steady-State Respiration Across Slow-Flow and Standard-Flow Nipples (Suck Burst-Steady State)

	Slow-Flow Difference (Range)	Sign of Difference +/-	p	Standard-Flow Difference (Range)	Sign of Difference +/-	p
Inspiratory Time (ms)	-10 (162)	5/8	0.133	-31 (182)	5/8	0.064
Period (ms)	328 (769)	12/1	.006*	359 (873)	10/3	.007*
Rhythmicity (SD)	0.8 (2.4)	13/0	.001*	0.6 (1.5)	13/0	.001*
Respiratory Rate (bpm)	-37 (105)	0/13	.001*	-34 (84)	0/13	.001*
Tidal Volume (% SS)	-32 (392)	5/8	0.152	-23 (342)	4/9	0.552
Minute Volume (% SS)	-53 (244)	1/12	.023*	-58 (236)	3/10	.039*

Difference reported as paired difference in median values.

* *$p < .05$ vs Steady-State*

Suck-Bursts: Examination of the temporal changes in respiration throughout a feed revealed respiration during the initial 30 seconds of sucking to be unique from the subsequent sucking period. In addition to the significant reductions in steady-state inspiratory period, rhythmicity, rate, and minute volume that were also observed during the subsequent sucking period, the initial 30 seconds of sucking also exhibited a significant reduction in steady-state inspiratory time (SF= -60, p=.016; STD= -94, p=.004) that was not found in the subsequent sucking period (SF= -10, p= .152; STD= -21, p=.101) (*Table 5.6-5.7*).

Table 5.6. Median Difference in Respiration Between the Initial Suck-Burst and Steady-State Across Slow-Flow and Standard-Flow Nipples (Initial Suck Burst-Steady State)

	Slow-Flow Difference (Range)	Sign of Diff. +/-	p	Standard-Flow Difference (Range)	Sign of Diff. +/-	p
Inspiratory Time (ms)	-60 (220)	2/11	.016*	-94 (220)	2/11	.004*
Period (ms)	484 (2240)	10/3	.011*	33 (1320)	10/3	.152*
Rhythmicity (SD)	1.2 (3.5)	13/0	.001*	1.1 (4.6)	13/0	.001*
Respiratory Rate (bpm)	-50 (109)	0/13	.001*	-38 (88)	0/13	.001*
Tidal Volume (% SS)	-31 (449)	4/9	0.133	-36 (457)	4/9	0.463
Minute Volume (% SS)	-65 (242)	1/12	0.023*	-63 (350)	3/10	.039*

Difference reported as paired difference in median values.
** p < .05 vs Steady-State*

Table 5.7. Median Difference in Respiration Between the Subsequent Suck-Burst and Steady-State Across Slow-Flow and Standard-Flow Nipples (Subsequent SB-Steady State)

	Slow-Flow Difference (Range)	Sign of Diff. +/-	p	Standard-Flow Difference (Range)	Sign of Diff. +/-	p
Inspiratory Time (ms)	-10 161	5/8	0.152	-21 175	5/8	0.101
Period (ms)	355 760	11/2	.011*	354 873	10/3	.009*
Rhythmicity (SD)	0.7 2.3	13/0	.001*	0.5 1.5	13/0	.001*
Respiratory Rate (bpm)	-36 104	0/13	.001*	-31 85	0/13	.001*
Tidal Volume (% SS)	-34 388	6/7	0.507	-22 335	5/8	0.650
Minute Volume (% SS)	-55 244	2/11	0.028*	-54 232	3/10	0.039*

Difference reported as paired difference in median values.
** p < .05 vs Steady-State*

This finding was supported by those findings obtained from direct comparison of the initial 30 seconds of sucking to the subsequent sucking period during which time the initial 30 seconds of sucking was found to have a significantly lower inspiratory time across both nipples (SF= -60, p=.005; STD= -94, p=.002). Other observed differences between the initial 30 seconds of sucking and the subsequent sucking period were solely observed on the slow-flow nipple. During slow-flow feeds, the initial 30 seconds of sucking was found to have a significantly reduced respiratory rate (-50, p=.006) and rhythmicity (1.2, p=.028) from the subsequent sucking period. No difference in respiratory rate (-38, p= .173) or rhythmicity (1.1, p=.075) between the initial 30 seconds of sucking and the subsequent sucking period was observed on the standard-flow nipple (*Table 5.8*).

Table 5.8. Median Difference in Respiration Between Initial 30 Seconds of Sucking and Subsequent Sucking Period Across Slow-Flow and Standard-Flow Nipples (Initial 30 Sucking– Subsequent Sucking)

	Slow-Flow Difference (Range)	Sign of Diff. +/-	p	Standard-Flow Difference (Range)	Sign of Diff. +/-	p
Inspiratory Time (ms)	-60 (221)	1/12	.005*	-94 (219)	1/12	.002*
Period (ms)	484 (2241)	8/5	0.087	33 (1324)	4/9	0.221
Rhythmicity (SD)	1.2 (3.5)	10/3	.028*	1.1 (4.6)	8/5	0.075
Respiratory Rate (bpm)	-50 (109)	2/11	.006*	-38 (88)	4/9	0.173
Tidal Volume (% SS)	-31 (449)	7/6	0.861	-36 (457)	4/9	0.507
Minute Volume (% SS)	-65 (242)	4/9	0.133	-63 (350)	3/10	0.152

Difference reported as paired difference in median values.

*$p < .05$

Direct examination of the differences in respiratory performance between the slow-flow and standard-flow nipple during the initial 30 second of sucking revealed respiration during feeds on the slow-flow nipple to have a significantly higher inspiratory period than on the standard-flow nipple (1252, p= .006) (*Table 5.9*). No differences in respiratory performance between slow-flow and standard-flow nipples were observed in the subsequent sucking period (*Table 5.9-5.10*).

Table 5.9. Median Difference in Respiration Between Slow-Flow and Standard-Flow Feeds During the Initial Suck-Burst (SF-STD)

	Slow-Flow Median (Range)	Standard-Flow Median (Range)	Difference (SF-STD)	Sign of Diff. +/-	p
Inspiratory Time (ms)	264 (200)	248 (240)	28	10/3	0.064
Period (ms)	1252 (2343)	794 (1112)	321	11/2	0.006*
Rhythmicity (SD)	1.3 (3.6)	1.2 (4.7)	.2	7/6	0.917
Respiratory Rate (bpm)	36 (56)	38 (78)	-6	4/8	0.289
Tidal Volume (% SS)	69 (449)	64 (457)	4	8/5	0.917
Minute Volume (% SS)	35 (242)	37 (350)	-1	6/7	0.507

Difference reported as paired difference in median values.
* $p < .05$

Table 5.10. Median Difference in Respiration Between Slow-Flow and Standard-Flow Feeds During the Subsequent Suck-Burst (SF-STD)

	Slow-Flow Median (Range)	Standard-Flow Median (Range)	Difference (SF-STD)	Sign of Diff. +/-	p
Inspiratory Time (ms)	286 (171)	289 (188)	0	5/7	0.695
Period (ms)	976 (1037)	1055 (1059)	68	9/4	0.861
Rhythmicity (SD)	.8 (2.4)	0.7 (1.5)	.0	8/5	0.382
Respiratory Rate (bpm)	43 (67)	43 (55)	-5	5/8	0.65
Tidal Volume (% SS)	66 (388)	78 (335)	-8	5/8	0.6
Minute Volume (% SS)	45 (244)	46 (232)	-9	5/8	0.507

Difference reported as paired difference in median values.
* $p < .05$

Suck-Burst Breaks: Comparison of respiration between suck-bursts and suck-burst breaks revealed suck-burst breaks to have significantly greater performance in all measures of respiration than during suck-bursts. Specifically, suck-burst breaks were found to have a heightened inspiratory time (SF= -11 , p=.017; STD= -38, p=.011), respiratory rate (SF= -23, p=.001; STD= -21, p=.001), respiratory rhythmicity (SF=.3, p=.002; STD=.3, p=.007) tidal volume (SF= -24, p= .001; STD= -33, p=.005), and minute volume (SF= -46, p=.002; STD= -59, p=.004), as well as a significant reduction in inspiratory period

(SF=252, p=.002, STD=235, p=.005) across both slow-flow and standard-flow nipples (*Table 5.11*).

Table 5.11. Median Difference in Respiration Between Cumulative Suck-Bursts and Suck-Burst Breaks Across Slow-Flow and Standard-Flow Nipples (Suck Burst-Suck Burst Break)

	Slow-Flow Difference	(Range)	Sign of Diff. +/-	p	Standard-Flow Difference	(Range)	Sign of Diff. +/-	p
Inspiratory Time (ms)	-11	(60)	3/10	.017*	-38	(74)	3/10	.011*
Period (ms)	252	(584)	12/1	.002*	235	(524)	12/1	.005*
Rhythmicity (SD)	0.3	(2.7)	12/1	.002*	0.3	(1.7)	10/3	.007*
Respiratory Rate (bpm)	-23	(37)	0/13	.001*	-21	(31)	0/13	.001*
Tidal Volume (% SS)	-24	(155)	0/13	.001*	-33	(258)	1/12	.005*
Minute Volume (% SS)	-46	(167)	1/12	.002*	-59	(229)	1/12	.004*

Difference reported as paired difference in median values.

* *p* < .*05*

Despite the observed improvement in respiration during the suck-burst break when compared to the suck-burst, suck-burst breaks continued exhibit reductions from baseline respiratory performance. This was observed in measures of respiratory rhythmicity (SF=.4, p=.001; STD=.4, p=.001) and rate (SF= -15, p= .039; STD= -12, p=.009) across both slow-flow and standard-flow nipples. The only measure to show elevations from baseline steady-state respiration was tidal volume during feeds on the standard-flow nipple, which was significantly greater than at baseline (24, p=.028). No significant difference in tidal volume during the suck-burst break on the slow-flow nipple was observed (-46, .463) (*Table 5.12*). Direct comparison of respiration during suck-burst breaks between slow-flow and standard-flow nipples revealed no significant difference in any measure of respiration (*Tables 5.12- 5.13*).

Table 5.12. Median Difference in Respiration Between Suck-Burst Breaks and Steady-State Respiration Across Slow-Flow and Standard-Flow Nipples (Suck Burst Break-Steady State)

	Slow-Flow Difference (Range)	Sign of Diff. +/-	p	Standard-Flow Difference (Range)	Sign of Diff. +/-	p
Inspiratory Time (ms)	-9 (203)	6/7	0.311	-6 (202)	6/7	0.422
Period (ms)	-16 (460)	6/7	0.701	72 (500)	9/4	0.221
Rhythmicity (SD)	0.4 (1.0)	13/0	.001*	0.4 (0.5)	13/0	.001*
Respiratory Rate (bpm)	-15 (89)	4/9	.039*	-12 (80)	3/10	.009*
Tidal Volume (% SS)	46 (457)	7/6	0.463	24 (337)	9/4	.028*
Minute Volume (% SS)	-2 (399)	6/7	0.753	22 (317)	8/5	0.345

Difference reported as paired difference in median values.

* $p < .05$ *vs Steady-State*

Table 5.13. Median Difference in Respiration Between Slow-Flow and Standard-Flow Feeds During the Suck-Burst Breaks (SF-STD)

	Slow-Flow Median (Range)	Standard-Flow Median (Range)	Difference (SF-STD)	Sign of Diff. +/-	p
Inspiratory Time (ms)	301 (175)	317 (212)	-11	5/8	0.345
Period (ms)	754 (555)	792 (577)	-46	5/8	0.087
Rhythmicity (SD)	.5 (.9)	0.4 (0.5)	.0	5/8	0.6
Respiratory Rate (bpm)	63 (60)	63 (57)	1	7/6	0.701
Tidal Volume (% SS)	105 (457)	124 (337)	-37	4/9	0.382
Minute Volume (% SS)	98 (399)	122 (317)	-20	5/8	0.6

Difference reported as paired difference in median values.

* $p < .05$

RESEARCH QUESTION 2

What is the difference in rate of transfer (mL/min) and proficiency (%) of oral intake between slow-flow and standard-flow nipples in the preterm infant?

Measures of milk ingestion were reviewed prior to statistical analysis to determine sample dispersion. It was determined that assessment of normality was limited by the small sample size and single, composite outcome measures within each infant. (See *Appendix 5.10* for histograms of all variables.) Data was therefore treated conservatively as nonparametric with comparisons performed using the Wilcoxon signed rank test and reported in terms of sample median.

Prescribed milk volume ranged from 29-47mL, with a median prescribed volume of 36mL. High variability in measures of milk ingestion were observed within and across infants. *Table 5.14* provides feeding volume and duration characteristics. No significant difference between slow-flow and standard-flow nipples were observed in measure of feeding duration (1, p=.969), anterior bolus loss (0, p= 1.000), five minute consumption (-1, p= .292), total ingestion (2, p= .583), and overall transfer (-4, p= .583).

Table 5.14. Volume and Duration Characteristics of Infant Feeding Between Slow-Flow and Standard-Flow Nipples

	Slow-Flow *Median (Range)*	Standard-Flow *Median (Range)*	Difference SF-STD	Sign of Diff. +/-	p
Feeding Duration (min.)	12 (6-22)	12 (7-25)	1	7/5	0.969
Anterior Bolus Loss (mL)	1 (0-2)	0 (0-6)	0	3/1	1.000
Five Minute Ingestion (mL)	14 (8-26)	14 (6-27)	-1	4/9	0.292
Total Ingestion (mL)	27 (12-33)	27 (13-58)	2	7/5	0.583
Overall Transfer (%)	69 (30-110)	73 (28-141)	6	7/5	0.583

Difference reported as paired difference in median values.

Rate of milk transfer was calculated during the first 5 minutes of feeding and the subsequent feeding period. A cumulative total feed rate of transfer was then calculated to summarize rate of transfer throughout the entire feed. Infants demonstrated a significantly faster rate of milk transfer during the initial 5 minutes of oral intake as they did during the subsequent portion of their feed across both slow-flow (1.2, p = .002) and standard-flow nipples (.8, p=.005). Direct comparison of rate of transfer between slow-flow and standard-flow nipples revealed no significant difference in rate of transfer during any portion of the feed. Consistent findings were observed in comparison of measures of proficiency between slow-flow and standard-flow nipples, in which no significant differences were observed (-4, p= .249). (See *Table 5.15* for values pertaining to rate of transfer and proficiency.) OFS scores generated from measures of rate of transfer and proficiency ranged from 1-4. Median OFS score was 4.0 during both slow-flow and standard-flow feeds (p=.914).

Table 5.15. Differences in Measures of Rate of Transfer and Proficiency Between Slow-Flow and Standard-Flow Nipples (SF-STD)

	Slow-Flow *Median (Range)*		Standard-Flow *Median (Range)*		Difference SF-STD	Sign of Diff. +/-	p
Rate of Transfer (mL/min.)							
First Five Minute	2.80	(1.6-5.2)	2.80	(1.2-5.4)	-0.20	4/9	0.292
Subsequent Feed	1.60	(.6-3.7)	2.00	(0-3.3)	-0.33	5/8	0.701
Cumulative Feed	2.10	(1-4.5)	2.20	(1.16-4.6)	-0.17	5/8	0.552
Proficiency (%)	36.00	(20-90)	39.00	(15-93)	-4.00	4/9	0.249

Examination of the relationship between the above measures of milk ingestion revealed proficiency to be strongly correlated with rate of transfer during the first five minutes (SF r =.78, p=.002; STD r =.92, p=<.001), and rate of transfer throughout the entire feed (SF r=.71, p= .006; STD r=.74, p=.004) across both nipples. Proficiency also demonstrated a moderate-to-strong association with overall transfer on both the slow-flow (r=.59, p=.032) and standard-flow nipple (r =.65, p=.015).

In contrast to the above associations common to both the slow-flow and standard-flow nipples, other associations were found to be unique to either the slow or standard-flow nipple. Specifically, while a negative association between rate of transfer in the first five minutes and total duration of feeding time was observed on the slow-flow nipple (r= -.68, p=.01), no association between these measures was observed on the standard-flow nipple (r= -.115, p=.708). Further differences were observed in comparisons of the association between overall transfer and the above measures of milk ingestion. Rate of transfer during the first five minutes (r=.59, p=.033) subsequent rate of transfer (r= .75, p= .003) and total rate of transfer (r= .74, p= .004) were all found to be moderate-to-strongly associated with overall transfer on the standard-flow nipple, but were not found to have any association on the slow-flow nipple. (See *Tables 5.16-5.18* for a full listing of association values.) Scatterplots of discussed associations are provided in *Appendices 5.11-13.*

Table 5.16. Spearman's Correlation Between Proficiency and Measures of Milk Ingestion Across Slow-Flow and Standard-Flow Nipples

	Slow-Flow		Standard-Flow	
	r	p	r	p
5 Rate (mL/min)	0.78	0.002*	0.92	<0.001*
Subsequent Rate (mL/min)	0.37	0.207	0.39	0.194
Total Rate (mL/min)	0.71	0.006*	0.74	0.004*
Overall Transfer (%)	0.59	0.032*	0.65	0.015*

$* p < .05$

Table 5.17. Spearman's Correlation Between Feeding Duration and Measures of Milk Ingestion Across Slow-Flow and Standard-Flow Nipples

	Slow-Flow		Standard-Flow	
	r	p	r	p
5 Rate (mL/min)	-0.68	0.01*	-0.12	0.708
Subsequent Rate (mL/min)	-0.44	0.135	0.04	0.886
Total Rate (mL/min)	-0.79	0.001*	-0.23	0.457
Proficiency (%)	-0.47	0.103	-0.02	0.95

$* p < .05$

Table 5.18. Spearman's Correlation Between Overall Transfer and Measures of Milk Ingestion Across Slow-Flow and Standard-Flow Nipples

	Slow-Flow		Standard-Flow	
	r	p	r	p
5 Rate (mL/min)	0.26	0.395	0.59	0.033*
Subsequent Rate (mL/min)	0.26	0.399	0.75	0.003*
Total Rate (mL/min)	0.17	0.571	0.74	0.004*
Duration (min)	0.28	0.347	0.40	0.175

* $p < .05$

Although sample size prohibited multivariate regression, case-by-case analysis demonstrated the relationship between characteristics of milk ingestion (rate of transfer in the first five minutes, subsequent rate of transfer and feeding duration) and total milk ingestion. As illustrated in *Table 5.19*, infants were able to obtain approximately equal volumes of milk ingestion using two different methods. In Case 1 the infant demonstrated a high rate of transfer during the initial 5 minutes, but the subsequent portion of the feed was short in duration and reduced in rate of milk transfer. In contrast, the infant depicted in Case 2 demonstrated much lower initial rate of transfer, but was able to maintain this rate during the subsequent feeding period for a longer duration that enabled the infant to ingest similar volumes of milk. Case 3 illustrates the effect of reductions in all characteristics on volume of milk ingestion.

Table 5.19. Case-by-case Analyses of the Relationship Between Measures of Feeding Performance and Total Consumed Volume

Case	First 5 Rate (mL/min)	Subsequent Rate (mL/min)	Feeding Time (min)	Volume Consumed (mL/% Rx)
1	5.2	1	6	27 (63%)
2	1.2	1.2	25	29 (73%)
3	1.6	0.57	12	12(30%)

RESEARCH QUESTION 3

What is the association between inspiratory time (ms), respiratory period (ms) respiratory cycle rhythmicity (SD), respiratory rate (bpm), tidal volume (% SS), and minute volume (% SS) on the slow-flow and standard-flow nipple and time to discharge?

Hospital discharge characteristics of the sample and were found to be variable in distribution, therefore it was decided to report the results as medians, and examine associations using the Spearman's correlation coefficient across all measures. Median time to achieve full oral feeds from the initiation of oral feeding was 10 days. Oral feeding was the last achieved developmental milestone required for discharge in 85% of the sample (n=11). Of these infants, the median difference in time between the achievement of full oral feeds and the previous achievement of all other milestones was 1 week. (See *Table 5.20* for a summary of the sample's time to achieve relevant developmental milestones.)

Table 5.20. Sample Hospital Discharge Characteristics

	Median	Minimum	Maximum
PMA at other Milestones	34 0/7	33 0/7	35 5/7
PMA at Full PO	34 5/7	33 5/7	36 1/7
Days from PO Initiation to Full PO	10	6	19
PMA at Discharge	34 6/7	33 6/7	36 3/7

A moderate association was found between days to acquisition of full oral intake and days to hospital discharge (r= .68 p=.011)(*Figure 5.2*). To further examine the relationship between these clinical outcomes, separate Spearman's correlations were performed between measures of feeding performance and time to full oral intake, as well between measures of feeding performance and time to hospital discharge.

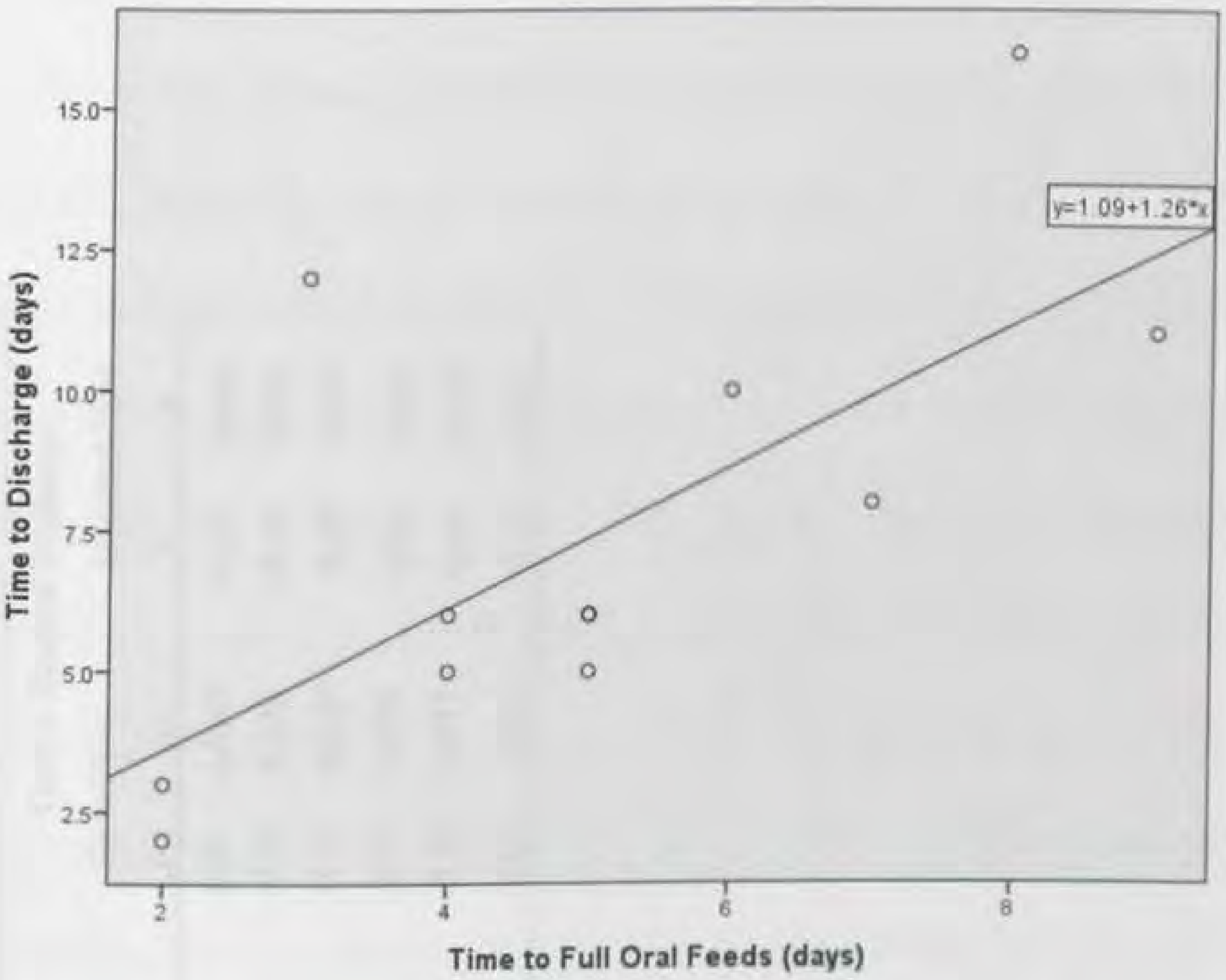


Figure 5.2. Relationship Between Time to Full Oral Feeds and Time to Hospital Discharge Significant positive association exists (r=.675, p=.011)with increased time to full oral feeds correlated with increased time to hospital discharge.

Characteristics of Milk Ingestion: Correlations between characteristics of milk ingestion were found to differ across nipples and clinical outcomes. Feeding duration was moderate-to-strongly associated with both time to achieve full oral feeds (r=.78, p=.002) and time to hospital discharge on the slow-flow nipple(r= .59, p=.034), but demonstrated no association with either clinical outcome on the standard-flow nipple. In contrast, while 5 minute rate of transfer (SF r= -.78, p=.002; STD r= -.67, p=.013) and total rate of transfer (SF r= -.84, p<.001; STD r= -.68, p=.011) demonstrated strong negative associations with time to full oral feeds on both slow-flow and standard flow nipples, neither measure had any association with time to hospital discharge.(See *Table 5.21* for full listing of values and *Appendix 5.14* for scatterplots.)

Table 5.21. Spearman's Correlation Between Characteristics of Milk Ingestion and Clinical Feeding Outcomes Across Slow-Flow and Standard-Flow Nipples

	Time to Full Oral Feeds				Time to Hospital Discharge			
	Slow-Flow		Standard-Flow		Slow-Flow		Standard-Flow	
	r	p	r	p	r	p	r	p
Duration	0.78	0.002*	0.06	0.841	0.59	0.034*	-0.22	0.481
5 Rate (mL/min)	-0.77	0.002*	-0.67	0.013*	-0.36	0.229	-0.25	0.414
Subsequent Rate (mL/min)	-0.52	0.07	-0.47	0.108	-0.36	0.229	-0.20	0.505
Total Rate (mL/min)	-0.84	<.001*	-0.68	0.011*	-0.54	0.058	-0.15	0.623
Proficiency (%)	-0.53	0.062	-0.50	0.082	-0.10	0.737	-0.05	0.871
Overall Transfer (%)	0.06	0.852	-0.48	0.099	0.49	0.09	-0.11	0.73

$^{*}p < .05$

Characteristics of Respiration: Differences in associations between characteristics of respiratory performance and clinical outcomes were observed throughout the feed, across nipples, and across outcomes. Associations between respiratory measures and time to full oral intake were isolated to the initial suck-burst during slow-flow feeds. During this time, infants with higher weight adjusted tidal volumes were found to take longer to achieve full oral nutrition (r=.657, p= .015). This was not observed during feeds on the standard-flow nipple (r=.489, p=.09). While this association was also observed when comparing time to hospital discharge, it was found to be universal across both slow-flow (r= .69, p= .009) and standard-flow nipples (r=.77, p= .002). Weight adjusted tidal volume continued to show moderate-strong positive associations with time to hospital discharge during the subsequent suck-burst (r= .64, p= .019) and suck-burst break (r= .66, p=.014). In contrast to the initial suck-burst, however, these associations were isolated to the standard-flow nipple. Weight adjusted minute volume and respiratory rhythmicity during the suck-burst break on the standard-flow nipple were the only other respiratory measures found to be associated with time to hospital discharge. Infants with higher minute volume (r=.57, p= .041) and rhythmicity (worse) (r=.6, p=.049) were found to have a longer time to hospital discharge.(See *Tables 5.22-5.24* for full reports and *Appendices 5.15-5.17* for scatterplots.)

Further examination of potential covariates of volumes and clinical outcomes was performed using steady-state volume measures. Weight adjusted steady-state tidal volume was moderately correlated with time to full oral feeds (r = .556, p=.049) and strongly correlated with time to hospital discharge (r = .809, p=.001). Weight adjusted steady-state minute volume was also moderately correlated with time to hospital discharge (r=.622, p=.012) but not correlated with time to full oral feeds (r=.472, p=.103). Neither weight adjusted tidal volume nor weight adjusted minute volume were correlated with gestational age (v_T= -.20, p= .52; V_E r = -.19, p=.55), birth weight (v_T= -.42, p=.156; V_E r = -.38, p=.201), or postmenstrual age (v_T=.498, p=.083; V_E r = -.415, p=.159) (*Table 5.25*, *Appendix 5.18*).

Table 5.22. Initial Suck-Burst Spearman's Correlation Between Respiratory Measures and Clinical Feeding Outcomes Across Slow-Flow and Standard-Flow Nipples

	Time to Full Oral Feeds				Time to Hospital Discharge			
	Slow-Flow		Standard-Flow		Slow-Flow		Standard-Flow	
	r	p	r	p	r	p	r	p
Inspiratory Time (ms)	0.52	0.067	0.01	0.986	0.41	0.161	0.01	0.986
Period (ms)	-0.05	0.87	-0.08	0.785	-0.11	0.717	-0.02	0.957
Rhythmicity (SD)	0.01	0.978	-0.02	0.949	0.23	0.452	-0.41	0.170
Respiratory Rate (bpm)	0.22	0.462	0.22	0.479	0.03	0.916	0.07	0.831
Tidal Volume (µV/g)	0.66	.015*	0.48	0.094	0.69	0.009*	0.77	.002*
Minute Volume (µV/g/min)	0.43	0.139	0.25	0.418	0.55	0.052	0.50	0.082

** p <.05*

Table 5.23. Subsequent Suck-Burst Spearman's Correlation Between Respiratory Measures and Clinical Feeding Outcomes Across Slow-Flow and Standard-Flow Nipples

	Time to Full Oral Feeds				Time to Hospital Discharge			
	Slow-Flow		Standard-Flow		Slow-Flow		Standard-Flow	
	r	p	r	p	r	p	r	p
Inspiratory Time (ms)	0.32	0.28	0.2	0.571	0.37	0.208	0.17	0.578
Period (ms)	-0.13	0.682	-0.2	0.429	0.10	0.744	0.07	0.828
Rhythmicity (SD)	-0.36	0.234	-0.2	0.59	-0.33	0.276	-0.33	0.272
Respiratory Rate (bpm)	0.24	0.424	0.1	0.863	0.13	0.663	0.01	0.964
Tidal Volume (µV/g)	0.27	0.371	0.344	0.25	0.35	0.247	0.64	.019*
Minute Volume (µV/g/min)	0.46	0.118	0.257	0.397	0.54	0.059	0.52	0.067

** p <.05*

Table 5.24. Suck-Burst Break Spearman's Correlation Between Respiratory Measures and Clinical Feeding Outcomes Across Slow-Flow and Standard-Flow Nipples

	Time to Full Oral Feeds				Time to Hospital Discharge			
	Slow-Flow		Standard-Flow		Slow-Flow		Standard-Flow	
	r	p	r	p	r	p	r	p
Inspiratory Time (ms)	0.34	0.25	0.16	0.603	0.32	0.285	0.30	0.314
Period (ms)	0.22	0.462	0.15	0.629	0.43	0.141	0.26	0.392
Rhythmicity (SD)	0.43	0.148	0.31	0.298	0.51	0.077	0.56	0.049*
Respiratory Rate (bpm)	-0.31	0.312	0.00	0.996	-0.46	0.111	-0.14	0.646
Tidal Volume (µV/g)	0.43	0.145	0.35	0.238	0.47	0.102	0.66	.014*
Minute Volume (µV/g/min)	0.03	0.935	0.19	0.534	0.10	0.751	0.57	.041*

* $p < .05$

Table 5.25. Spearman's Correlation Between Steady-State Volume Characteristics and Potential Covariates

	GA (wks./days)		Birth Weight (grams)		PMA (wks./days)		Time to Full Oral Feeds (days)		Time to D/C (days)	
	r	p	r	p	r	p	r	p	r	p
Tidal Volume (µV/g)	-0.20	0.52	-0.42	0.156	0.50	0.083	0.56	0.049*	0.81	0.001*
Minute Volume (µV/g/min)	-0.19	0.55	-0.38	0.201	-0.42	0.159	0.47	0.103	0.62	0.023*

* $p < .05$

SUPPLEMENTAL FINDINGS: NURSE PERCEPTION OF FEEDING PERFORMANCE

All nurses were blind to nipple type during qualitative evaluation of feeding performance using a subjective comparative feeding assessment scale (Appendix 5.19). There were approximately equal number of nurses who reported infants fed better during the slow-flow feed, infant's fed better during the standard-flow feed, and that there was no difference in feeding performance between feeds (*Table 5. 26*). Of those nurses who indicated they perceived a difference, approximately half of the nurses (44% n=4) correctly identified which feed was completed with a slow-flow nipple and which feed was completed with a standard-flow nipple. Qualitative comments regarding the differences in feeding performance between nipples was provided for 6 subjects. The number of comments reflecting positive perceptions of feeding performance on the slow-flow nipple was approximately equal to the number of comments reflecting negative perceptions of feeding performance on the standard-flow nipple. Nurse comments reflecting their perception of infant feeding performance while blinded to nipple are summarized in *Table 5.27*.

Table 5.26. Nurse Perception of Feeding Performance Across Feeds

Outcome Measure	Nurse Assessment	Number of Infants
Overall Quality	Slow-Flow Better	4
	Standard-Flow Better	6
	No Difference	3
Endurance	Slow-Flow Better	4
	Standard-Flow Better	6
	No Difference	3
Milk Containment	Slow-Flow Better	3
	Standard-Flow Better	2
	No Difference	8
Coordination	Slow-Flow Better	4
	Standard-Flow Better	4
	No Difference	5
Respiratory Stability	Slow-Flow Better	5
	Standard-Flow Better	3
	No Difference	5

Table 5.27. Nurse Qualitative Comments of Feeding Performance Across Feeds

Slow-Flow Comments	Standard-Flow Comments
▪ More consistent sucking	▪ Less pacing required
▪ Better endurance	▪ Fast rate at first then quickly fatigued
▪ Nipple collapsed	▪ More anterior bolus loss
▪ More gulping	▪ More pacing required
	▪ Better performance
	▪ More pacing required. If pacing provided infant fed better than SF, if not then infant fed worse

CHAPTER 6: DISCUSSION

The alteration of milk flow rate through bottle-nipple modification is a widespread clinical intervention that is used to improve feeding performance in the preterm infant. Despite its common use among healthcare providers, there is limited evidence to support its clinical effectiveness as a dysphagia treatment modality. The primary aims of the present investigation were to fill this void by testing the effect of laser-cut, slow-flow nipples on measures of respiratory performance and milk ingestion during preterm oral intake in the clinical setting. We also sought to elucidate the functional implications of preterm dysphagia through a third aim that examined the association between measures of preterm feeding performance and time to hospital discharge.

EFFECT OF SLOW-FLOW NIPPLES ON PRETERM FEEDING PERFORMANCE

Findings from this investigation indicate that few differences exist in preterm feeding performance within the clinical setting between slow-flow and standard-flow nipples. Differences that were observed were likely of low clinical significance, as they were primarily isolated to differences in slow-flow and standard-flow internal associations (temporal changes in feeding performance) and external associations (steady-state changes in respiration), without carry-over to direct slow-flow and standard-flow nipple comparisons. Specifically, temporal changes in respiratory-rate and rhythmicity throughout a feed were solely observed on the slow-flow nipple, while significant elevations in steady-state tidal volume were solely observed during suck-burst breaks on the standard-flow nipple. The only measure to exhibit significant differences in direct comparison of respiration between slow-flow and standard-flow feeds was inspiratory period during the initial 30 seconds of sucking. Inspiratory period on the slow-flow nipple was found to be significantly longer than on the standard-flow nipple. Slow-flow and standard-flow nipples were also found to have similar ingestion characteristics, with no significant difference in any of the identified measures.

While the observed similarities in milk ingestion between slow-flow and standard-flow nipples are consistent with findings of past investigators, the observed reductions in respiratory performance during oral intake on the slow-flow nipple are in direct opposition of previously reported findings. In the laboratory setting, Matthew et al. (1991) reported respiration during oral intake on a custom-made, laser-cut, slow-flow nipple to be significantly improved when compared to respiration on a faster-flow nipple. These improvements in respiration included elevations in respiratory rate and minute volume.(O. Mathew, 1991) Neither our indirect comparison of slow-flow and standard-flow nipples to internal or external measures of respiration, nor our direct comparison of slow-flow and standard–flow nipples to each other support this finding. Instead, although likely not of strong clinical significance, our findings indicate worse respiratory performance during feeds on a slow-flow nipple when compared to feeds on a standard-flow nipple.

Nurse Imposed Adaptations to Feeding Method Based on Infant Feeding Performance

Nurse-imposed compensatory feeding techniques in the clinical setting are hypothesized to account for these differences in findings. Visual review of the acquired signals revealed suck-bursts on the standard-flow nipple to regularly exhibit periods of 2-3 uninterrupted respiratory cycles coinciding with a reduction in the angle of bottle inversion. Unlike traditional pacing methods that completely void the nipple of all milk to maintain infant cardiopulmonary stability, the observed changes in inversion solely reduced the volume of liquid within the nipple. Such alterations have the potential to compensate for reductions in respiratory-swallow coordination during suck-bursts by periodically reducing or eliminating milk flow based on infant respiratory performance to enable respiration when needed. It is likely that our observations of improved respiratory performance on the standard-flow nipple may not reflect its beneficial effect on suck-burst respiratory performance, but instead, primarily reflect the increased provision of modified pacing techniques.(See *Appendix 6.1* for a schematic of observed signals and observed pacing techniques.)

Neuromotor Response to Reductions in Ventilation

The observed elevation in steady-state volume during the suck-burst break on the standard-flow nipple is also hypothesized to reflect reduced suck-burst feeding performance. Complex feedback loops between arterial and medullary chemoreceptors, and motor-programing respiratory muscle modulators, enables even the most premature infant to rapidly adapt respiratory mechanics to increase respiratory rate and tidal volume in response to perturbations in systemic oxygen and carbon dioxide levels. (G. M. Davis

& Bureau, 1987) To our knowledge there has been no work to examine how this translates to respiration during suck-burst breaks. It is plausible, however, that reductions in suck-burst respiratory-swallow coordination, potentially caused by increased milk flow rate, may significantly perturb systemic oxygen and carbon dioxide levels that are manifested as elevations in tidal volume during the subsequent suck-burst break. This hypothesis was supported by secondary signal review which revealed higher tidal volumes during the initial breaths of suck-burst breaks were frequently observed following respiratory cessation in the preceding suck-burst. In contrast, infants with rhythmic respiration throughout the preceding suck-burst were frequently observed to have greater stability in tidal volume during the subsequent suck-burst break. (See *Appendix 6.2* for sample nasal airflow and sucking tracings.) Rapid fluctuations in blood gas levels caused by reduced ventilation in the animal and adult models have been found to have deleterious effects on intracranial pressure, and perfusion from the heart, kidney, and gut. (Cardenas et al., 1996; Gitelman, Prohovnik, & Tatemichi, 1991; McIntyre, Haenel, & Moore, 1994) Future investigations examining the effect of impaired respiratory-swallow coordination on refined measures of cardiopulmonary function in the preterm infant are needed to determine its short and long-term effects for feeding and underlying systemic function.

External and Internal Feeding Modifications Stifle Theoretic Milk Transfer Benefits

Reduced respiratory performance on the standard-flow nipple may also contribute, in part, to the observed similarities in characteristics of milk transfer across nipples. Theoretically, an elevated rate and volume of milk transfer can be achieved using a faster-flow nipple if all other variables are held constant. If the resulting cardiopulmonary implications of this elevated milk flow rate require the provision of milk flow rate-reducing feeding modifications and heightened recovery suck-burst break periods, the milk ingestion benefits may be void. Another likely source of the observed similarity in milk ingestion, however, is an infant-imposed alteration to sucking kinematics. It is well established that while the preterm infant is unable to achieve adequate respiratory-swallow coordination by altering sucking kinematics alone, these alterations are sufficient to change the presented milk-flow to a rate more favorable to the infant's capacities. While the present investigation did not examine the differences in sucking kinematics between laser-cut slow-flow and standard-flow nipples, it is likely that infant-imposed alterations to sucking kinematics contributed to the observed similarities in volume and rate of milk ingestion, and minimized the effect of the nipple on respiratory variables. Future controlled investigations are needed to further investigate the effect of external and internal feeding modifications on measures of feeding physiology and milk ingestion.

RELATIONSHIP BETWEEN CHARACTERISTICS OF PRETERM FEEDING PERFORMANCE AND CLINICAL OUTCOMES

Findings from this investigation also elucidate the relationship between preterm feeding impairment and time to hospital discharge. According to the American Academy of Pediatrics, it is recommended the preterm infant meet four primary developmental milestones prior to hospital discharge: 1) sustained weight gain; 2) maintenance of body temperature; 3) stable cardiopulmonary function; and 4) oral feeding without cardiopulmonary compromise. (Committee on Fetus and Newborn, 2008) In the current study, variability in medical charting prohibited the identification of the date that milestone four was fully achieved, but was sufficient to identify the date infants obtained full oral nutrition. Obtaining full oral nutrition was the last developmental milestone to be achieved in 85% of our sample, lagging behind other milestones by an average of 7 days. The breadth of this gap is likely even greater in a true clinical setting consisting of both healthy preterm infants, such as those that were included in the current investigation, as well as unhealthy preterm infants with complex respiratory and neurologic comorbidities.

Although this delay in the preterm infant's obtainment of full oral feeds is a primary cause of delayed hospital discharge, the characteristics of preterm feeding performance that best predicted each of these outcomes were different. Time to achieve full oral feeds was primarily associated with measures of milk ingestion including feeding duration, 5 minute rate of transfer, and total rate of transfer. In contrast, associations found with time to hospital discharge were primarily comprised of measures of respiratory performance including tidal volume, minute volume, and respiratory rhythmicity. Because hospital discharge requires the infant to not only ingest an adequate volume of milk, but to do so without cardiopulmonary compromise, our findings suggest that poor respiratory performance during feeds may continue to prohibit hospital discharge once milk ingestion goals have been obtained. Further exploration of these relationships is needed to focus the targets of future interventions to achieve greatest clinical impact.

Limitations of Indirect Measures of Feeding Performance as Indicators of System Integrity

Also of interest was the observed heterogeneity in the above associations across nipples. Comparison of measures of milk ingestion revealed that infants who exhibited longer feeding durations on a slow-flow nipple had longer times to reach both full oral feeds and hospital discharge than those infants who exhibited shorter feeding durations. No association between feeding duration and either clinical outcome, however, was observed on the standard-flow nipple. Findings on the slow-flow nipple are consistent with work by Lau who identified maturation of the feeding system to be correlated with improvements in sucking kinematics, higher rates of milk ingestion, and shorter feeding durations.(Amaizu et al., 2008; Lau et al., 2000; Lau & Smith, 2011; Lau et al., 1997)

Hanlon et al.(1997) revealed that while this association may reflect the relationship between feeding duration and feeding maturation for the majority of preterm infants, this relationship may not hold true for select infants with the greatest level of feeding impairment. In the laboratory setting, Hanlon et al. (1997) found that the presentation of a milk flow-rate that exceeded the infant's ingestion capacities resulted in a complete cessation of sucking efforts.(Hanlon et al., 1997) Although Hanlon et al. (1997) did not directly examine how sucking cessation translated to feeding duration, typical clinical management of such behavior would result in the early termination of the feeding attempt. We hypothesize that the milk flow rate provided by the slow-flow nipple did not exceed the capacities of even the poorest feeder in the sample, and enabled the observation of the direct relationship between feeding duration and feeding maturation.

The milk flow-rate provided by the standard-flow nipple was likely beyond feeding capacities of select infants within our sample, resulting in the early termination of the feed due to infant sucking cessation and the inability to observe the discussed linear correlation.

Effect of Lung Function on Preterm Feeding Performance

We also observed differences in correlations between time to hospital discharge and measures of respiratory performance. Differences in the observed correlations across slow-flow and standard-flow nipples were predominately isolated to measures of weight adjusted tidal volume throughout the feed, where infants with higher tidal volumes were found to have longer times to hospital discharge. Both the nature of the observed associations, and their isolation to the standard-flow nipple were unexpected. Exploration of potential covariates outside of feeding maturation that may account for the observed relationship indicated this trend was not isolated to tidal volume during feeding, but was also observed in even greater strength during pre-feeding steady-state respiration. Of interest however, was that none of the commonly appreciated variables traditionally identified as covariates to hospital discharge were found to account for this association.

It is hypothesized that the observed association between steady-state weight adjusted tidal volume and time to hospital discharge may reflect the manner in which underlying lung function impacts the infant's ability to reach the oral intake milestone required for hospital discharge. Past investigators have demonstrated differences in weight adjusted tidal volume across infants with varying levels of lung function.(Durand & Rigatto, 1981;

Hjalmarson & Sandberg, 2002) Hjalmarson et al. (2002) revealed larger dead space in the lung of the healthy preterm infant contributes to higher weight adjusted tidal and minute volumes when compared to full-term infants of the same postmenstrual age.(Hjalmarson & Sandberg, 2002) Earlier work by Durand et al. (1981) indicated this elevation in healthy preterm tidal volume was not universal to all preterm infants, but instead, restricted to those who were hypercapnic.(Durand & Rigatto, 1981) It is suggested that these subtle deficits in the healthy preterm infant's pulmonary function may pose a greater barrier to bottle-feeding than previously appreciated.

Although there have been no investigations to the author's knowledge that directly examine the effect of baseline hypercapnia on tidal volume during feeding in the preterm infant, work by Durand et al. (1981) in the term infant revealed similar trends to exist. These investigators found that while infant's increased tidal volume in response to elevations in inspired CO_2 concentrations during feeding, the magnitude of these elevations was significantly diminished from those occurring at rest.(Durand et al., 1981) The failure to observe the steady-state correlation between tidal volume and time to hospital discharge on the slow-flow nipple is potentially the result of the current investigations small sample size, as well as differences in preterm ventilation during feeding when compared to the term infant. Likewise, observation of this correlation on the standard-flow nipple may be a true translation of the observed steady-state correlation during active feeding, but instead, the translation of this correlation to the initial uninterrupted breaths after the provision of modified pacing events. This theory is consistent with our previously stated post hoc findings that indicated observations of improved respiratory performance on the standard-flow nipple were likely attributable to the provision of modified pacing events.

CONCLUSIONS

Dysphagia is a highly prevalent condition in the preterm infant that carries negative developmental, social, and financial implications. Clinical practice often governs the management of preterm dysphagia through the provision of broad treatment approaches across all infants. One such treatment is the reduction of milk flow rate through the use of slow-flow nipples. While the provision of such broad intervention approaches is effective in the management of disorders that share a common underlying source, this practice is ineffective when varying etiologies exist. Such is the case for preterm dysphagia. Preterm dysphagia shares a common clinical manifestation that is characterized by the infant's inability to meet nutritional needs without cardiopulmonary compromise. The underlying sources and resulting physiologic attributes that result in this manifestation, however vary across infants. Effective dysphagia management requires the medical team to depart from broad intervention approaches, and instead, provide interventions based on each infant's unique, underlying impairment and clinical presentation.

Our findings suggest that while the slow-flow nipple may reduce the need for feeders that are skilled in the provision of external feeding modifications, when broadly applied in a clinical setting where nurses adapt their feeding method based on the infant's presenting level of performance, its clinical benefits are in question. It is likely that select infants with specific underlying feeding deficits may obtain greater benefit from the slow-flow nipple than was observed across all healthy preterm infants in the current investigation. The physiologic attributes and clinical presentations that distinguish those infants who will benefit from the use of a slow-flow nipple from those who it may inhibit or be ineffective remain unknown. Current clinical determination of the bottle-nipple that will best optimize preterm feeding performance warrants refined case-by-case assessment of objective measures of milk ingestion and subjective measures of sucking, swallowing, and respiration until future objective clinical assessment modalities become available.

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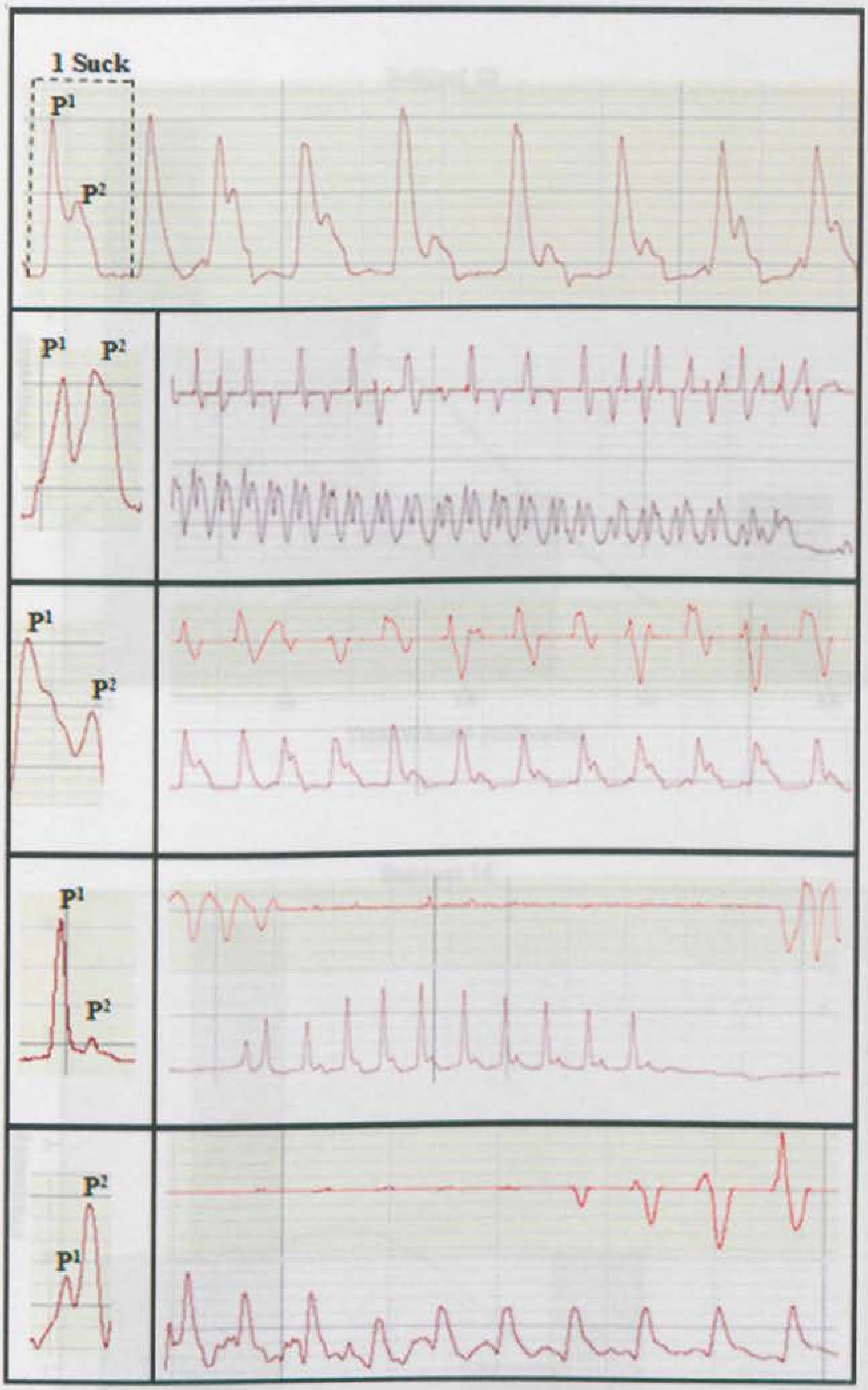
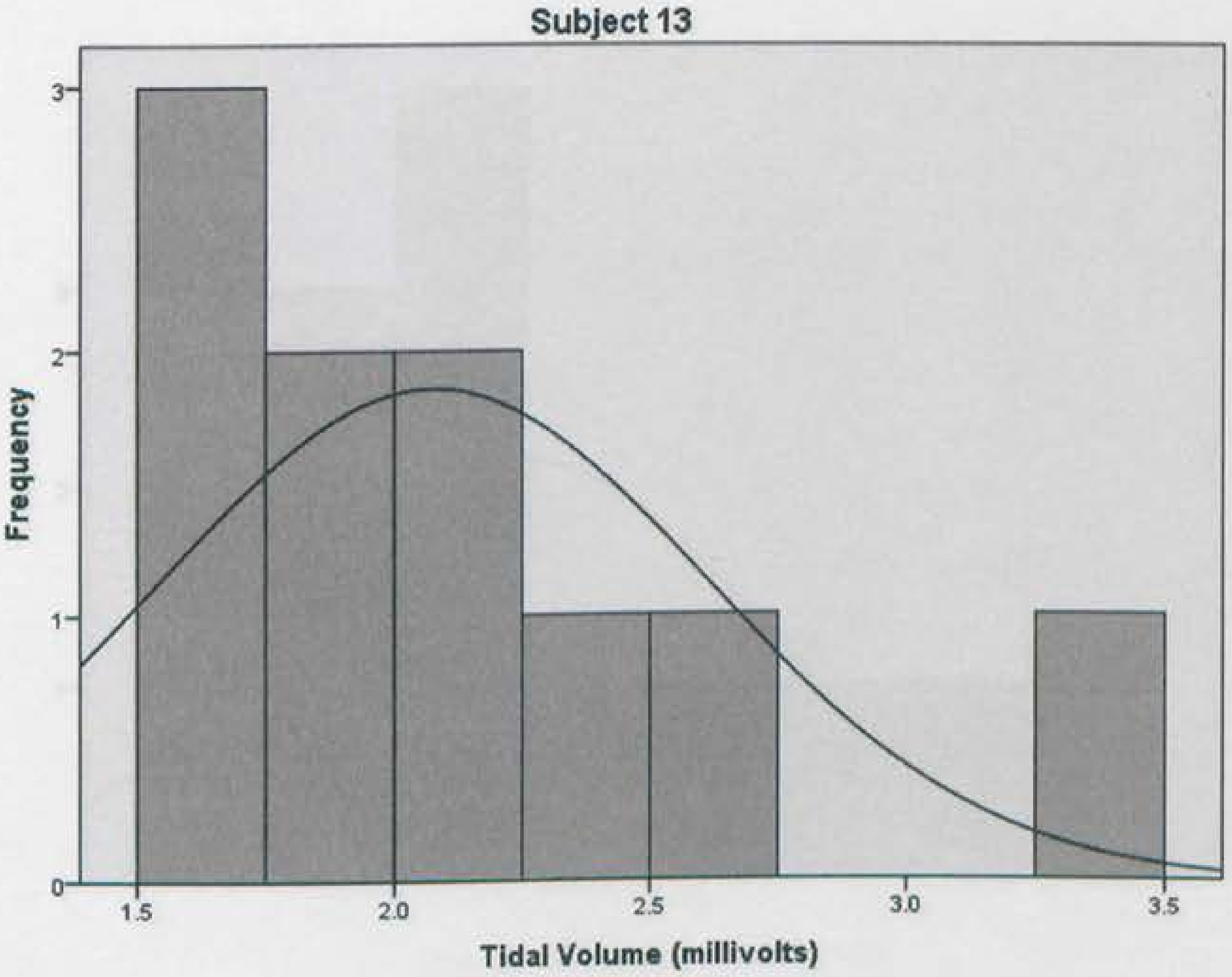
APPENDIX 4.1.
SUCKING SIGNAL ATTRIBUTES AND THEIR RELATIONSHIP TO RESPIRATION

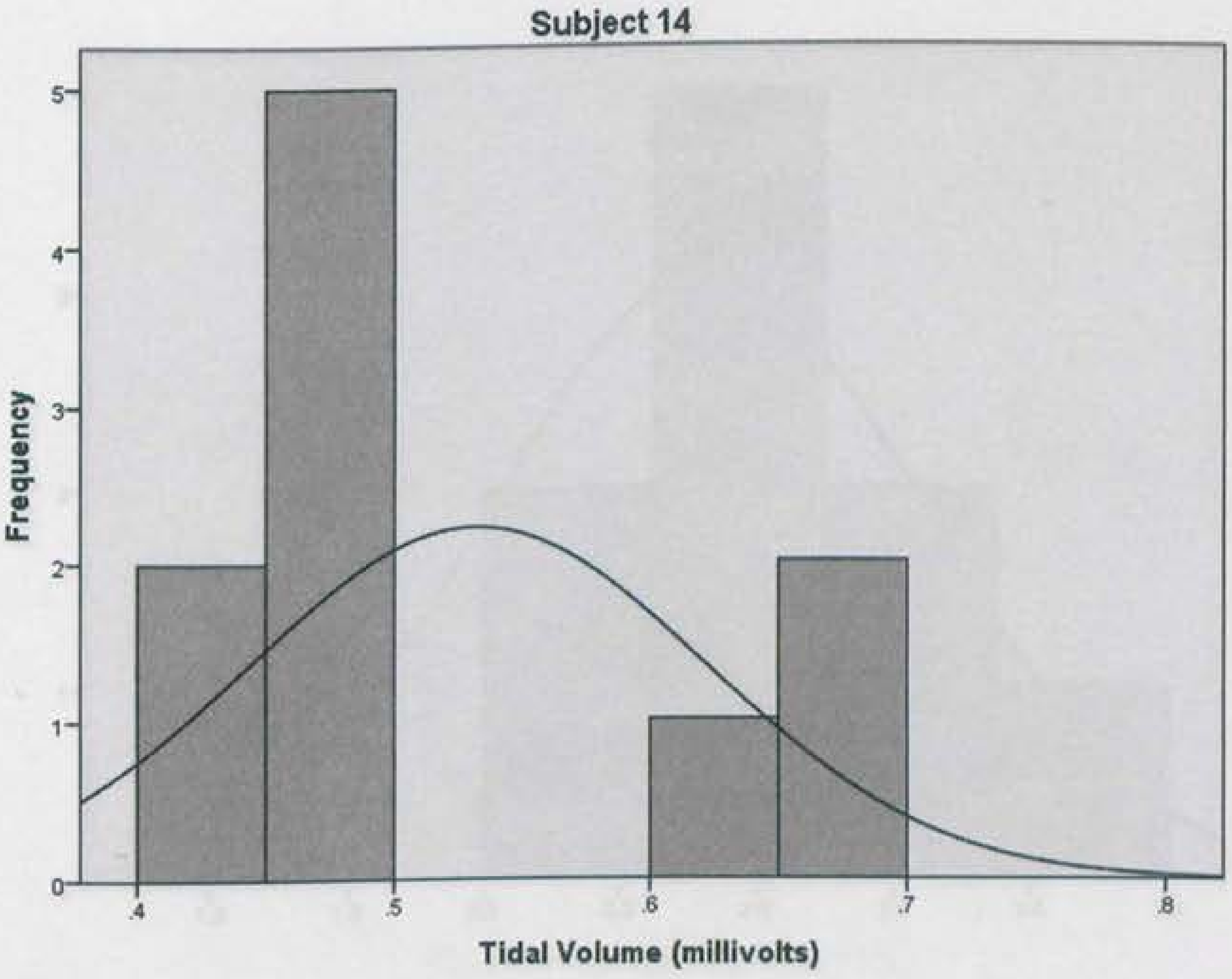


Suck composed of two peaks (P^1, P^2) with varying amplitude and temporal relationships. Top channel indicating respiration, bottom channel indicating sucking. Patterns of improved respiratory performance in infants who suck with a) P^2 initiating prior P^1 amplitude reaching baseline; and b) P^2 amplitude of lower voltage than P^1.

APPENDIX 5.1.
INDIVIDUAL HISTOGRAMS: STEADY-STATE

TIDAL VOLUME

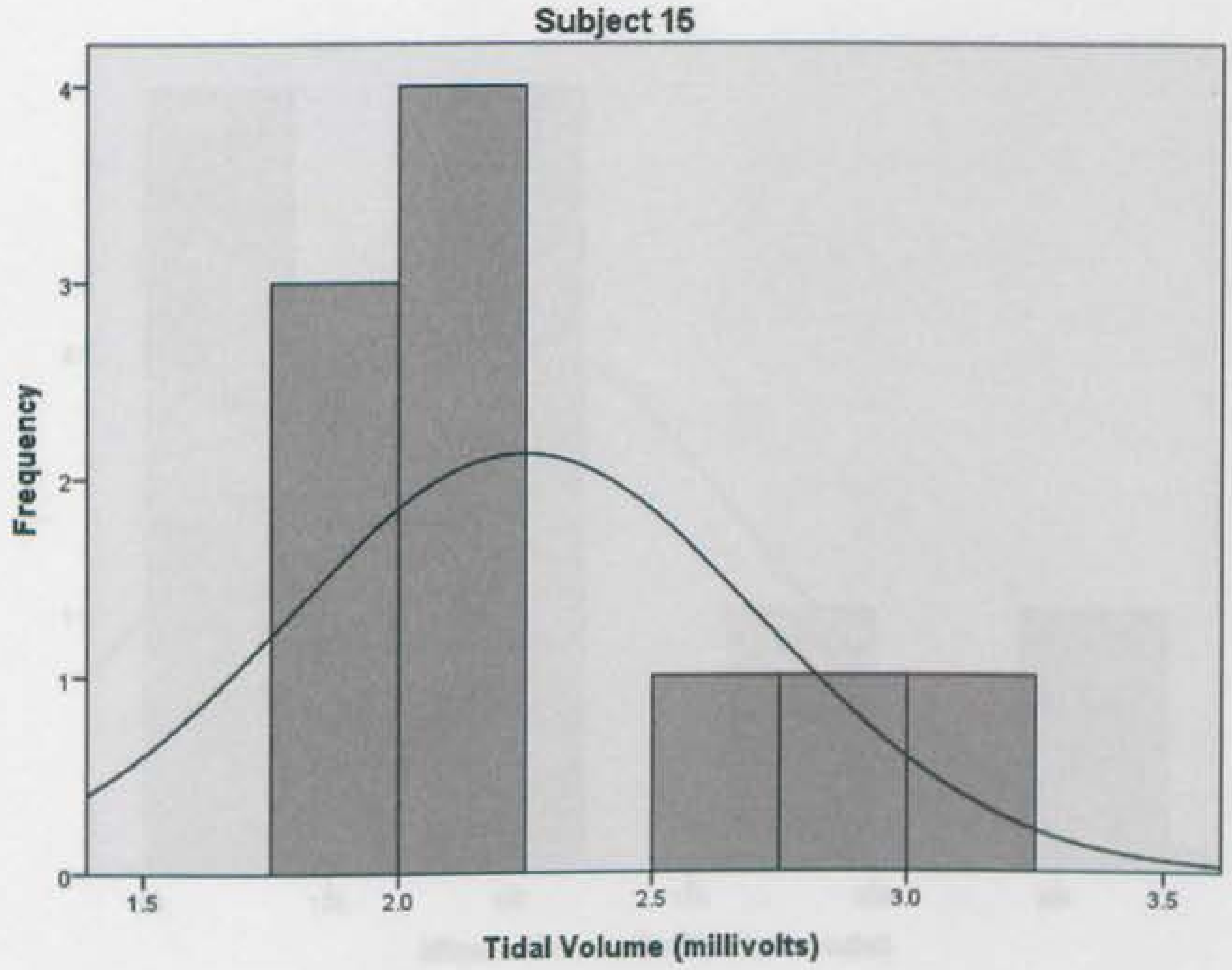




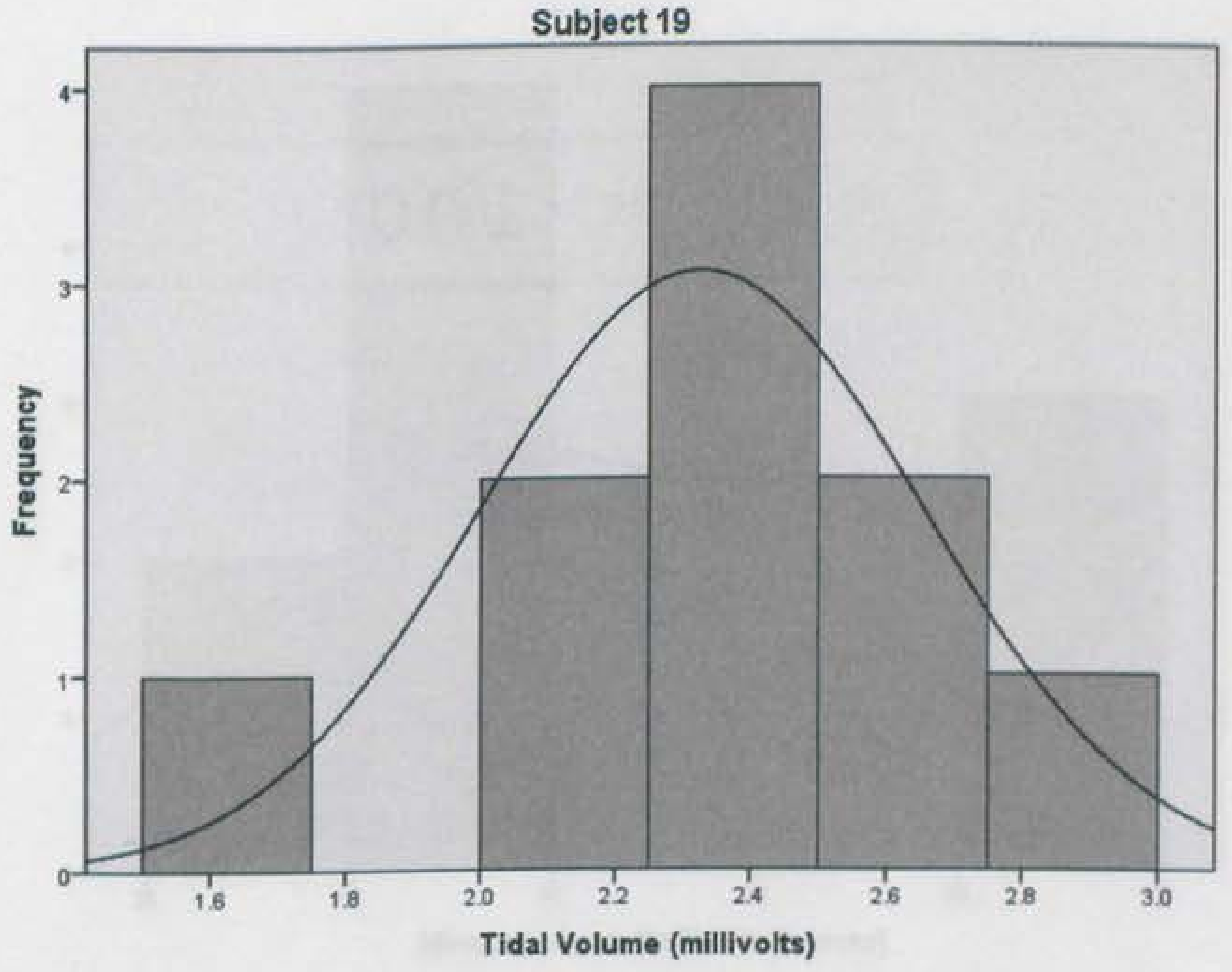
* *Outcome measures with multiple data points for each subject are summarized by median value.*

APPENDIX 5.1. *Continued*

TIDAL VOLUME



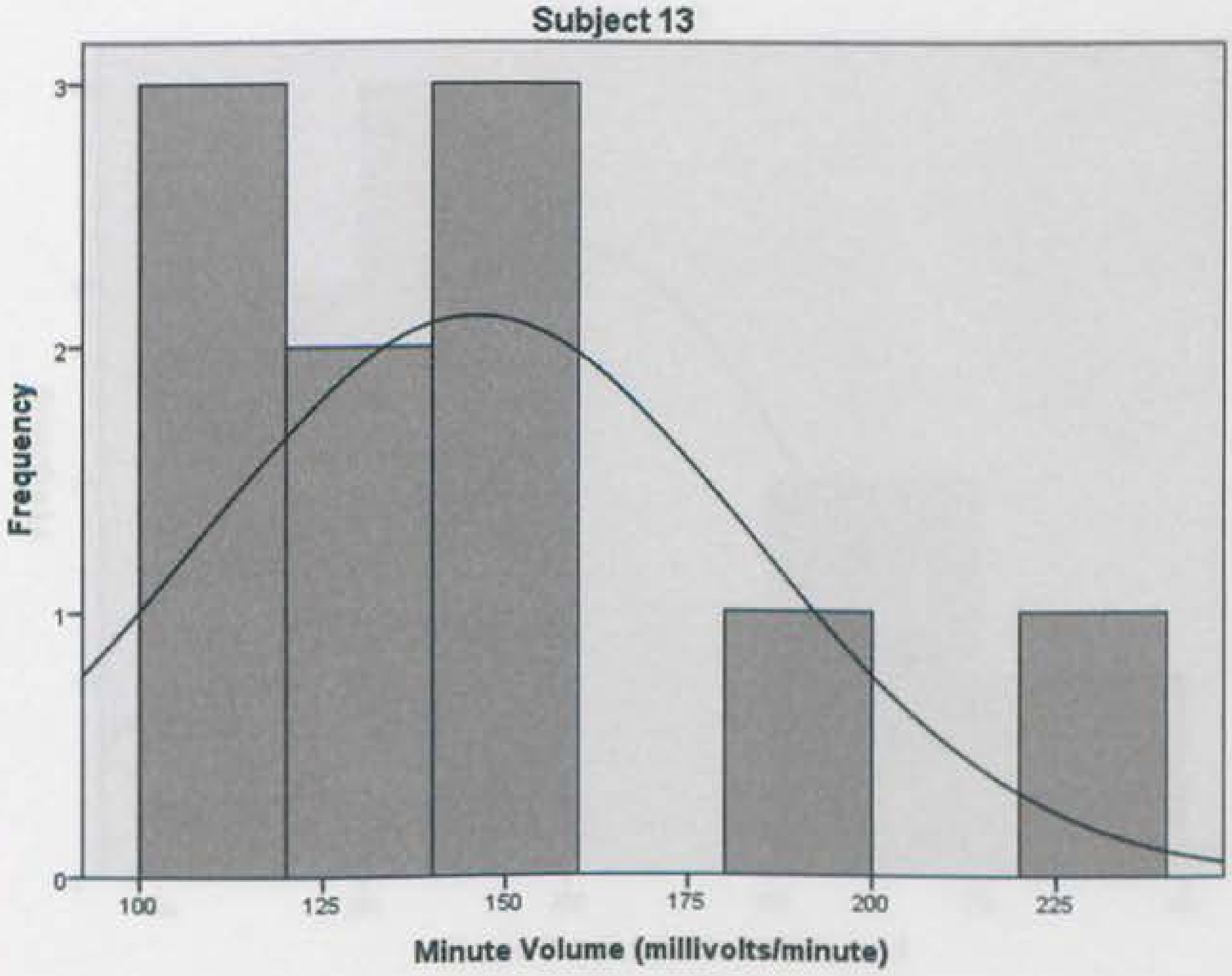
Subject 15

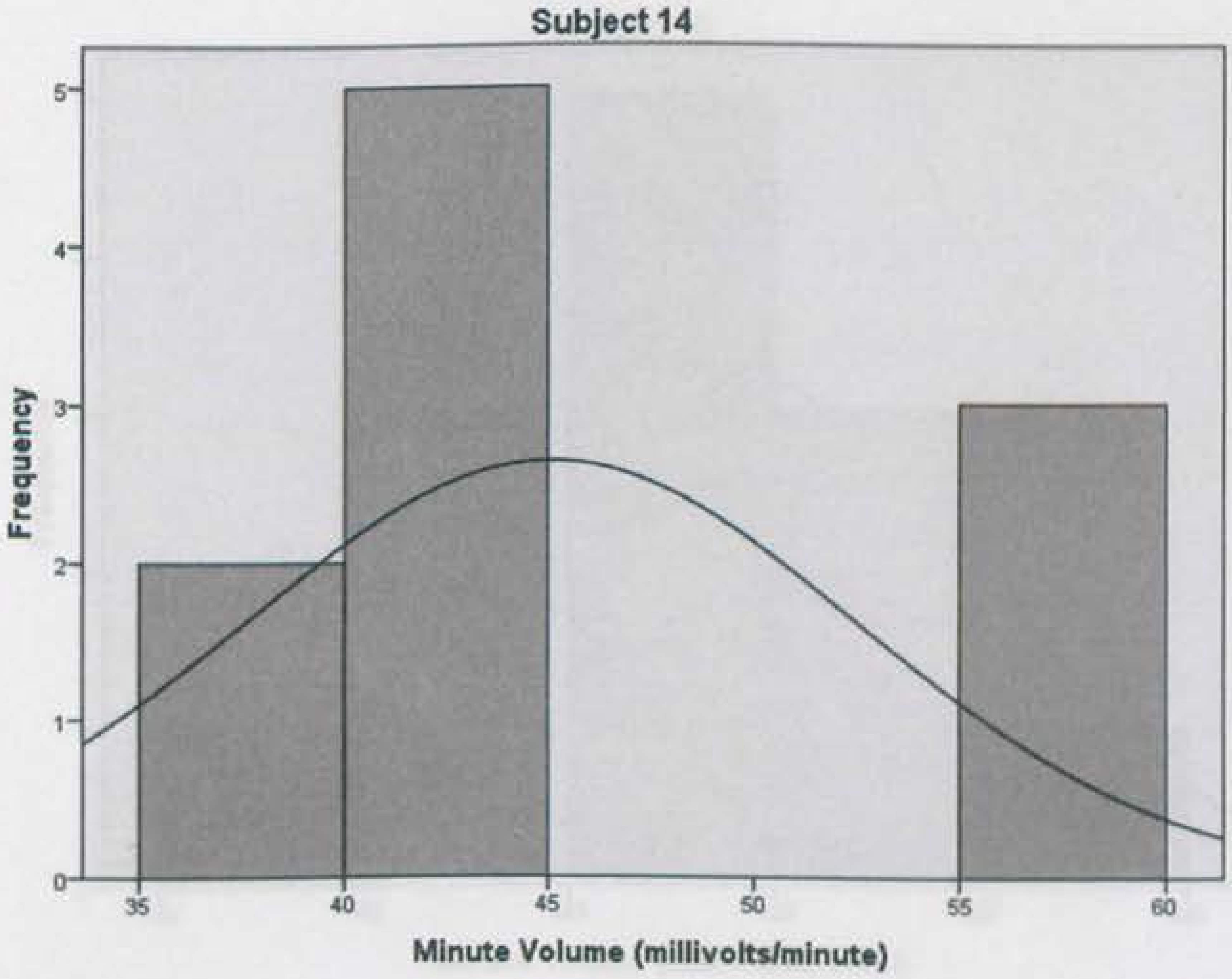


Subject 19

APPENDIX 5.1. Continued

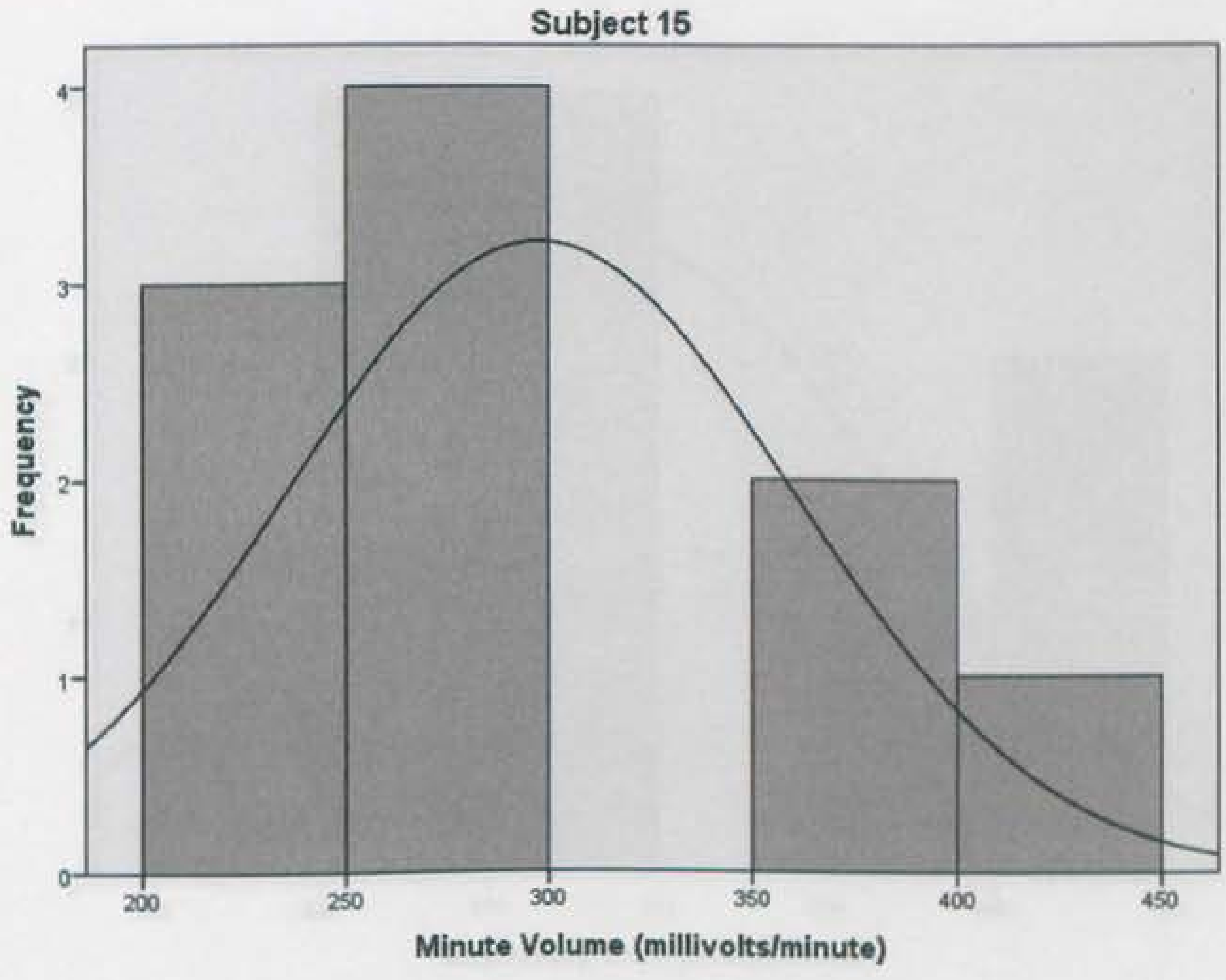
MINUTE VOLUME

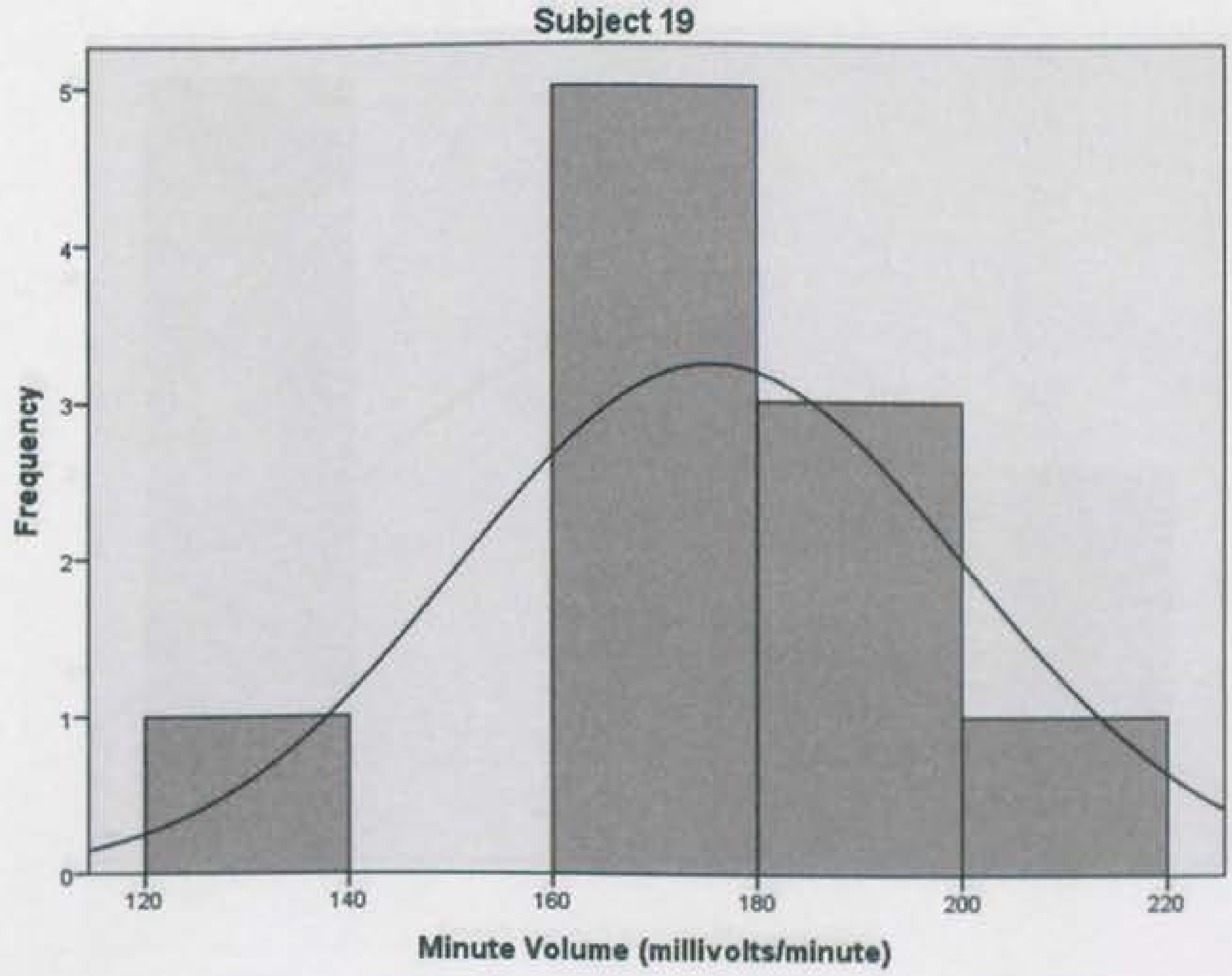




APPENDIX 5.1. Continued

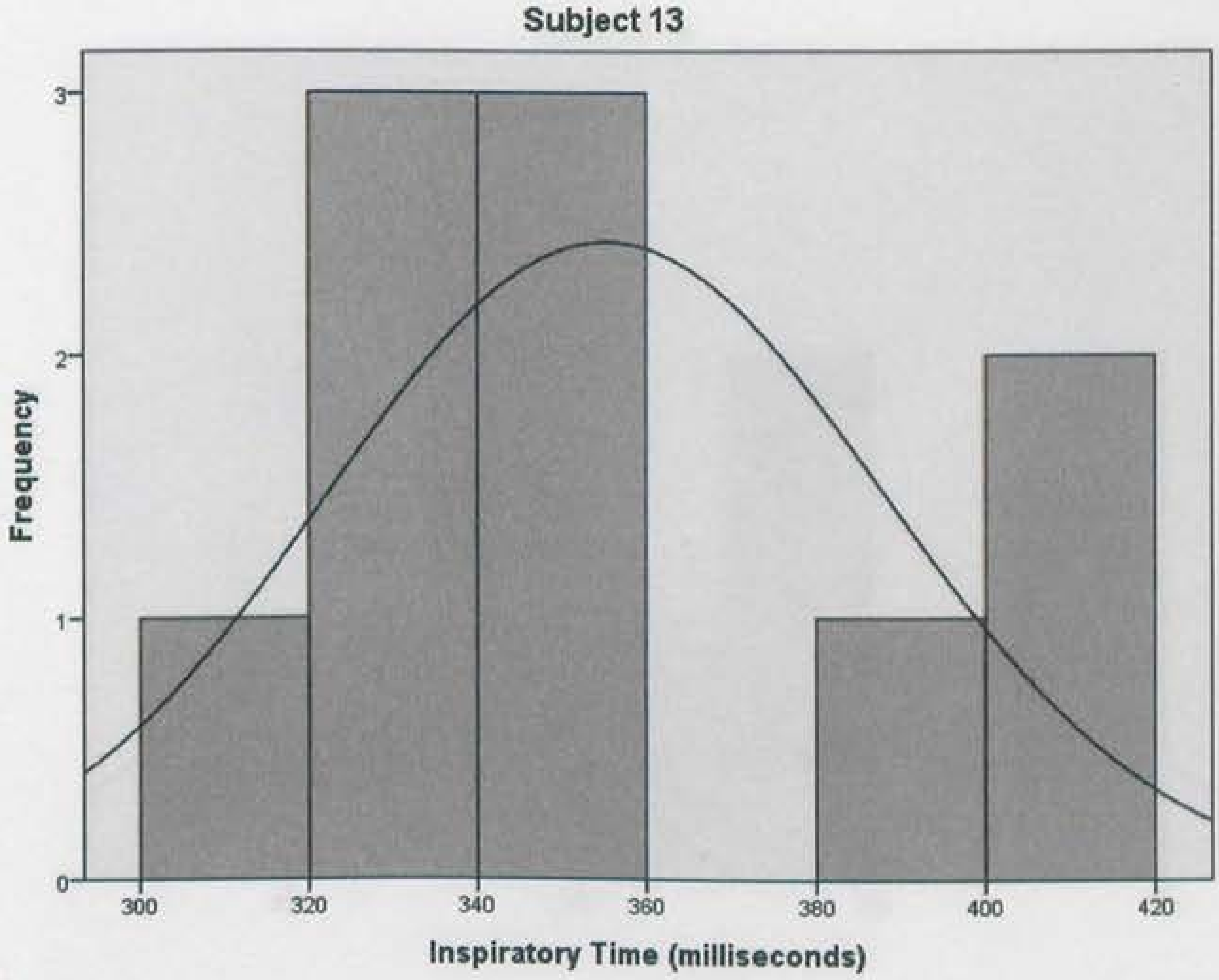
MINUTE VOLUME

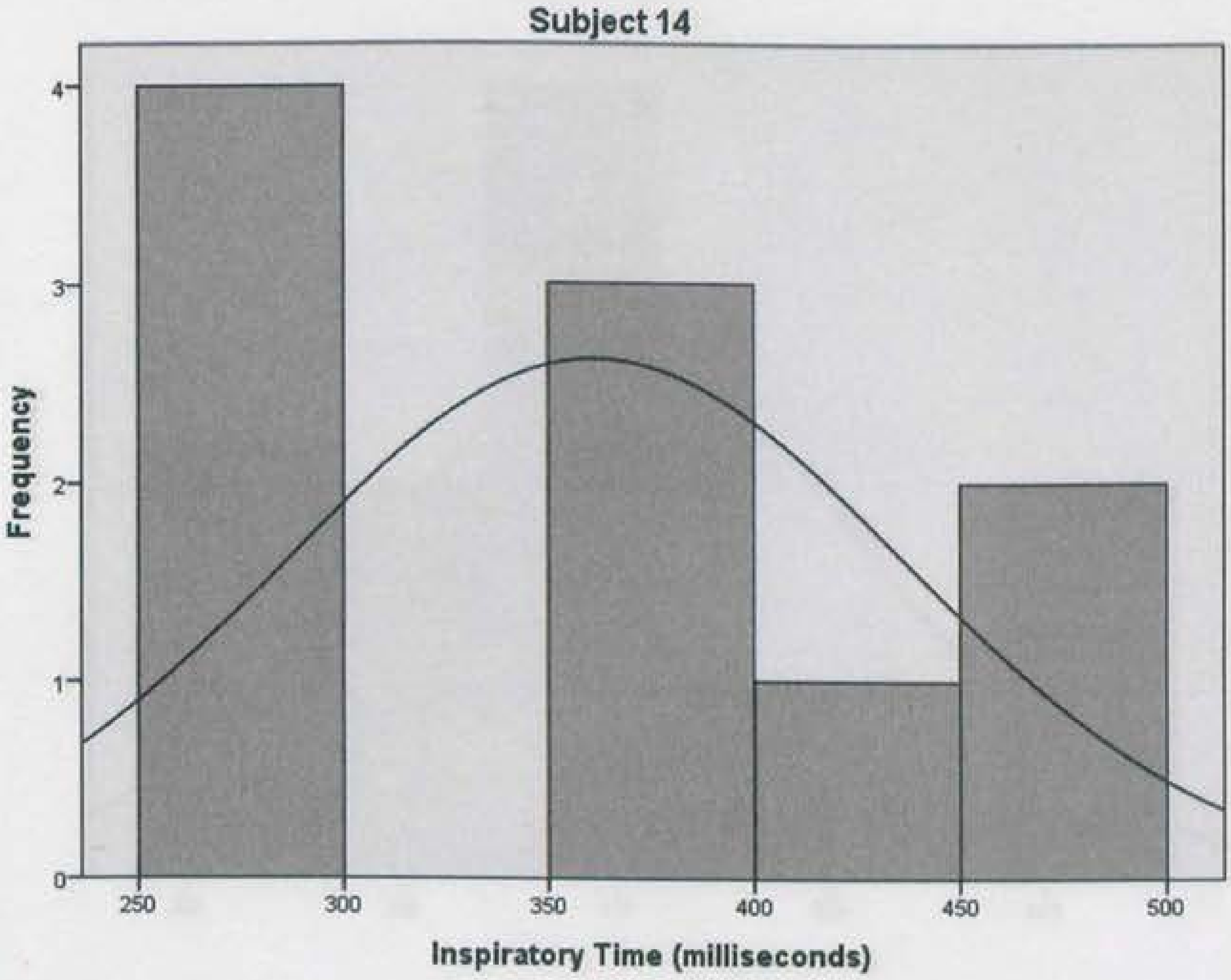




APPENDIX 5.1. Continued

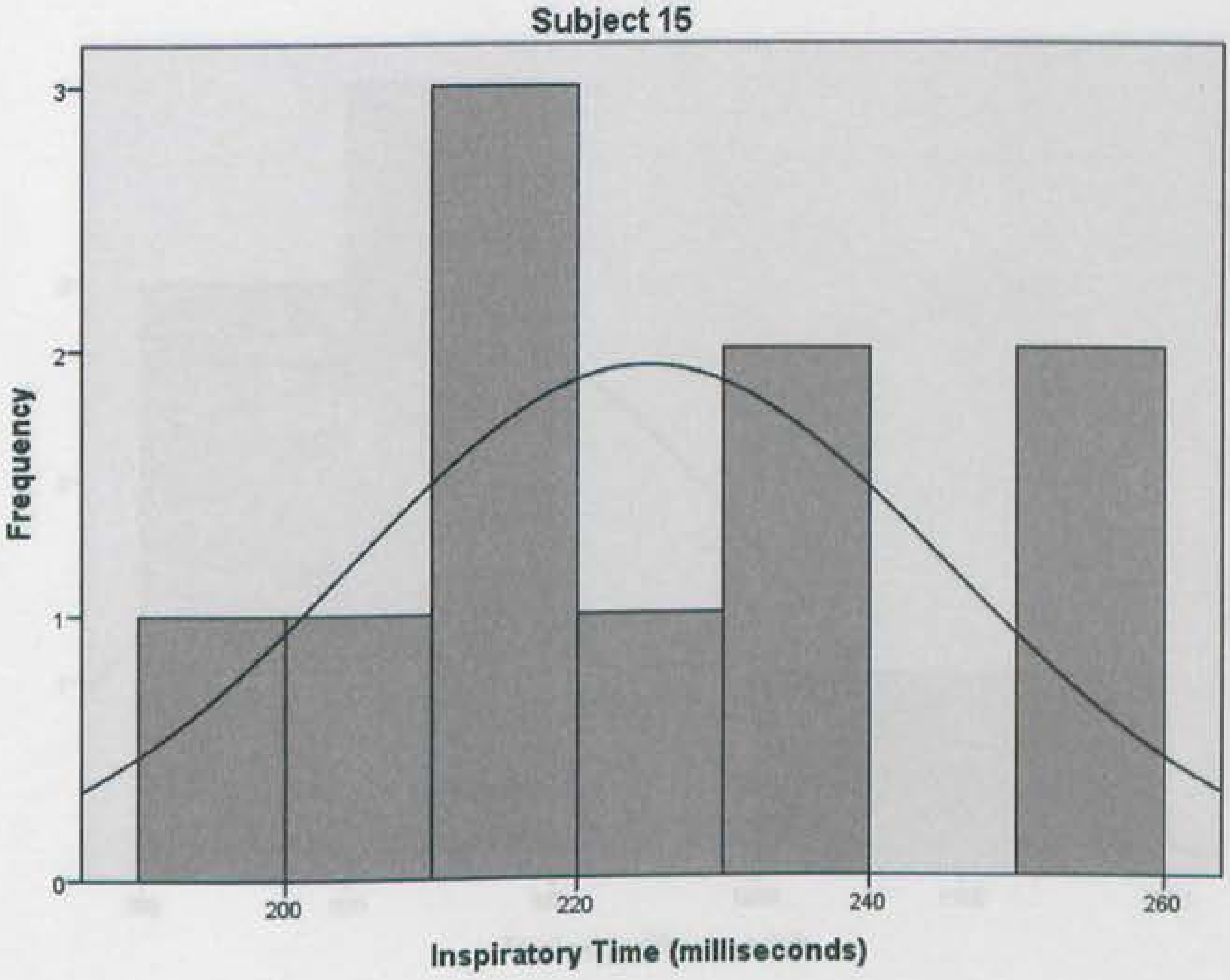
INSPIRATORY TIME

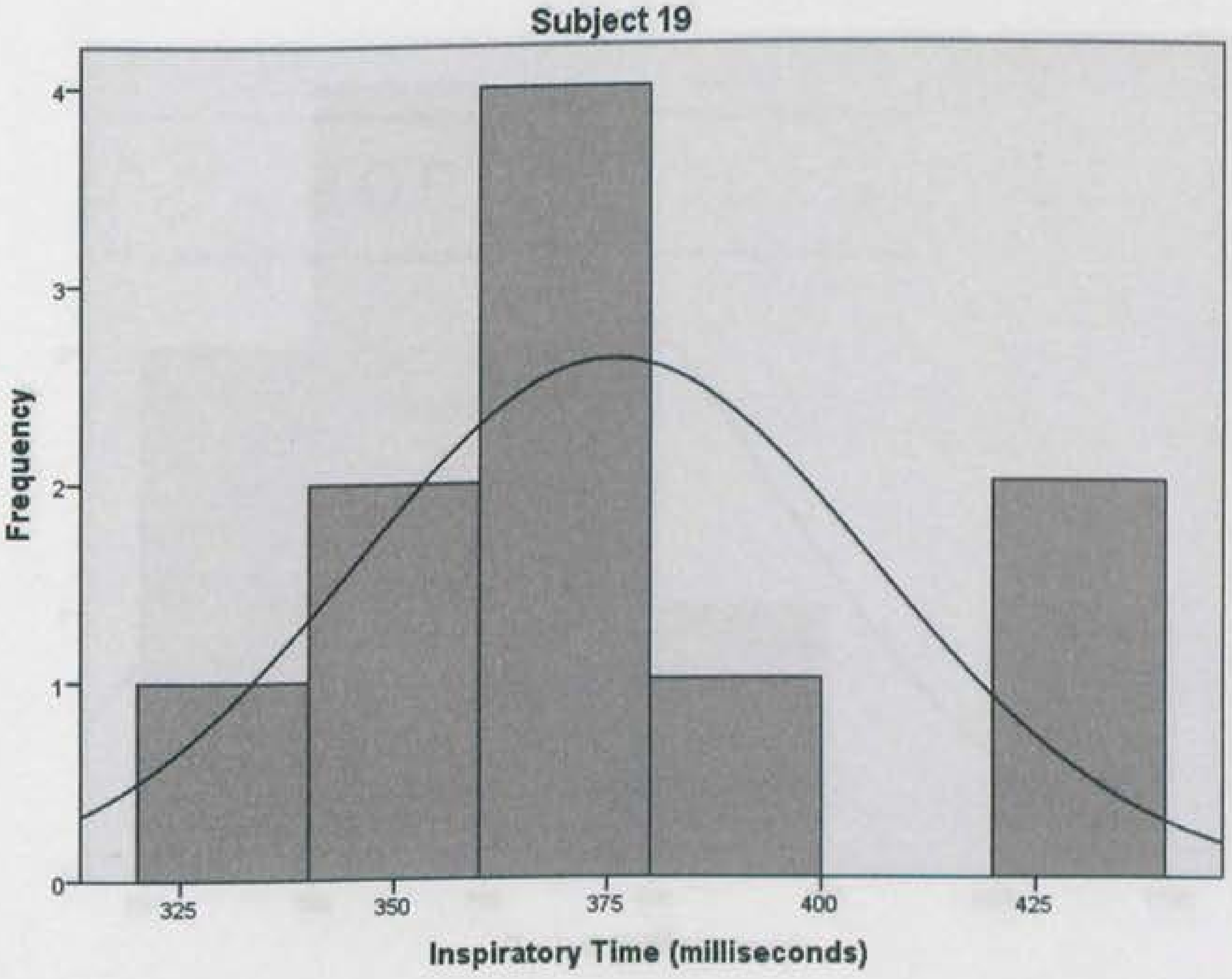




APPENDIX 5.1. *Continued*

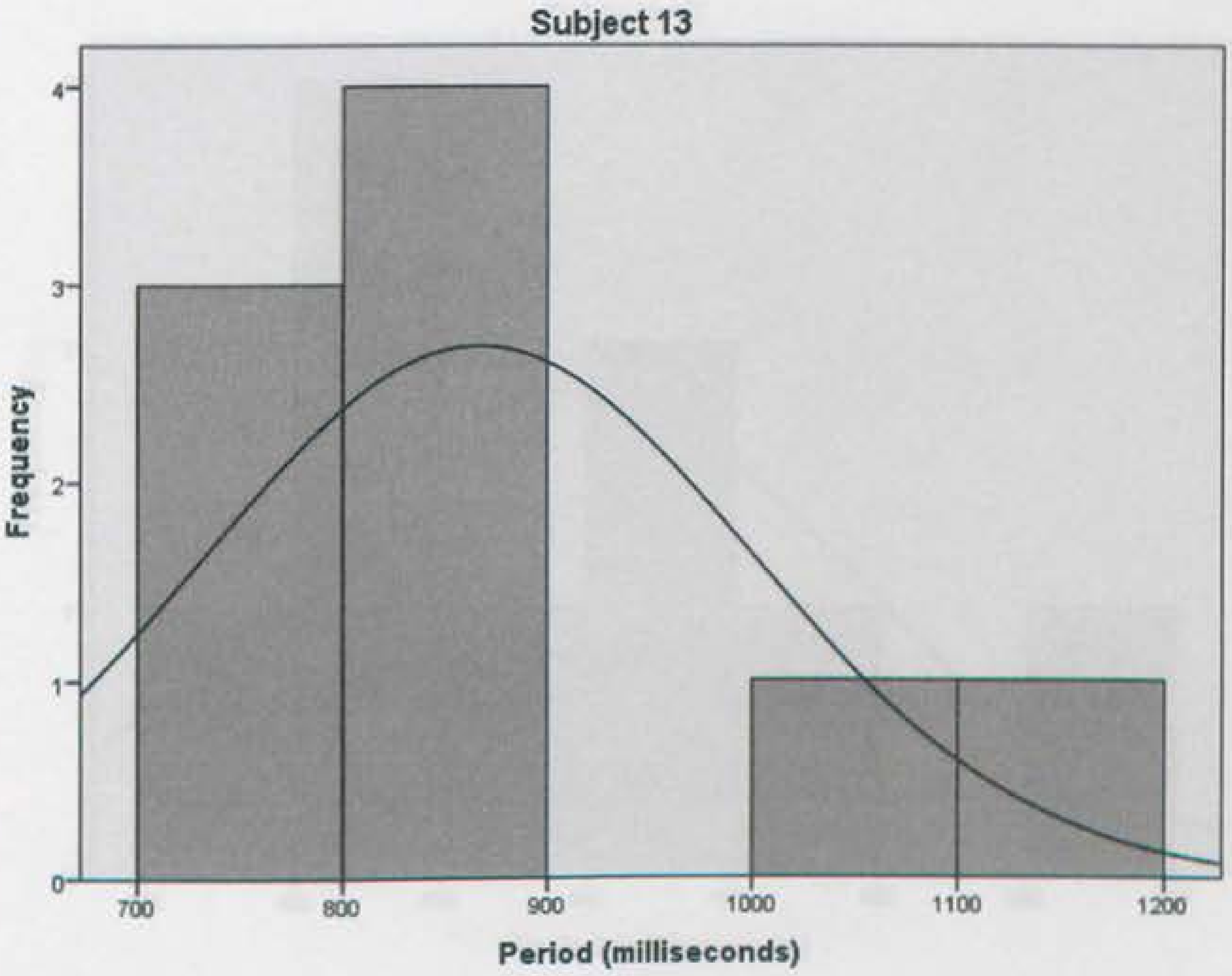
INSPIRATORY TIME

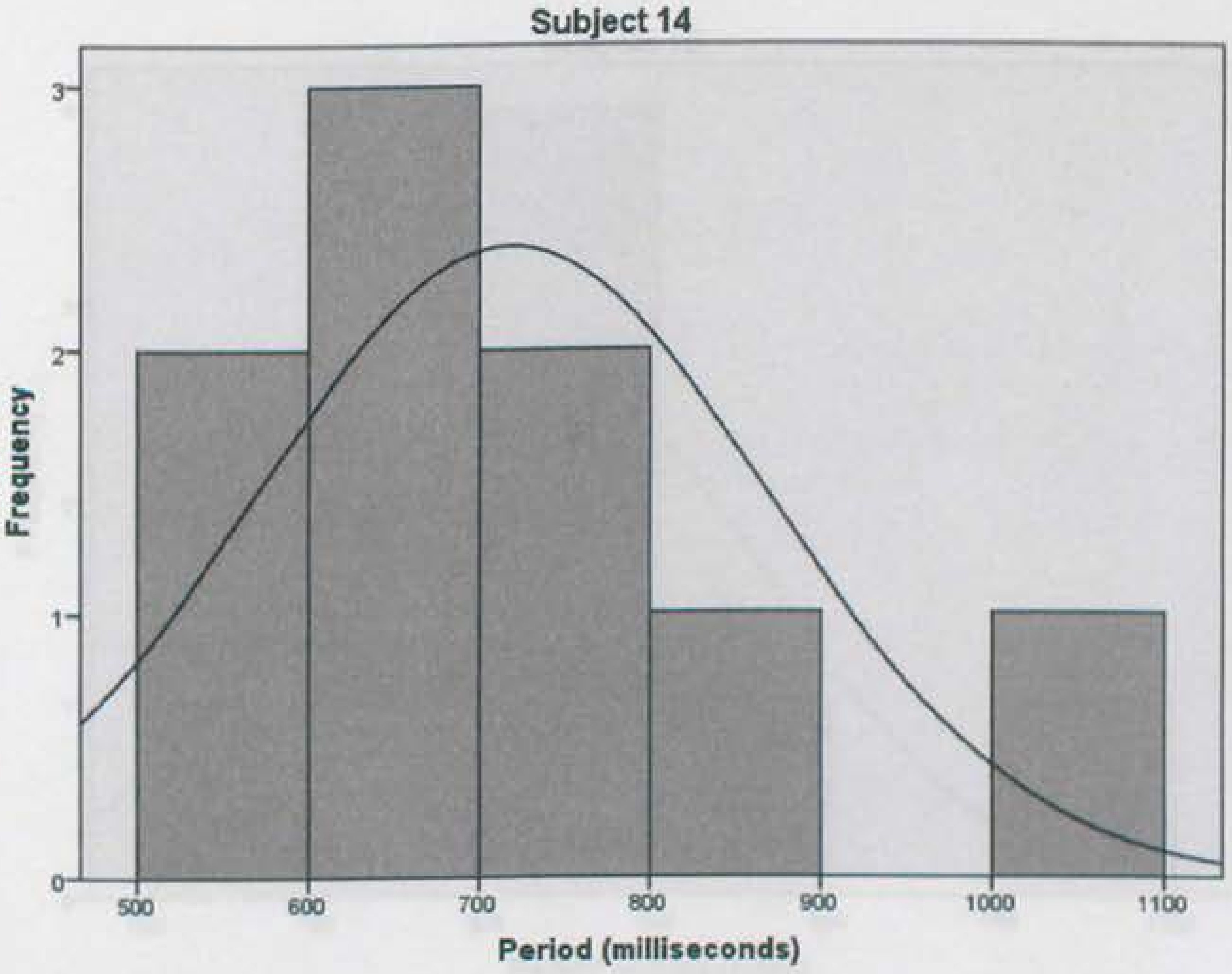




APPENDIX 5.1. *Continued*

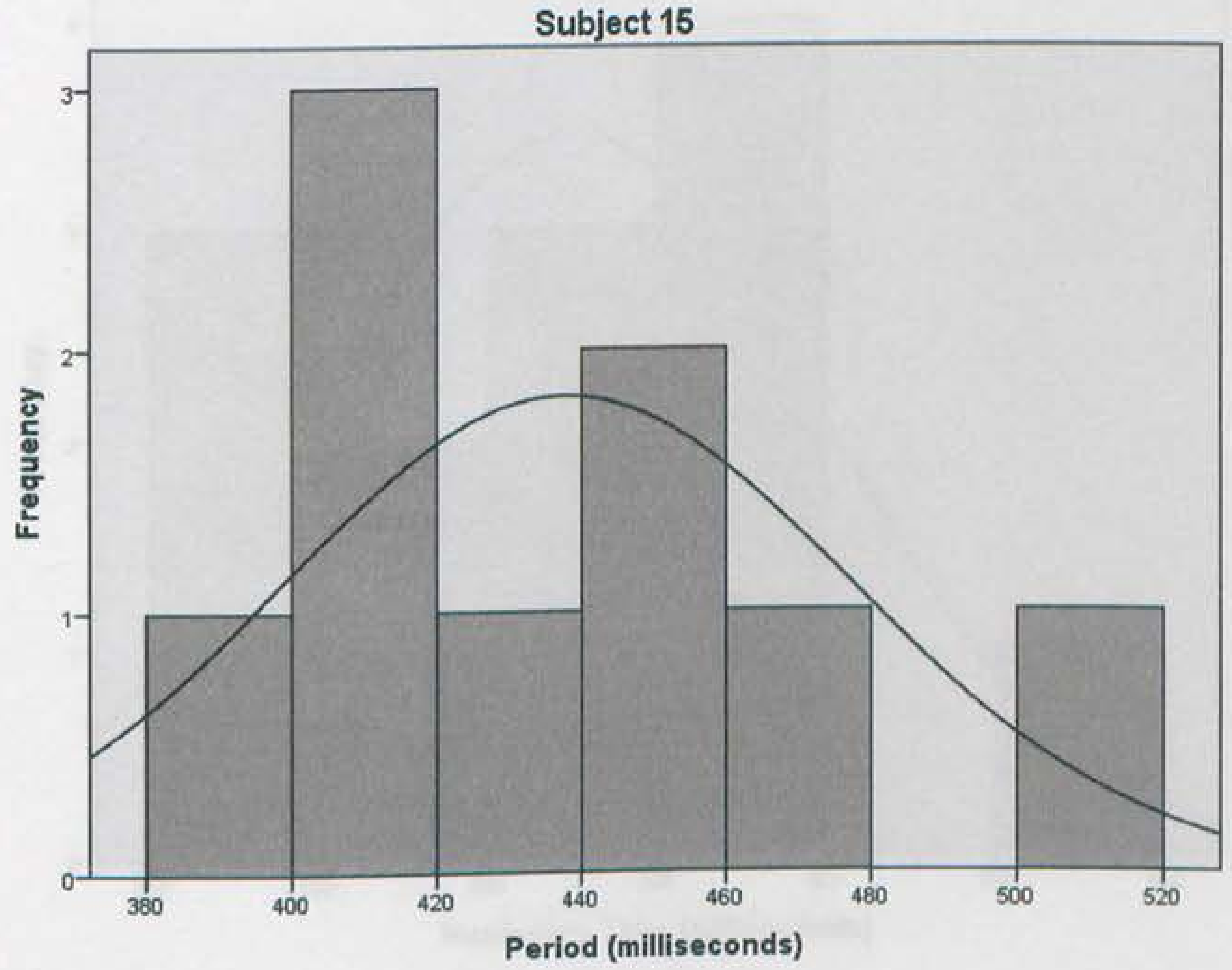
PERIOD

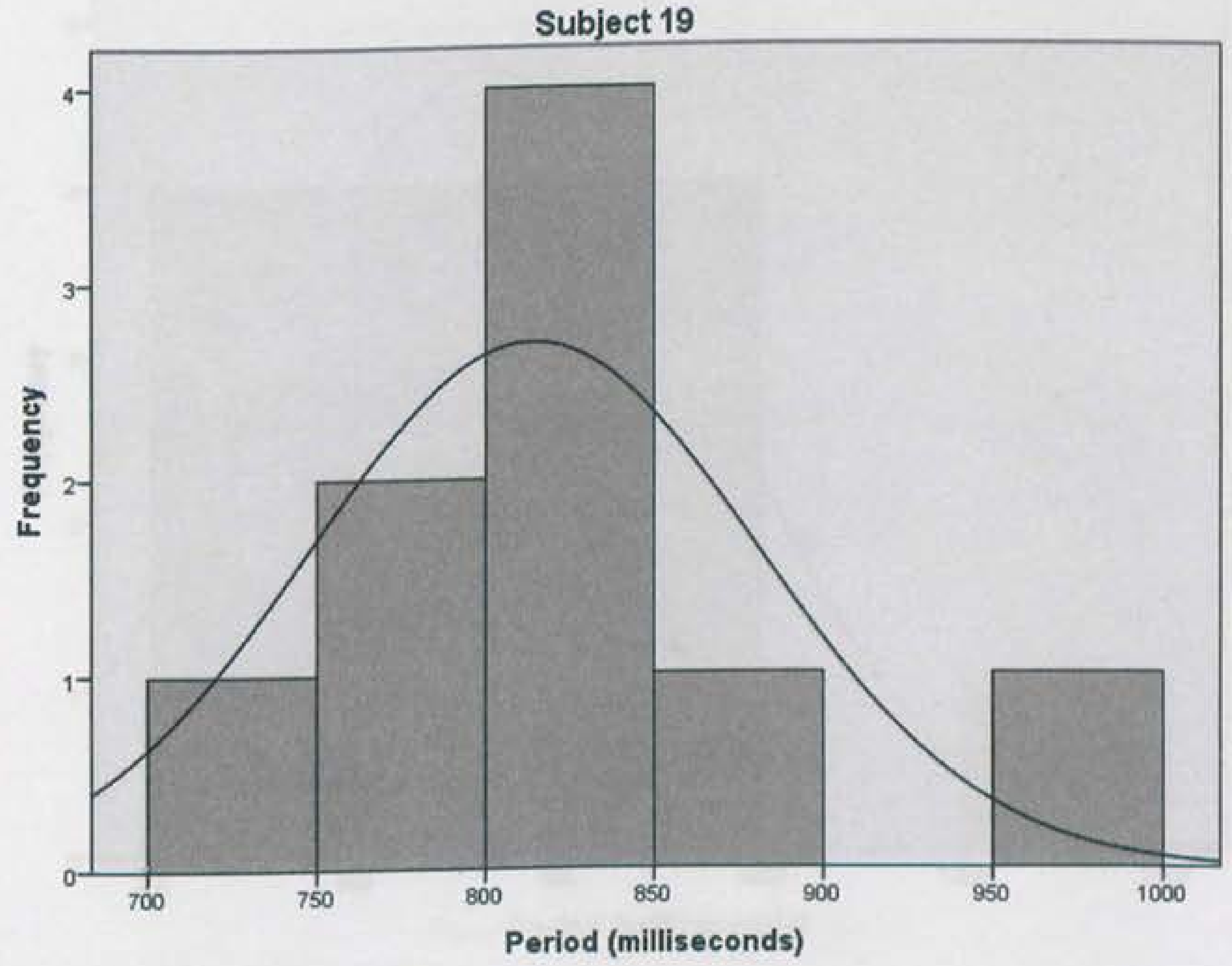




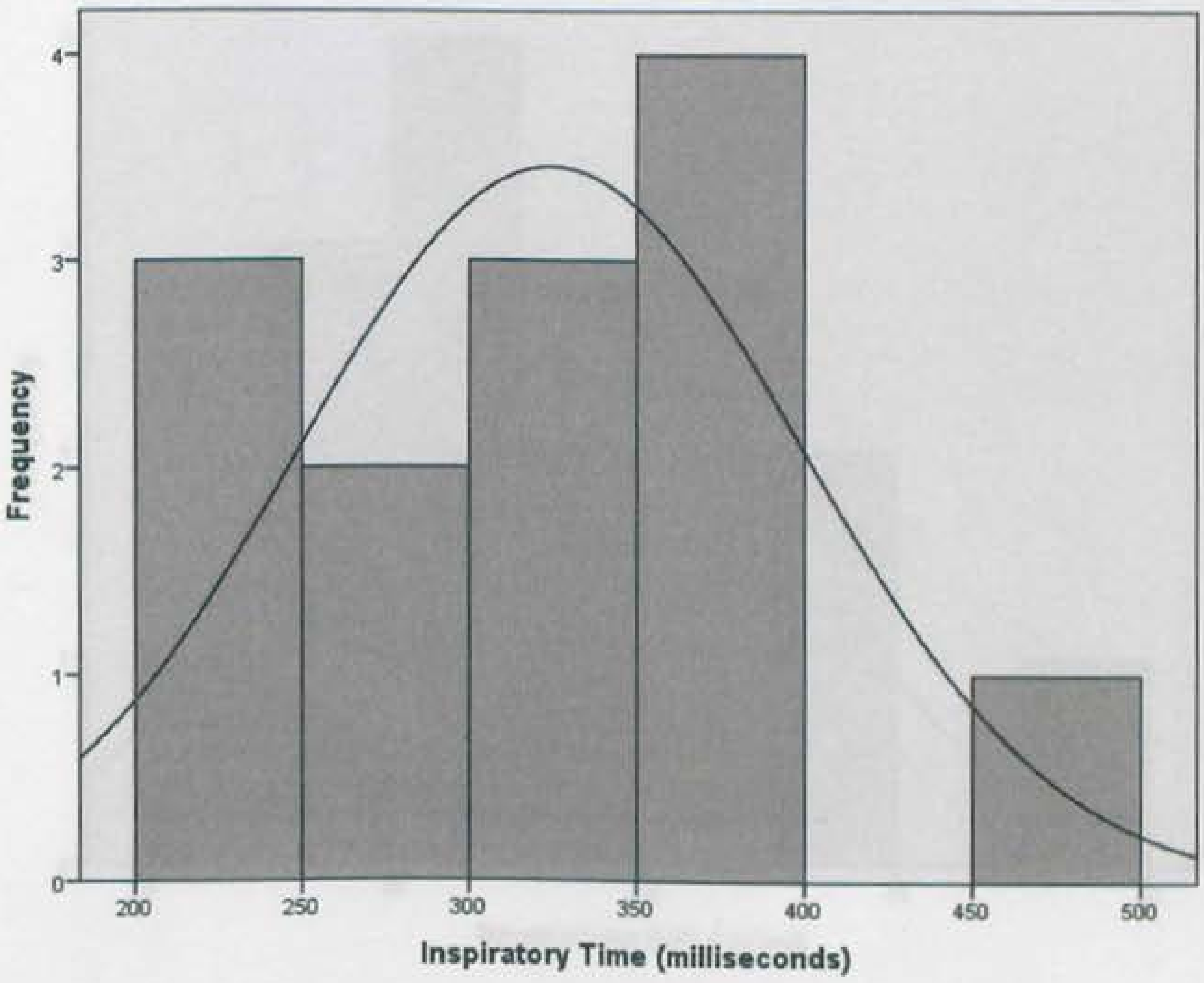
APPENDIX 5.1. *Continued*

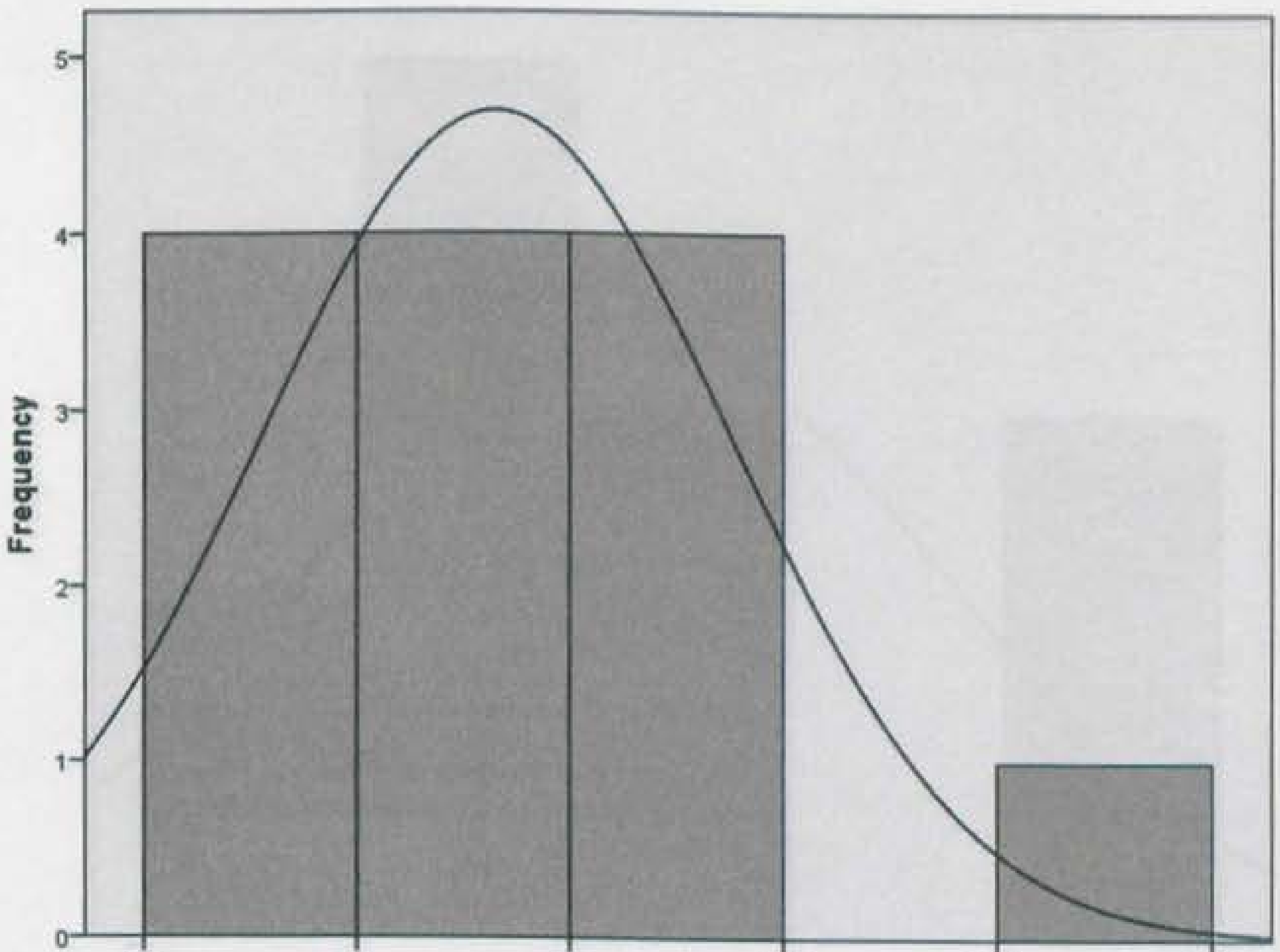
PERIOD





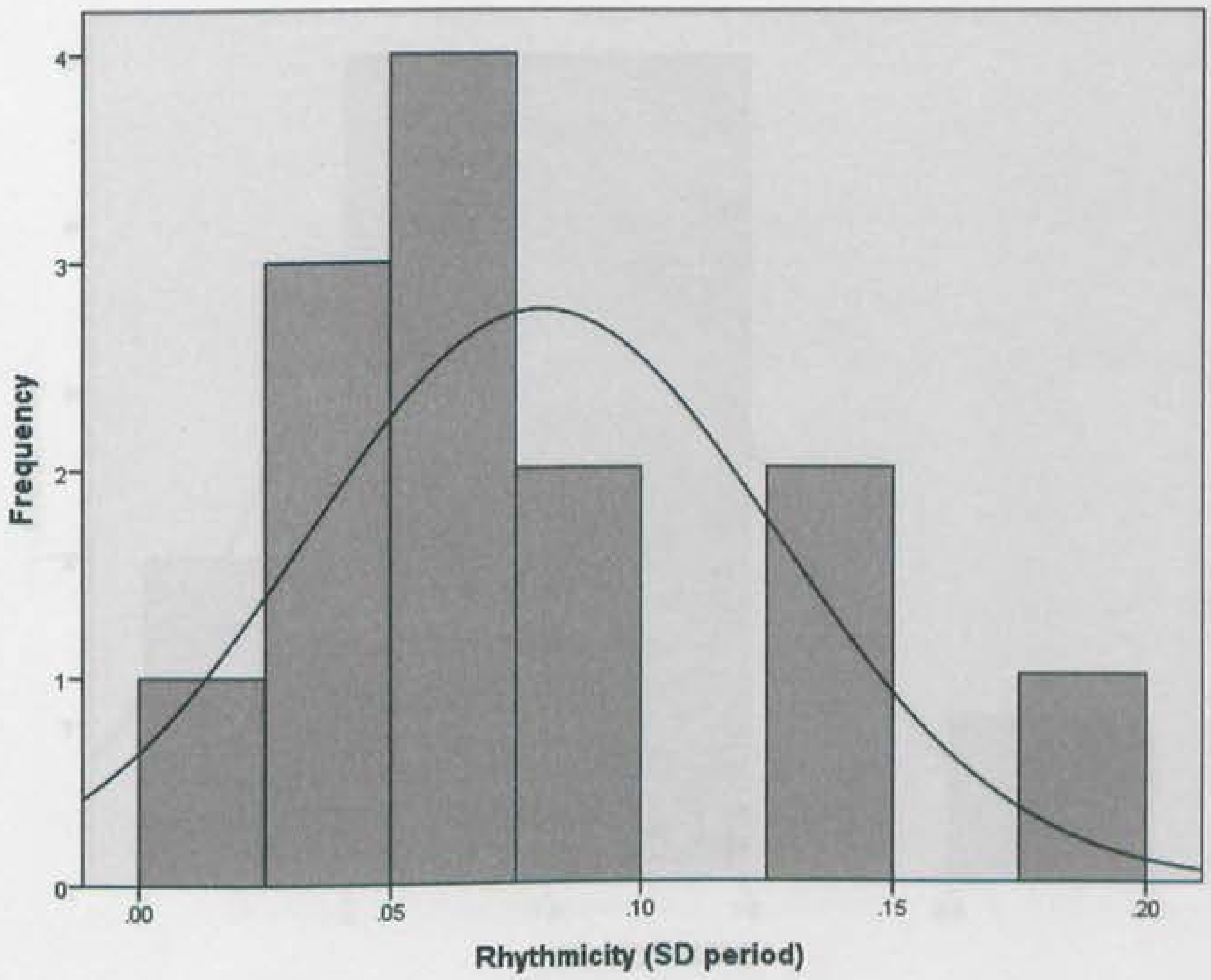
APPENDIX 5.2.
SAMPLE HISTOGRAMS: STEADY-STATE

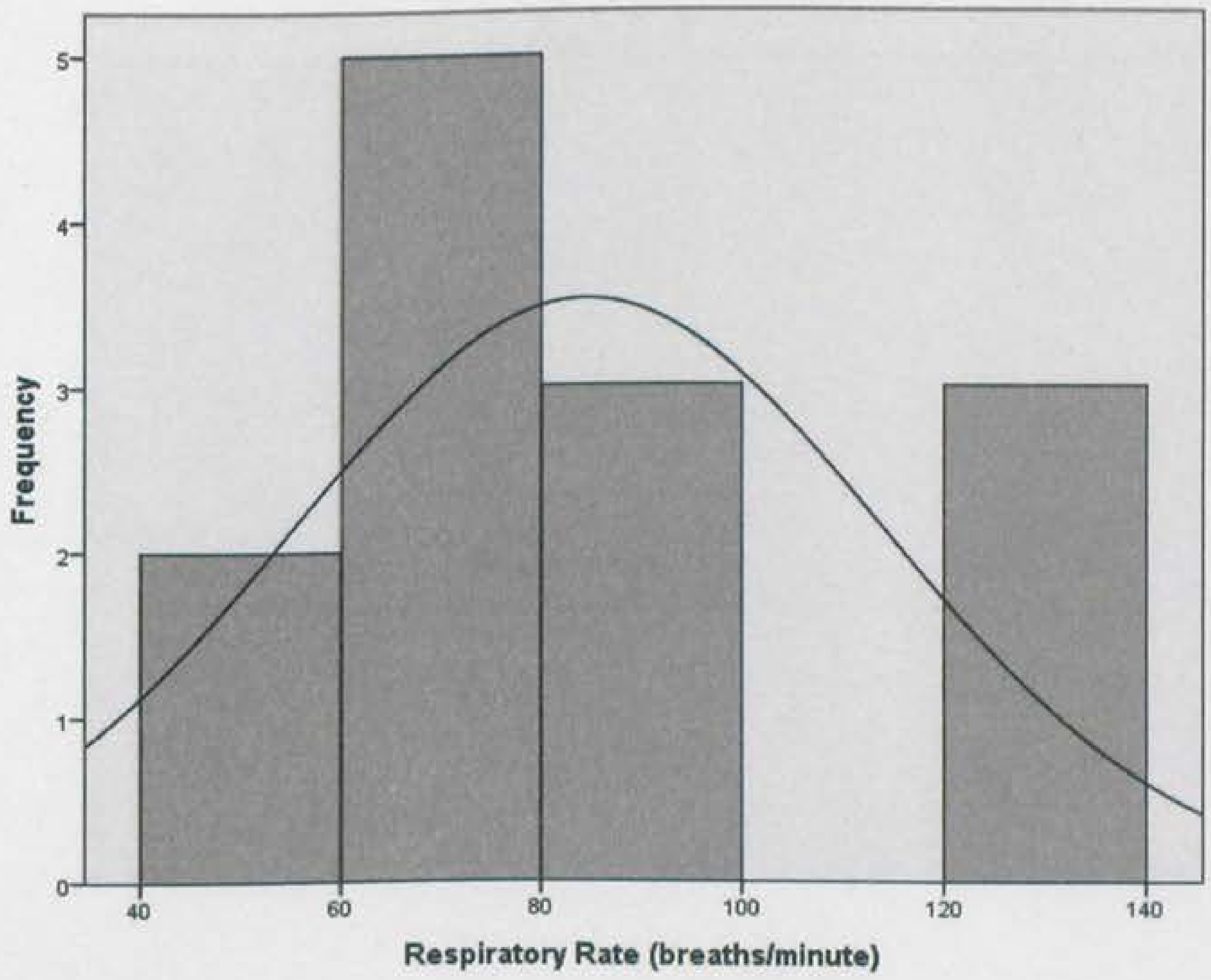




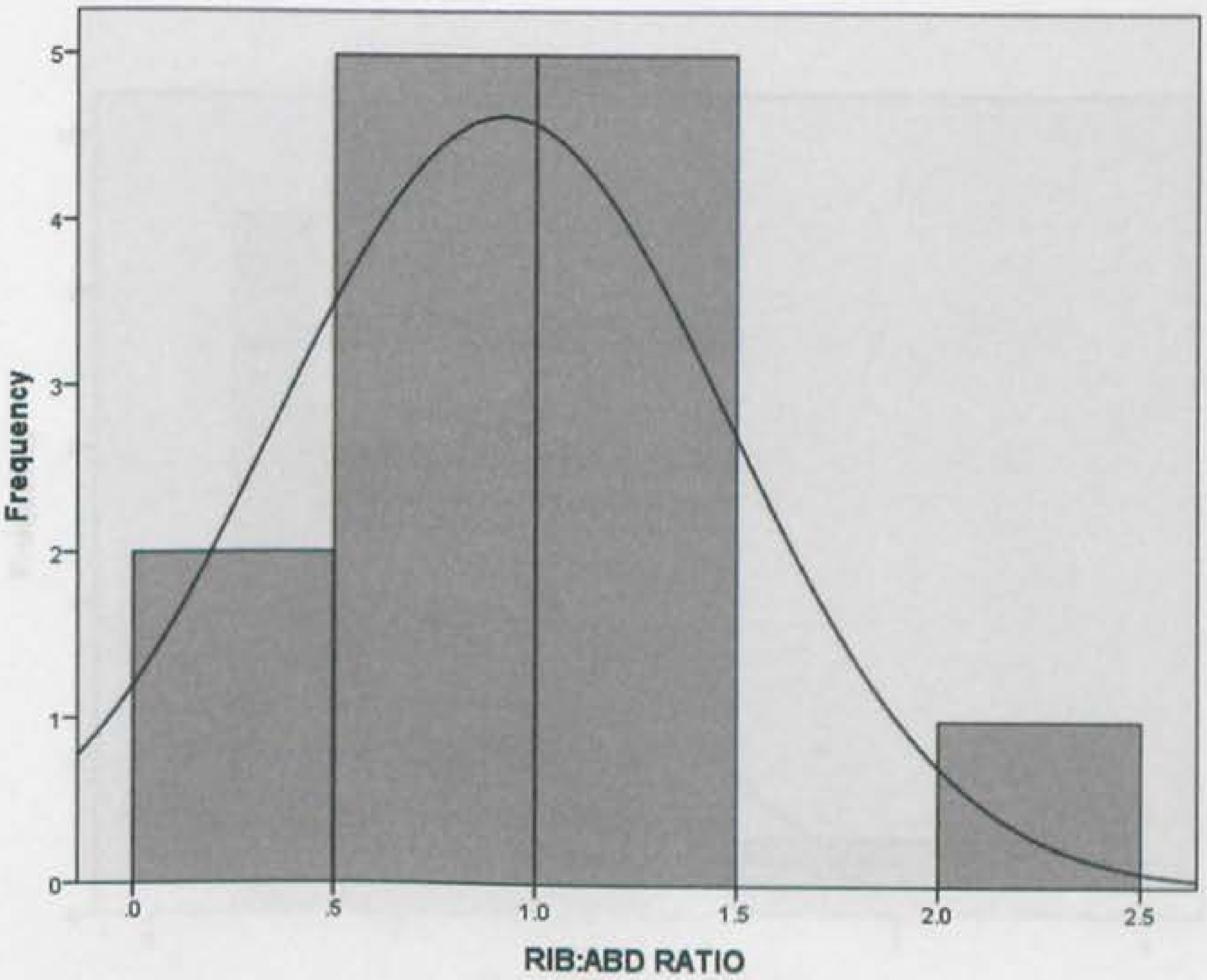
** Outcome measures with multiple data points for each subject are summarized by median value*

APPENDIX 5.2. Continued



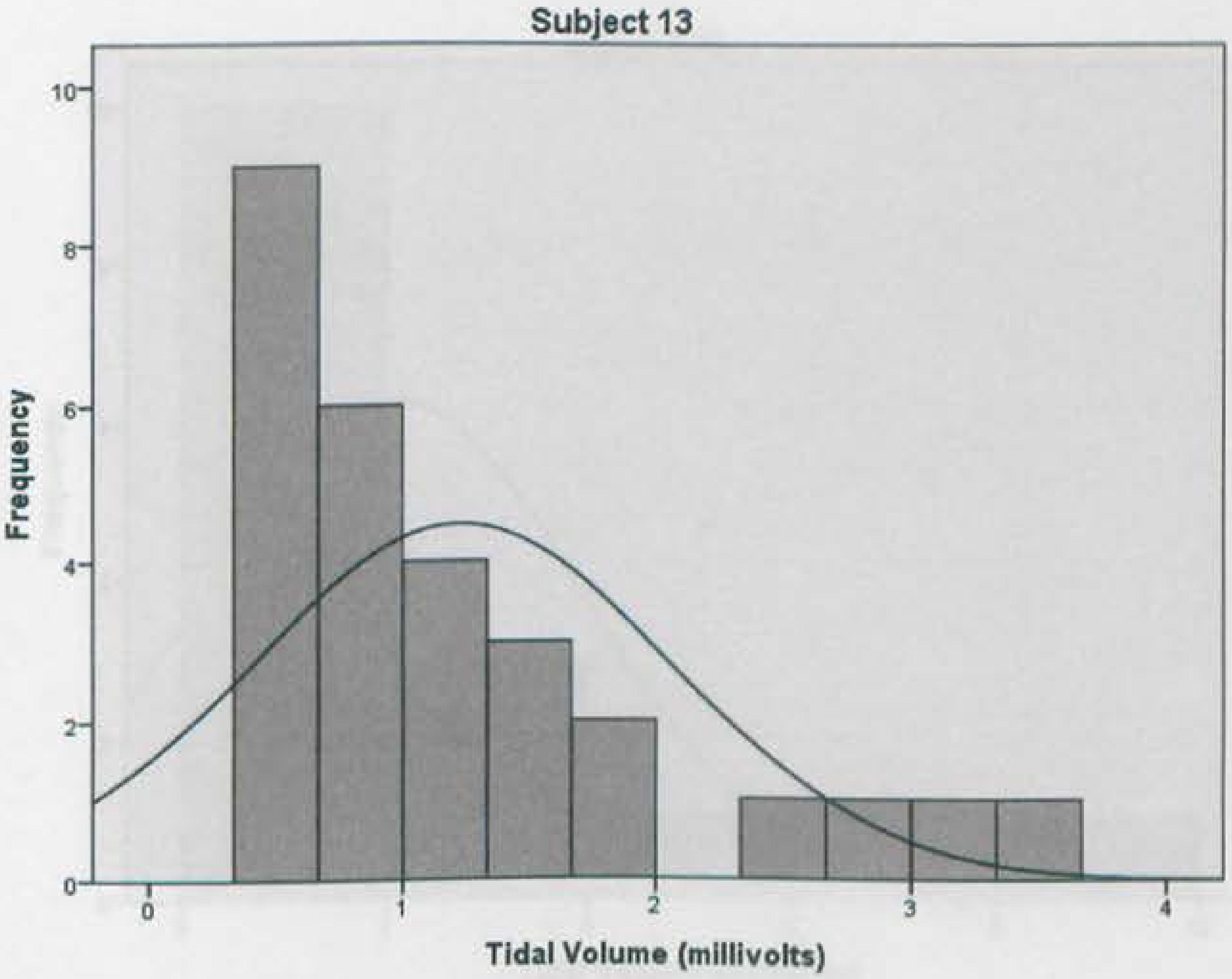


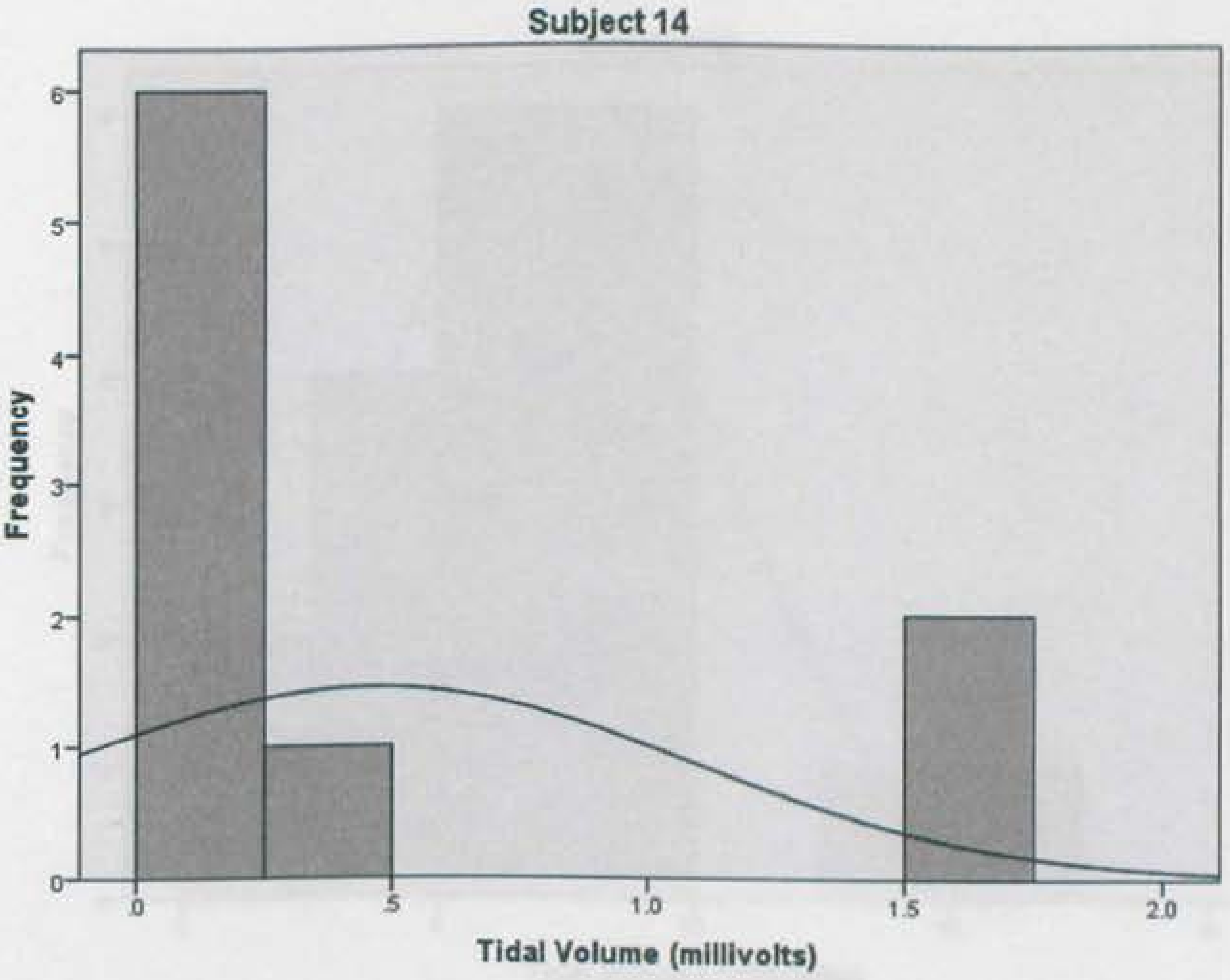
APPENDIX 5.2 . Continued



APPENDIX 5.3.
INDIVIDUAL HISTOGRAMS: FEEDING TIDAL VOLUME

INITIAL SUCK-BURST

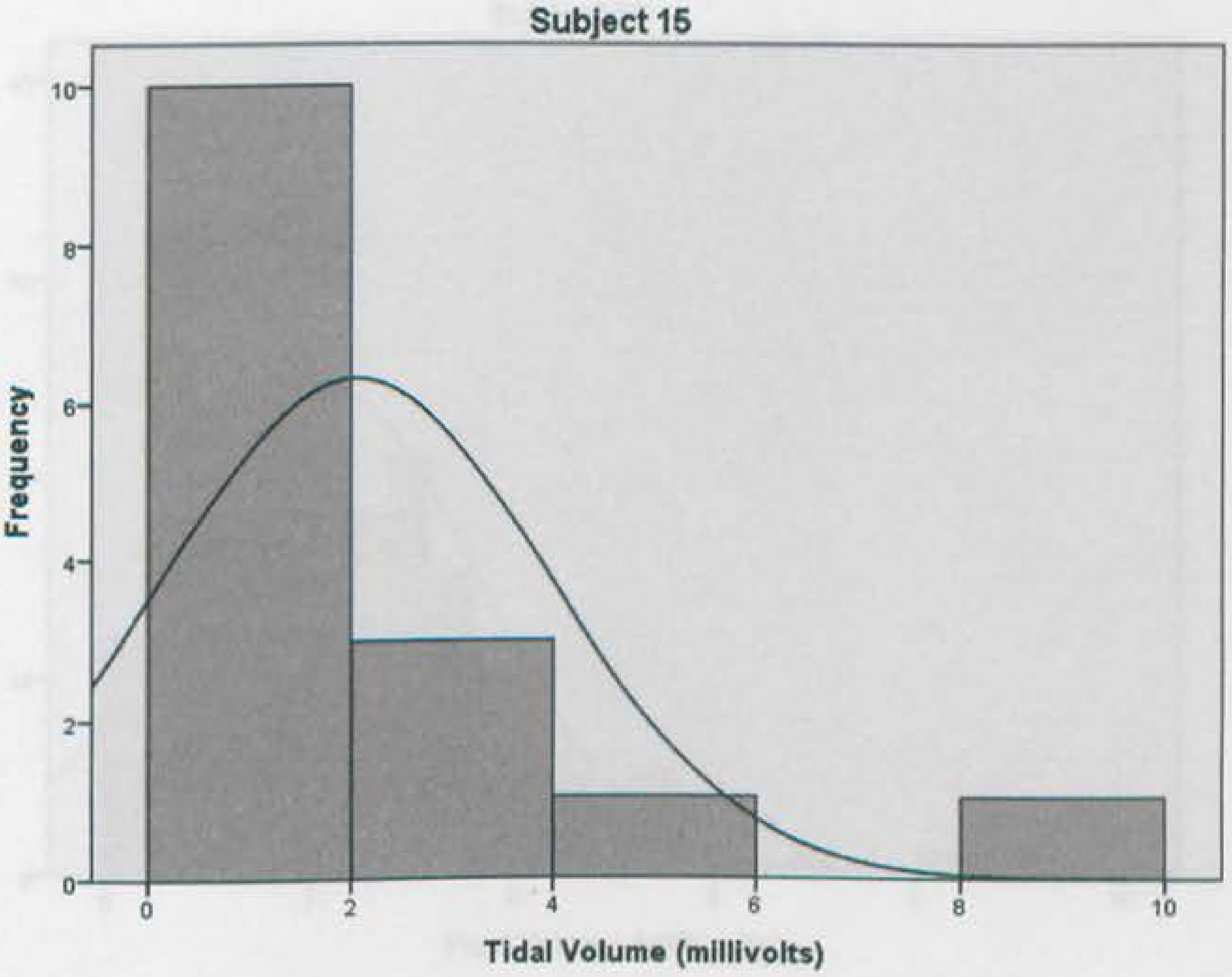


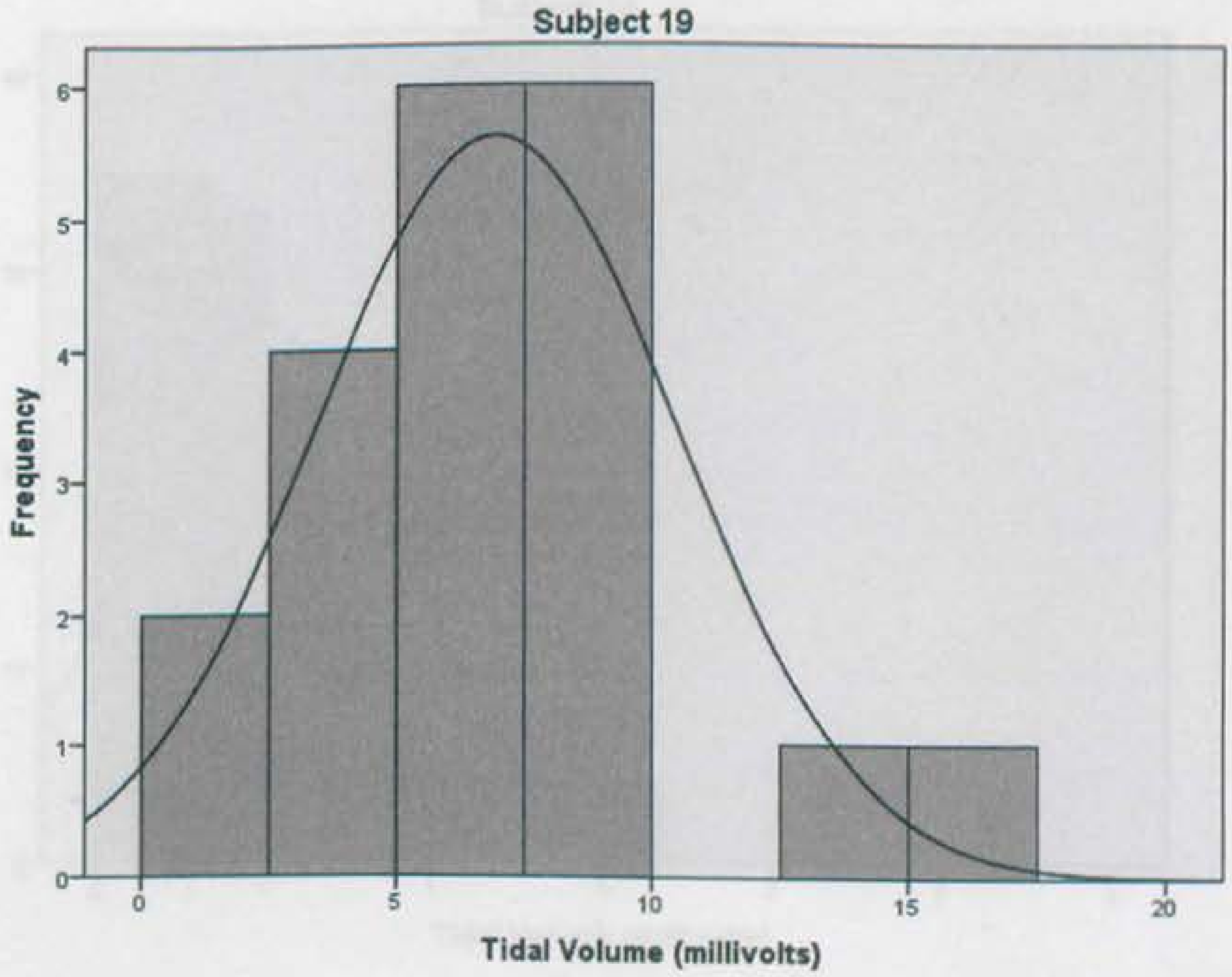


**All volumes represent respiration on the standard-flow nipple.*

APPENDIX 5.3. *Continued*

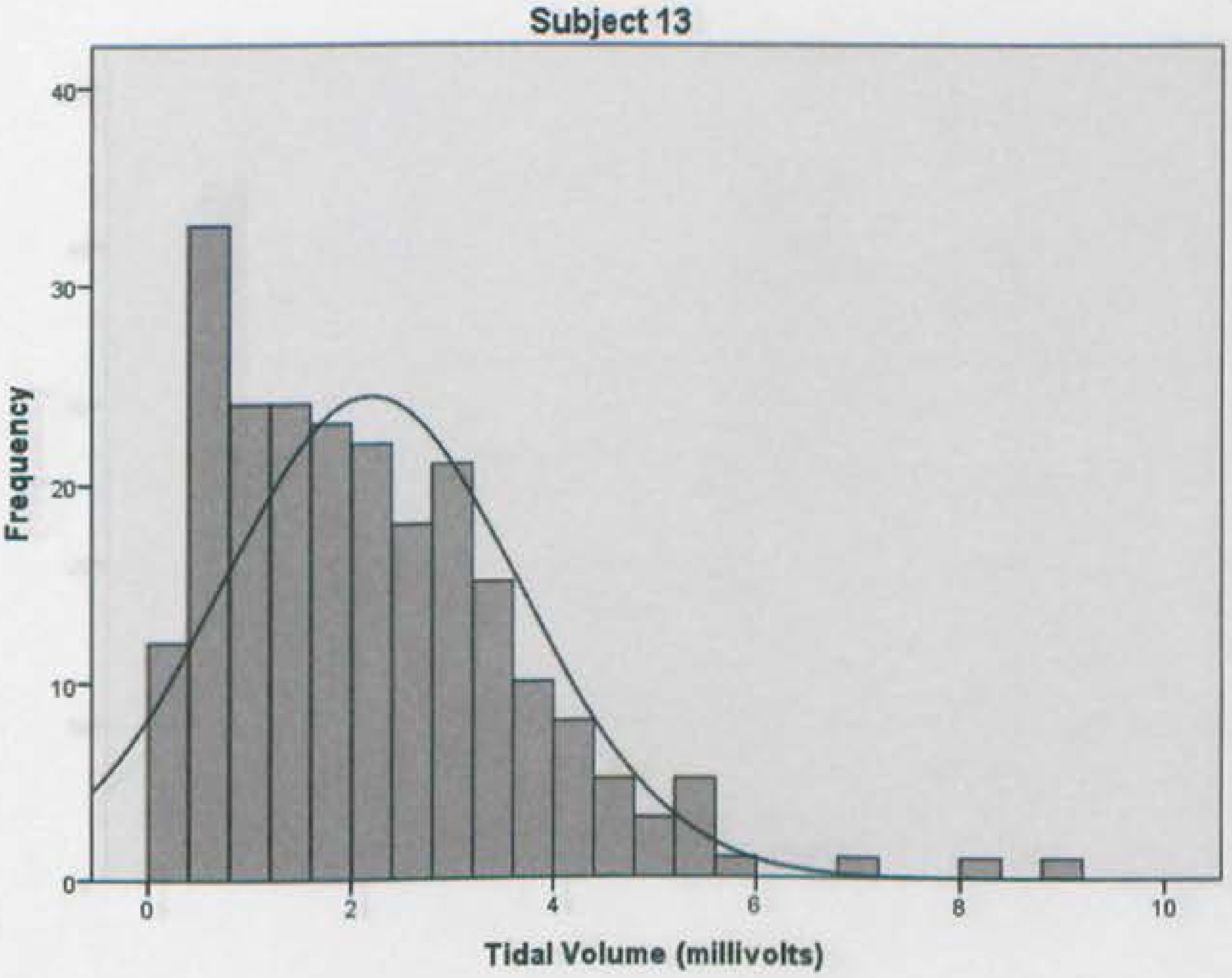
INITIAL SUCK-BURST

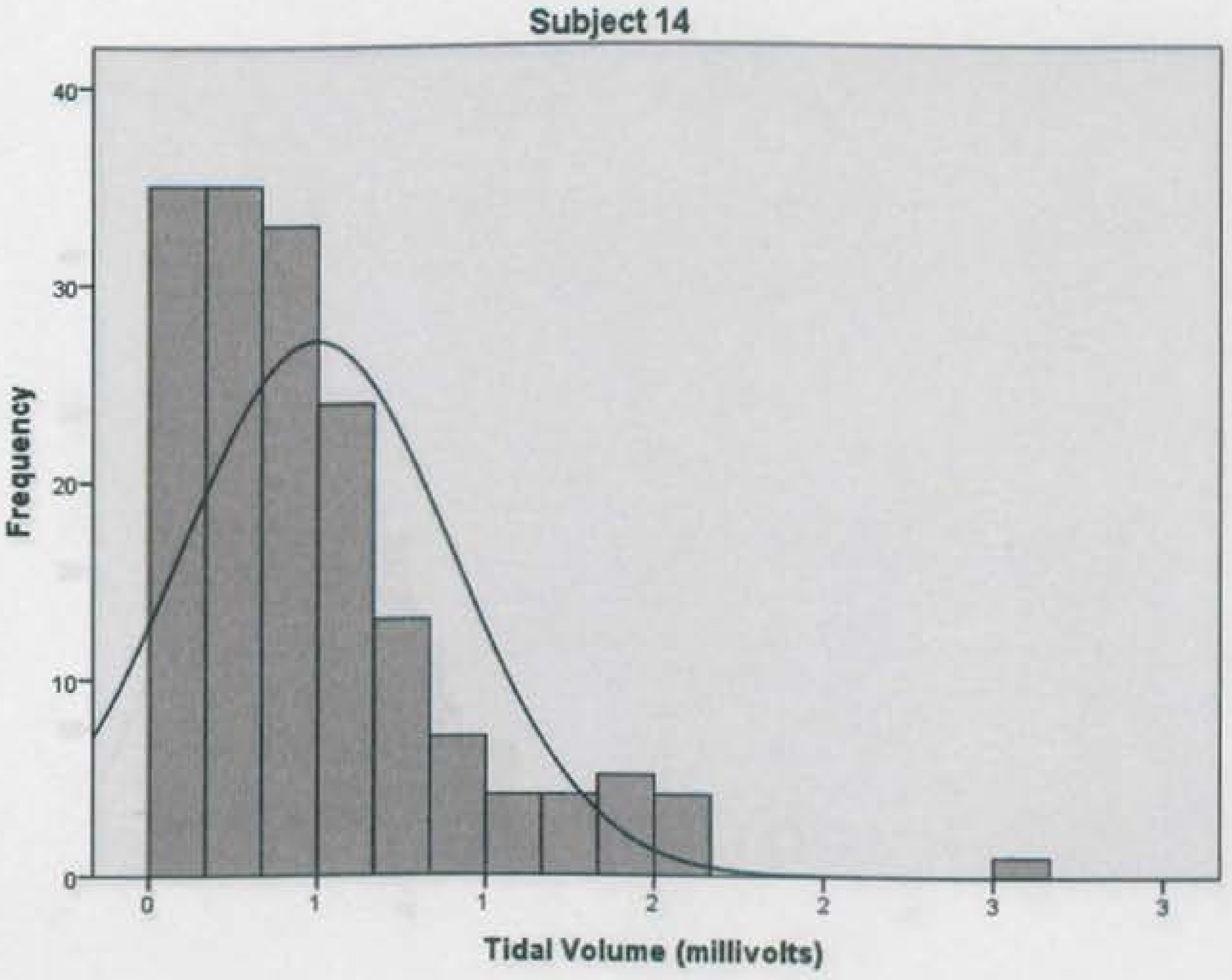




APPENDIX 5.3. Continued

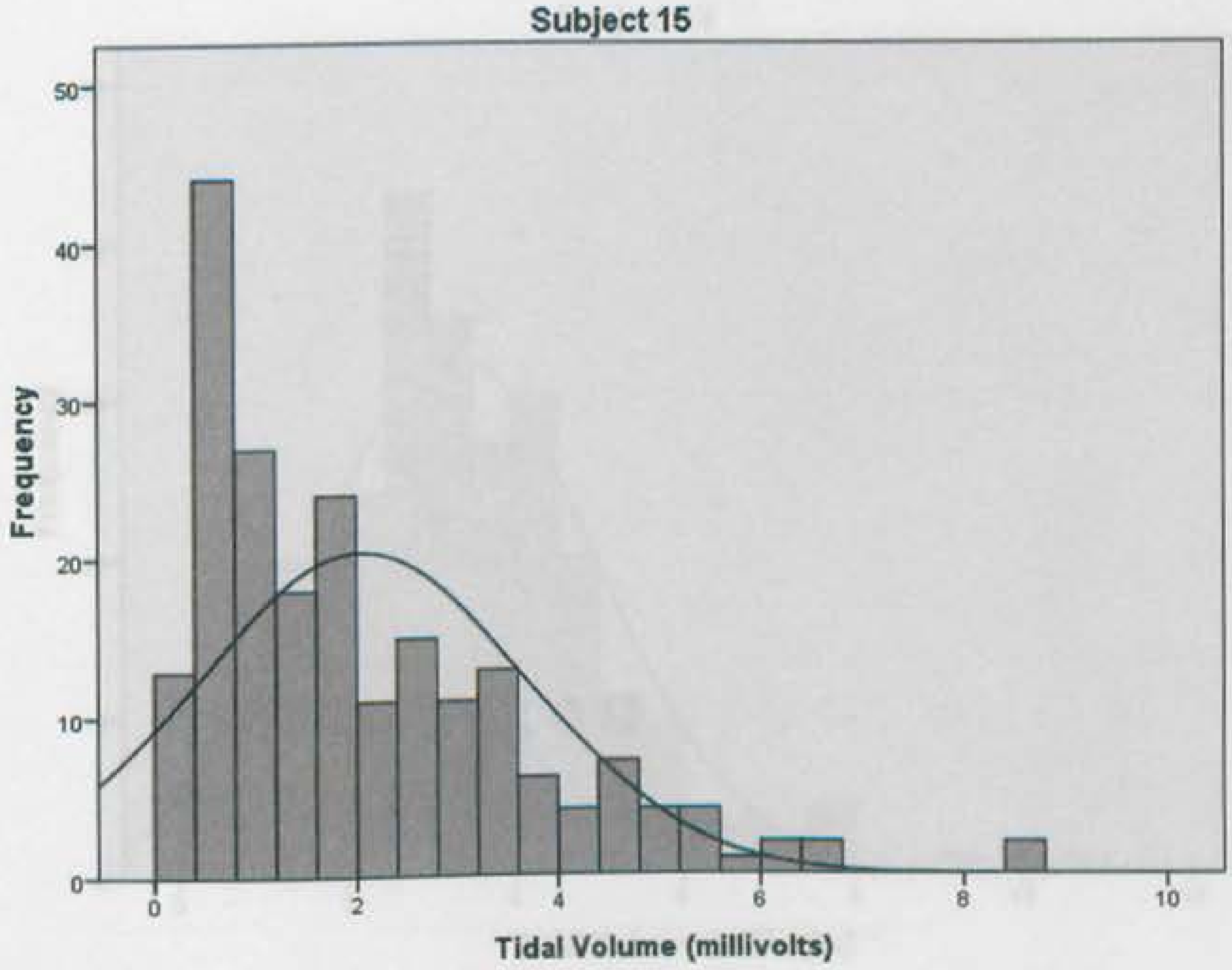
SUBSEQUENT SUCK-BURST

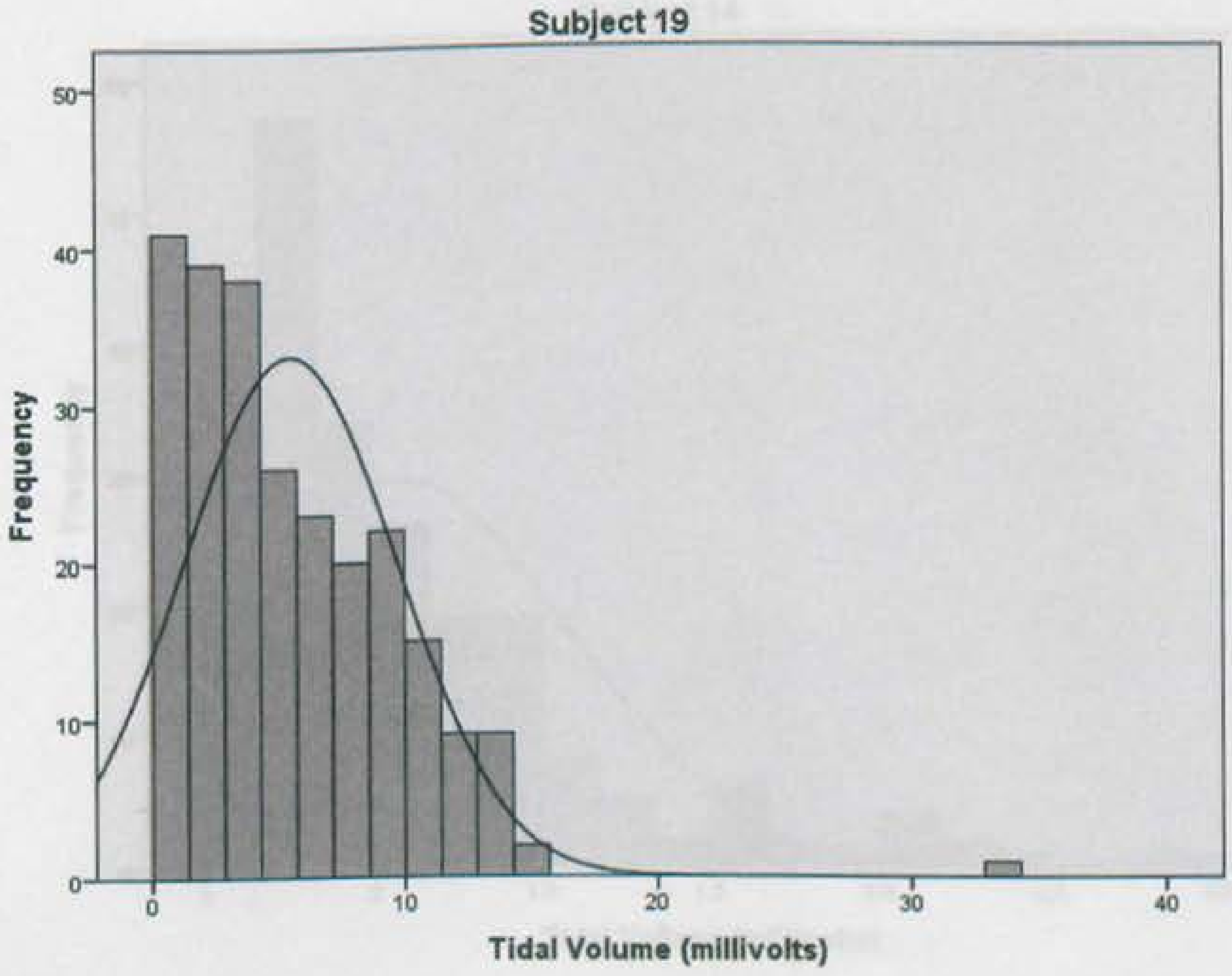

Subject 13


Subject 14

APPENDIX 5.3. Continued

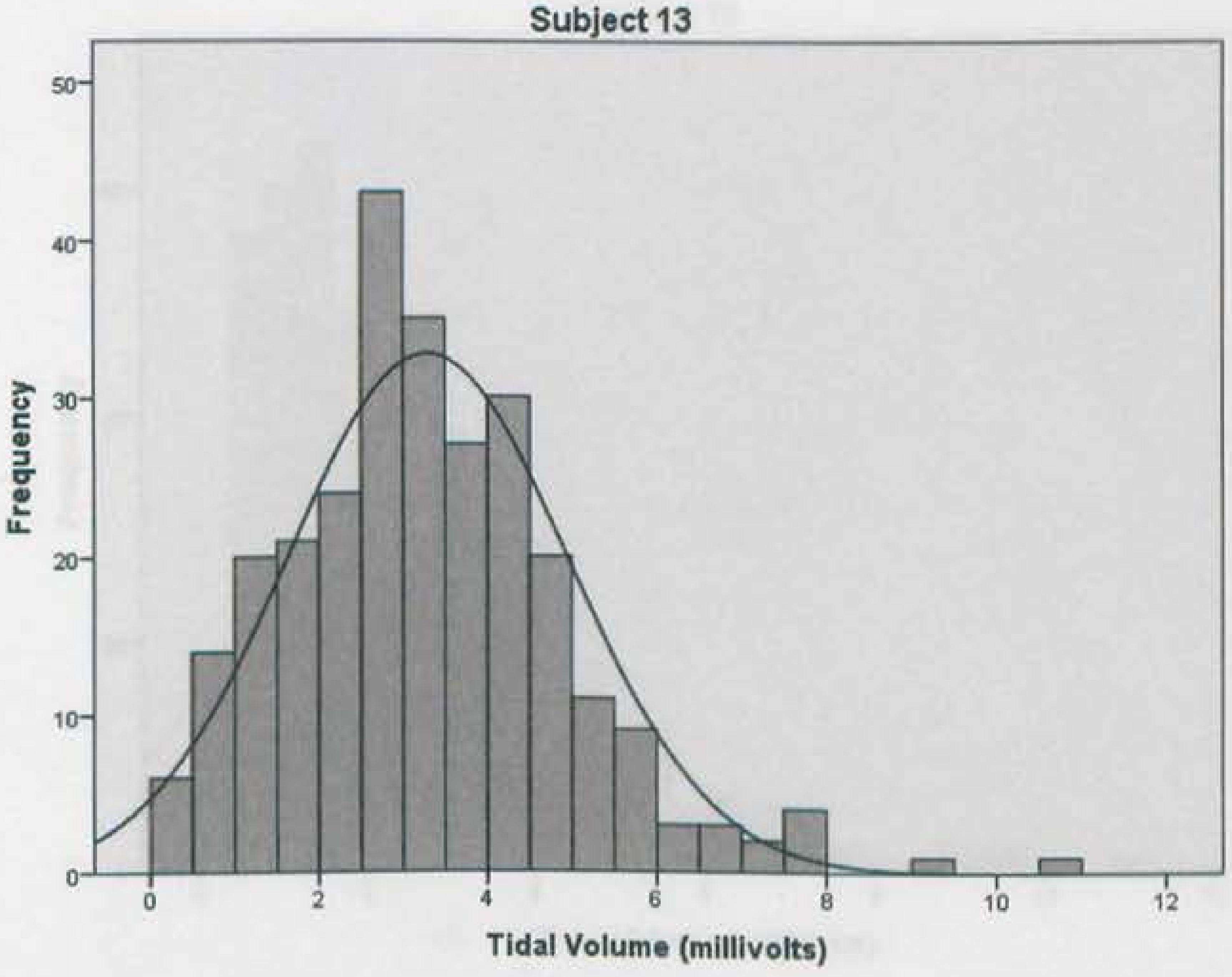
SUBSEQUENT SUCK-BURST





APPENDIX 5.3. *Continued*

SUCK-BURST BREAK



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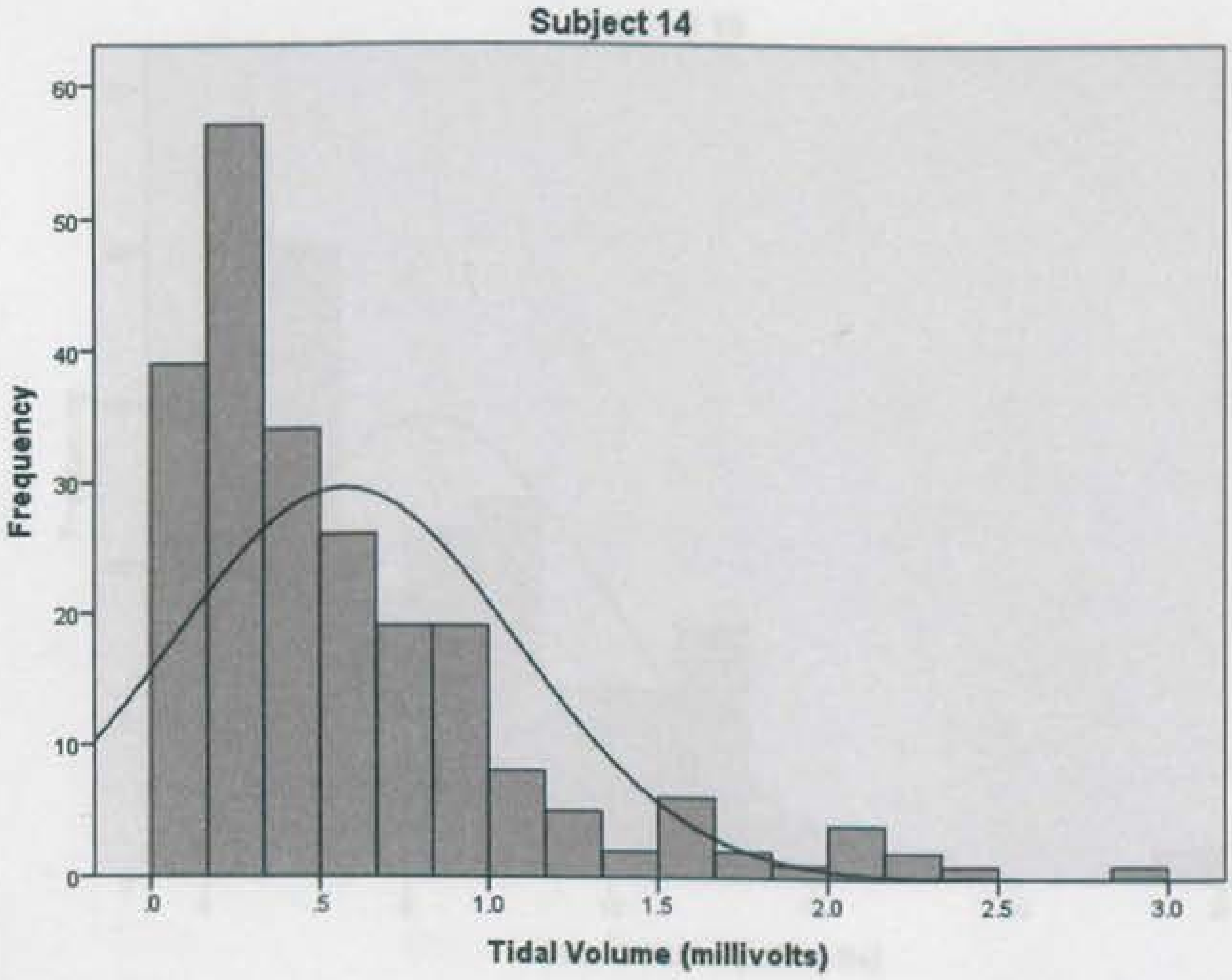
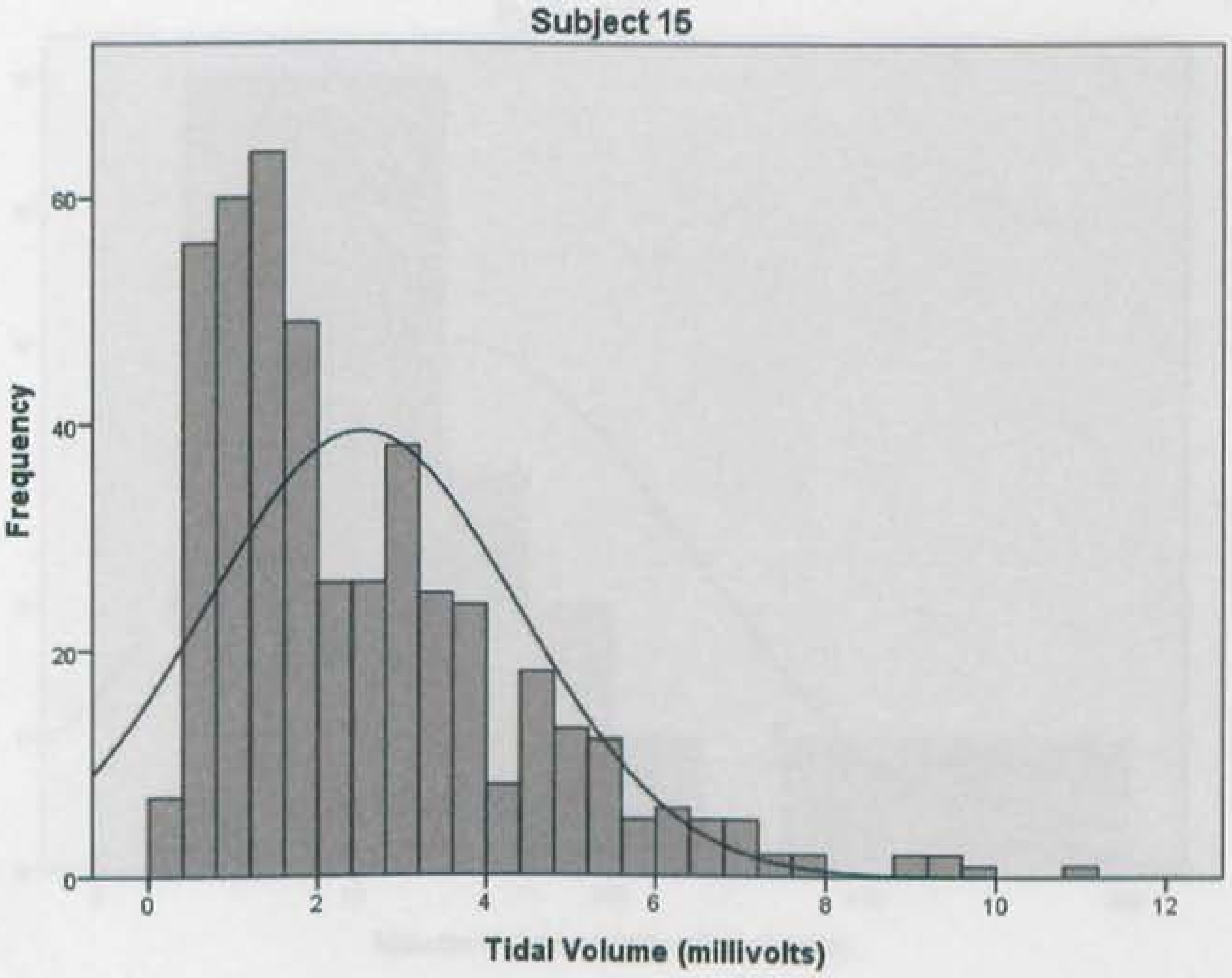
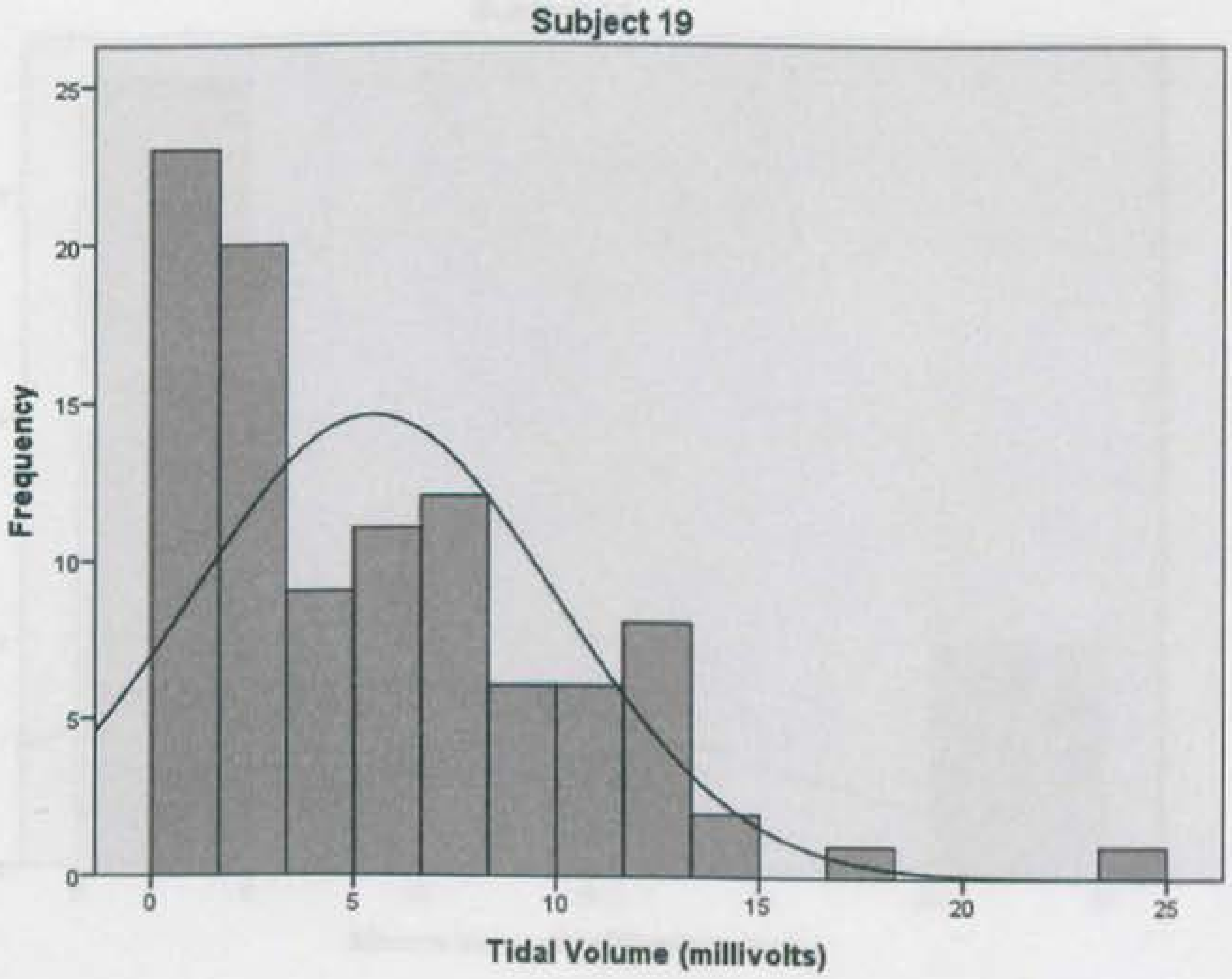


Subject 14

APPENDIX 5.3. Continued

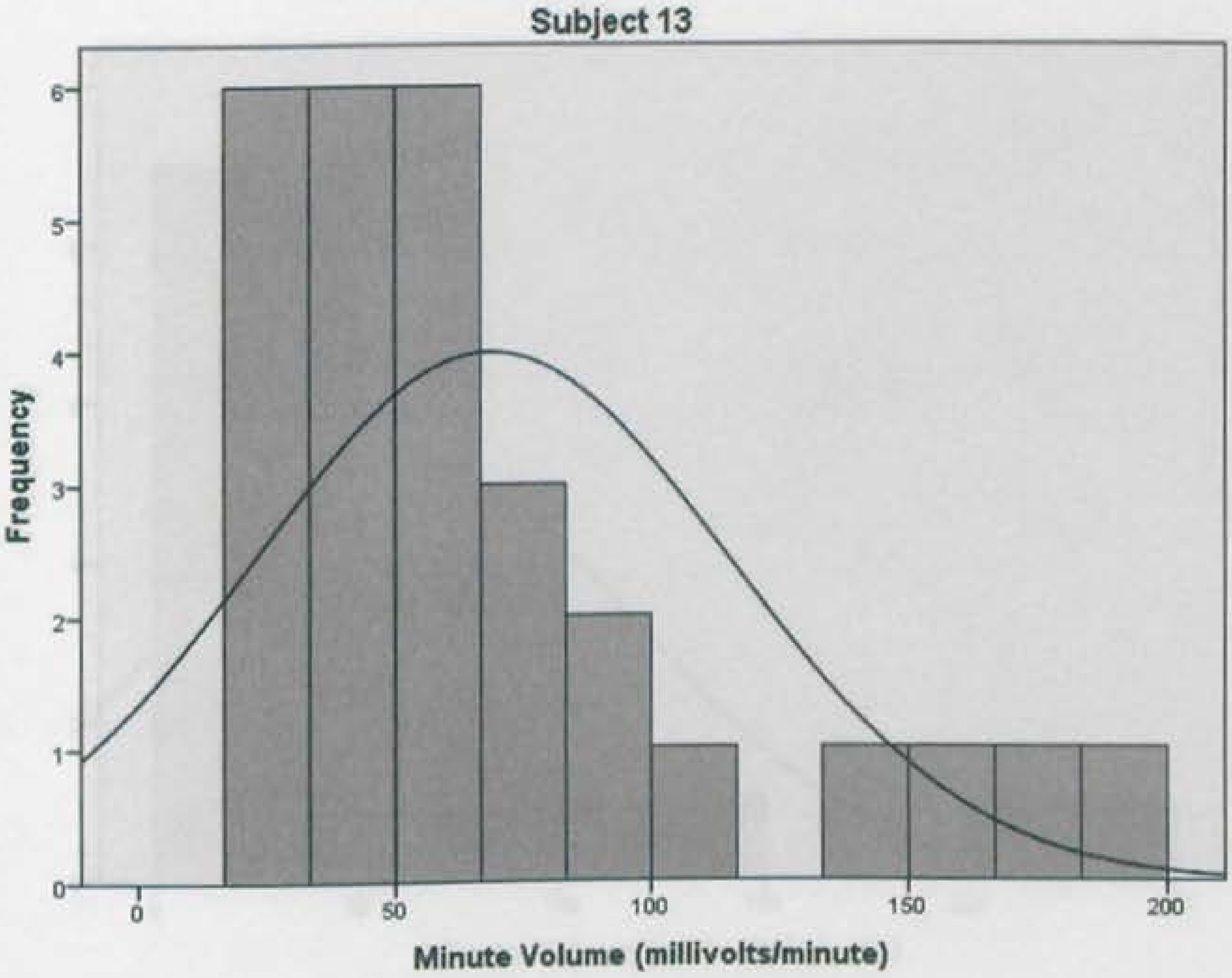
SUCK-BURST BREAK

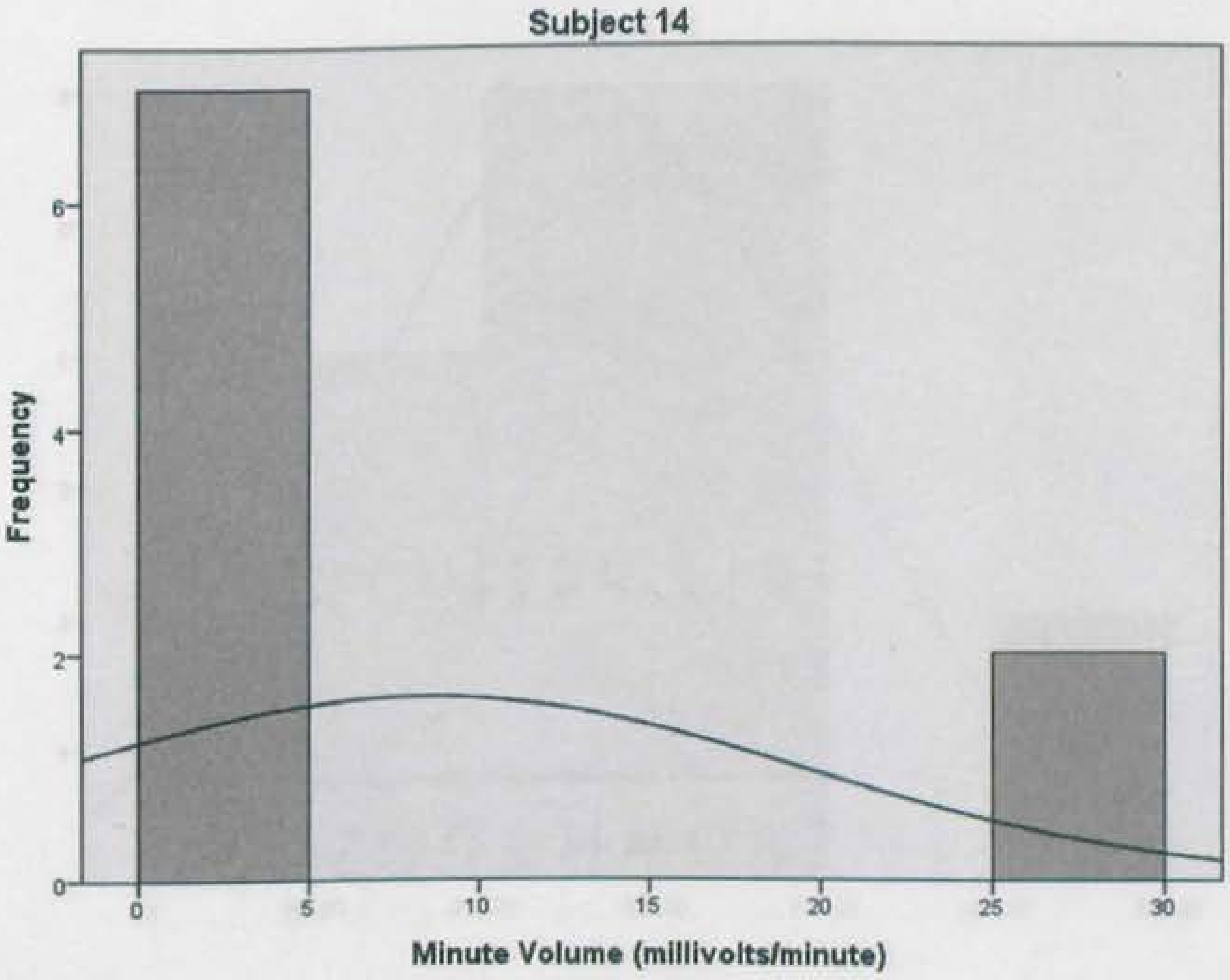




APPENDIX 5.4.
INDIVIDUAL HISTOGRAMS: FEEDING MINUTE VOLUME

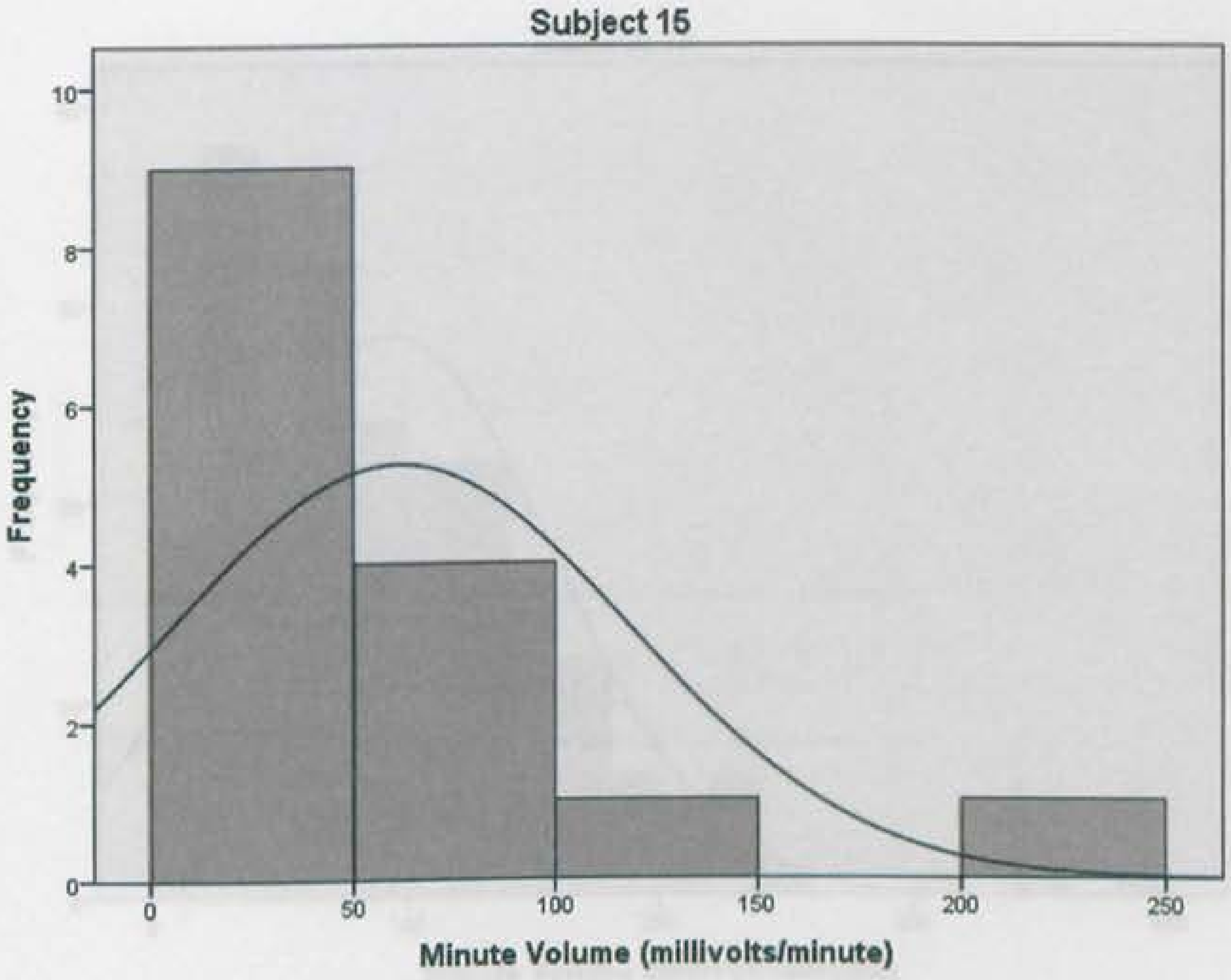
INITIAL SUCK- BURST

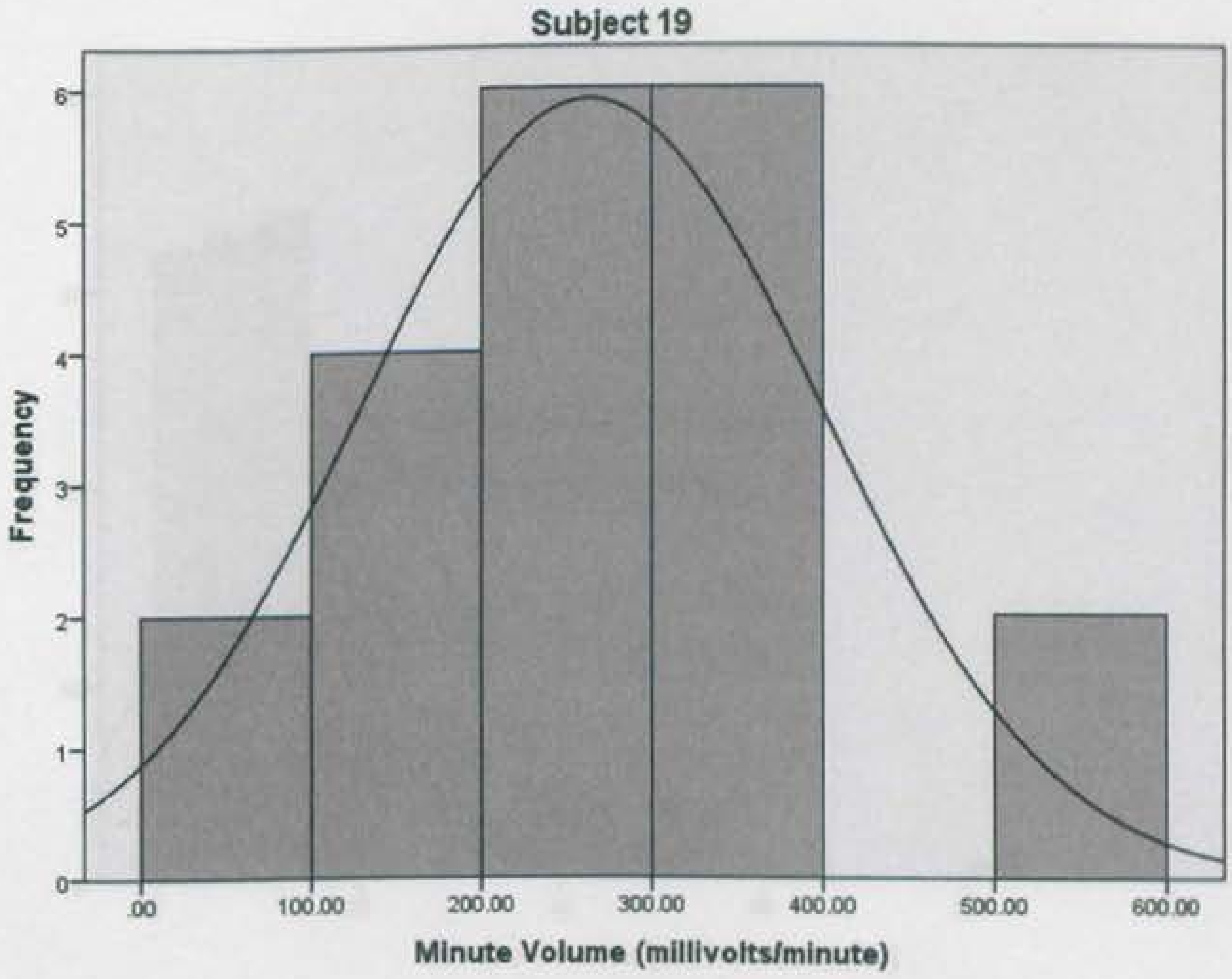




APPENDIX 5.4. *Continued*

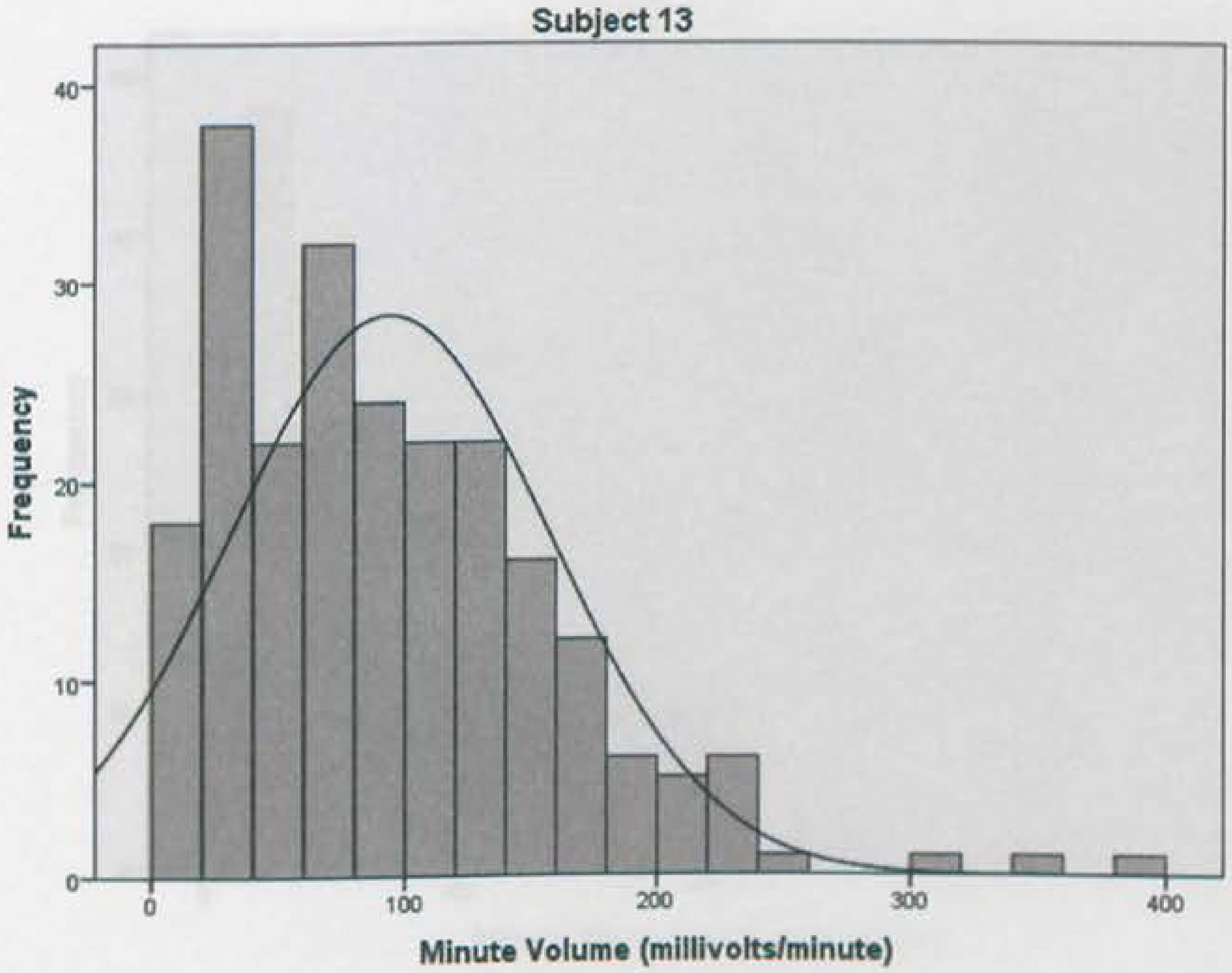
INITIAL SUCK- BURST

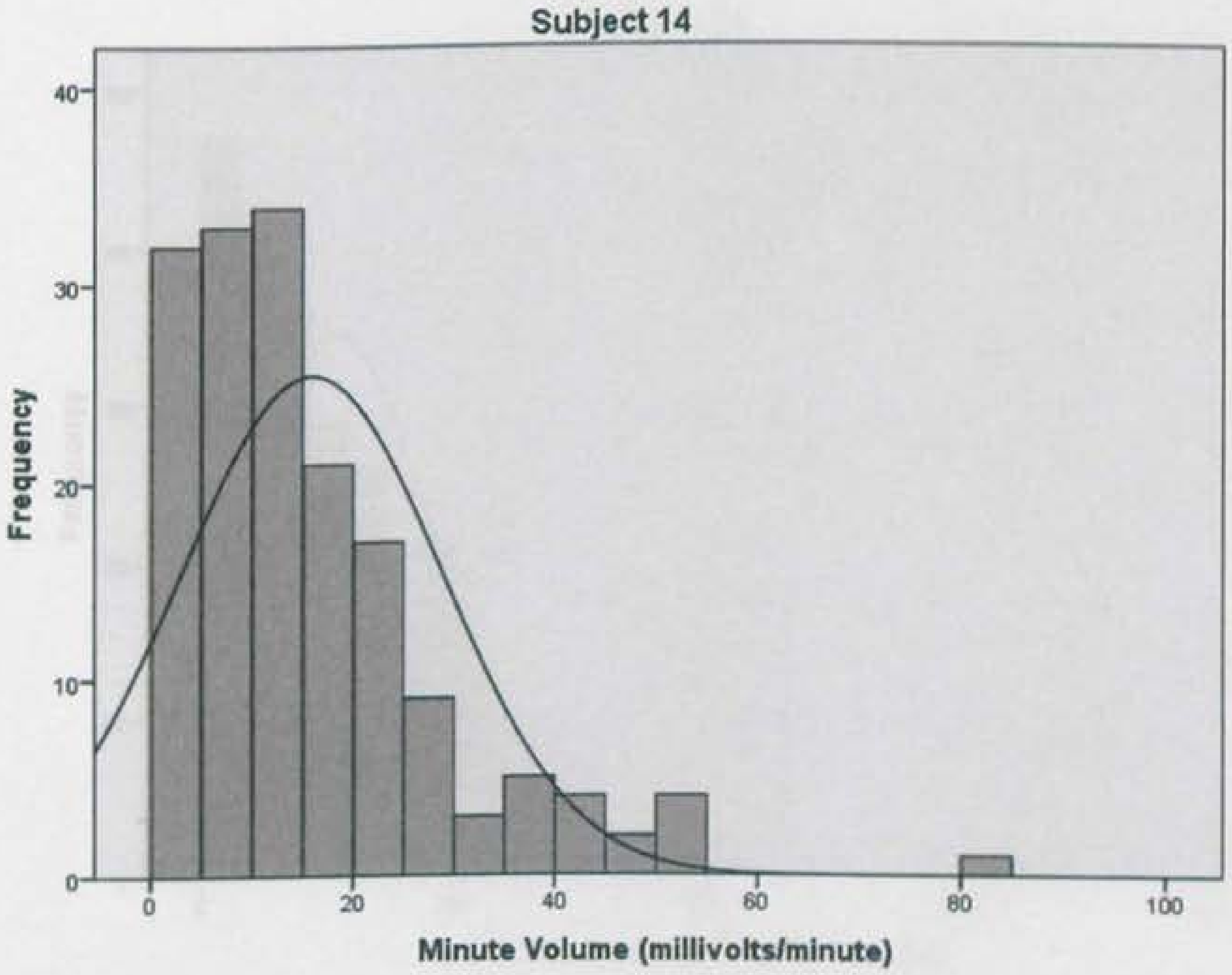




APPENDIX 5.4. *Continued*

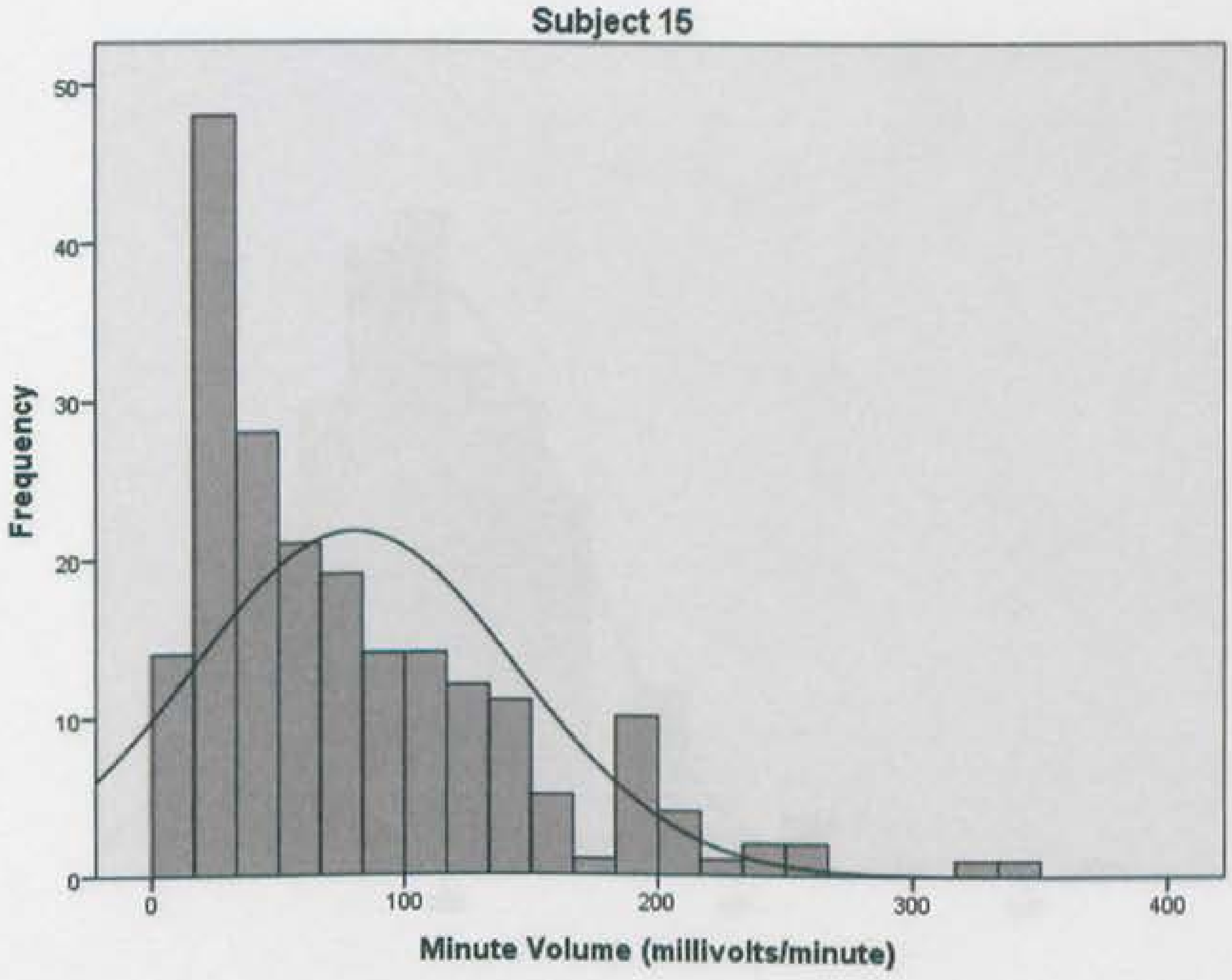
SUBSEQUENT SUCK- BURST

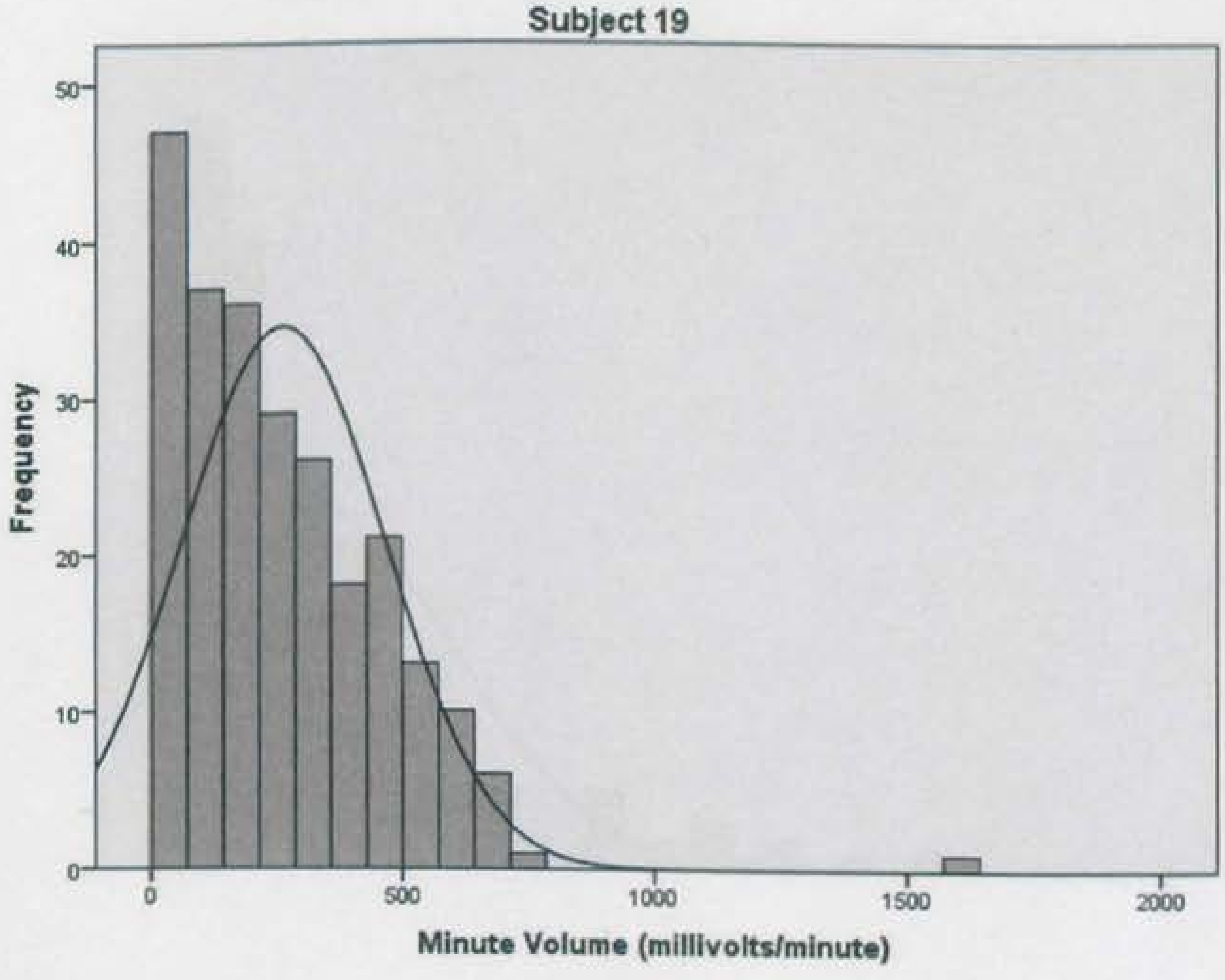




APPENDIX 5.4. Continued

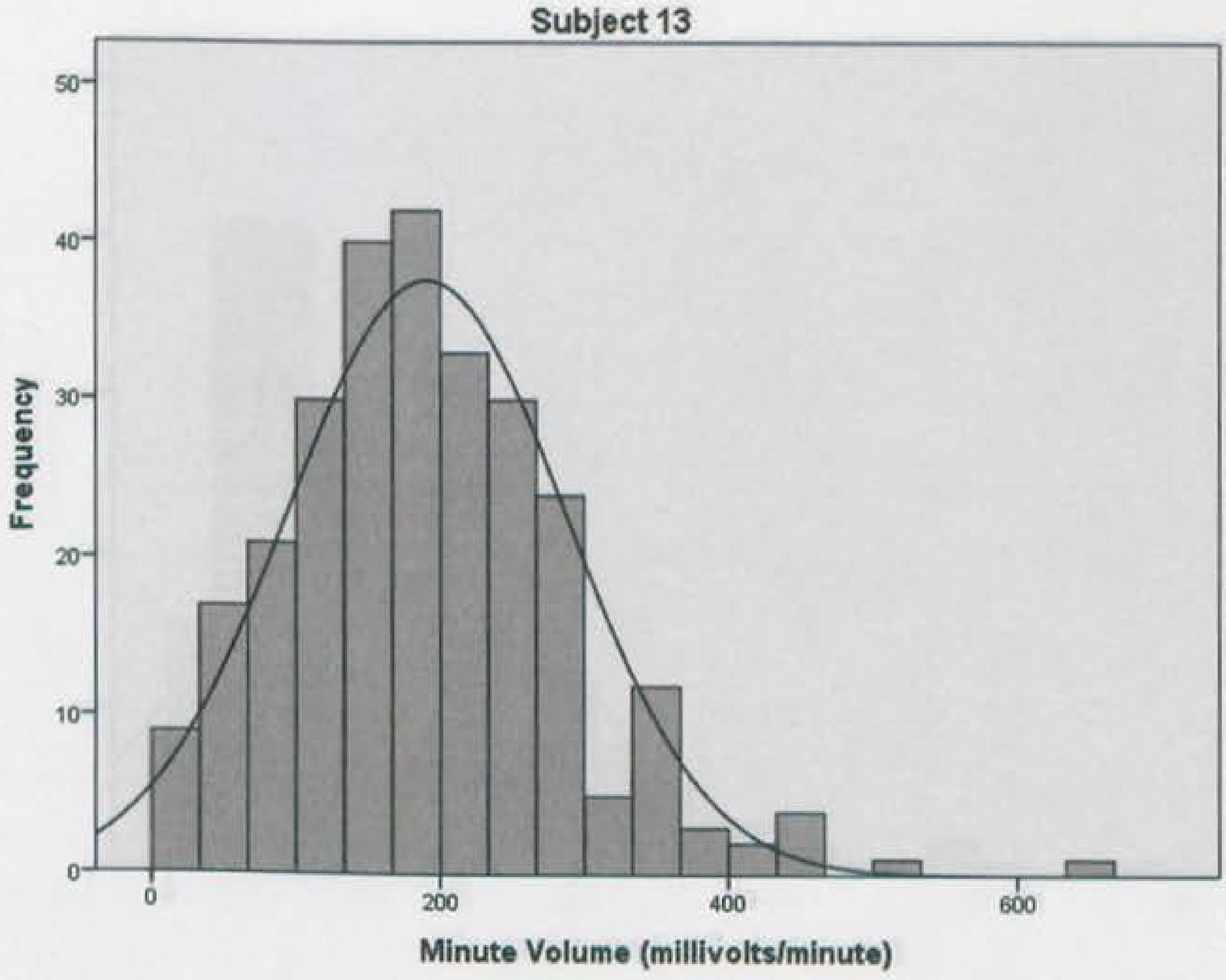
SUBSEQUENT SUCK- BURST



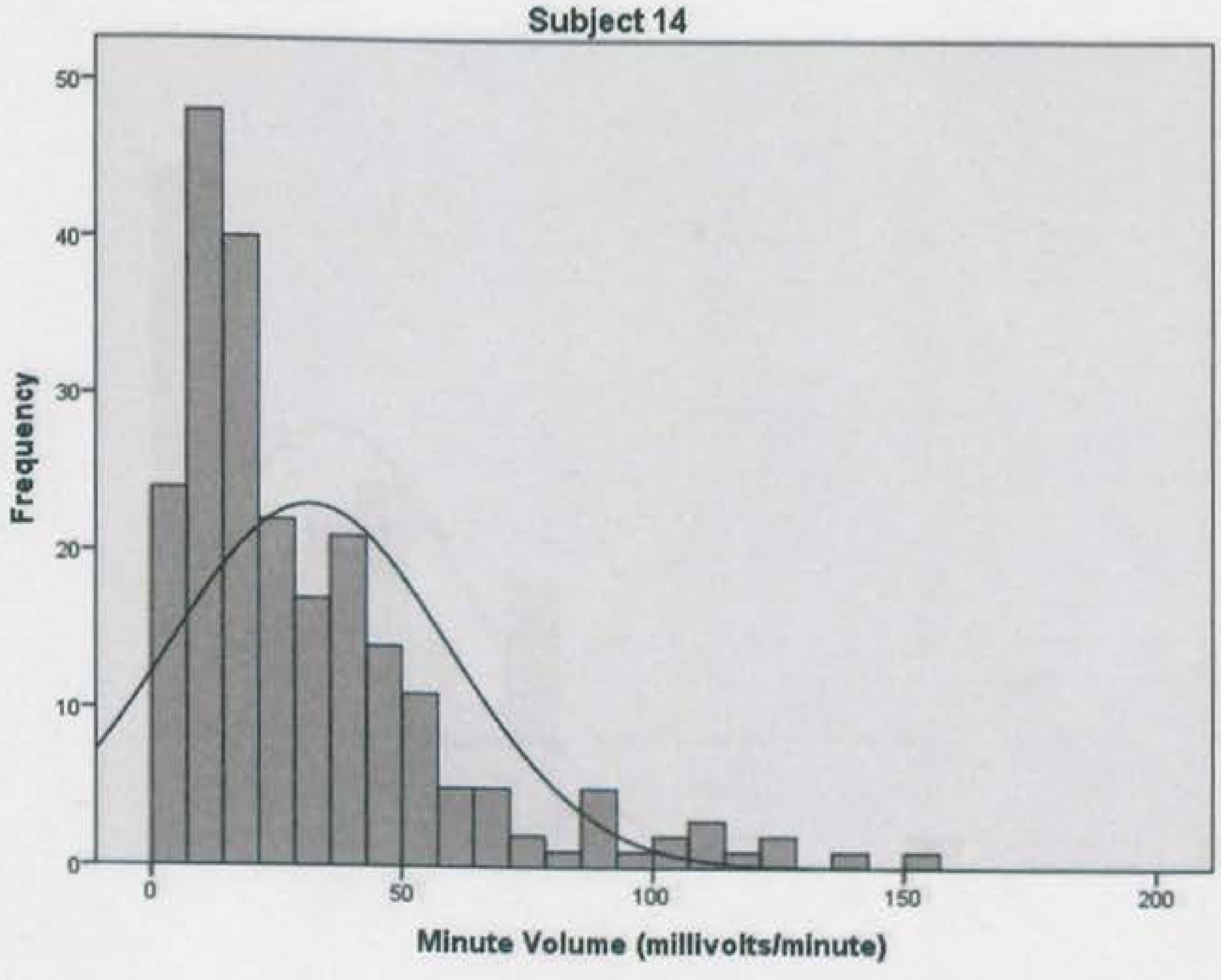


APPENDIX 5.4. *Continued*

SUCK- BURST BREAK



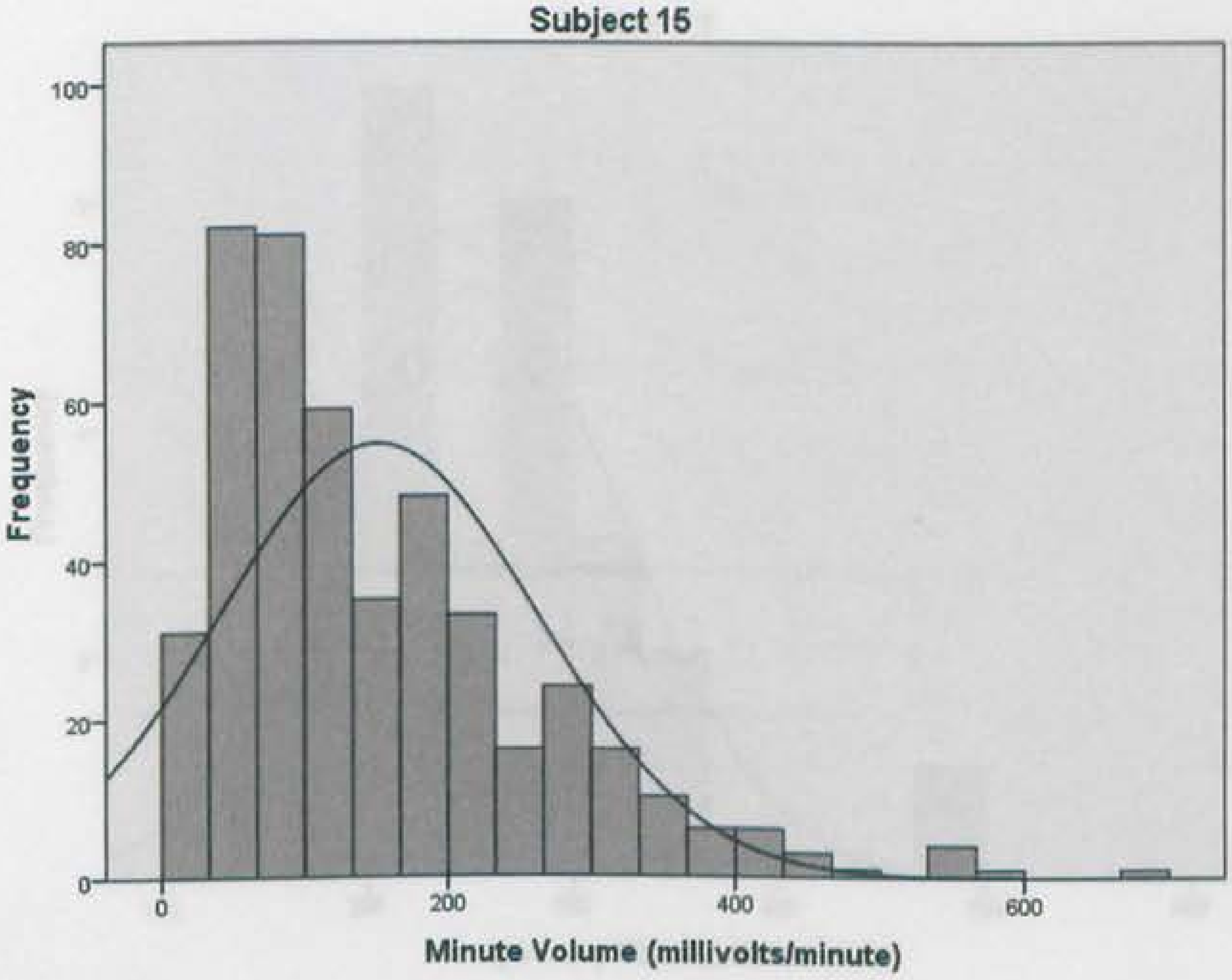
Subject 13

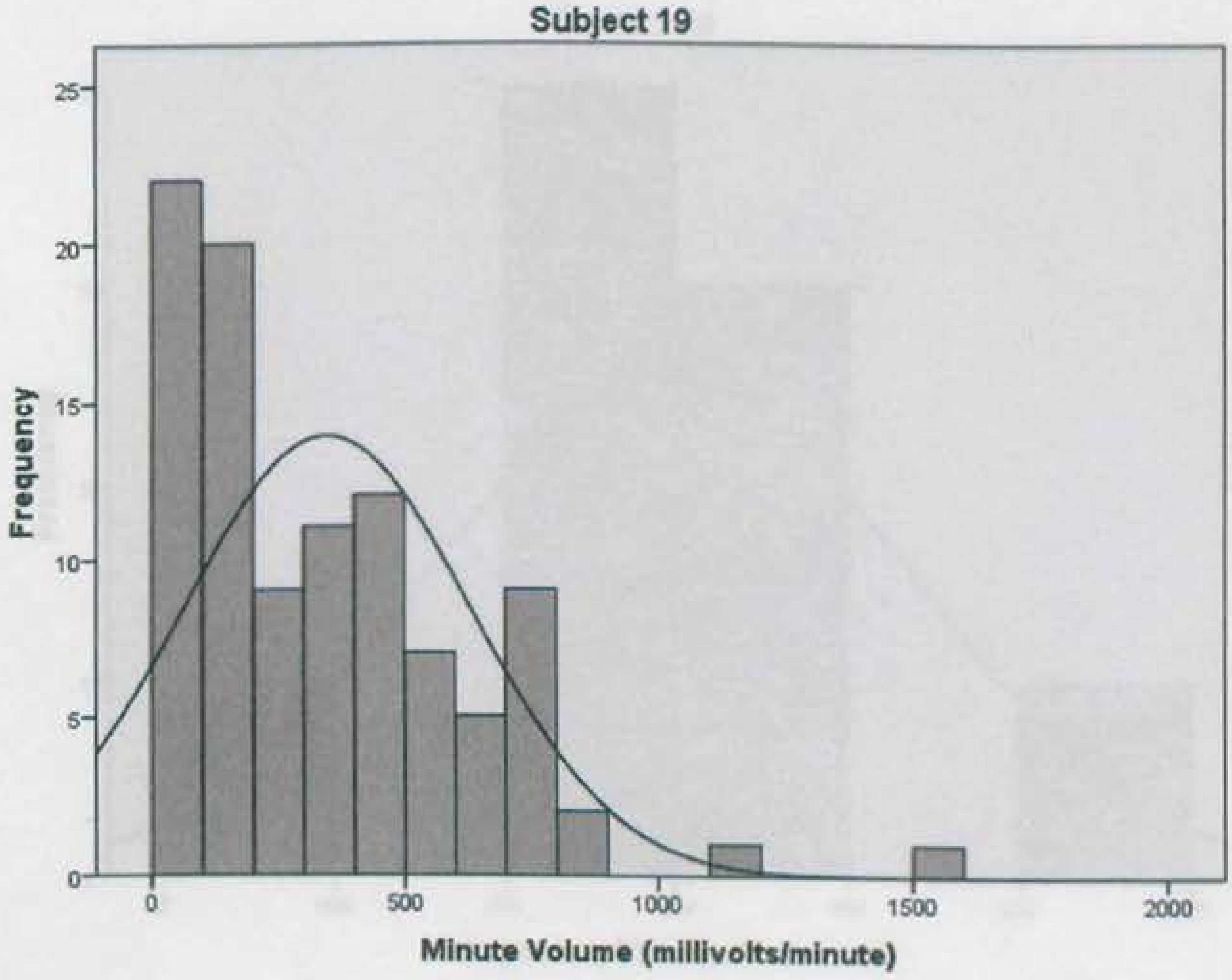


Subject 14

APPENDIX 5.4. Continued

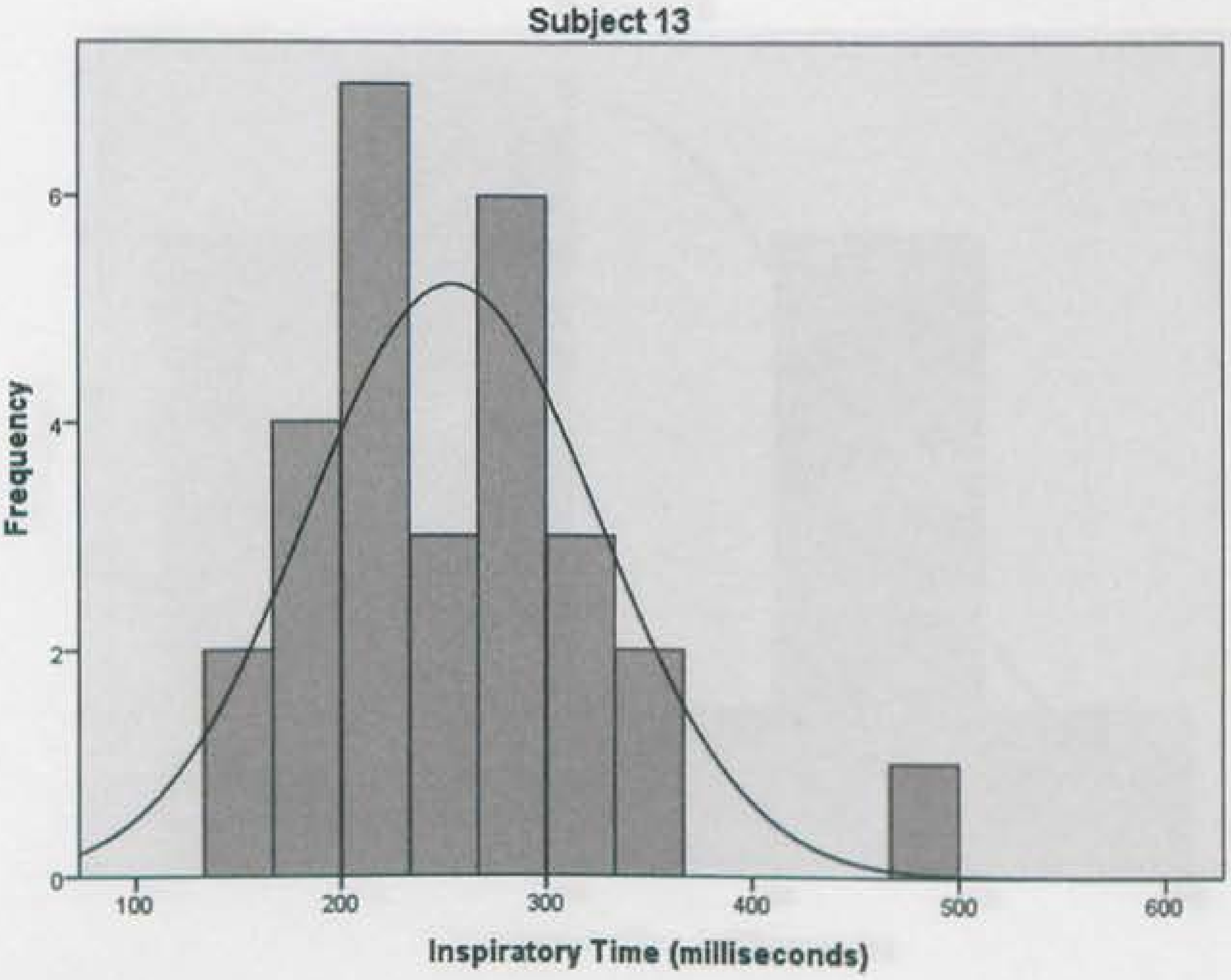
SUCK- BURST BREAK

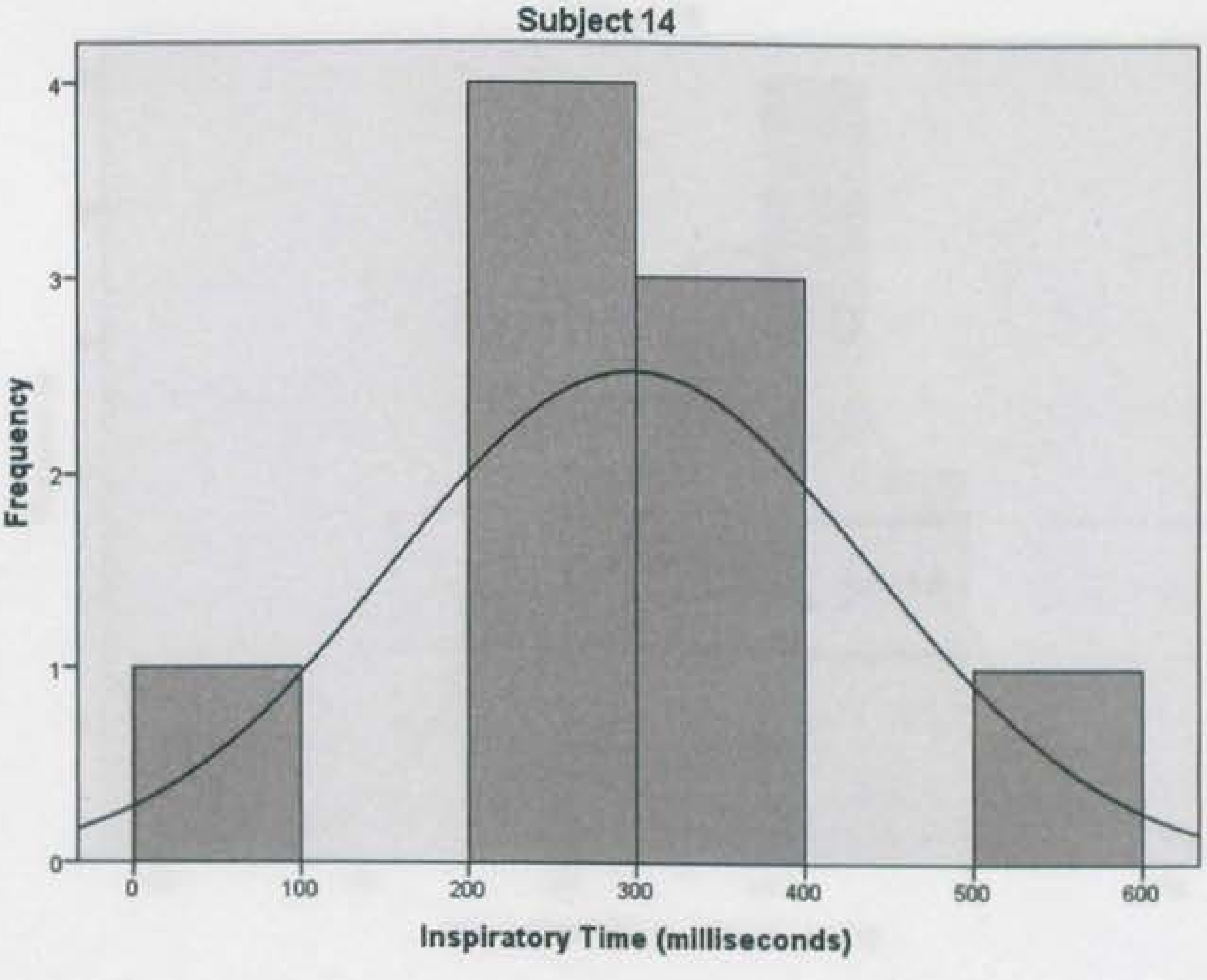

Subject 15


Subject 19

APPENDIX 5.5.
INDIVIDUAL HISTOGRAMS: FEEDING INSIPRATORY TIME

INITIAL SUCK-BURST

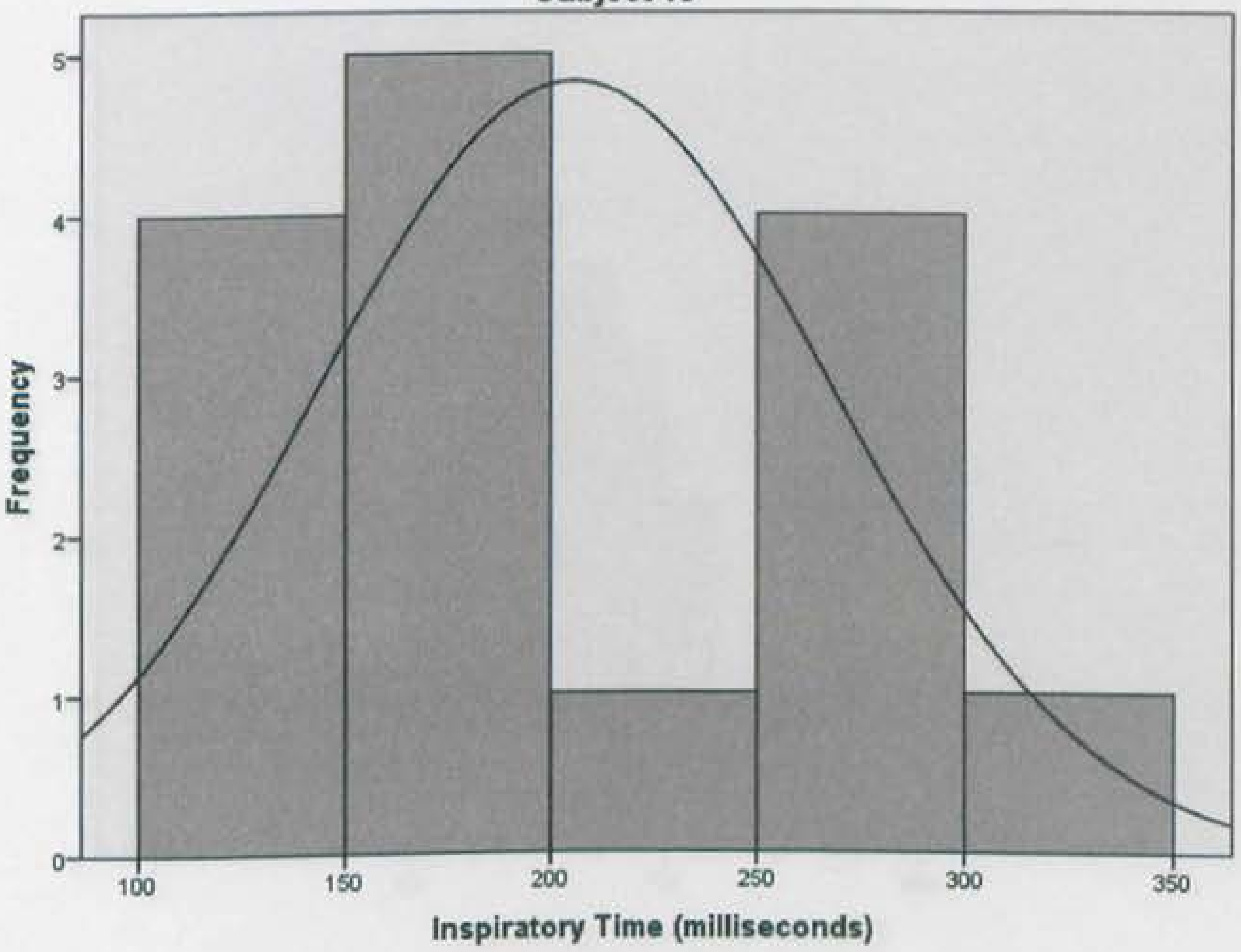




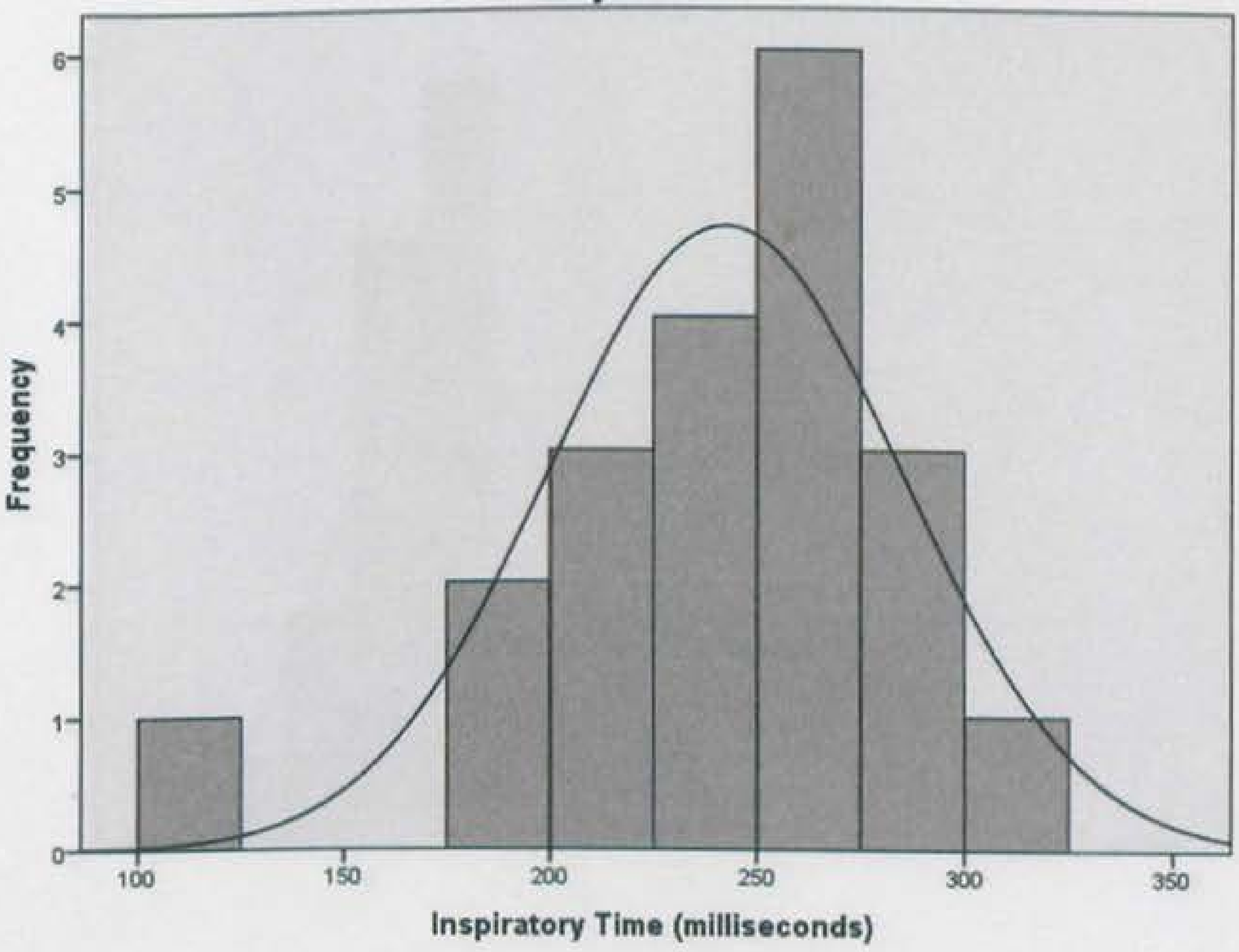
**All times represent respiration on the standard-flow nipple.*

APPENDIX 5.5. Continued

INITIAL SUCK-BURST



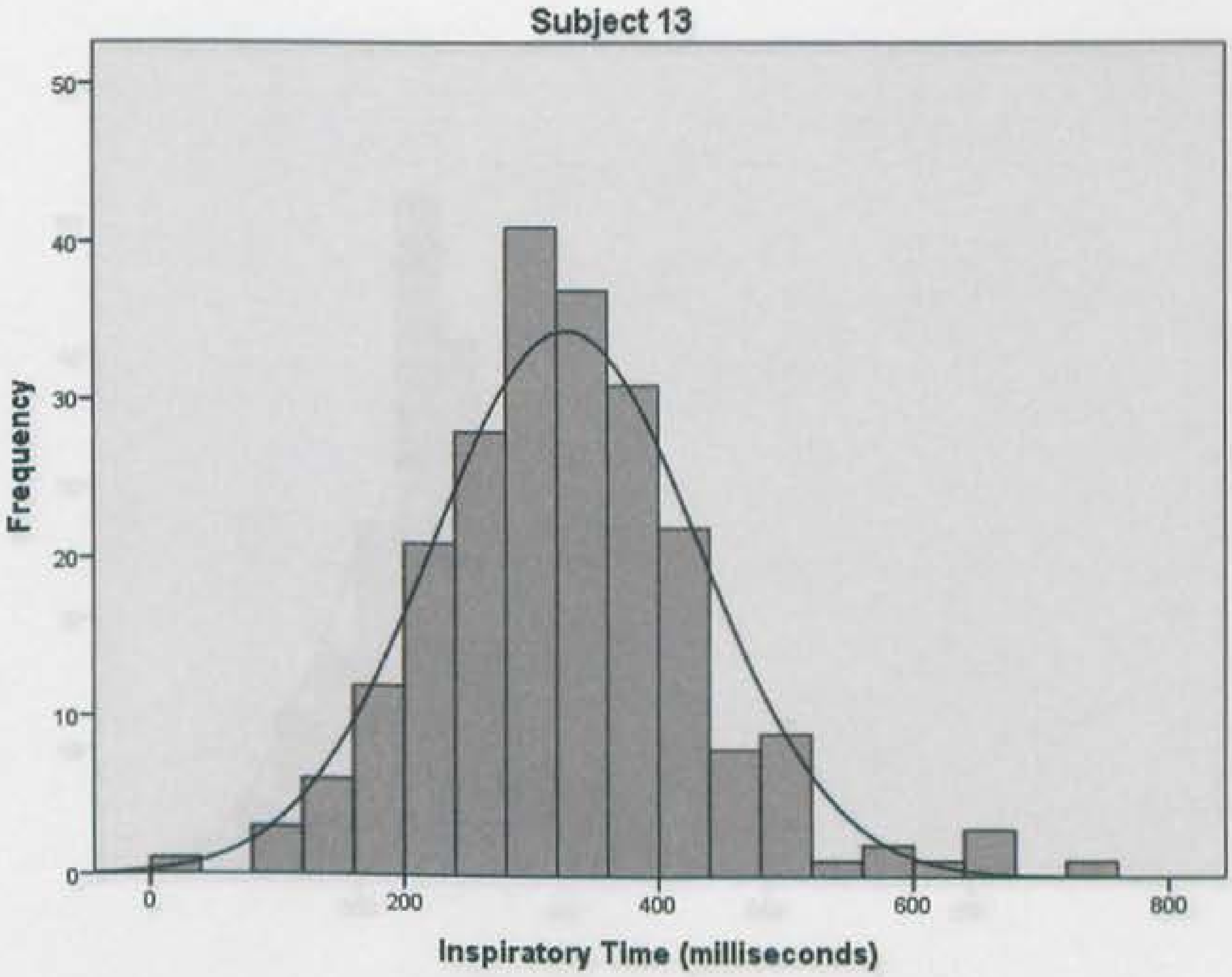
Subject 15

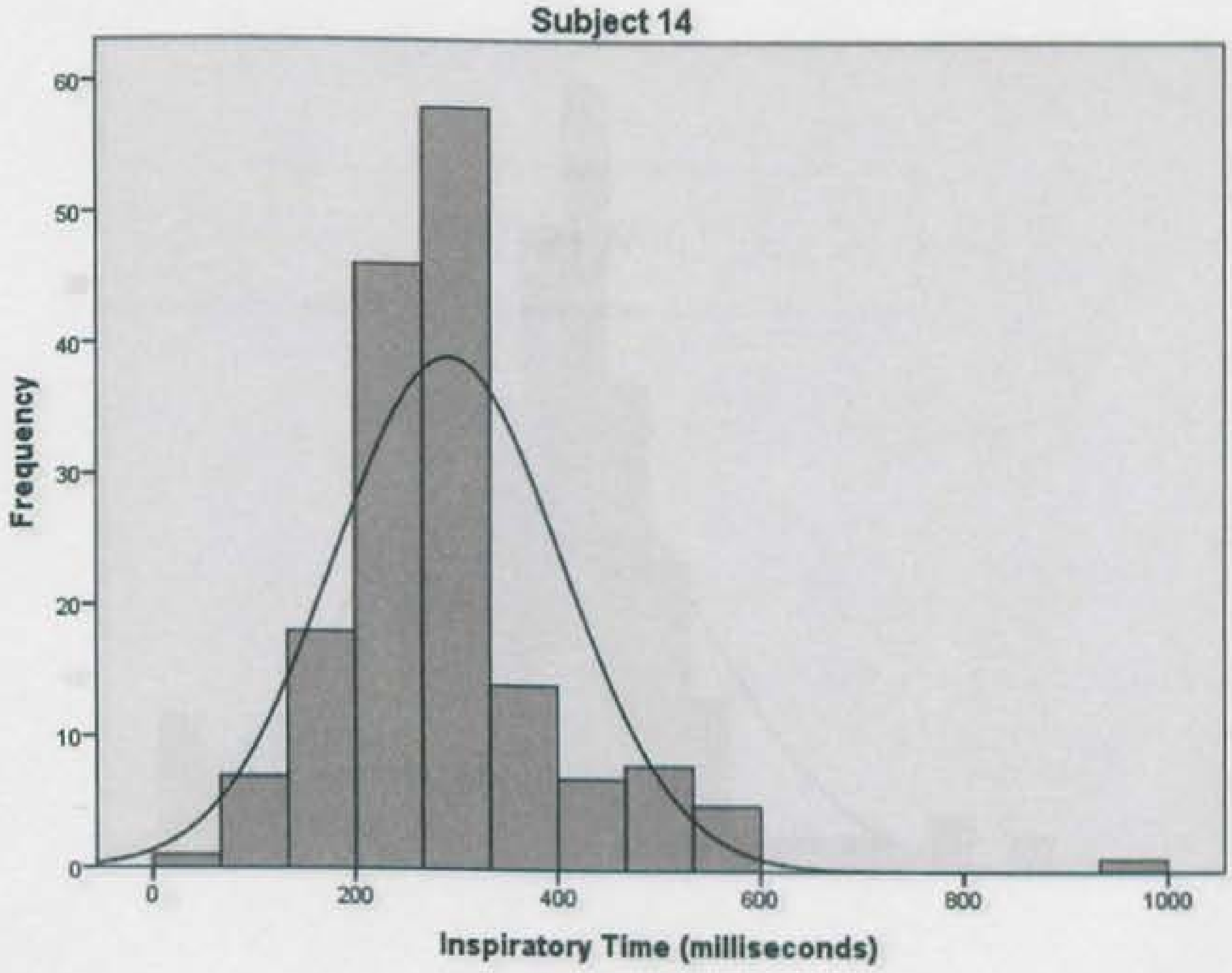


Subject 19

APPENDIX 5.5. Continued

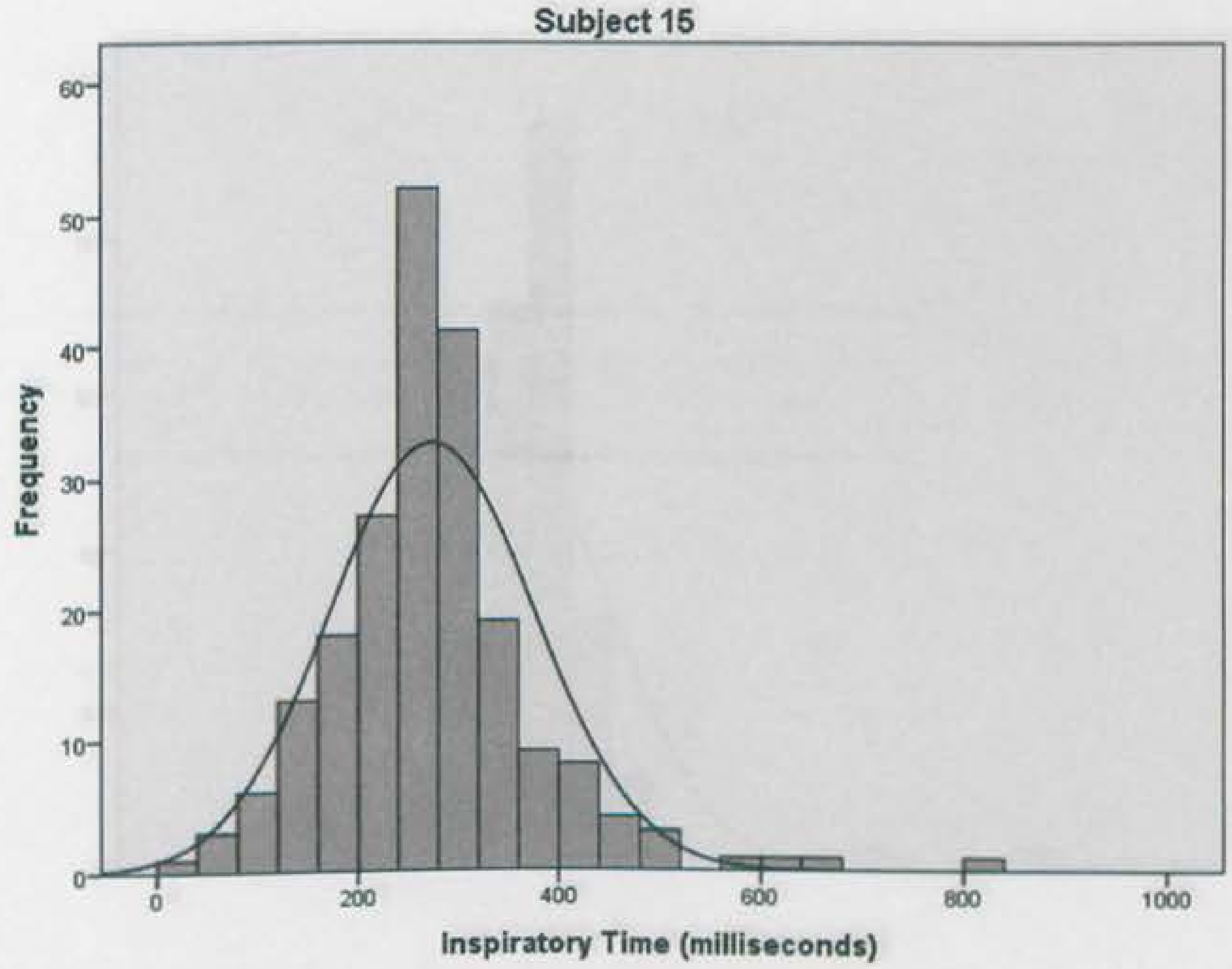
SUBSEQUENT SUCK-BURST

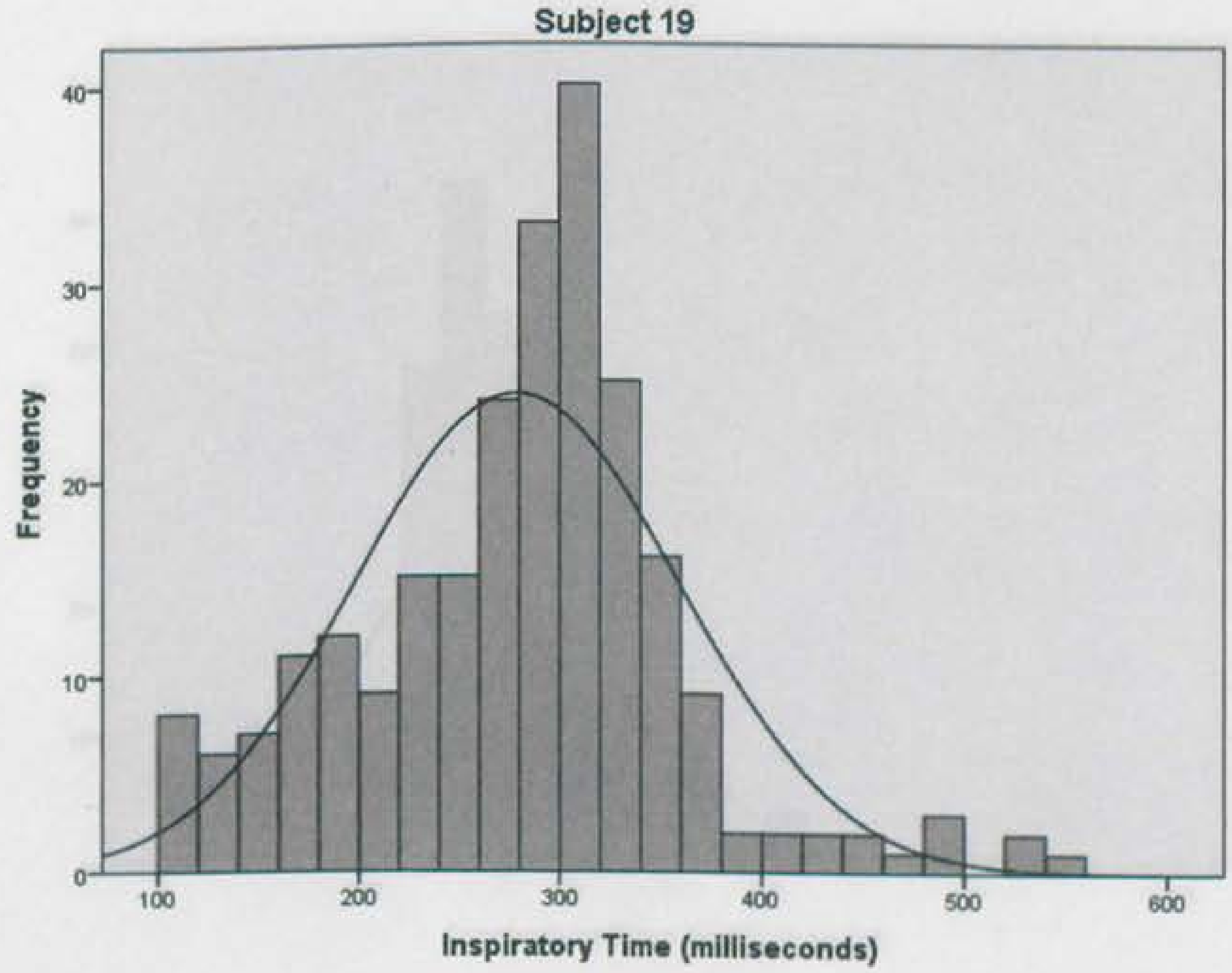




APPENDIX 5.5. Continued

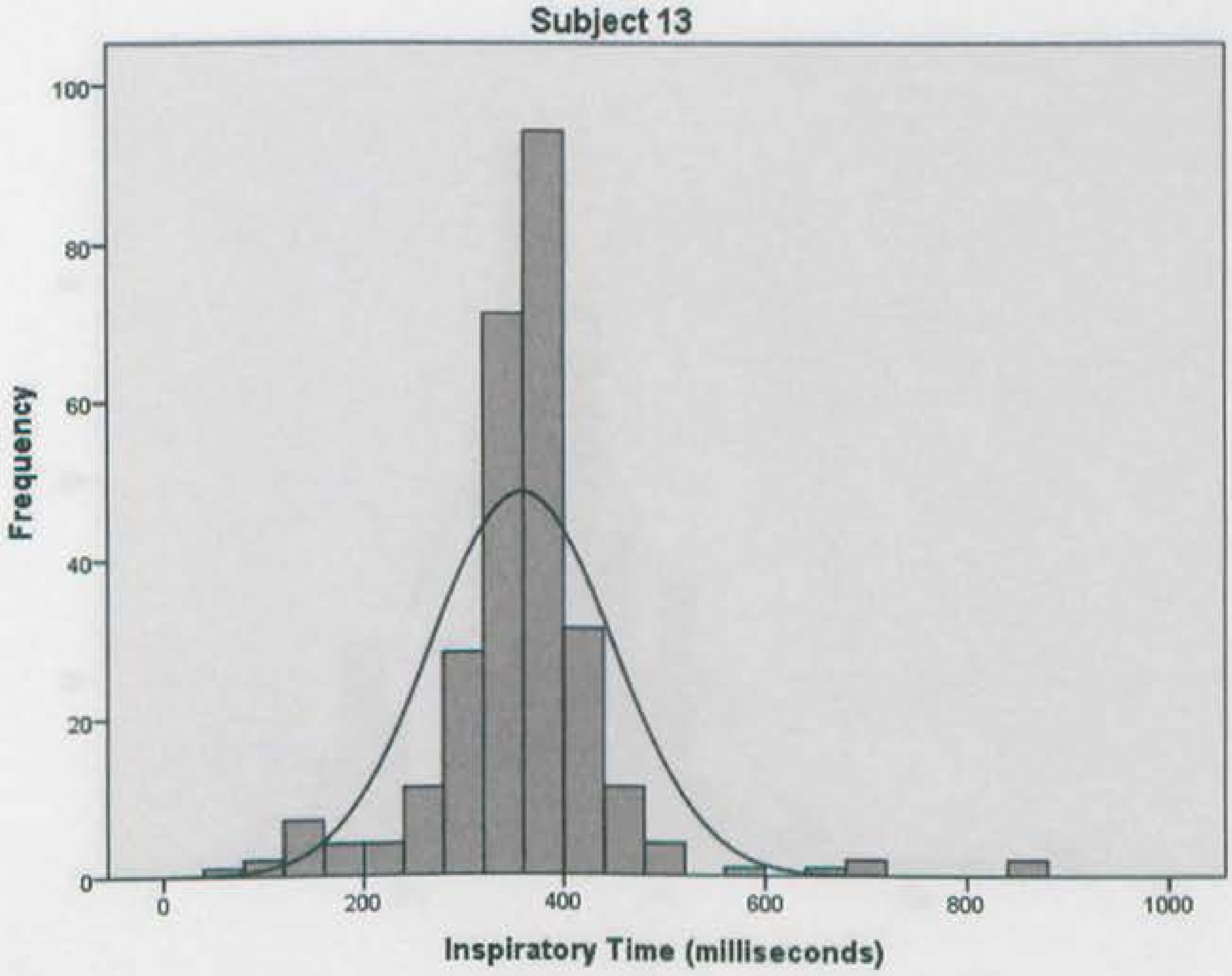
SUBSEQUENT SUCK-BURST

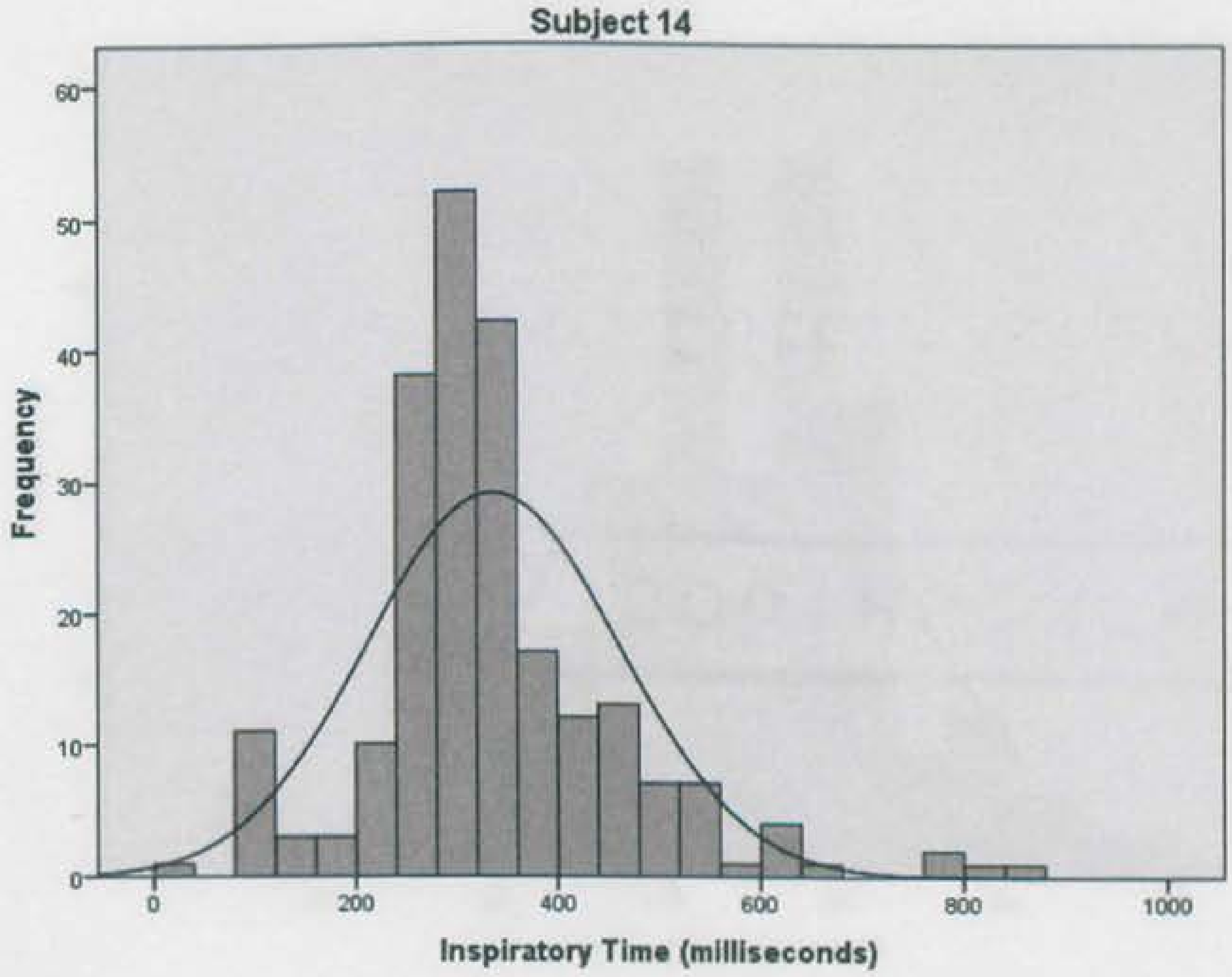




APPENDIX 5.5. *Continued*

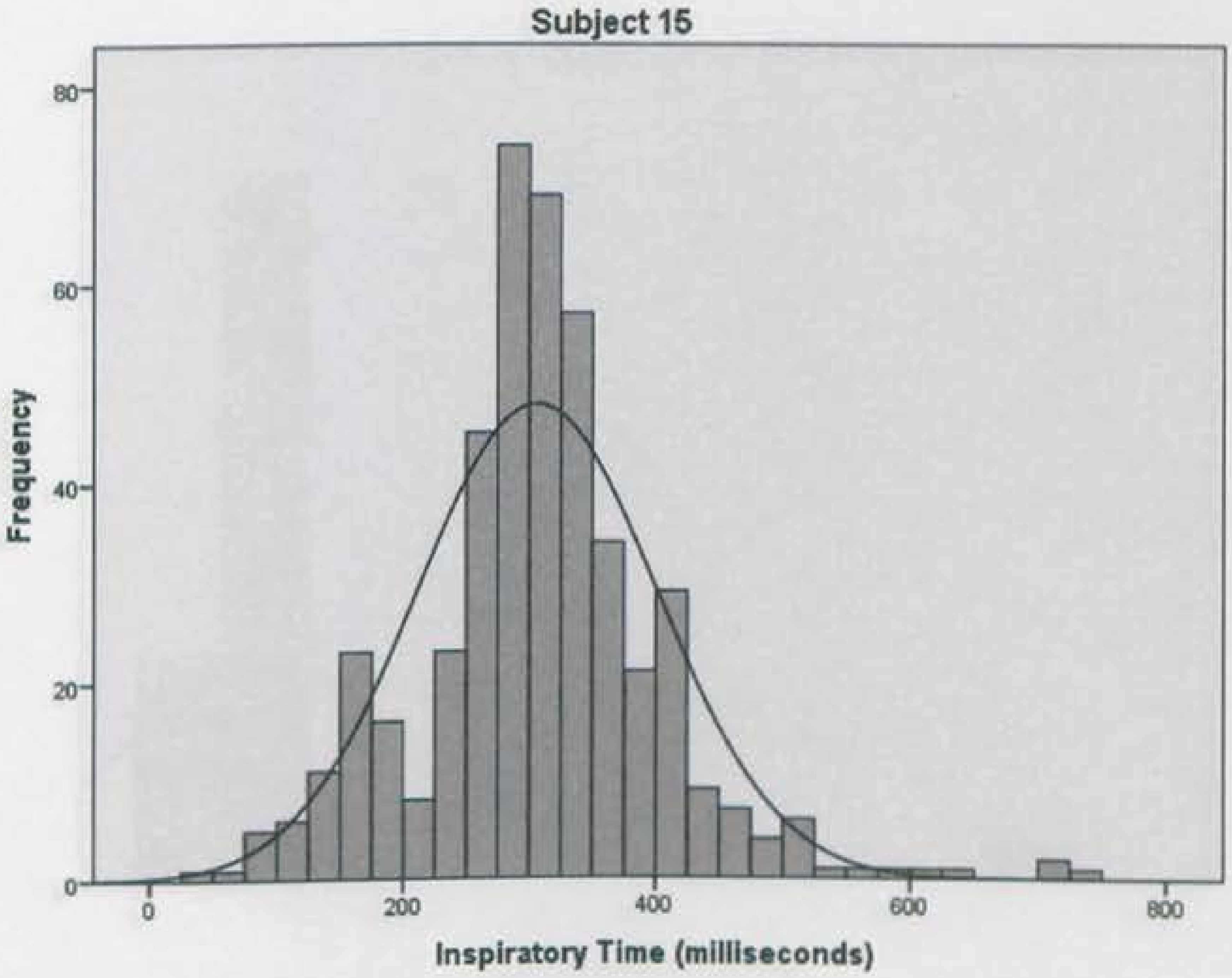
SUCK-BURST BREAK

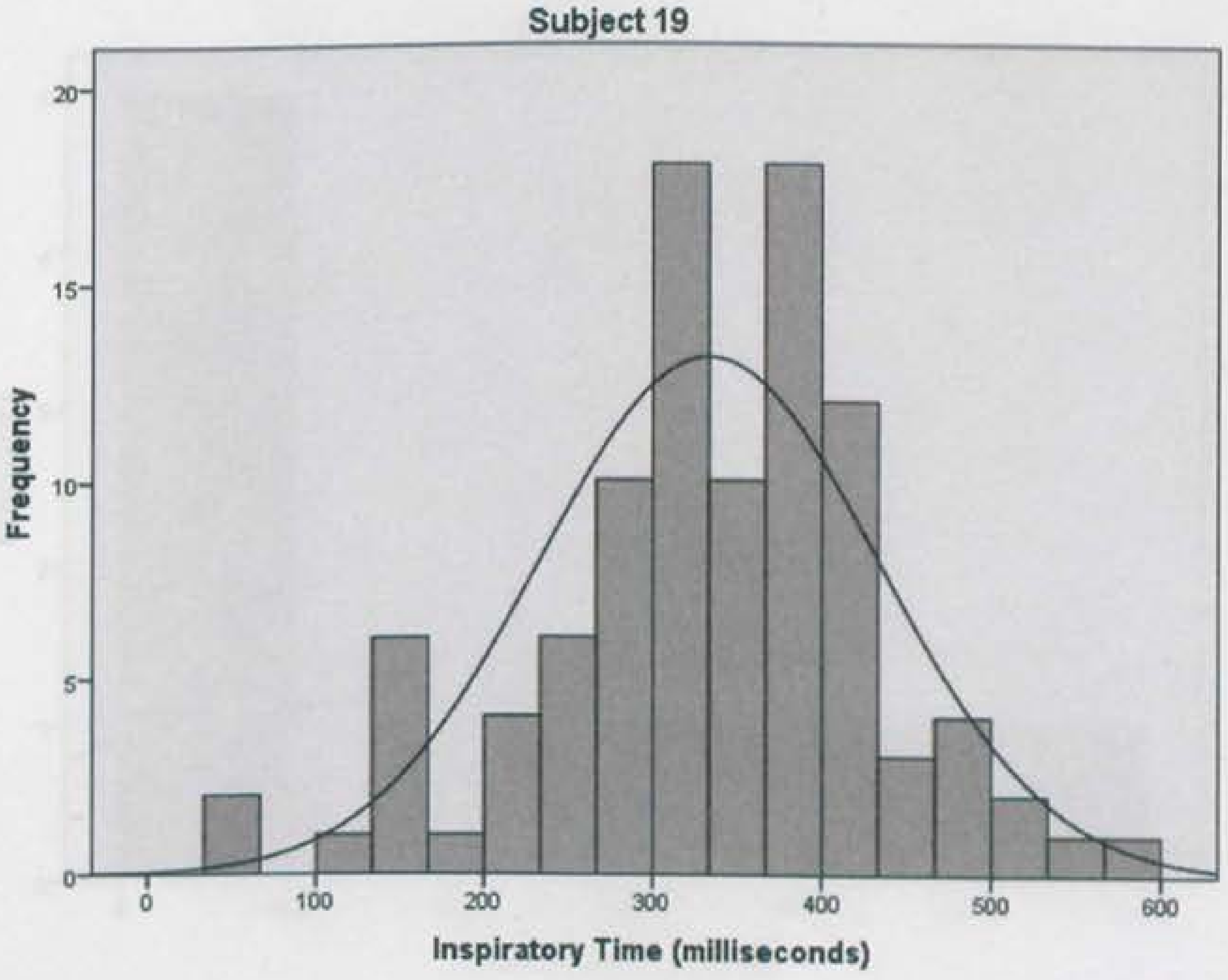




APPENDIX 5.5. Continued

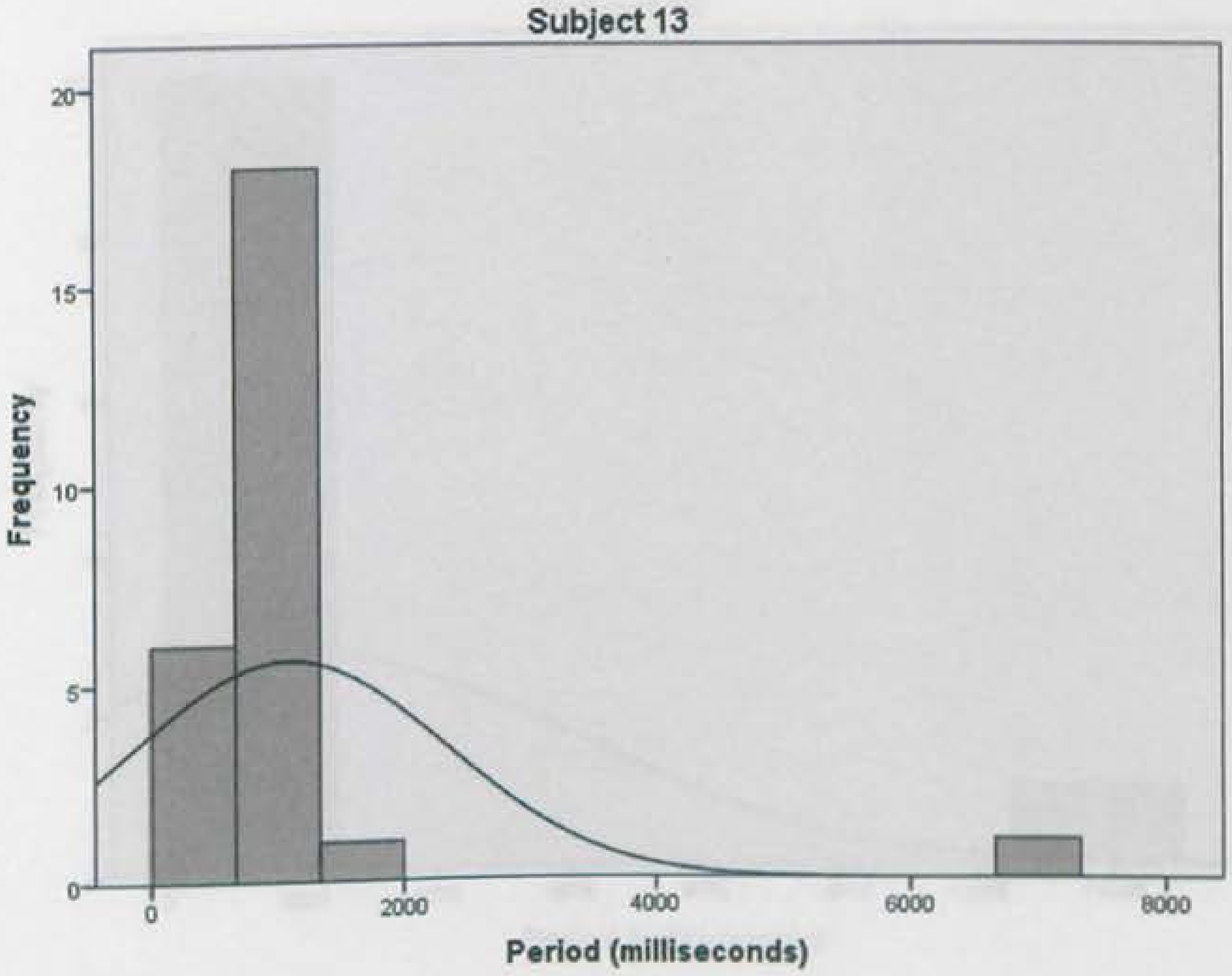
SUCK-BURST BREAK

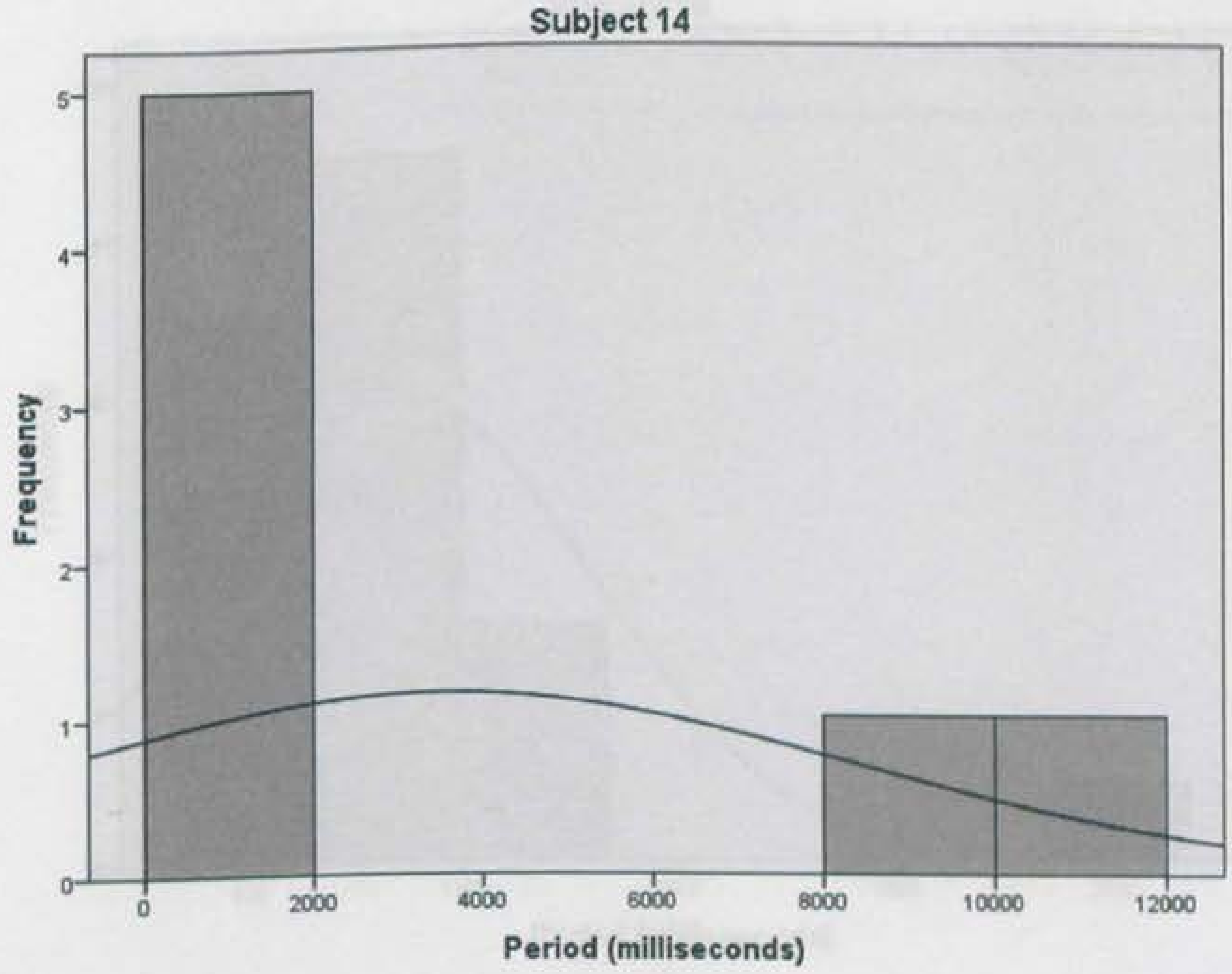




APPENDIX 5.6.
INDIVIDUAL HISTOGRAMS: FEEDING PERIOD

INITIAL SUCK- BURST

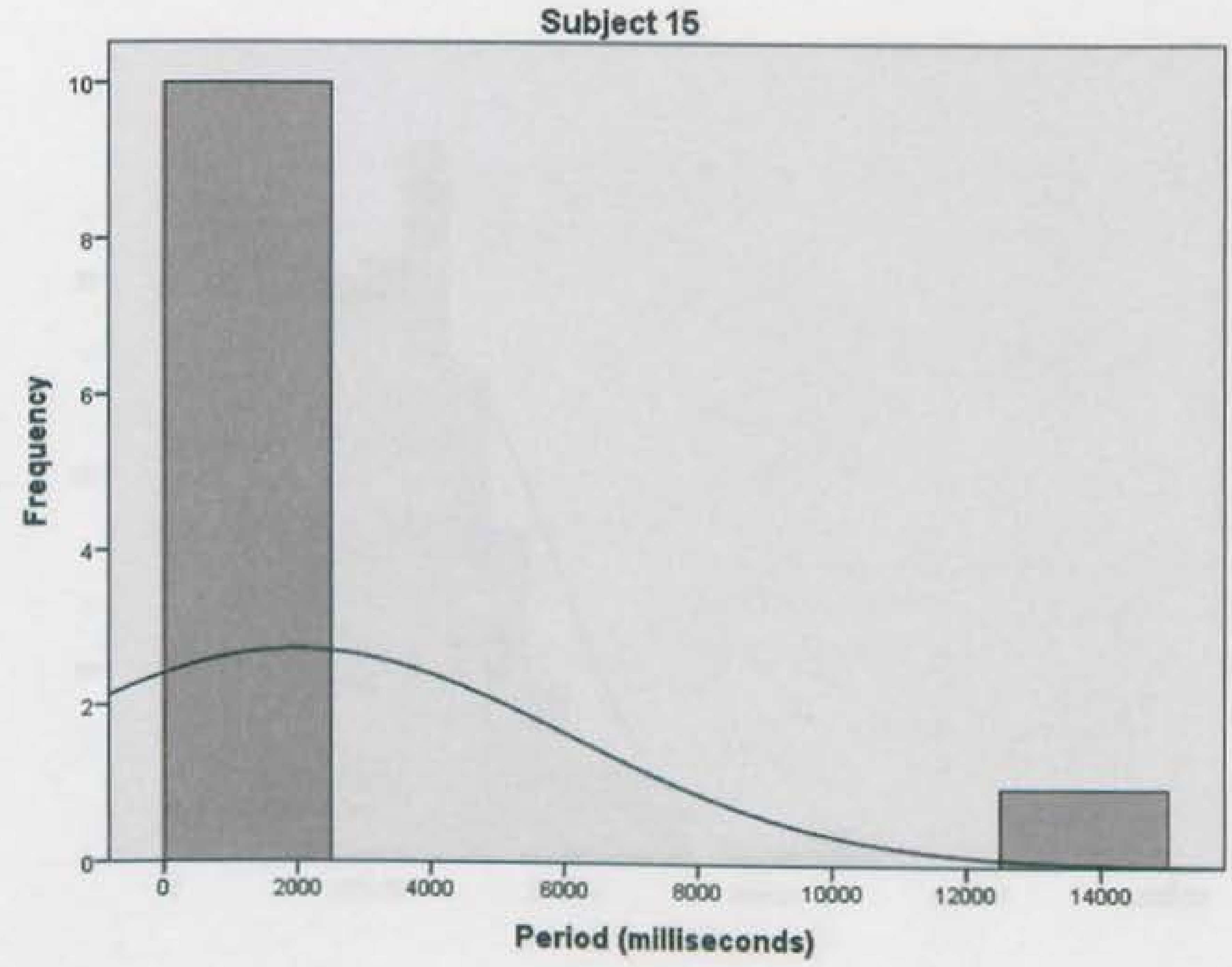


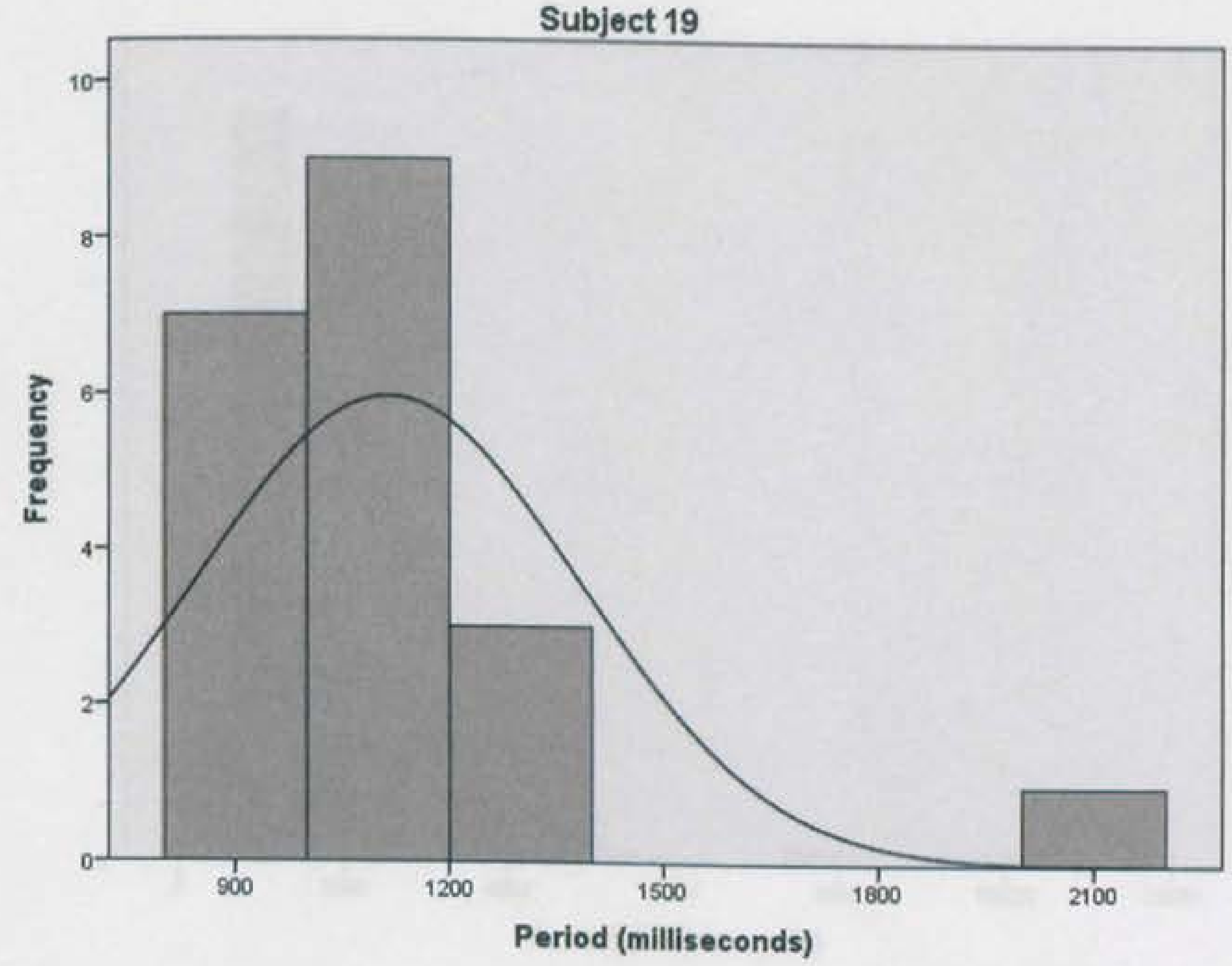


**All times represent respiration on the standard-flow nipple.*

APPENDIX 5.6. *Continued*

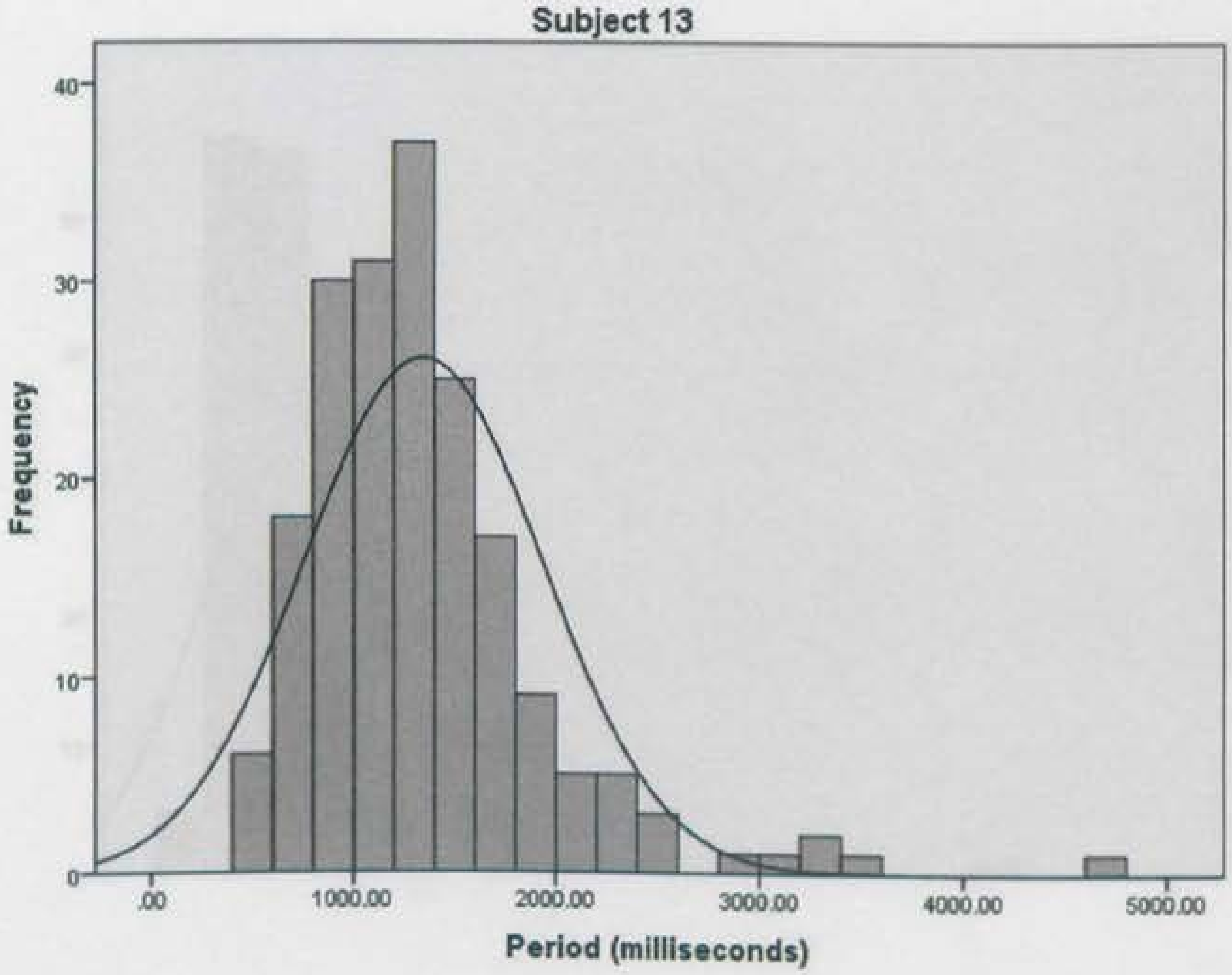
INITIAL SUCK- BURST

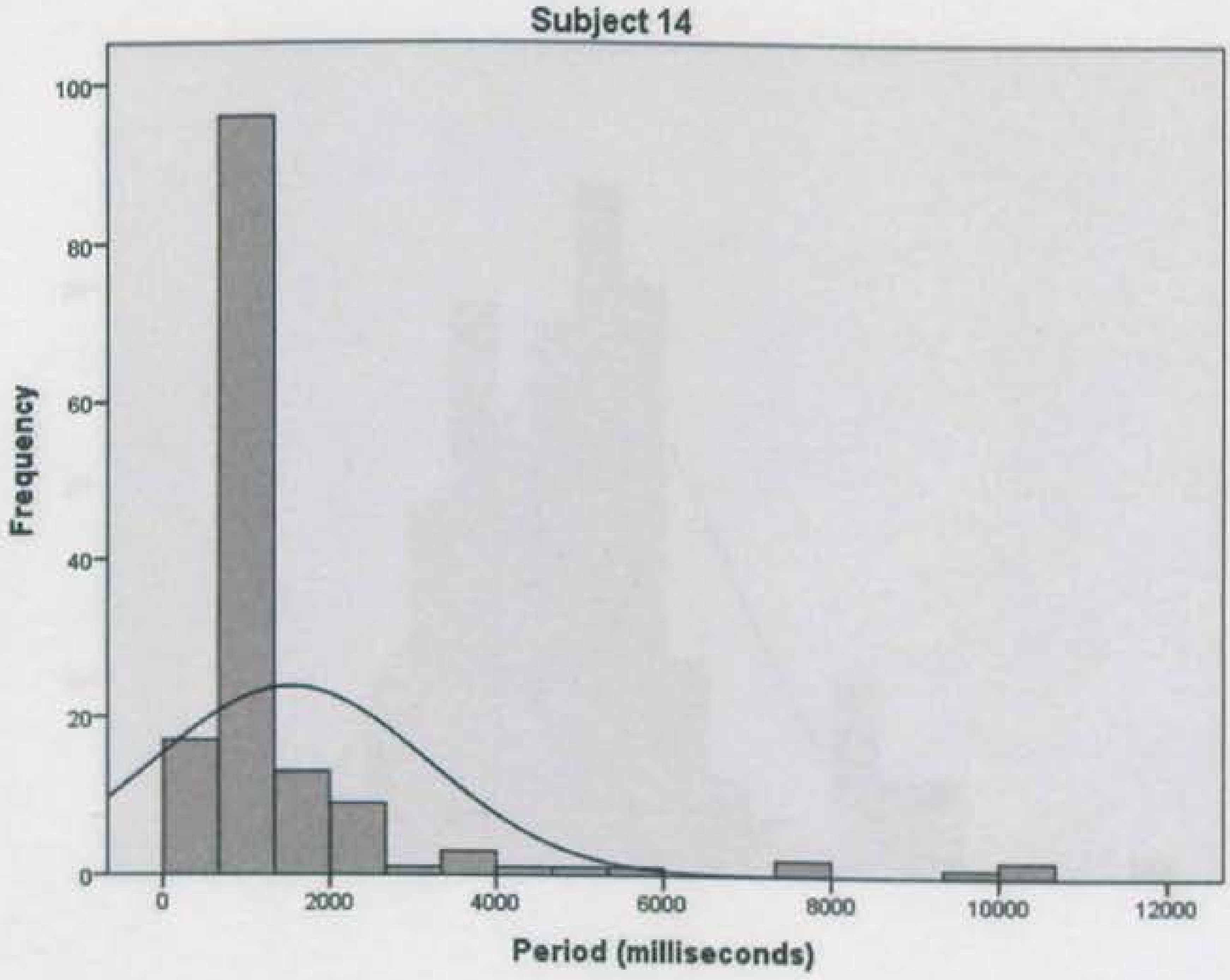




APPENDIX 5.6. *Continued*
INDIVIDUAL HISTOGRAMS: FEEDING PERIOD

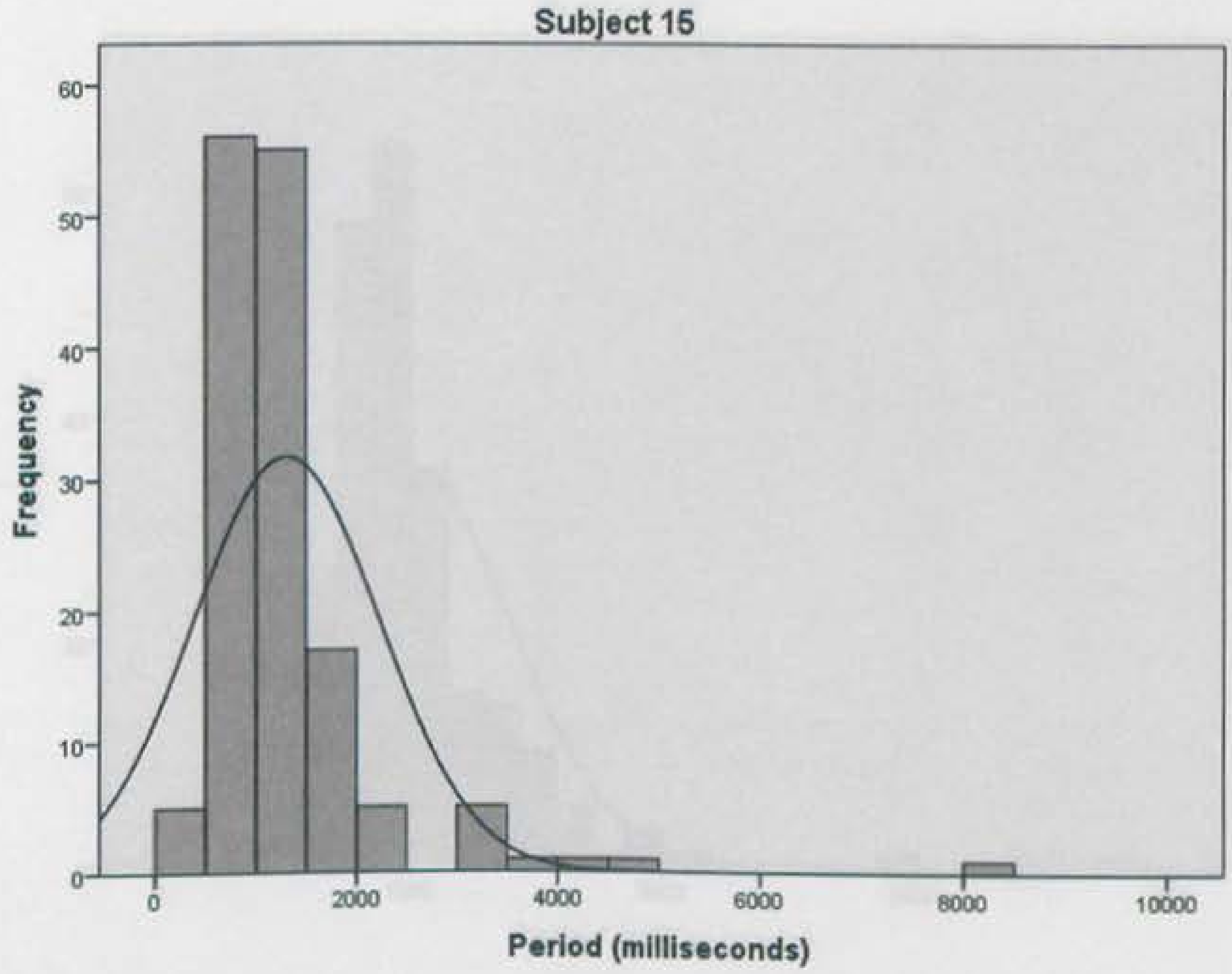
SUBSEQUENT SUCK- BURST

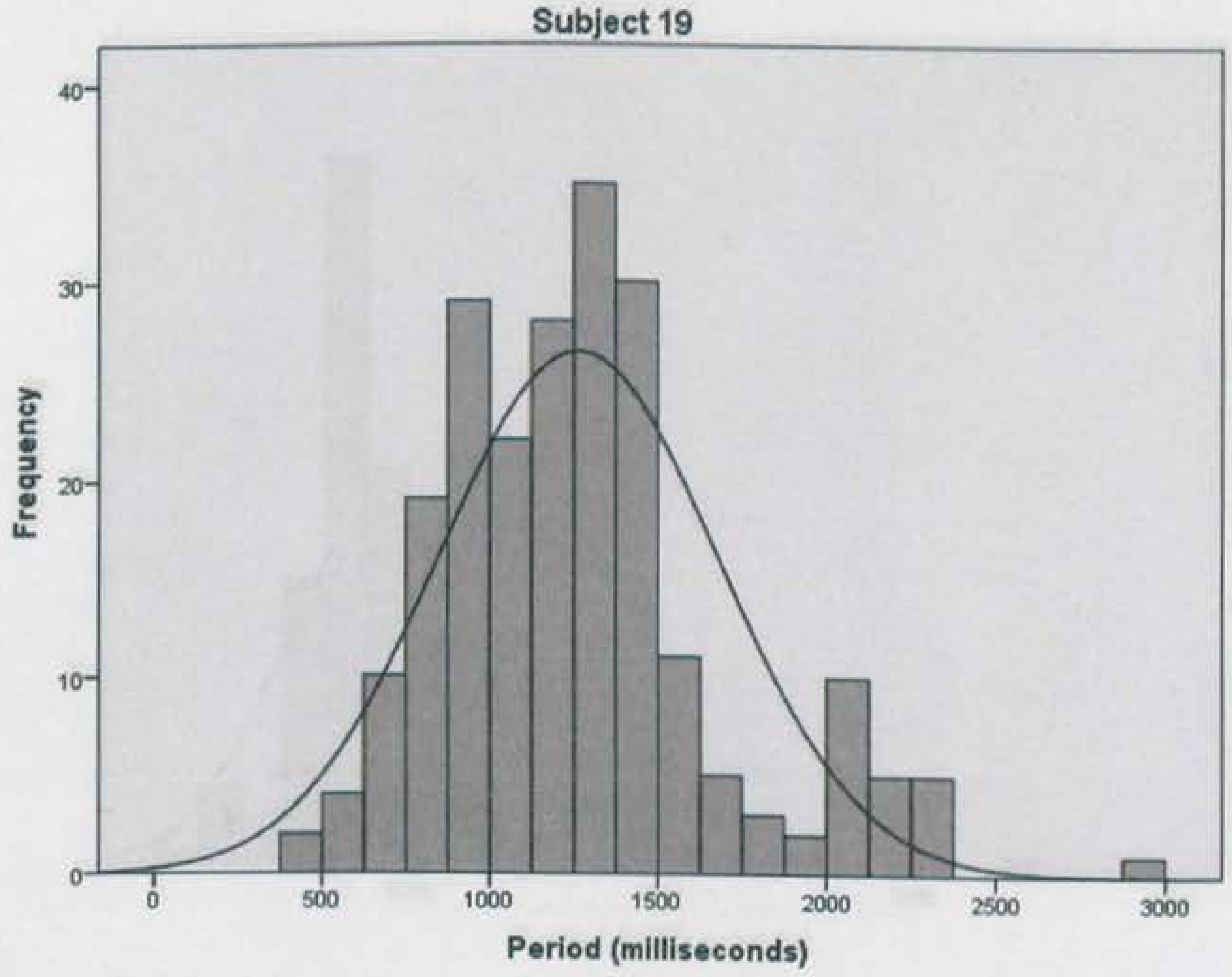




APPENDIX 5.6. Continued

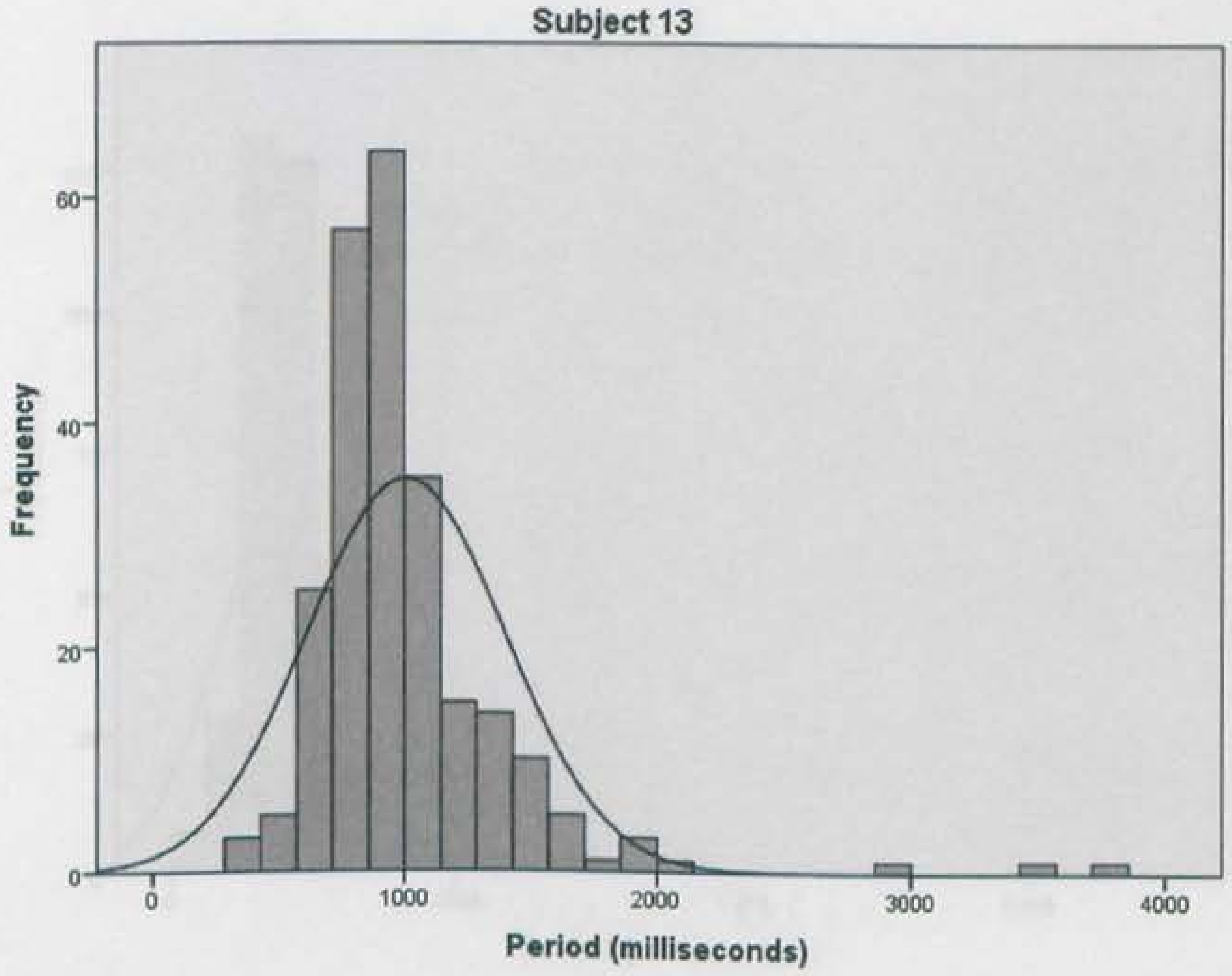
SUBSEQUENT SUCK- BURST

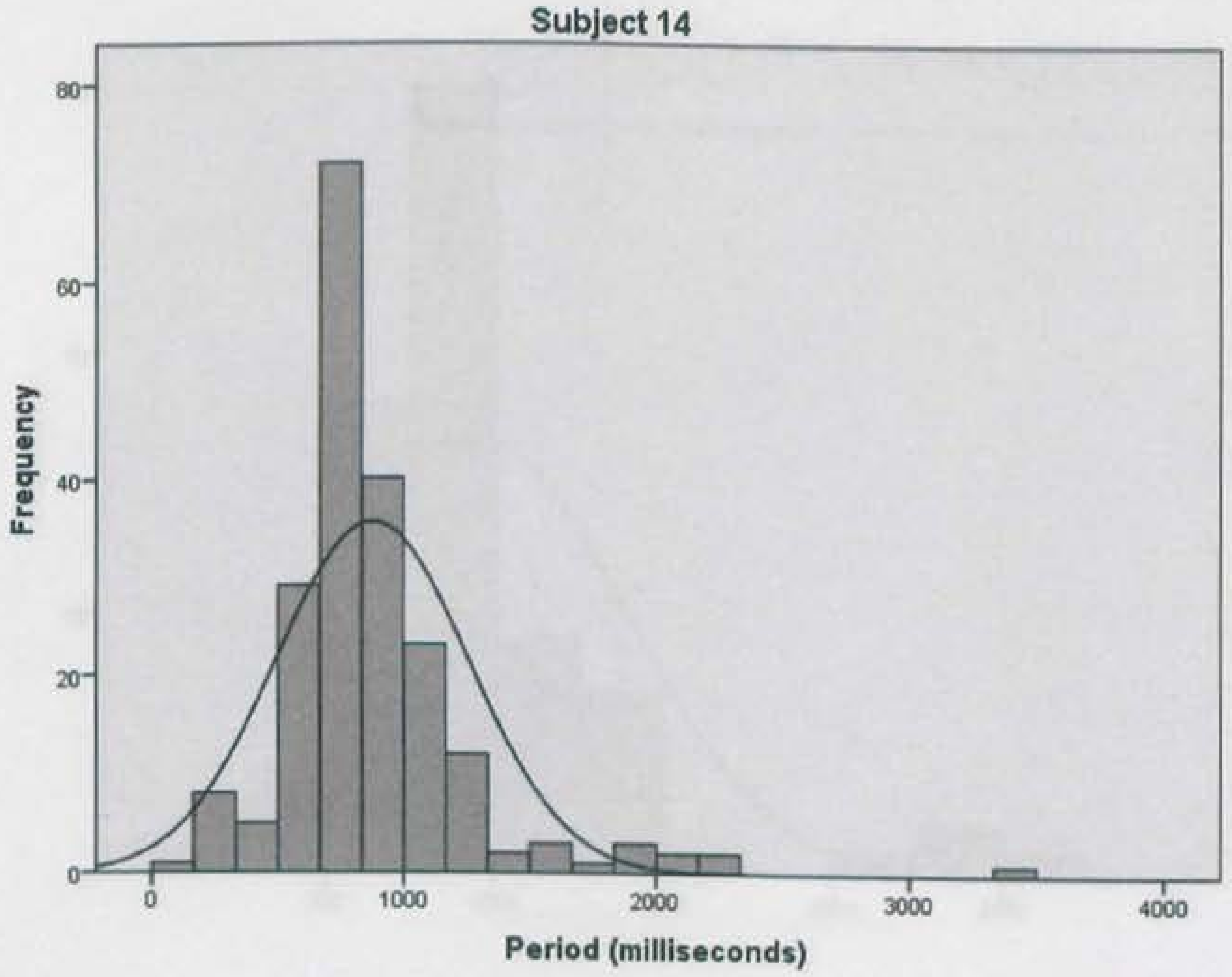

Subject 15


Subject 19

APPENDIX 5.6. Continued

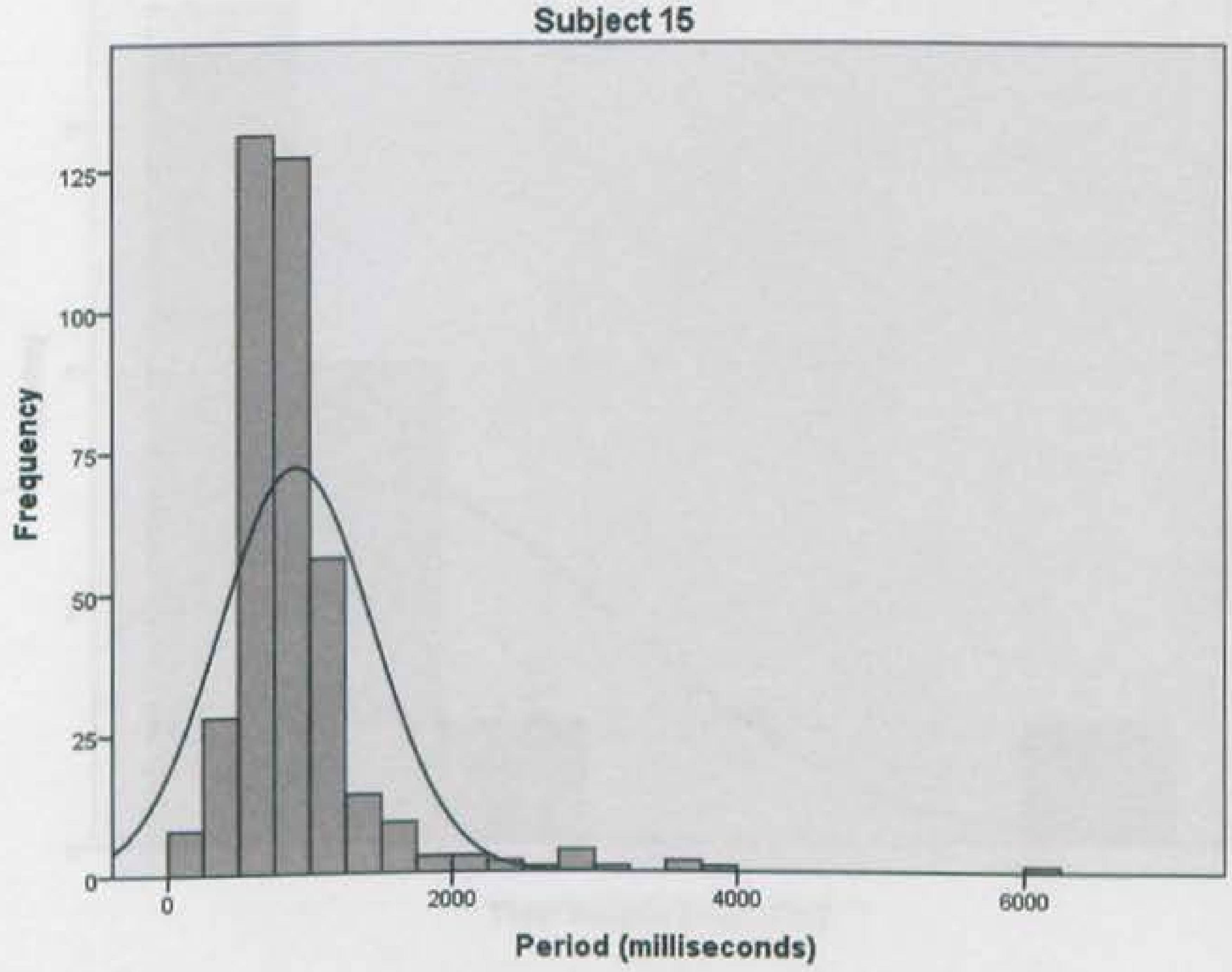
SUCK- BURST BREAK

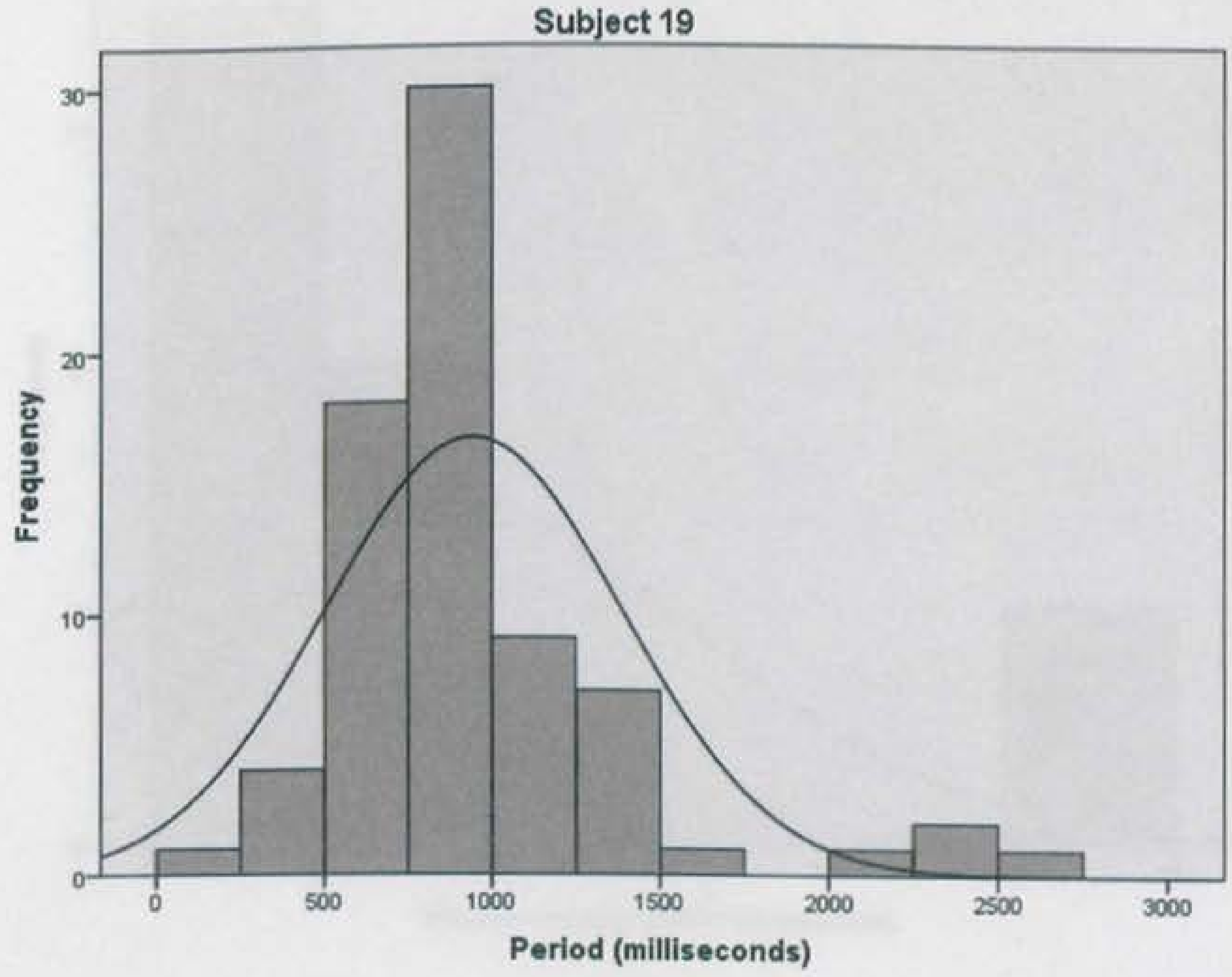




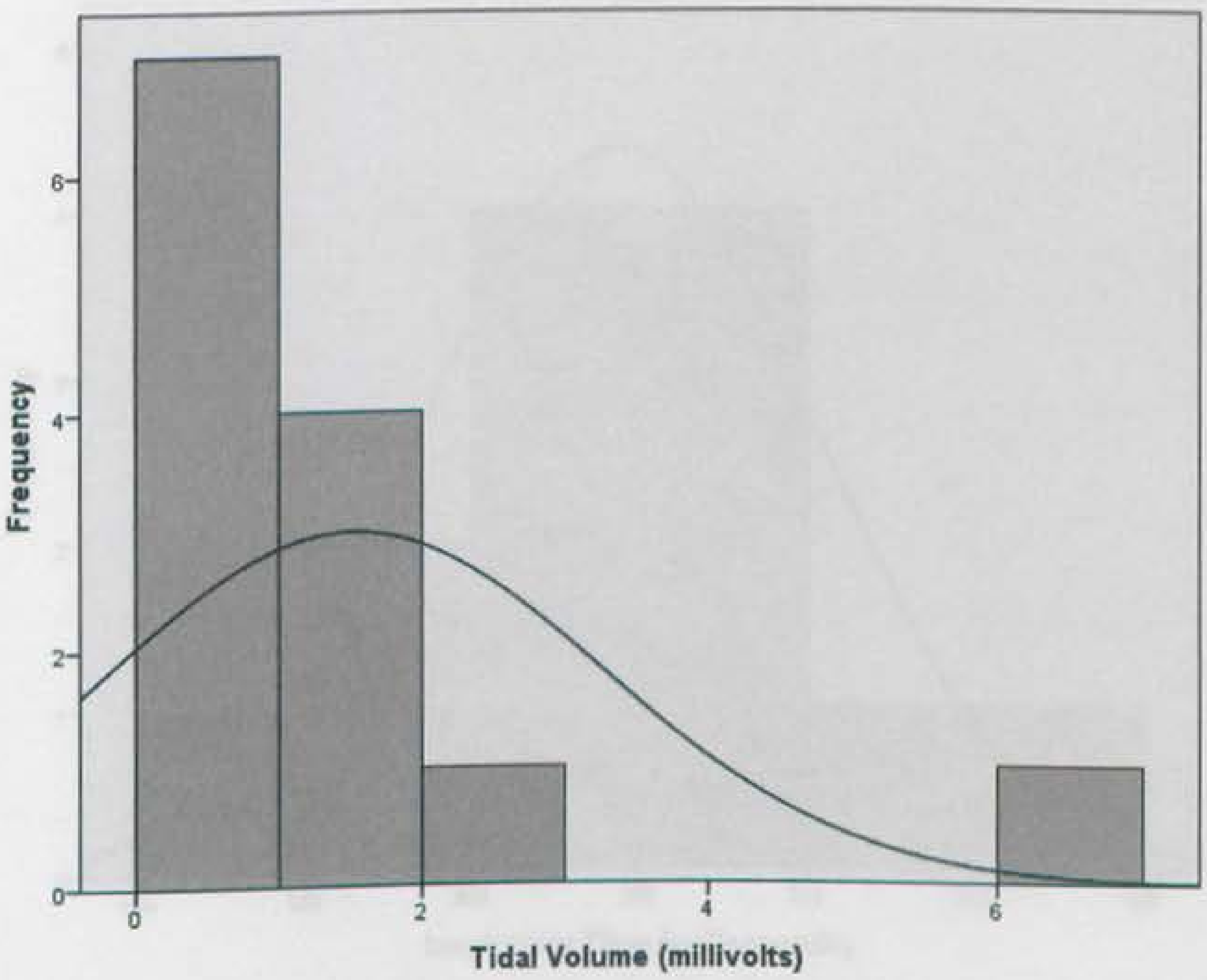
APPENDIX 5.6. *Continued*

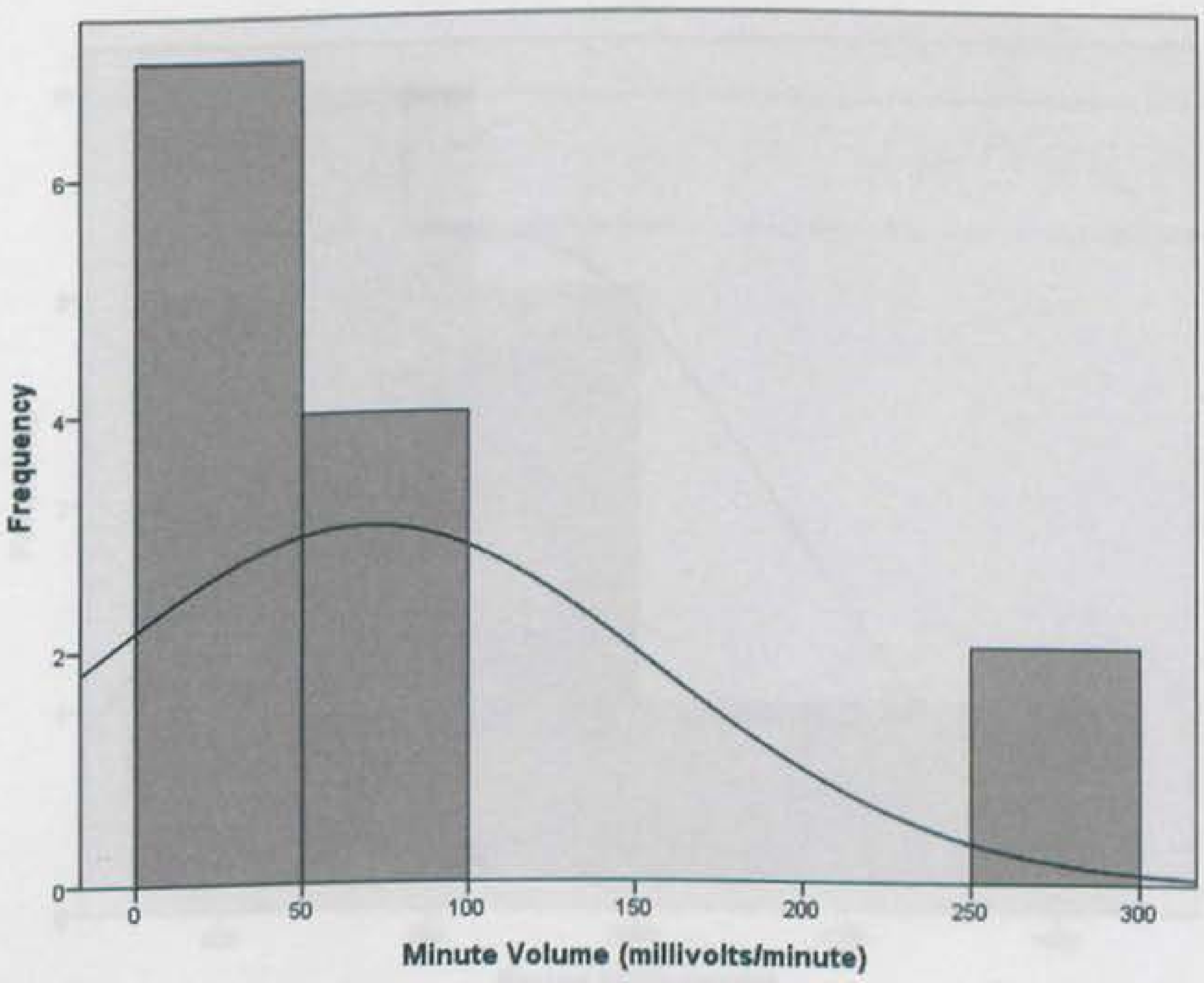
SUCK- BURST BREAK





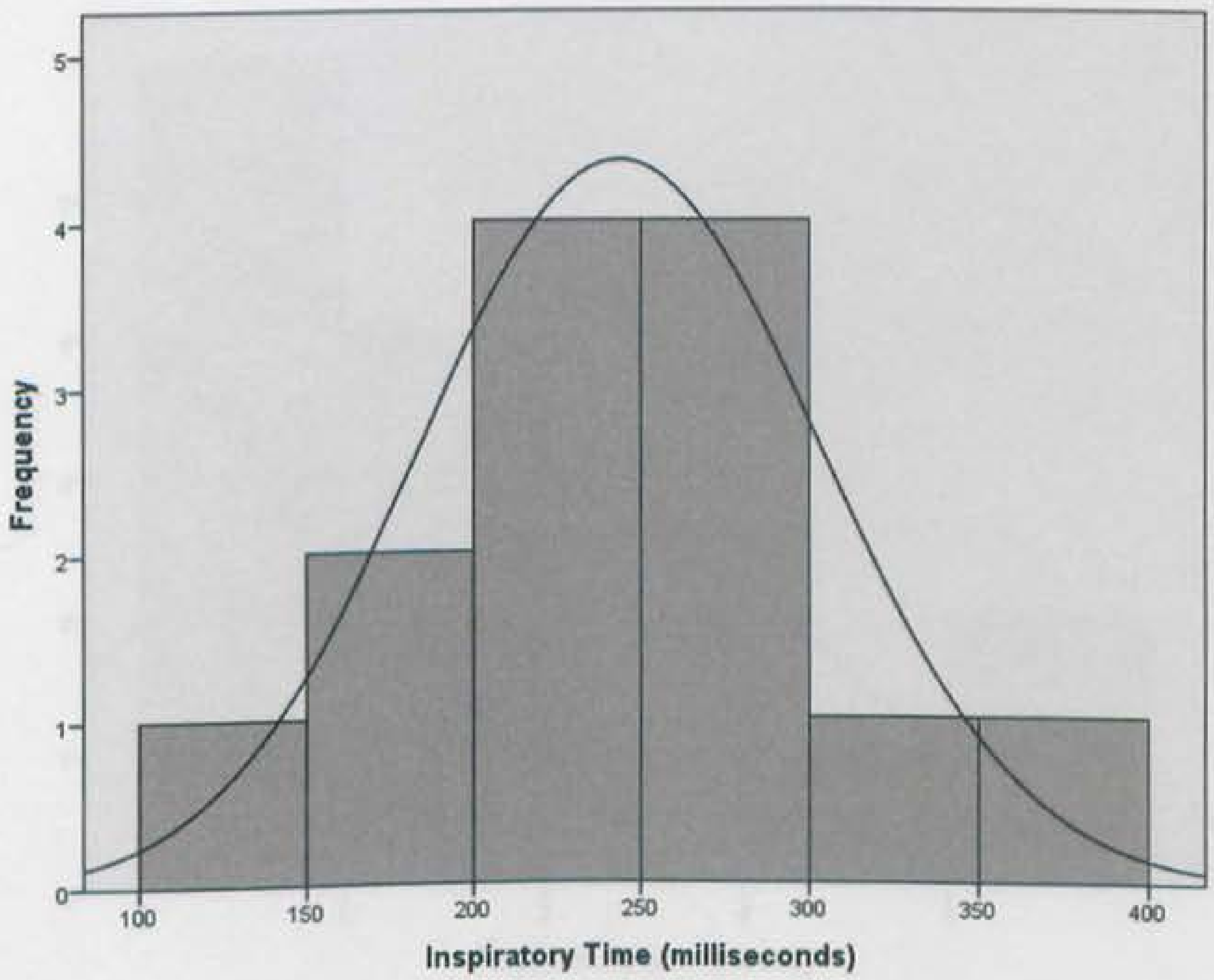
APPENDIX 5.7.
SAMPLE HISTOGRAMS: INITIAL SUCK-BURST

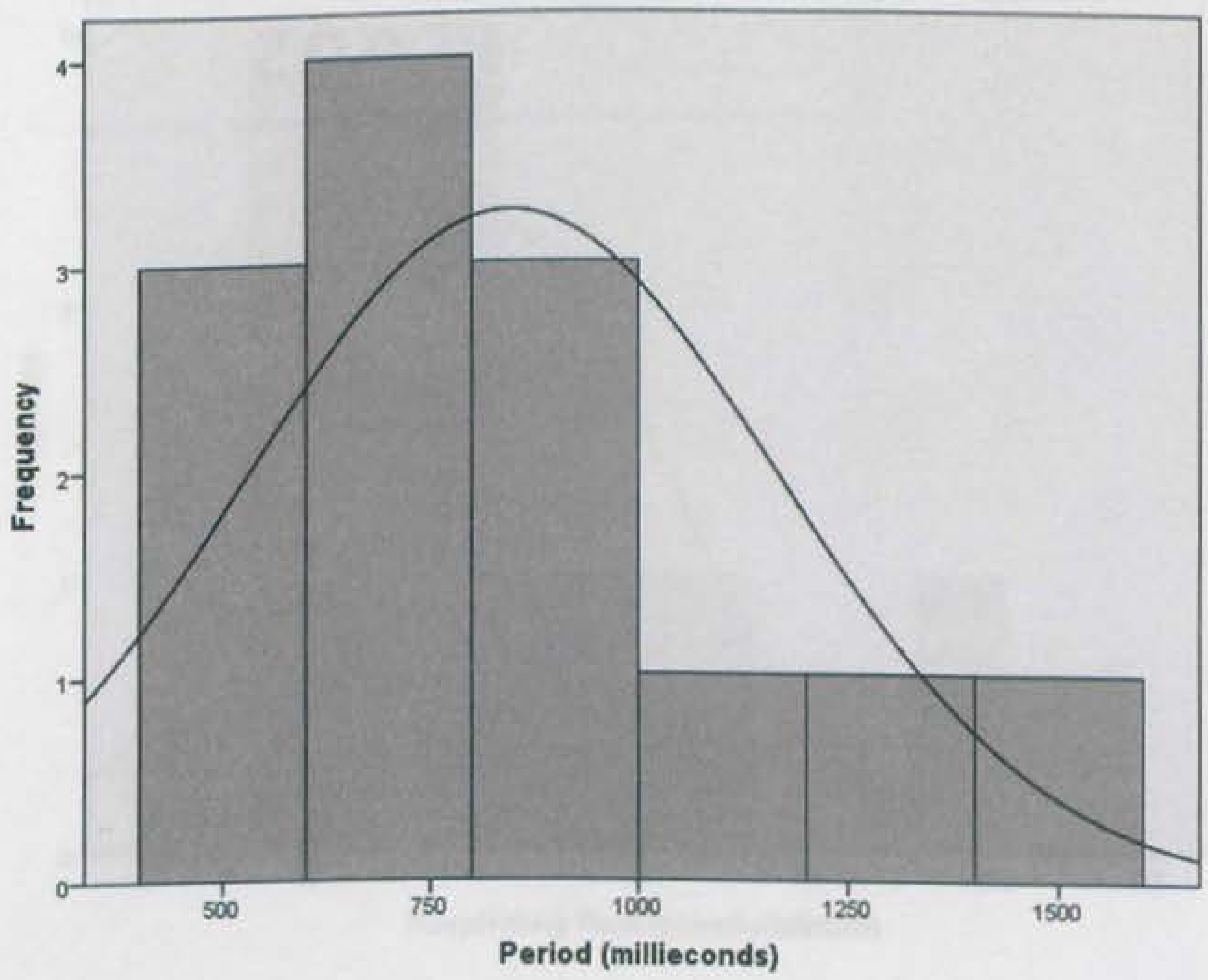




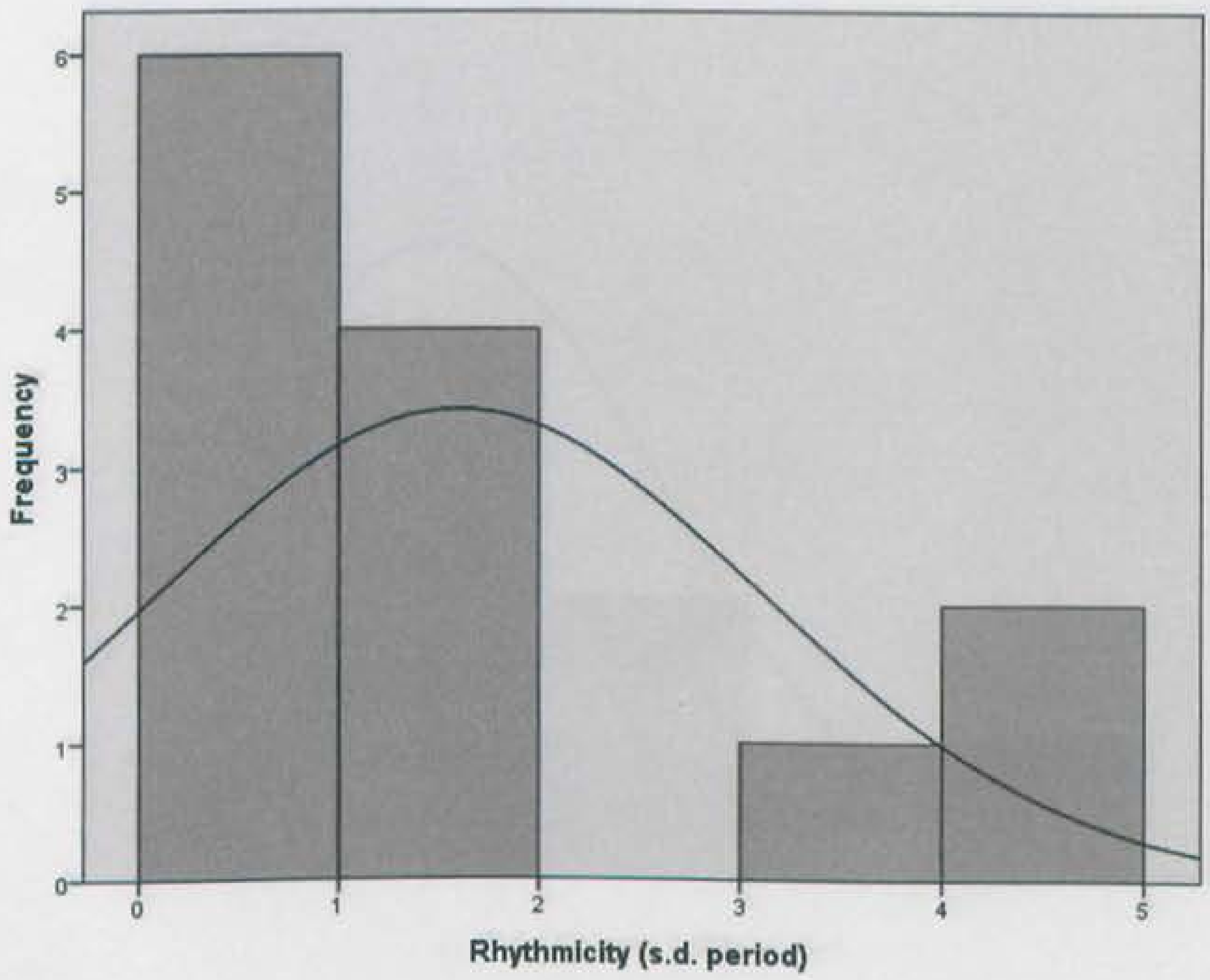
**All values represent respiration on the standard-flow nipple. Outcome measures with multiple data points for each subject are summarized by median value.*

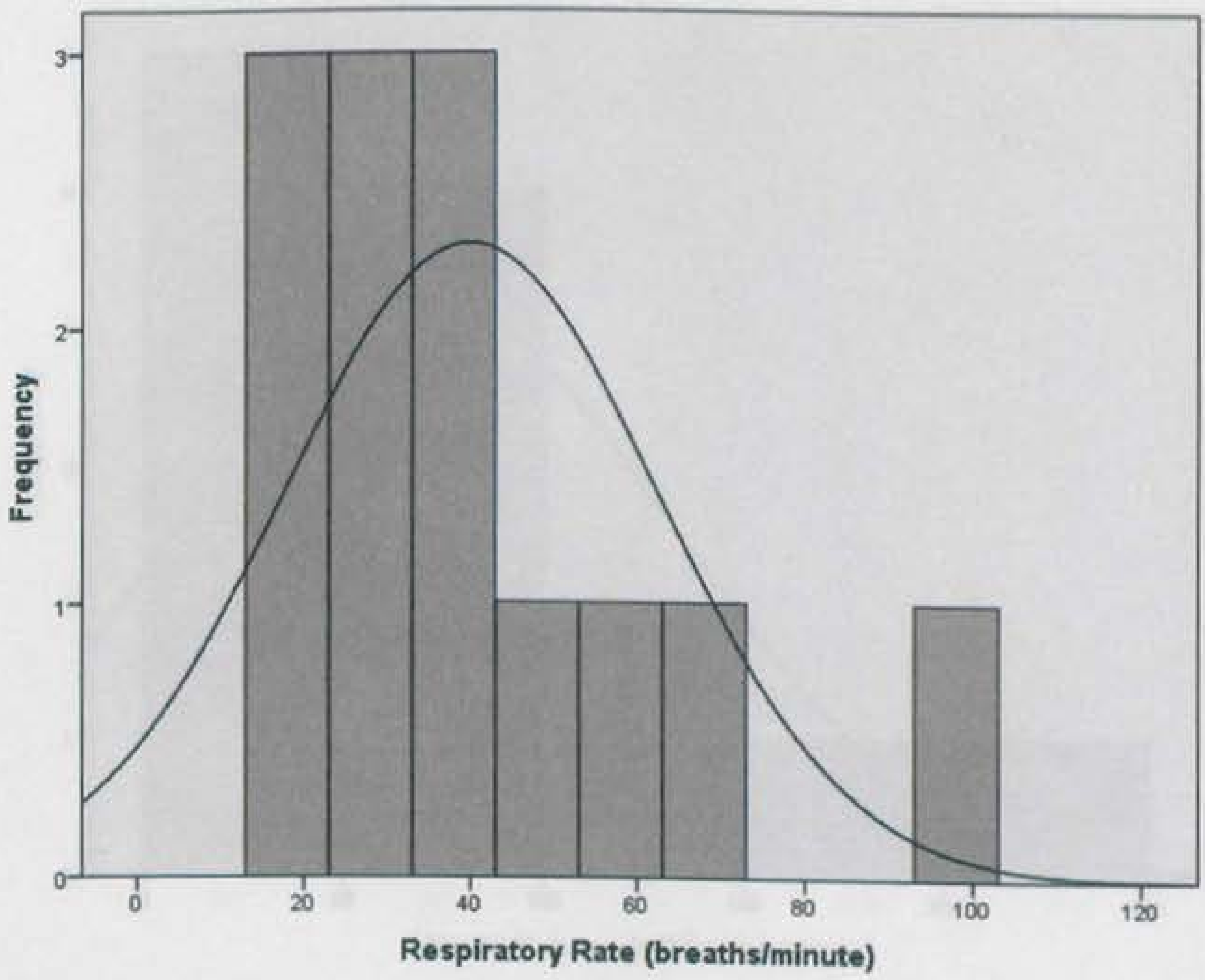
APPENDIX 5.7. *Continued*



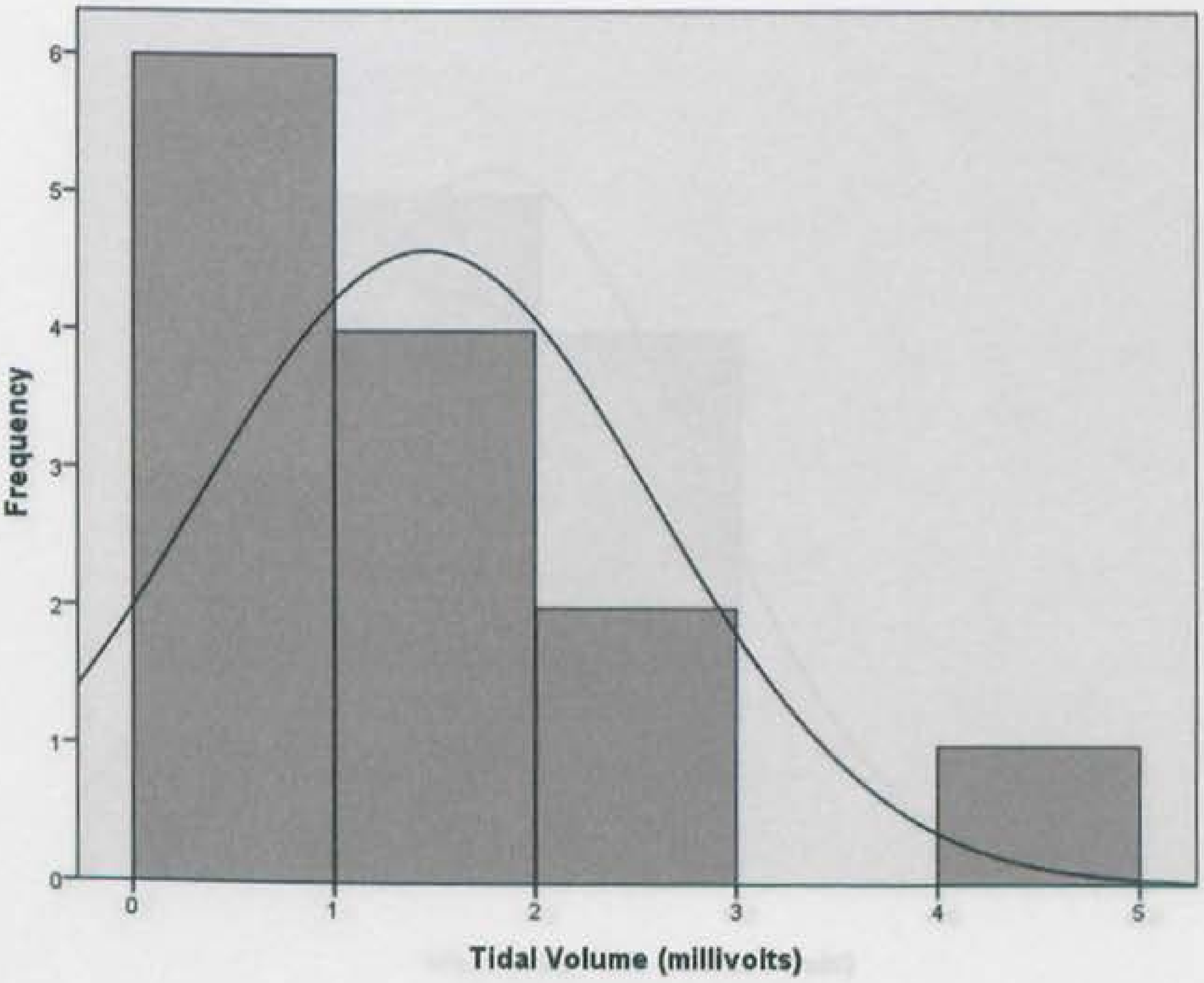


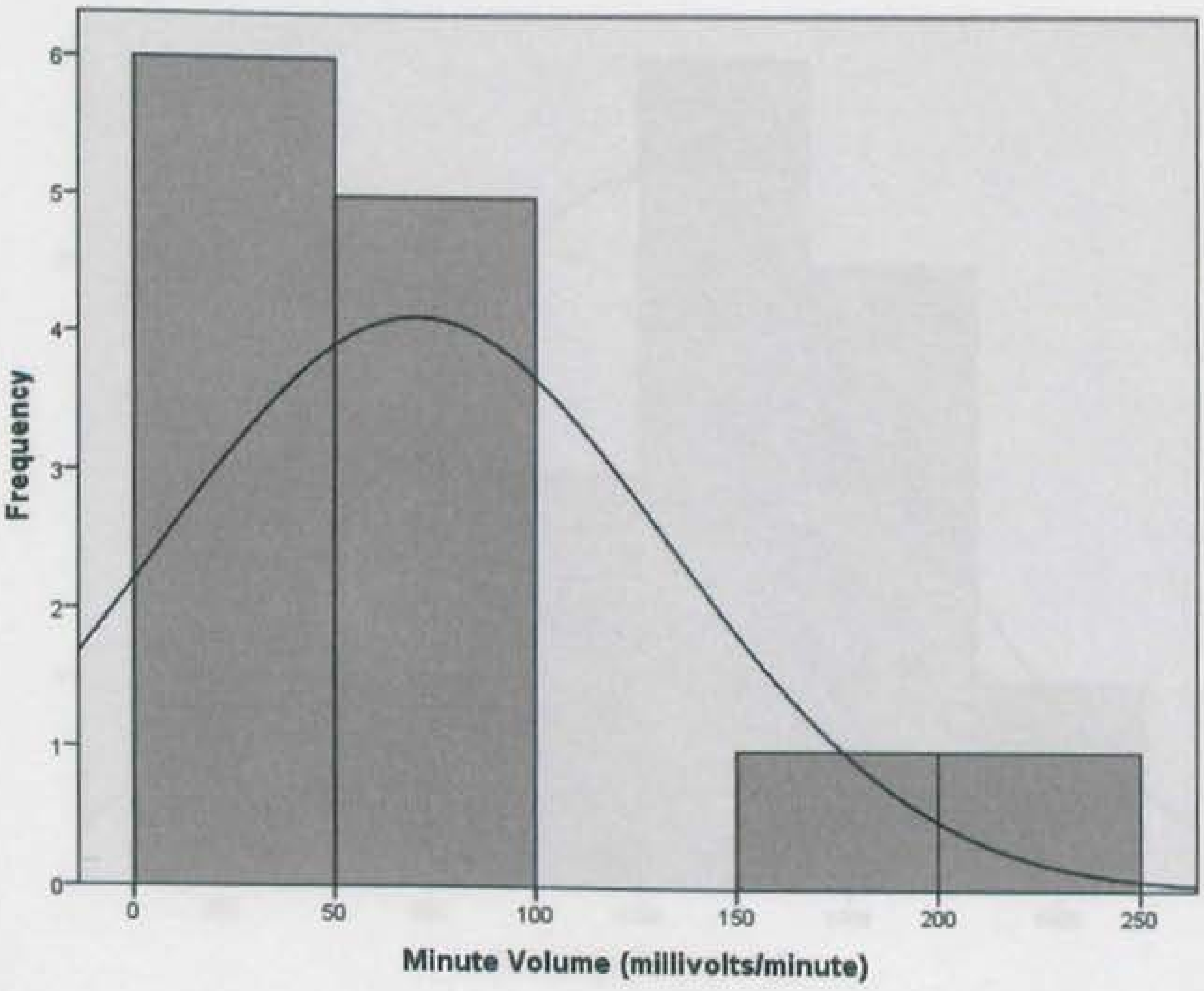
APPENDIX 5.7. *Continued*





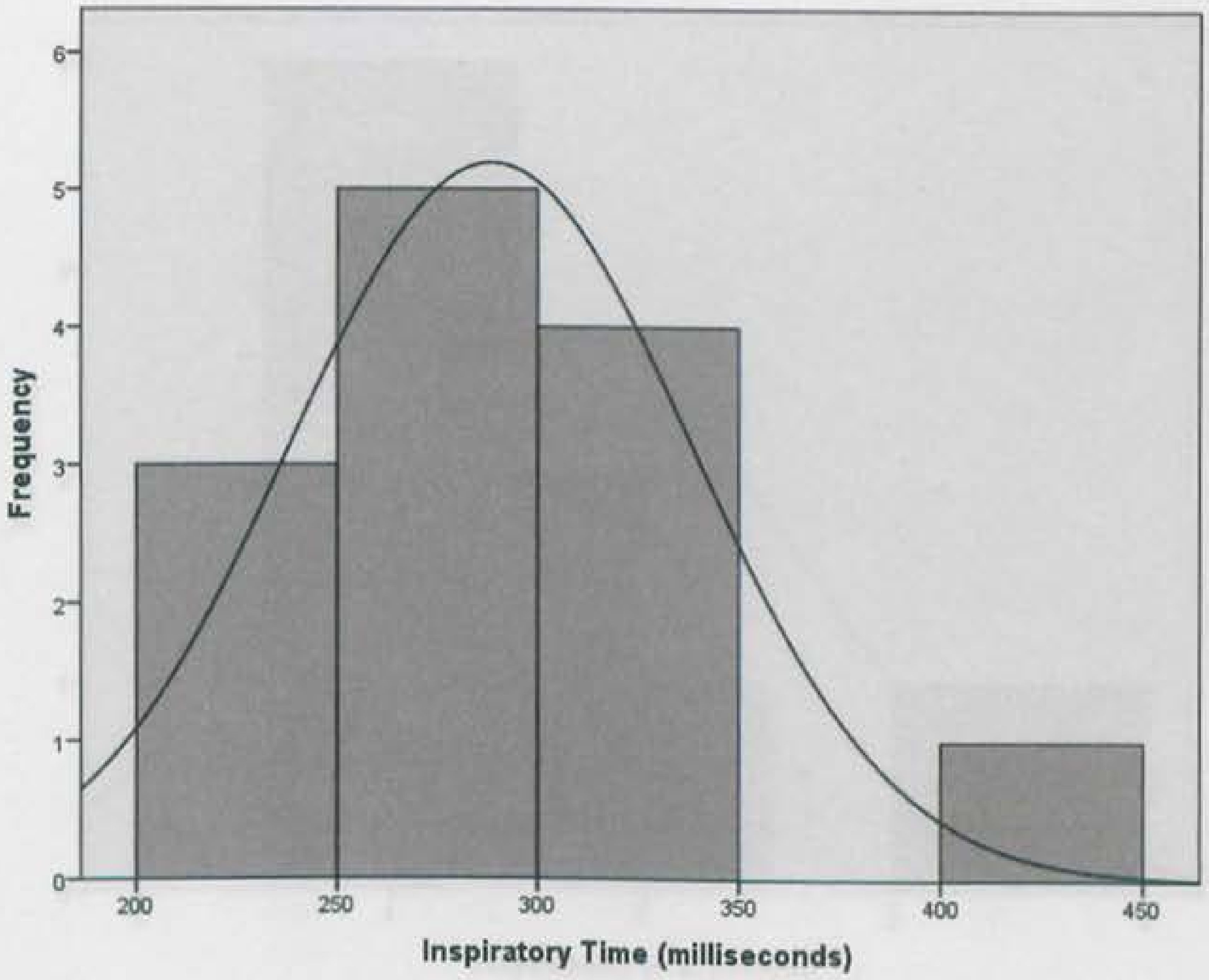
APPENDIX 5.8.
SAMPLE HISTOGRAMS: SUBSEQUENT SUCK-BURST

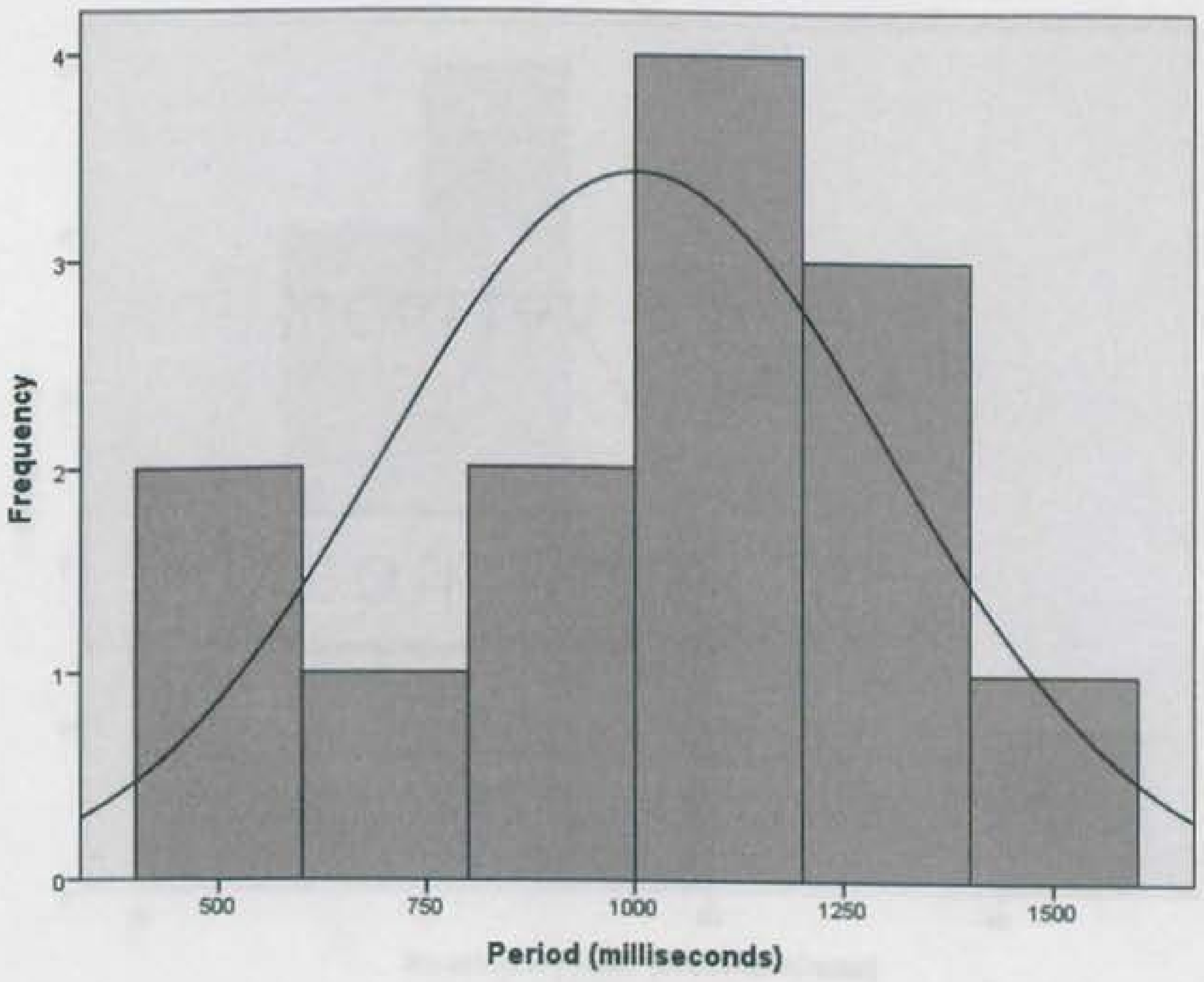




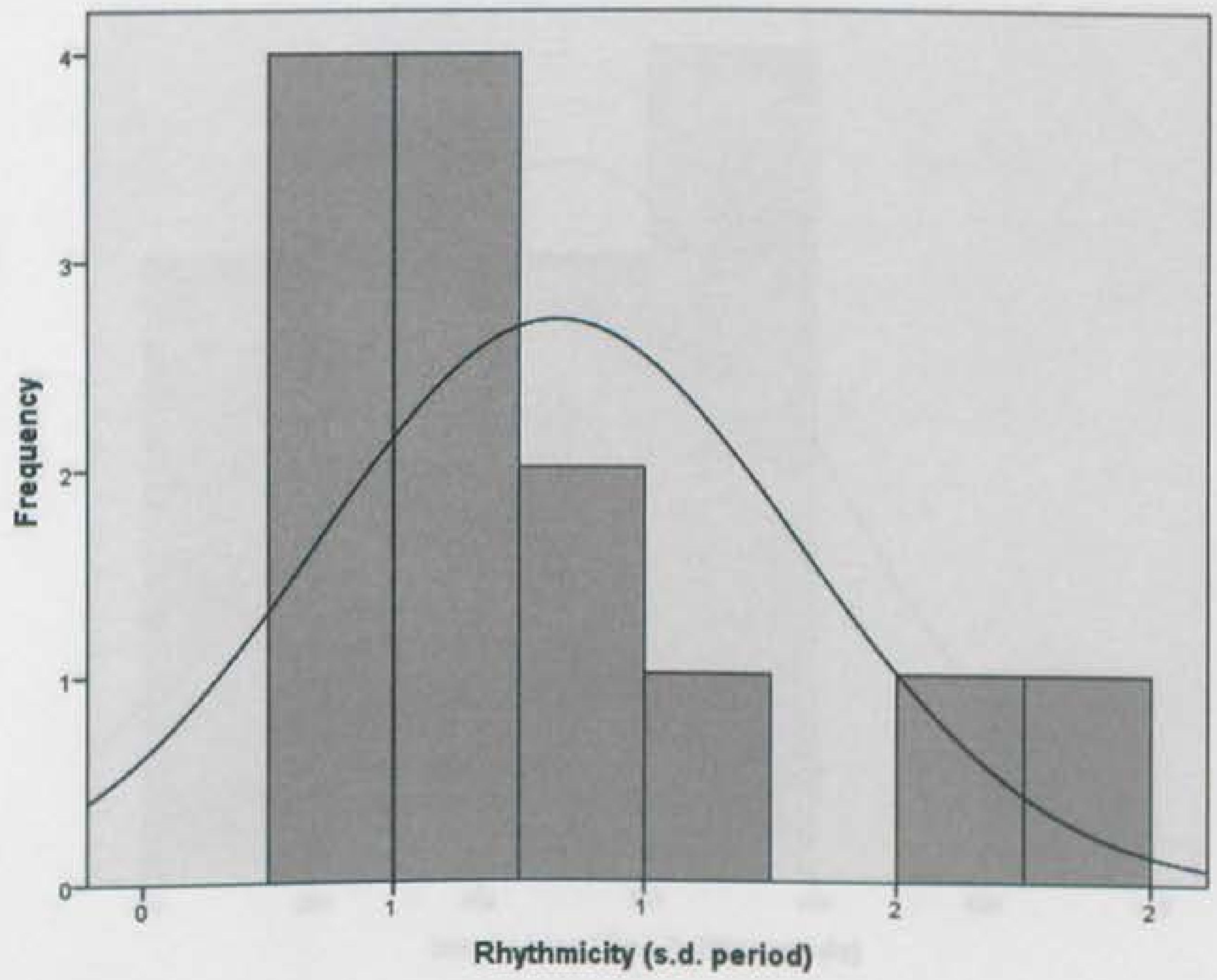
**All values represent respiration on the standard-flow nipple. Outcome measures with multiple data points for each subject are summarized by median value.*

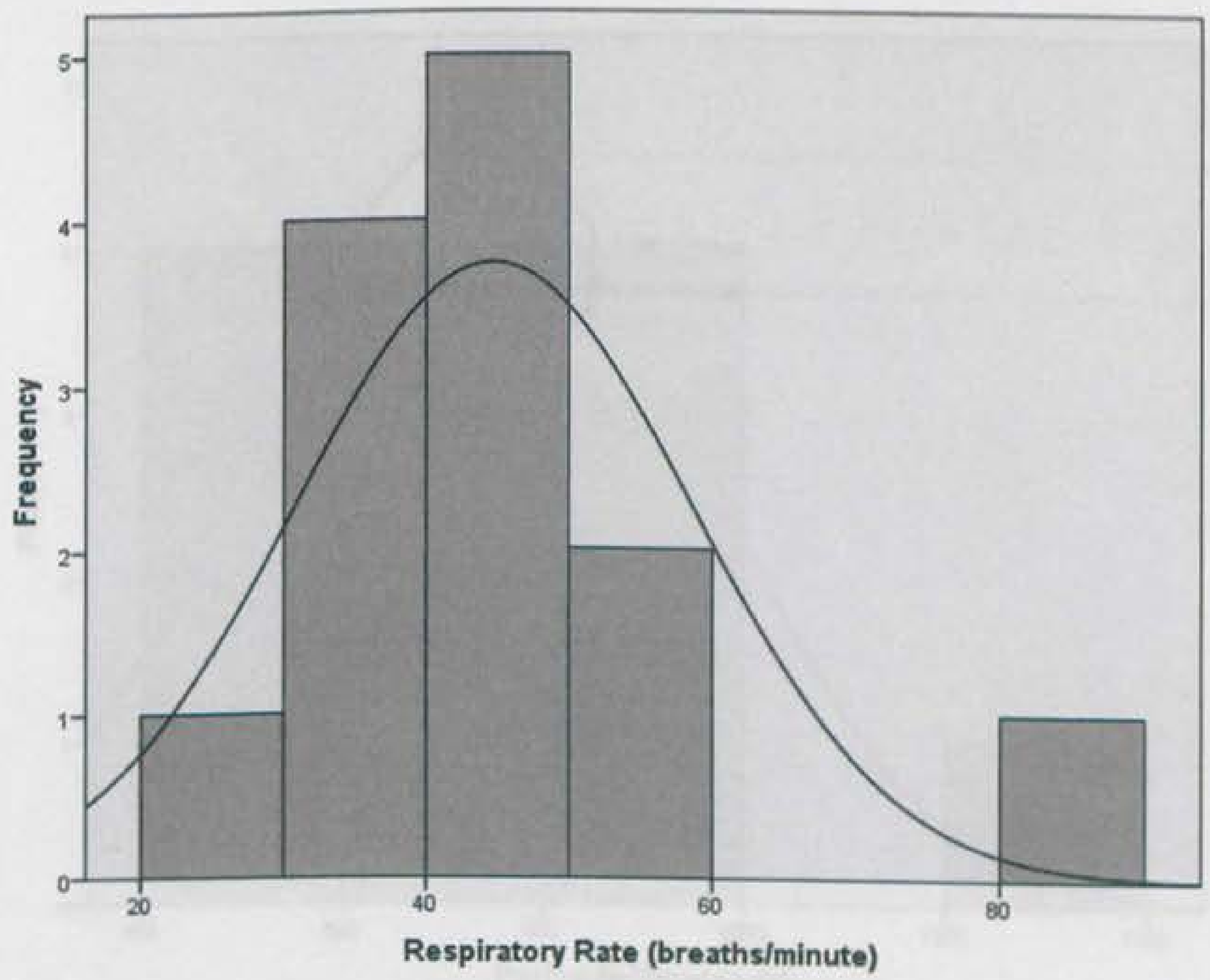
APPENDIX 5.8. *Continued*



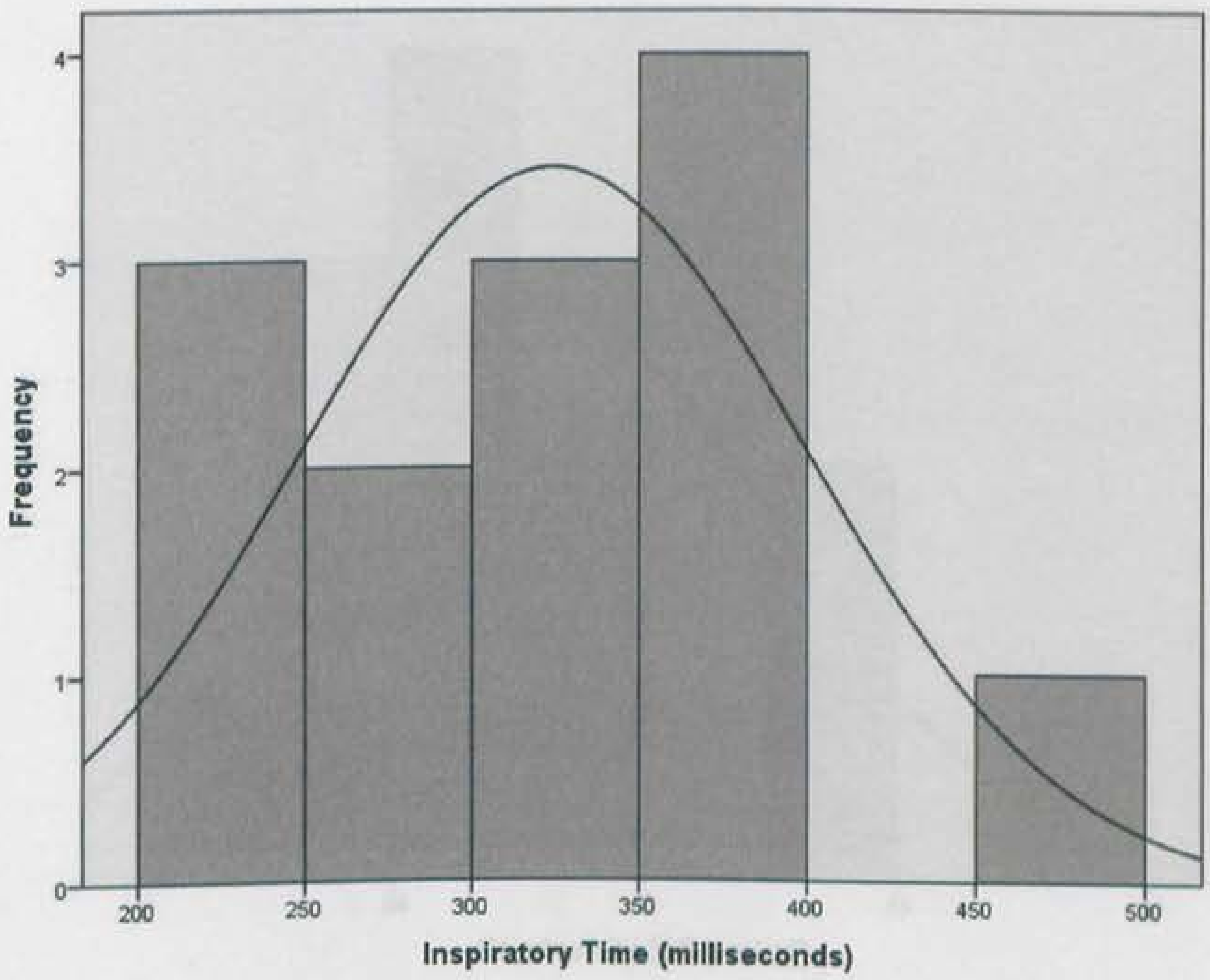


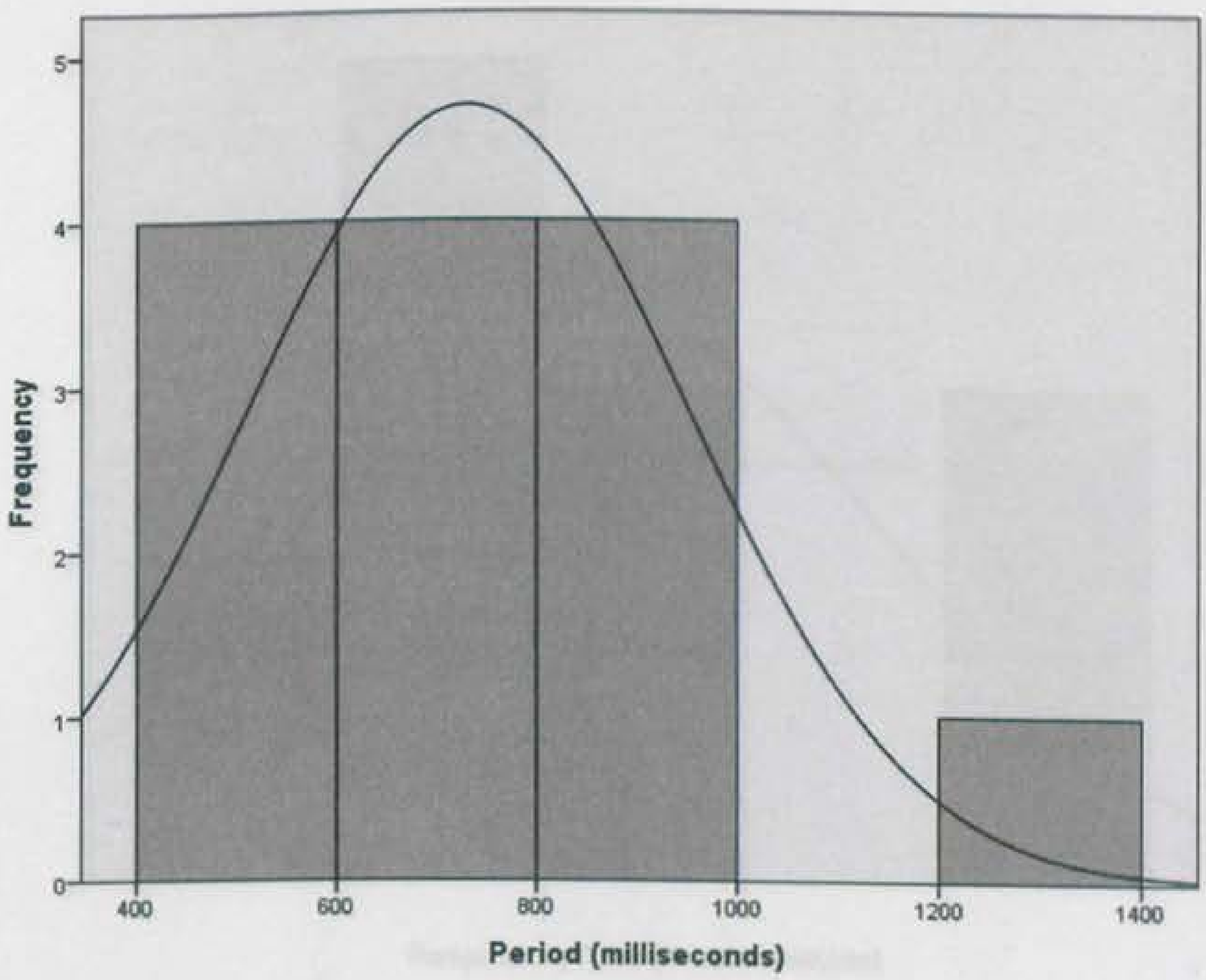
APPENDIX 5.8. *Continued*





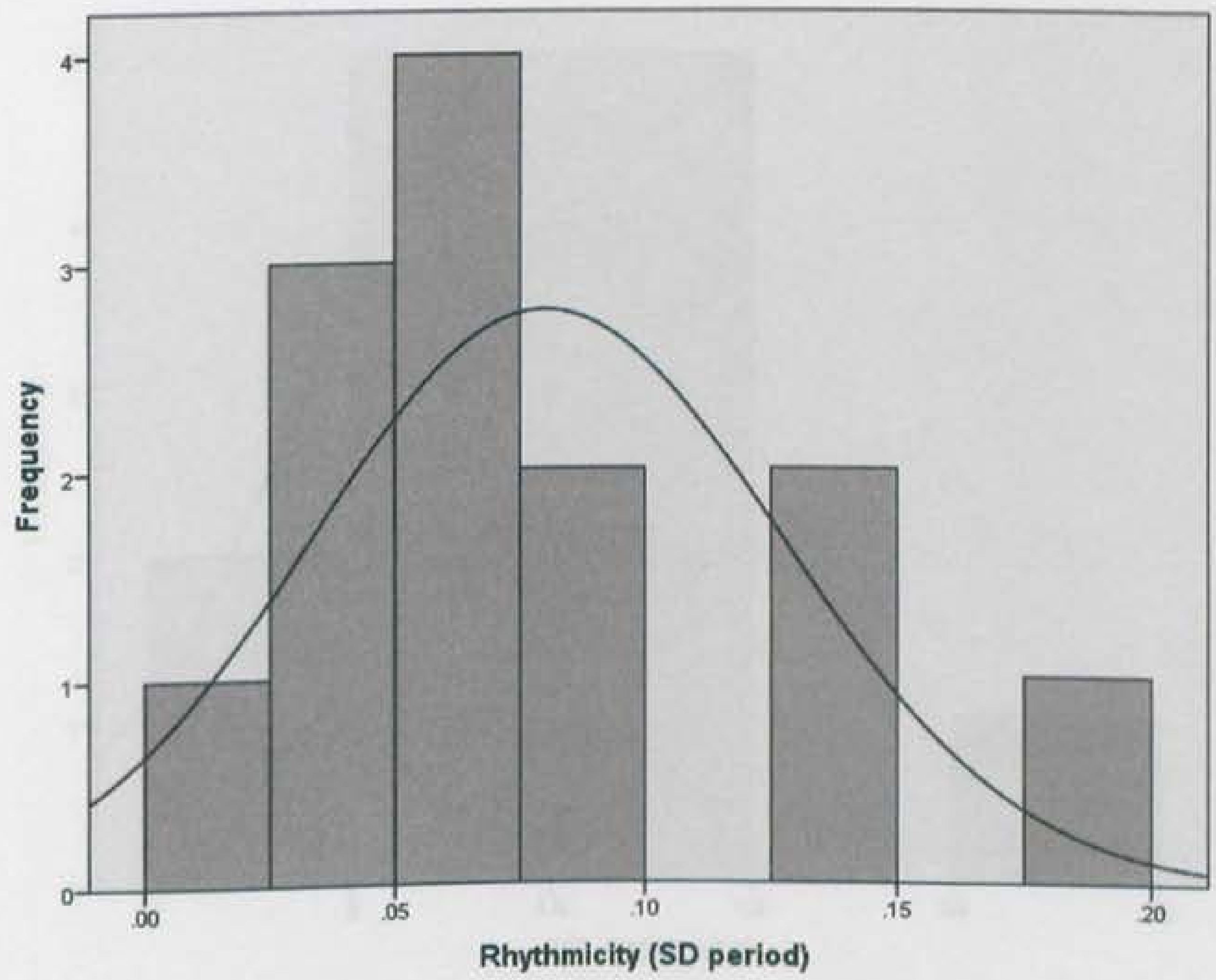
APPENDIX 5.9.
SAMPLE HISTOGRAMS: STEADY-STATE

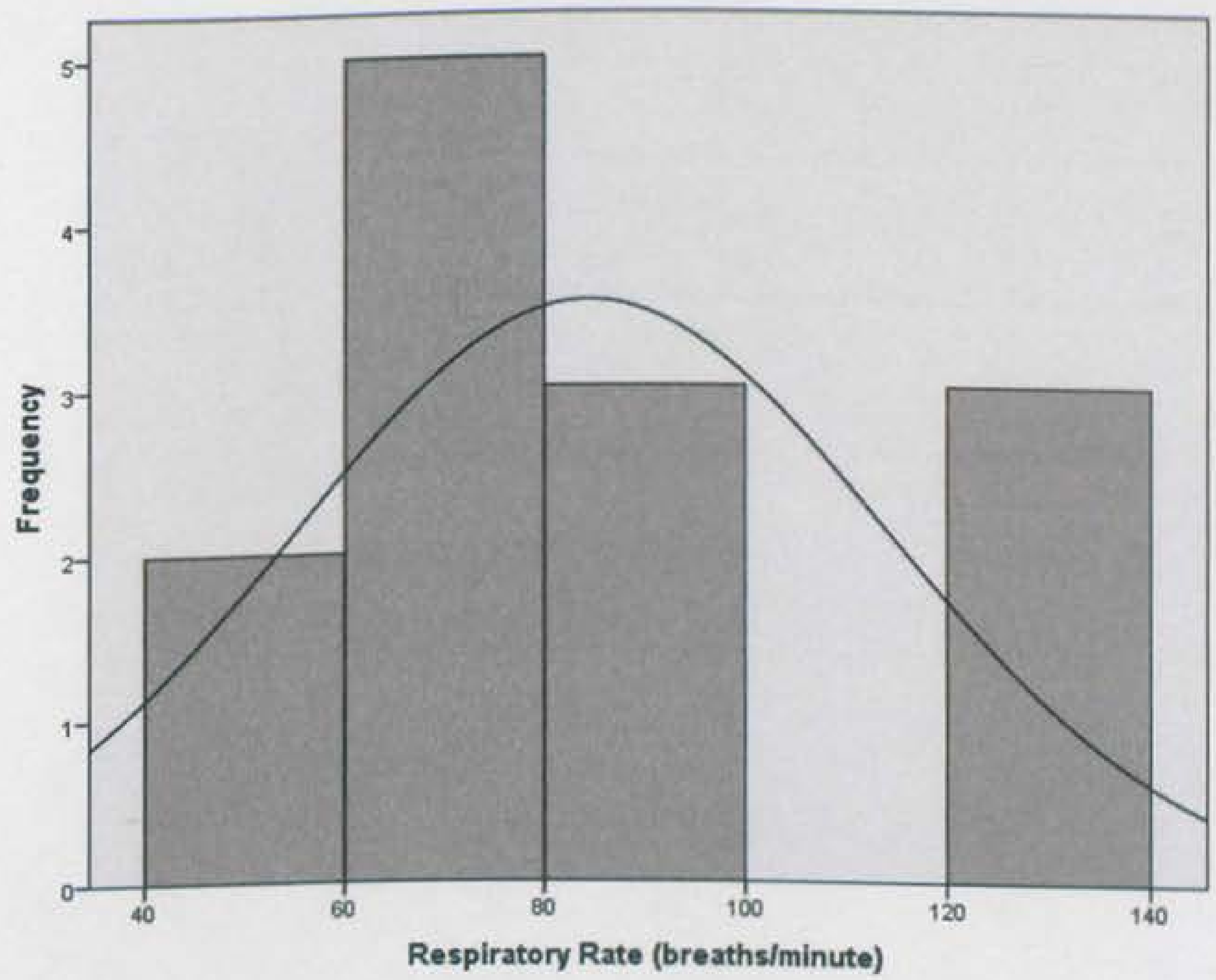




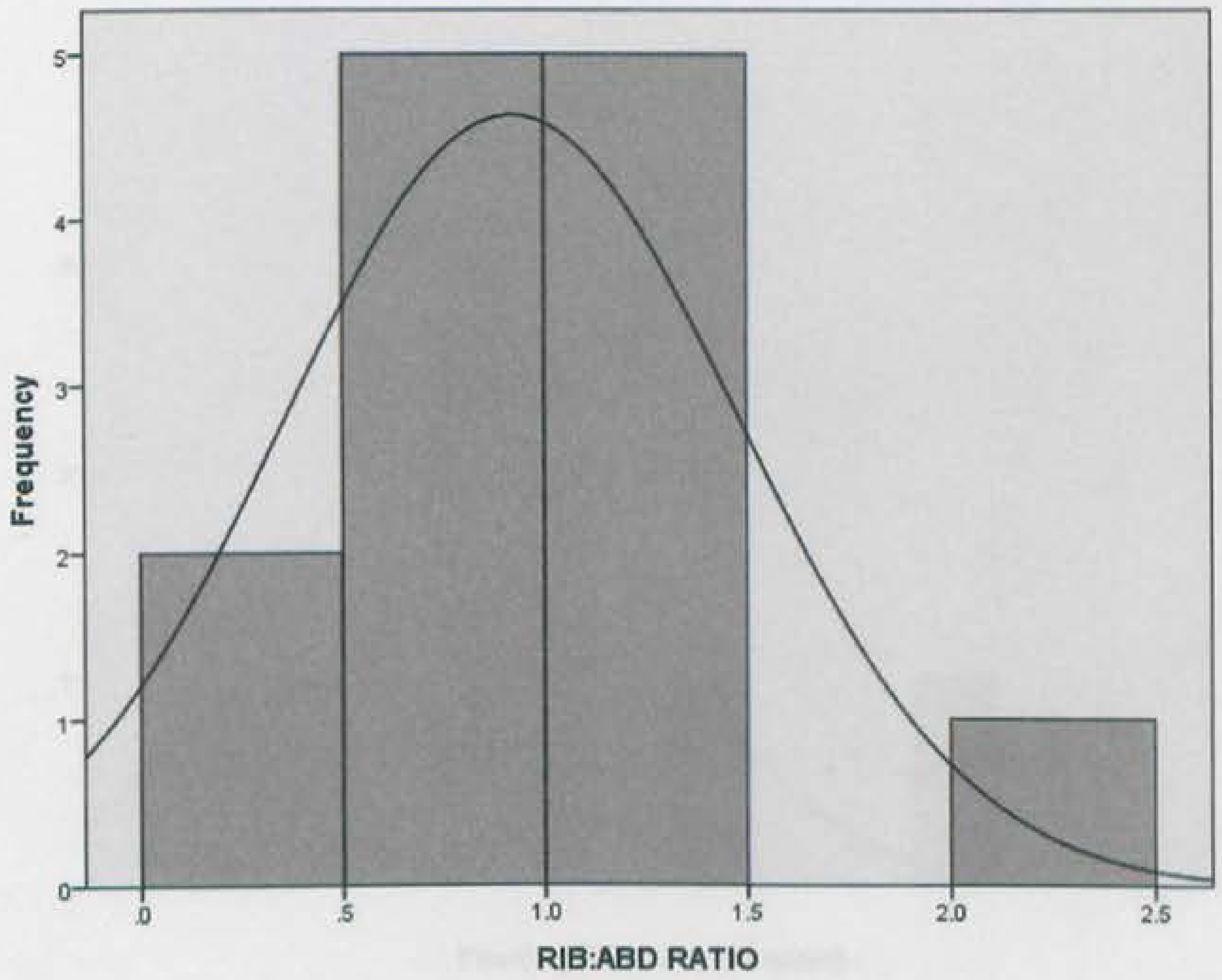
** All values represent respiration on the standard-flow nipple. Outcome measures with multiple data points for each subject are summarized by median value.*

APPENDIX 5.9. *Continued*

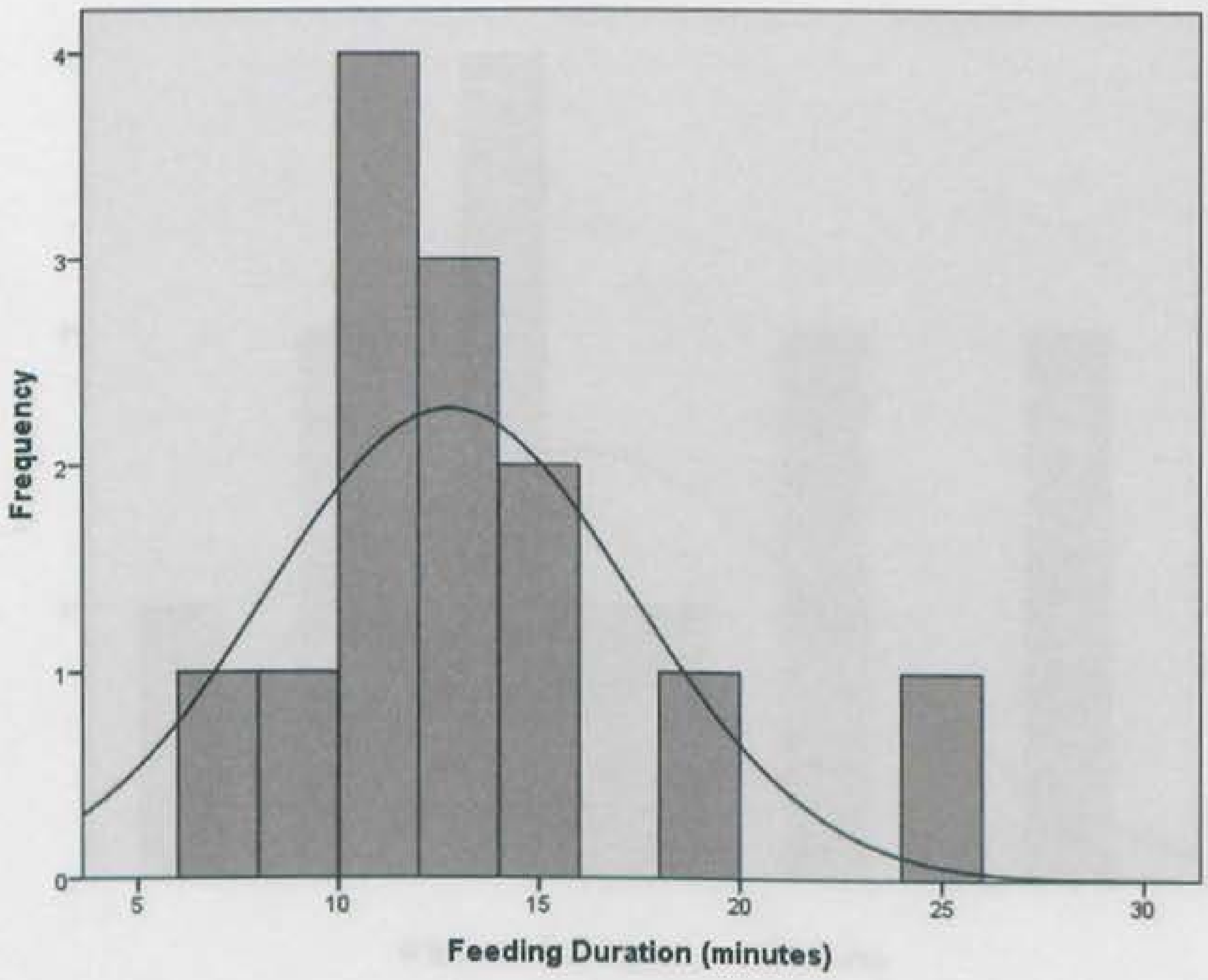


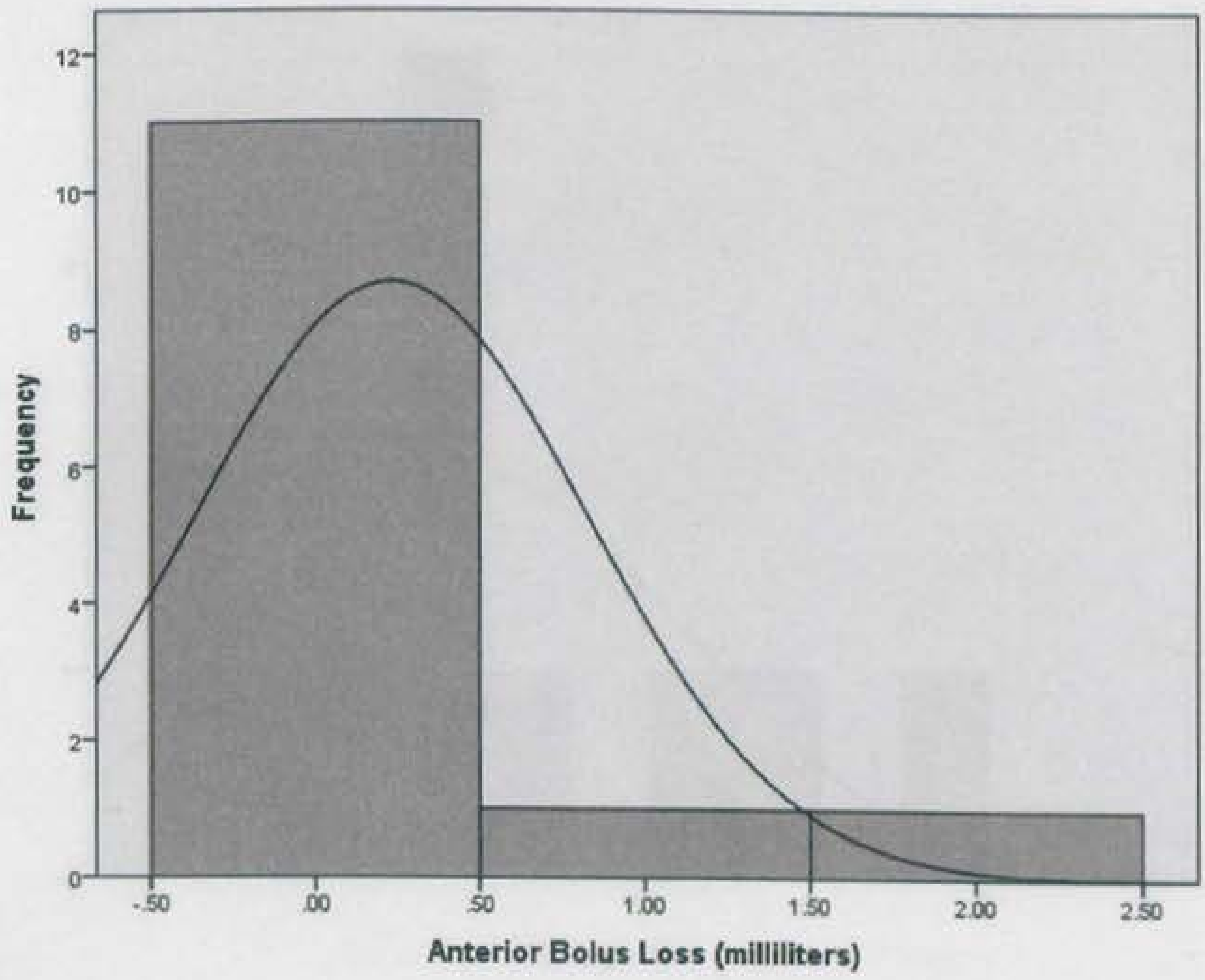


APPENDIX 5.9. *Continued*



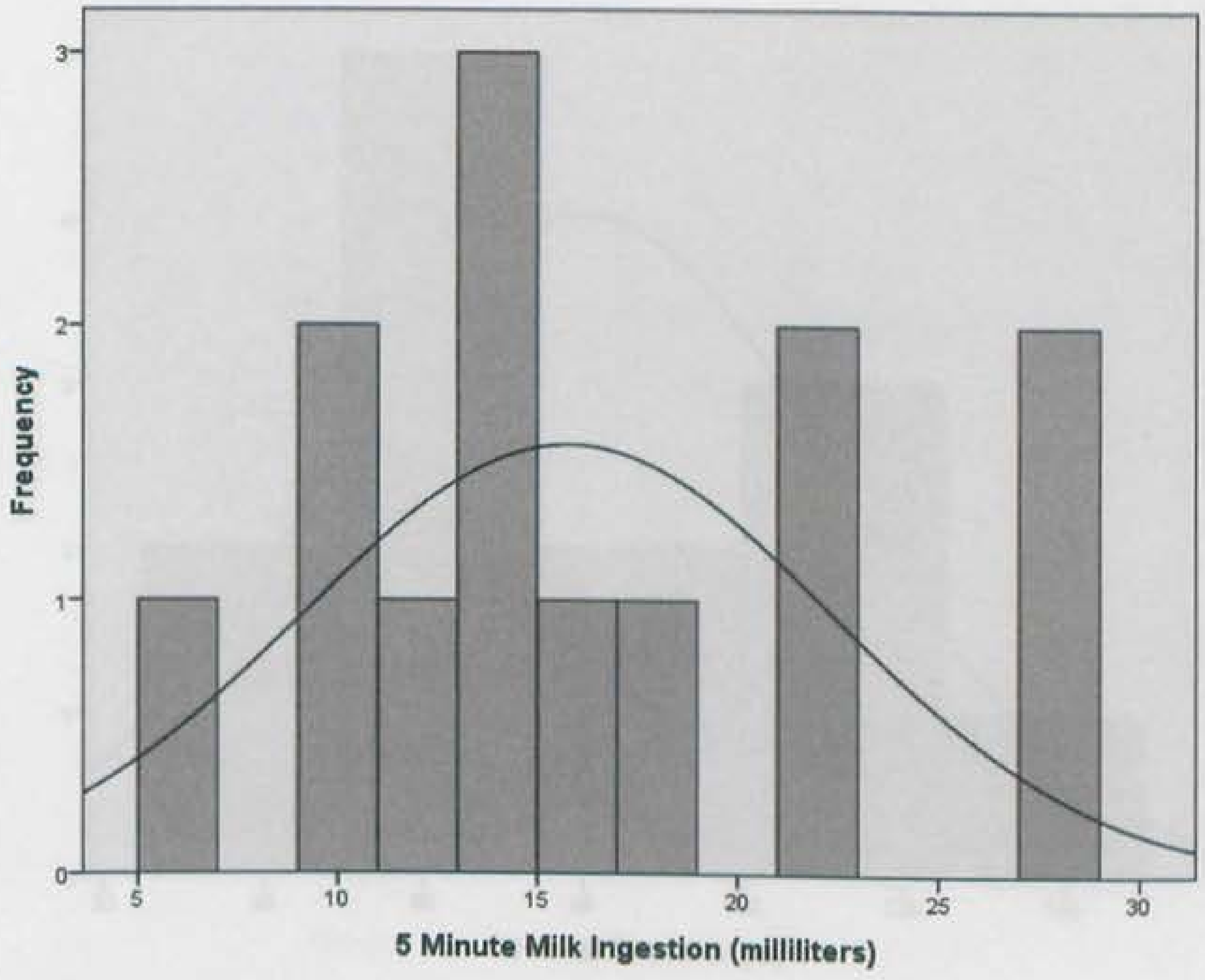
APPENDIX 5.10.
SAMPLE HISTOGRAMS: MILK INGESTION

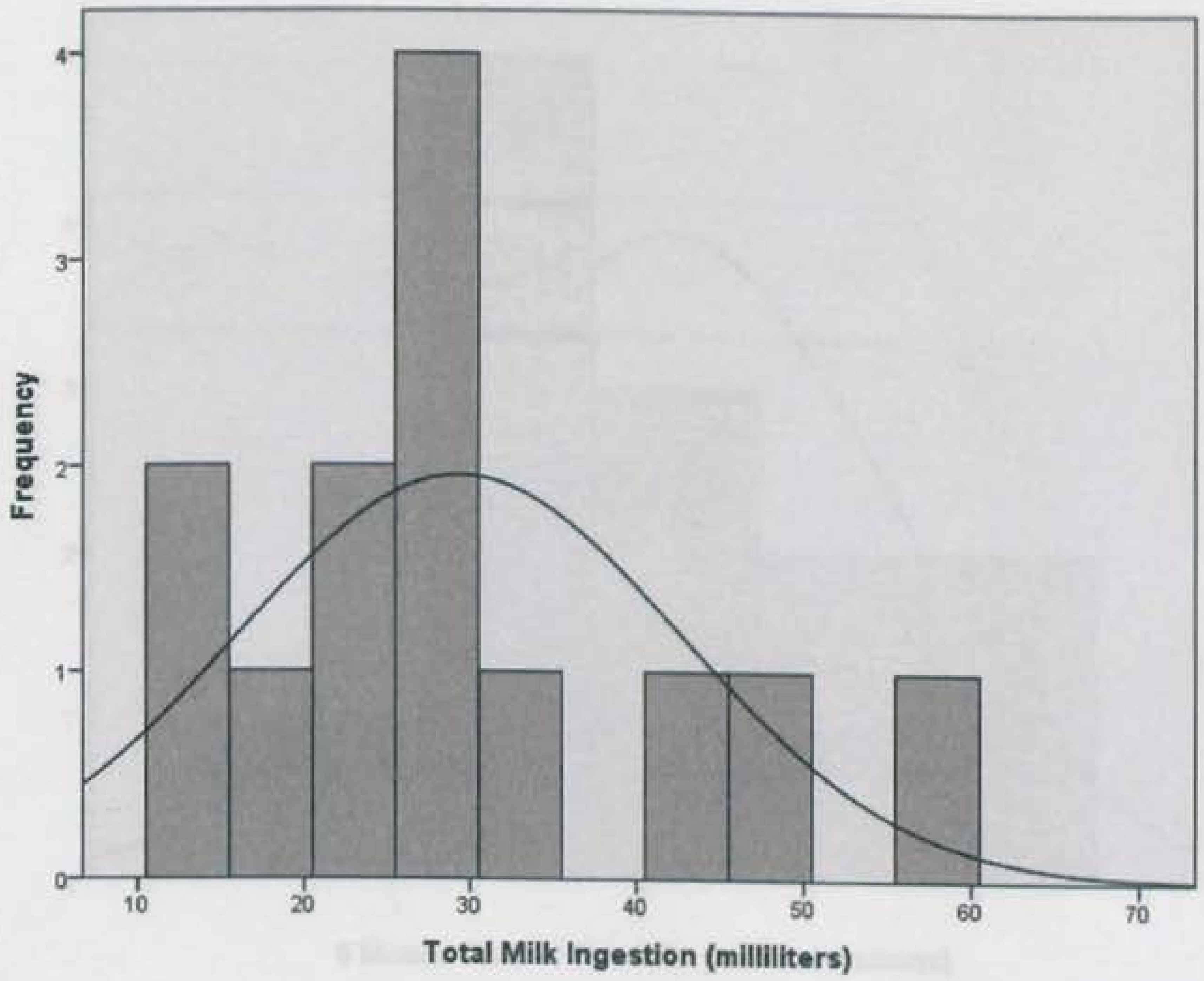




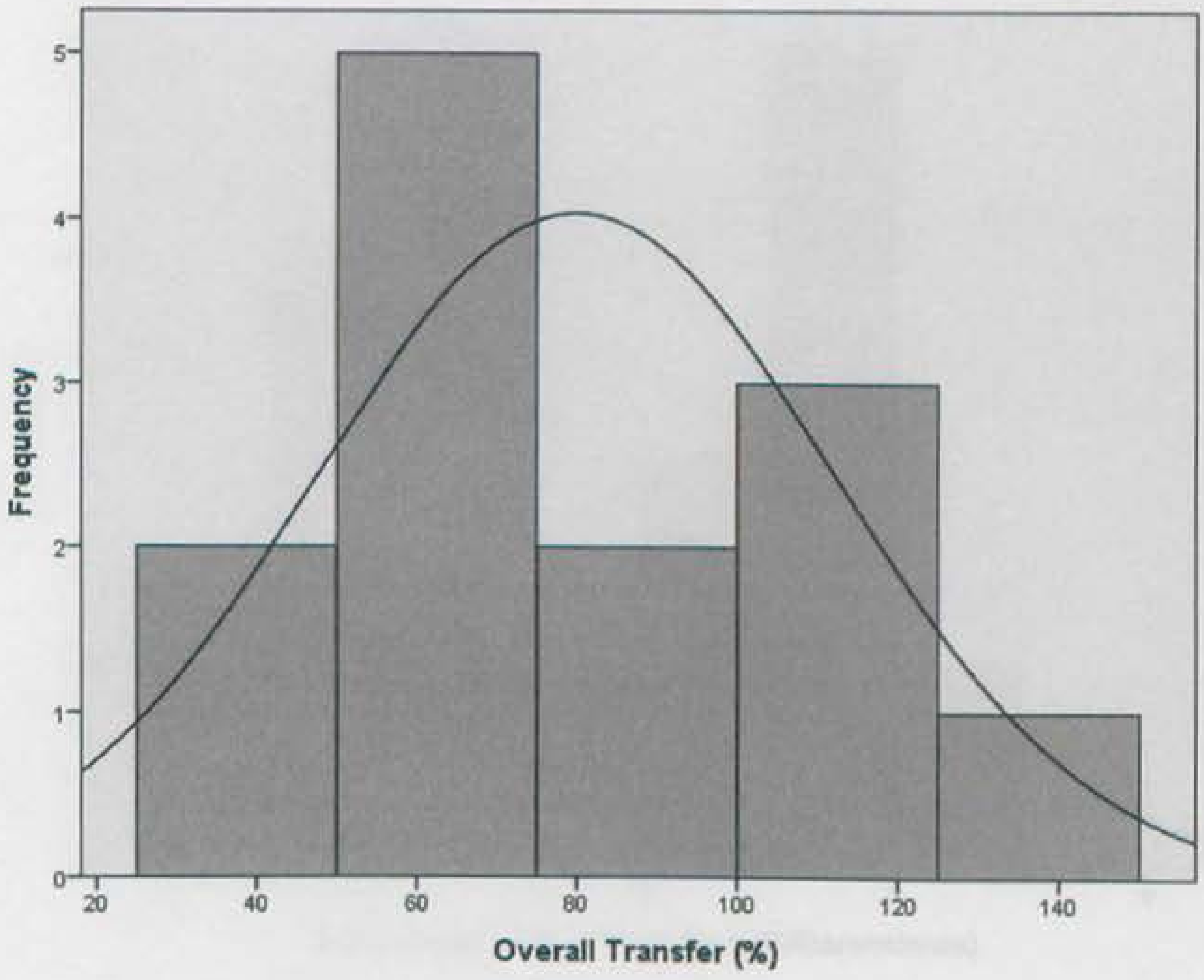
**All values represent milk ingestion on the standard-flow nipple.*

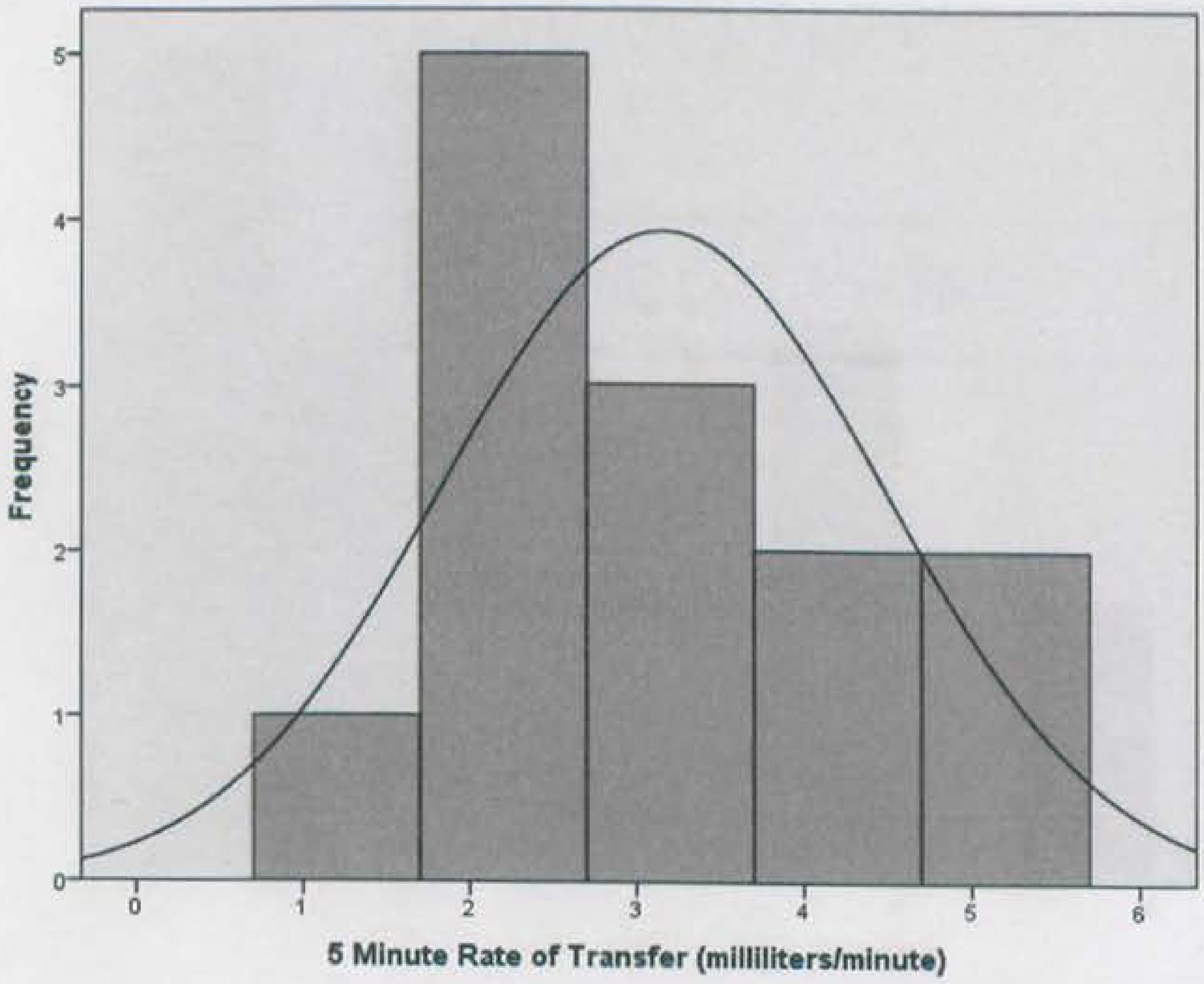
APPENDIX 5.10. *Continued*



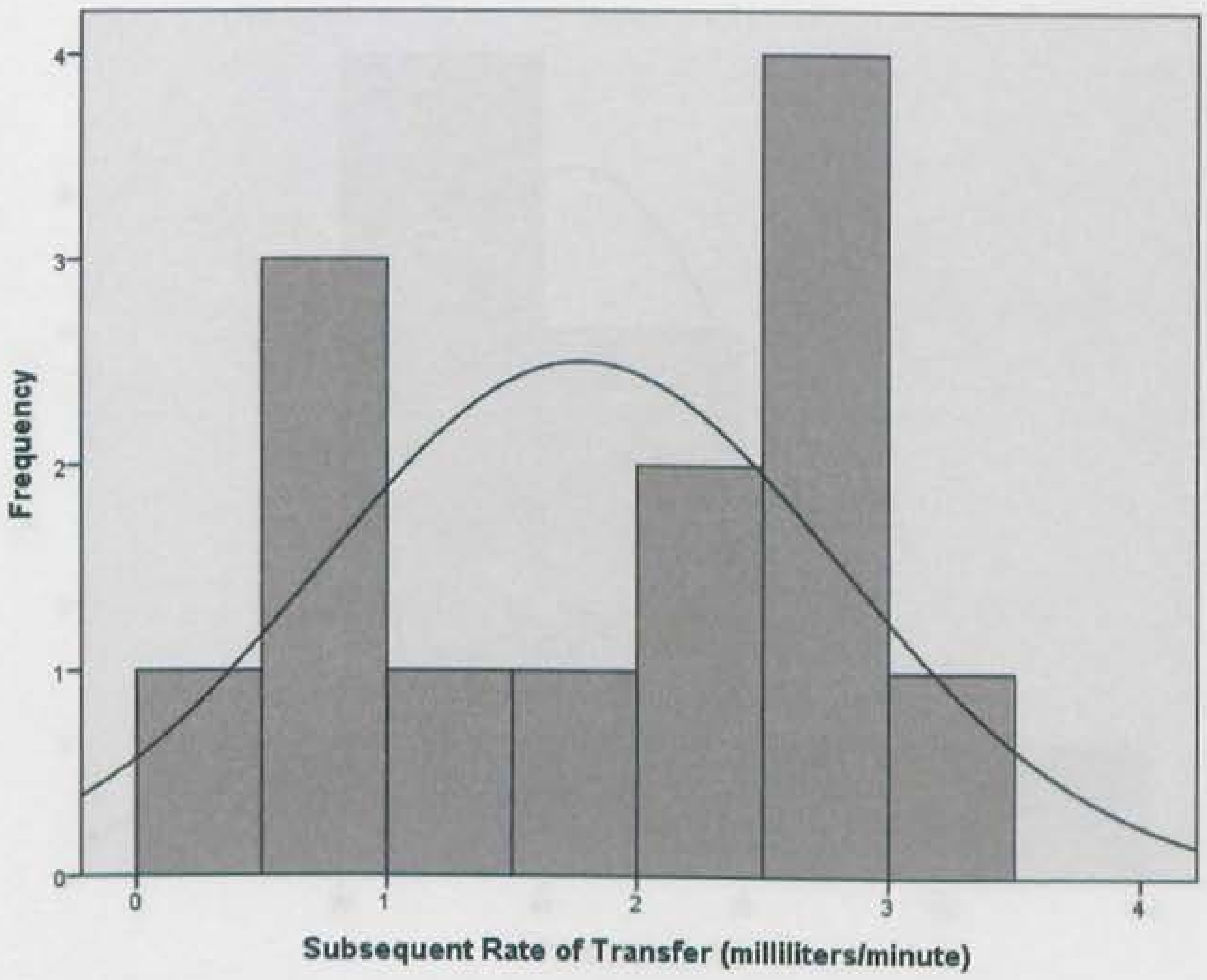


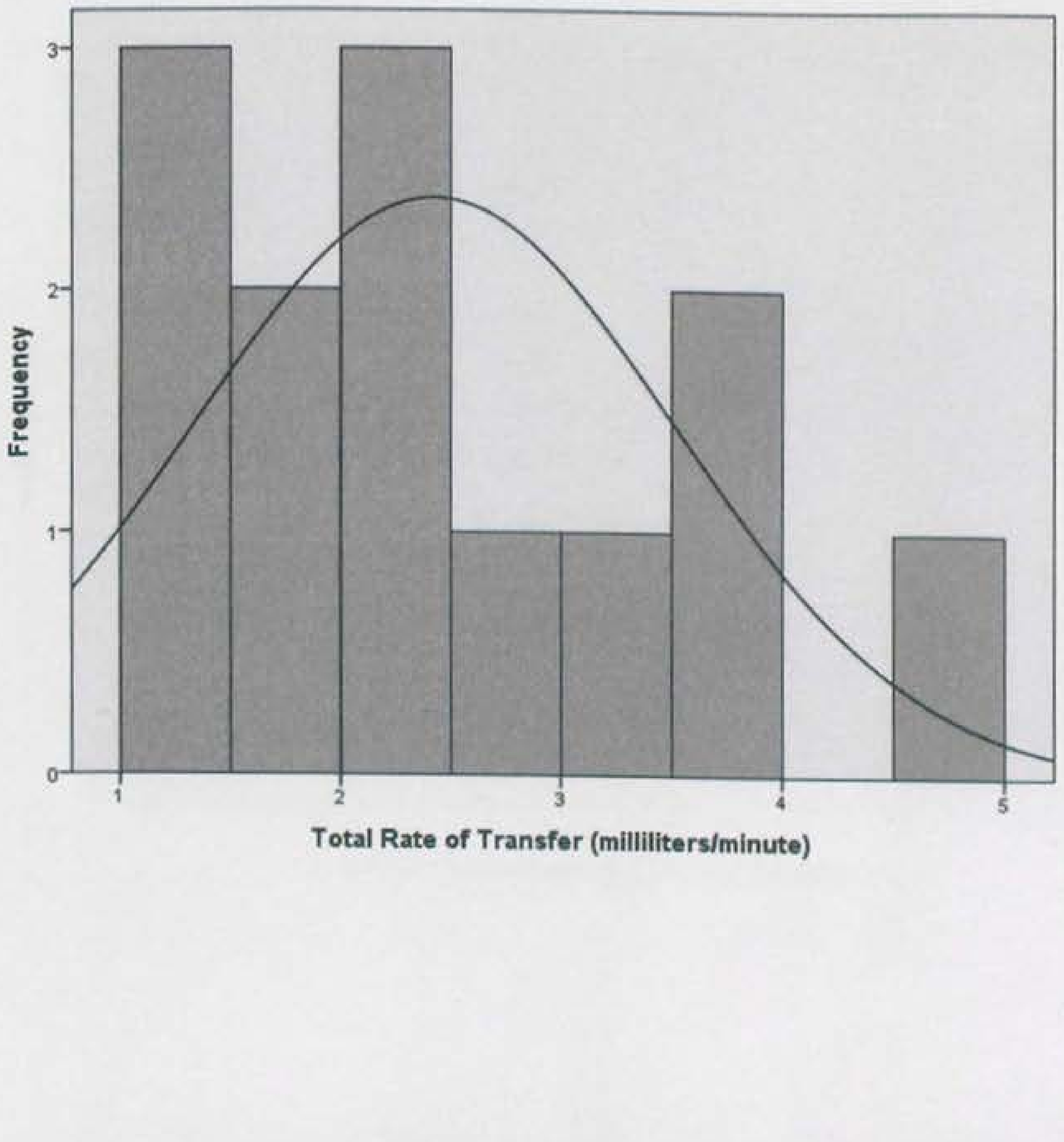
APPENDIX 5.10. *Continued*



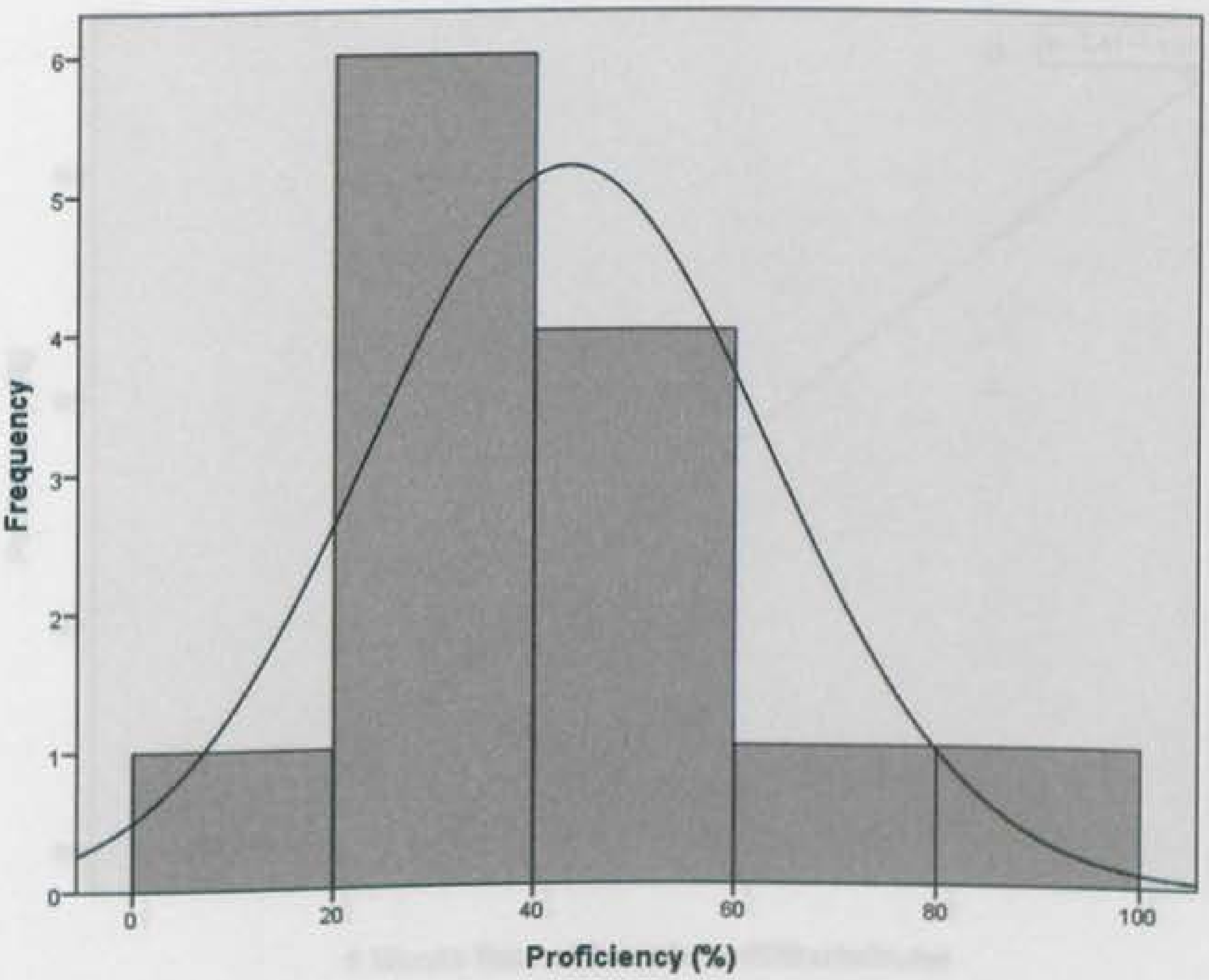


APPENDIX 5.10. *Continued*



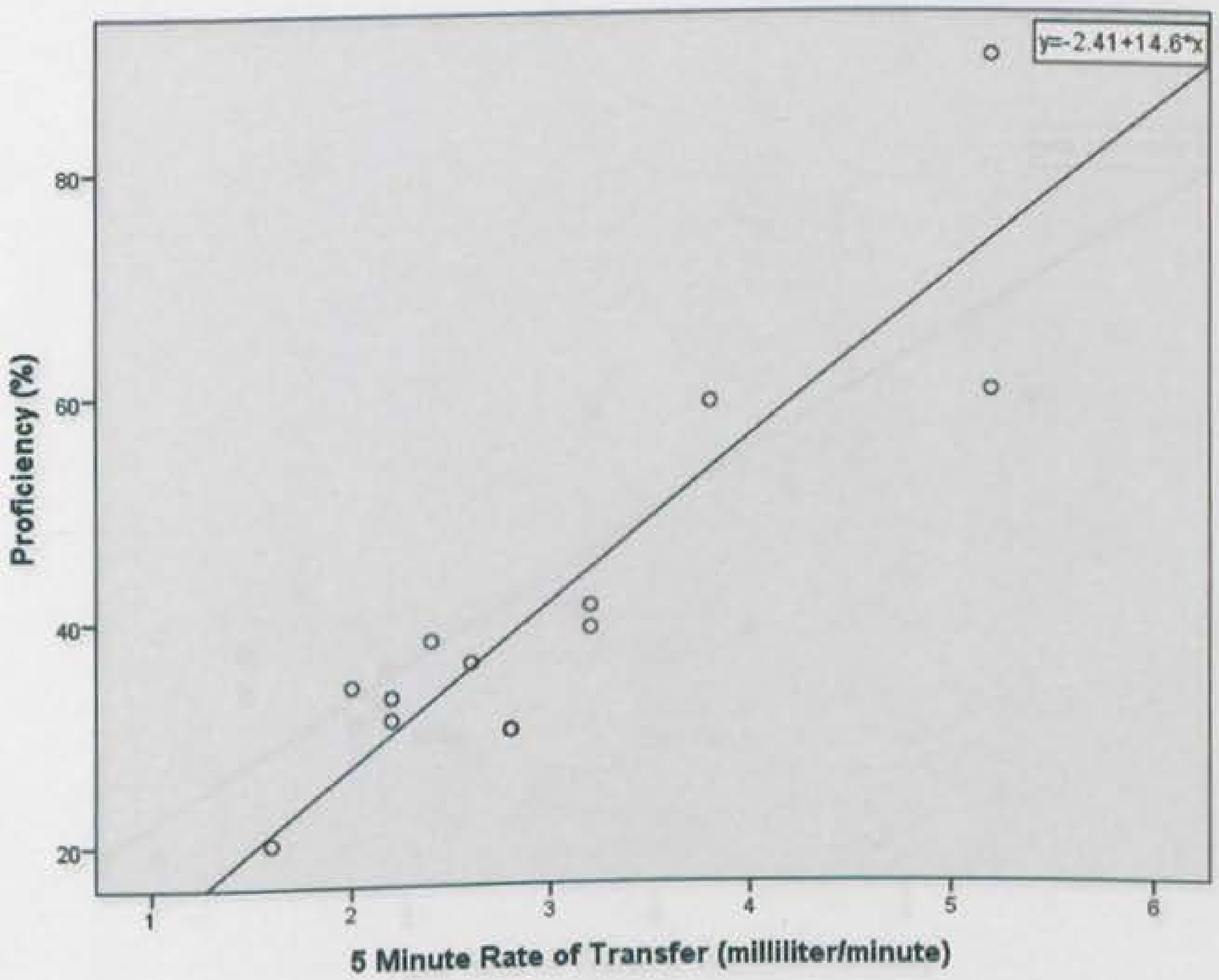


APPENDIX 5.10. *Continued*

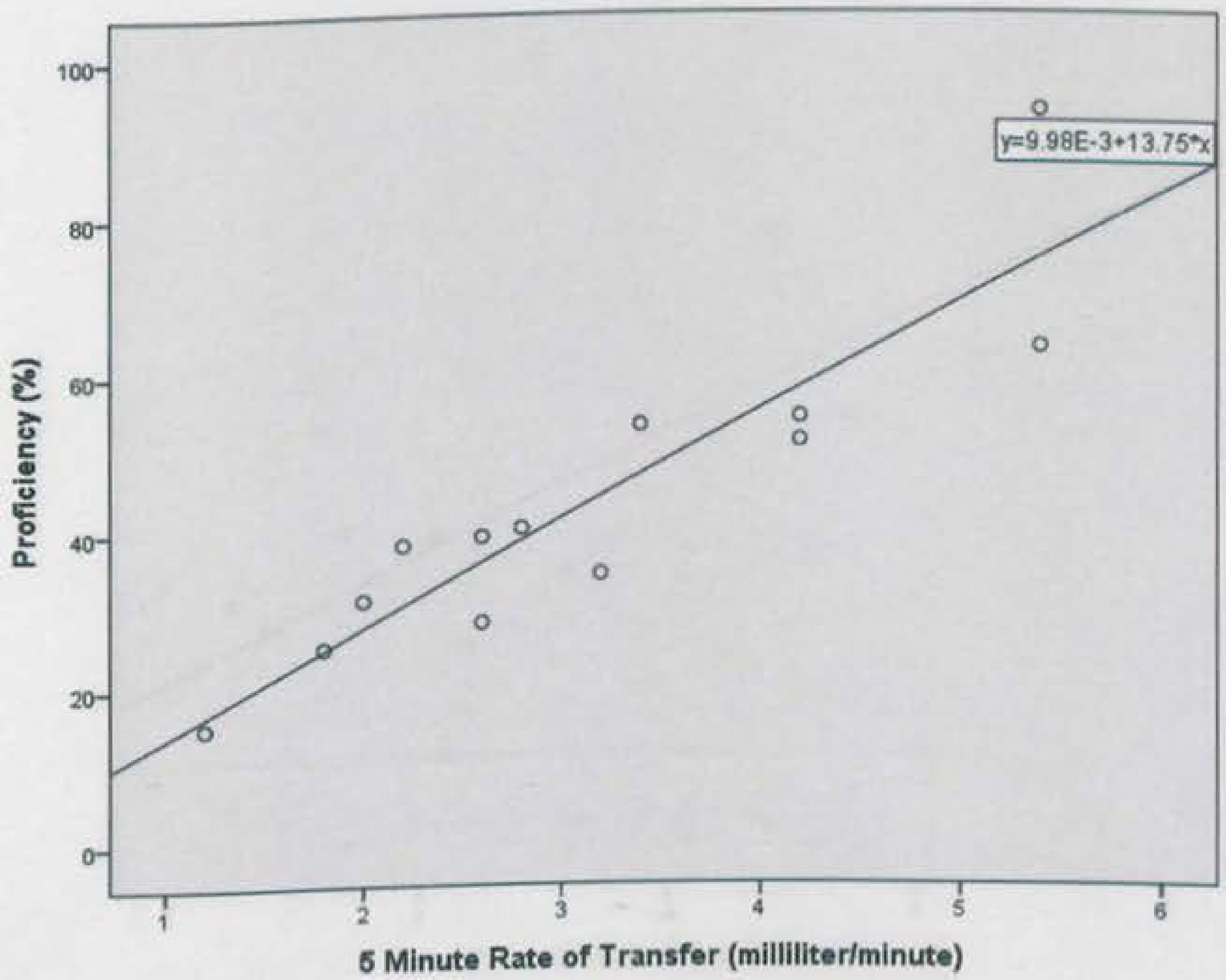


APPENDIX 5.11.
MILK INGESTION CORRELATIONS: PROFICIENCY

SLOW-FLOW

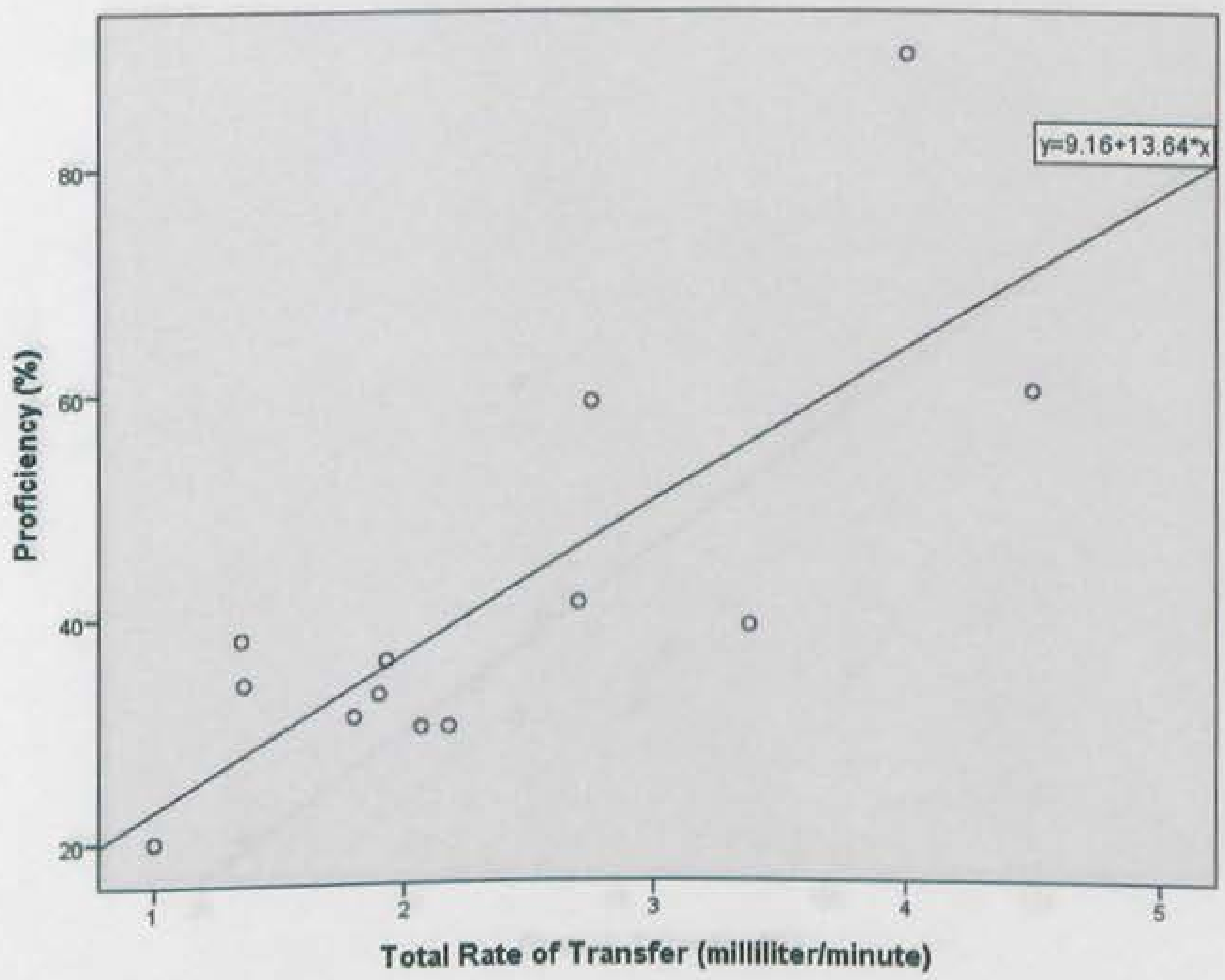


STANDARD-FLOW

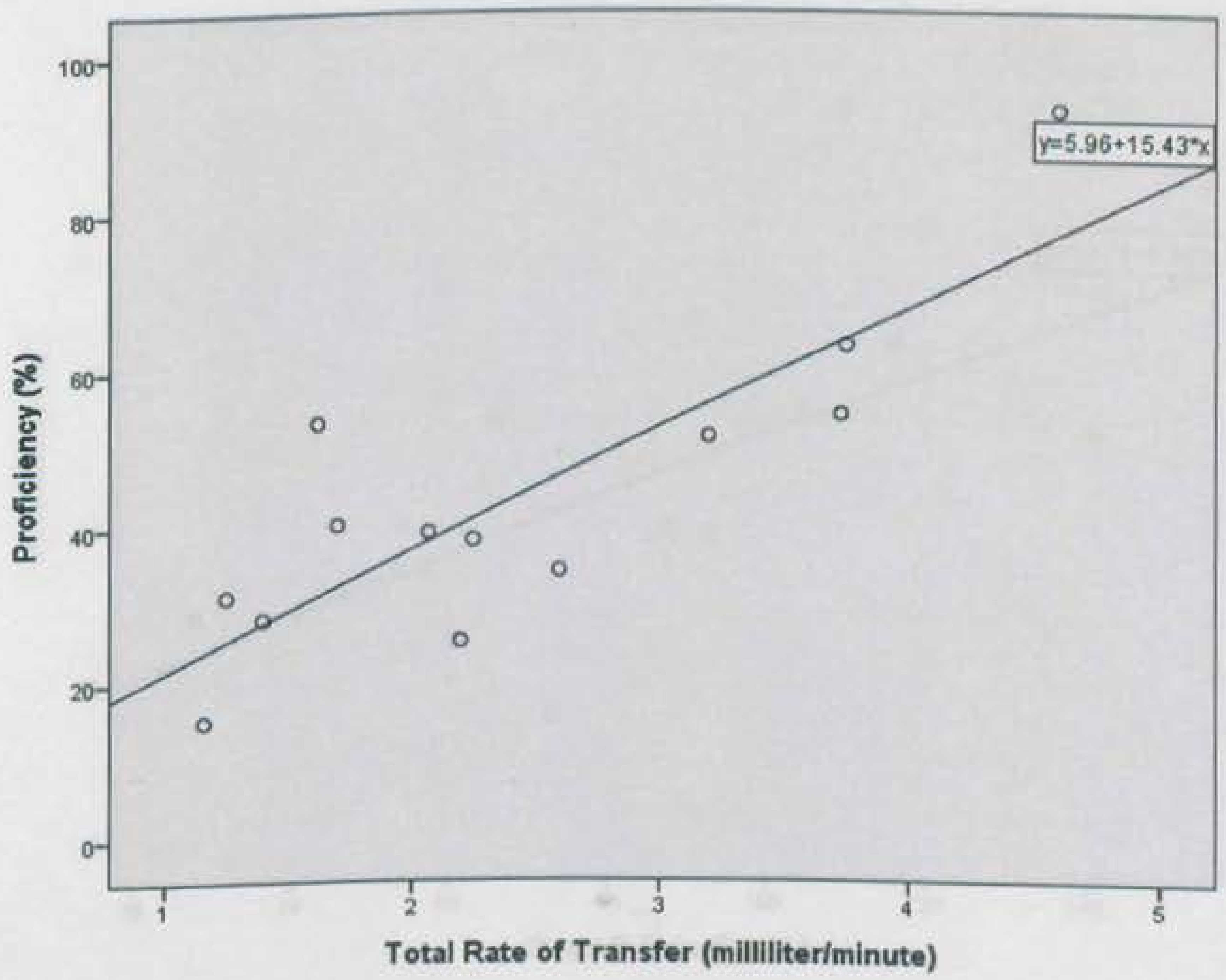


APPENDIX 5.11. *Continued*

SLOW-FLOW

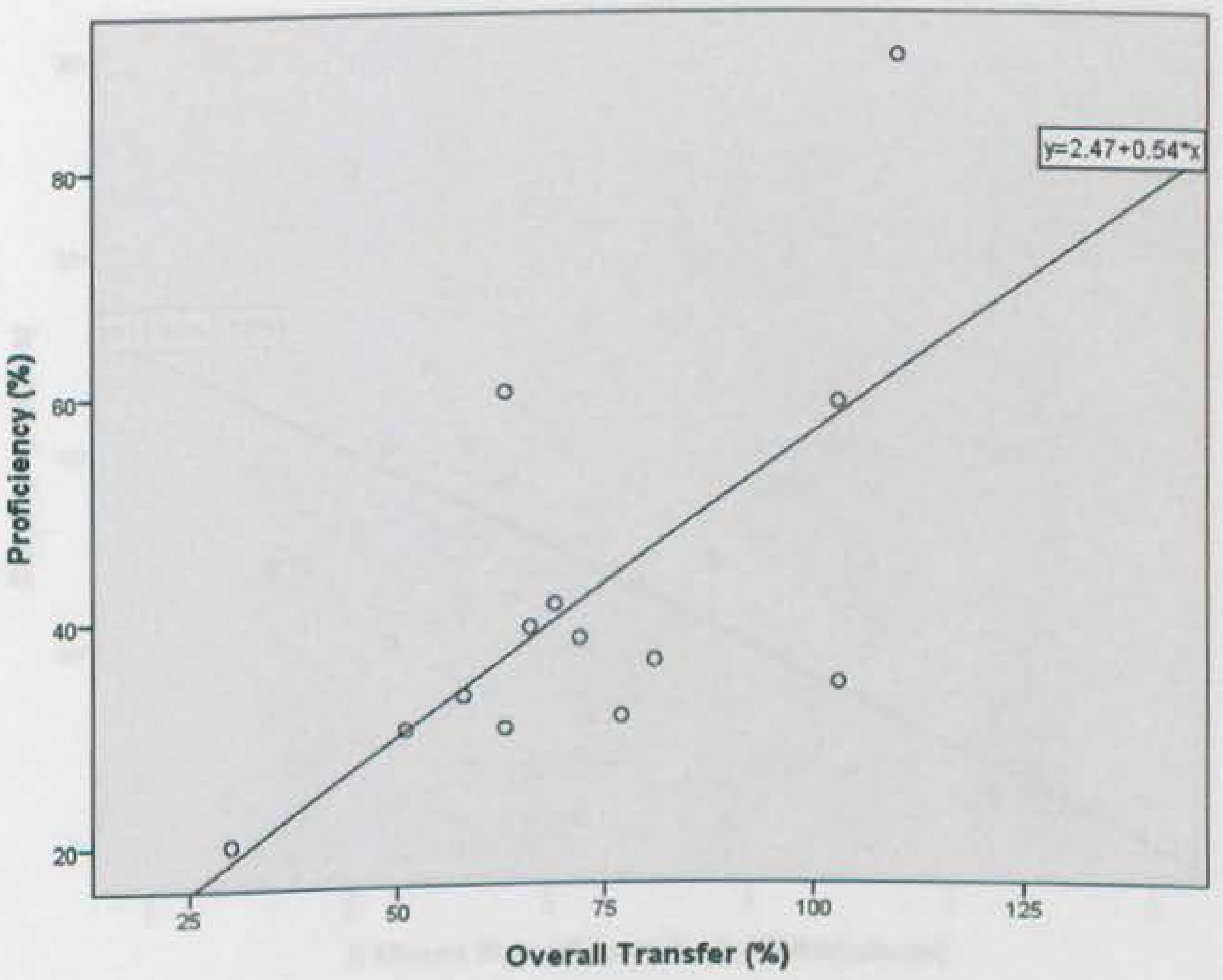


STANDARD-FLOW

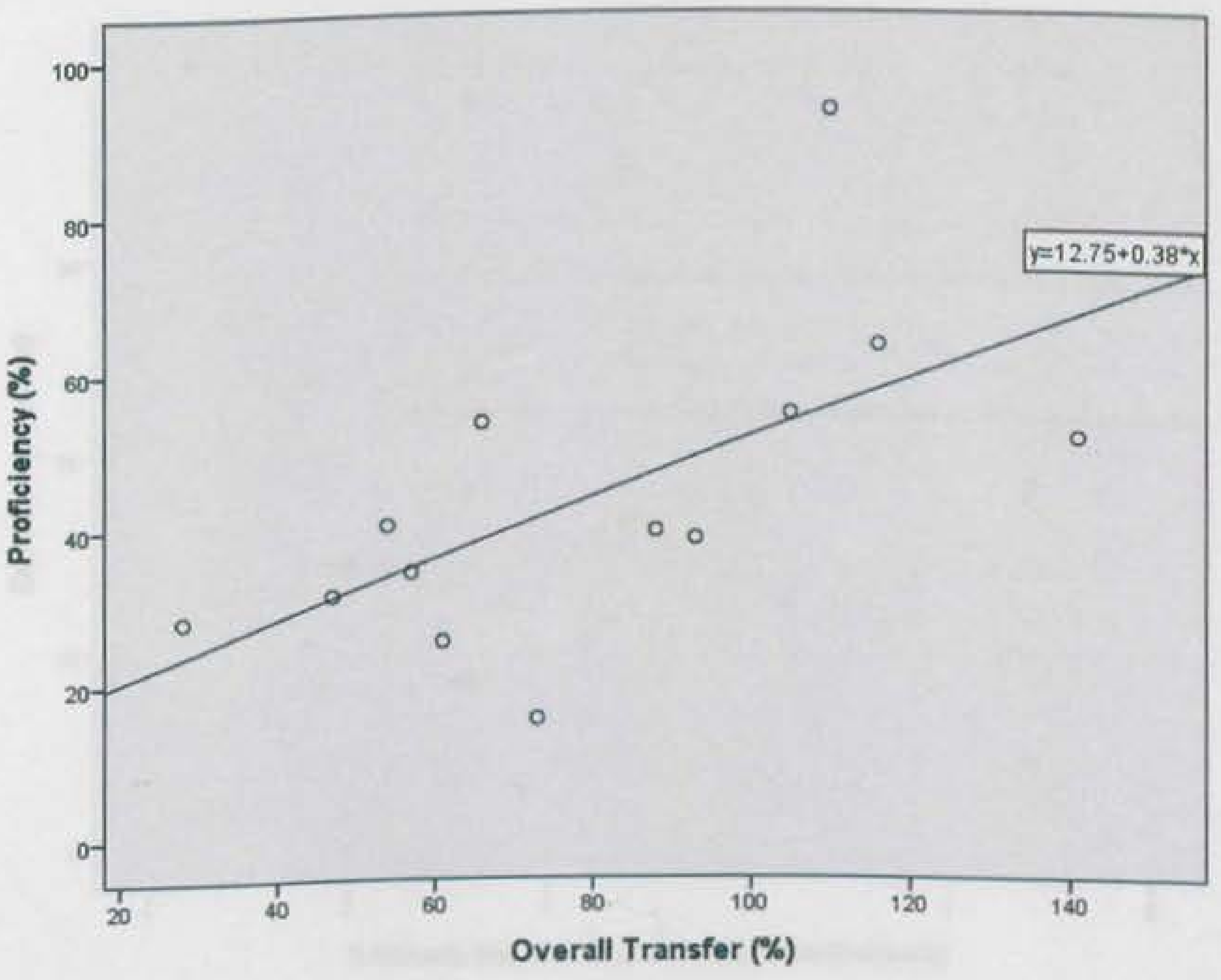


APPENDIX 5.11. *Continued*

SLOW-FLOW

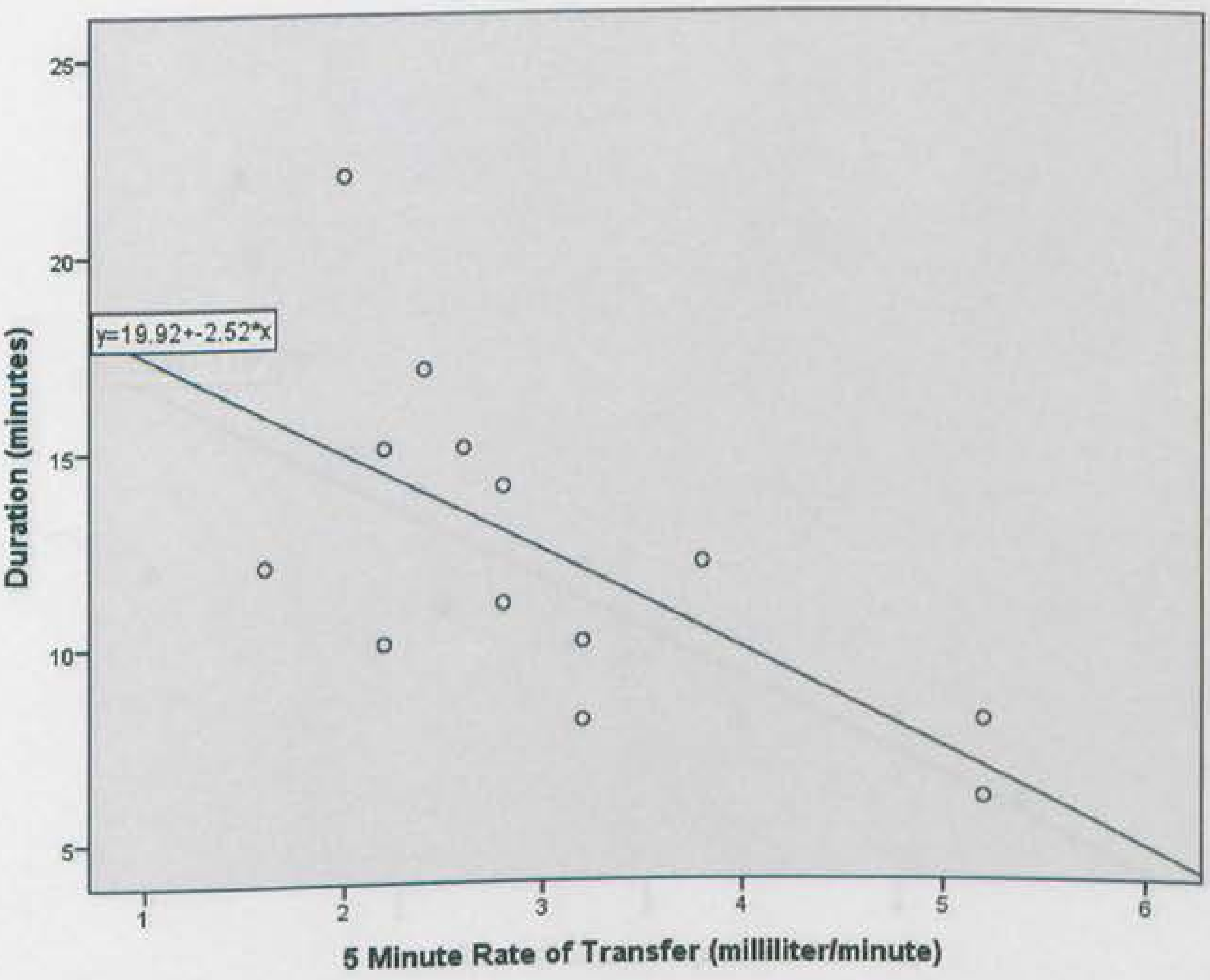


STANDARD-FLOW



APPENDIX 5.12.
MILK INGESTION CORRELATIONS: DURATION

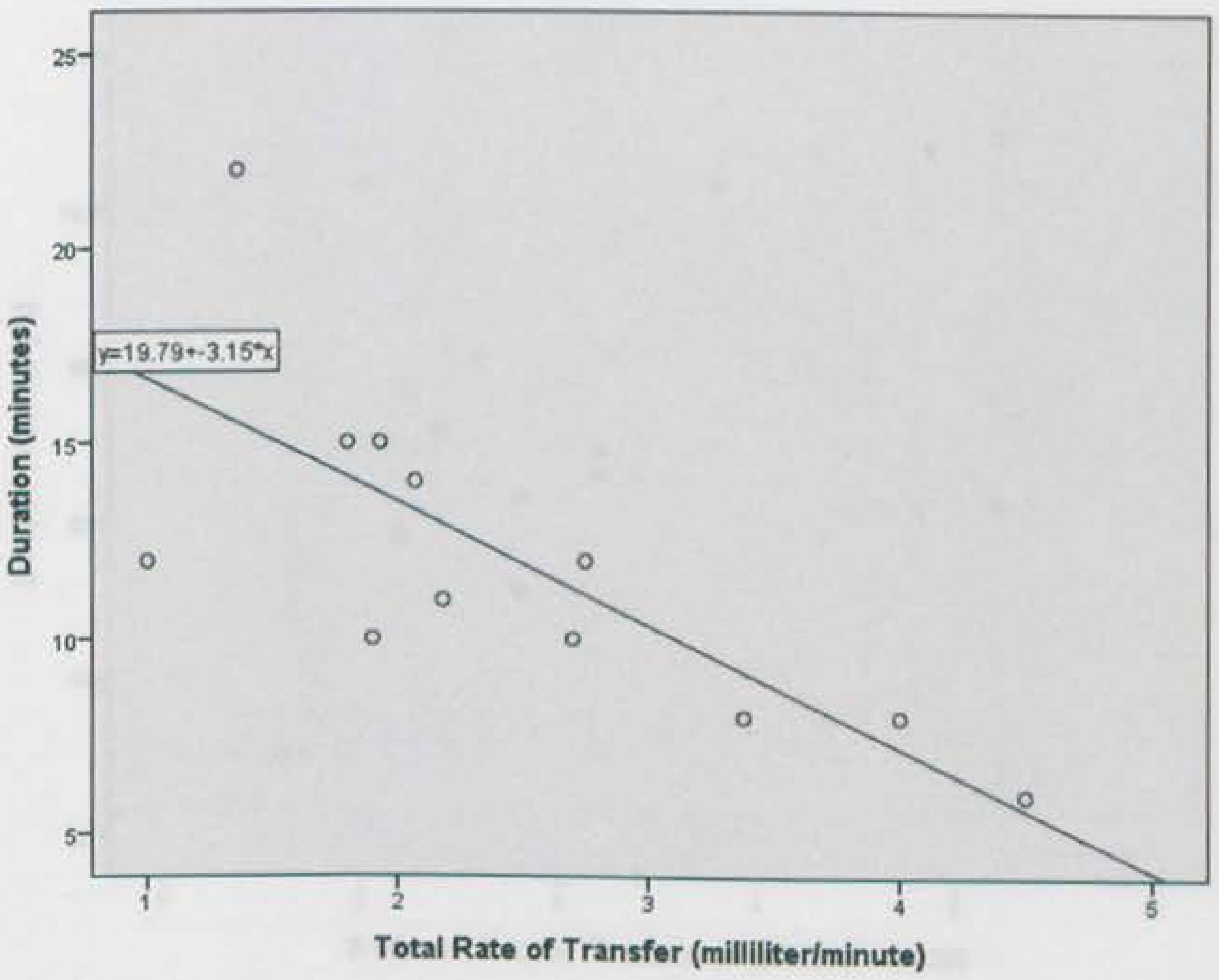
SLOW-FLOW



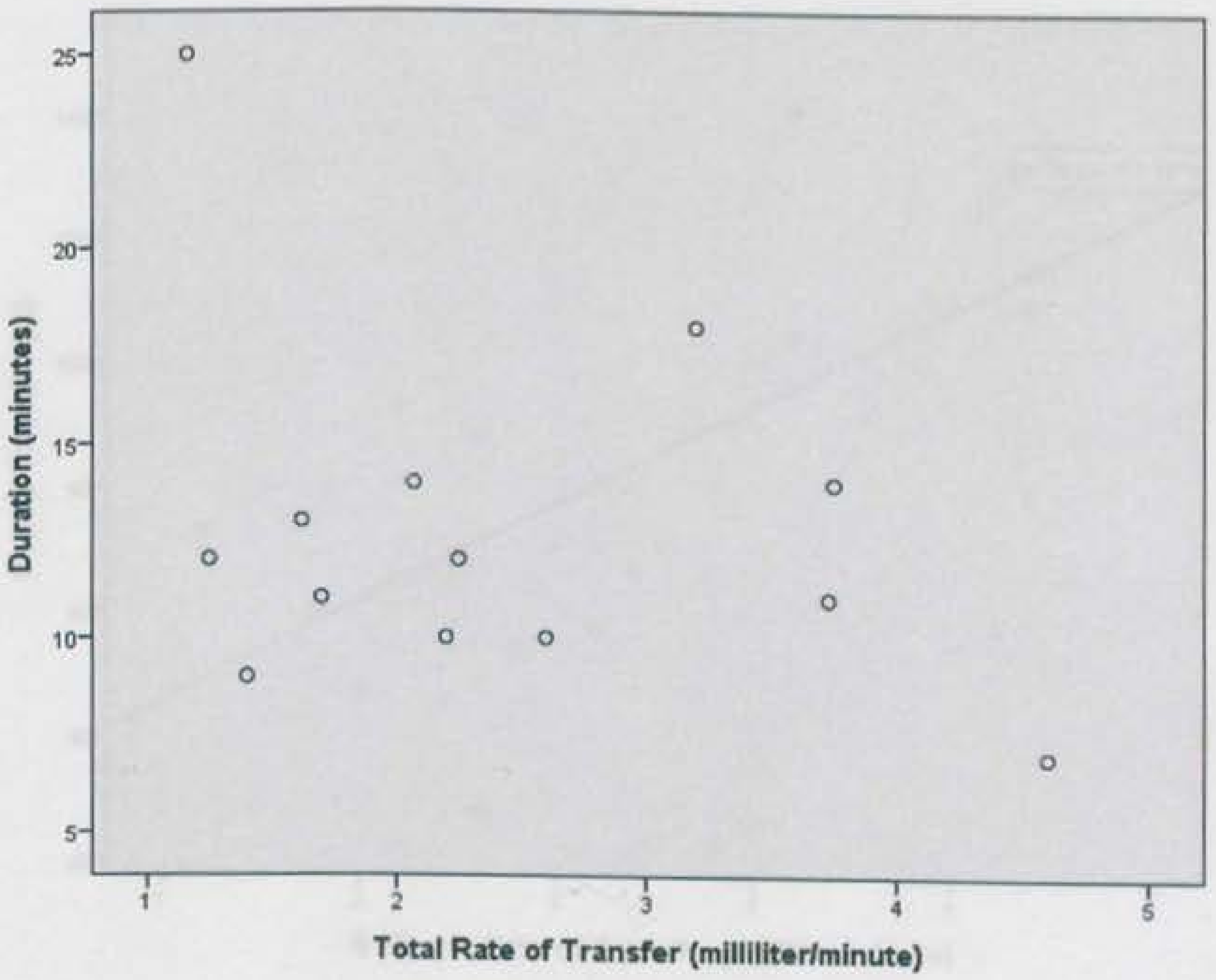
STANDARD-FLOW

APPENDIX 5.12. *Continued*

SLOW-FLOW

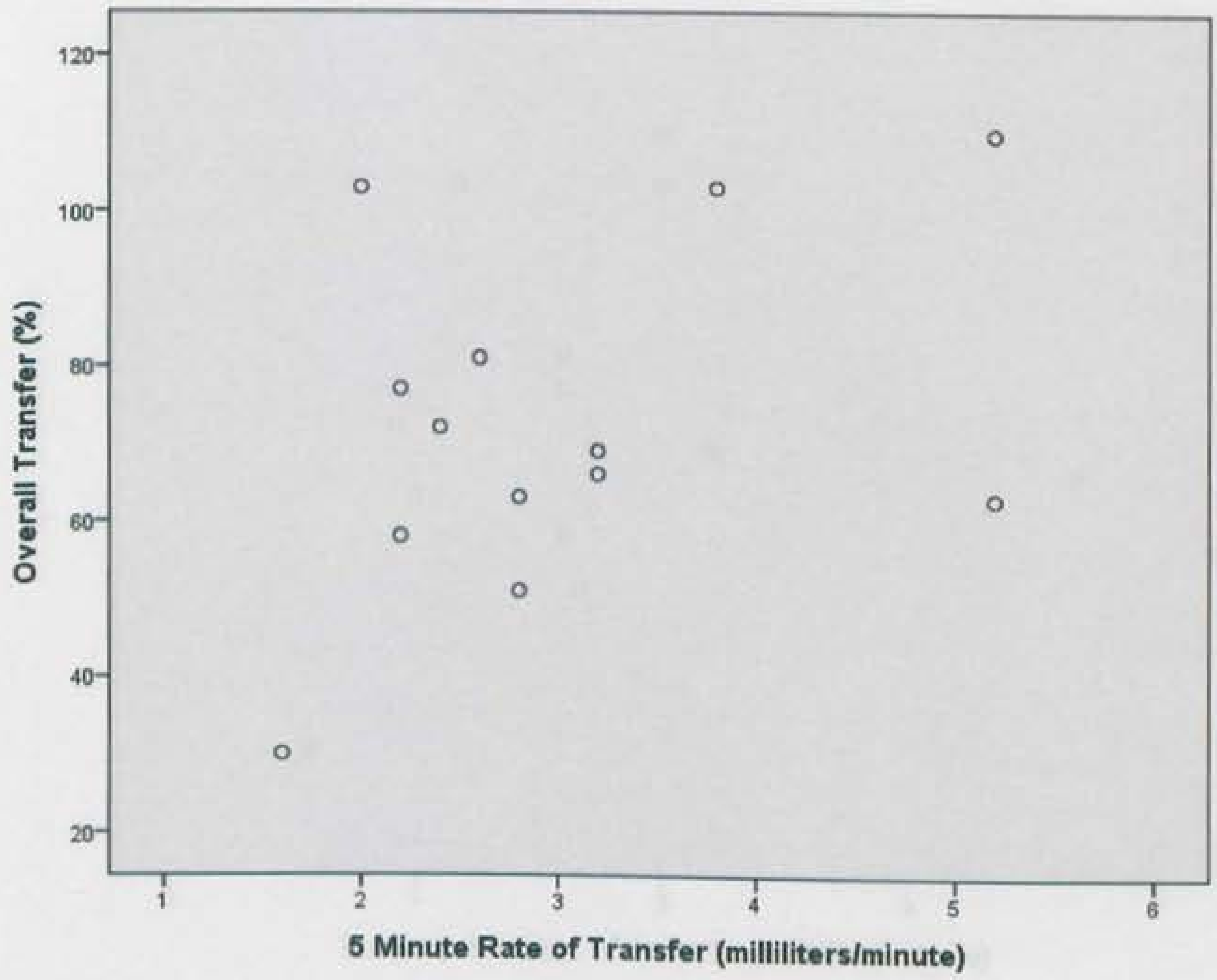


STANDARD-FLOW

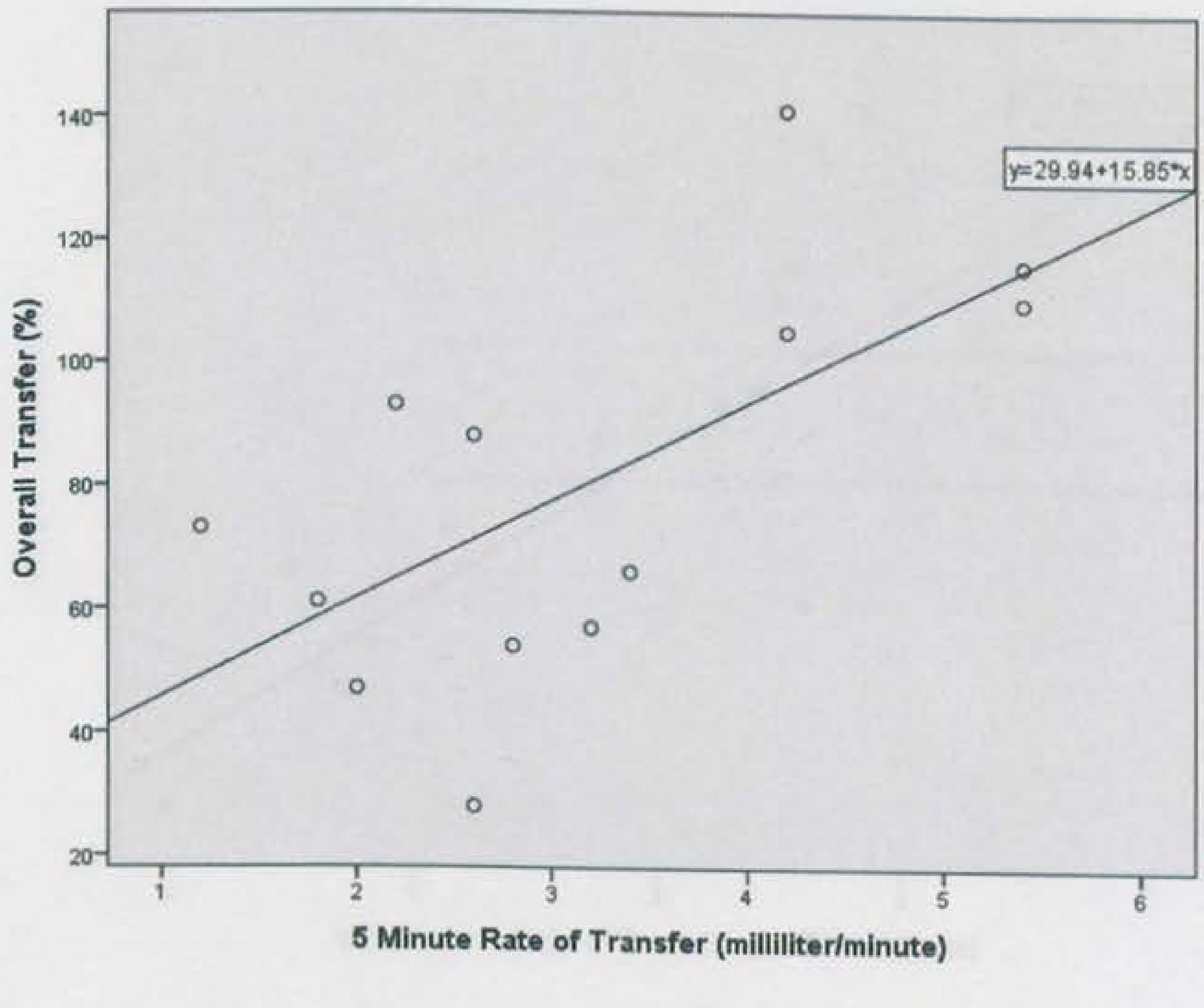


APPENDIX 5.13.
MILK INGESTION CORRELATIONS: OVERALL TRANSFER

SLOW-FLOW

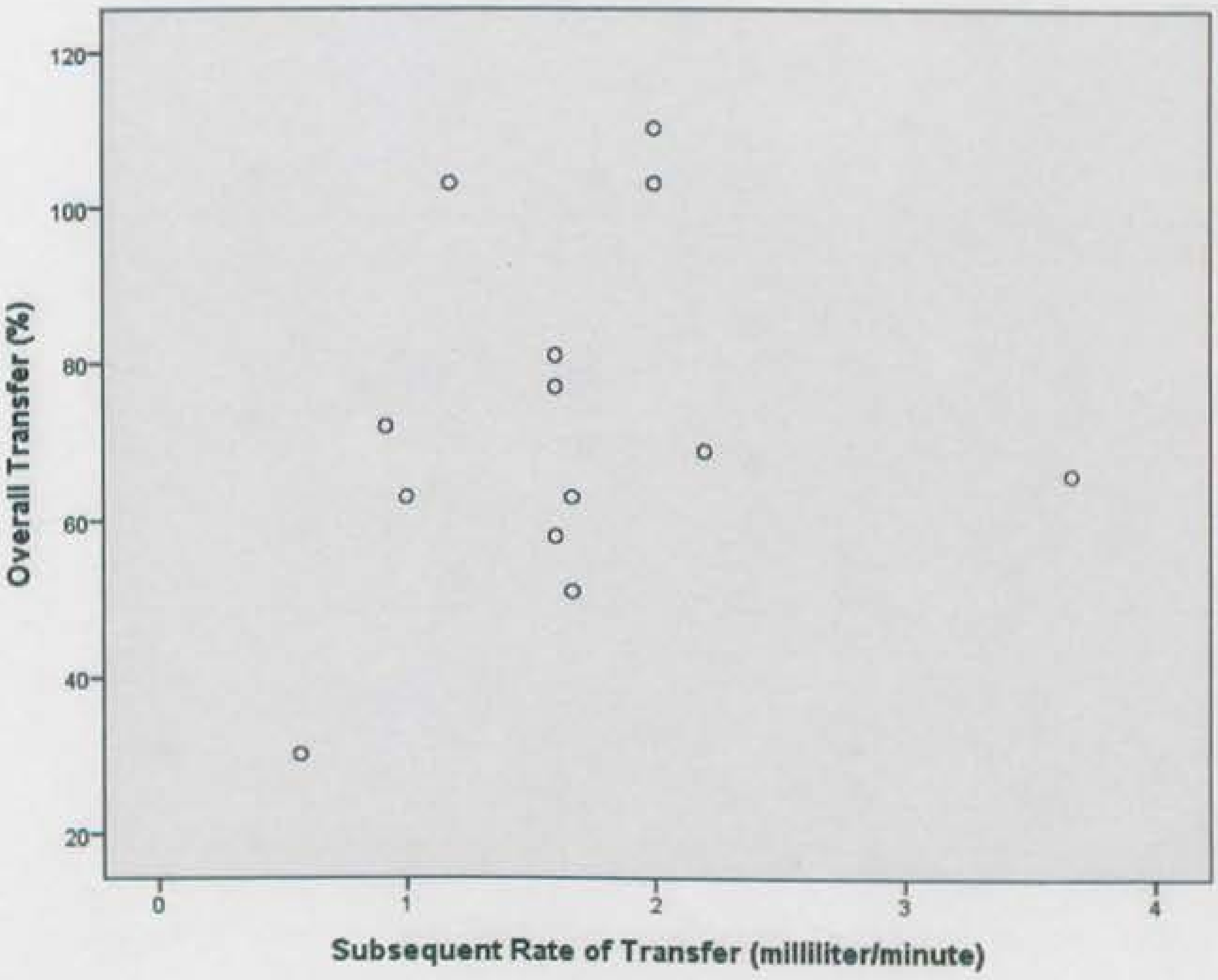


STANDARD-FLOW

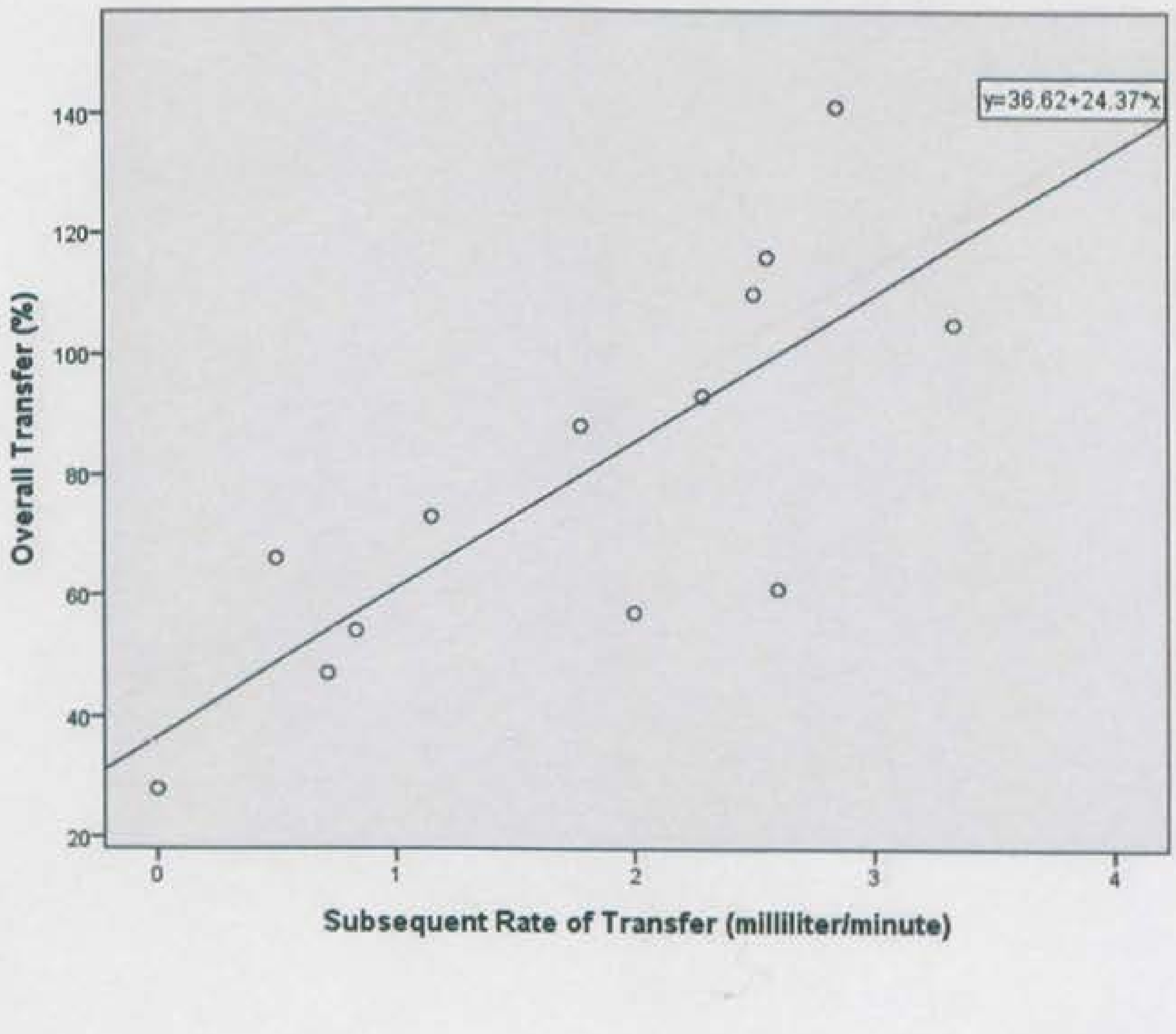


APPENDIX 5.13. *Continued*

SLOW-FLOW

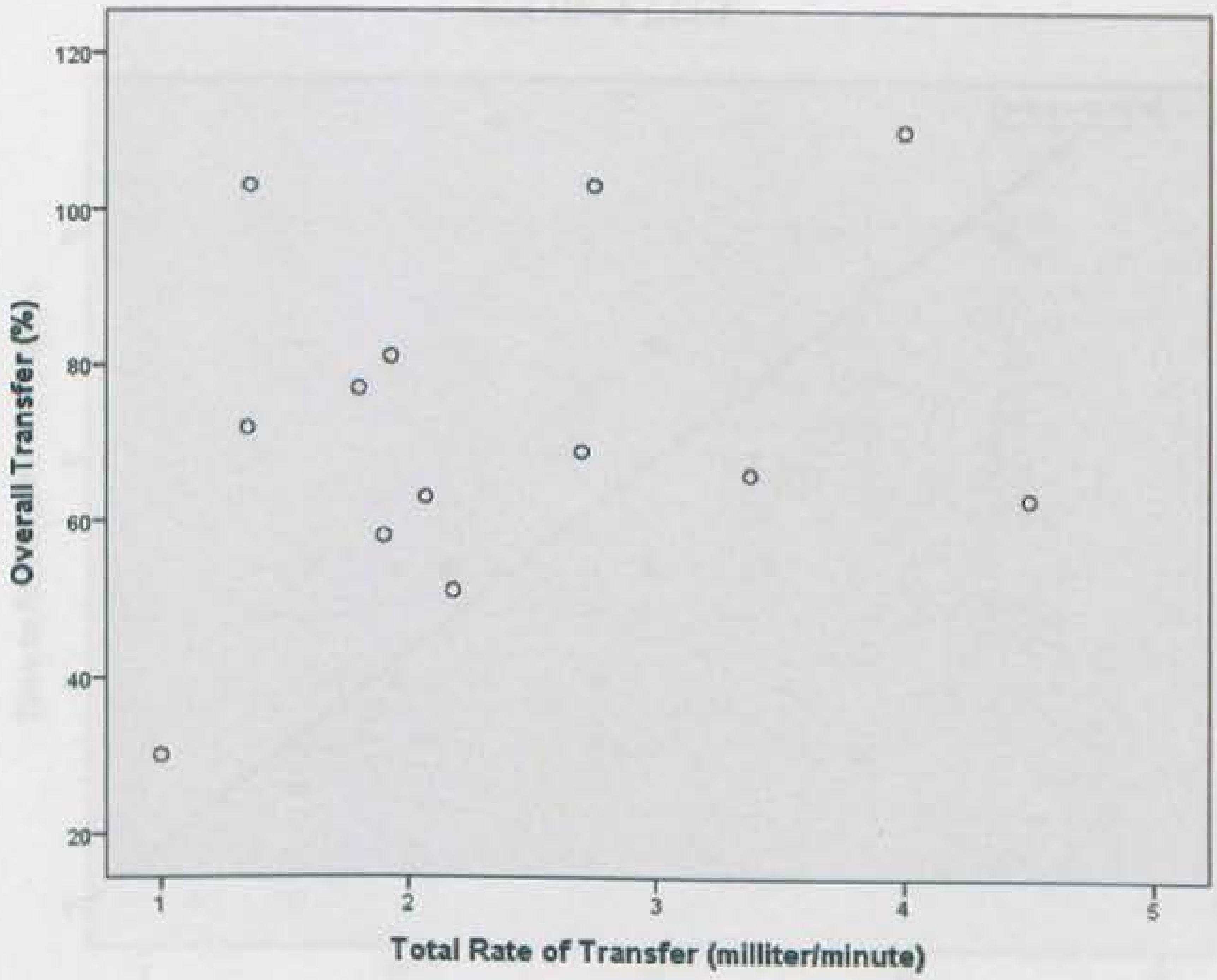


STANDARD-FLOW

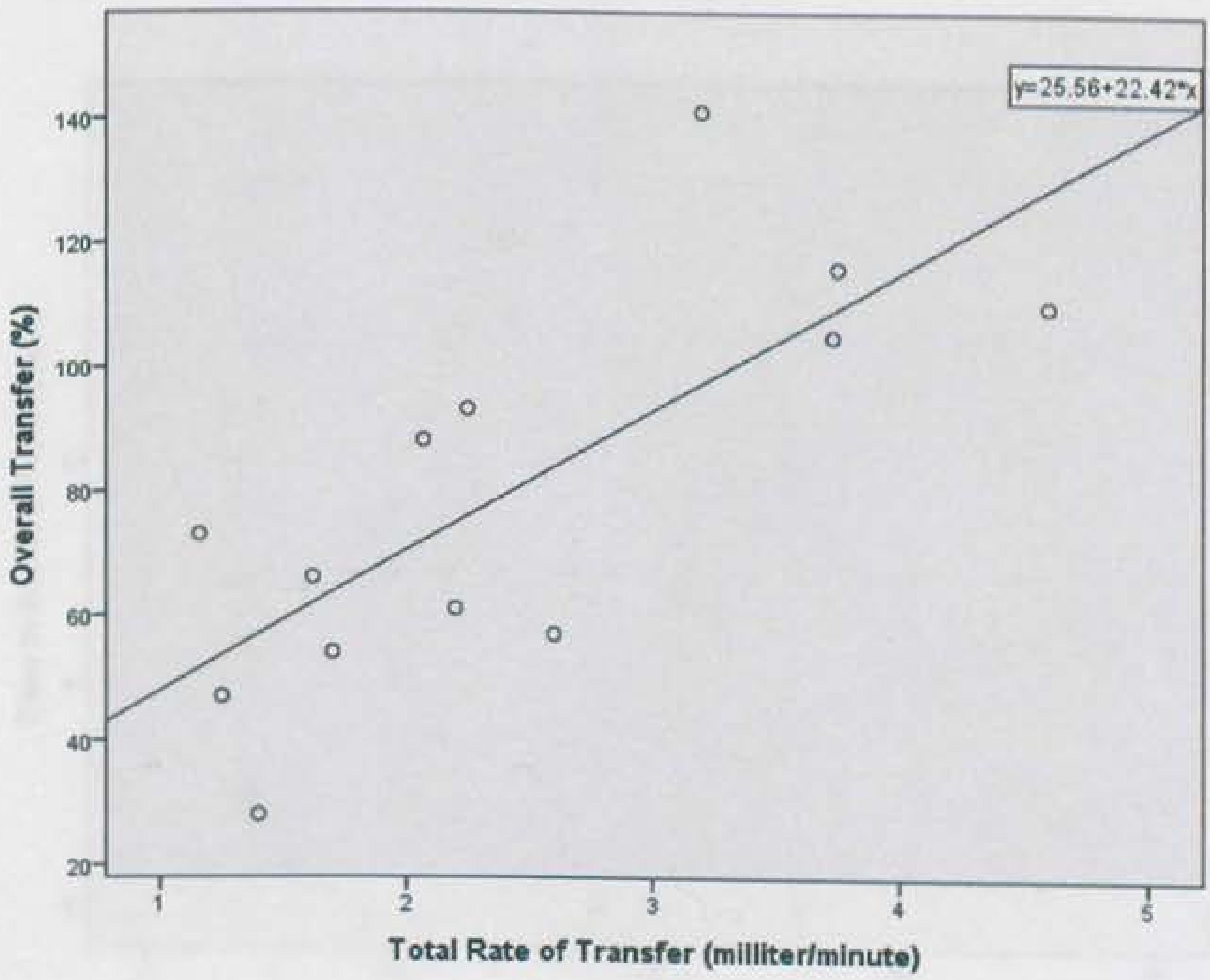


APPENDIX 5.13. *Continued*

SLOW-FLOW



STANDARD-FLOW

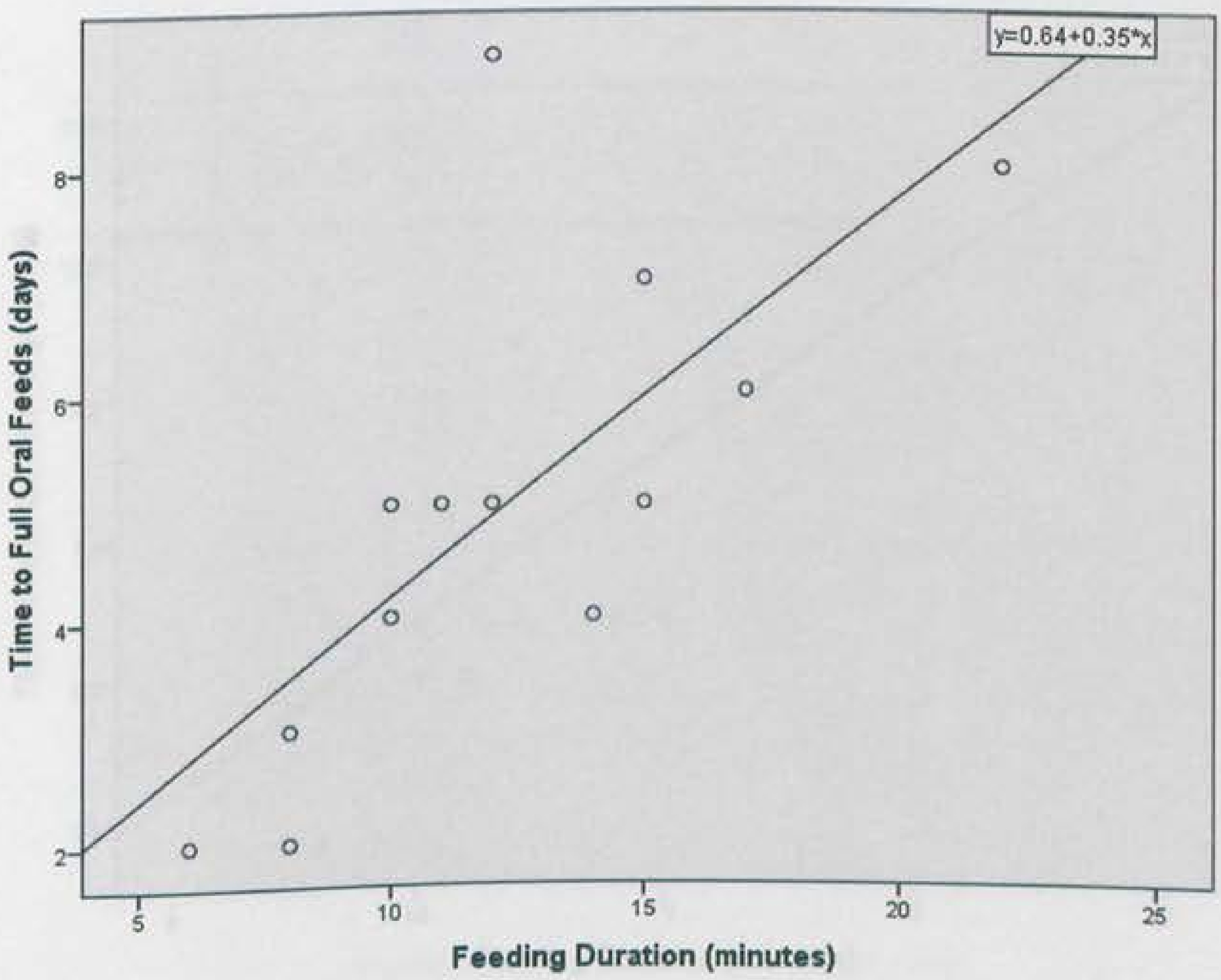


APPENDIX 5.14.

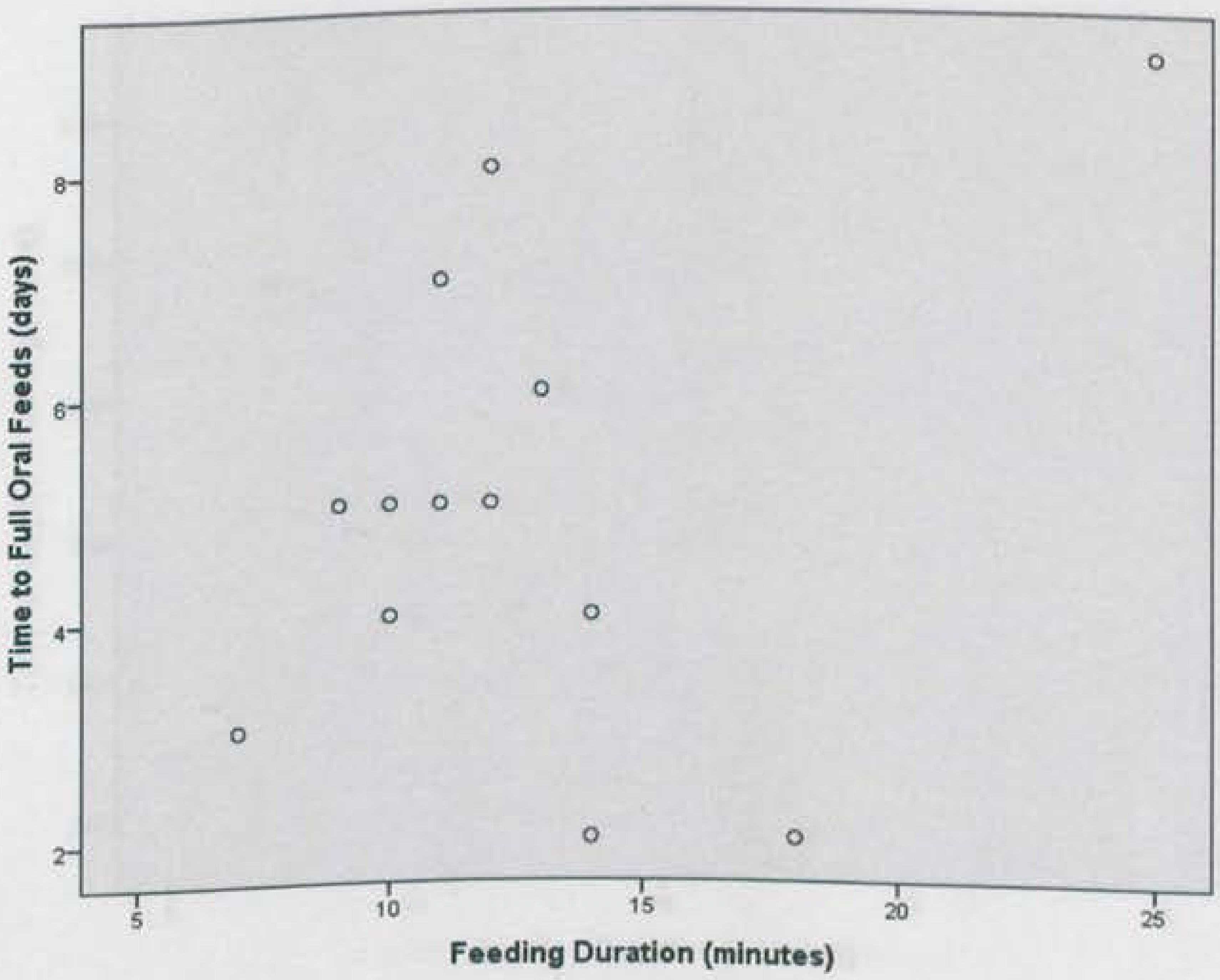
CLINICAL OUTCOME CORRELATIONS: MILK INGESTION

FEEDING DURATION

SLOW-FLOW



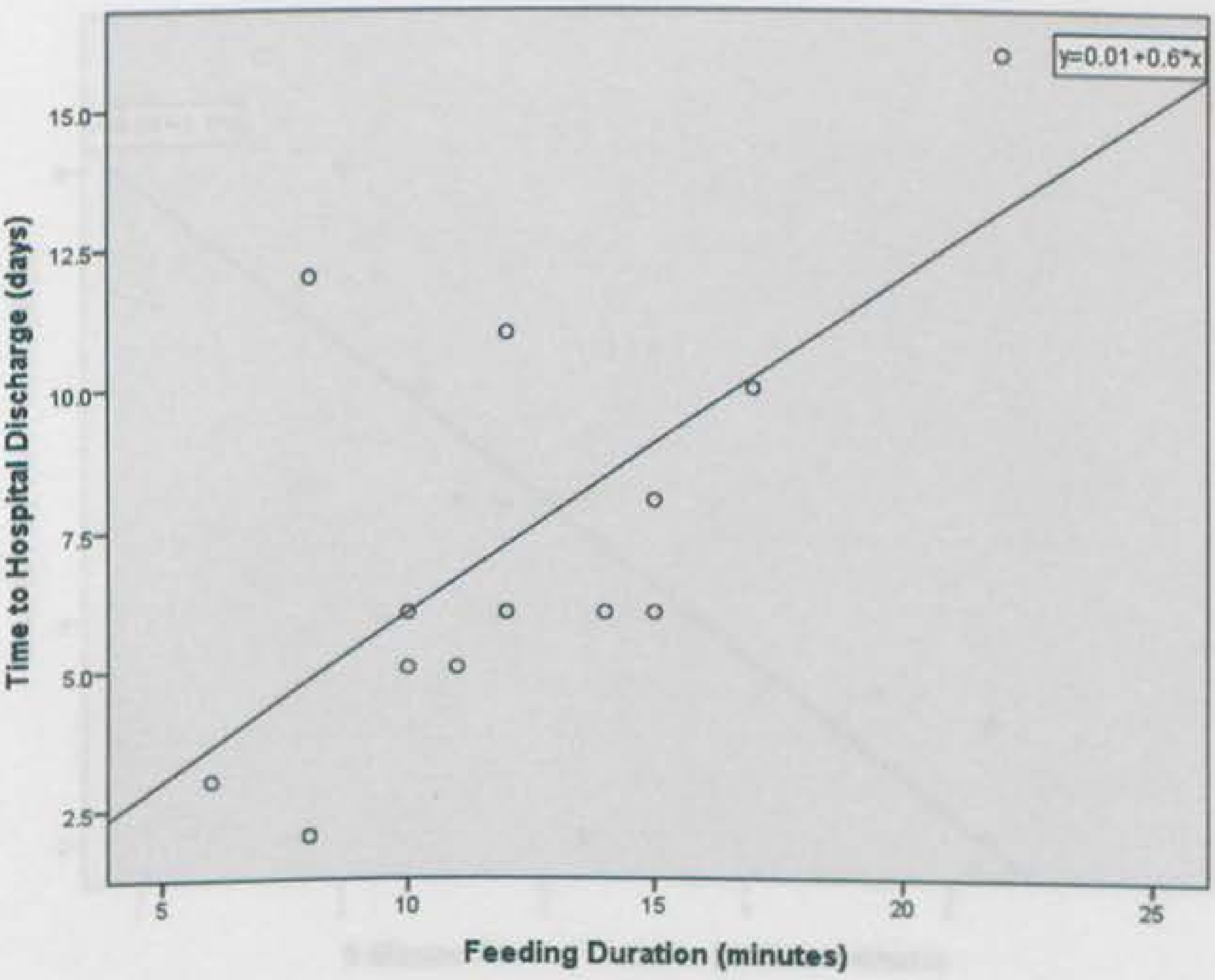
STANDARD-FLOW



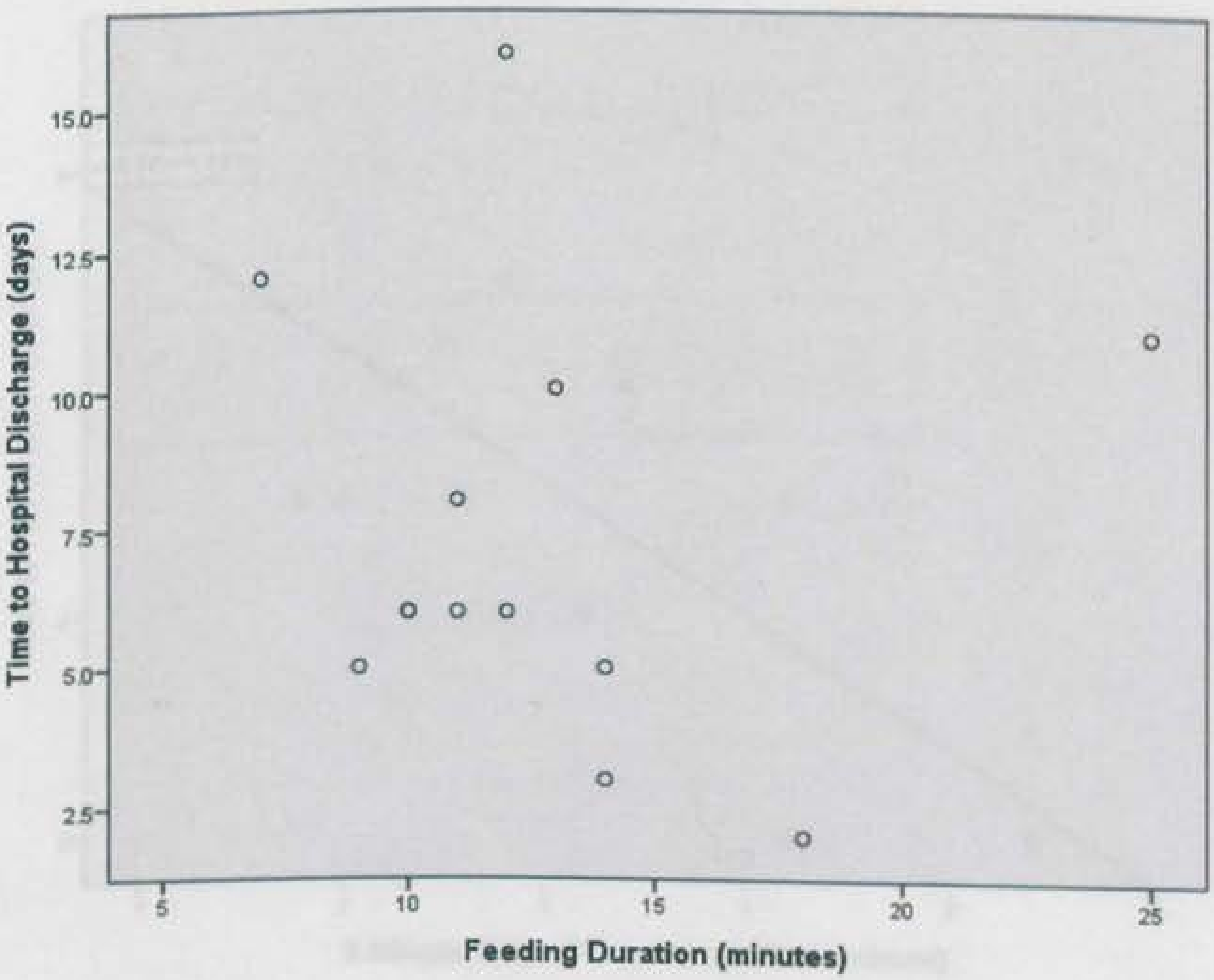
APPENDIX 5.14. *Continued*

FEEDING DURATION

SLOW-FLOW



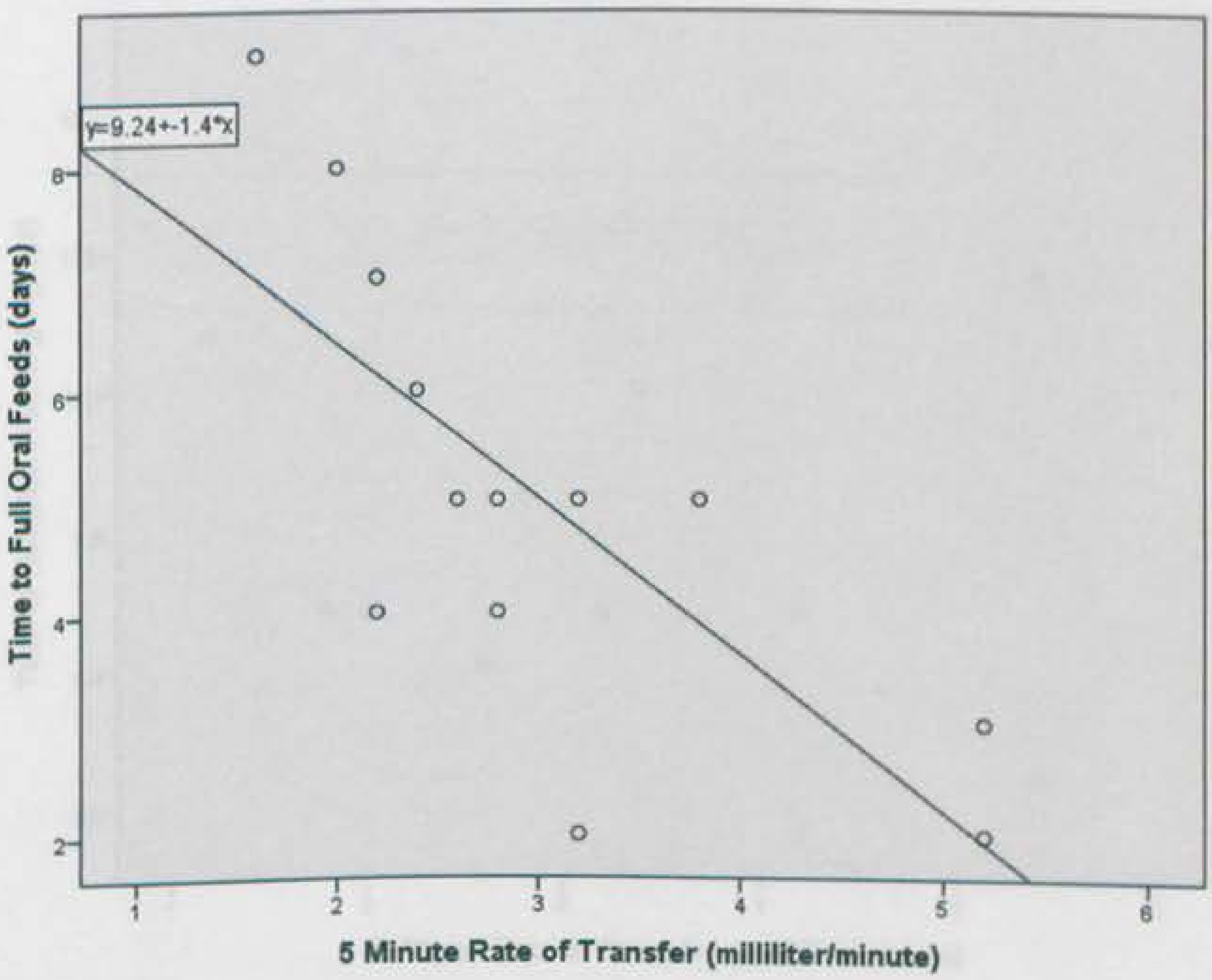
STANDARD-FLOW



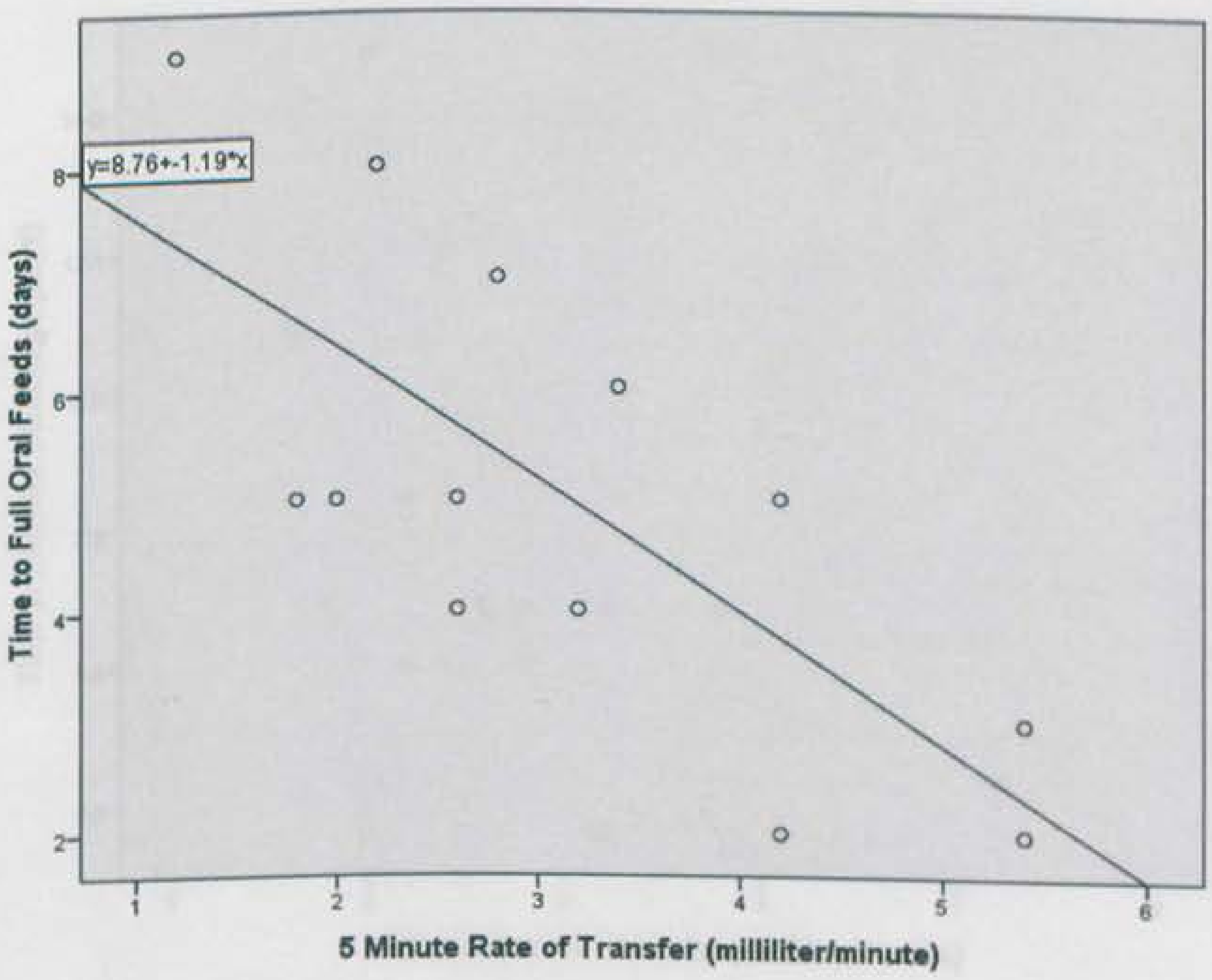
APPENDIX 5.14. *Continued*

5 MINUTE RATE OF TRANSFER

SLOW-FLOW



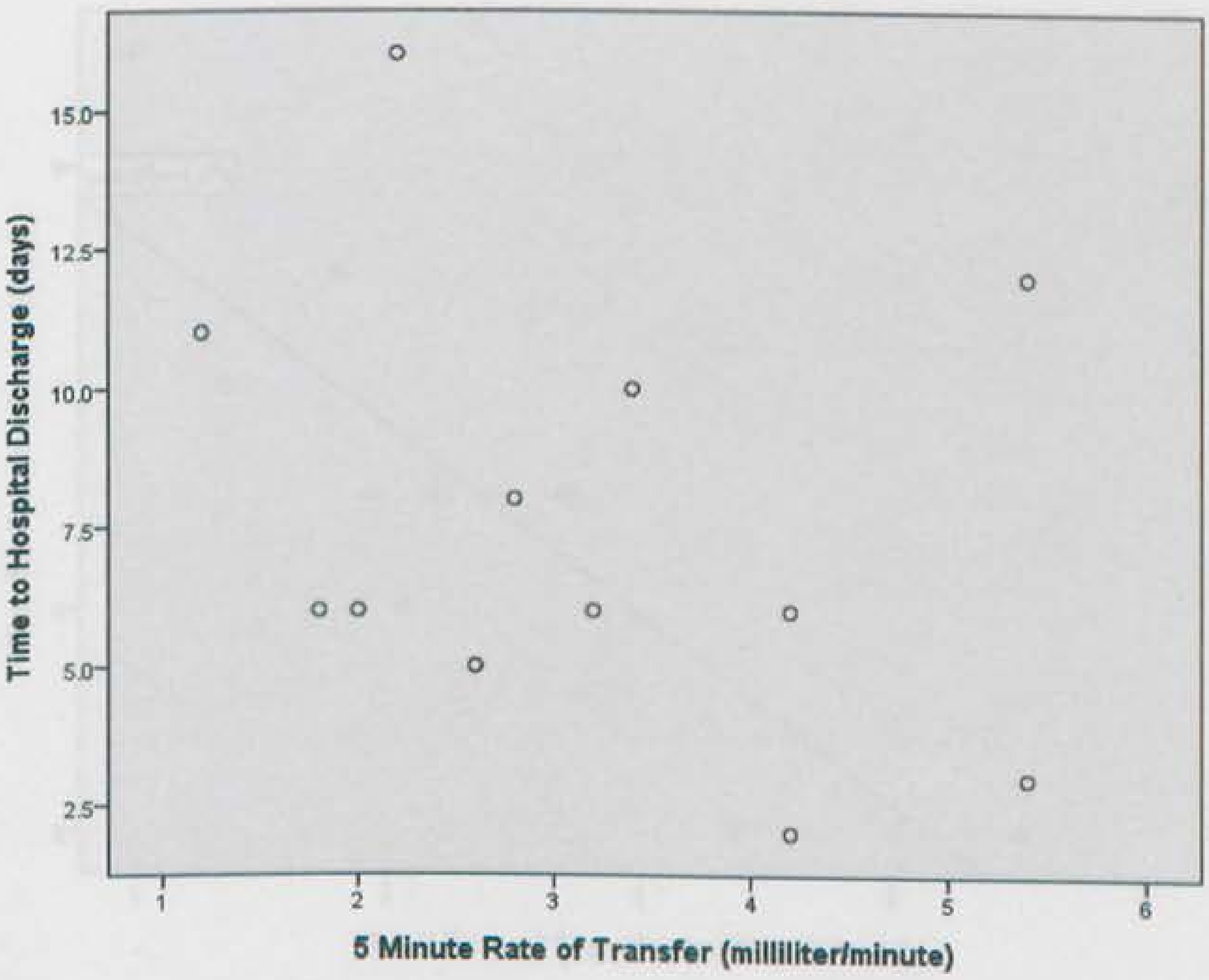
STANDARD-FLOW



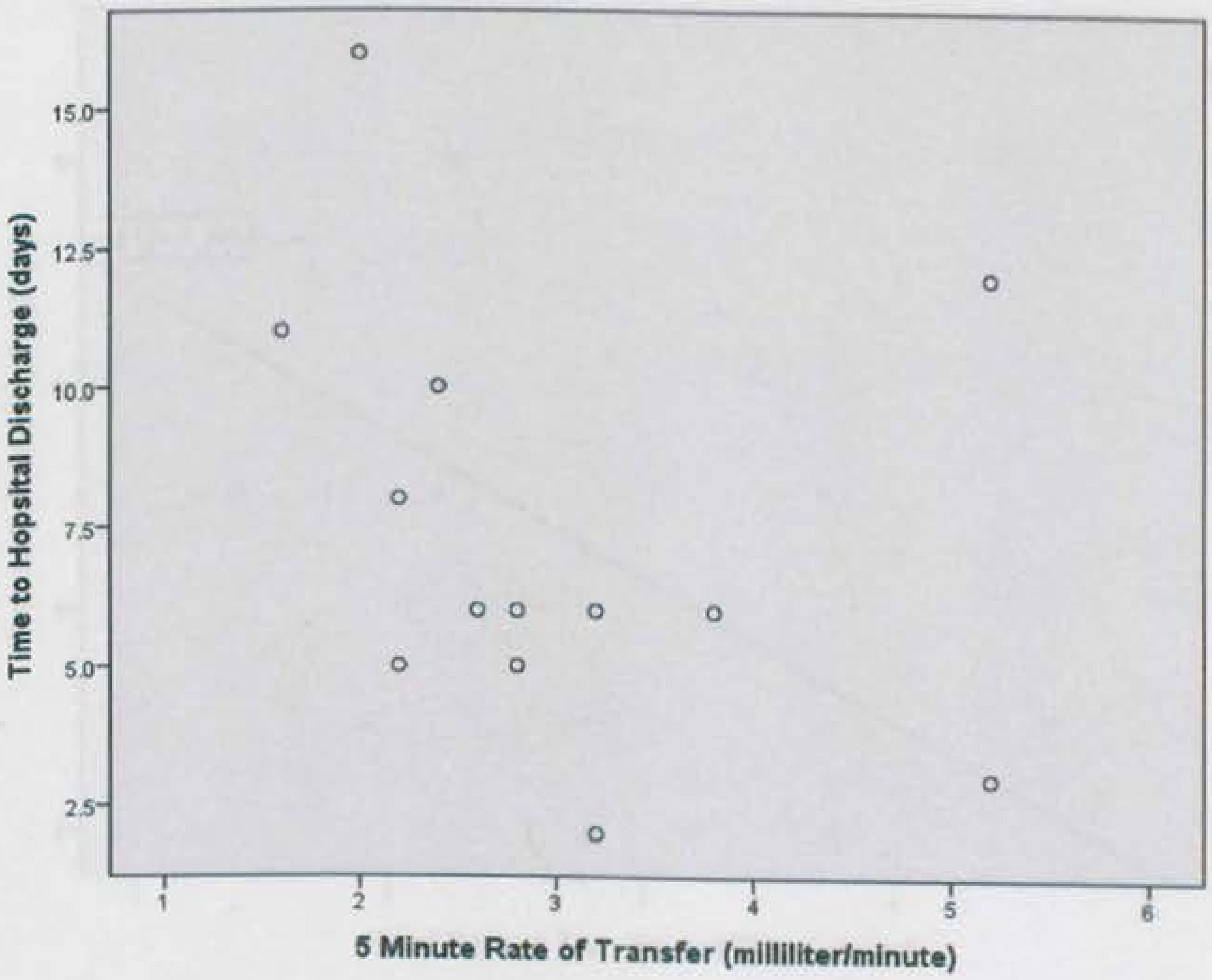
APPENDIX 5.14. *Continued*

5 MINUTE RATE OF TRANSFER

SLOW-FLOW



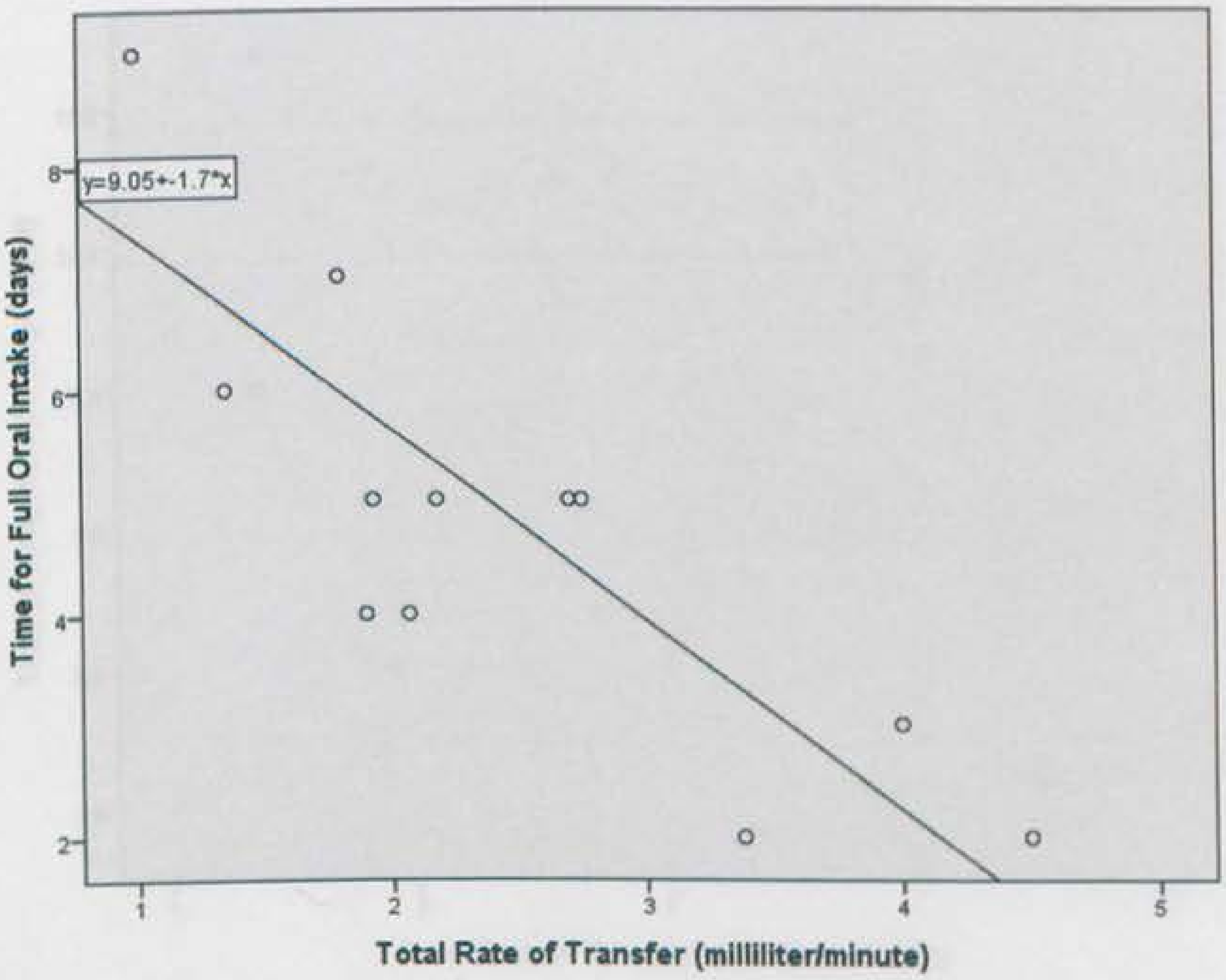
STANDARD-FLOW



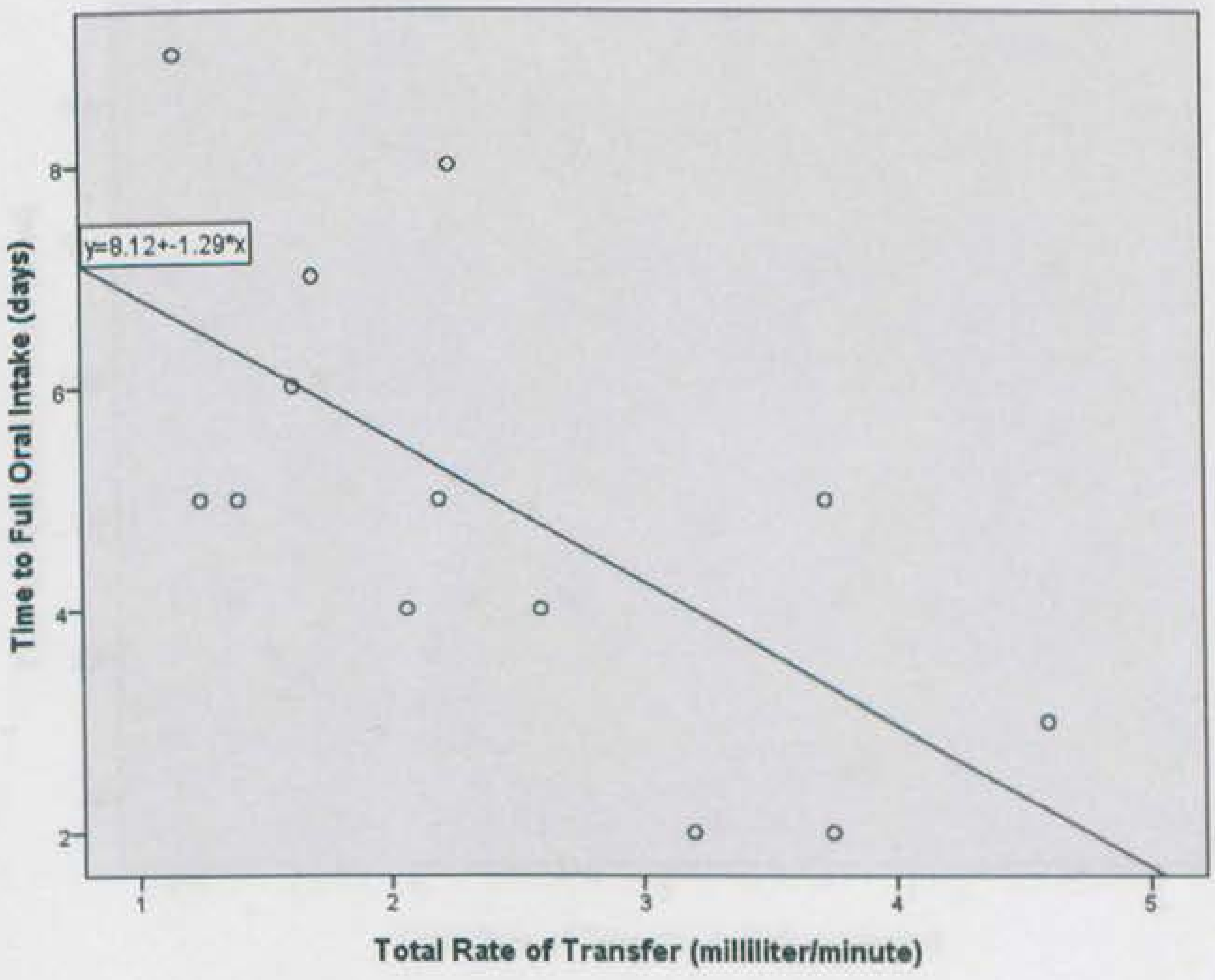
APPENDIX 5.14. *Continued*

TOTAL RATE OF TRANSFER

SLOW-FLOW



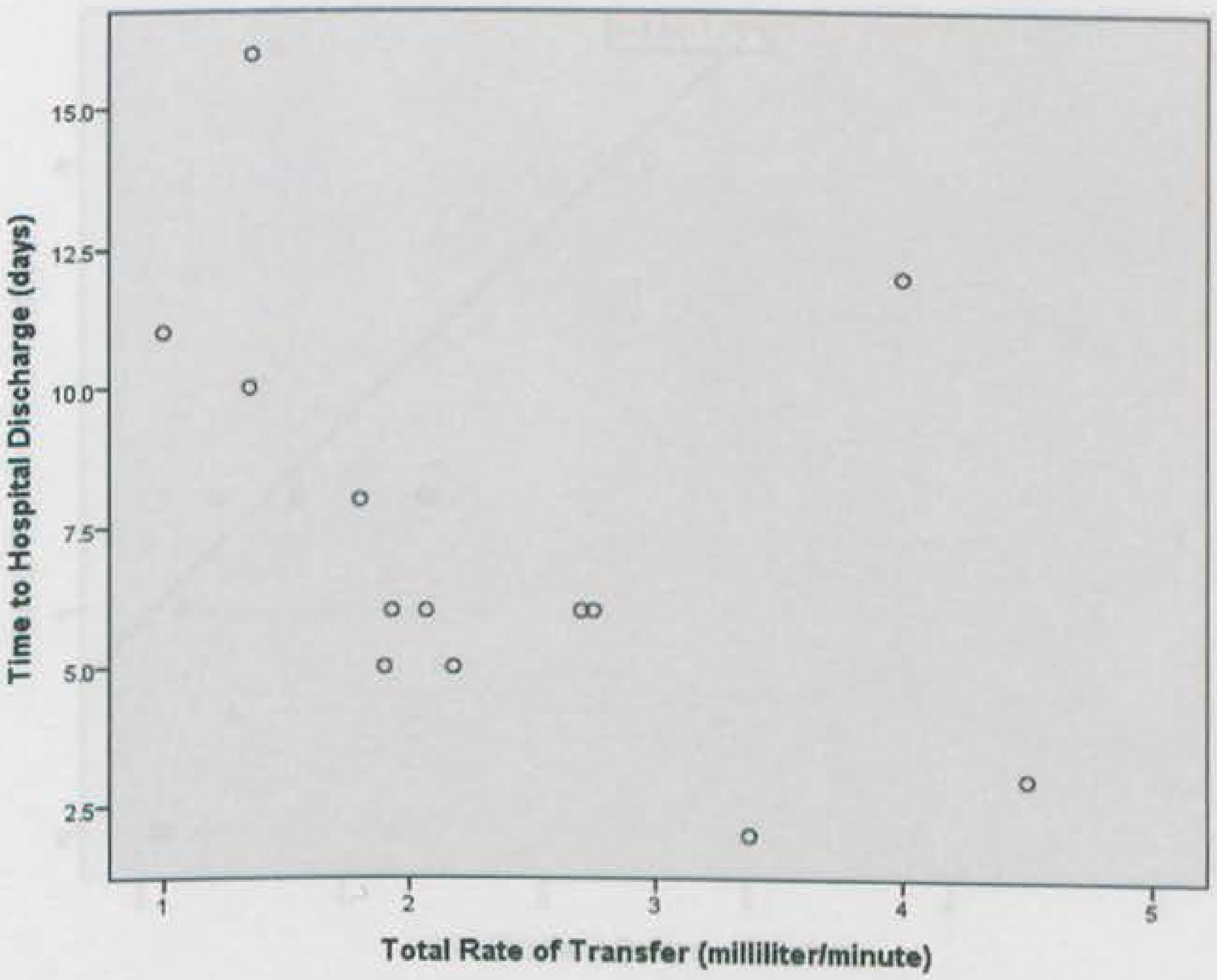
STANDARD-FLOW



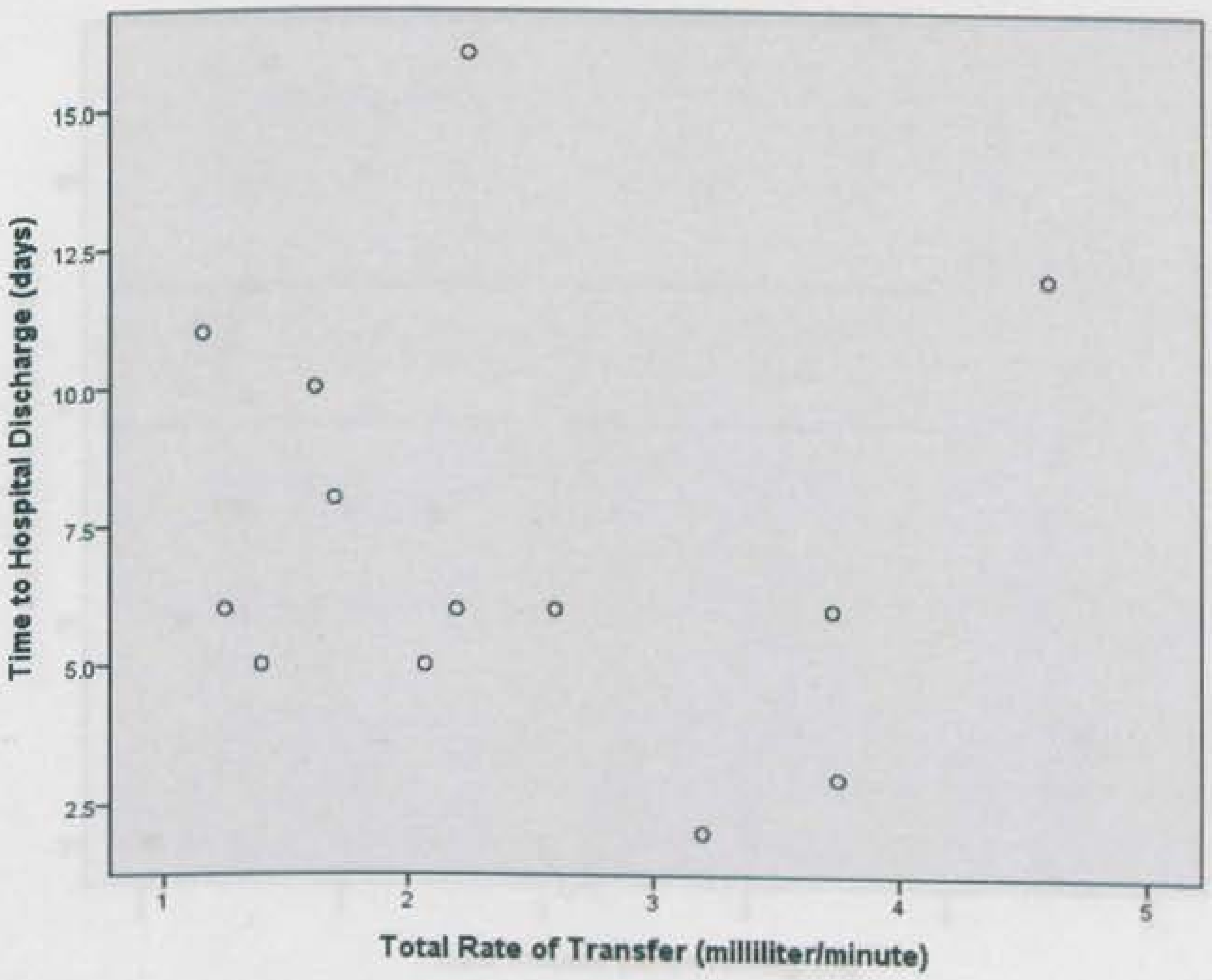
APPENDIX 5.14. *Continued*

TOTAL RATE OF TRANSFER

SLOW-FLOW



STANDARD-FLOW

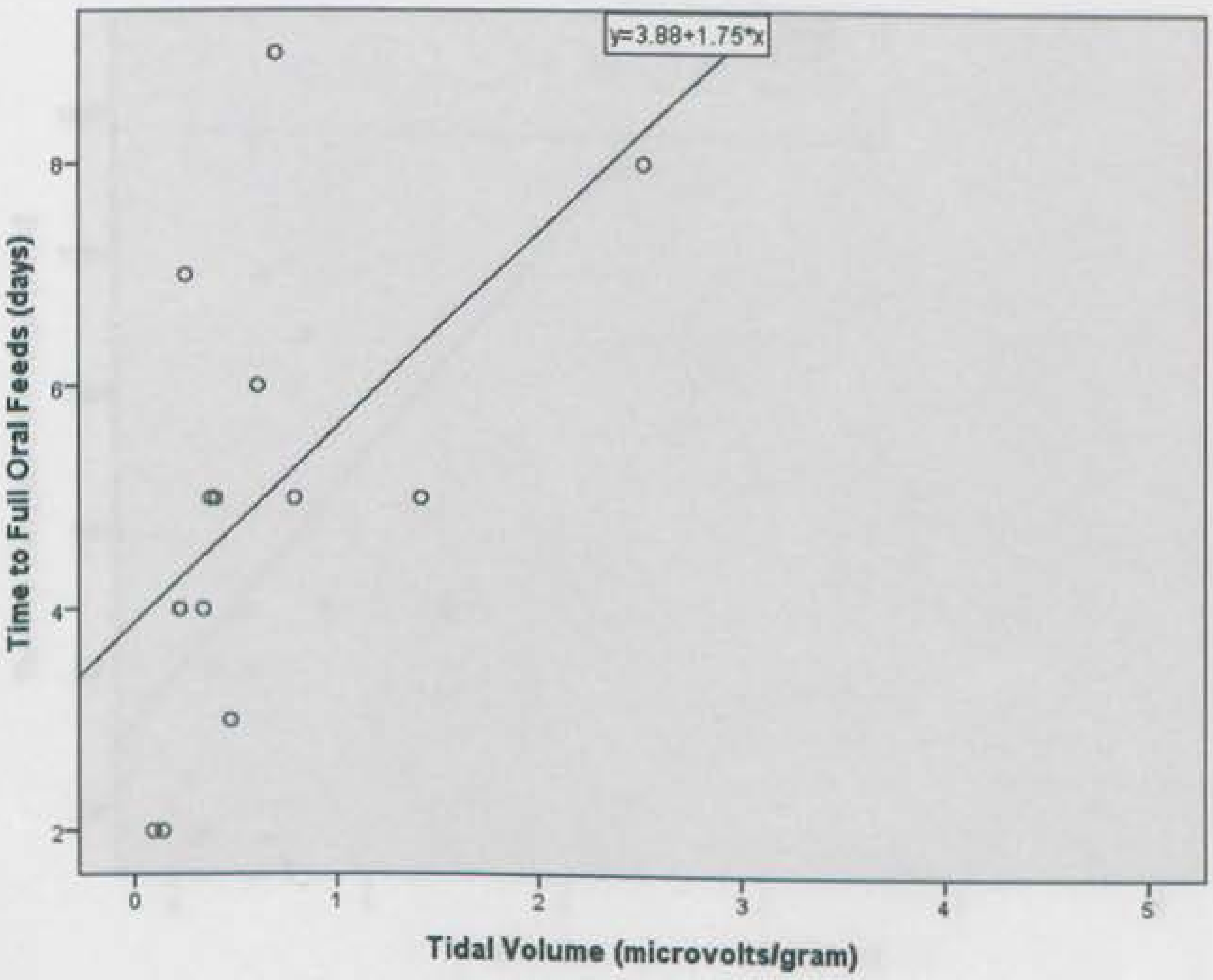


APPENDIX 5.15.

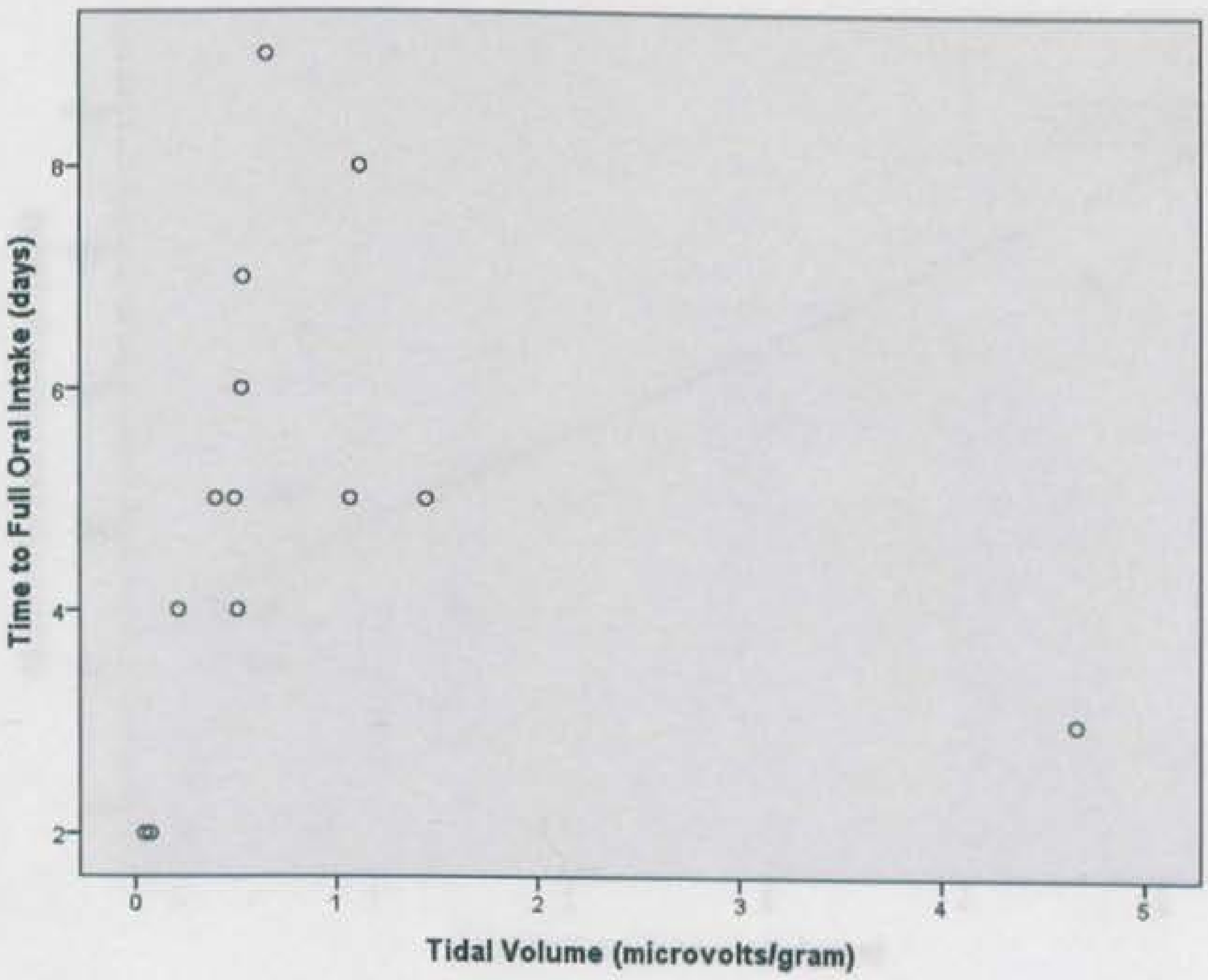
CLINICAL OUTCOME CORRELATIONS: TIDAL VOLUME

INITIAL SUCK-BURST

SLOW-FLOW



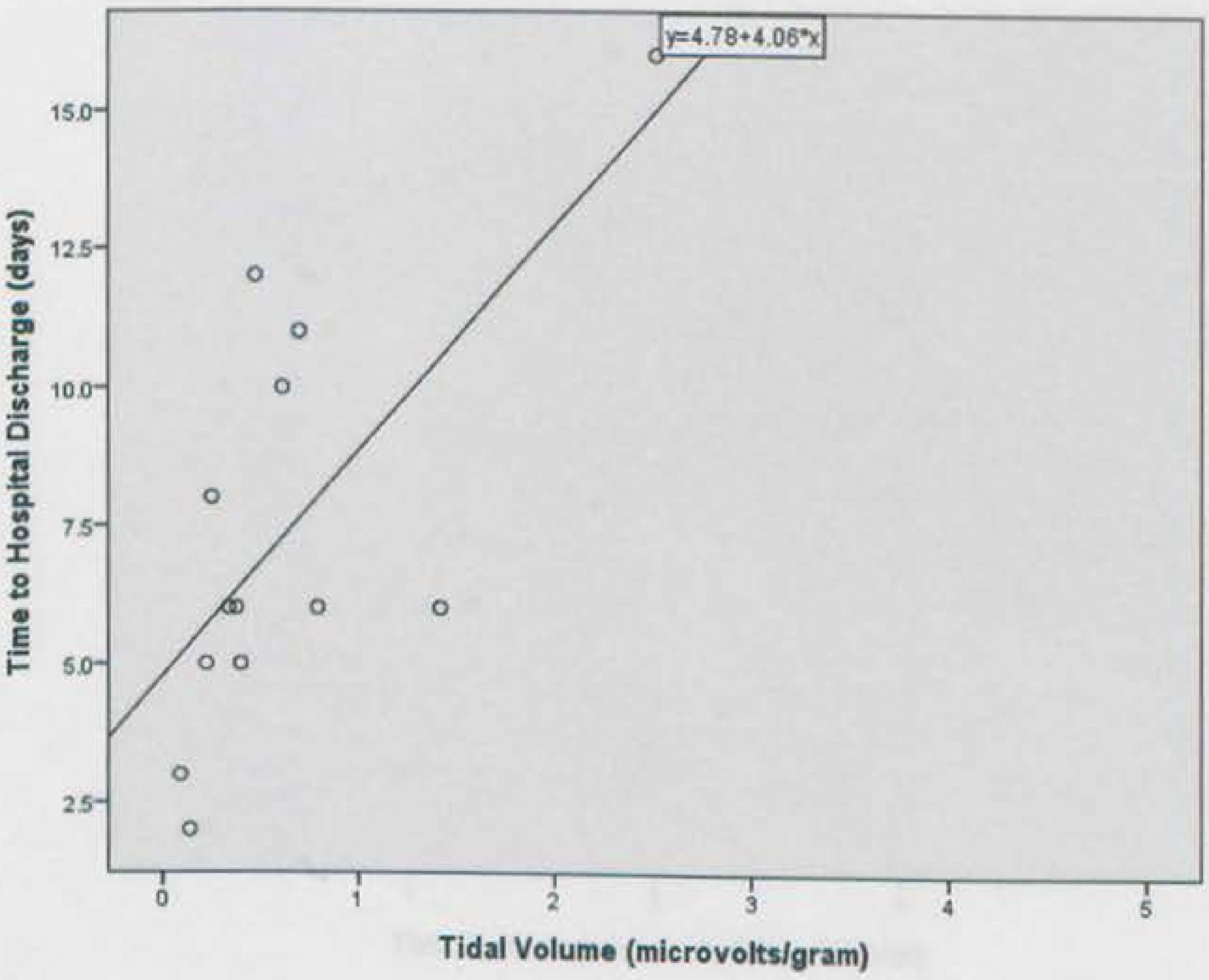
STANDARD-FLOW



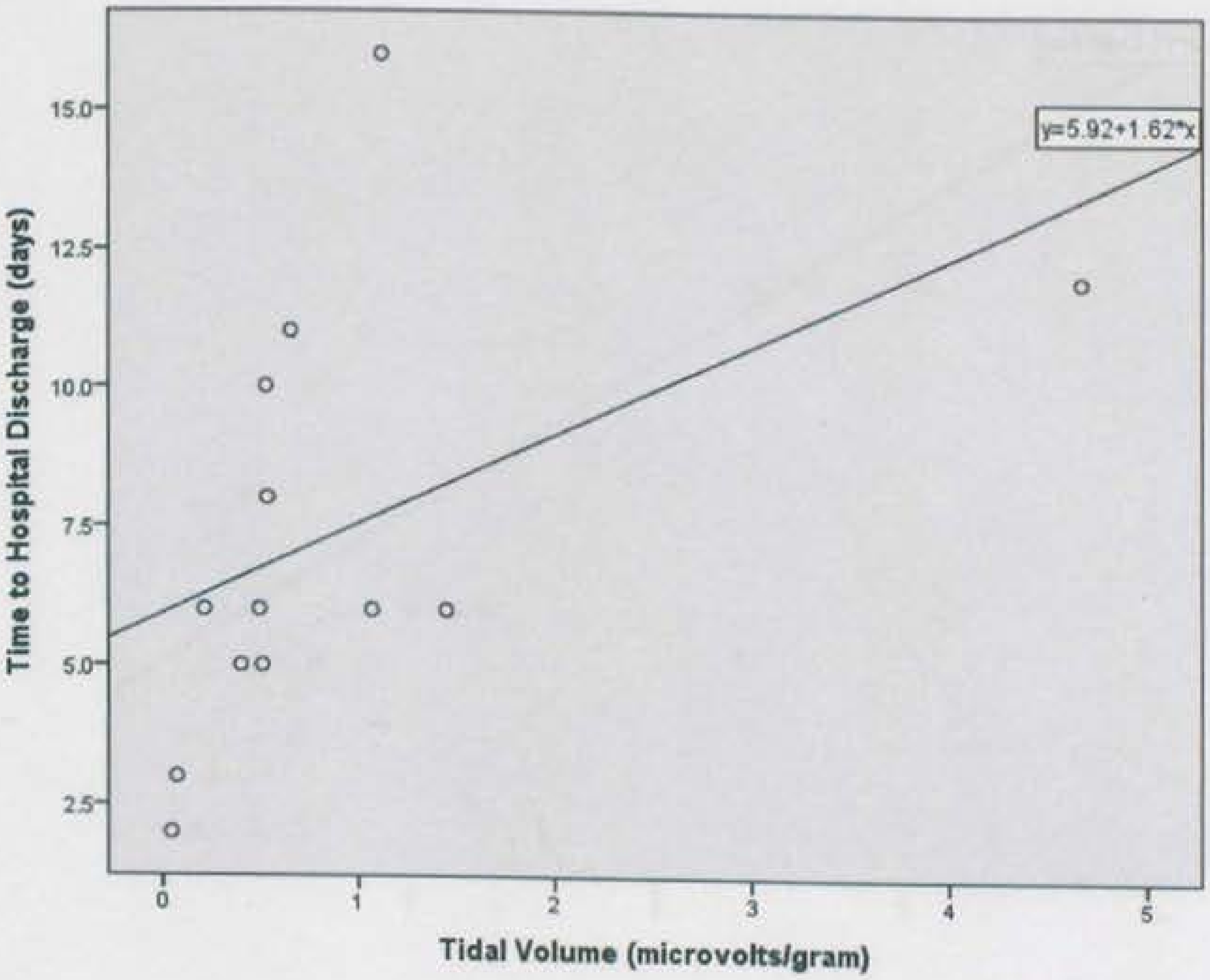
APPENDIX 5.15. *Continued*

INITIAL SUCK-BURST

SLOW-FLOW



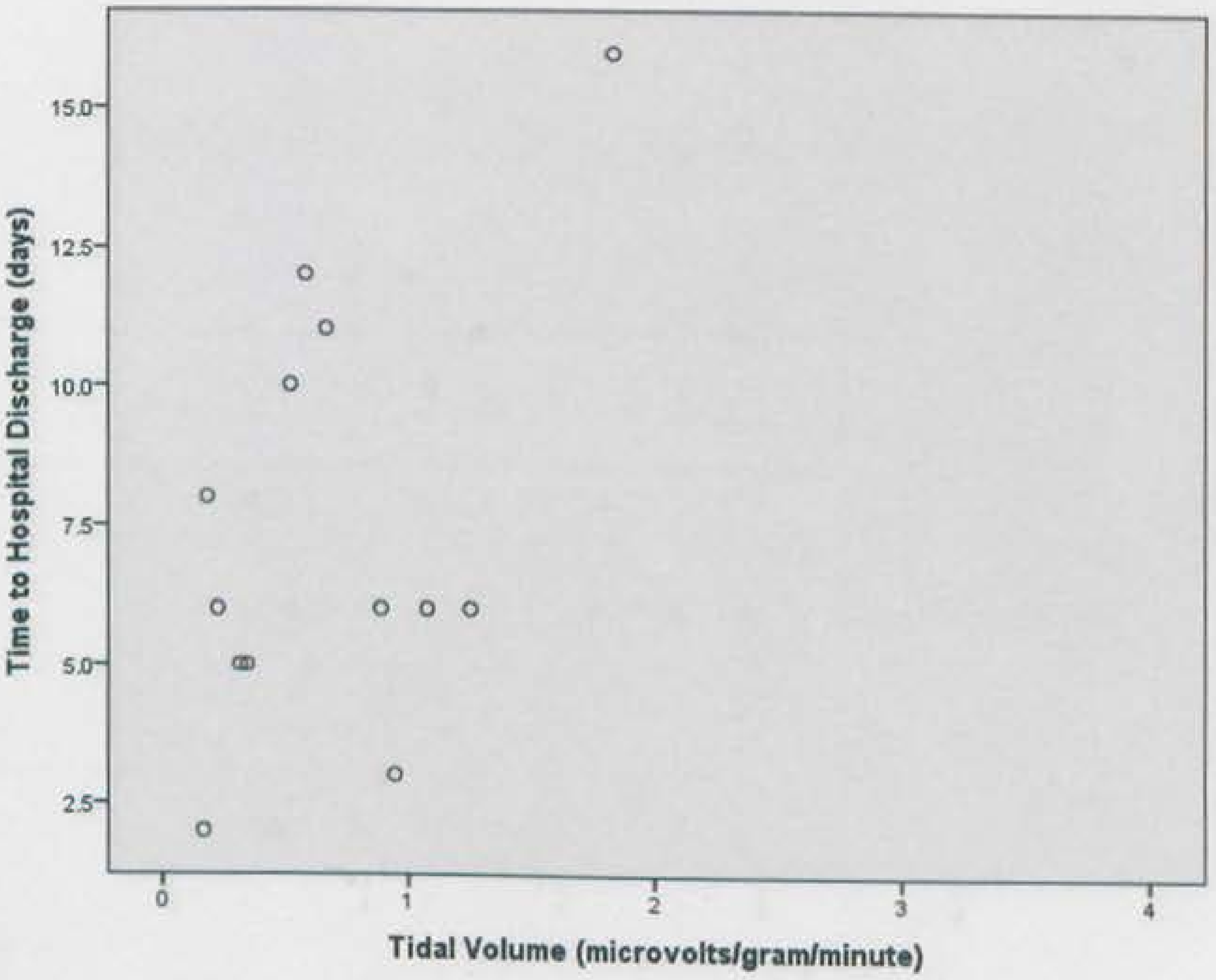
STANDARD-FLOW



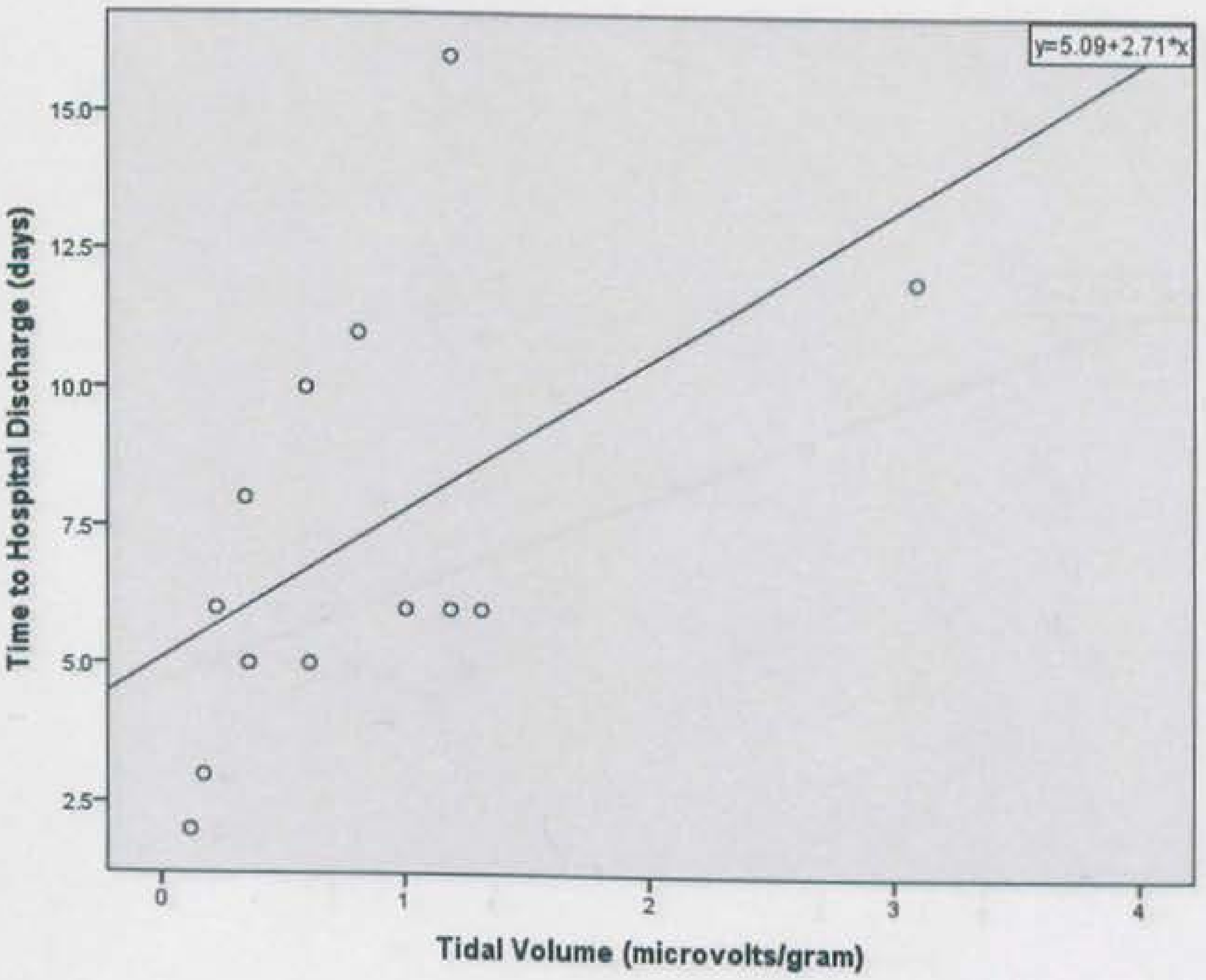
APPENDIX 5.15. *Continued*

SUBSEQUENT SUCK-BURST

SLOW-FLOW



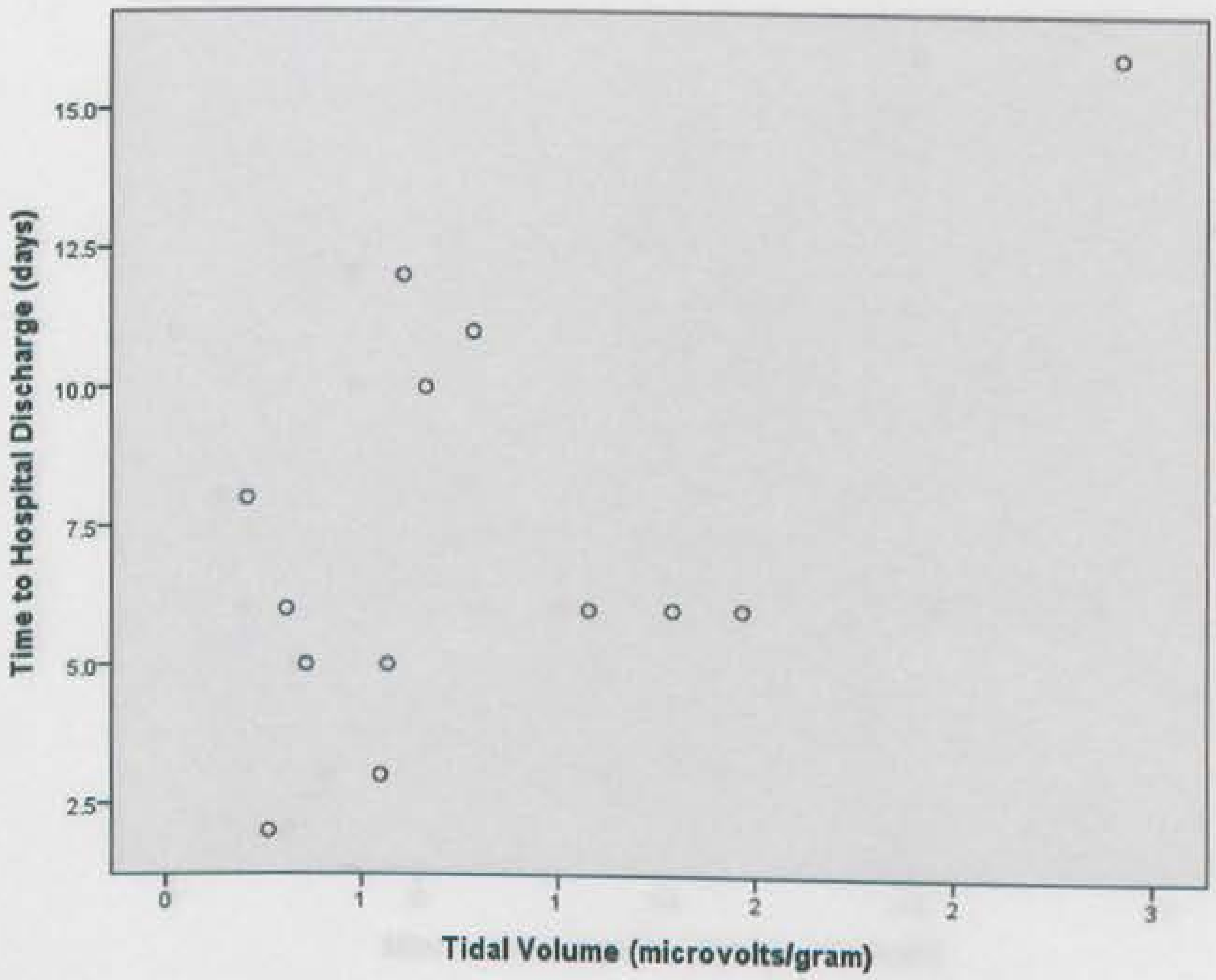
STANDARD-FLOW



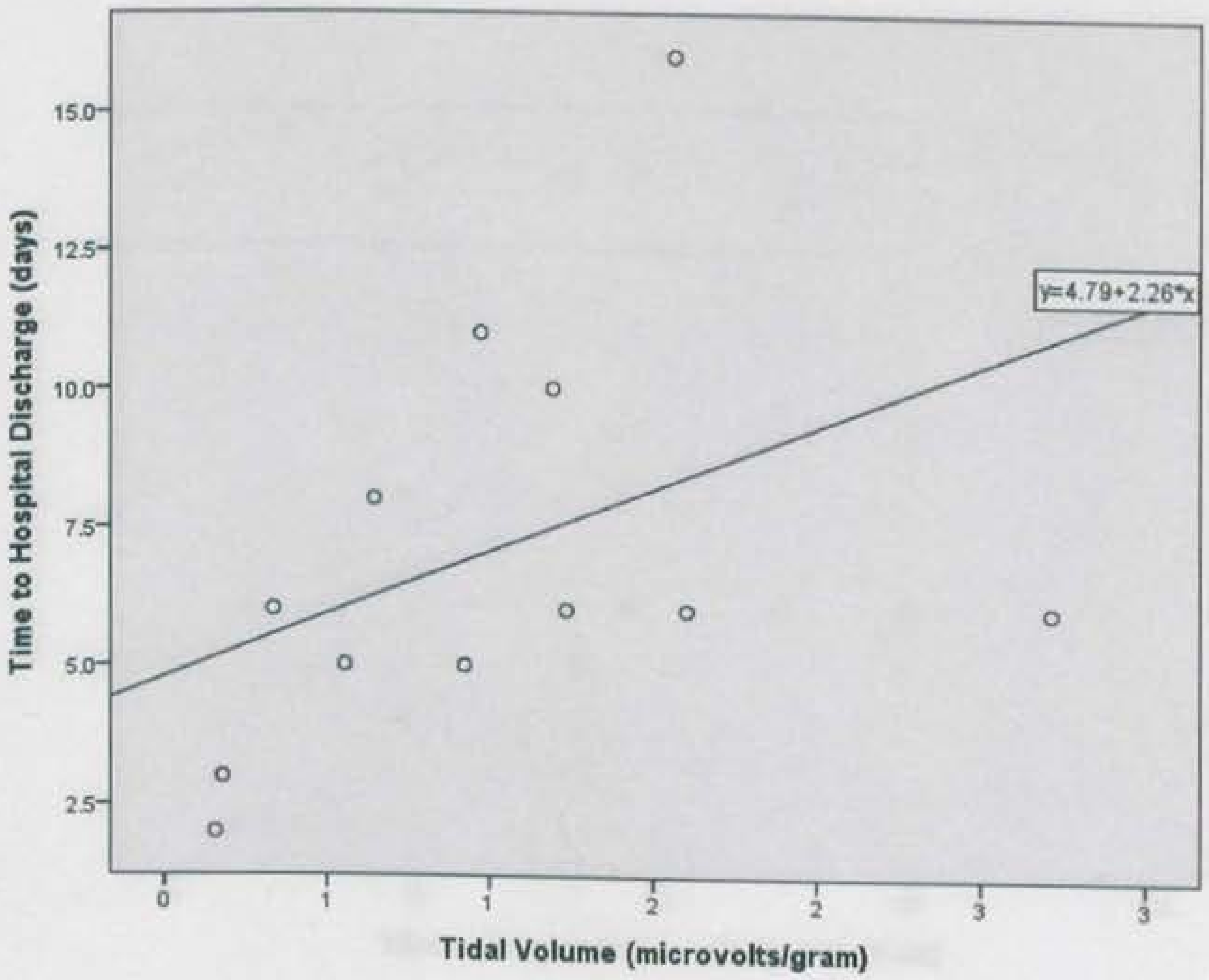
APPENDIX 5.15. *Continued*

SUCK-BURST BREAK

SLOW-FLOW



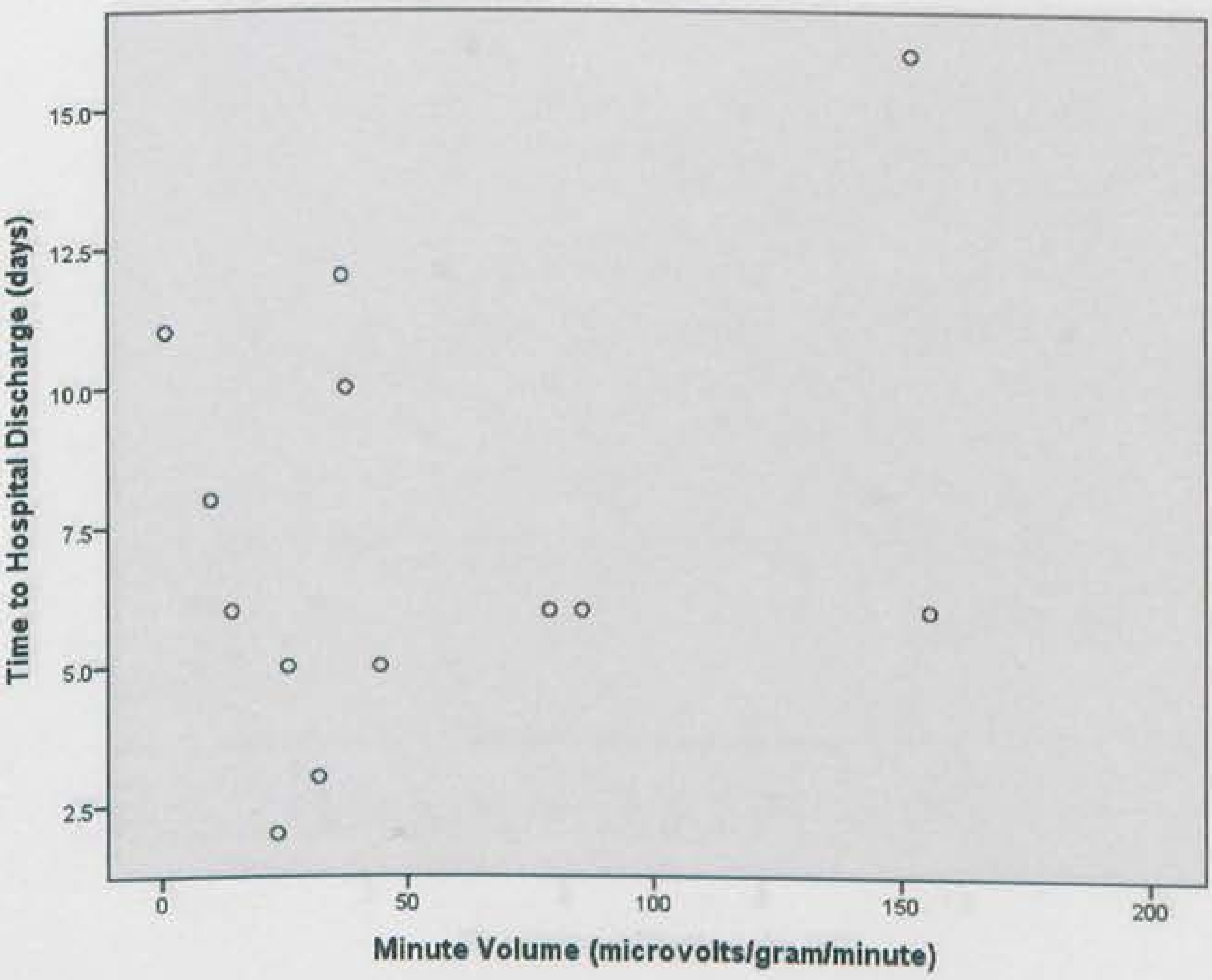
STANDARD-FLOW



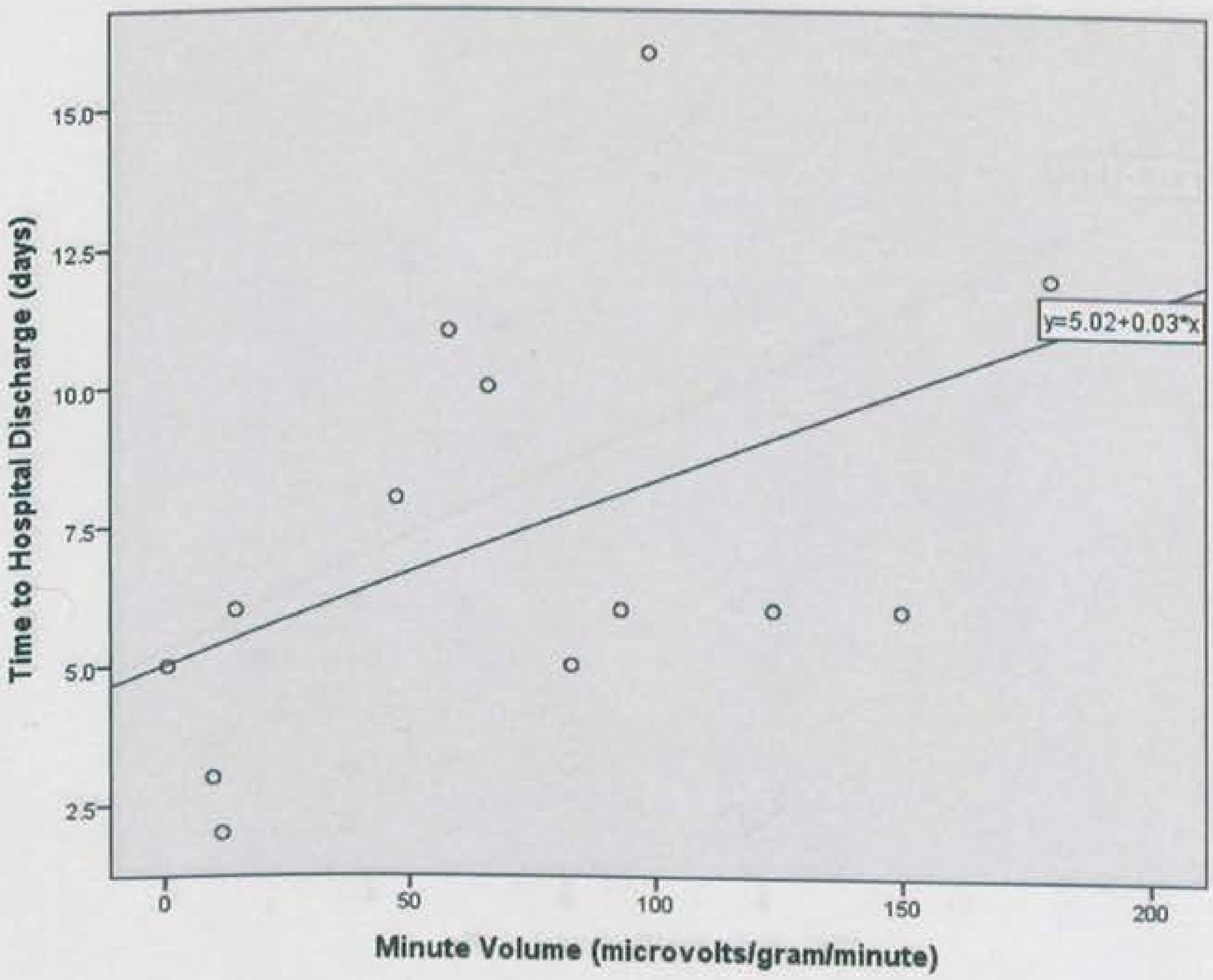
APPENDIX 5.16.

CLINICAL OUTCOME CORRELATIONS: MINUTE VOLUME SUCK-BURST BREAK

SLOW-FLOW



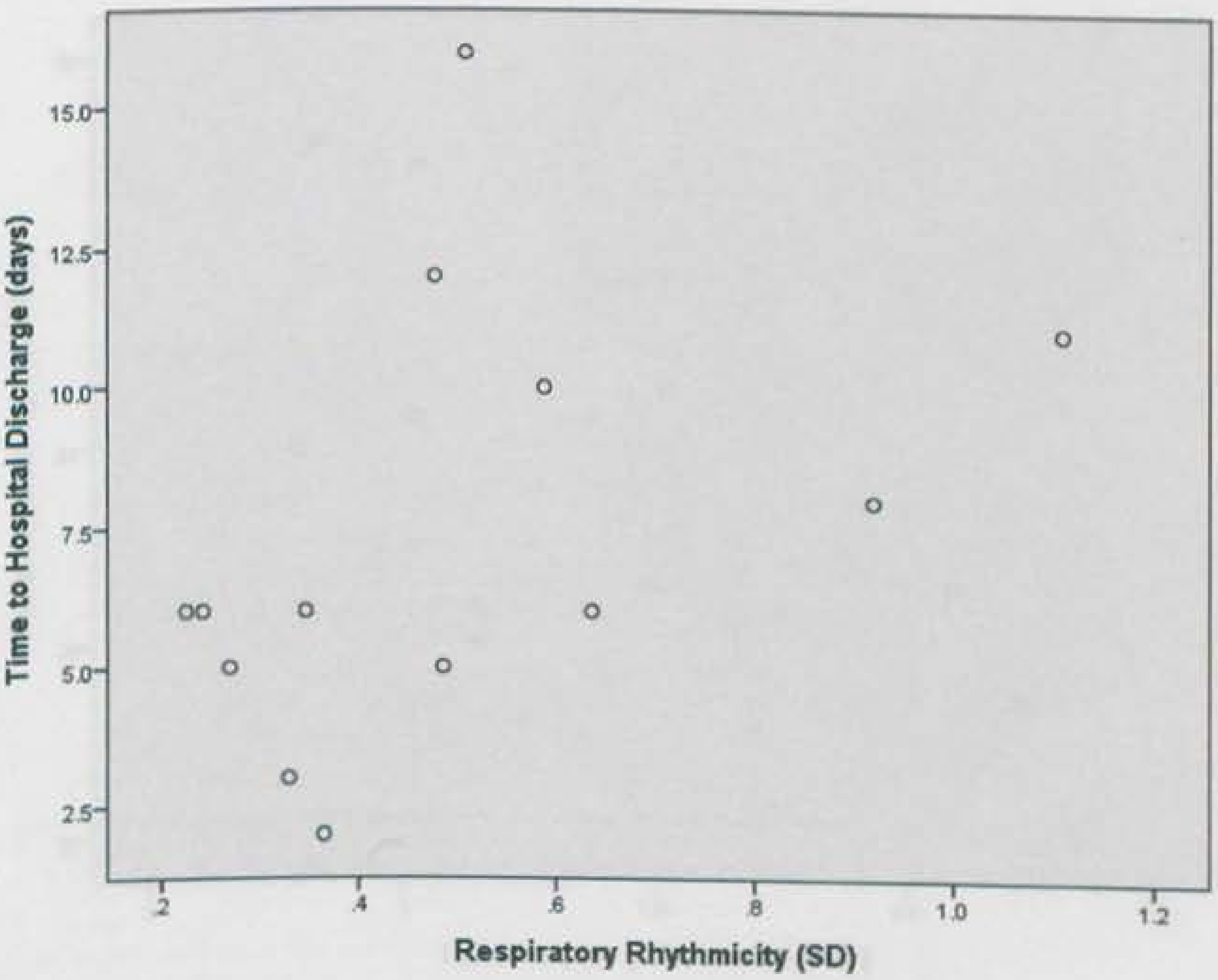
STANDARD-FLOW



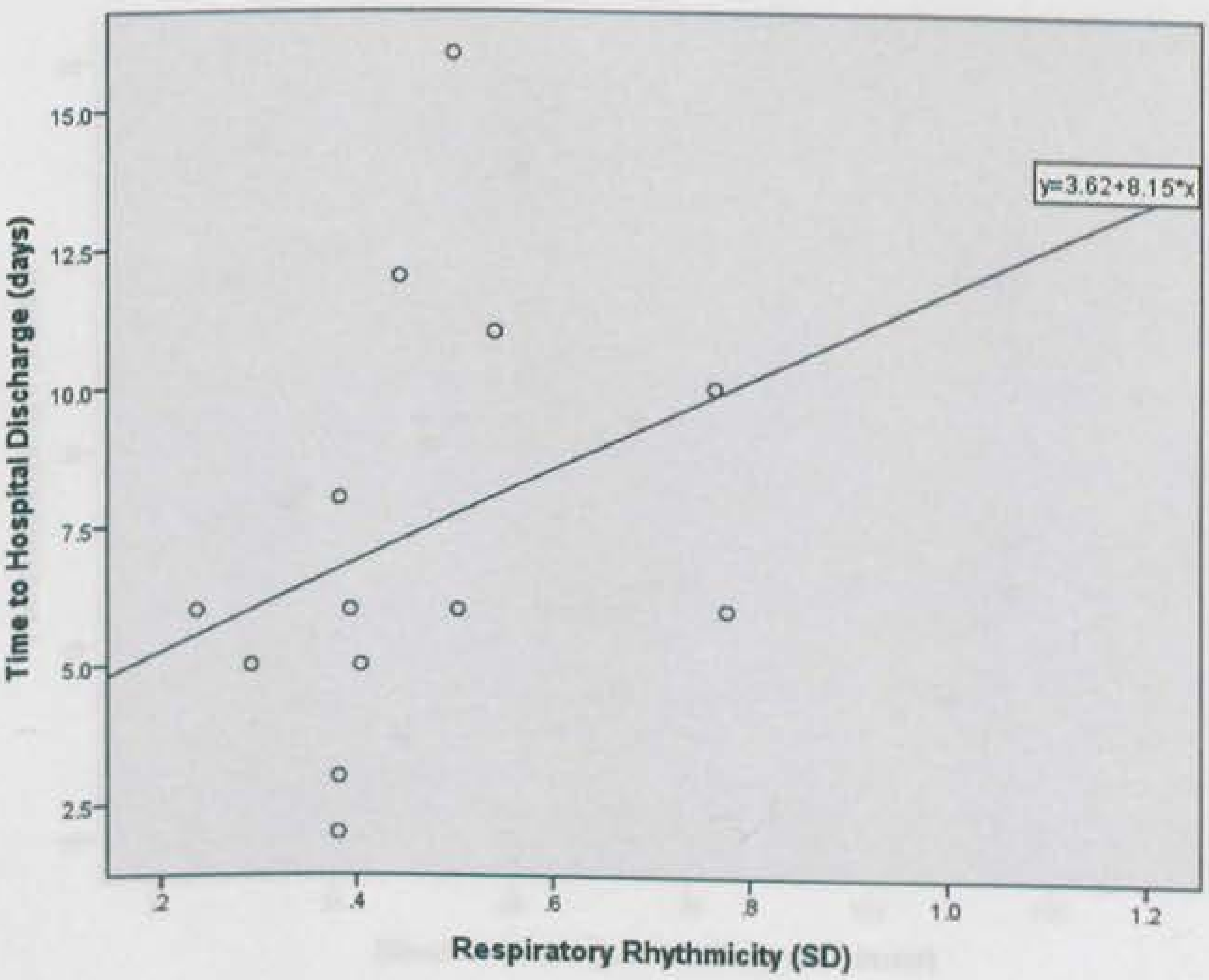
APPENDIX 5.17.

CLINICAL OUTCOME CORRELATIONS: RESPIRATORY RHYTHMICITY
SUCK-BURST BREAK

SLOW-FLOW

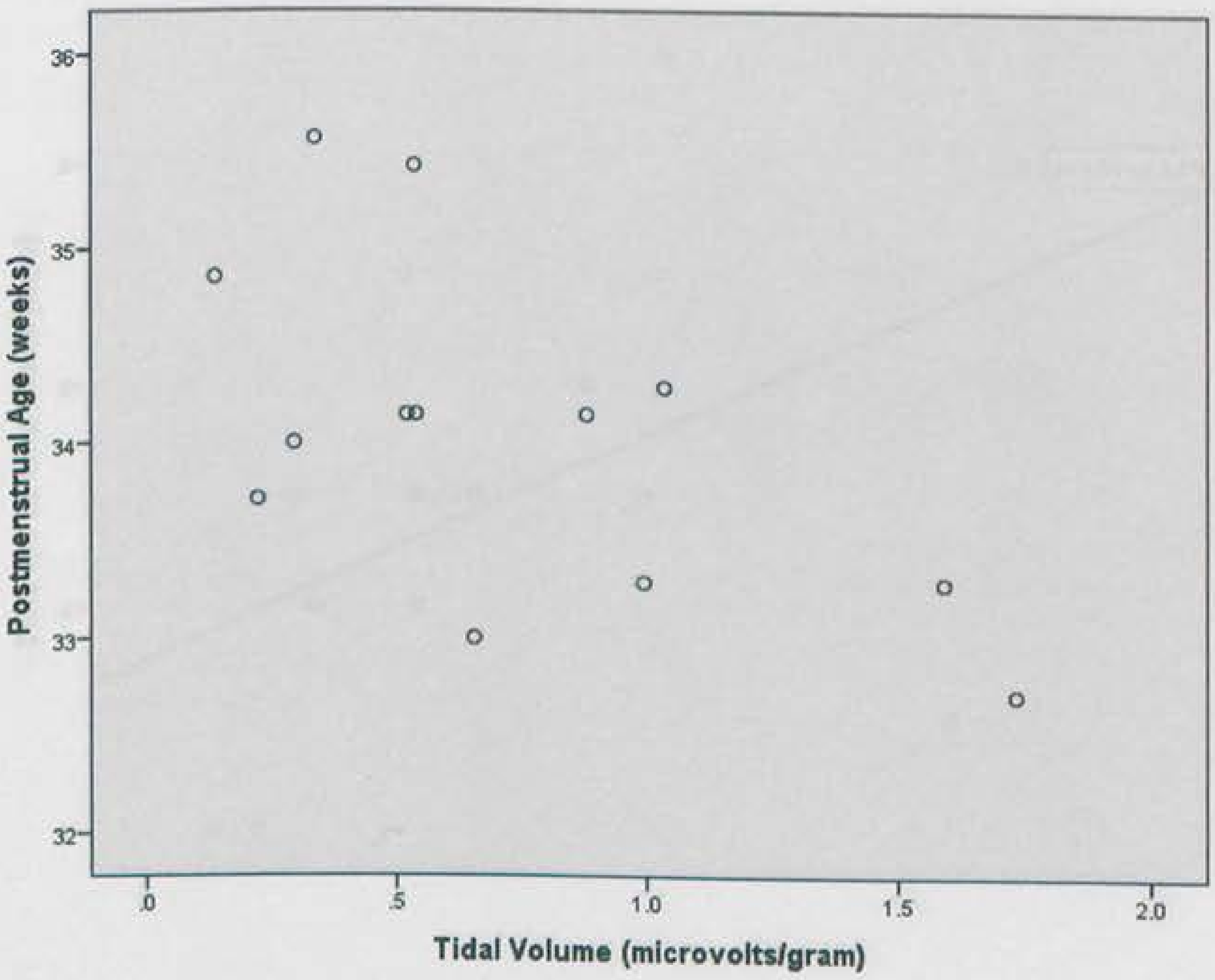


STANDARD-FLOW

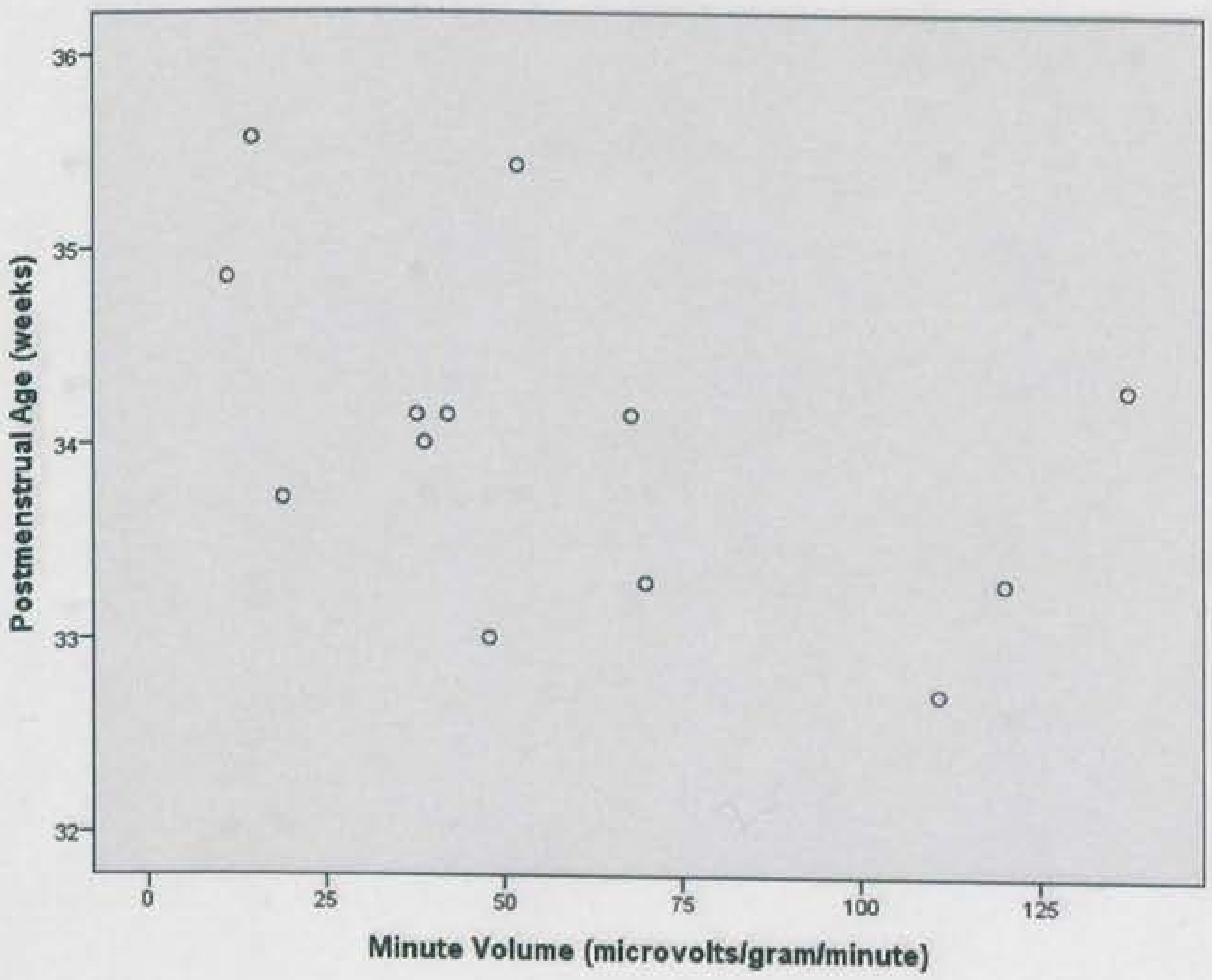


APPENDIX 5.18.
ADJUSTED STEADY-STATE VOLUME CORRELATIONS
POSTMENSTRUAL AGE

TIDAL VOLUME



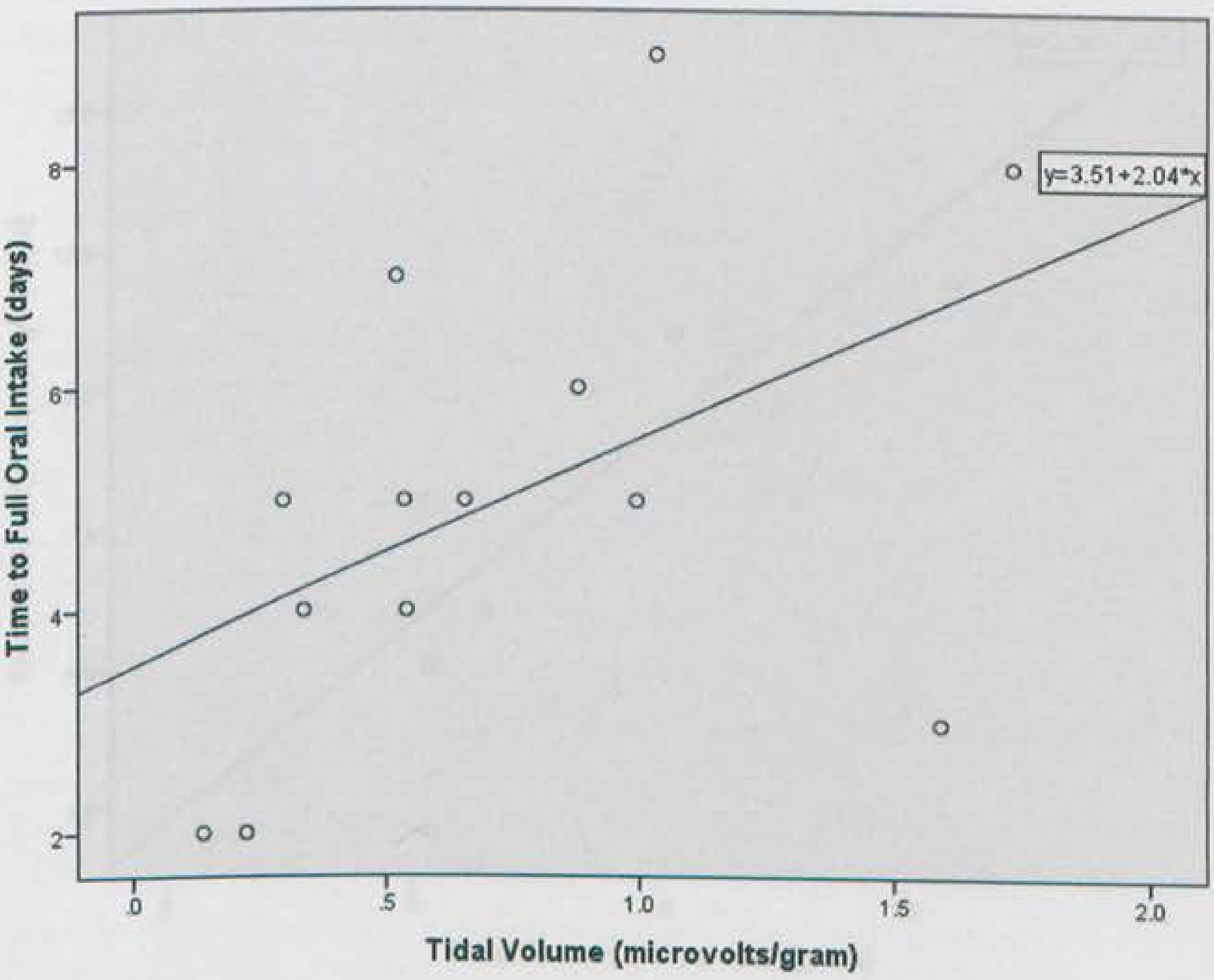
MINUTE VOLUME



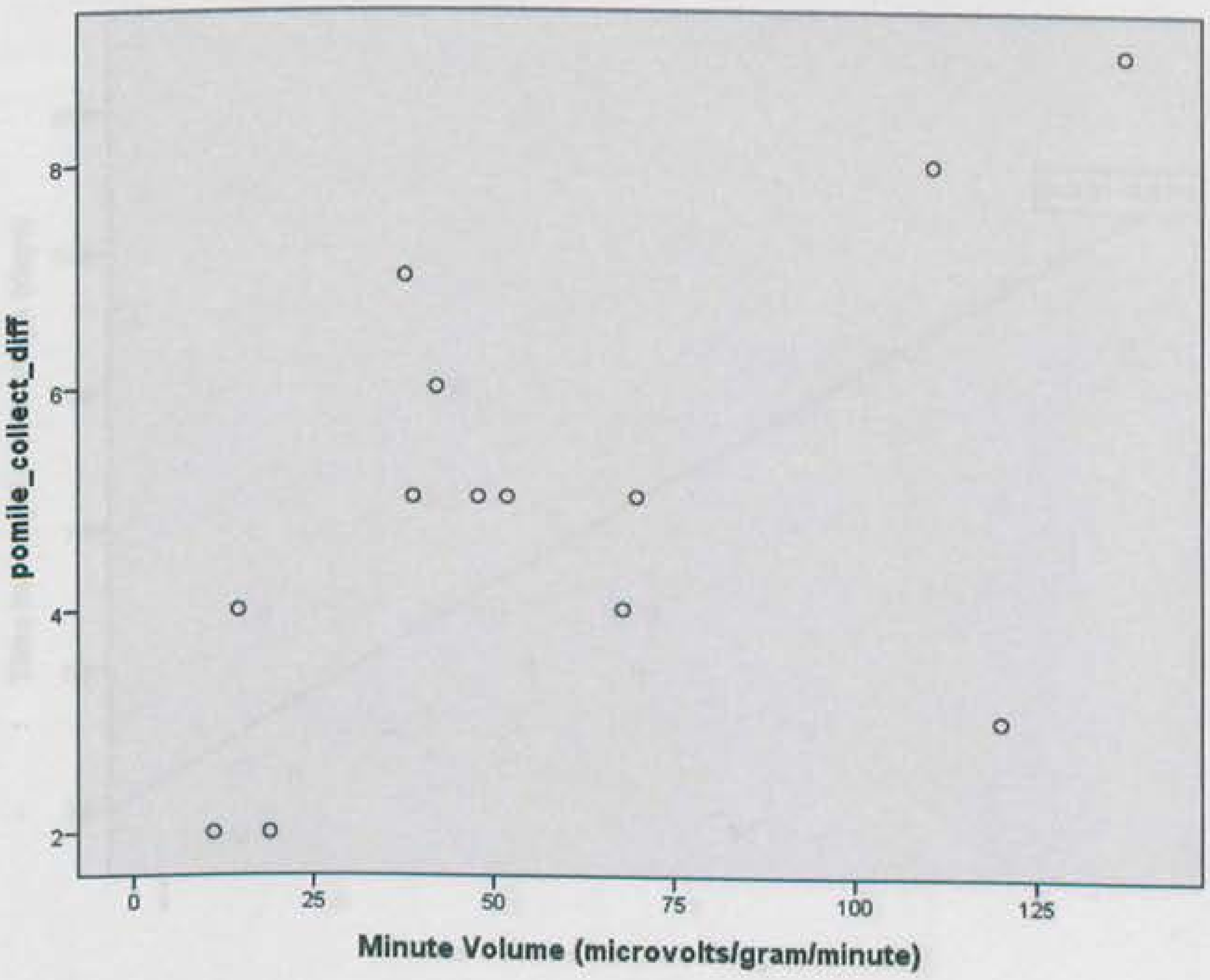
APPENDIX 5.18. *Continued*

TIME TO FULL ORAL INTAKE

TIDAL VOLUME



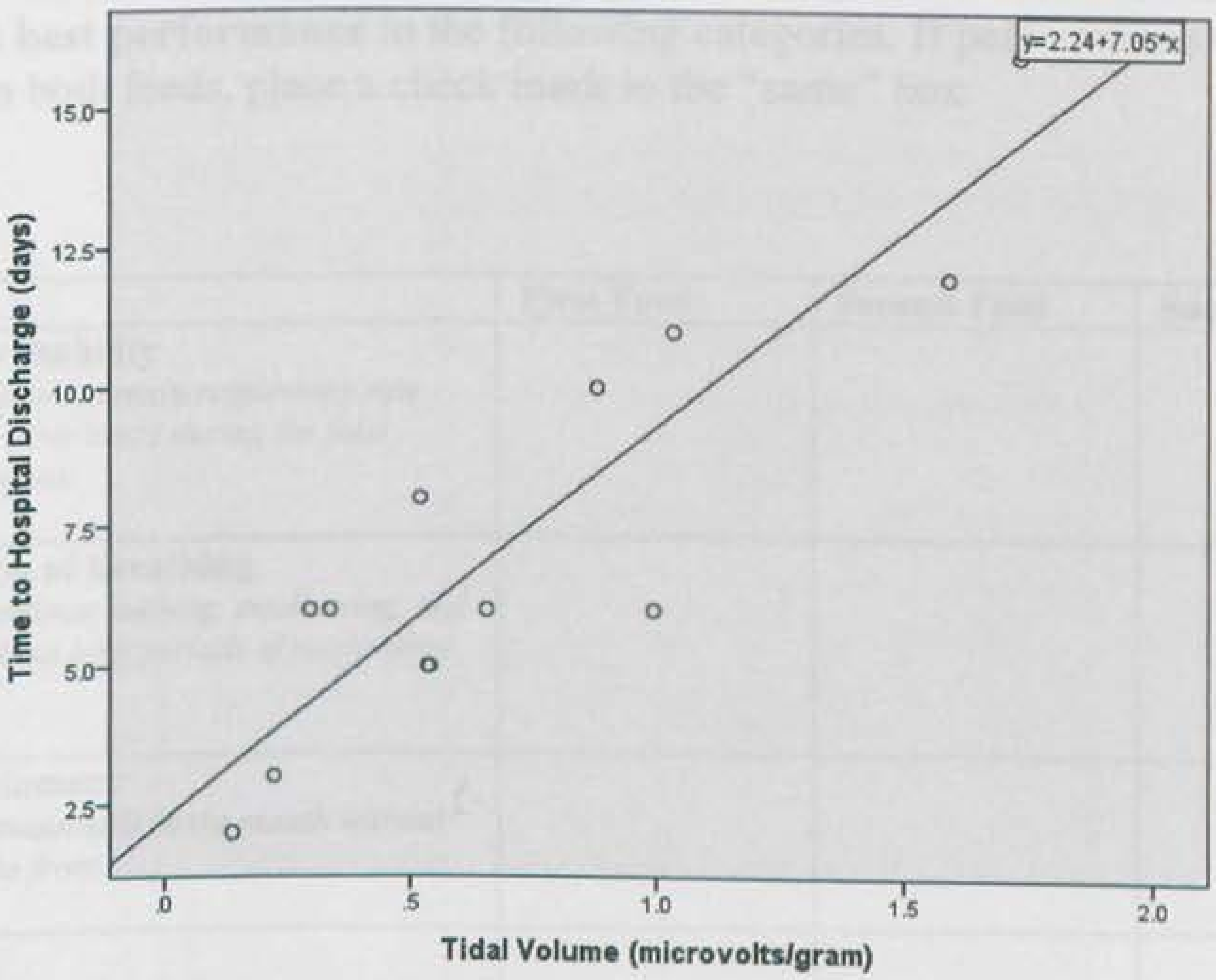
MINUTE VOLUME



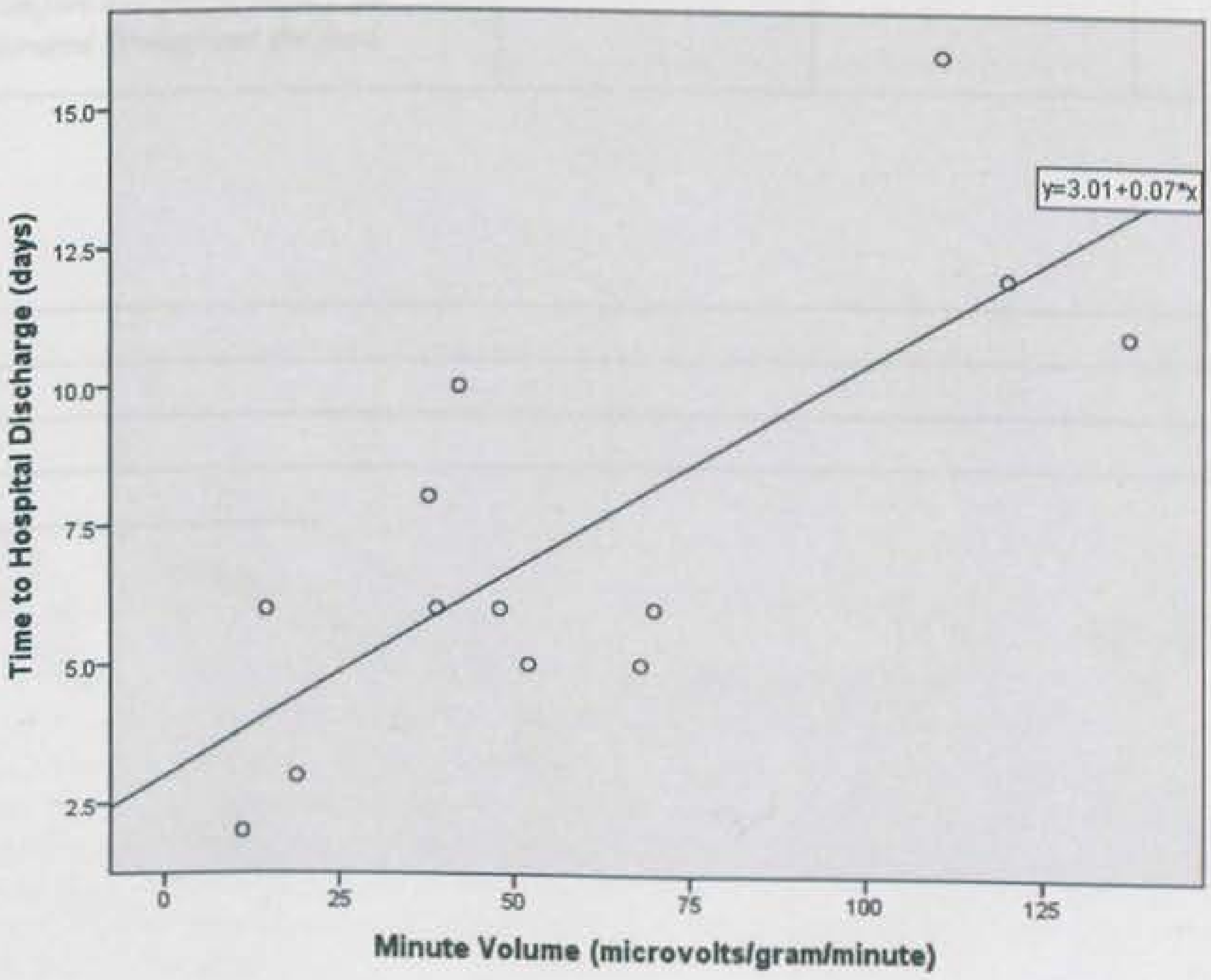
APPENDIX 5.18. *Continued*

TIME TO HOSPITAL DISCHARGE

TIDAL VOLUME



MINUTE VOLUME



APPEDIX 5.19 .
FEEDING PERFORMANCE EVALUATION

Place a check mark in the box that identifies which assessment feed the infant demonstrated **best performance** in the following categories. If performance was the same between both feeds, place a check mark in the "same" box.

	First Feed	**Second Feed**	**Same**
Respiratory Stability *Infant's ability to maintain respiratory rate within comfortable limits during the feed without tachypnea.*			
Coordination of Breathing *Ability to coordinate sucking, swallowing, and breathing without long periods of respiratory cessation.*			
Milk Containment *Ability to maintain milk in the mouth without spilling out the front.*			
Endurance *Ability to continue eating for the duration of the feed.*			
Overall Quality *The overall comfort and performance the infant demonstrated throughout the feed.*			

Comments:

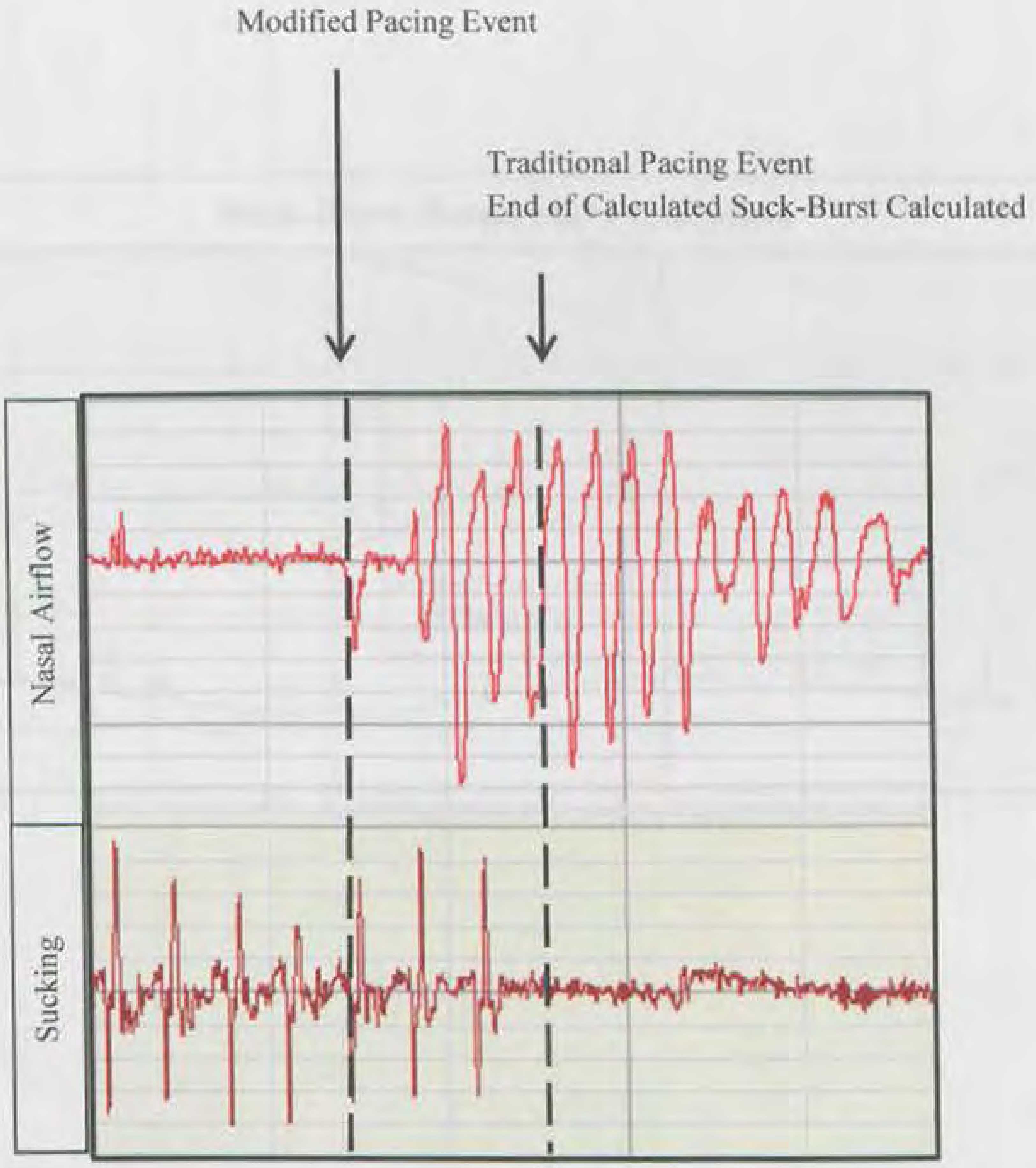
APPEDIX 5.19 .
FEEDING PERFORMANCE EVALUATION

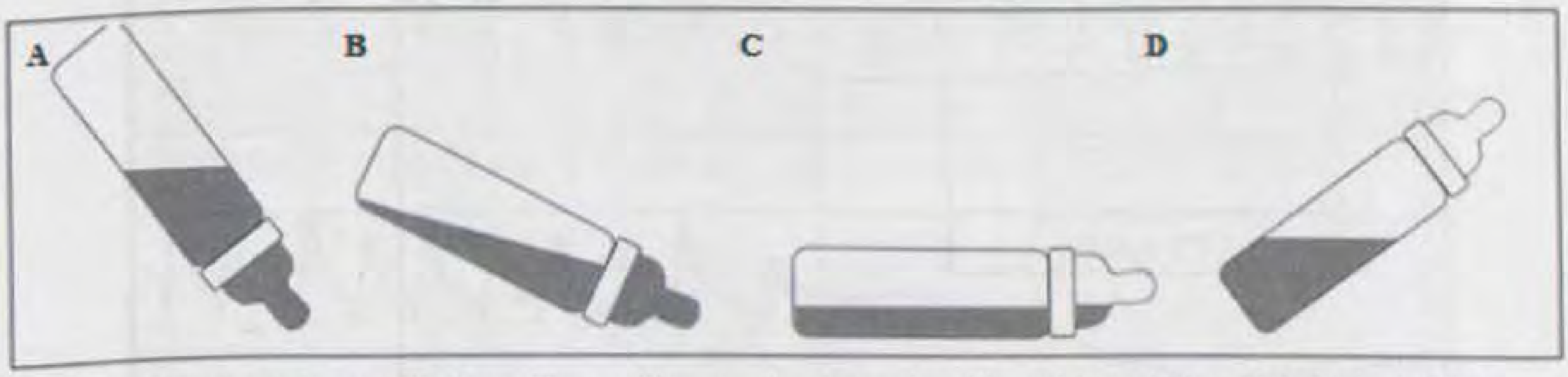
Place a check mark in the box that identifies which assessment feed the infant demonstrated **best performance** in the following categories. If performance was the same between both feeds, place a check mark in the "same" box.

	First Feed	**Second Feed**	**Same**
Respiratory Stability *Infant's ability to maintain respiratory rate within comfortable limits during the feed without tachypnea.*			
Coordination of Breathing *Ability to coordinate sucking, swallowing, and breathing without long periods of respiratory cessation.*			
Milk Containment *Ability to maintain milk in the mouth without spilling out the front.*			
Endurance *Ability to continue eating for the duration of the feed.*			
Overall Quality *The overall comfort and performance the infant demonstrated throughout the feed.*			

Comments:

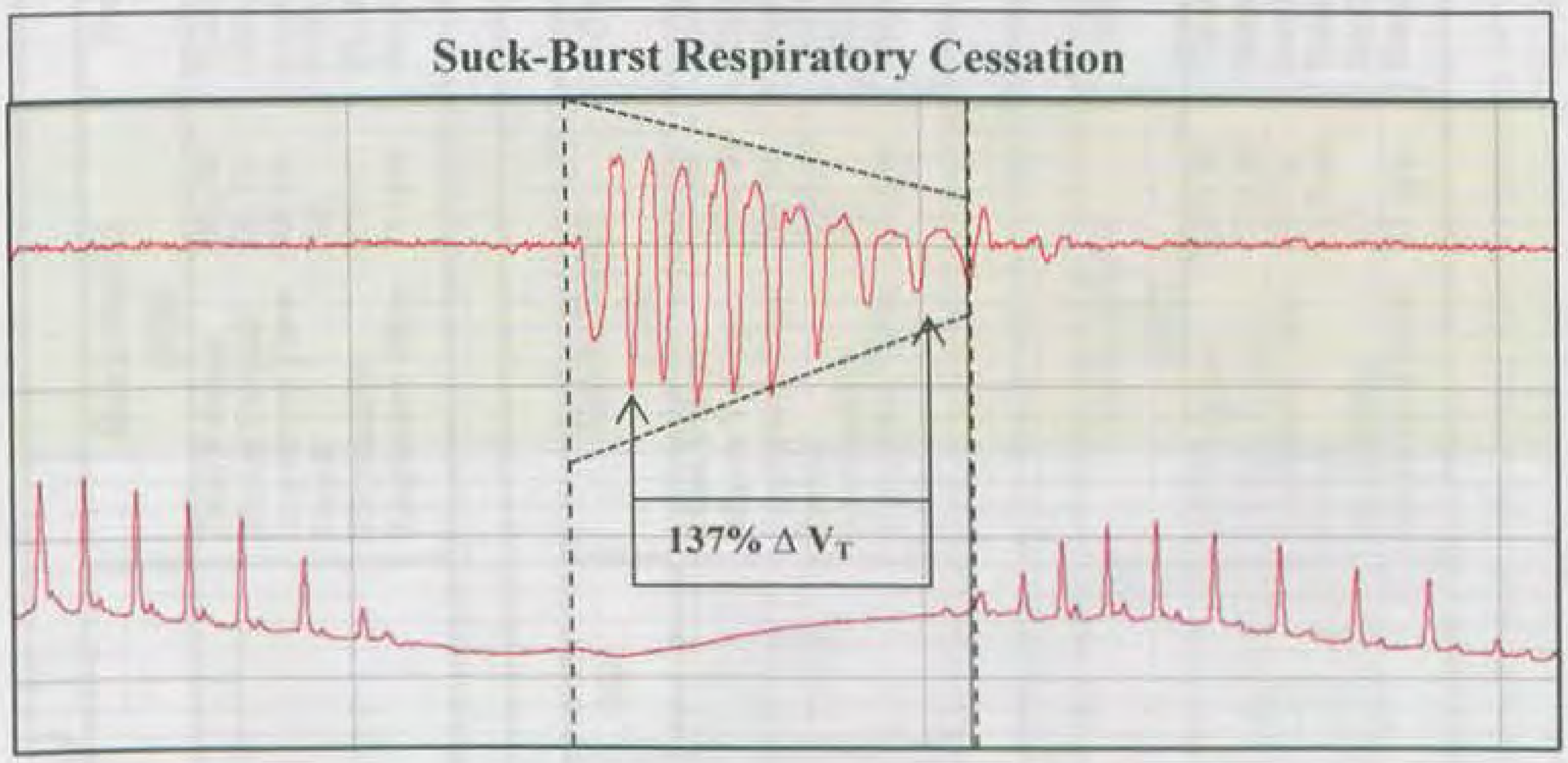
APPENDIX 6.1.
MODIFIED PACING THEORY



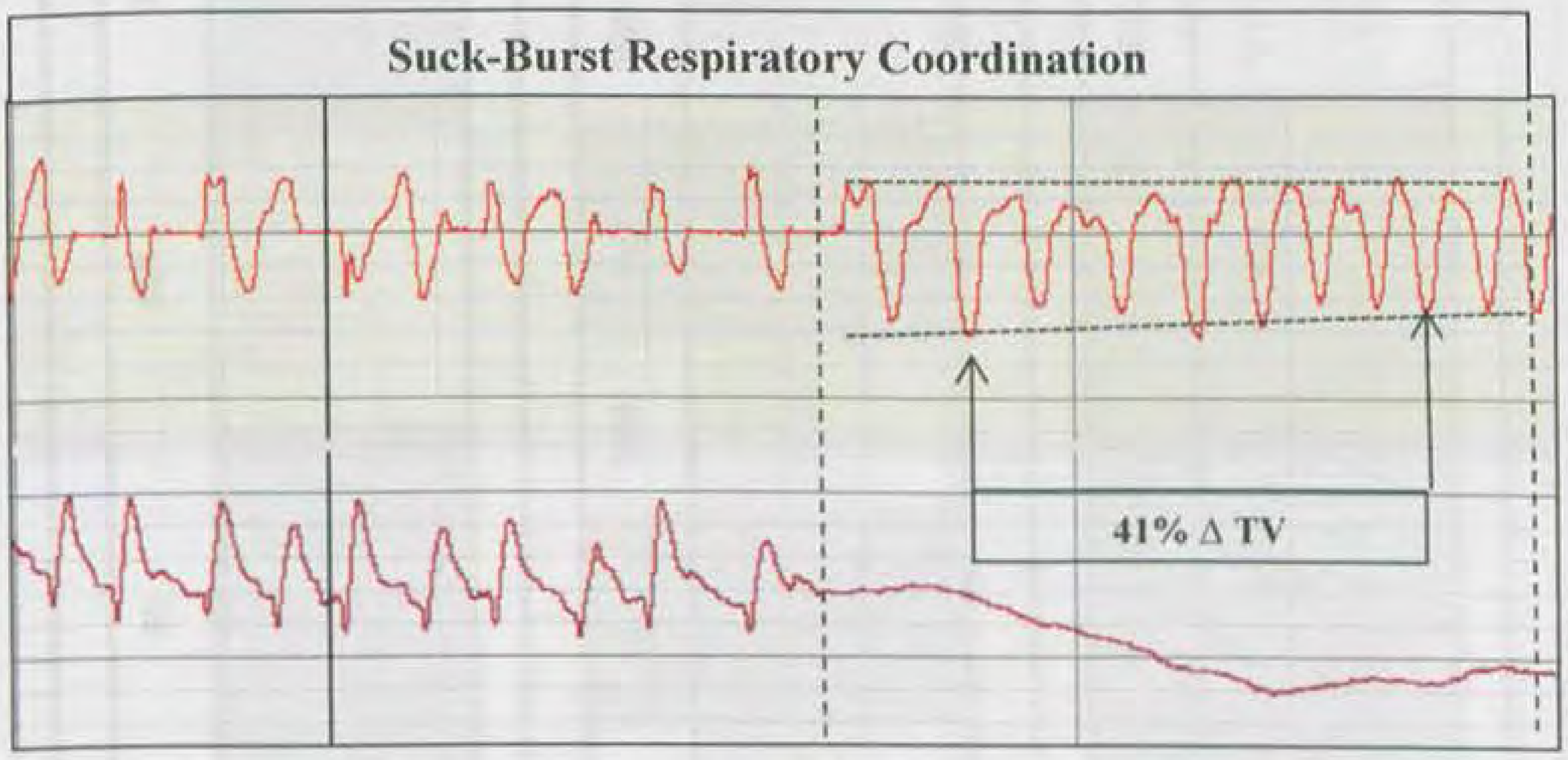


Effect of bottle angle on milk flow Figures illustrate the change in milk position within a Volufeeder® filled with 36mL milk. **A**. Fastest milk flow rate due to hydrostatic pressure **B.** Milk flow rate reduced by modified pacing type I which decreases the angle of inversion to reduce hydrostatic pressure. **C.** Cessation of milk flow regardless of sucking using modified pacing type II through displacement of milk from the nipple orifice without bottle tip elevation **D.** Cessation of milk flow using traditional pacing methods of elevating the bottle tip to remove all milk from the nipple.

APPENDIX 6.2.
CHANGES IN SUCK-BURST BREAK RESPIRATION BY SUCK-BUST COORDINATION



Suck-Burst Respiratory Cessation

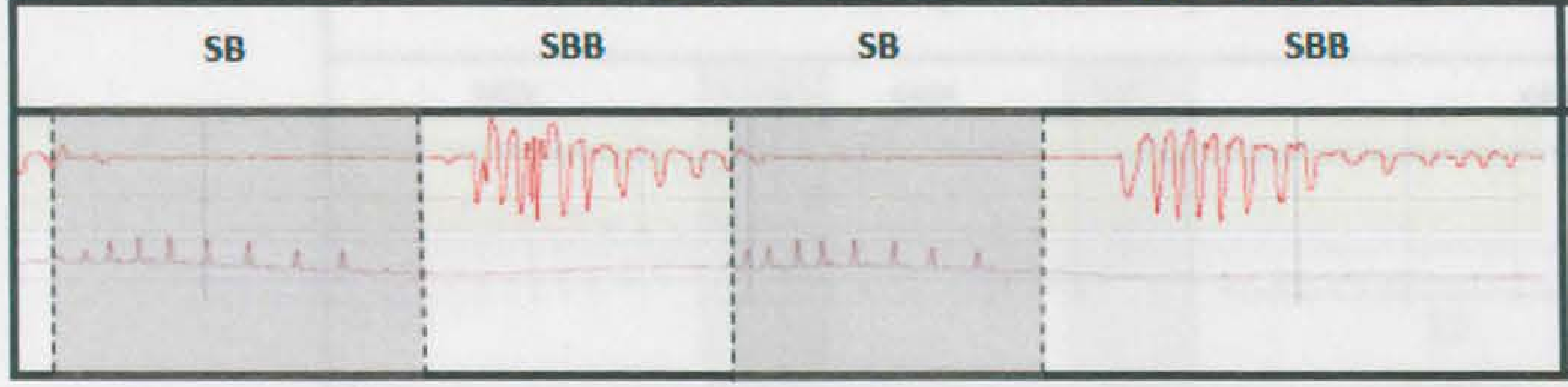


Suck-Burst Respiratory Coordination

Increased tidal volume and respiratory rate in the initial breaths of the suck-burst break following prolonged respiratory cessation compared to steady respiratory pattern during the suck-burst break following a suck-burst with respiratory control.

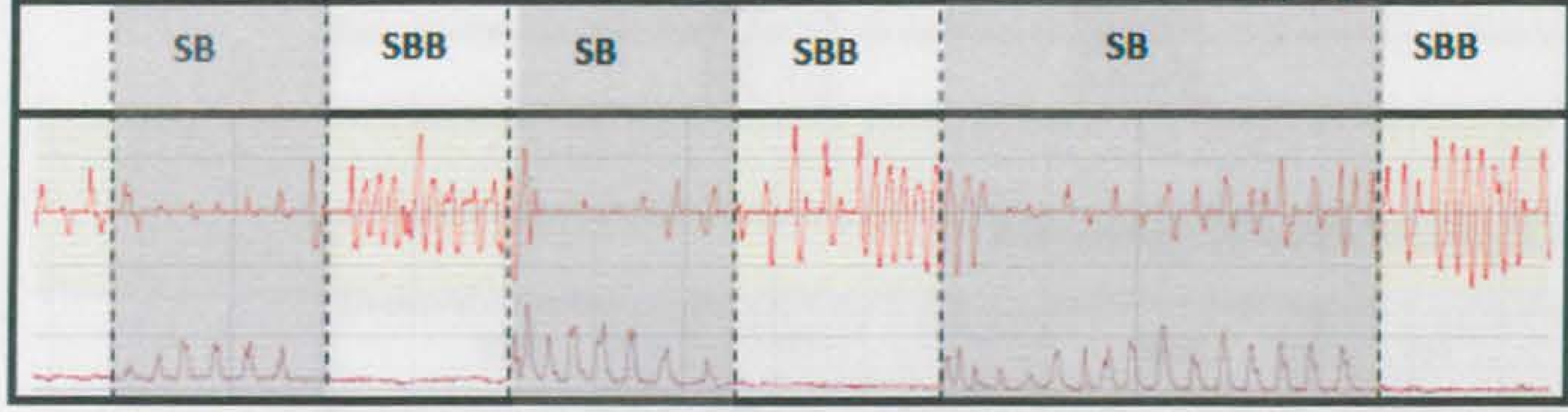
APPENDIX 6.3.
PATTERNS OF INFANT RESPIRATORY COORDINATION

Uncoordinated



Suck-Burst (SB)		Suck-Burst Break (SBB)	
Tidal Volume:	48% SS	**Tidal Volume:**	269% SS
Minute Volume:	6% SS	**Minute Volume:**	216% SS
Inspiratory Time:	300 ms	**Inspiratory Time:**	300 ms
Period:	N/A	**Period:**	800 ms
Rhythmicity:	N/A	**Rhythmicity:**	.18
Respiratory Rate:	11 bpm	**Respiratory Rate:**	59 bpm

Emerging



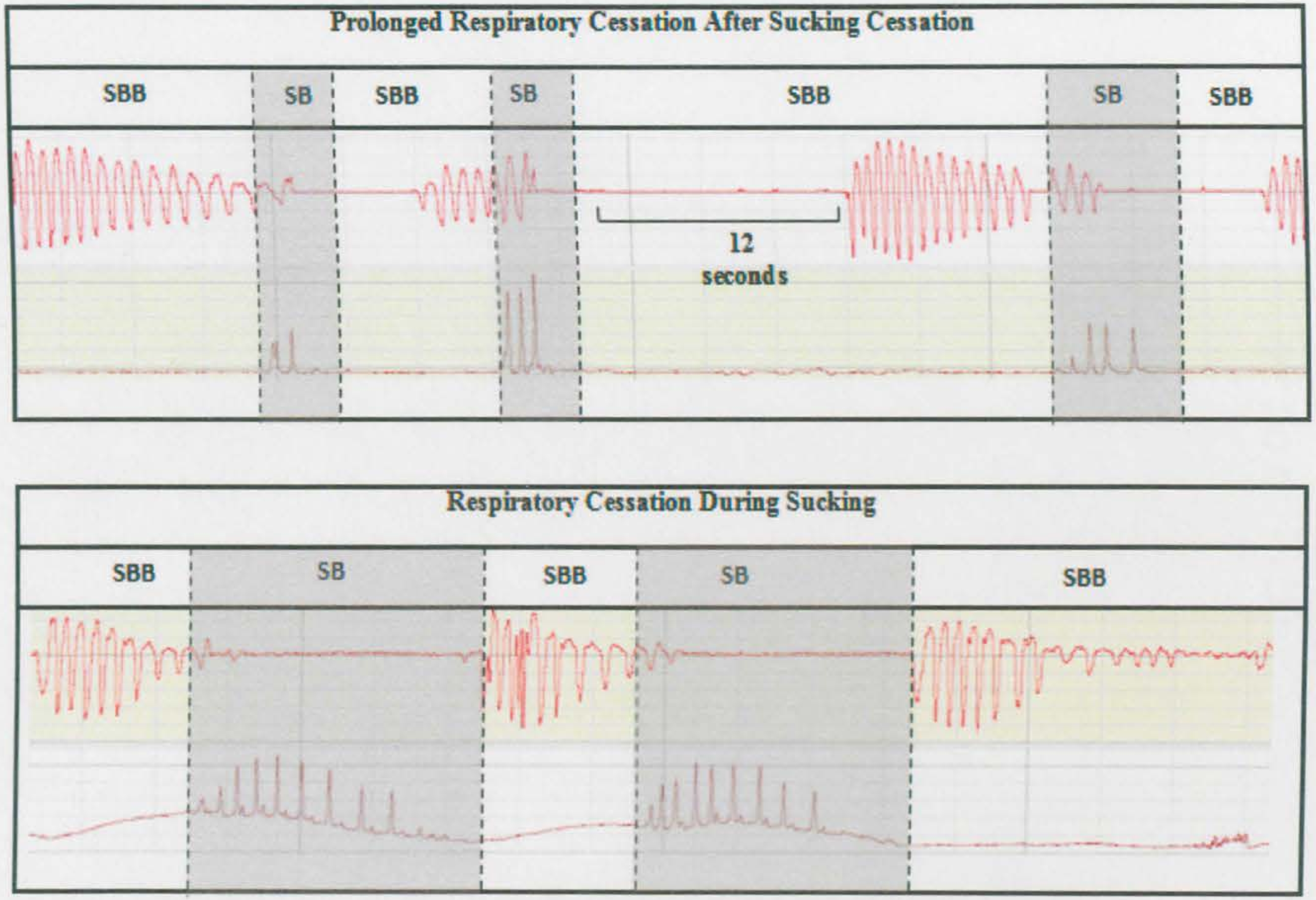
Suck-Burst (SB)		Suck-Burst Break (SBB)	
Tidal Volume:	94% SS	**Tidal Volume:**	275% SS
Minute Volume:	36% SS	**Minute Volume:**	210% SS
Inspiratory Time:	258 ms	**Inspiratory Time:**	239 ms
Period:	1088 ms	**Period:**	501 ms
Rhythmicity:	.86	**Rhythmicity:**	.22
Respiratory Rate:	48 bpm	**Respiratory Rate:**	96 bpm

Coordinated

Suck-Burst (SB)		Suck-Burst Break (SBB)	
Tidal Volume:	88% SS	**Tidal Volume:**	178% SS
Minute Volume:	53% SS	**Minute Volume:**	152% SS
Inspiratory Time:	280 ms	**Inspiratory Time:**	370 ms
Period:	1270 ms	**Period:**	960 ms
Rhythmicity:	.47	**Rhythmicity:**	.12
Respiratory Rate:	42 bpm	**Respiratory Rate:**	60 bpm

Synchronized respiratory (top red) and sucking (bottom maroon) tracings with extracted values representing infant respiratory performance during suck-bursts and suck-burst breaks. Respiratory-rate during suck-bursts found to be the most representative single measure of impairment, however when supplemented with measures of lung volume, inspiratory time, respiratory rhythmicity, and inspiratory period, greater precision in infant-specific impairments can be identified.

APPENDIX 6.4.
PATTERNS OF RESPIRATORY CESSATION


Prolonged Respiratory Cessation After Sucking Cessation

Respiratory Cessation During Sucking

Synchronized respiratory (top red) and sucking (bottom maroon) tracings depicting two patterns of respiratory cessation. The top pattern is characterized by respiratory cessation isolated to periods of sucking and the immediate swallow period following. The bottom pattern is characterized by prolonged respiratory cessation once sucking has stopped.