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Fresh stillborn and severely asphyxiated neonates share a common hypoxic–ischemic pathway

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Abstract

Objective: To characterize, among non-breathing flaccid neonates at delivery, immediate heartrate and responses to ventilation in relation to the clinical diagnosis of fresh stillbirth (FSB) or early neonatal death (END) within 24 hours.

Methods: The present cross-sectional study included all deliveries at Haydom Hospital in rural Tanzania between July 1, 2013, and July 31, 2016. Ventilation parameters and heartrate were recorded by monitors with ventilation and dry-electrocardiography sensors. Perinatal characteristics were recorded on data forms by trained research assistants.

Results: Among 12 789 neonates delivered, 915 were ventilated; among ventilated neonates, there were 53 (6%) FSBs and 64 (7%) ENDs. Electrocardiography was used in 46 FSBs and 55 ENDs, and these neonates were included in a subanalysis. Initial heartrate was detected in 27 (59%) of 46 FSBs and 52 (95%) of 55 ENDs, and was lower in FSBs (52 ± 19 vs 76 ± 37 bpm; P=0.003). More ENDs responded to ventilation (53% vs 9%; P<0.001), with heartrate increasing above 100 bpm. Heartrate at ventilation discontinuation was higher among ENDs (115 ± 49 vs 52 ± 33 bpm; P<0.001).

Conclusion: Progression to FSB or END after intrapartum hypoxia/anoxia is probably part of the same circulatory end-process. Distinguishing FSB from severely asphyxiated newborns is clinically difficult and probably influences estimated global perinatal mortality rates.

KEYWORDS

Birth asphyxia; Early neonatal death; Fetal monitoring; Fresh stillbirth; Helping Babies Breathe; Neonatal resuscitation; Perinatal mortality; Perinatal outcome

1 | INTRODUCTION

Globally, an estimated 2.7 million neonatal deaths occur annually, constituting almost 45% of child mortality among under 5-year-olds.[1,2] Approximately 23% of neonatal deaths are reported to be intrapartum-related, occurring secondary to birth asphyxia.[3] In addition, an estimated 1.3 million neonates are reported to be “fresh stillborn” (FSB), indicating intrapartum demise shortly before delivery.[4,5] Intrapartum-related deaths such as FSB, or early neonatal death (END) secondary to asphyxia (interruption of placental blood flow) may represent the same hypoxic–ischemic end-process.[6] These neonates invariably appear similar at delivery: flaccid, white/bluish, and non-breathing. Several studies have reported a decline in FSB after the introduction of basic neonatal resuscitation training programs.[7–9]

Most non-breathing flaccid newborns are in so-called “primary apnea” with a heartrate above 60 bpm, and will respond to basic interventions including drying, stimulation, and/or bag-mask ventilation (BMV) if implementation is timely.[6,8,10] Secondary apnea, often with a heartrate below 60 bpm at delivery, is suggestive of a more prolonged asphyxial process that invariably requires intensive interventions including cardiopulmonary resuscitation to restore cardiorespiratory function.[6] In a "true" FSB with cardiac arrest (no perceived heartrate activity at delivery), the return of spontaneous circulation is unlikely. Nevertheless, implementation of the Helping Babies Breathe[11] training program in Tanzania has demonstrated a 47% reduction in END and a 24% reduction in FSB.[8] However, no newborn heartrate data were available in that report, and we speculate that the observed decline in apparent FSB was probably due to prior misperception and misclassification of "asphyxiated" newborns as FSB.[7,12]

There is great disparity in the incidence of FSB in high- and low-resource settings.[5,7–10,13–19] Understanding the timing and/or pathogenesis of FSB is an important first step to reducing this disparity. The ability to immediately measure newborn heartrate, using novel dry-electrode electrocardiography (ECG) technology,[20] coupled with non-invasive measurements of ventilatory changes at birth, has afforded the opportunity to accurately study heartrate in flaccid non-breathing newborns. Therefore, the aim of the present study was to characterize the immediate heartrate and the cardiorespiratory responses to BMV among non-breathing flaccid neonates with a clinical diagnosis of FSB or END within 24 hours of delivery.

2 | MATERIALS AND METHODS

The present cross-sectional study included all deliveries from July 1, 2013, to July 31, 2016, at Haydom Hospital, Haydom, Tanzania. All neonatal deliveries were observed by research assistants during this period and included in the analyses. Ethical approval was granted before the study by the National Institute for Medical Research in Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434) and the Regional Committee for Medical and Health Research Ethics in Norway (Ref. 2013/110). Informed consent was not required by the ethical committees because the study was descriptive.

Haydom Hospital is a rural referral hospital in northern Tanzania that provides comprehensive emergency obstetric care and basic emergency newborn care to approximately 500 000 individuals. Midwives largely conduct deliveries and resuscitations; doctors are on 24-hour call.

During the study period, three or four trained research assistants were continuously present in the labor ward, working in three shifts over 24 hours covering the labor ward, operating theatre, and adjacent neonatal area. Every delivery and subsequent neonate was observed, and intervals from delivery to different events were timed via a stopwatch. In addition, neonatal characteristics, fetal heartrate (FHR), labor complications and management, neonatal resuscitation, and outcomes were recorded on data collection forms. All data collection forms were controlled for quality issues, and double-entered into the database by two different data clerks.

FHR was determined intermittently by using a fetoscope (Pinard) or a handheld Doppler monitor (FreePlay). FHR anomalies were defined as 120 bpm or below, or above 160 bpm. Gestational age was based on measurements of the symphysis pubis to the fundus. Death at a gestational age below 28 weeks was classified as spontaneous abortion in the study setting. A normal outcome was defined as survival beyond 24 hours without any perceived medical issues. FSB was defined clinically by the midwives as an Apgar score of 0 at both 1 and 5 minutes with intact skin and suspected death during labor and/or delivery.

Neonatal resuscitation monitors (developed for research by Laerdal Global Health, Stavanger, Norway) were available in each delivery room and operating theatre, and used during most neonatal resuscitations. The monitor included a ready-to-use self-inflating neonatal resuscitator without a positive end-expiratory pressure valve and no external gas-source, and a dry-electrode ECG sensor for rapid application over the abdomen of the neonate.[20] The monitor could be readily operated by a single healthcare provider. The heartrate was displayed on the wall-mounted monitor in front of the provider (Fig. 1A). Heartrate was automatically calculated via an algorithm based on zero-crossing counts.[21]

Ventilation pressure, flow, and volume were measured through a pressure and a flow sensor (Acutronic Medical Systems, Hirzel, Switzerland). Expired CO_2, as a percentage of atmospheric pressure, was measured as a marker of both circulation and respiration using a side-stream sensor (ISA; Masimo, Irvine, CA, USA). All sensors were placed between the facemask and the resuscitator bag. Heartrate, applied ventilation pressures and volumes, and expired CO_2 were synchronously recorded (Fig. 1B). All ECG recordings included in the study were analyzed by two researchers (HLE and JE) and noted to show a regular rhythm with narrow QRS complexes.

Before the study, all midwifes were trained in Helping Babies Breathe and how to use the monitor. During the study period, 10-minute training sessions were conducted on a weekly basis, emphasizing the importance of initiating BMV within 1 minute for non-breathing neonates not responding to stimulation. Intubation, cardiac compressions, and medications are not included in the Helping Babies Breathe algorithm.[11]

Data analysis was performed by using Matlab R2016b (MathWorks, Natick, MA, USA) and SPSS version 23 (IBM, Armonk, NY, USA). Values were presented as mean ± SD or median (interquartile range). Categoric data were compared by χ^2 or Fisher exact test as appropriate. Continuous data were compared by independent-sample t test for normally distributed data and Mann-Whitney U test for non-parametric data.

Binary logistic regression modeling was used to identify factors influencing the clinical classification of FSB or END among neonates born with heart activity. First, univariate regression was performed with all relevant cofactors. Next, a likelihood ratio test based on backward and forward variable selection in a multivariate regression analysis was performed. The model showed a satisfactory fit as per the Hosmer-Lemeshow test. Statistical significance was set at $P<0.05$.

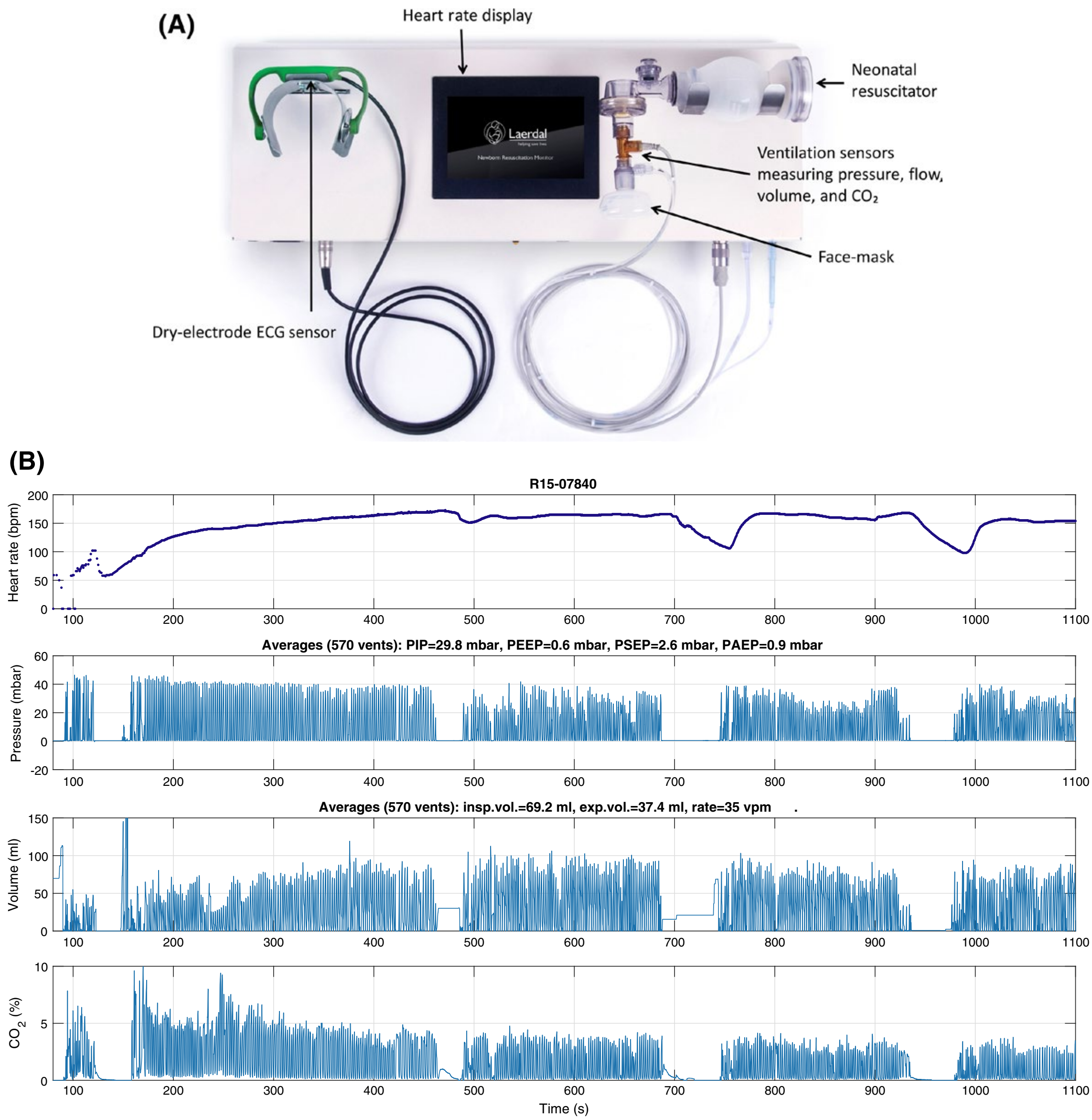

FIGURE 1 The newborn resuscitation monitor with signal outputs. (A) Monitor with an easy-to-apply dry-electrode ECG sensor, a heartrate display, and a ready-to-use resuscitator with ventilation sensors. (B) Signal outputs from a representative early neonatal death. The top tracing represents the course of the heartrate in beats per minute. The upper middle tracing represents the PIP in millibar; the mean PIP approximates 30 millibar for the whole episode (571 ventilations). The lower middle tracing represents the corresponding inflated volumes in mL. The delivered (tidal) volume is equal to the expired volume. The bottom tracing represents expired CO_2 (1% ≈1 kPa=7.5 mm Hg). The *x*-axis presents the time in seconds. Abbreviations: ECG, electrocardiogram; PIP, peak inflation pressure.

3 | RESULTS

During the study period, 12 789 neonates were delivered with a mean delivery weight of 3245 ± 529 g and a gestational age of 38 ± 2 weeks (Fig. 2). At 24 hours, the outcomes included 11 919 (93.2%) normal neonates, 428 (3.3%) admissions to the neonatal unit, 175 (1.4%) FSBs, 97 (0.8%) ENDs, and 170 (1.3%) macerated stillbirths. Most neonates (9816/12 789; 76.8%) initiated spontaneous respiration without any intervention at a median of 4 seconds (IQR 2–14 seconds) after delivery; 2681 (21.0%) of 12 789 neonates failed to initiate spontaneous respiration. Of these, 1766 (65.9%) responded to stimulation and/or suctioning by initiating breathing at a median of 54 seconds (28–93 seconds) after delivery. For 915 (7.2%) of the 12 789 neonates, BMV was initiated at a median of 112 seconds (79–156 seconds) after delivery.

The mean delivery weight and gestational age were significantly greater for normal neonates as compared with FSB and END (Table 1). FHR on admission to the labor suite was not detectable in 87 (49.7%) neonates of subsequent 175 FSBs. During labor, FHR was not assessed in 28 (16.0%) and 16 (16.5%) neonates of the subsequent 175 FSBs and 97 ENDs, respectively. The time interval from the final FHR measurement to delivery was similar between normal neonates and ENDs, but significantly longer for FSBs. In FSBs and ENDs, the fetus was likely to be in the breech presentation compared with the

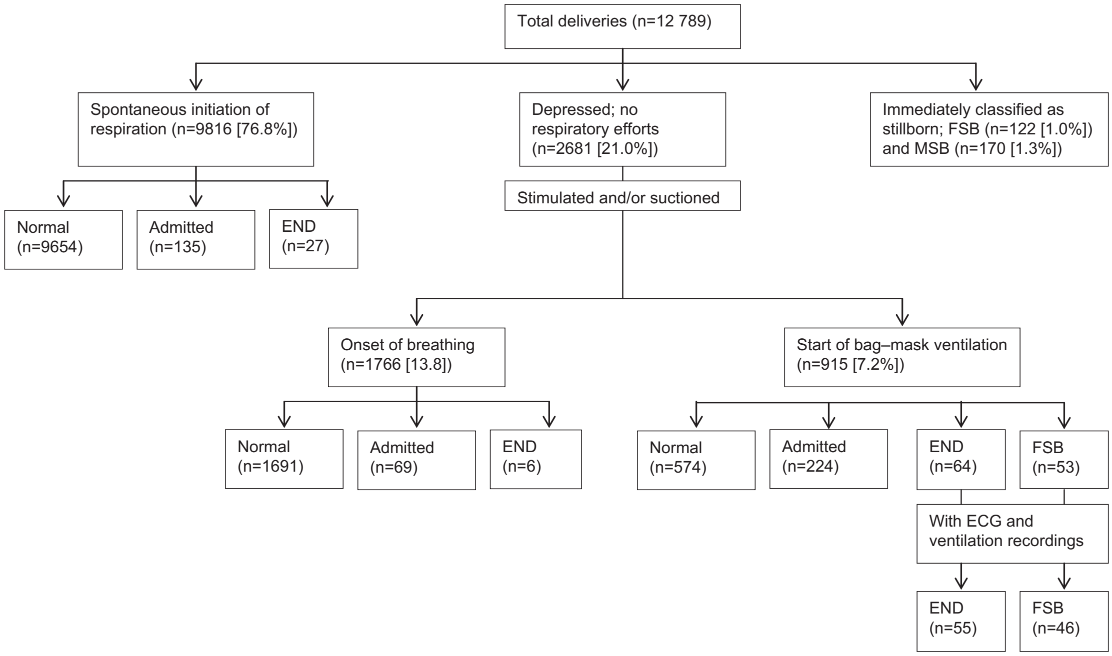

FIGURE 2 Overview of the study cohort. Abbreviations: END, early neonatal death; FSB, fresh stillbirth; MSB, macerated stillbirth.

other deliveries, and labor adverse events (uterine rupture, cord prolapse, prepartum bleeding) were significantly more common among FSBs or ENDs (Table 1).

A subanalysis was carried out for FSBs and ENDs where ventilation was administered and ECG monitoring was used. The ECG-sensor was used during the resuscitation of 46 of 53 (87%) and 55 of 64 (86%) neonates that received ventilation and were subsequently classified as FSB or END, respectively (Fig. 2). Among the 55 neonates who died, the timing of death was within 30 minutes (n=17), 30 minutes to 12 hours (n=8), and 12–24 hours (n=30) after delivery. The 46 FSB neonates were recorded as such by the provider within 30 minutes of delivery. There were no differences in labor and newborn characteristics between the two groups (Table 2). The time from the last FHR measurement to delivery was longer for FSB than for END. Most resuscitative actions were similar between the two groups.

In the subanalysis, an initial heartrate was detected in 27 (59%) of 46 FSBs and 52 (95%) of 55 ENDs; the heartrate was significantly lower in FSBs than in ENDs (P=0.003). A rapid increase in heartrate (<40 seconds) to more than 100 bpm in response to BMV was more common among ENDs than FSBs. A heartrate was detected at BMV discontinuation among a greater proportion of ENDs than FSBs (Table 2).

Higher inflation and expired volumes were recorded among ENDs compared with FSBs. There were no differences in mask leak, ventilation frequency, or peak inflation pressure. In comparison with FSBs, ENDs were more likely to have an expired CO_2 above 3% and less likely to have an expired CO_2 below 1%. At discontinuation of BMV, 42 (76%) ENDs initiated spontaneous breathing. Among those classified as FSBs, 1 (2%) neonate was recorded to have some gasping efforts (Table 2).

FSBs and ENDs with heart activity at initiation of BMV were included in a logistic model to determine potential factors influencing the clinical diagnosis of FSB or END. Failure to initiate breathing at discontinuation of BMV was the only factor significantly related to an FSB diagnosis (odds ratio 92, 95% confidence interval 11–759; P<0.001).

4 | DISCUSSION

The present study provided insight into the pathophysiologic mechanisms occurring in flaccid neonates with a subsequent clinical diagnosis of FSB or END. Heart activity, where recorded, was detected in 59% of neonates subsequently classified as FSB and almost all classified as END. An increase in heartrate after initiation of BMV was more common and rapid among END neonates than among FSB neonates. At the time of discontinuation of ventilation, the heartrate was unchanged from baseline and remained profoundly bradycardic for those classified as FSB, whereas it was more than 100 bpm for those subsequently classified as END. Providers achieved higher expired volumes and CO_2 values in END neonates than in apparent FSBs. This was despite a lack of differences in mask leak, applied peak inflation pressure, or ventilation frequency. Almost all FSB neonates (98%) had no respiratory effort at discontinuation of ventilation.

A major strength of the study was the unique research infrastructure that was established in parallel to clinical operation. The systems for data collection, control, and management were meticulous, facilitating the study of a large cohort population with detailed, continuous, observer monitoring of events as they occurred in real time, coupled with automatic recording of biomedical signal data. The findings

TABLE 1 Labor, delivery, and resuscitation characteristics of neonates classified as normal, fresh stillbirth, and early neonatal death within 24 h.[a]

Characteristics	Normal (n=11 919)	END (n=97)	FSB (n=175)	*P* value	
				Normal vs END	END vs FSB
Referral from other facility	389 (3.2)	10 (10.3)	26 (14.9)	<0.001[b]	0.291[b]
Birth weight, g	3281 ± 485	2473 ± 813	2881 ± 757	<0.001[c]	<0.001[c]
Birth weight ≤2500 g		46 (47.4)	48 (27.4)		0.001[b]
Gestational age, wk	38.2 ± 1.7	35.3 ± 4.0	36.7 ± 3.2	<0.001[c]	0.007[c]
Gestational age ≤34 wk		31 (32.0)	30 (17.1)		0.005[b]
FHR on admission					
Normal	10 757 (90.3)	79 (81.4)	66 (37.7)	0.004[b]	<0.001[b]
Abnormal	89 (0.7)	9 (9.3)	8 (4.6)	<0.001[b]	0.129[b]
Not detectable	5 (0.1)	0	87 (49.7)	0.181[d]	<0.001[b]
Not measured	1077 (9.0)	9 (9.3)	14 (8.0)	0.934[b]	0.723[b]
Cervical dilatation on admission, cm	6.0 ± 2.4	6.11 ± 2.7	6.31 ± 2.9	0.842[c]	0.633[c]
Fetal presentation					
Cephalic	11 463 (96.2)	80 (82.5)	136 (77.7)	<0.001[b]	0.347[b]
Breech	371 (3.1)	16 (16.5)	26 (14.9)	<0.001[b]	0.717[b]
Other (transverse, prolapse)	92 (0.8)	1 (1.0)	13 (7.4)	0.997[d]	0.027[d]
Maternal infection	1885 (15.8)	18 (18.6)	19 (10.9)	0.463[b]	0.068[b]
FHR during labor					
Normal	10 025 (84.1)	58 (60.0)	43 (24.6)	<0.001[b]	<0.001[b]
Abnormal	434 (3.6)	23 (23.7)	20 (11.4)	<0.001[b]	0.008[b]
Not detectable	8 (0.1)	0	84 (48.0)	0.274[d]	<0.001[b]
Not measured	1461 (12.3)	16 (16.5)	28 (16.0)	0.270[b]	0.902[b]
Amniotic fluid					
Clear	8083 (67.8)	40 (41.2)	65 (37.1)	<0.001[b]	0.514[b]
Slight meconium	1852 (15.5)	19 (19.6)	38 (21.7)	0.274[b]	0.643[b]
Thick meconium	713 (6.0)	26 (26.8)	42 (24.0)	<0.001[b]	0.614[b]
Blood stained	47 (0.4)	1 (1.0)	8 (4.6)	0.636[d]	0.219[d]
Missing	1233 (10.3)	11 (11.3)	22 (12.6)		
Final FHR before delivery					
Normal	9743 (81.7)	60 (61.9)	37 (21.1)	<0.001[b]	<0.001[b]
Abnormal	1021 (8.6)	26 (26.8)	23 (13.1)	<0.001[b]	0.005[b]
Not detectable	5 (0.1)	0	74 (42.2)	0.998[d]	<0.001[d]
Not measured	1159 (9.7)	11 (11.3)	41 (23.4)	0.952[b]	<0.001[b]
FHR among those with detectable FHR, bpm	134 ± 11	133 ± 20	126 ± 19	0.704[c]	0.031[c]
Interval between final FHR and delivery, min	67 ± 166	67 ± 162	210 ± 310	0.999[c]	<0.001[c]
Excluding neonates with no FHR on admission		67 ± 162	174 ± 324		0.011[c]
Labor complications	771 (6.5)	19 (20.6)	54 (30.9)	<0.001[b]	0.043[b]
Obstructed	569 (4.8)	7 (7.2)	8 (4.6)	0.372[d]	0.524[d]
Uterine rupture	11 (0.1)	1 (1.0)	9 (5.1)	0.089[d]	0.147[d]
Pre-eclampsia	29 (0.3)	0	1 (0.6)	0.734[d]	0.976[d]
Eclampsia	21 (0.2)	0	3 (1.7)	0.701[d]	0.810[d]
Cord prolapse	62 (0.5)	5 (5.2)	18 (10.3)	<0.001[d]	0.203[d]
Prepartum bleeding	47 (0.4)	6 (6.2)	13 (7.4)	<0.001[d]	0.913[d]
Shoulder dystocia	32 (0.3)	0	2 (1.1)	0.742[d]	0.858[d]

(Continues)

TABLE 1 (Continued)

Characteristics	Normal (n=11 919)	END (n=97)	FSB (n=175)	*P* value	
				Normal vs END	END vs FSB
Mode of delivery					
Spontaneous vaginal	9277 (77.8)	45 (46.4)	104 (59.4)	<0.001[b]	0.040[b]
Cesarean	2551 (21.4)	45 (46.4)	61 (34.9)	<0.001[b]	0.057[b]
Assisted breech	77 (0.6)	7 (7.2)	8 (4.6)	<0.001[d]	0.504[d]
Vacuum extraction	18 (0.2)	0	2 (1.1)	0.998[d]	0.992[d]
Apgar score assigned by attending midwife					
1 min	9 (9–9)	5 (3–7)	0	<0.001[e]	<0.001[e]
5 min	10 (10–10)	9 (5–10)	0	<0.001[e]	<0.001[e]
Apgar score ≤7					
1 min	659 (5.5)	76 (78.4)	0	<0.001[b]	
5 min	41 (0.3)	36 (37.1)	0	<0.001[b]	
Time to spontaneous breathing, s	4 (2–14)	11 (5–22)		0.003[e]	
Time to cord clamping, s	58 (25–93)	21 (12–56)	42 (14–73)	<0.001[e]	0.011[e]
Resuscitation attempted	2270 (19.0)	70 (72.3)	53 (30.3)	<0.001[b]	<0.001[b]
Stimulation	2256 (18.9)	69 (71.1)	52 (39.7)	<0.001[b]	<0.001[b]
Suction	2110 (17.7)	65 (67.0)	47 (26.9)	<0.001[b]	<0.001[b]
Ventilation	574 (4.8)	64 (66.0)	53 (30.3)	<0.001[b]	<0.001[b]
Time to start ventilation, s	110 (78–153)	128 (81–159)	111 (76–162)	0.131[e]	0.364[e]
Time of ventilation, s	141 (78–243)	425 (174–1074)	359 (130–669)	<0.001[e]	0.127[e]

Abbreviations: END, early neonatal death; FHR, fetal heart rate; FBS, fresh stillbirth.
[a]Values given as number (percentage), mean ± SD, or median (interquartile range), unless indicated otherwise.
[b]χ^2 test.
[c]Student *t*. Normal distribution was verified by using the Shapiro–Wilk test.
[d]Fisher exact test.
[e]Mann-Whitney *U* test.

should be applicable to other resource-limited settings. In addition, they might serve as a substrate for understanding the pathway to FSB and birth asphyxia. The study also had limitations, including its observational methodology, and the fact that the data represent a single center in a resource-limited setting. In addition, no causal conclusions can be drawn.

For several reasons, the present observations strongly suggest that many of the neonates classified as FSB were in secondary apnea with cardiovascular collapse because of a severe asphyxial process (Fig. 3). First, the labor course was pertinent for conditions likely to compromise placental blood flow, including obstructed labor, uterine rupture, cord prolapse, and prepartum hemorrhage. Second, the cardiovascular state was pertinent for asystole noted at initiation or cessation of ventilation in 42% of neonates, or for profound unrelenting bradycardia in the remaining neonates. The unresponsive heartrate response to ventilation probably reflects a stunned myocardium secondary to hypoxia–ischemia, with presumed profound acidosis. Importantly, no cardiac compressions or medications were provided. In addition, the inability to establish effective ventilation might have been an important contributing factor.[22] Alternatively, the recorded heartrate signal might have reflected pulseless electrical activity, although all ECG recordings showed a regular rhythm and narrow QRS complexes. Last, almost all apparent FSB neonates had no respiratory effort by the time ventilation was discontinued. Indeed, lack of breathing efforts at discontinuation of BMV increased the likelihood of being classified as FSB by 92-fold.

The neonates progressing to END, and in particular the 17 (30%) where this occurred within 30 minutes of delivery (including 13 where breathing was never established), were also likely to be in secondary apnea, in part related to the same medical conditions that resulted in an interruption of placental blood flow (Fig. 3).[7,12]

The onset of spontaneous respiration after delivery has been suggested as a marker of the duration and/or severity of an asphyxial insult. Dawes[6] reported that, if resuscitation is immediately instituted, for each 1-minute duration of total asphyxia it takes approximately 2 minutes to elicit a gasp and 4 minutes to achieve spontaneous respiratory effort.[6] All neonates who died beyond 30 minutes in the present cohort exhibited spontaneous respiratory effort by the time ventilation was discontinued after a median of 8 minutes.

The timing and etiology of FSB remains poorly defined. In the present study, at least 50% of neonates classified as FSB had no FHR activity on admission, and 42% had a FHR noted before delivery (Table 1).

TABLE 2 Labor, delivery, and resuscitation characteristics among neonates classified as early neonatal death and fresh stillbirth with ECG and ventilation recordings.[a]

Characteristic	END (n=55)	FSB (n=46)	*P* value
Birth weight, g	2815 ± 583	2919 ± 634	0.394[d]
Gestational age, wk	37.3 ± 2.7	37.2 ± 2.6	0.876[d]
FHR on admission			
Normal	43 (78)	31 (68)	0.315[e]
Abnormal	8 (15)	4 (9)	0.554[f]
Not detectable	0	4 (9)	0.346[f]
Not measured	4 (7)	7 (15)	0.339[f]
Cervical dilatation on admission, cm	6.2 ± 2.7	5.5 ± 2.5	0.262[d]
Fetal presentation			
Cephalic	49 (89)	40 (87)	0.721[e]
Breech	5 (9)	5 (11)	0.942[f]
Other (transverse, prolapse)	1 (2)	1 (2)	0.998[f]
FHR during labor			
Normal	30 (55)	24 (52)	0.733[e]
Abnormal	18 (33)	10 (22)	0.264[e]
Not detectable	0	3 (7)	0.642[f]
Not measured	7 (11)	9 (20)	0.349[e]
Amniotic fluid			
Clear	18 (33)	20 (44)	0.241[e]
Slight meconium	13 (24)	5 (11)	0.248[f]
Thick meconium	22 (40)	19 (41)	0.997[e]
Final FHR before delivery			
Normal	31 (56)	21 (46)	0.246[e]
Abnormal	19 (35)	14 (30)	0.734[e]
Not detectable	0	2 (4)	0.804[f]
Not measured	5 (9)	9 (20)	<0.001[f]
FHR among those with detectable FHR, bpm	134 ± 23	127 ± 21	0.155[d]
Interval between final FHR and delivery, min[b]	18 (10–38)	39 (20–65)	0.006[h]
Labor complications	10 (18)	18 (39)	0.019[e]
Mode of delivery			
Spontaneous vaginal	21 (38)	20 (45)	0.547[e]
Cesarean	33 (60)	26 (57)	0.681[e]
Assisted breech	1 (2)	0	0.987[f]
Vacuum extraction	0	0	
Resuscitation attempted			
Stimulation	54 (98)	45 (98)	0.997[f]
Suction	55 (100)	44 (96)	0.649[f]
Ventilation	57 (100)	47 (100)	
Time from delivery to cord clamping, s	18 (9–45)	21 (10–42)	0.438[h]
Time from delivery to placement of ECG, s	118 (68–150)	88 (68–124)	0.216[h]
Time from delivery to ventilation start, s	128 (84–160)	112 (78–173)	0.373[h]
Heartrate present at start of ventilation	52 (95)	27 (58)	<0.001[e]
Heartrate at start of first ventilation, bpm	76 ± 37	52 ± 19	0.003[d]
Ventilation parameters			
Inflated volume, mL	47 ± 21	39 ± 17	0.038[d]

(Continues)

TABLE 2 (Continued)

Characteristic	END (n=55)	FSB (n=46)	*P* value
Expired volume, mL	28 ± 15	21 ± 14	0.033[d]
Mask leakage, %	38 ± 19	44 ± 23	0.161[d]
Expired volume, mL/kg	10.0 ± 5.3	7.4 ± 4.7	0.011[d]
Ventilation frequency, per min	56 ± 21	64 ± 23	0.076[d]
Peak inflation pressure, mbar	32 ± 7	32 ± 7	0.926[d]
Duration from first to final ventilation, s	484 (174–1091)	363 (131–688)	0.410[h]
Neonates with expired CO_2, %[c]	55 (100)	45 (99)	<0.001[e]
<1	13 (24)	37 (81)	<0.001[e]
1–3	20 (36)	8 (17)	0.033[e]
≥3	22 (40)	1 (2)	<0.001[f]
Expired CO_2, %	2.44 ± 1.60	0.75 ± 0.76	<0.001[d]
Neonatal responses			
Started breathing at cessation of ventilation	42 (76)	1 (2)	<0.001[f]
Heartrate present at cessation of ventilation	53 (96)	27 (59)	<0.001[e]
Heartrate at cessation of ventilation, bpm	115 ± 49	52 ± 33	<0.001[d]
Rapid (<40 s) increase in heartrate	29 (53)	4 (9)	<0.001[e]
Heartrate increase from first to final ventilation, bpm	40 ± 54	0.03 ± 24	<0.001[d]
Apgar score assigned by attending midwife			
1 min	4 (3–5)	0	<0.001[h]
5 min	8 (5–10)	0	<0.001[h]

Abbreviations: END, early neonatal death; FHR, fetal heart rate; FBS, fresh stillbirth.
[a]Values are given as mean ± SD, number (percentage), or median (interquartile range), unless indicated otherwise.
[b]Excluding neonates with no FHR on admission.
[c]1% ≈1 kPa=7.5 mm Hg; 3% ≈3 kPa=22.5 mm Hg.
[d]Student *t* test. Normal distribution was verified by using the Shapiro-Wilk test.
[e]χ^2 test.
[f]Fisher exact test.
[h]Mann-Whitney *U* test.

Among the neonates classified as FSB with ECG recordings at delivery, 42% were asystolic from the beginning and the remainder were persistently bradycardic despite basic resuscitation. This latter observation supports the concept of a misclassification of flaccid newborns as FSB (Apgar score of zero at 1 and 5 minutes). Moreover, one of the neonates classified as FSB had some gasping effort. Assignment of Apgar scores has previously been reported to be unreliable in this setting.[23]

Previous findings from the same rural hospital indicate that an abnormal and/or absent FHR before delivery is a strong predictor and highly specific for a newborn in need of resuscitation at birth and/or delivery of a FSB.[18] Therefore, careful assessment of FHR and detection of FHR abnormalities are important first steps in preventing intrapartum hypoxia/ischemia, a presumed precursor to FSB. Other data from an urban low-resource setting indicate that approximately 60% of FSBs occur in the context of three clinical categories: acute interruption of placental blood flow, pre-eclampsia, and fetal distress.[19] These observations suggest that improved obstetric and immediate neonatal care could prevent many intrapartum-related FSBs.

A critical issue is whether enhanced FHR monitoring during labor can identify fetuses at increased risk of FSB or asphyxia-related END. In the present study, FHR abnormalities as a first sign of hypoxia/ischemia may have been missed because the mean time interval from the final recorded FHR to delivery was almost 3 hours for FSB neonates with a detectable FHR on admission to the labor ward, and more than 1 hour for END neonates (Table 1). However, improved FHR monitoring is unlikely to prevent fatal outcomes unless coupled with timely obstetric actions. For example, 22% of FSB and 12% of END neonates were secondary to acute events such as uterine rupture, cord prolapse, and prepartum bleeding, which necessitates an immediate response to avoid adverse outcomes. A second critical issue is whether intensive resuscitation including immediate (within the first minute) initiation of ventilation, cardiac compression, and medication might have restored cardiovascular integrity.[24,25]

In conclusion, progression to FSB and/or asphyxia-related END is probably part of the same end-process of circulatory collapse following intrapartum hypoxia/anoxia, and could be modulated by delayed delivery, ineffective/delayed ventilation, and/or absence of cardiac compression. Distinguishing a true FSB from a severely asphyxiated newborn in the delivery room is clinically difficult and probably influences the global rates of reported perinatal mortality.[12]

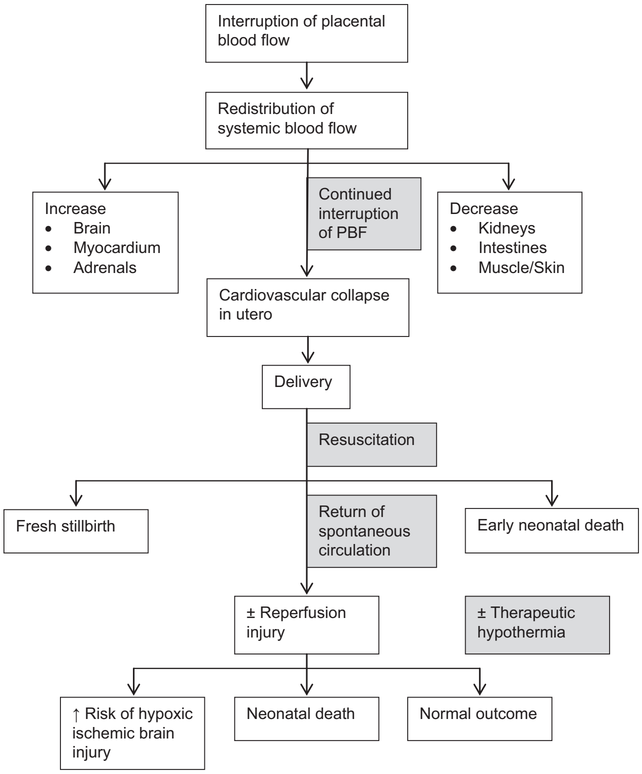

FIGURE 3 Proposed common pathway to a fresh stillbirth or asphyxia-related early neonatal death. Abbreviation: PBF, placental blood flow.

AUTHOR CONTRIBUTIONS

HLE contributed to the conception and design of the study, data collection, analyses and interpretation, and manuscript writing. JE contributed to data processing, analyses and interpretation, and manuscript revisions. JEL contributed to data collection, analyses, and manuscript revisions. AY, ERM, and HK contributed to data collection and manuscript revisions. JP contributed to the design of the study, analyses and interpretation, and manuscript revisions. All authors approved the final manuscript.

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CONFLICTS OF INTEREST

JE is an employee of Laerdal Medical. JEL is married to an employee of Laerdal Global Health. JEL has received an unrestricted research grant from the Laerdal Foundation for Acute Medicine, JP has received a travel grant from the Laerdal Foundation for Acute Medicine, and Haydom Lutheran Hospital has received project funds from the Laerdal Foundation for Acute Medicine. The authors have no other financial relationships from the 3 years preceding publication with any organizations that might have an interest in the submitted work, or other relationships or activities that could have influenced the submitted work.

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