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● *Original Contribution*

DETECTION OF CEREBRAL HIGH-INTENSITY TRANSIENT SIGNALS BY NEODOPPLER DURING CARDIAC CATHETERIZATION AND CARDIAC SURGERY IN INFANTS

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Abstract—There is a risk of gaseous and solid micro-embolus formation during transcatheter cardiac interventions and surgery in children with congenital heart disease (CHD). Our aim was to study the burden of high-intensity transient signals (HITS) during these procedures in infants. We used a novel color M-mode Doppler (CMD) technique by NeoDoppler, a non-invasive ultrasound system based on plane wave transmissions for transfontanellar continuous monitoring of cerebral blood flow in infants. The system displays CMD with 24 sample volumes and a Doppler spectrogram. Infants with CHD undergoing transcatheter interventions (n = 15) and surgery (n = 13) were included. HITS were manually detected based on an "embolic signature" in the CMD with corresponding intensity increase in the Doppler spectrogram. Embolus-to-blood ratio (EBR) defined HITS size. A total of 1169 HITS with a median EBR of 9.74 dB (interquartile range [IQR]: 5.10−15.80 dB) were detected. The median number of HITS in the surgery group was 45 (IQR: 11−150), while in the transcatheter group the median number was 12 (IQR: 7−24). During cardiac surgery, the highest number of HITS per hour was seen from initiation of cardiopulmonary bypass to aortic X-clamp. In this study we detected frequent HITS and determined the feasibility of using NeoDoppler monitoring for HITS detection. (E-mail: martin.leth-olsen@ntnu.no)

Key Words: **High-intensity transient signals, Micro-embolic signals, Brain embolisms, Doppler ultrasound monitoring, Color M-mode Doppler, Congenital heart disease.**

INTRODUCTION

Approximately 25% of infants with congenital heart disease have critical heart defects, many of which will require an interventional procedure or surgery within the first year of life (Virani et al. 2020). Long-term neurological disabilities are still common in this population (Gaynor et al. 2015; Marelli et al. 2016; Feria-Kaiser et al. 2020).

Children with congenital heart disease (CHD) are at risk of gaseous and solid embolus formation with embolization to the cerebral circulation during transcatheter cardiac interventions and cardiac surgery with cardiopulmonary bypass (CPB) (O'Brien et al. 1997; Rodriguez et al. 1998; Itoh et al. 2011; Wallace et al. 2016; Larovere et al. 2017). Many children with CHD have venous-to-systemic shunts predisposing to passage of emboli to the brain. The clinical implications of cerebral micro-emboli in the pediatric population are unclear (Naik et al. 2014). There is also conflicting evidence in the adult population (Martin et al. 2009; Kruis et al. 2010). Peri-operative brain injuries in children with CHD are common (Mahle et al. 2002; Chen et al. 2009; Chung et al. 2019), and are associated with neurodevelopmental disease in children of school age (Claessens et al. 2018). Modifications of procedures to reduce the embolic load could potentially be advantageous but require reliable monitoring equipment. Near-infrared spectroscopy for cerebral monitoring is used to

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some degree in this patient group but cannot detect micro-emboli (Durandy et al. 2011).

Transcranial Doppler (TCD) to detect micro-emboli has been used for research purposes for decades (Padayachee et al. 1987) and in stroke diagnostics (Spence et al. 2005). High-intensity transient signals (HITS) in the Doppler spectrum represent both gaseous and solid emboli. Pulse-waved, single-gated TCD (sgTCD) equipment with monitoring of the middle cerebral artery has been the standard, but HITS detection algorithms and HITS criteria have varied. A consensus on micro-embolus detection and reporting has been proposed (Ringelstein et al. 1998). However, TCD devices are not well suited for continuous monitoring of neonates and young infants because of the size and shape of the transducers, which require a large, rigid head accessory to hold them in position. A dedicated cerebral monitoring system is needed for this vulnerable population. Our aim was to investigate whether a new ultrasound monitoring system specially designed for neonates and infants, NeoDoppler (Vik et al. 2020), could detect and quantify HITS in children with CHD during transcatheter interventions and cardiac surgery. We hypothesized that the color M-mode Doppler (CMD) used in NeoDoppler could provide continuous information on HITS; thus, we also aimed to describe the burden of HITS during transcatheter cardiac interventions and cardiac surgery in infants with CHD.

METHODS

Patient selection

This study was conducted at the Department of Pediatric Cardiology, Oslo University Hospital (OUS), Oslo, Norway, in close collaboration with the ultrasound group at The Norwegian University of Science and Technology (NTNU). The Regional Committee for Medical and Health Research Ethics, REC Central (Reference 2017/314), the Norwegian Directorate of Health (Reference 17/15181-11) and The Norwegian Medicines Agency (Reference 19/05458) approved the study. Informed written consent was obtained from the parents of all participants.

In Norway, all pediatric cardiac catheterizations and surgeries are centralized to OUS, and for our prospective observational study we recruited participants at OUS from February 2019 to December 2019. Neonates and infants (<1 y of age) with CHD who were scheduled for transcatheter intervention or cardiac surgery with CPB were eligible for enrollment. The first author was present during the full inclusion period of all patients. Relevant procedures and events were documented. Consent was obtained from the parents of 31 children.

Study protocol

The participants were monitored with NeoDoppler during transcatheter cardiac interventions or surgery from after intubation until the end of the procedure or surgery. A customized soft hat with a probe attachment mechanism fixed the probe over the anterior fontanelle before the start of the procedure. The investigator made sure that adequate signal was obtained, and the NeoDoppler display interface was then blinded to avoid any impact on the clinical staff. The NeoDoppler display was used only for periodic signal quality checks. Recordings were made in intervals with pre-set recording times 1 to 30 min long with up to 1-min pauses. The recording intervals were selected based on the phases of the intervention or surgery, with the longest continuous recordings in the more critical phases and the shorter recordings during phases of surgery in which no surgical or anesthetic procedures were performed.

Equipment, image acquisition, processing and safety

NeoDoppler is a non-invasive ultrasound Doppler system developed by the ultrasound group at NTNU, Trondheim, Norway. A small lightweight probe (Imasonic SAS, France) integrated into a cap (Fig. 1A) is connected to an ultrasound scanner (Manus EIM-A, Aurotech Ultrasound AS, Tydal, Norway) and a PC with a user interface (Vik et al. 2020). The probe operates at a frequency of 7.8 MHz, with plane wave transmissions that cover a cylindrical shape with a diameter of 10 mm, in a depth range down to 38 mm with a 1.5-mm axial extension of the 24 sample volumes (SVs). The signal is processed in real time, and received echo data are transferred through a network cable to a PC with a user interface. The real-time high-frame-rate CMD and Doppler spectrogram are displayed simultaneously. The CMD indicates direction of flow (*red* toward and *blue* away) and the intensity of the signal (brightness) of the blood vessels intersecting the ultrasound beam. A corresponding pulse wave Doppler spectrogram is displayed based on the selected SV, as illustrated in Figure 1. If the selected SV covers multiple vessels the Doppler trace in the spectrogram represents the vessel with the highest velocity.

An in-house MATLAB (The MathWorks, Natick, MA, USA) application was used for offline post-processing and analysis and allowed detailed digital reviewing of the recordings. The SV position and size can also be adjusted during offline processing based on region of interest. Basic adjustments such as gain, vertical scale, horizontal sweep, SV size and depth are adjusted through a menu system. Doppler velocity data and indices are displayed for the selected SV and time interval.

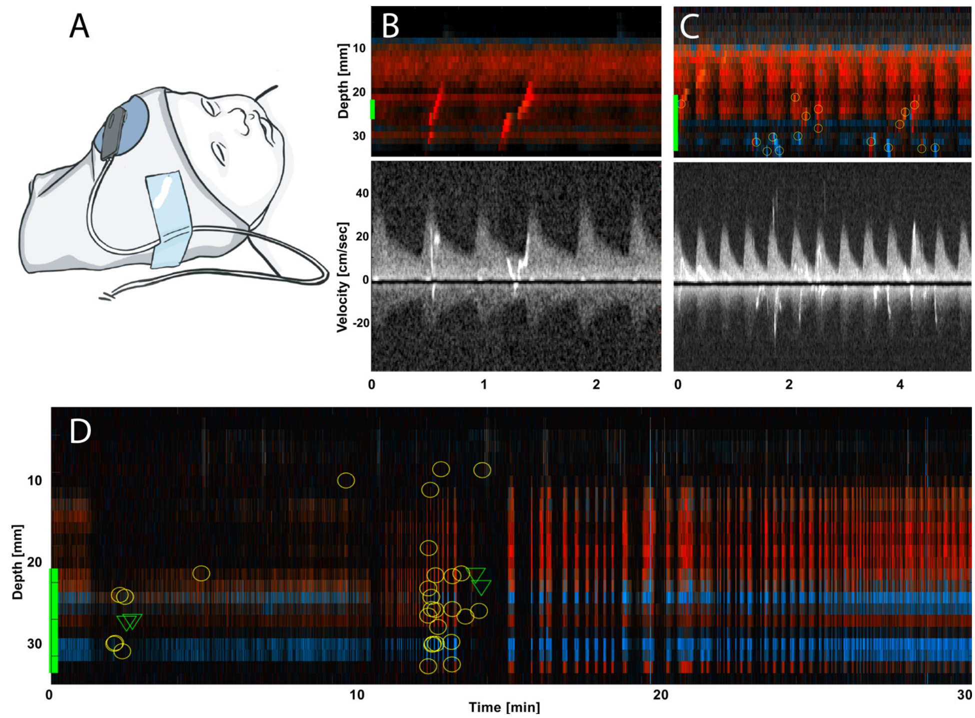

Fig. 1. NeoDoppler high-intensity transient signal (HITS) detection. (A) Soft hat with the attachment mechanism for fixation of the probe. (B) Color M-mode Doppler (CMD) in the top panel with a sample volume (SV), the *green marker*, placed at a depth around 23−26 mm. Skewed *red* HITS are seen in the CMD. The spectrogram in the panel below corresponds to the spatial position selected by the SV. (C) How HITS were marked in the CMD. *Yellow circles* labeled single HITS, while uncertain events were marked with a *triangle*. (D) CMD in a 30-min recording of a patient undergoing cardiac surgery with HITS marked as in (C).

The safety of NeoDoppler has previously been described (Vik et al. 2020). In standard ultrasound, the temperature increase is highest at the focus depth. In NeoDoppler, the temperature increase is highest at the skin surface and diminishes with increasing depth because of the unfocused beam. Recordings were done in intervals with short pauses to further reduce the bioeffects of ultrasound. According to ter Haar (2012), a thermal index <0.7 and mechanical index <0.3 have no time limitation and are considered safe for continuous recordings. The skin was examined after removal of the probe to assess for any local adverse effects from the probe.

Data acquisition protocol

The insonated arteries cannot be truly identified anatomically based on CMD. Arteries at multiple depths can be shown simultaneously in a cylindrical 10 × 38-mm (diameter × depth) volume. The high pass filter is set to 170 Hz. Doppler data are automatically saved to the hard drive intermittently after each defined recording interval.

In this study, HITS were manually detected by the investigator based on the CMD and the corresponding Doppler spectrogram. Manually detected HITS were defined as high-intensity signals in the CMD with an "embolic signature" and a corresponding intensity increase in the Doppler spectrogram from the same spatial position for confirmation. The "embolic signature" in the CMD consists of a skewed line of high-intensity signal moving away or toward the probe (Fig. 1B). A unidirectional high-intensity signal in the spectrogram from the same spatial position confirms the embolic trace in the CMD. By changing SV depth, a time delay of the high-intensity signal can be observed in the spectrogram corresponding to the skewed line in the CMD (Supplementary Video S1, online only). Complex patterns where the change in directionality was seen in the CMD and in the spectrogram as a "to and from" continuous signal, were counted as a single embolus. "To and from" signals that could not be continuously traced in time in the spectrogram with SV adjustment were counted as separate emboli. Multiple embolic signatures in different spatial positions at the same time were counted as separate discrete emboli if they had spatial separation in the CMD and could not be traced continuously in depth in the spectrogram while the SV depth or size was being adjusted.

HITS analysis protocol

Episodes of HITS were grouped into single HITS, HITS with a curtain effect and HITS with uncertain events, as described previously (Larovere et al. 2017). Single HITS events were defined as single episodes with an "embolic signature" in the CMD with a corresponding single intensity spike in the spectrogram. HITS with a curtain effect had a broad or chaotic embolic pattern in the CMD with a corresponding intensity increase that filled the entire Doppler curve or were so numerous that they could not be distinguishable separately in the spectrogram. Uncertain events were defined as events that did not fill the criteria for HITS or artifacts. Artifacts caused by electromagnetic distortion or probe motion have a high intensity signal in several depths simultaneously with no time delay in the CMD and a corresponding bidirectional spike in the spectrogram. HITS were manually marked in the CMD according to these categories, creating temporal and spatial coordinates for all events.

In the patients undergoing cardiac surgery with CPB, HITS were further grouped into the following periods: pre-cannulation, from the start of NeoDoppler registration to the moment before aortic cannulation; cannulation, from aortic cannulation to before aortic X-clamp; CPB, from initiation of CPB to aortic X-clamp; X-clamp on, from the moment of aortic X-clamp to the moment immediately before declamping; X-clamp off, from the moment of declamping of the aorta to the end of CPB; decannulation, the period from the end of CPB to decannulation of the aorta; and after decannulation, from the period after decannulation to the end of surgery. The total count of single HITS for the defined periods as well as HITS count rate (HITS per hour) were calculated.

Embolus-to-blood ratio (EBR, in decibels [dB]) of single HITS were automatically calculated based on the difference in intensity between the manually marked single HITS and the mean background signal during the 5 s before and after all single HITS. HITS with a curtain effect were not included in this analysis. Negative EBRs were excluded from the statistics but were studied in detail manually to try to explain the phenomenon and further understand potential errors in the calculations. A theoretical relation between air embolus diameter and EBR is illustrated in Figure 2. The scattering cross

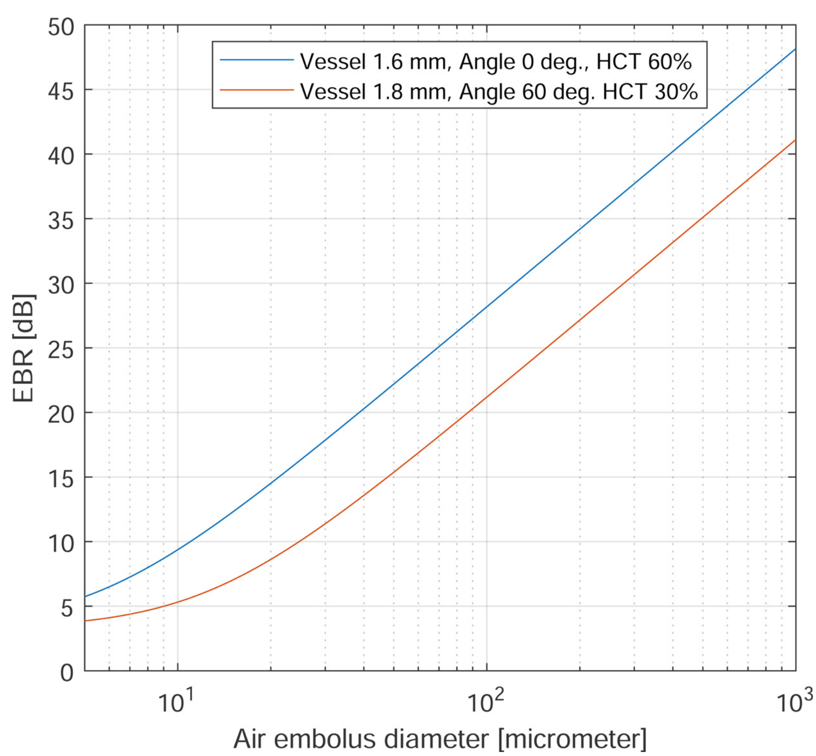

Fig. 2. Theoretical relationship between embolus-to-blood ratio (EBR) and air embolus diameter. A theoretical model of air embolus diameter in micrometers, related to EBR in decibels (dB), for two cases: one with maximum expected blood signal amplitude, and one with minimum blood signal amplitude If it is assumed that the anterior cerebral artery is insonated, the diameter of the vessel is in the range 1.6−1.8 mm for infants from birth to 6 mo of age. With a variation of angle of insonation between 0 and 60° degrees and of hematocrit (HCT) between 0.3 and 0.6, an EBR of 15 dB would correspond to an air embolus diameter in the range 22−48 μm.

Table 1. Basic patient and procedure measures for transcatheter interventions and surgery*

	Total (n = 28)	Transcatheter intervention (n = 15)	Surgery (n = 13)
Male sex (n)	15 (61%)	9 (60%)	8 (61.5%)
Age (mo)	3.2 (0.6−6.0)	3 (0.5−6)	3.5 (1.9−6.3)
Weight (g)	5303.7 ± 1822.8	5084.8 ± 2001.2	5556.5 ± 1635.2
Body surface area (m^2)	0.29 ± 0.07	0.29 ± 0.08	0.31 ± 0.06
Hematocrit (fraction)	0.35 (0.32−0.38)	0.33 (0.31−0.39)	0.36 (0.33−0.38)
Heart rate (bpm)	140 ± 20.8	134 ± 24.6	147 ± 12.9
Mean arterial pressure (mm Hg)	59 ± 8.9	62 ± 9.2	56 ± 7.7
Duration of operation (min)	81.3 ± 39.4	55.7 ± 21.7	110.9 ± 34.4
Duration of cardiopulmonary bypass (min)		n.a.	61 (54.0−85.5)
Duration of NeoDoppler monitoring (min)	112.0 (59.6−249.3)	60.8 (45.8−86.9)	254.2 (194.7−300.2)

* Values are expressed as n (%) and median (first to third quartiles) for non-normally distributed data and as the mean ± standard deviation for normally distributed data.

section of air embolus was assumed to be equal to the geometrical cross section. The backscattering coefficient of human blood varies between 5^{-4}/m and 10^{-4}/m, depending on hematocrit (Cobbold 2006). The volume of blood contributing to the background signal depends on the vessel diameter and the angle of insonation. In Figure 2, the theoretical EBR is calculated for two different cases; one with maximum expected blood signal amplitude, and one with minimum blood signal amplitude. We have used vessel diameter in the range 1.6−1.8 mm (Arat et al. 2015). We chose to characterize HITS with EBR ≥15 dB as large. We used this cutoff value to determine the number of large air emboli for all individual cases, for the transcatheter interventions and the surgery group, and the distribution of large air emboli during the different surgical phases.

Reproducibility: Intra- and inter-observer variability

To evaluate the reproducibility of the manual HITS detection, three patients from transcatheter intervention group and one patient from the cardiac surgery group were randomly selected. The data were re-analyzed by the same investigator (M.L.O) and by a second investigator (S.A.N.). The investigators registered single HITS, HITS with a curtain effect and uncertain events in these data sets.

Statistical analysis

This was an exploratory pilot study. We did not know what to expect regarding the HITS count and what difference in HITS count was clinically relevant. Power calculations were therefore not performed *a priori*. SPSS Statistics version 27 (IBM, Armonk, NY, USA) was used for statistical analyses. Data for continuous variables are expressed as the mean ± standard deviation (SD) if normally distributed or as the median and interquartile range if non-normally distributed.

RESULTS

Patient selection

In this study we included 28 patients with 15 participants (54%) undergoing transcatheter interventions and 13 participants (46%) undergoing cardiac surgery with CPB. The infants had a median age of 3.2 mo (range: 0.1−8 mo). Four patients (14.3%) received pre-operative prostaglandin E infusion. The patient characteristics are further summarized in Table 1.

Feasibility

Three infants (8, 7 and 6 mo of age, respectively) for whom consent had been received could not be included: one because of a closed fontanelle, one because of thick hair where the cap that fixes the probe slipped off and one infant for whom the investigator could obtain only venous Doppler signal. The remaining 28 patients displayed high-quality Doppler signals during the whole study period except for procedure-specific artifacts as described below. Diathermia typically introduced artifacts in the Doppler spectrogram (Fig. 3), making automatic tracing of the velocity curve difficult. Still, HITS could be detected in the CMD between interference from the diathermia, but also during diathermia. Anesthetic procedures and transesophageal echocardiograms occasionally caused minor direct probe movement that could introduce artifacts, especially at shallower depths. X-Ray and other electronic equipment could introduce mild continuous artifacts. These artifacts were considered manageable when it came to HITS detection.

The signal quality was approved by the investigator in all included Doppler data during manual HITS detection.

High-intensity transient signals

High-intensity transient signals were detected in 13 of 15 patients during transcatheter interventions and in all patients during cardiac surgery. In all patients, a total

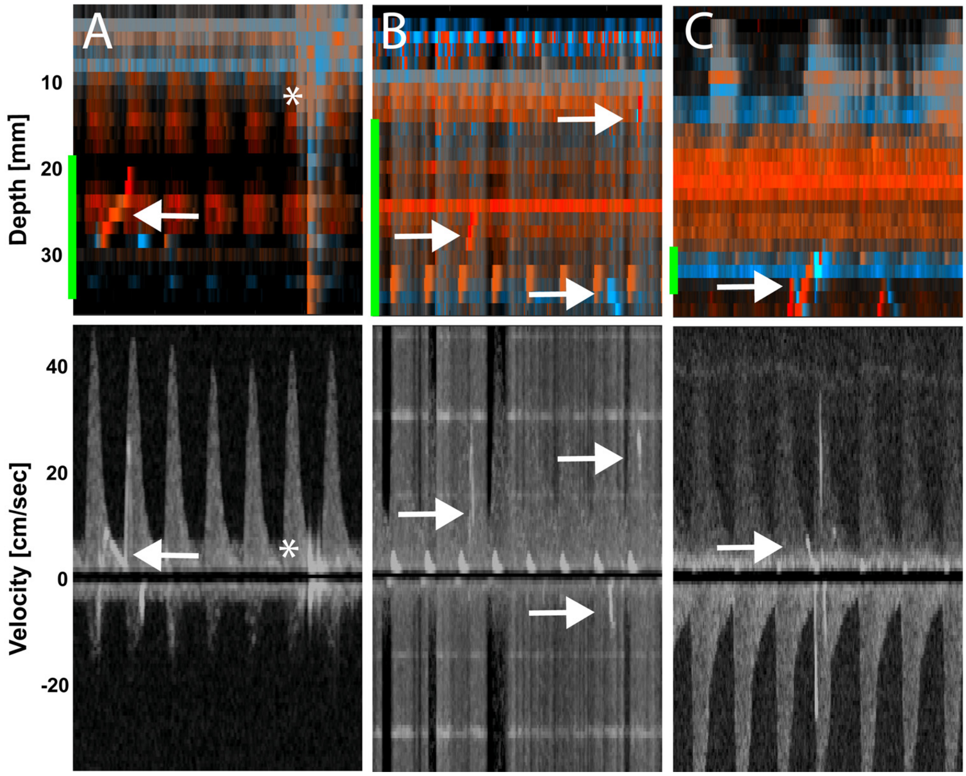

Fig. 3. High-intensity transient signals (HITS) and artifacts. (A) A HITS event seen as a skewed line of high intensity in the color M-mode display (CMD) marked with an *arrow*, while artifacts are vertical lines in the CMD marked with an *asterisk*. The corresponding intensity findings are in the spectrogram (lower panel). (B) HITS, marked with *arrows*, seen in the CMD and corresponding spectrogram with simultaneous artifacts from diathermia in a patient undergoing arterial switch. (C) HITS events marked with an *arrow* in the CMD with corresponding findings in the spectrogram (lower panel), where a continuous artifact/interference with a slow oscillating pattern with quite high velocity in the spectrogram is also seen. HITS can still be recognized in this recording from this transcatheter device closure of a secundum atrioseptal defect.

of 1169 HITS (median = 23.5, interquartile range [IQR]: 11.25−73.5) were detected Table 2. summarizes HITS events for all patients. The median total numbers of HITS in the surgery group and in the transcatheter intervention group were 45 (IQR: 11−150) and 12 (IQR: 7−24), respectively. Most HITS were single HITS, while HITS with a curtain effect were seen in only 6 patients.

For patients undergoing cardiac surgery, the HITS count rate was highest from initiation of CPB to aortic X-clamp with a rate of 65.9 HITS per hour, but the highest number of HITS was seen during the X-clamp on period. The total number of HITS and the HITS rate during all surgical periods are illustrated in Figure 4.

HITS embolus-to-blood ratio

The HITS had an EBR for all included patients with a median of 9.74 dB (IQR: 5.10−15.80 dB), where transcatheter interventions had a median of 14.90 dB (IQR: 7.87−21.90 dB) and cardiac surgery had a median of 7.79 dB (IQR: 4.27−21.30 dB) Figure 5. illustrates the distribution of HITS based on EBR for both transcatheter interventions and surgery. Eleven HITS had a negative value that could be explained by proximity to embolic showers that caused the background intensity to be higher than the selected single HITS, curtains or diathermia and/or a more intense venous signal simultaneously in the same SV (Fig. 6).

Intra- and inter-observer analysis of manual HITS detection

Investigator 1 (M.L.O) registered a total of 128 single HITS, 4 HITS with curtain effect and 15 uncertain events in the primary analysis. One hundred thirty single HITS, 4 HITS with curtain effect and 14 uncertain events were registered in the reanalysis by the same investigator. Investigator 2 (S.A.N) registered 128 single HITS, 3 HITS with curtain effect and 13 uncertain events.

Selected patient examples

We selected patient examples to illustrate how NeoDoppler typically displayed the “embolic signature” of

Table 2. HITS detection during transcatheter interventions and surgery related to cardiac diagnosis and type of procedure

Diagnosis	Procedure	HITS Single - n	HITS Single ≥15 dB - n (%)	HITS Curtain effect - n
	Transcatheter intervention (n = 15)	Median: 12 IQR: 7−24	Mean: 35% SD: ±26.8%	Median: 0 IQR: 0−0
vPS	PV balloon valvuloplasty	7	3 (42.9)	0
ReCoA	Aortic balloon dilatation	29	4 (13.8)	0
vPS	PV balloon valvuloplasty	13	9 (69.2)	0
HLHS	Sano shunt test occlusion and SVC-PA balloon dilatation	77	51 (66.2)	14
vPS	PV balloon valvuloplasty	12	3 (25.0)	0
vPS	PV balloon valvuloplasty	1	0 (0)	0
ReCoA	Aortic balloon dilatation	9	4 (44.4)	3
Ebstein's anomaly	Ductal stenting	7	1 (14.3)	0
LPA stenosis	LPA balloon dilatation	0	0 (0)	0
PDA	Device occlusion	0	0 (0)	0
vAS	AoV balloon valvuloplasty	24	13 (54.2)	0
vAS	AoV balloon valvuloplasty	21	10 (47.6)	0
PA/IVS	PV radio frequency ablation	147	64 (43.5)	2
LPA stenosis	LPA balloon dilatation	19	16 (84.2)	0
ASD	Device occlusion	8	2 (25.0)	0
	Surgery (n = 13)	Median: 41 IQR: 11−150	Mean: 16.3% SD: ±13.3%	Median 0 IQR: 0−0.5
cAVSD	Repair	21	3 (14.3)	0
cAVSD	Repair	41	9 (22.0)	4
TGA	Arterial switch operation	150	22 (14.7)	0
CoA	Repair	23	1 (4.3)	0
pAVSD	Repair	36	4 (11.1)	0
DORV-TOF	Repair	74	5 (6.8)	0
TAPVC	Repair	11	4 (36.4)	0
TOF	Repair	31	1 (3.2)	0
cAVSD	Repair	112	25 (22.3)	1
tAVSD	Re-operated mitral valve plasty	72	33 (45.8)	0
DORV-TOF	Repair	91	9 (9.9)	7
pmVSD + mVSD	Closed pmVSD, PA banding	24	5 (20.8)	0
pmVSD	Repair	78	0 (0)	0

Description of each case with single HITS, single HITS with embolus-to-blood ratio (EBR) ≥15 decibels (dB) and HITS with curtain effect. AoV = aortic valve; ASD = atrial septal defect; cAVSD = complete atrioventricular septal defect; CoA = coarctation of the aorta; DORV-TOF = double-outlet right ventricle of tetralogy of Fallot type; HITS = high-intensity transient signal(s); HLHS = hypoplastic left heart syndrome; IQR = interquartile range; LPA = left pulmonary artery; mVSD = muscular VSD; PA = pulmonary artery; PA/IVS = pulmonary atresia with intact ventricular septum; pAVSD = partial atrioventricular septal defect; PDA = patent ductus arteriosus; pmVSD = perimembranous VSD; PV = pulmonary valve; ReCoA = re-coarctation of the aorta; SVC-PA = superior vena cava to pulmonary artery; TAPVC = total anomalous pulmonary venous connection; tAVSD = transitional atrioventricular septal defect; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; vAS = valvular aortic stenosis; vPS = valvular pulmonary stenosis.

HITS in infants during transcatheter interventions and surgery, as illustrated in Figure 7.

Safety

Values for mechanical index and thermal index were continuously displayed during recordings and were within the recommended limits for neonatal transcranial ultrasound (ter Haar 2012). The mean thermal index for soft tissue in the patients in this study was 0.5 (SD: ±0.17) at the skin surface with reduction to 0.1 (SD: ±0.04) at 3.0-cm depth. The mean thermal index for bone and cranial bone was 0.35 (SD: ±0.12). The mean mechanical index was 0.063 (SD: ±0.01). Transient, mild local skin impression from the probe fixation area could be seen in most patients right after probe removal but normalized within minutes to hours. There were no serious skin reactions. No patients had remaining signs of skin irritation after 3 h.

DISCUSSION

In this study, we describe HITS detection with NeoDoppler and determine its feasibility in infants less than 8 mo of age. We found that this technique detects frequent HITS. A large variety of CHD diagnoses and procedures were included; although most patients had HITS during transcatheter interventions and surgery, the total HITS burden varied from case to case. Single HITS were most often detected in this study, with HITS with a curtain effect being more rarely detected. We described

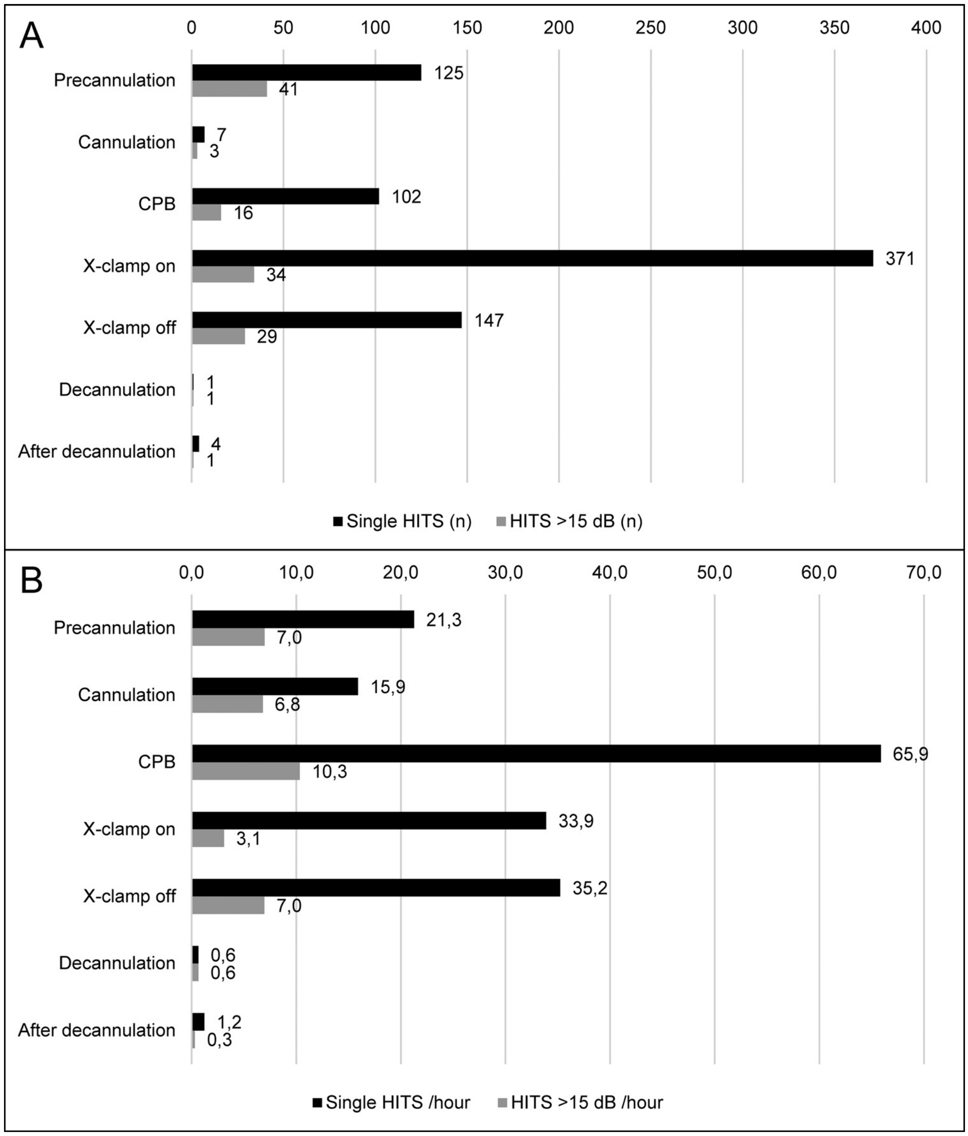

Fig. 4. Single high-intensity transient signals (HITS) and single HITS with embolus-to-blood ratio (EBR) ≥15 dB during cardiac surgery. (A) Total numbers of single HITS and HITS with EBR ≥15 dB during the different periods of surgery in the 13 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). (B) Corresponding HITS rate (HITS/hour).

different HITS patterns and signatures in CMD and spectrograms. We also described different HITS counts and count rates during different phases of surgery.

The NeoDoppler systems allows for a more in-depth evaluation of HITS than is possible with traditional sgTCD. A sgTCD sample volume covers only a small part of the embolic path while NeoDoppler uses the combination of a broad ultrasound beam that permits prolonged scanning time of each embolus as it moves through the ultrasound beam and a high frame rate in the CMD to track an embolus in depth to gain more information about these patterns. Discriminating HITS from artifacts with sgTCD equipment can be challenging. There could be potential advantages of newer Doppler technologies such as power M-mode Doppler (PMD) that allow for tracking emboli in a broad depth range (Moehring and Spencer 2002; Saqqur et al. 2004; Choi et al. 2010). Like NeoDoppler, PMD allows for better recognition of the "embolic signature." Dual-gated Doppler has also exhibited time delay of the embolic signal as a key feature of emboli (Molloy and Markus Hugh 1996). NeoDoppler further allows for more detailed evaluation of emboli as the SV can be adjusted in size and depth to the spatial region of interest during both live recording and post-recording to evaluate spectrograms in detail. We believe that evaluation of these

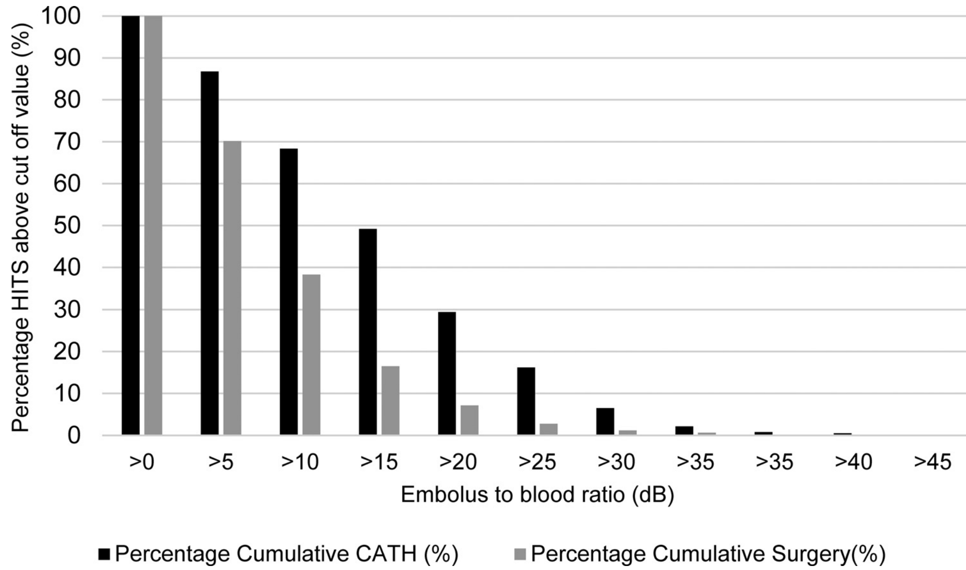

Fig. 5. Cumulative histogram: embolus-to-blood ratio. This cumulative histogram illustrates the distribution of high-intensity transient signals (HITS) with respect to embolus-to-blood ratio cutoff values in decibels for transcatheter interventions (CATH) and cardiac surgery (Surgery).

patterns and "embolic signatures" is a key to making embolus detection more reliable and separation from artifacts easier. Furthermore, complex patterns with "to and from" signatures are seen more often with a broad ultrasound beam that is more likely to insonate the change of direction in a blood vessel or a bifurcation. The embolic patterns and embolic signatures seen in this study are in line with studies using PMD (Moehring and

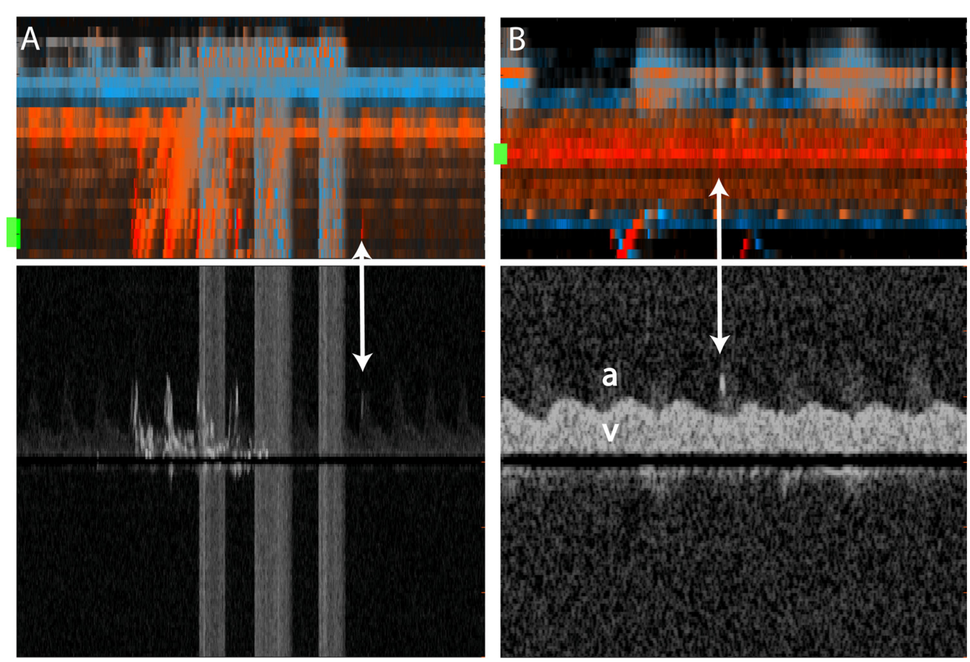

Fig. 6. High-intensity transient signals (HITS) with negative embolus-to-blood ratio (EBR). EBR was automatically calculated from the maximum intensity of the manually marked HITS and compared with the mean intensity of the 5 s prior to and after the HITS in the same depth. These examples illustrate potential sources of error in these calculations. (A) A HITS (*arrowhead*) where a shower of HITS with curtain effect and artifact from diathermia prior to the marked HITS event, resulting in negative EBR. (B) Another example (*arrowhead*). There are two Doppler signals in the spectrogram, including a venous signal (v) with higher intensity than the arterial signal (a) where the HITS (*arrowhead*) is seen.

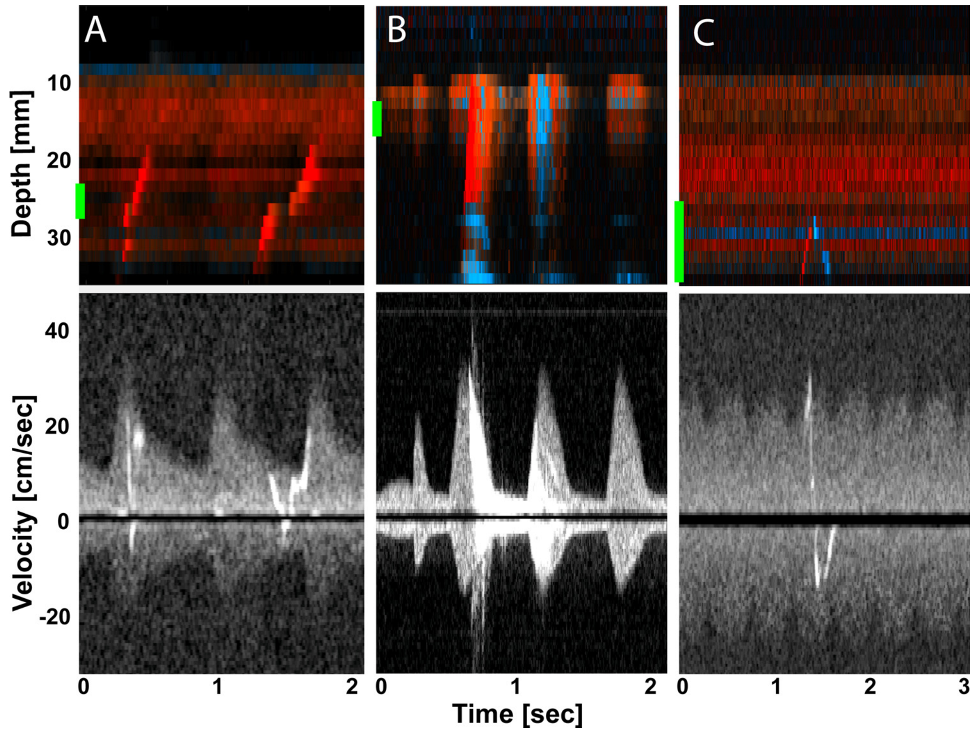

Fig. 7. Selected patient examples with high-intensity transient signals (HITS). (A) Single HITS with skewed lines of high-intensity increase in the color M-mode display (CMD) in the upper panel, with corresponding intensity increase in the spectrogram in the lower panel. (B) HITS with curtain effect creating a broad intensity increase in CMD with a corresponding intensity increase in the spectrogram that fills the entire Doppler curve in a patient with re-coarctation of the aorta undergoing transcatheter balloon dilatation during which the balloon ruptured. (C) HITS with a complex pattern with change of directionality during cardiopulmonary bypass.

Spencer 2002). Single HITS were observed in clusters in this study, as has also been described in previous studies (Wallace et al. 2015).

A recent study found no definitive association with surgical maneuvers and HITS detected during pediatric cardiac surgery, although declamping of the aorta was associated with the greatest number of HITS (Twedt et al. 2020). During surgery, the period with the highest number of HITS in our study was the CPB period and the highest HITS rate was seen from initiation of CPB to aortic X-clamp.

Cerebral air embolus diameter estimation with TCD in humans has previously been studied but the clinical implications have remained unclear (Chung et al. 2015). Variations in hematocrit could influence the backscatter of blood (Yuan and Shung 1988). We recorded pre-operative hematocrit values but did not adjust for hematocrit as variations during CPB are commonly seen. During CPB, an arterial 40-μm filter was used. It has previously been found that arterial filters could reduce embolic load in the CPB period (Pugsley et al. 1994). During surgery, the period with the highest number of large air emboli was seen prior to aortic cannulation. The pre-cannulation period includes several anesthetic interventions such as administration of intravenous medication and saline flushing in lines without filters. High-risk patients with right-to-left shunts or mixing would be more susceptible to larger cerebral air emboli in this period. Transcatheter interventions had more HITS with EBR $\geq$15 dB compared with cardiac surgery. Transcatheter interventions have the same risk factors as the pre-cannulation period of surgeries with administration of medications in venous lines, but also contrast studies that are associated with air emboli (Wallace et al. 2016).

Limitations

This study has several limitations. First, the sample size is small. Second, there is heterogenicity in diagnosis, interventions and surgeries performed. Interventions, surgical procedures and anesthetic procedures were also personnel dependent. Although the same ultrasound and scattering principles apply to NeoDoppler as to TCD, an in vitro HITS detection validation would be beneficial. NeoDoppler cannot differentiate between solid material emboli and air emboli; thus, embolus diameter estimation theories used in this study apply for air emboli only.

In this study, emboli were registered in all depths and were considered separate if they could be separated in the CMD or in the spectrogram. This means that more emboli could be detected with NeoDoppler than with sgTCD as more vessels are monitored simultaneously. However, one embolus moving in and out of the ultrasound beam could potentially be counted more than once. This is exemplified in Figure 7B, where an episode of multiple emboli during two subsequent heartbeats was registered as two separate curtain events by one investigator and as one curtain event by the other investigator. The exact vessels being monitored with this system are not known. The high frequency of the NeoDoppler probe does not penetrate the skull bone, limiting the NeoDoppler system to transfontanellar monitoring of neonates and infants. Lastly, we do not have pre- and post-intervention cerebral magnetic resonance imaging as this was not performed routinely in these patients. Furthermore, we do not have data on long-term neurodevelopmental outcome.

Future perspectives

We aim to perform *in vitro* validation of HITS detection in future work, but special equipment such as a high-frame-rate/high-resolution camera would be needed to accomplish this task. NeoDoppler is also capable of monitoring other cerebral instant hemodynamic events during transcatheter interventions and cardiac surgery in infants as reported in a recent abstract from our group (Leth-Olsen M et al. 2021. NeoDoppler−Continuous cerebral blood flow monitoring during cardiac surgery and interventions in children with congenital heart disease. [Poster presentation]. AEPC 2021 - 54th annual meeting for European Paediatric and Congenital Cardiology, Gothenburg). As manual HITS detection, as presented in this study, is time consuming and requires expertise, automatization of this process would be beneficial. Automated software embolus detection algorithms have previously been described (Cullinane et al. 2000). We have initiated work on automatization of HITS detection, but further development is needed to create a valid automated software. An "embolus monitor" could be helpful to further improve our intervention and surgery methods to avoid unnecessary embolic load on children with CHD. We believe that NeoDoppler CMD HITS detection could be useful in patients on extracorporeal membrane oxygenation to detect circuit embolization, but studies to confirm this theory are warranted.

CONCLUSIONS

We found that NeoDoppler detects frequent HITS in infants with CHD undergoing surgery or transcatheter interventions. The broad ultrasound wave permits prolonged scanning time for each transient event. Furthermore, the frame rate is high, and the CMD allows for distinction between artifacts and emboli. This may indicate that NeoDoppler could become a useful tool for improved monitoring of HITS during surgery or interventions in infants. Potentially the technique could become a guide to reduce the burden of HITS during intervention and surgery. The implications of HITS in children with CHD are still unclear, and long-term follow-up studies are needed.

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Conflict of interest disclosure——NTNU and St. Olav's Hospital, Trondheim University Hospital, may benefit financially from a commercialization of the ultrasound equipment through future possible intellectual properties; this may include financial benefits to authors of this article. H.T and S.A.N are co-inventors of NeoDoppler. S.A.N. is a board member of CIMON Medical. H.T. and S.A.N. have part-time positions and are among shareholders in CIMON Medical, the company responsible for commercialization of NeoDoppler. The technology used in this study is a prototype/research setup only, and a miniaturized product is expected to be launched in 2022. G.D. and M. L.O. declare no conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2022.02.021.

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