［委員会報告］

Late preterm児（34〜36週）の低酸素性虚血性脳症

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はじめに

低酸素性虚血性脳症（hypoxic ischemic encephalopathy：HIE）は，脳性麻痺，精神発達遅滞，てんかんなどの神経学的後障害の原因となる疾病であり，周産期医療においては，最も重要な疾病の一つである。

2012年に日本周産期・新生児学会の周産期学シンポジウム運営委員会が中心となり本邦における中等度〜重度のHIEの発症状況ならびにそのリスク因子の解析を行うことを目的としてアンケートによる全国調査を行った。第31回周産期学シンポジウムプレコングレスにて，調査結果の一部を「周産期学シンポジウムアンケート調査報告　〜本邦における新生児低酸素性虚血性脳症の現状と病態に関する研究〜」として，在胎37週以上の児の概要について報告した[1]。わが国における在胎37週以上の中等度〜重度のHIEは出生1,000に対して0.38であり，中等度〜重度のHIEにおける予後は，臍帯異常，院外出生，蘇生の程度，Apgarスコア，入院時血液ガス所見，入院時検査における白血球数，乳酸値，LD値，CK値，AST値，頭部MRI所見と関連があることを明らかにした[2]。

在胎34〜36週出生の児は，正期産に近いためほとんどの症例で出生体重が2,000gを超えており，"near-term"とよばれて正期産児と準じて管理されていた。しかしながら，これらの児は正期産児と比べ新生児合併症が多く，発達予後が悪いことが報告されており[3, 4]，早産児であることを認識するために"late preterm"とよばれるようになった[3]。HIEにおいても，late

preterm児と正期産児に差異があることが予想されるが，late preterm児におけるHIEの報告はわずかに散見されるのみである[5, 6]。今回は，「周産期学シンポジウム運営委員会報告　Late preterm児（在胎34〜36週）の低酸素性虚血性脳症」として，late preterm児におけるHIEの概要について検討した。

対象と方法

日本周産期・新生児医学会の周産期専門医研修施設（基幹施設：136施設，指定施設：145施設）に対して，施設調査および平成20年出生の在胎34週0日以上の児で下記の条件に該当する症例について調査を行った。

仮死出生が原因のHIEまたは明らかな仮死出生がなくとも，生後72時間以内に意識障害，筋トーヌスの異常，原始反射の異常，新生児発作の症状のいずれかが24時間以上持続した症例，または，新生児発作もしくは無呼吸発作で人工換気療法を必要とした症例を対象とした。先天奇形症候群（染色体異常を含む），電解質異常（低Ca血症，低Na血症等），低血糖症，代謝異常症（有機酸代謝異常，アミノ酸代謝異常等），神経変性疾患，神経筋疾患，神経皮膚症候群，中枢神経異常（脳奇形等），中枢神経感染症，特発性脳梗塞，頭蓋内出血，その他の中枢神経疾患（TORCH等を含む）等が原因の急性脳症であり，HIEでないことが明らかな場合は除外した。施設概要としては，平成20年12月31日時点でのNICU病床数を調査した。

291施設に調査用紙を送付し，263施設（NICU：2,138

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床）から回答を得た（回答率90.7％）。263施設で370例の該当症例があり，在胎期間が記載されていなかった2例，出生体重が記載されていなかった4例を除外した。在胎34週以上36週未満は75症例，在胎37週以上は289症例であった。今回はlate preterm（在胎34週以上36週未満）の75例を対象にHIE発症のリスク因子の解析を行った。

本研究における胎児心拍数モニタリング所見は日本産科婦人科学会周産期委員会の分類に準じて，徐脈，病的一過性徐脈（遅発一過性徐脈，変動一過性徐脈，遷延一過性徐脈），基線細変動減少および消失に群分けをした。頭部MRIについては，入院中に撮像された画像所見でHIEに起因する病変を有するものを異常とした。

1歳6カ月の神経学的予後が正常である症例を正常群，神経学的後障害のある症例または死亡症例を異常群とし，2群間における，母体因子，周産期因子，新生児検査所見などについて検討した。統計学的検討は連続変数の解析にはMann-Whiteny U 検定，名義変数の解析には χ^2 検定，PosthocにはBonferroni検定を用いた。p値が0.05未満の場合を統計学的に有意とした。

本調査内容については，国立成育医療研究センター倫理委員会にて審査され承認を得て施行した。

結果

母体の基本情報については，年齢は31.0歳（19〜44歳），妊娠歴がない例は30例（40％），分娩歴がない例

は38例（51％）であった。出生場所は院内出生が43例（57％），院外出生が32例（43％）であった。性別については，男児48例（64％），女児27例（36％）であった。1歳6カ月の転帰では，生存が56例（75％），死亡が2例（3％），不明が17例（22％）であり，転帰不明の17例を除く1歳6カ月の予後は19例（35％）が正常発達，34例（62％）が神経学的後障害，2例（3％）が死亡であった。

1歳6カ月の予後と母体因子の検討では，母体合併症は有意に予後と関連を認めたが，母体年齢，妊娠歴，分娩歴，不妊治療の有無，長期服薬については2群間に有意差を認めなかった（表1）。出生場所，分娩様式，誘発の有無，器械分娩の有無については両群間で差は認めなかった。羊水混濁の有無，臍帯胎盤因子についても両群間で差は認めなかった（表2）。胎児機能不全，胎児心拍数モニタリング所見では両群間で差は認めなかった（図1）。

新生児については，正常群で男児が多かったが，在胎期間，出生体重に差は認めなかった（表3）。臍帯血液ガス分析，Apgarスコアについても両群間で差は認めなかった（図2，3）。出生時の蘇生については異常群で有意に高度の蘇生を受けていた（図4）。入院時血液検査ではASTが異常群で有意に高値であったが，他の検査値については有意差を認めなかった（図5〜7）。頭部MRIが撮像された症例は64例であった。頭部MRI所見は，正常が16例（25％），両側基底核視床病変（basal ganglia thalamic lesion：BGTL）が10例（15％），皮質下白質病変（cortical white matter lesion：C-WM）が

表1　母体因子

	正常群	異常群	p値
母体年齢（範囲）	32（25〜41）	31（20〜44）	0.606
妊娠歴 なし／あり（なしの割合）	4/14（22.2％）	16/20（44.4％）	0.111
分娩歴 なし／あり（なしの割合）	7/11（38.9％）	19/17（52.8％）	0.336
自然妊娠／不妊治療（自然妊娠の割合）	18/1（94.7％）	32/1（97.0％）	0.687
母体合併症 なし／あり（なしの割合）	17/2（89.5％）	21/14（60.0％）	0.024
長期服用薬 なし／あり（なしの割合）	18/0（100％）	30/5（85.7％）	0.092

表2　分娩に関する因子

	正常群	異常群	p値
院内／院外（院内の割合）	9/10（47.4％）	24/12（66.7％）	0.165
病院／病院以外（病院の割合）	13/6（68.4％）	32/4（88.9％）	0.061
経腟分娩／帝王切開（経腟分娩の割合）	4/15（21.1％）	5/31（13.9％）	0.495
自然／誘発（自然分娩の割合）	7/1（87.5％）	9/0（100％）	0.274
器械分娩 なし／あり（なしの割合）	14/1（93.3％）	23/1（95.8％）	0.731
羊水混濁 なし／あり（なしの割合）	15/2（88.2％）	23/8（72.4％）	0.251
臍帯異常 なし／あり（なしの割合）	15/1（97.8％）	30/2（97.8％）	1.000
胎盤異常 なし／あり（なしの割合）	5/13（27.8％）	11/22（33.3％）	0.683
早期剥離 なし／あり（なしの割合）	7/11（38.9％）	14/19（42.4％）	0.806

10例（15%），混合型が11例（17%），多嚢胞性脳軟化症（multicystic encephalomalacia：MCE）が3例（5%），脳室周囲白質軟化症（periventricular leukomalacia：PVL）が4例（6%），頭蓋内出血（intracranial hemorrhage：ICH）が7例（11%），その他が3例（5%）であった。予後との関連については，MRI異常所見は正常群で63%，異常群で94%と予後異常群で有意にMRI異常が多かった（p = 0.005）。

図1　胎児機能不全

□：所見あり
■：所見なし

胎児機能不全　p=0.206
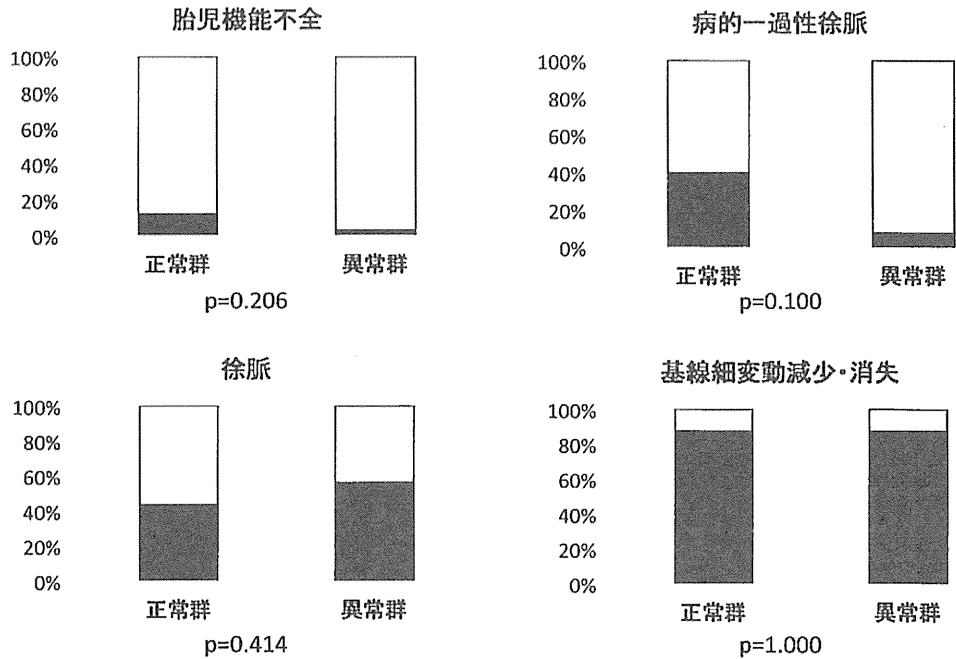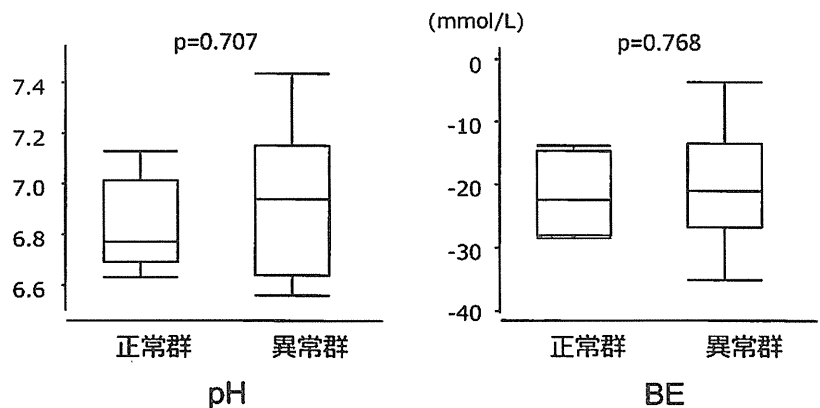
病的一過性徐脈　p=0.100

徐脈　p=0.414

基線細変動減少・消失　p=1.000

表3　新生児因子

	正常群	異常群	p値
男児／女児 （男児の割合）	16/3 (84.2%)	18/18 (50.0%)	0.013
在胎期間 （範囲）	36.0週 (34.4～36.9)	35.4週 (34.0～36.9)	0.204
出生体重 （範囲）	2204g (1035～2866)	2872g (1412～2890)	0.265

図2　臍帯血液ガス分析

上の横線：最大値，箱の上の線：第3四分位点，箱の中央の線：中央値，箱の下の線：第1四分位点，下の横線：最小値

p=0.707　pH

p=0.768　BE（mmol/L）

考察

　調査回答があった263施設のNICU病床の合計は2,138床であり，平成23年医療施設（静態・動態）調査・病院報告の概況[7]では国内のNICU病床総数が2,765床であることから，本調査は国内NICUの77.3%をカバーしていると推測された。したがって，平成20年出生のlate preterm児における中等症～重症のHIE症例数は75例÷0.773＝97例と推計された。

　1歳6カ月時における予後と母体因子，分娩時因子，

新生児因子は在胎37週以上の児とは在胎34～36週の児とでは異なっていた。在胎37週以上の児においては，臍帯異常，院外出生，蘇生の程度，Apgarスコア，入院時血液ガス所見，入院時検査における白血球数，乳酸値，LD値，CK値，AST値，入院中に撮像された頭部MRI所見が予後不良と関連があった。その一方で，late preterm児では性別，蘇生の程度，入院時検査におけるAST，入院中に撮像された頭部MRI所見が予後と関連があった。

　在胎37週以上の児とlate pretermで共通している因子

図3　Apgar スコア
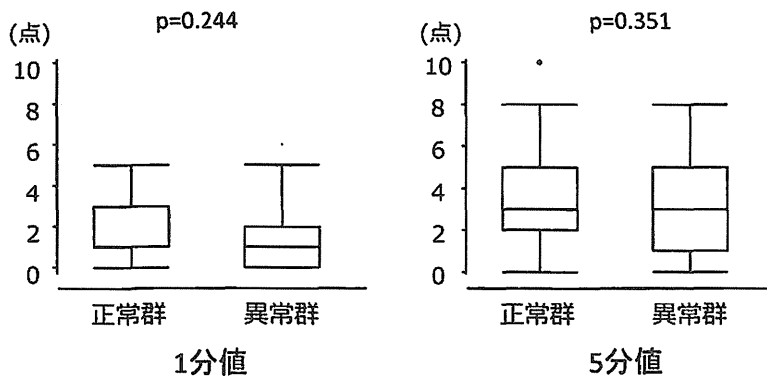上の横線：最大値，箱の上の線：第3四分位点，箱の中央の線：中央値，箱の下の線：第1四分位点，下の横線：最小値，丸：はずれ値

1分値　　　　　　5分値

図4　出生時の蘇生レベル
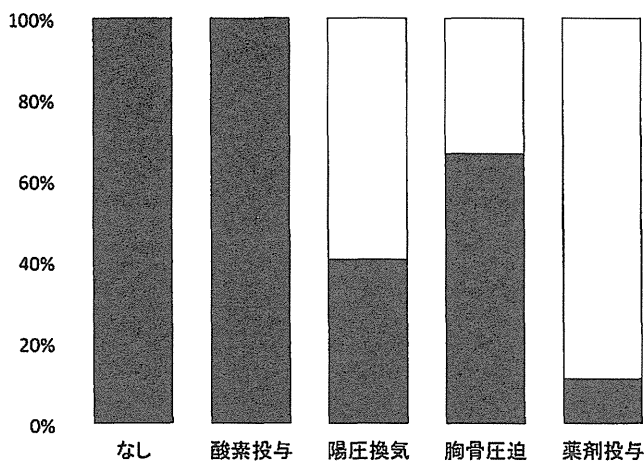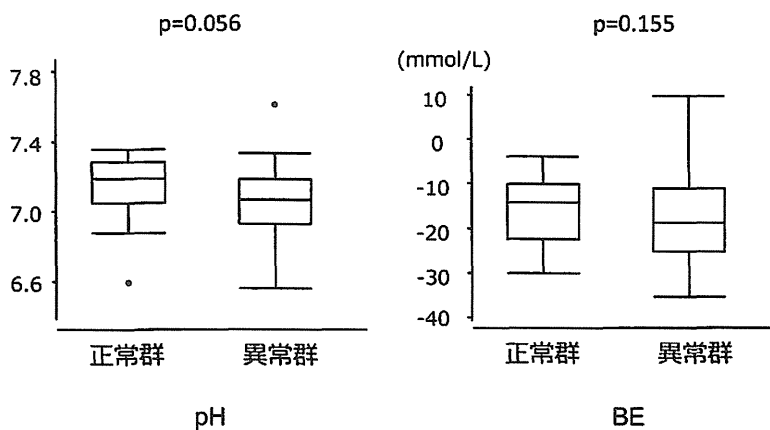■：正常群　□：異常群　p＝0.040

図5　入院時の血液ガス分析
上の横線：最大値，箱の上の線：第3四分位点，箱の中央の線：中央値，箱の下の線：第1四分位点，下の横線：最小値，丸：はずれ値

pH　　　　　　BE

は蘇生の程度，AST，頭部MRIのみであった[2]。これらの結果はHIEの受傷様式の違い，低酸素虚血に対する児の脆弱性の違いなどを反映している可能性が考えられたが，更なる臨床的検討，基礎的検討が必要である。

　頭部MRI所見は，正常が25%，BGTLが15%，C-WMが15%，混合型が17%，MCEが5%，PVLが6%，ICHが11%，その他が5%であった。一方で，在胎37週以上の児においては，正常が32%，BGTLが

22%，C-WMが17%，混合型が10%，MCEが11%，8%がその他の所見であり，頭部MRI所見の違いが明らかになった。Late preterm児では，解剖学，生化学的に正期産児とは異なるため，それらの要因が頭部MRIに反映されたことが考えられた。

利益相反について

・今回の論文に関連して，開示すべき利益相反状態はありません。

図6　入院時検査所見①
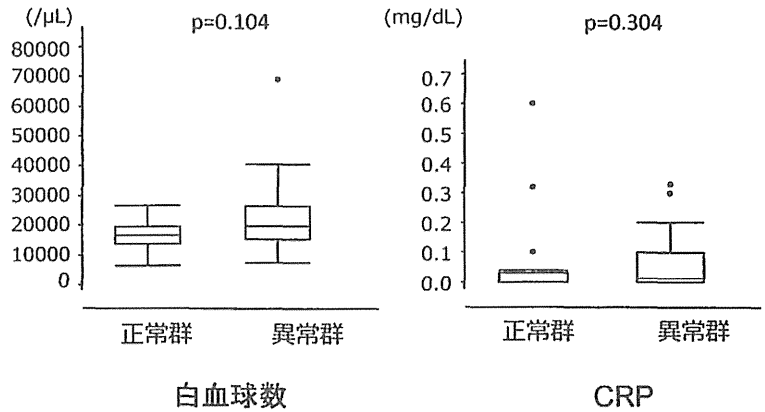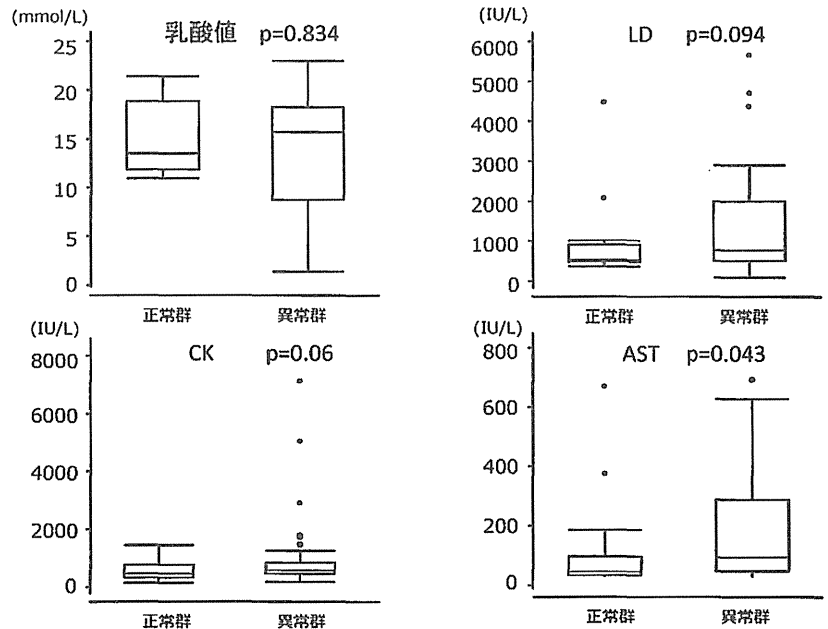上の横線：最大値，箱の上の線：第3四分位点，箱の中央の線：中央値，箱の下の線：第1四分位点，下の横線：最小値

白血球数　　　　CRP

図7　入院時検査所見②
上の横線：最大値，箱の上の線：第3四分位点，箱の中央の線：中央値，箱の下の線：第1四分位点，下の横線：最小値，丸：はずれ値

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神経症候群（第2版）
―その他の神経疾患を含めて―

V

IX　周産期障害

新生児低酸素性虚血性脳症

早川昌弘

IX 周産期障害

新生児低酸素性虚血性脳症
Neonatal hypoxic ischemic encephalopathy

早川昌弘

Key words：低酸素性虚血性脳症，低体温療法，MRI，
amplitude-integrated EEG

1. 概念・定義

低酸素性虚血性脳症(hypoxic ischemic encephalopathy: HIE)は，低酸素血症および虚血によって中枢神経系が障害され，意識障害，新生児発作，筋緊張低下をきたす重篤な疾病である．臨床症状，画像検査，脳波検査などにより重症度分類が行われ，中等症以上では予後不良であることが多い．

2. 疫　　学

先進国におけるHIEの発症率は1-3/1,000出生と報告されている[1-3]．我が国においては，2008年出生の在胎37週以上の児における中等度〜重度のHIEの実態調査を行ったところ，その発症率は0.38/1,000出生であった[4]．胎児への血流供給を完全に破綻させる常位胎盤早期剥離や臍帯脱出など原因が明らかになっている事例ばかりではなく，胎児心拍モニター所見がそれほど重篤ではない事例においても発症するため，HIEの臨床診断は難しく正確な発症数を把握するのは極めて困難と思われる．

3. 病　　因

HIEはその受傷様式により，臨床症状や頭部MRI所見などの病像が異なることが特徴である．短時間ではあるが強い低酸素性虚血性イベントは，total asphyxia(profound asphyxia)と呼ばれ，新生児期にエネルギー需要が高い脳幹部・基底核・視床が受傷する．基底核視床病変では，後にアテトーゼ型脳性麻痺の臨床像を呈する．一方，比較的軽度ではあるが長時間に及ぶ低酸素性虚血性イベントは，partial asphyxia(prolonged asphyxia)と呼ばれる．total asphyxia症例の多くは，いわゆる分娩時仮死で出生するが，partial asphyxia症例では分娩時に典型的な仮死出生の症状を呈しないことがある．著者らが行った後方視的検討では，全例が新生児発作で発症しているが，出生直後に神経症状を呈した症例は約20％であった．1分後のアプガースコアについては，半数以上の症例で5点以上であり，臍帯血pHが7.0未満の症例は10％足らずであり，出生直後では新生児仮死・新生児脳症の臨床像を呈していない症例が多数みられた[5]．遅発性エネルギー障害から遅発性神経細胞死を引き起こし遅れて神経症状をきたすことを理解していないと，患者の病状把握を誤る可能性もあり，十分な注意が必要である．当然のことながら，臨床的にtotal asphyxiaとpartial asphyxiaを明確に区別することができない症例は多数存在する．

4. 病　　態

HIEの興味深いところは，神経細胞の受傷時期が低酸素性虚血性イベントの直後のみならず，遅発性にエネルギー代謝不全を引き起こし神経細胞のアポトーシスを誘導することである．低酸素・虚血により生体膜電位の維持ができなく

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なると，大量の興奮性神経伝達物質が放出され，神経細胞は脱分極状態となる．脱分極に伴いCaチャネルが開放されて，多量のCaイオンが細胞内に流入する．通常では，Caイオンを細胞外にくみ出し恒常性を保っているが，低酸素性虚血性イベントの後では電子伝達系の活動が停止しており，細胞内の恒常性を保つことが困難である．細胞内Caイオンの濃度が増加し，カルシウム依存性の酵素系が活性化することで，細胞死をきたす．その後，低酸素性虚血性イベントに対して蘇生処置を行うことで，細胞内のエネルギー状態は一時的に改善する．しかしながら，低酸素性虚血性イベントに伴い細胞内に流入したCaイオンは膜電位や酵素活性の回復を阻害し，ラディカルの産生を引き起こすことで，重要な細胞内小器官の一つであるミトコンドリアを障害させる．ミトコンドリア障害が原因でエネルギー供給が絶たれる現象は遅発性エネルギー障害と呼ばれており，アポトーシスを中心とした遅発性神経細胞死の原因であると考えられている[6]．出生直後には神経症状を認めなかった児が，生後数時間以上経過してから新生児発作などの新生児脳症の症状を呈する症例を時に経験するが，これは遅発性神経細胞死が原因であると考えられている．

5. 診断と鑑別診断

病歴，理学的所見，画像所見，血液検査所見などを総合して診断を行う．理学的所見では，筋緊張・姿勢・腱反射および原始反射の異常を評価する．また自律神経機能異常を反映した瞳孔異常やバイタルサインの異常を評価する．血算，血液生化学，血液ガス分析を行い全身状態および合併する多臓器障害の程度を評価する．

画像検査としては，頭部エコーおよびMRIが有用である．頭部エコーでは，重症例では深部灰白質の輝度上昇が認められ，また，実質などの出血も検出しうるが，軽症や中等症では病変の検出は困難である．ドプラ法で拡張期血流の増加を認めることが多いが，動脈管血流，脳圧，酸素/炭酸ガス分圧などの影響も受けるため，予後予測の根拠とはならない．HIEの頭部
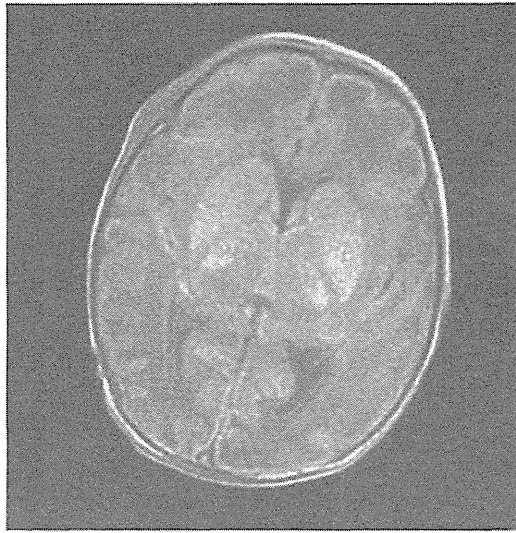

図1　Total asphyxia

図2　Partial asphyxia

MRIは，受傷機転によって異なった像をとる．total asphyxiaでは，基底核や視床，海馬，皮質脊髄路，中心回などが障害され，両側基底核視床病変と称される（図1）．一方，partial asphyxiaでは動脈の分水嶺が受傷するため，前大脳動脈と中大脳動脈，中大脳動脈と後大脳動脈の灌流境界や（図2），皮質下白質に病変を認める．早

期にMRIの撮像が可能ならば，拡散強調画像やADCマップが有用である．拡散能低下を反映して，拡散強調画像で高輝度，ADCマップで低輝度となる．

脳波では，重症度に応じた急性期異常を認め，急性期異常の程度から神経学的予後を推測することができる[7]．近年，amplitude-integrated EEG(aEEG)が新生児医療に普及してきた．aEEGは脳機能を簡便かつ連続的にモニタリングする器機である．HIE児の脳機能評価や新生児発作の診断に有用である．経時的変化を評価することで予後予測に有用であるが[8,9]，受傷直後のaEEG所見からでは予後予測が困難であることに注意をするべきである[10]．

6. 治療と予後

現時点で，HIEに対して有効な治療法は低体温療法のみである．中等症のHIEの児では，低体温療法を施行することで，死亡および18カ月での重度の神経学的後遺症の合併を軽減できることが，複数の無作為化比較試験によって示されている[11]．2010年に国際蘇生法連絡委員会が，正期産もしくは正期産に近い児のHIEに対して，低体温療法を標準治療として推奨することを発表した[12]．これを受けて，日本蘇生協議会のNCPRガイドライン2010において同様の推奨が発表された．これによると，全身冷却法/選択的頭部冷却法のいずれも適切な方法であり，生後6時間以内に開始し，冷却時間は72時間，少なくとも4時間かけて復温する手順で行うことが推奨されている．低体温療法の適応となるのは，正期産近くの成熟した新生児であり，出生直前に低酸素虚血のオンセットがあったと考えられ，従来の治療法のみでは死亡または重度の後遺障害を残す可能性が高く，低体温療法によるメリットがデメリットを上回る症例である．

HIEに対する薬物療法として様々な脳保護薬が考案されてきたが，いずれも大規模な臨床試験における有効性を示すには至っていない．一方で，近年その効果が期待されている薬剤として，エリスロポエチン，メラトニン，トピラメイトなどが挙げられる．また，キセノンやブメタニドの神経保護作用も注目されるところであり，これらと低体温療法の併用による相乗効果の実現が期待される[13,14]．

分娩時仮死に伴う症例では，低酸素血症および循環不全のために多臓器に障害を生じるため，患児の状態に応じて，呼吸管理，循環管理，水分・電解質管理が必要となる．中等症以上のHIEでは新生児発作を生じることがある．新生児発作に対しては，呼吸抑制や循環動態に注意しながら，抗てんかん薬を使用する．退院後の神経学的フォローアップが重要であることは言うまでもない．

7. 予　　後

中等症以上のHIEの予後は不良であることが多い．先進国におけるHIE症例の10-15％が死亡，10-15％が脳性麻痺となり，40％が失明，難聴，広範性発達障害，てんかん，発達遅滞，認知や行動の異常などを合併すると報告されている[1-3]．我が国における調査では1歳6カ月の転帰では，正常発達が39％，神経学的後障害が49％，死亡が12％であり[15]，HIEは新生児医療が進歩した現在においても極めて神経学的予後が不良である疾病である．

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Original article

Cystatin C and body surface area are major determinants of the ratio of N-terminal pro-brain natriuretic peptide to brain natriuretic peptide levels in children

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A B S T R A C T

Background: Production of N-terminal pro-brain natriuretic peptide (NT) and BNP is equimolar. Although NT clearance occurs only in the kidneys, BNP clearance occurs in the kidneys and other organs. This study tested the hypothesis that NT/BNP ratio in children may be independently related to cystatin C (CysC), a glomerular filtration rate marker, when diastolic function and age/body size are taken into consideration.

Methods: The study included 430 children (5.3 ± 4.9 years) with heart disease who had undergone cardiac catheterization and simultaneous BNP, NT, and CysC measurements. Pulmonary capillary wedge pressure (PCWP) was used as a ventricular diastolic stretch marker. Variables showing skewed distribution were transformed into a common logarithm.

Results: Univariate regression revealed that log NT/BNP was affected by PCWP ($r = -0.12$) and log CysC ($r = 0.57$). When age and the log of body surface area (BSA) were added to the stepwise regression, age was not adopted because of multicollinearity to log BSA, but PCWP ($\beta = -0.10$), log CysC ($\beta = 0.22$), and log BSA ($\beta = -0.66$) were independent factors of log NT/BNP.

Conclusions: Renal dysfunction independently increased NT/BNP, whereas high BSA decreased it and is the greatest determinant of NT/BNP. The observation that high PCWP decreased NT/BNP may suggest that worsening heart failure slows BNP clearance from other organs, a compensatory pathway of heart failure. These factors need to be considered when assessing BNP and NT.

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Introduction

Brain natriuretic peptide (BNP) is a hormone secreted by the ventricular myocardium during increased wall stress caused by excessive volume or pressure loading of the heart [1]. Plasma BNP concentrations are elevated in patients with congestive heart failure (HF) [2] and reflect the severity of HF and diastolic stretch [3]. The plasma BNP concentration is useful in predicting mortality and hospital readmission [4] in many etiologies of HF.

N-terminal pro-BNP (NT) [5–7] is another recent option for such use. NT can be measured from the serum, whereas BNP measurement requires plasma. NT is much more stable than BNP in blood samples at room temperature. Thus, NT use has been greatly increasing, and there is a growing body of evidence about the usefulness of NT. Moreover, the required amount of serum for NT measurement is only about 20 µL, which may promote further use in neonatal and pediatric settings. NT also correlates with BNP in pediatric patients [8,9]. The ratio of NT to BNP (NT/BNP) increases with renal impairment [10] and decreases with increasing age [11].

However, the relationship between NT and BNP levels appears more complicated, and the factors contributing to it are not yet established. Because of the equimolar production of NT and BNP, NT/BNP depends on the clearance rate of each hormone. NT

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clearance occurs only in the kidneys [1] via unknown mechanisms [12]. In contrast, BNP clearance occurs in the kidneys, liver, lungs, and vascular endothelium [1] via the clearance receptor (natriuretic peptide receptor-C) and neutral endopeptidases [13]. Thus, NT/BNP should be determined by the clearance rate between the kidneys and other organs. If this relationship becomes clear, each value of BNP or NT can be approximately converted to the other.

The clearance balance of both hormones may be affected by maturation-related and maturation-unrelated functional states of the kidneys and other organs. HF by itself may affect the clearance of both hormones. Thus, this study tested the hypothesis that NT/BNP may be determined by cystatin C (CysC) [14–17], a muscular mass-independent glomerular filtration rate marker, maturation, and severity of HF in children.

Methods

Patients

The study included 430 consecutive pediatric patients with heart disease (age <20 years, 198 male and 232 female) who had undergone cardiac catheterization and simultaneous measurements of pulmonary capillary wedge pressure (PCWP), BNP, NT, and CysC at Saitama Medical University International Medical Center. Their ages ranged from 0.16 to 19.1 years [mean ± standard deviation (SD), 5.3 ± 4.9 years; median, 3.3 years]. Patients underwent diagnostic or interventional cardiac catheterization at Saitama Medical University, with written informed parental consent obtained for all the patients. This study was approved by the Institutional Review Board of Saitama Medical University.

Measurements

PCWP was regularly measured during cardiac catheterization. We used PCWP as a representative measure of diastolic function and ventricular stretch. Systemic output (Qs) was calculated using the Fick method and Qs index (QsI) was calculated as Qs/body surface area (BSA). Blood sampling to determine CysC levels was performed 1 day before cardiac catheterization as part of routine blood testing. Blood samples of BNP and NT were withdrawn from the inferior vena cava at the beginning of cardiac catheterization. Measurements of BNP were performed using enzyme immunoassay, NT using electrochemiluminescence immunoassay, and CysC using latex-enhanced turbidimetric immunoassay.

Statistical analysis

All data are presented as mean ± SD, unless otherwise stated. Variables showing skewed distribution were transformed into a common logarithm before the correlation analysis. Pairwise comparisons were performed using the paired t-test. The correlation between two variables was assessed using Pearson's correlation coefficient. After univariate regression, to determine the independent variables that correlate with BNP, NT, NT/BNP, stepwise multivariate linear regression analysis was performed using the following variables: gender, log BSA, log CysC, and PCWP. Subsequently, we performed subgroup analysis to assess whether the difference between left- or right-sided volume load may relate to log NT/BNP, and whether the difference between pressure and volume load may affect NT/BNP. Atrial septal defect (ASD) patients were used as a right-sided volume overload group, and ventricular septal defect (VSD) and patent ductus arteriosus (PDA) patients as a left-sided volume overload group. Coarctation of the aorta (CoA) and aortic stenosis (AS) patients were used as a left-sided pressure overload group. We compared log NT/BNP values between right- and left-sided volume overload groups,

and between left-sided pressure and volume overload groups. Statistical significance was assumed at an error level of 5%. Statistical analyses were performed using JMP 8 (SAS, Cary, NC, USA).

Results

As summarized in Table 1, patients with various underlying heart diseases (N = 430) were included in this study. The range and distribution of each parameter are shown in Table 2.

Univariate regression

Table 3 summarizes the results of univariate regression. Gender did not relate to log NT, log BNP, or log NT/BNP. In contrast, age, body size (body weight, body height, and BSA), log CysC, and PCWP significantly correlated to log NT, log BNP, and log NT/BNP. Log NT/BNP negatively correlated with age ($r = -0.71, p < 0.0001$), and the relation was a convex downward curve (Fig. 1a). There was strong negative linear correlation between log NT/BNP and log BSA ($r = -0.79, p < 0.0001$) (Fig. 1b). Log NT/BNP positively correlated with log CysC ($r = 0.57, p < 0.0001$) (Fig. 1c), and negatively correlated with PCWP ($r = -0.12, p < 0.05$) (Fig. 1d). BNP was much less influenced by age, BSA, and CysC compared with NT, as indicated by a smaller correlation coefficient in Table 3.

Multivariate regression

Table 4 summarizes the results of multivariate regression. When age, log BSA, log CysC, and PCWP were added as independent variables into stepwise regression to correlate to log NT/BNP, age was not adopted because of multicollinearity to log BSA, but PCWP ($\beta = -0.10$), log CysC ($\beta = 0.22$), and log BSA ($\beta = -0.66$) were independent factors of log NT/BNP (Table 4). Not only body size and renal function, but also PCWP, independently related to the log NT/BNP. Higher PCWP negatively affected log NT/BNP.

Log NT/BNP can be approximated with the regression by $-0.66 \times \log$ BSA $- 0.10 \times$ PCWP $+ 0.22 \times \log$ CysC $+ 0.86$. There was significant correlation between the measured and estimated log NT/BNP calculated by this approximation [RMSE = 0.18, R^2 (coefficient of determination) = 0.66, $p < 0.0001$]. Residual plot showed no tendency between residuals and estimated values.

Fig. 2 shows the results of subgroup analysis assessing whether the difference between pressure or volume load may relate to

Table 1
Diagnoses of included patients.

Disease (N = 430)	Number of patients
Atrial septal defect	82
Single ventricle	55
Tetralogy of Fallot	41
Patent ductus arteriosus	31
Ventricular septal defect	29
Pulmonary atresia with/without other CHD	25
Transposition of great arteries	26
Double outlet right ventricle	19
Congenitally corrected transposition of great arteries	15
Coarctation of aorta	13
Hypoplastic left heart syndrome	12
Aortic stenosis	8
Atrioventricular septal defect	8
Tricuspid atresia	7
Post-heart transplantation	6
Pulmonary stenosis	6
Total anomalous pulmonary venous connection	5
Hypoplastic left ventricle	4
Others	38
Total	**430**

CHD, congenital heart disease.

Table 2
Distribution of each parameter (N = 430).

	Mean ± SD	Range	Median (interquartile range)
Age (years)	5.35 ± 4.93	0.16 to 19.1	3.31 (1.65–7.21)
Male (%)	197 (45.9%)		
Body weight (kg)	19.0 ± 15.1	3.8 to 86.0	13.0 (9.2–21.5)
Body height (mL/m²)	101 ± 31	49 to 181	91.8 (77–119.3)
Body surface area (m²)	0.71 ± 0.39	0.22 to 2.0	0.71 (0.43–0.85)
CysC (mg/L)	0.95 ± 0.22	0.59 to 1.88	0.91 (0.79–1.07)
Qs index (L/min/m²)	3.65 ± 1.07	1.49 to 7.84	3.58 (2.91–4.31)
Qp/Qs	1.36 ± 0.74	0.42 to 4.5	1.0 (0.96–1.62)
PCWP (mmHg)	9.73 ± 3.2	2 to 24	9.25 (7.5–12)
NT-pro BNP (pg/mL)	428 ± 991	7 to 14600	186 (78–418)
log NT-pro BNP	2.27 ± 0.53	0.85 to 4.16	2.27 (1.90–2.62)
BNP (pg/mL)	43.5 ± 142	4 to 2655	20 (10.6–35.1)
log BNP	1.33 ± 0.43	0.60 to 3.42	1.30 (1.02–1.54)
NT/BNP	11.2 ± 10.0	0.76 to 97.3	8.62 (5.37–8.62)
log NT/BNP	0.94 ± 0.31	−0.12 to 1.99	0.94 (0.73–1.10)

Data are presented as mean ± standard deviation, median (interquartile range), or frequency (within-group percentage).
CysC, cystatin C; Qs, systemic output; Qp, pulmonary output; PCWP, pulmonary capillary wedge pressure; NT, N-terminal; BNP, brain natriuretic peptide.

Table 3
Univariate analysis of NT-pro BNP, BNP, and NT/BNP.

	log NT-pro BNP		log BNP		log NT/BNP	
	r	p	r	p	r	p
Age (years)	−0.61	<0.0001	−0.25	<0.0001	−0.71	<0.0001
Gender		0.65		0.89		0.29
log Body weight (kg)	−0.72	<0.0001	−0.34	<0.0001	−0.78	<0.0001
log Body height (mL/m²)	−0.69	<0.0001	−0.30	<0.0001	−0.79	<0.0001
log Body surface area (m²)	−0.71	<0.0001	−0.32	<0.001	−0.79	<0.0001
log CysC (mg/L)	0.46	<0.0001	0.16	0.001	0.57	<0.0001
PCWP (mmHg)	0.23	<0.0001	0.38	<0.0001	−0.12	0.011

CysC, cystatin C; PCWP, pulmonary capillary wedge pressure; NT, N-terminal; BNP, brain natriuretic peptide.
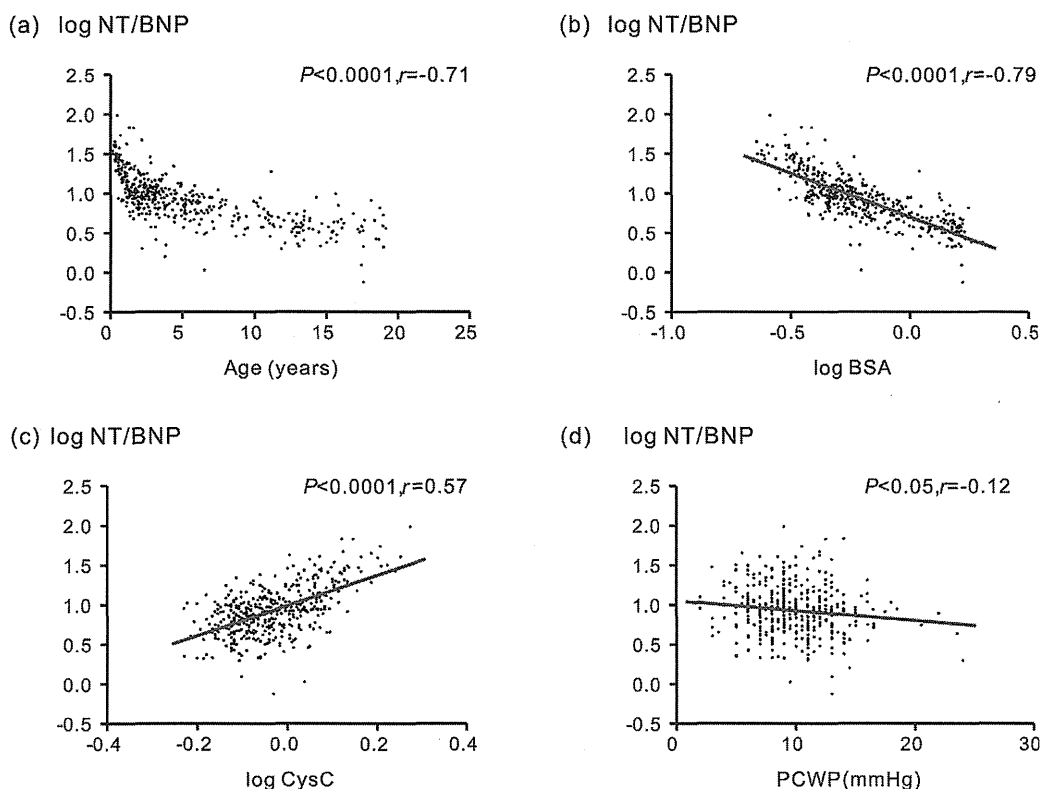

Fig. 1. Correlation between logarithm of the ratio between N-terminal pro-BNP and BNP (log NT/BNP) and other factors. (a) Log NT/BNP negatively correlates with age; the relation is a convex downward curve. (b) There is a strong negative linear correlation between log NT/BNP and log BSA. (c) Log NT/BNP positively correlates with log CysC. (d) Log NT/BNP negatively correlates with PCWP. BNP, brain natriuretic peptide; BSA, body surface area; CysC, cystatin C; NT, N-terminal pro-BNP; PCWP, pulmonary capillary wedge pressure.

Table 4
Multivariate regression analysis of NT-pro BNP, BNP, and NT/BNP.

	log NT-pro BNP		log BNP		log NT/BNP	
	β	p	β	p	β	p
Gender		0.60		0.87		0.48
log Body surface area (m²)	−0.73	<0.0001	−0.41	<0.0001	−0.66	<0.0001
log CysC (mg/L)		0.38	−0.12	0.021	0.22	<0.0001
PCWP (mmHg)	0.28	<0.0001	0.42	<0.0001	−0.10	0.0005

CysC, cystatin C; PCWP, pulmonary capillary wedge pressure; NT, N-terminal; BNP, brain natriuretic peptide.
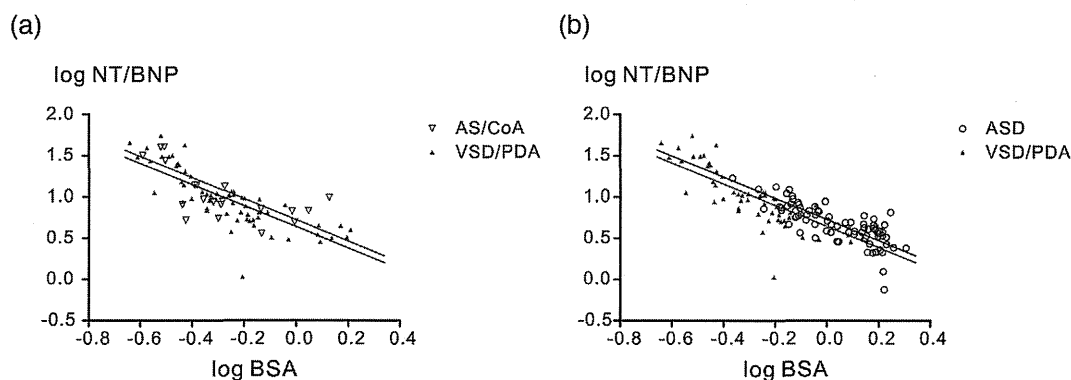

Fig. 2. Subgroup analysis to assess whether different types of heart disease relate to log NT/BNP. (a) Left ventricular pressure load vs. volume load. Log NT/BNP was not significantly affected ($p = 0.76$) by the differences between the AS/CoA ($n = 21$) and VSD/PDA ($n = 60$) groups. (b) Left- vs. right-sided volume load. Multivariate comparison showed that log NT/BNP in the ASD ($n = 82$) was slightly ($\beta = 0.13$) but significantly ($p < 0.05$) higher than that in the VSD/PDA ($n = 60$) group when log BSA was taken into consideration. This significance was preserved ($p < 0.05$) when we matched the body size between the two groups by only including data from VSD/PDA patients with log BSA >0.4 ($n = 41$). However, when we added Qp/Qs into the multivariate analysis, the difference between the ASD and VSD/PDA groups was no longer significant, but Qp/Qs was shown to be a significant independent factor for log NT/BNP ($p < 0.05$, $\beta = 0.16$). AS, aortic stenosis; BNP, brain natriuretic peptide; BSA, body surface area; CoA, coarctation of the aorta; NT, N-terminal pro-BNP; PDA, patent ductus arteriosus; Qp/Qs, pulmonary-to-systemic output ratio; VSD, ventricular septal defect.

log NT/BNP, and whether the difference between left- or right-sided volume load may relate to log NT/BNP. As shown in Fig. 2a, log NT/BNP was not significantly affected ($p = 0.76$) by the differences between the AS/CoA ($n = 21$) and VSD/PDA ($n = 60$) groups. Fig. 2b shows that log NT/BNP in ASD ($n = 82$) was slightly ($\beta = 0.13$) but significantly ($p < 0.05$) higher than that in VSD/PDA ($n = 60$). This significance was preserved ($p < 0.05$) when we matched the body size between the two groups by only including data from VSD/PDA patients with log BSA >0.4 ($n = 41$). However, in this subgroup analysis, the pulmonary-to-systemic output ratio (Qp/Qs) in ASD was significantly higher than that in VSD/PDA (2.2 ± 0.8 vs. 1.4 ± 0.4, $p < 0.0001$). When we added Qp/Qs into the multivariate analysis, the difference between the ASD and VSD/PDA groups was no longer significant, but Qp/Qs was found to be a significant independent factor for log NT/BNP ($p < 0.05$, $\beta = 0.16$).

Discussion

The major findings in this pediatric study regarding NT/BNP were: (1) renal dysfunction increased NT/BNP levels, (2) high BSA levels decreased NT/BNP as the greatest and powerful determinant of NT/BNP ($\beta = -0.66$), and (3) high PCWP decreased NT/BNP. This is the first study, to our knowledge, to reveal a detailed relationship between NT and BNP with body size, renal function, and invasive diastolic measurements taken into consideration. Simultaneous measurements of both hormones may provide an insight into NT and BNP clearance in the kidneys and other organs. Factors that affect the clearance of both hormones need to be considered when assessing HF severity using NT or BNP.

Renal contribution

Renal dysfunction independently increased NT/BNP (Fig. 1c and Tables 3 and 4). In adults, one of the most important factors affecting the NT/BNP ratio is renal function [18]. NT/BNP ratio increases exponentially with the stage of renal disease [10]. NT/BNP ratios in a population of patients receiving long-term hemodialysis were much higher than those found in patients with end-stage renal disease not receiving dialysis [19]. Thus, the result of our study in children, which used a sufficient number of patients with body size and diastolic function taken into account, was consistent with those of aforementioned studies in adults [10]. Renal dysfunction predominantly slowed the clearance of NT relative to BNP and increased the NT/BNP ratio regardless of whether this was a child or adult population.

Although observations that NT/BNP increases as renal function decreases have been consistently reported in previous [10,18,20] and current studies, mechanistic studies surprisingly demonstrated that the kidney clears NT and BNP equally [13] in various subjects [20–22]. Other possible mechanisms to explain the NT/BNP increase in patients with renal dysfunction may be the relative NT increase by saturable NT clearance [12], the relative BNP decrease by the upregulation of type C natriuretic receptor [20], and the accumulation of neutral endopeptidases [20,23]. These issues should be pursued in future studies.

Body size vs. age

High BSA decreased NT/BNP and was the greatest and most powerful determinant of NT/BNP (Fig. 1b and Tables 3 and 4). The results of a previous pediatric study [11] and the current study

demonstrated that NT/BNP decreased as children aged from childhood to adolescence. An age-dependent decrease of NT/BNP can be partly explained by the maturation of renal function. Our data also indicate the age-related decrease of CysC in patients <2 years (data not shown). However, multivariate regression in this study showed that body size was an independent greatest factor to determine NT/BNP with renal function taken into consideration. Importantly, the relationship between log NT/BNP and log BSA was tighter than that between log NT/BNP and age. These observations suggest that the proportion of the BNP clearance in other organs relative to that in kidney may be larger in smaller children in body-size related fashion.

HF

High PCWP decreased NT/BNP, indicating a relatively greater increase of BNP relative to NT. Importantly, only BNP, but not NT, has active anti-HF activities. Thus, the tendency to preserve BNP concentration in HF should serve as a compensatory mechanism. This effect was significant but not as strong ($\beta = -0.10$) as other factors. This BNP preservation may not be sufficient in some clinical HF situations in which exogenous BNP [24] or neutral endopeptidase inhibitor [25] administration is particularly effective.

Our observation suggests that worsening HF may relatively slow BNP clearance from organs other than kidney. Although "clearance" receptor upregulation [26,27] and neutral endopeptidase activation [28,29] in HF may work to decrease BNP, once the number of BNP receptors on the cell surface is maximized, they may become saturated by BNP, reducing the overall clearance rate for BNP [30]. However, the complete picture of HF effect on NT and BNP clearance remains to be elucidated. Future studies that examine the serial changes of two hormones and other factors between baseline and acute exacerbation in severe HF would help clarify the detailed effect of HF on the clearance of BNP and NT.

Levels of intact pro-BNP, a precursor of BNP and NT, are also increased in HF [31]. Because present BNP immunoassays also measure pro-BNP [31], this factor may partly explain the HF effect on NT/BNP. This issue warrants future study.

In subgroup analysis (Fig. 2), the difference between pressure and volume load did not relate to log NT/BNP. In this study, ASD patients had higher Qp/Qs than VSD/PDA patients. The slightly higher log NT/BNP in ASD than in VSD/PDA patients could be explained by the Qp/Qs differences between the two groups. This observation appears consistent with the theoretical prediction that higher Qp/Qs should increase the log NT/BNP because BNP clearance occurs also in the lungs, but NT clearance occurs only in the kidney. The group difference was no more significant when Qp/Qs was added into the multivariate comparison. Thus, our results did not indicate that the difference between right- and left-sided volume load is an important determinant of log NT/BNP.

The current study provided novel findings of two points: the effects of body size and potential HF compensation in natriuretic hormone dynamics. Of note, BNP is much less influenced by age, body size, or renal function, and much more influenced by PCWP in comparison to NT (Table 4). In this regard, BNP [32] may be appreciated as a more specific marker of HF, whereas NT with body size correction may represent the entire cardiorenal system. Current results underline the importance of standardizing NT by age or body size and assessing renal function in the assessment of both hormones in children. The reference value for NT in children decreases with age [33]. For the evaluation of NT in children, use of a *Z*-value of NT [33] is an important option for standardizing NT. When the NT value is within the normal range, it indicates that the cardiorenal system is functioning normally. In contrast, when the NT value is above the normal range, assessment should be

undertaken to determine whether cardiac dysfunction, renal dysfunction, or both caused the high NT value. A high NT value with body size or age correction should be assessed and followed up with consideration of renal function and its trend. Measurements of both hormone levels, if available, can be taken into consideration to enable the qualitative assessment of both cardiac and renal status.

Study limitations

Several issues should be considered in the interpretation of our data. First, this study employed PCWP as a substitute for ventricular stretch. PCWP is a stable measurement obtained by right heart catheterization, whereas PCWP more directly provides the effect of ventricular stretch than do echocardiographic indices. Future studies using other diastolic parameters such as stiffness, relaxation, and end-diastolic wall stress [3] are warranted to further clarify the effect of HF on natriuretic peptide dynamics. Second, in contrast to well-known BNP clearance mechanisms, NT clearance remains to be elucidated. NT clearance occurs only in the kidneys [1], but other clearance pathways other than the kidneys [13] cannot be fully excluded. However, such pathways, if they exist, would tend to suppress the NT/BNP increase in renal dysfunction, but we observed that renal dysfunction independently and significantly increased NT/BNP. Thus, the other clearance pathways of NT except the kidneys would not change our results or discussion.

In conclusion, renal dysfunction independently increased NT/BNP, whereas high BSA decreased it, and was the greatest determinant of NT/BNP in children with heart disease. Moreover, high PCWP decreased NT/BNP, a potential compensatory pathway of HF. These factors need to be considered in the assessment of BNP and NT.

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Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

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Oxygen Supply to the Fetal Cerebral Circulation in Hypoplastic Left Heart Syndrome: A Simulation Study Based on the Theoretical Models of Fetal Circulation

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Abstract Hypoxia due to congenital heart diseases (CHDs) adversely affects brain development during the fetal period. Head circumference at birth is closely associated with neuropsychiatric development, and it is considerably smaller in newborns with hypoplastic left heart syndrome (HLHS) than in normal newborns. We performed simulation studies on newborns with CHD to evaluate the cerebral circulation during the fetal period. The oxygen saturation of cerebral blood flow in newborns with CHD was simulated according to a model for normal fetal circulation in late pregnancy. We compared the oxygen saturation of cerebral blood flow between newborns with tricuspid atresia (TA; a disease showing univentricular circulation and hypoplasia of the right ventricle), those with transposition of the great arteries (TGA; a disease showing abnormal mixing of arterial and venous blood), and those with HLHS. The oxygen saturation of cerebral blood flow in newborns with normal circulation was 75.7 %, whereas it was low (49.5 %) in both newborns with HLHS and those with TA. Although the oxygen level is affected by the blood flow through the foramen ovale, the oxygen saturation in newborns with TGA was even lower (43.2 %). These data, together with previous reports,

suggest that the cerebral blood flow rate is decreased in newborns with HLHS, and the main cause was strongly suspected to be retrograde cerebral perfusion through a patent ductus arteriosus. This study provides important information about the neurodevelopmental prognosis of newborns with HLHS and suggests the need to identify strategies to resolve this unfavorable cerebral circulatory state in utero.

Keywords Cerebral circulation · Congenital heart disease · Fetus · Hypoplastic left heart syndrome

Background

In recent years, neuropsychiatric developmental delay has been recognized in patients with congenital heart disease (CHD) who require surgery during the neonatal period [6]. Most notably, the impacts of surgical invasion, including cardiopulmonary bypass, and of the state of heart failure during the perioperative period on the neonatal brain, have been considered the major factors underlying this delay [2]. However, the importance of congenital factors, such as hypoxia due to congenital cardiovascular structural anomalies that adversely affect brain development during the fetal period, has recently been pointed out [1]. This is also suggested by reports showing that head circumference at birth, which is closely associated with the neuropsychiatric developmental prognosis, is significantly smaller in newborns with hypoplastic left heart syndrome (HLHS), characterized by anomalous hemodynamics from the fetal period, than in normal newborns [16]. Furthermore, reports on Doppler ultrasound measurements of cerebral blood flow in HLHS during the fetal period have also shown a brain-sparing effect, a finding indicating decreased oxygen supply

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to the brain [8]. However, these findings are not consistently observed in many other forms of CHD showing hemodynamic derangement and hypoxia, and there are differences even in the descriptions of HLHS itself among reports [3]. In addition to the limited sample size of each study, one of the major reasons for this may be the difficulty in standardizing the effects of maternal factors including placental function and fetal factors affecting the cerebral circulation, such as developmental status, chromosomal abnormalities, and gestational age, in in vivo assessment. Thus, in this study, to eliminate potential confounding factors affecting the cerebral circulation and thereby assess the pure effects of hemodynamic factors due to cardiovascular structural anomalies in HLHS, we performed simulation studies of cerebral circulation in HLHS during the fetal period on the basis of the theoretical models of fetal circulation.

Methods

On the basis of a model of normal fetal circulation in late pregnancy that was introduced with preferential streaming of placental blood flow [18], the oxygen saturation of cerebral blood flow in HLHS fetuses was simulated. Moreover, with a model of Type Ia tricuspid atresia (TA, a disease showing univentricular circulation and hypoplasia of the right heart) and a model of type I transposition of the great arteries (TGA, a disease showing abnormal arteriovenous blood mixture), similar simulations were performed for comparison.

Model of Normal Fetal Circulation

Figure 1a shows the basic model of normal fetal circulation developed using the model proposed by Rudolph [18] on the basis of animal experiments. Data for blood flow distribution and oxygen saturations at each site used for calculating the oxygen saturation of cerebral blood flow are summarized in Table 1. Briefly, the oxygen saturation of umbilical venous blood ($S_{uv}O_2$) is 85 %, and the blood flow rate is 200 mL kg^{-1} min^{-1}, of which 130 mL kg^{-1} min^{-1} flows into the left atrium through the foramen ovale. The remaining umbilical venous blood of 70 mL kg^{-1} min^{-1} in combination with blood flow from the lower limbs ($S_{low \, IVC}O_2$, 35 %; blood flow rate, 100 mL kg^{-1} min^{-1}) and the upper limbs ($S_{SVC}O_2$, 35 %; blood flow rate, 170 mL kg^{-1} min^{-1}), a total of 340 mL kg^{-1} min^{-1}, flows into the right ventricle. Of the right ventricular output of 340 mL kg^{-1} min^{-1}, 300 mL kg^{-1} min^{-1} is distributed to the descending aorta through the arterial duct and 40 mL kg^{-1} min^{-1} is distributed to the pulmonary circu-

lation. In total, 130 mL kg^{-1} min^{-1} of blood flow from the foramen ovale and 40 mL kg^{-1} min^{-1} of the pulmonary venous return without being oxygenated in the lungs flows into and out of the left ventricle. All of this left ventricular output circulates throughout the upper body, and all of the blood flow from the arterial duct to the descending aorta circulates throughout the lower body.

From the data listed in Table 1, we can calculate the oxygen saturation of the right and left ventricle where blood with different oxygen saturations is mixed according to the flow distribution as follows:

Oxygen saturation in the right ventricle($S_{RV}O_2$)
= ([inferior vena cava(IVC)flow from the placenta
$\quad$ × oxygen saturation of the IVC flow from the placenta]
$\quad$ + [IVC flow from other organs
$\quad$ × oxygen saturation of the IVC flow from other organs]
$\quad$ + [superior vena cava(SVC) flow
$\quad$ × oxygen saturation of the SVC flow])/
(IVC flow from the placenta + IVC flow from other organs
$\quad$ + SVC flow)

Oxygen saturation in the left ventricle($S_{LV}O_2$)
= ([foramen ovale (FO) flow from the placenta
$\quad$ × oxygen saturation of FO flow] + [pulmonary artery(PA)flow
$\quad$ × oxygen saturation of the PA flow])/(FO flow + PA flow)

Similar calculations based on the flow and O_2 saturation were applied to fetal circulation with CHD.

Models of CHD

Data for blood flow distribution and oxygen saturations at each site used for calculating the oxygen saturation of cerebral blood flow in the models of CHD are also summarized in Table 1. Placental function was assumed to be normal, and thus the oxygen saturation of umbilical venous blood ($S_{uv}O_2$) was set at 85 %, and the blood flow rate was set at 200 mL kg^{-1} min^{-1}. The ventricular functions were presumed to be good enough to be capable of maintaining necessary systemic blood flow similar to the normal circulation. Furthermore, the blood flow rate from the upper limbs was hypothesized to be the same as the normal rate, 170 mL kg^{-1} min^{-1}. Because the pulmonary blood flow rates in HLHS (Fig. 1b) and TA (Fig. 1c) were expected to be slightly higher than the normal rate, the rates in both diseases were hypothesized to be 50 mL kg^{-1} min^{-1}. Because lower pulmonary vascular resistance and an even higher pulmonary blood flow rate were expected in TGA (Fig. 1d) [12], the rate was hypothesized to be 130 mL kg^{-1} min^{-1}. The blood flow rates from the lower
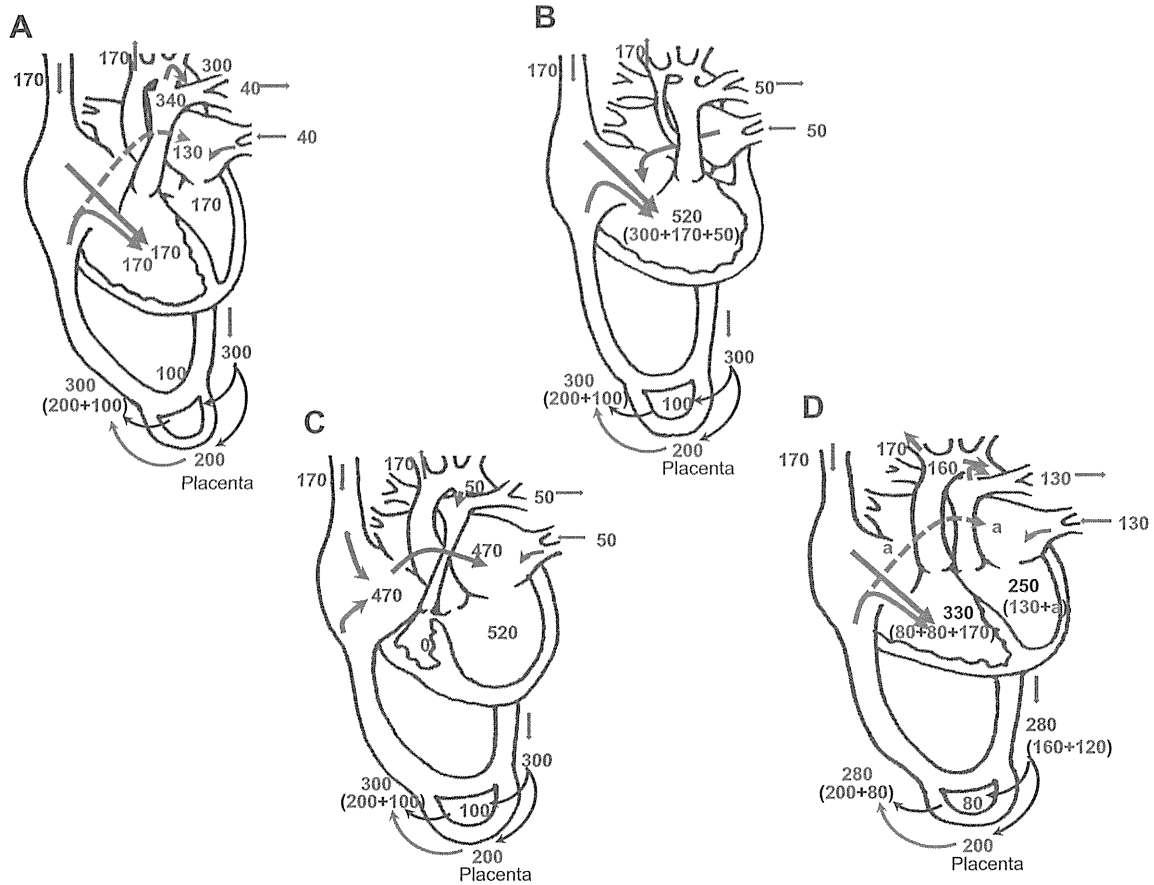
Fig. 1 Basic model of normal fetal circulation developed using the model proposed by Rudolph et al. (**a**). Model of fetal circulation in HLHS (**b**), TA (**c**), and TGA (**d**). The unit of blood flow is mL kg^{-1} min^{-1}

Table 1 Blood flow and the oxygen saturations in the main vessels used for simulation

	Normal	HLHS	TA	TGA
Blood flow (mL kg^{-1} min^{-1})				
UV	200	200	200	200
FO	130	50	470	[a]
IVC	100	100	100	80
SVC	170	170	170	170
PA	40	50	50	130
O$_2$ saturation (%)				
UV	85	85	85	85
FO	85			85
IVC[b]	35	35	35	35
SVC	35	35	35	35

UV umbilical vein, *FO* foramen ovale, *IVC* inferior vena cava, *SVC* superior vena cava, *PA* pulmonary artery

[a] The shunt flow rate from the right atrium to the left atrium through the foramen ovale was set as mL kg^{-1} min^{-1}

[b] IVC flow and O$_2$ saturation are those of blood from the lower limbs other than from the placenta

limbs in HLHS and TA were hypothesized to be similar to the normal rate of 100 mL kg^{-1} min^{-1}. Because high pulmonary blood flow was postulated in TGA, the blood flow rate from the lower limbs was hypothesized to be 80 mL kg^{-1} min^{-1}. The blood flow volume through the foramen ovale could be hypothesized to be the total volume of left atrial perfusion in HLHS and the total volume of right atrial perfusion in TA. Because the shunt volume varies substantially in TGA depending on the condition of the foramen ovale, the shunt flow rate was hypothesized to be (a) mL kg^{-1} min^{-1} only from the right atrium to the left atrium.

Furthermore, on the basis of the hypothesis that oxygen consumption in both the upper and the lower limbs was the same as that in the normal circulation, $S_{\text{low IVC}}O_2$, $S_{\text{SVC}}O_2$, and oxygen saturation in the right ventricle ($S_{\text{RV}}O_2$) (oxygen saturation in the left ventricle [$S_{\text{LV}}O_2$] in TA) were calculated. When this hypothesis did not fit the observations made, it was reexamined, and the analysis was attempted again.

Results

Oxygen Saturation at Each Site in the Normal Circulation

Oxygen saturation was calculated to be 45.3 % in the right ventricle and 75.7 % in the left ventricle, as follows:

$$S_{RV}O_2 = ([70 \times 85\%] + [100 \times 35\%] + [170 \times 35\%])/340$$
$$= 45.3\%$$

$$S_{LV}O_2 = ([130 \times 85\%] + [40 \times 45.3\%])/170 = 75.7\%$$

$$SVC = 35\%$$

Oxygen Saturation at Each Site in CHDs

HLHS

On the basis of the assumption that the blood flow rates and oxygen consumptions in the upper and the lower bodies were similar to those in the normal circulation, differences in arterial–venous oxygen saturation in both upper and lower bodies should be the same as in normal conditions:

$$S_{RV}O_2 - S_{SVC}O_2 = 41\%$$

$$S_{RV}O_2 - S_{low\,IVC}O_2 = 10\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the right ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{RV}O_2 = 45$ %, using the following equation:

$$S_{RV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\%]$$
$$+ [50 \times S_{RV}] + [170 \times S_{SVC}])/520.$$

Reexamination of the Hypothesis of HLHS

When the decrease in oxygen saturation was set at 41 % in the upper limbs and 10 % in the lower limbs, the equation in "HLHS" section yielded a nonphysiological value of $S_{SVC}O_2 = 4$ %. Because a portion of venous blood that had low oxygen saturation in simulation of the normal circulation passes through the foramen ovale, the actual oxygen saturation should be lower in the left ventricle and higher in the right ventricle than the values obtained in "HLHS" section. Thus, the decreases in oxygen saturation in the upper and lower limbs in the normal circulation were changed to 30 and 20 %, respectively, and simulations were then performed while the hypothesis that the blood flow rates and oxygen consumption in both the upper and lower limbs were similar to those in the normal circulation was maintained:

$$S_{RV}O_2 - S_{SVC}O_2 = 30\%$$

$$S_{RV}O_2 - S_{low\,IVC}O_2 = 20\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{LV}O_2 = 45$ %, using the following equation:

$$S_{RV} = ([100 \times S_{low\,IVC}] + [200 \times 85\%]$$
$$+ [50 \times S_{RV}] + [170 \times S_{SVC}])/520.$$

TA

On the basis of the assumption that the blood flow rates and oxygen consumptions in the upper and the lower bodies were similar to those in the normal circulation, differences in arterial–venous oxygen saturation in both the upper and lower bodies should be the same as in normal conditions:

$$S_{LV}O_2 - S_{SVC}O_2 = 41\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 10\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 4$ %, $S_{low\ IVC}O_2 = 35$ %, and $S_{LV}O_2 = 45$ %, using the following equation:

$$S_{LV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\%]$$
$$+ [50 \times S_{LV}] + [170 \times S_{SVC}])/520.$$

Reexamination of the Hypothesis of TA

When the decrease in oxygen saturation was set at 41 % in the upper limbs and 10 % in the lower limbs, the equation in "TA" section again yielded a nonphysiological value of $S_{SVC}O_2 = 4$ %. As is the case with "Reexamination of the Hypothesis of HLHS" section, the decreases in oxygen saturation in the upper and lower limbs in the normal circulation were changed to 30 and 20 %, respectively, and simulations were then performed while the hypothesis that blood flow rates and oxygen consumption in both the upper and the lower limbs were similar to those of the normal circulation was maintained:

$$S_{LV}O_2 - S_{SVC}O_2 = 30\%$$

$$S_{LV}O_2 - S_{low\,IVC}O_2 = 20\%$$

Furthermore, owing to the oxygen saturation of blood mixed in the left ventricle, oxygen saturations were calculated to be $S_{SVC}O_2 = 19.5$ %, $S_{low\ IVC}O_2 = 29.5$ %, and $S_{LV}O_2 = 49.5$ %, using the following equation:

$$S_{LV}O_2 = ([100 \times S_{low\,IVC}] + [200 \times 85\%]$$
$$+ [50 \times S_{LV}] + [170 \times S_{SVC}])/520.$$

TGA

The blood flow rates and oxygen consumption in both the upper and the lower limbs were hypothesized to be similar