19 腹痛 abdominal pain

腹痛は，日常診療の中でよくみられる症状の1つである．腹痛の診断にあたっては緊急性を判断しながら，患児の年齢，いつからの痛みか，どの程度の痛みか，どのあたりの痛みか，痛みの増強・軽減があるかなどに注目して鑑別を進めていく（表1-125）．

特に緊急性を要する疾患である可能性の高い症状は，急性の痛みで，①激痛，②下血・血便，③嘔吐（胆汁性・血性），④腹部膨満，⑤筋性防御・反跳痛，⑥全身状態不良，のいずれかがみられる場合である．これらの症例では急性腹症を疑い，早急な診断が必要である．

腹痛は，急激に発症する急性の腹痛と1〜2カ月以上持続してみられる慢性・反復性の腹痛に分けられる（表1-126）．なお，頻度の高い疾患を下線で示した．

腹痛の鑑別診断を図1-67に示す．図からわかるように，随伴症状（例えば，嘔吐・下痢・発熱など）の有無を十分問診することが大切である．

一方，腹痛の原因は必ずしも消化器疾患とは限らない．丁寧な問診および理学的所見から，診断を進めていく．

また，低年齢児ではその部位や程度を正確に表現できないことが多いことにも注意が必要である．例えば，乳児では，"激しく泣く，機嫌が悪い，ミルクの飲みが悪い"と母親が訴えるのみの場合や，幼児では頭痛・腹痛・四肢痛など他の部位の痛みを腹痛（ポンポンが痛い）と表現する場合がある．

診断に必要となることが多い検査を表1-127に示す．問診・視診・触診・聴診に加えて，これらの検査のいくつかを選択し診断の手助けとする．

血液検査では白血球数，CRPなどから炎症の程度を確認する．急性虫垂炎，細菌性腸炎などではこれら炎症反応の上昇がみられる．

表1-125 腹痛の診断のポイント

1. 緊急性の有無（本文参照）
2. 痛みが出現した時期
   　いつからか？
3. 痛みの部位
4. 痛みの強さ
   　体位や表情から推定
5. 痛みの持続時間
   　間欠的か？　持続するか？
6. 痛みの起こりやすい時
   　食事との関係があるか？　夜間も痛むか？
7. 全身状態
8. 脱水の有無は？　食欲はあるか？
9. 随伴症状
   　嘔吐・下痢・血便・便秘・発熱などを伴うか？
10. その他
   　内服薬の有無．年長女児では月経歴など．

表 1-126　腹痛の原因

	急性の腹痛	慢性の腹痛
乳幼児	腸重積☆ かぜ症候群 急性胃腸炎 尿路感染症 鼠径ヘルニア嵌頓☆ 腸閉塞☆ 総胆管拡張症☆	便秘 反復性腹痛症
学童期	急性胃腸炎 急性虫垂炎☆ 血管性紫斑病☆ かぜ症候群 卵巣腫瘍・茎捻転☆ 急性陰嚢症☆ 周期性嘔吐症 食中毒 尿路感染症 肝炎 膵炎	過敏性腸症候群 便秘症 胃・十二指腸潰瘍 炎症性腸疾患（クローン病） 神経性食思不振症 心因性腹痛

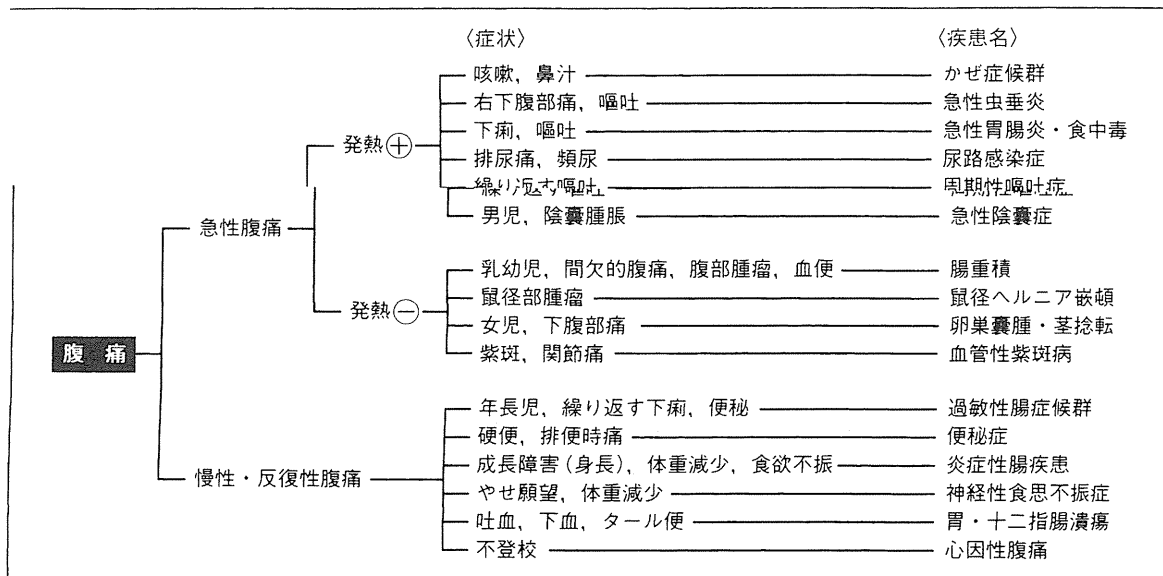＊下線（＿）は頻度の高い疾患，星印（☆）は急性腹症の疾患.

図 1-67　腹痛の鑑別診断

　生化学検査では，肝臓・胆嚢・胆道系疾患で AST，ALT などが，膵疾患でアミラーゼなどが上昇することが多い．また消化管出血では貧血に加えて，尿素窒素の上昇がみられることがある．

表 1-127　診断に必要となることが多い検査

1. スクリーニング検査
　　腹部 X 線検査
　　腹部超音波検査
　　血液検査
　　　血算，CRP，ビリルビン，ALT (GOT)，AST (GPT)，LDH，アミラーゼ
　　　尿素窒素，クレアチニン，血糖，電解質，赤沈
　　尿検査
　　　定性，沈渣
　　便
　　　潜血，培養
2. 確定診断のための検査
　　腹部 CT，腹部 MRI
　　注腸造影・上部消化管造影検査
　　消化管内視鏡検査
　　その他
　　　年長女児では婦人科受診．腹部疾患以外の精査．

　尿検査は簡便かつ低侵襲であり，尿路感染症の診断には必須である．便検査は腹痛の診断に重要であり，必要であれば浣腸を用いて，性状や血便の有無を確認する．イチゴゼリー様粘血便では腸重積を疑う．

　画像検査では単純 X 線検査は重要であり，腸閉塞や消化管穿孔の診断には第一選択である．腹部超音波検査は腸重積，急性虫垂炎，腸閉塞，総胆管拡張症，腫瘤性病変など，腹部 CT 検査は急性虫垂炎の診断，肝胆道系疾患および膵疾患の鑑別に有用である．

　慢性・反復性の痛みの場合には，食欲や体重の増減，便通の様子に加えて，日常生活への支障，患者・家族の気持ちについても聞き取り，治療計画を練ることが大切である．

20 悪心 nausea, 嘔吐 vomiting

　嘔吐は小児診療で多く遭遇する症状の1つであり，原因も様々である．診断のポイントとして，患児の年齢，時間経過，嘔吐の量・回数，嘔吐の勢い，水分摂取量・尿量・食欲など全身状態，腹痛・下痢・発熱を伴うかなどがあげられる（表 1-128）．

　急性の嘔吐には緊急を要する疾患が多く，①血性・胆汁性の嘔吐，②全身状態不良，③意識レベルの低下，④痙攣，⑤激腹痛・筋性防御，を伴う場合は早急な診断が必要である．

　なお，嘔吐は消化管の内容物を噴出する状態であり，乳幼児における解剖学的特徴（食道と胃壁のなす角度が鈍角であること）による逆流，すなわち溢乳とは異なるため区別して考えることが必要である．

　嘔吐は経過により急性と慢性に分類され年齢により好発疾患が異なる（表 1-129）．

　新生児期は，溢乳・空気嚥下・ミルク誤飲など生理的な原因による嘔吐が多いが，消化管閉塞による嘔吐の頻度が年長児に比べて高いのも特徴である．また，嘔吐の原因は必ずしも腹部疾患とは限らず，敗血症や髄膜炎・脳腫瘍・頭蓋内出血などの中枢性疾患，ガラクトー

表 1-128　嘔吐の診断のポイント

1. 緊急性の有無（本文参照）
2. 年齢
3. 嘔吐が出現した時期
   　いつからか？
4. 嘔吐の量・回数
5. 嘔吐の状況
   　悪心の有無は？　食事との関係があるか？
6. 嘔吐の勢い
7. 嘔吐物の性状
   　血液・胆汁の混入はあるか？
8. 全身状態
   　脱水の有無は？　尿量は？　哺乳量は？
9. 随伴症状
   　腹痛・下痢・発熱などを伴うか？
10. その他
    　虐待の可能性はないか？
    　家庭・保育園での流行疾患の有無.

表 1-129　嘔吐の原因

	急性の嘔吐	慢性・反復性の嘔吐
新生児期	初期嘔吐 敗血症・髄膜炎 先天性消化管閉鎖 頭蓋内出血 先天性代謝異常 総胆管拡張症 先天性副腎過形成	胃食道逆流症 ミルクアレルギー
乳幼児期	急性胃腸炎 急性中耳炎 腸重積 髄膜炎・脳炎・脳症 肝炎 腸閉塞 尿路感染症 アセトン血性嘔吐症	脳腫瘍 先天性代謝異常症 胃食道逆流症 肥厚性幽門狭窄症
学童期	急性胃腸炎 急性虫垂炎 肝炎 膵炎 血管性紫斑病 糖尿病性ケトアシドーシス	クローン病 神経性食思不振症 胃十二指腸潰瘍 アセトン血性嘔吐症

＊下線（＿＿）は頻度の高い疾患

ス血症をはじめとする代謝性疾患など全身疾患の鑑別を忘れてはならない．乳幼児期はウイルス性の胃腸炎の頻度が圧倒的に高い．髄膜炎・敗血症などの重症感染症，その他，尿路感染症・中耳炎などが見落とされやすく注意が必要である．学童期も，ウイルス性胃腸炎による嘔吐の頻度が高いが年長児では異物・薬物誤飲や胃十二指腸潰瘍，アセトン血性嘔吐症などの代謝内分泌疾患の頻度が高まる．

嘔吐の鑑別診断を図 1-68 に示す．図からわかるように，随伴症状（例えば，腹痛・下痢・発熱など）についても十分問診することが大切である．

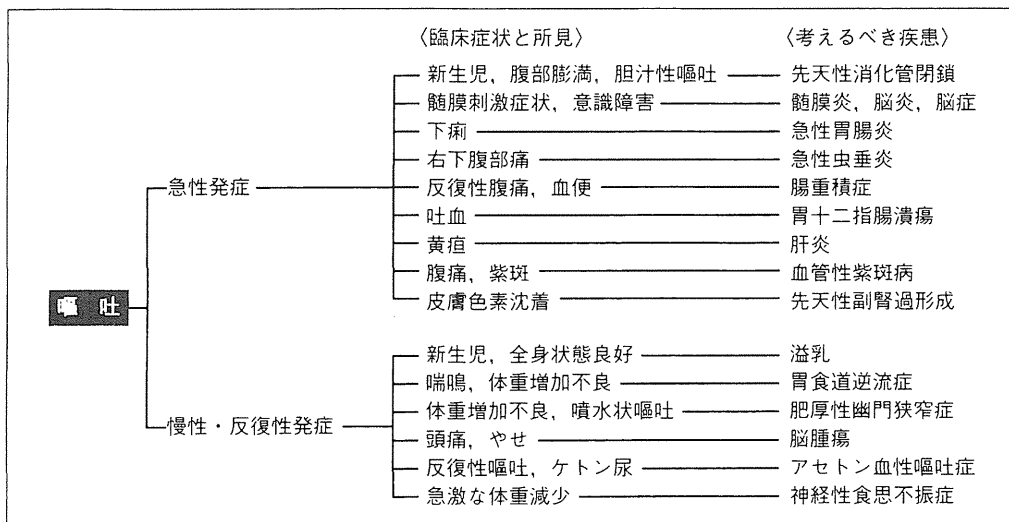診断に必要となることが多い検査を表 1-130 に示す．問診・視診・触診・聴診に加えて，これらの検査のいくつかを選択し診断の手助けとする．

	〈臨床症状と所見〉	〈考えるべき疾患〉

急性発症
- 新生児，腹部膨満，胆汁性嘔吐 ── 先天性消化管閉鎖
- 髄膜刺激症状，意識障害 ── 髄膜炎，脳炎，脳症
- 下痢 ── 急性胃腸炎
- 右下腹部痛 ── 急性虫垂炎
- 反復性腹痛，血便 ── 腸重積症
- 吐血 ── 胃十二指腸潰瘍
- 黄疸 ── 肝炎
- 腹痛，紫斑 ── 血管性紫斑病
- 皮膚色素沈着 ── 先天性副腎過形成

嘔吐

慢性・反復性発症
- 新生児，全身状態良好 ── 溢乳
- 喘鳴，体重増加不良 ── 胃食道逆流症
- 体重増加不良，噴水状嘔吐 ── 肥厚性幽門狭窄症
- 頭痛，やせ ── 脳腫瘍
- 反復性嘔吐，ケトン尿 ── アセトン血性嘔吐症
- 急激な体重減少 ── 神経性食思不振症

図 1-68 嘔吐の鑑別診断

表 1-130 診断に必要となることが多い検査

1. スクリーニング検査
   体重測定
   腹部 X 線検査
   腹部超音波検査
   血液検査
   　血算，CRP，ビリルビン，ALT（GOT），AST（GPT），LDH，アミラーゼ
   　尿素窒素，クレアチニン，血糖，電解質，赤沈
   尿検査
   　定性・沈渣：特に尿ケトン，尿糖など
2. 確定診断のための検査
   腹部 CT，腹部 MRI
   注腸造影・上部消化管造影検査
   消化管内視鏡検査
   その他
   　腹部疾患以外の精査（頭部 CT・MRI など）

　血液検査では白血球数, CRP は急性虫垂炎, 細菌性腸炎の他, 髄膜炎・中耳炎・肺炎などでも, これら炎症反応の上昇がみられる.

　生化学検査では, 腹痛の場合と同様, 肝臓・胆嚢・胆道系疾患では AST, ALT などを, 膵疾患ではアミラーゼなどを参考とする. 代謝疾患を疑った場合には血液ガス分析・電解質・血糖, アンモニア, 尿ケトン体をまず検査することが多い. 尿中ケトン体が病初期より認められるのはアセトン血性嘔吐症の特徴である.

　先天性消化管閉鎖症の診断には単純 X 線検査が第一選択であることが多い. 腹部超音波検査は侵襲性が少なく, スクリーニング精査として位置づけられる. 腸重積, 急性虫垂炎, 腸閉塞, 総胆管拡張症, 腫瘤性病変など様々な疾患の鑑別に有用である. 腹部 CT 検査は急性虫垂炎の診断, 肝胆道系疾患および膵疾患の鑑別に有用である.

21 嚥下困難・障害 dysphagia

　嚥下は食物や液体を口に取り込み, 咽頭と食道を経て胃内へ送り込む運動である. 口から食べられなくなることは, 楽しみの消失であり生活の質を著しく低下させることを忘れてはならない.

　小児の摂食・嚥下障害の原因として器質的原因, 神経学的原因, 心理的原因に大きく分類される (表 1-131).

　嚥下障害の具体的症状として, 食べこぼす, むせる, 食事に時間がかかる, 口に溜める, 噛めない, 流涎, 喉がゴロゴロ鳴る, 誤嚥, 窒息などがあげられる. 特に緊急性を要する可能性の高い症状は, ①発熱, ②咽頭痛, ③嚥下障害, ④喘鳴などの呼吸障害, がみられる場合である. これらの症例では咽後膿瘍, 急性喉頭蓋炎を疑い, 早急な診断が必要である.

　嚥下障害児に対するリハビリテーションを表 1-132 に示す. 訓練は食物を直接使う方法と使わず口唇・頬の伸展マッサージや口腔周囲の可動域訓練を行う間接法がある. 肺理学療法として, ①呼吸訓練, ②誤嚥と気道分泌貯留を防ぐために体位変換とポジショニング, ③

表 1-131　嚥下障害の原因

器質的原因	口腔	口蓋裂
	舌	巨舌 (Down 症候群, 先天性リンパ管腫)
	鼻腔	鼻炎・副鼻腔炎, 先天性後鼻孔閉鎖症
	下顎	小顎症
	咽頭	扁桃腫大, 腫瘍, 喉頭蓋炎, 喉頭軟化症, 咽後膿瘍
	食道	先天性食道閉鎖症, 血管輪
神経学的原因	中枢神経	脳性麻痺, 染色体異常
		脳血管障害, 腫瘍, 脳炎
	末梢神経	腫瘍, 外傷性, 感染症, 血管性, 脱髄
	筋障害	筋ジストロフィー症, 重症筋無力症, 皮膚筋炎・多発筋炎
		先天性代謝異常症, 甲状腺機能低下症
心理的原因		神経性食思不振症, 拒食, 食事恐怖症, 反芻
その他		口腔乾燥, 口内炎, 薬剤・中毒症

表 1-132　嚥下障害のリハビリテーション

1. 訓練
1）直接訓練
食物を使う訓練．誤嚥のリスクあり
2）間接訓練
食物を使わない訓練．
口唇・頬のマッサージ．舌・口腔周囲の可動域訓練
2. 肺理学療法
1）呼吸訓練
2）体位変換
3）排痰法
3. 運動療法
4. 理学療法
5. 口腔ケア

咳嗽訓練，があげられる．また，活動性の低下に伴い，筋力低下をまねき誤嚥性肺炎のリスクを高めるため運動療法による活動性の向上は重要である．

　口腔内は，微生物が繁殖しやすい条件がそろっていることから，呼吸器感染症をはじめ全身疾患と関連している．したがって，歯牙のブラッシング・粘膜の清掃やマッサージ，舌のブラッシングなどの口腔ケアはそれら疾患の予防に必要不可欠である．

　小児が成人と大きく異なる点は，成長・発達期であること，重症児が多いこと，全身状態や心理面への配慮が重要になる点である．したがって，医師，歯科医師，看護師，言語療法士，理学療法士，作業療法士，栄養士など小児の嚥下障害に関わるスタッフの連携が重要であると思われる．

〈龍城真衣子，宮沢麗子，友政　剛〉

　小児の食思不振は，成人と異なる点に留意する．成人の食思不振は本人の主観が中心であるが，小児では本人の食欲とは無関係に保護者の主観による哺乳量・摂取量の低下も食思不振となりうる．したがって，期待どおりの哺乳量・摂食量がみられない場合も食思不振と捉えられることがある．そして，食思不振の訴えの中には哺乳障害，嚥下障害，摂食障害なども含まれる．患児の年齢，性別，随伴症状の有無，症状を認めた期間，成長（体重・身長），生活環境などの社会心理的背景を的確に捉えることが大切である．

　新生児期では，妊娠・分娩歴，仮死の有無などの情報とともに，哺乳回数と哺乳量（1回・1日量），栄養法（母乳・混合・人工乳），哺乳にかかる時間，および体重増加を確認する（表 1-133）．乳幼児期では，感染症（消化器・呼吸器感染症）によるものが多いが，親子関係に起因するものもある．乳児では，離乳食の開始時期・内容・量，よだれの有無などを確認する．幼児期以降では，食思不振を認める時間・場所とともに食事記録（内容・重量）を分析する．数日間のデータを記録から，栄養士による1日摂取カロリー，および糖質・蛋白質・脂質の摂取状況を算出する．学童期，特に思春期では心理的問題などを確認す

ORIGINAL ARTICLE

Association of lymphocyte crossmatch and the outcome of intestinal transplantation in swine

Makoto Hayashida · Toshiharu Matsuura · Isamu Saeki · Yusuke Yanagi ·
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Abstract

Background The effect of preformed antidonor antibodies have been demonstrated in various types of solid organ transplantation. However, the significance of anti-donor antibodies in intestinal transplantation remains unclear. The aim of this study is to evaluate the impact that the extent of T cell crossmatch has on the outcome of swine intestinal transplantation.

Materials and methods All studies were performed on outbred domestic male pigs weighing from 15 to 20 kg. Intestinal transplantation was performed orthotopically with an exchange of grafts between white and black pigs. FK506 was administered intravenously (0.1 mg/kg per day, POD 0–7) for immunosuppression. A lymphocyte crossmatch test was performed using the direct CDC crossmatch. The results were considered positive when more than 10% of the donor lymphocytes were killed by the recipient's serum. In addition, 0–10, 11–20, 21–30, 31–80 and 81–100% of the killed lymphocytes were classified as grade 1, 2, 4, 6 and 8, respectively.

Result A total of 34 intestinal transplantations were performed. All but one case had positive donor specific T cell crossmatches. The number of grade 2, 4, 6 and 8 cases was 11, 14, 6 and 2, respectively. Although there was a tendency towards a decreased survival according to the grade,

the survival rate was not statistically different among each different grade. Moreover, the rates of acute cellular rejection and vascular complications were not significantly different among the four grades.

Conclusion These results suggest that the extent of positive T cell crossmatch is not associated with the outcome of swine intestinal transplantation.

Keywords Intestinal transplantation · Lymphocyte crossmatch · Antidonor antibody

Introduction

The progress of perioperative management and immunosuppressive therapy has allowed an increase in the numbers of intestinal transplantations for irreversible intestinal failure. However, the incidence of cellular rejection is still high and graft survival is unsatisfactory [1]. The effect of preformed anti-donor antibodies has been demonstrated in various types of solid organ transplantation. However, the significance of anti-donor antibodies in intestinal transplantation remains unclear. The aim of this study was to evaluate the impact that the extent of T cell crossmatch has on the outcome of swine intestinal transplantation.

Materials and methods

Animals

All studies were performed on outbred domestic male pigs weighing from 15 to 20 kg. All animals were given water but no solid food for 12 h before the operation. All animals received human care, in compliance with the Guidelines

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The procedure of intestinal transplantation

Intestinal transplantation was performed orthotopically with an exchange of grafts between white and black pigs. General anesthesia was induced with intravenous administration of 10 mg/kg ketamine HCl (Ketaral; Daiichi Sankyo Co., Ltd, Tokyo, Japan), 0.2 mg/kg atropine intramuscular, and pentobarbital sodium (Nembutal; Dainippon Sumitomo Pharma, Co., Ltd, Osaka, Japan) intravenous administration. Anesthesia was maintained with 0.5–2% isoflurane (Forane; Abbott Japan Co., Ltd, Tokyo, Japan) inhalation. A 3-m length of the ileal segment, located 10 cm proximal from the ileocecal valve, was harvested using vascular pedicles. The intestinal allograft was implanted after systemic heparinization (100 U/kg), using end-to-side anastomosis of the SMA to the infrarenal aorta and of the SMV to the IVC [2].

Postoperative management and immunosuppression

All animals were allowed to drink only water ad libitum during the period from postoperative day 1 to day 4. In addition, they were intravenously administered maintenance infusion therapy of Taclorimus (0.05 or 0.1 mg/kg day^{-1}), heparin (100 U/kg day^{-1}) and antibiotics. Full oral feeding, including solid food, was started on postoperative day 5.

Lymphocytotoxic cross-match test

A crossmatch test between the donor's isolated T lymphocytes and the recipient's sera was performed using a standard lymphocytotoxicity test. The crossmatch test results were interpreted based on the percentages of donor lymphocytes killed: 0–10% was negative, grade 1. When more than 10% of lymphocytes were killed, the result was defined as positive. In addition, 0–10, 11–20, 21–30, 31–80 and 81–100% of the killed lymphocytes were classified as grades 1, 2, 4, 6 and 8, respectively. In addition, grades 2 and 4 were defined as weak positive, and grade 6 and 8 were defined as strong positive.

Results

A total of 34 intestinal transplantations were performed. All but one case were positive donor specific T cell crossmatches. The number of grade 2, 4, 6 and 8 cases was 11, 14, 6 and 2, respectively. In addition, the median survival was 15.18, 14.93, 8, and 5.5 days, respectively
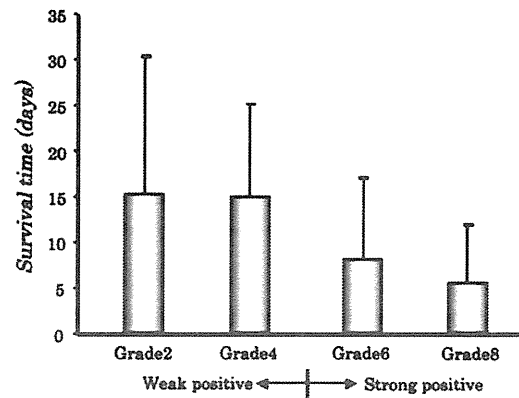

Fig. 1 The grade of crossmatch and survival. There was a tendency of decreased survival rate, however, the survival rate was not statistically different among each different grade
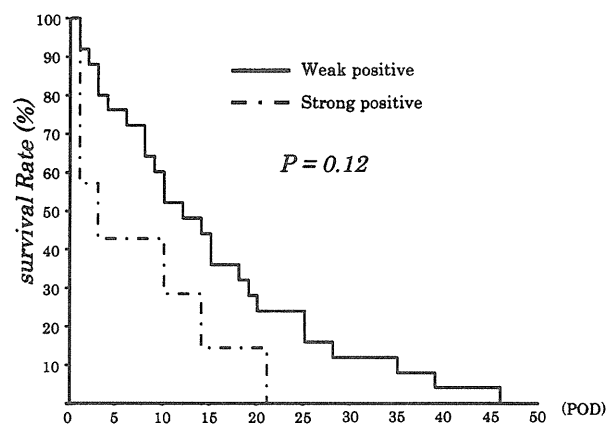

Fig. 2 The cumulative survival rate of crossmatch weak positive and strong positive intestinal graft recipients. There was no significant difference in the recipient's survival between both groups

(Fig. 1). Although there was a tendency towards a decreased survival, there was no statistical difference in the survival rate between each different grade. There was no significant difference between the cumulative survival rate of crossmatch weak positive and strong positive intestinal graft recipients (Fig. 2). The rate of rejection and vascular complications are shown in Table 1. The rates of acute cellular rejection and vascular complications among the four grades were not significantly different.

Discussion

Transplantation across a positive T cell crossmatch is performed in various types of solid organ transplantation, however, the effect of pre-transplant crossmatch on overall rejection and graft survival is controversial. Recent advances in immunosuppressive therapy, surgical technique

Table 1 The rate of rejection and vascular complication

	Grade 2	Grade 4	Grade 6	Grade 8	*P* value
n	11 (34.4%)	14 (43.8%)	5 (15.6%)	2 (6.3%)	NS
Rejection	4 (36.4%)	4 (28.6%)	0	1 (50%)	NS
Vascular complication	2 (18.2%)	3 (21.4%)	0	0	NS

The rates of acute cellular rejection and vascular complications were not significantly different among the four grades

and post-operative management improve the short-term outcome of intestinal transplantation; however, the significance of anti-donor antibodies in intestinal transplantation still remains unclear. The detrimental effects of preformed anti-donor antibodies in intestinal transplantation are limited. Ruiz et al. [3] described a possible correlation of humoral sensitization with allograft vascular alteration in human intestinal transplantation. Kato et al. [4] showed that posttransplant HLA-antibodies are associated with an episode of acute rejection in multivisceral recipients. These results suggest that anti-donor antibodies seemed to have some effects on allografts.

Several approach to desensitization to overcome positive crossmatch, associated with high rates of sever rejection and infection have been reported [5]. A general approach to desensitization is to remove or neutralize anti-HLA IgG. Plasmapheresis and high-dose IgG therapy are generally used to remove or neutralize anti-HLA IgG. Moreover, it is important to prevent formation of new anti-HLA IgG after transplantation. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed at the CD20 antigen found on normal and malignant B lymphocytes. Rituximab is used in sensitized recipients [6]. Rituximab is widely used for the treatment of B cell lymphoma. Rituximab prevents the formation of new plasma cell and inhibits B cell driven antigen presentation and co-stimulation of T cell. These effects allow rituximab to reduce the alloimmune response [5]. Splenectomy is another strategy for sensitized recipients. Splenectomy reduces the number of plasma cells and the B cell surveillance capabilities.

Al but one case of swine intestinal transplantation in the current series, had positive donor specific T cell crossmatches. There was a tendency that the survival time for weak positive crossmatches was longer than that for strong positive crossmatches; however, the survival rate was not statistically different among each different grade. These results suggest that the extent of positive T cell crossmatch is not associated with the outcome of swine intestinal transplantation. Further studies are required to investigate the influence of preformed antibodies in the outcome of intestinal transplantation.

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ORIGINAL ARTICLE

Ischemic preconditioning and remote ischemic preconditioning have protective effect against cold ischemia–reperfusion injury of rat small intestine

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Abstract

Purpose To investigate the protective effect of ischemic preconditioning (IPC) and remote ischemic preconditioning (RIPC) against cold ischemia–reperfusion injury (IRI) associated with small bowel transplantation (SBT).

Methods Male Lewis rats weighing 200–300 g were used for this study. The rats were assigned to three groups: control, ischemic preconditioning (IPC), or remote ischemic preconditioning (RIPC). Heterotopic SBT was thereafter performed. The recipient rats were killed 3, 6, 12 and 24 h after transplantation. Specimens from the intestine were histologically scored according to a grading system (Park et al.). Serum lactate dehydrogenase (LDH), aspirate aminotransferase (AST), alanine aminotransferase (ALT) were examined and heme oxygenase-1 (HO-1) were analyzed by ELISA where HO-1 served as an indicator of protection against IRI.

Results The values of tissue injury were significantly lower in the IPC and RIPC groups than in control group at 3 h after SBT. The serum LDH, AST and ALT levels also significantly decreased in the IPC and RIPC groups at 3 h after SBT, but these protective effects against cold IRI diminished by 12 and 24 h after SBT. The serum HO-1 level significantly increased in the IPC and RIPC groups 3 h after SBT.

Conclusion Both IPC and RIPC were found to ameliorate ischemia–reperfusion injury after rat SBT in the early phase. HO-1 may therefore play a protective role against cold IRI.

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Abbreviations

IPC Ischemic preconditioning
RIPC Remote ischemic preconditioning
SBT Small bowel transplantation
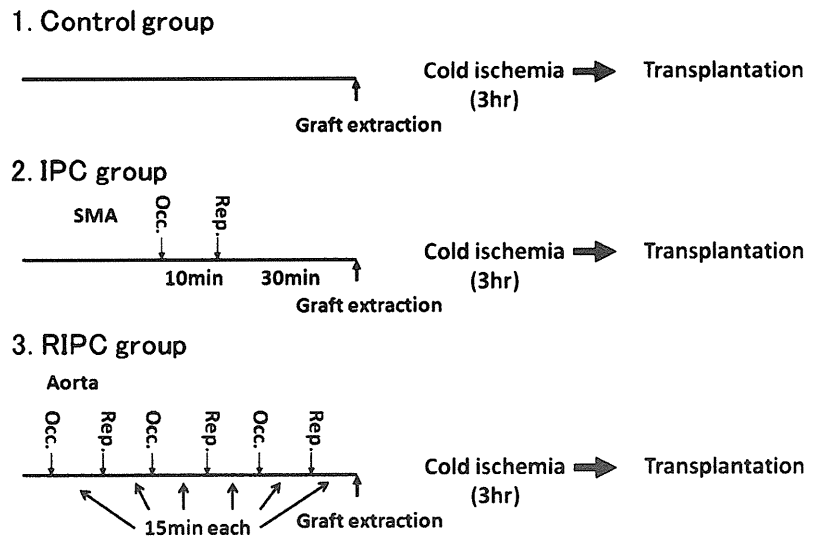IRI Ischemia–reperfusion injury
HO-1 Heme oxygenase-1

Introduction

The small intestine is highly susceptible to ischemia–reperfusion injury (IRI) of intestine after small bowel transplantation (SBT), thus leading to bacterial translocation, endotoxemia, acute respiratory distress syndrome, and multiple organ failure [1–3]. In 1986, Murry et al. [4] first reported ischemic preconditioning (IPC) as a novel method to protect organs from IRI. They introduced five or six cycles of short-period coronary ischemia (5 min) and reperfusion (5 min) to protect against a long period of myocardial ischemia in dog. Recently, IPC protocols have been changed to one cycle of ischemia (10 min) and reperfusion (15 min) and thus have been demonstrated to successfully protect many other organs including the intestine [5–7]. Many clinical studies of IPC were already performed in some organ transplantation [8, 9].

IPC protects not only the organ directly targeted by IPC, but also other distally located organs against IRI, and this phenomenon is called remote ischemic preconditioning (RIPC) [10]. The effect of RIPC has been demonstrated in

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1. Control group

Cold ischemia ➡ Transplantation (3hr)

Graft extraction

2. IPC group

SMA   Occ.   Rep.

10min   30min   Graft extraction

Cold ischemia ➡ Transplantation (3hr)

3. RIPC group

Aorta

Occ. Rep. Occ. Rep. Occ. Rep.

15min each   Graft extraction

Cold ischemia ➡ Transplantation (3hr)

many organs using various sites and cycles of ischemia–reperfusion [11, 12]. RIPC is easily and safely monitored in humans and skeletal muscle ischemia is induced using a blood pressure cuff or tourniquet. Clinical studies of RIPC have already been performed in the field of vascular surgery [13], but no reports have so far addressed the protective effect of RIPC against cold IRI in the small intestine.

The beneficial effect of IPC and RIPC is associated with the induction of heat shock proteins (Hsp). Hsp32, also known as heme oxygenase-1 (HO-1), is induced in the protection of the intestine in the IRI and endotoxic shock models [14, 15]. HO-1 is a rate-limiting enzyme that oxidizes heme to biliverdin and carbon monoxide. Biliverdin is further metabolized to bilirubin and both bilirubin and carbon monoxide have a strong antioxidative activity [16]. HO-1 expression has also been reported to be associated with cytoprotection of intestinal IRI [17].

The aim of this study is to identify the level of protection by IPC and RIPC against cold IRI using the rat SBT model and to determine whether this protective effect occurs through HO-1 induction.

Materials and methods

Animals

Inbred Lewis rats weighing 200–300 g were used as donors and recipients. The animals were housed in conventional facilities under a day/night cycle with free access to food and water. The experiments were conducted according to the Animal Protection Guidelines of Kyushu University School of Medicine.

Experimental design

The rats were randomly divided into three groups. SBT was performed on the control group according to a previous work [18]. In the IPC group, the donor's superior mesenteric artery (SMA) was clamped for 10 min by a microvascular clamp following 30 min of reperfusion before harvesting the intestinal graft. In RIPC group, three cycles of RIPC were performed before harvesting the intestinal graft. The donor rat's infrarenal aorta was clamped for 15 min by a micro-bulldog clamp following 15 min of three cycles of reperfusion (Fig. 1).

The donor rats were operated on for 90–110 min in each group ($n = 20$).

Small bowel transplantation (SBT)

Heterotopic SBT was performed with a technique modified from a previously described report by Matsuura et al. [18]. A segment of the small intestine, located 30 cm distal from the Treitz ligament, was harvested from the donor rat and stored at 4°C in lactate Ringer's solution for 3 h. SBT was performed using micro-vascular techniques. During transplantation, warm ischemia was induced for 22–30 min. For histopathological evaluations and biochemical analysis, the recipient animals were killed at 3, 6, 12 and 24 h after SBT.

Histopathological analysis

The harvested grafts were formalin-fixed and stained with hematoxylin–eosin. Degree of IRI was assessed by a pathologist. A grading system described by Park et al. [19] was used for histological scoring.

Serum chemistry

Arterial blood samples were obtained 3, 6, 12 and 24 h after transplantation. The serum levels of LDH, AST and ALT were examined.

HO-1 ELISA

The serum HO-1 level was measured using the Rat HO-1 ELISA kit (Stressgen, Assay Designs, Inc. USA).

Statistical analysis

Statistical analysis was performed using the unpaired Student's t test and error bars indicated standard deviations. Statistical significance was set at a threshold of $p < 0.05$ in the analysis.

Results

Effect of IPC and RIPC on cold IRI in small intestinal graft

At 3 h after SBT, the small intestine exhibited histopathologies in Fig. 2. The villi were extensively denuded in the control group, but were well preserved in the IPC and RIPC groups. In Fig. 3, the transplanted small intestinal graft was significantly protected from IRI in IPC and RIPC groups at 3 and 6 h after SBT ($p < 0.05$). Although the protective effects were observed to diminish at 12 and 24 h after SBT in the IPC and RIPC groups, and the Park score was surprisingly slightly elevated.

Effect of IPC and RIPC on serum chemistry and HO-1 level

The serum levels of LDH, AST and ALT were significantly reduced in both IPC and RIPC groups compared to control group at 3 h after SBT, but subsequently, there was no significant difference between any of the groups (Fig. 4). The serum HO-1 levels were significantly higher in the IPC and RIPC groups than in the control group at 3 h after reperfusion, but subsequently the difference diminished (Fig. 5).

Discussion

The present study demonstrates that IPC and RIPC provide comparable protection to the small intestine against cold IRI in the early phase. The serum levels of LDH, which are used as a marker of intestinal injury [5, 20, 21], are
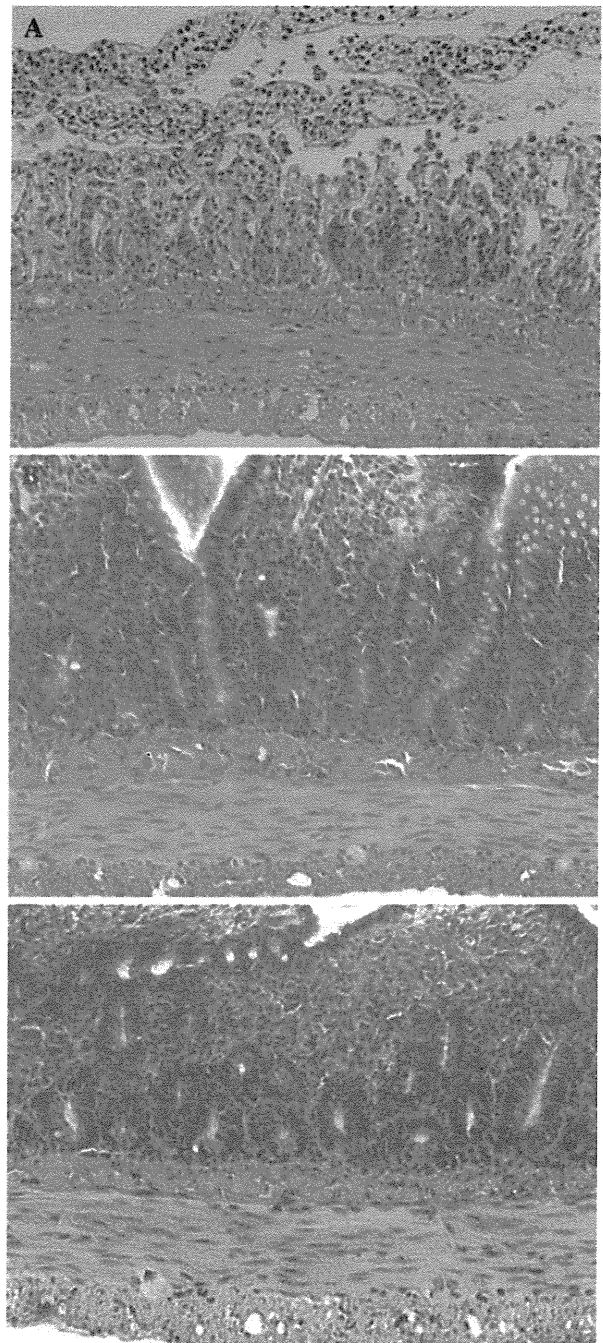

Fig. 2 Histopathological appearance of graft small intestine at 3 h after SBT. The villi were denuded in **a** the control group. In contrast, the villi were preserved well in **b** the IPC group and **c** RIPC groups. Hematoxylin and eosin staining was used

elevated in the control group in comparison to the IPC and RIPC groups. This result correlates with the histological analysis.

The protective effect of IPC was initially described in the heart [4], and applied to many other organs including
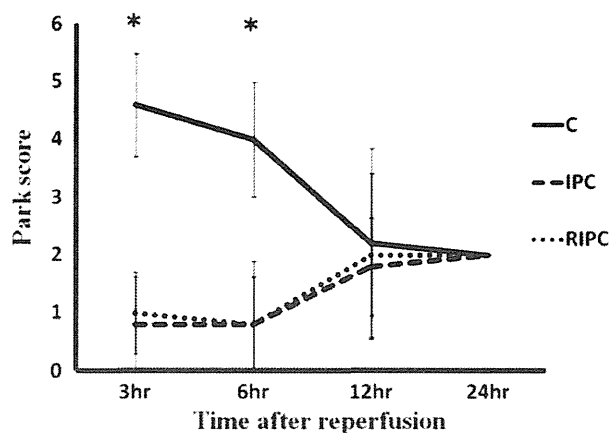
Fig. 3 Park score of intestinal injury after SBT. The intestinal mucosa was protected against IRI during 6 h after SBT (early phase). Each value was reported as the mean of a sample size of five rats. $*p < 0.05$ relative to the control group

intestine [8, 9, 22, 23], but so far few reports describe the protective effect of IPC against intestinal cold ischemia [7, 20]. The optimal protective protocol for IPC remains to be determined [24], but many reports in the literature use one cycle of 10 min of IPC in the rat intestinal IRI. In the present study, we used one cycle of IPC (10 min ischemia followed by 30 min reperfusion) and thus observed this protocol to be effective against cold IRI in the small intestine.

There are no reports of RIPC-mediated protection against intestinal cold IRI in rats. Vlasov et al. [23] performed 30 min of limb ischemia with 15 min of reperfusion (single cycle RIPC) to protect the small intestine from warm IRI, but they did not achieve a sufficient protective effect. In many organs, multiple cycles of RIPC are more effective than a single cycle [10]. Ren et al. [11] show that limb RIPC protected against rat brain focal ischemia, and 3 cycles of 15 min of RIPC provides better protection than 2 cycles of 15 min or 2 cycles of 5 min of RIPC. In the present study, we used 3 cycles of 15 min infrarenal aorta clamping ischemia with 15 min reperfusion (multiple cycle RIPC), and the protocol is equally effective compared to that of IPC. This is the first report indicating the effectiveness of RIPC against cold IRI in a rat intestinal graft.

Although the mechanisms of IPC and RIPC are still not completely understood, it has been shown that some mediators like NF-κB, NO and heat shock proteins are released [6–10]. Mallick et al. [5] show the protective effect of IPC against warm IRI through the higher HO-1 activity in the IPC group than in the control group. The protective effect is diminished by the administration of zinc protoporphyrin (ZnPP) which is an inhibitor of heme production. Secondly, Lai et al. [12] report the protective role of HO-1 to rat liver ischemia using limb RIPC. In the
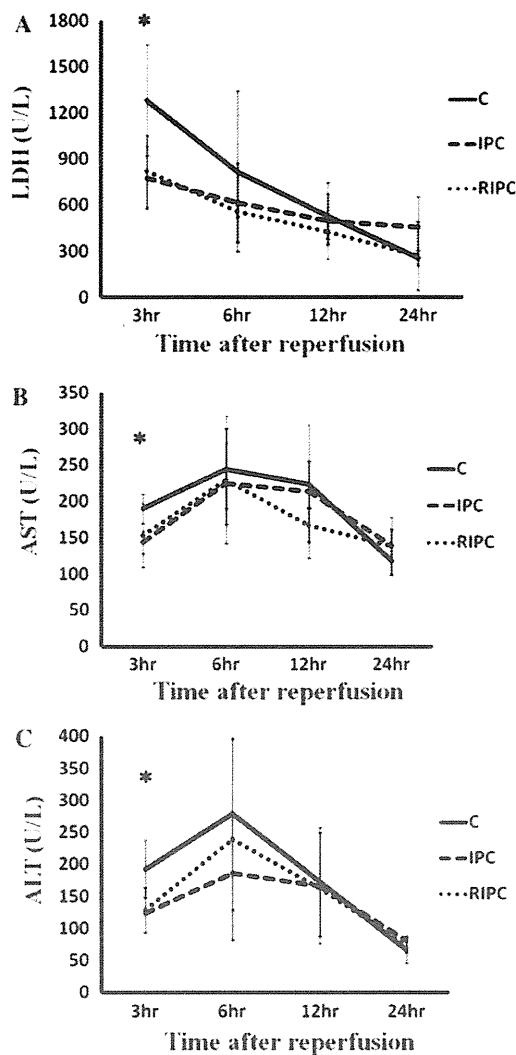

Fig. 4 Effect of IPC and RIPC on the serum a LDH, b AST, and c ALT. Serum LDH and transaminase were decreased in the IPC and RIPC groups compared to the control group at 3 h after reperfusion. Each value was reported as the mean of a sample size of five rats. $*p < 0.05$ relative to the control group

present study, serum HO-1 levels are significantly higher in the IPC and RIPC groups compared to the control group 3 and 6 h after reperfusion. The protective effect of IPC and RIPC are thought to be associated with the activation of HO-1.

In this study, LDH, as well as AST and ALT, are significantly lower in the IPC and RIPC groups at 3 h after SBT. LDH, AST and ALT are widely distributed throughout many organs. The protective effects of IPC and RIPC on the graft intestine therefore appear to be spread to other organs of the recipient rat. It is reported that the effect of IPC on the heart can spread by the infusion of coronary effluent [25]. Oltean et al. [26] show that the transplantation of
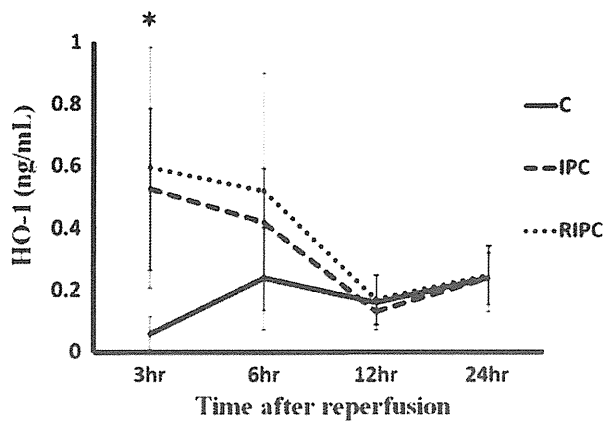
Fig. 5 Effect of IPC and RIPC on the serum HO-1 level. HO-1 in systemic blood samples was elevated in the IPC and RIPC groups compared to the control group at 3 h after reperfusion. Each value was reported as the mean of a sample size of five rats. *$p < 0.05$ relative to the control group

tacrolimus-preconditioned intestine could reduce liver injury and cytokine release. In the application of IPC or RIPC to donor rat, HO-1 in the intestinal graft may be activated, and transferred into blood of recipient rats so as to protect other organs. This hypothesis may be confirmed by the administration of ZnPP to the recipient rat in further studies.

The protective period of IPC is divided into two phases, namely, the early phase and late phase. The early phase of protection against IRI appears at 1–3 h after reperfusion, and the late phase of protection appears at 24 h after reperfusion and lasts from 2 to 3 days [8, 9]. In the present study, we demonstrate the early phase of protection against intestinal IRI. The protective effect lasts 3–6 h after reperfusion and subsequently diminishes 12–24 h after SBT. This protective period is suitable for the early phase of protection. In the IPC and RIPC groups, the serum HO-1 level decrease 6–12 h after SBT. There may be some relationship between the reduction in the serum HO-1 level and the disappearance of a protective effect. In the present study, the protective effect on the intestine at 24 h after SBT is slight or moderate even in the control group. Due to the remarkable rate of turnover and regenerative speed of the intestinal epithelial layer [27], the modification of this study protocol will be necessary to investigate the late phase protective effect of IPC and RIPC against intestinal IRI.

IPC and RIPC are brief and convenient methods to protect organs against IRI without any special medications or tools. In particular RIPC can be safely applied to clinical practice using a blood pressure cuff or tourniquet [10, 28]. In the present study, we provide the first demonstration that RIPC is equally effective on rat intestinal IRI compared to IPC. These results may therefore be helpful in intestinal

transplantations using RIPC. Further studies will be needed to determine the role of intestinal IPC and RIPC in humans.

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The utility of muscle sparing axillar skin crease incision for pediatric thoracic surgery

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Tatsuro Tajiri · Risa Teshiba · Genshiro Esumi · Yuji Karashima ·
Sumio Hoka · Kouji Masumoto

Abstract

Background Posterolateral or standard axillar incisions for the pediatric thoracic surgery are occasionally associated with poor motor as well as cosmetic results, including chest deformities and large surgical scars. A muscle sparing axillar skin crease incision (MSASCI) was initially proposed by Bianchi et al. (in J Pediatr Surg 33:1798–1800, 1998) followed by Kalman and Verebely (in Eur J Pediatr Surg 12:226–229, 2002) resulting in satisfactory cosmetics. However, they performed operations through the third or fourth intercostals space (ICS), therefore the target organs were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old). There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. A thoracotomy was performed through the appropriate ICS (from third to eighth).

Results In all patients, the expected procedures, including pulmonary lower lobectomy, were successfully performed by MSASCI throughout the thoracic cavity. A good operational field was easily obtained in neonates and infants. Most of the patients achieved excellent motor and aesthetic outcomes.

Conclusions MSASCI may become the standard approach for the thoracic surgery for small children.

Keywords Axillar skin crease · Thoracotomy · Pulmonary lobectomy · Neonate · Infant

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Introduction

Advances in antenatal diagnosis, surgical technique and perioperative care have improved survival rate for neonatal surgical diseases. The mortality rate has become less than 10% [1]. It is now important to consider the long-term good "quality of life" (QOL) in neonatal surgical disease. Therefore, surgeons have sought to establish procedures that leave no scars, using the natural skin crease such as axillar crease and umbilical crease [2–4].

Posterolateral or standard axillar incisions for the pediatric thoracic surgery sometimes cause poor functional as well as cosmetic results, including chest deformities (scoliosis, shoulder deformity, and winged scapula) and large surgical scars. Muscle sparing axillar skin crease incision (MSASCI) was initially proposed for neonates by Bianchi et al. [5] in 1998, and then Kalman and Verebely [6] extended this approach for children in 2002, thus resulting

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in a good postoperative cosmetic results. However, they performed surgery through the third or fourth intercostals space (ICS), therefore the performed operations were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods

Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old) from December 2006 to February 2011. There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. The performed operations were 10 primary esophageal anastomoses, 12 pulmonary lobectomies (including lower lobectomies) or partial resections, 2 subtotal neuroblastoma resections, 1 diaphragmatic repair, 1 pulmonary biopsy, and 1 exploratory thoracotomy.

This study was performed, according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on 30 July 2003 and complies with the Helsinki Declaration of 1975 (revised 1983). Regarding this retrospective study, properly informed consent was obtained from the parents.

The patient was placed in the lateral position. The uppermost arm was extended to about 130°, drawn forward, and placed on an arm-rest. A pulse-oxymeter was applied on hand of the extended arm.

A skin incision was made just on the axillar skin crease, and the pectoralis major and latissimus dorsi muscles were retracted superiorly and medially, respectively. Either of these muscles could be partially incised in case. The incision was deepened and the axillary fat pad and lymph nodes were pushed upward. The long thoracic nerve was preserved in the posterior part of the wound (Fig. 1). The anterior serratus muscle was split along its fibers just on the targeted costa. The thoracic cavity was entered through the appropriate ICS. The peripheral pulse was monitored by the pulse-oxymeter of the extended arm avoid a circulatory failure of the arm.

Thoracotomy for esophageal atresia was performed through the fourth ICS and the upper and lower esophagus was exposed via an extrapleural approach. After cutting The azygos vein was cut and the Tracheoesophageal fistula (TEF) was closed by 5-0 polydioxanon (PDS) transfixing sutures and cut. Esophageal end-to-end anastomosis was performed with one layer stitch sutures. Both lateral sides were approximated using 5-0 PDS, and a transanastomotic tube was inserted from the nose to the stomach through the anastomosis. The anterior and the posterior aspects were sutured with 6-0 PDS in stitch.

One-lung ventilation was attempted in order to obtain adequate operational field for pulmonary lower lobectomy [7]. Briefly, bronchial blockade with a 4Fr or 5Fr Fogarty embolectomy catheter was attempted in each case. Children were initially intubated with a Fogarty embolectomy catheter under direct laryngoscopy. Then, immediately, an endotracheal tube was placed alongside the catheter in the trachea. After securing the tube, a pediatric fiberoptic bronchoscope (2.2 mm in diameter) was passed through to set a Fogarty embolectomy catheter to the mainstem bronchus. And then, bronchial blockade was performed with its balloon inflated with an appropriate volume of normal saline. Thoracotomy was done through the fifth or sixth ICS, and then the lung was deflated. The pulmonary arteries were ligated and cut and then the bronchus was cut and closed with 5-0 PDS sutures. Finally, the pulmonary vein was doubly ligated and cut, and the pulmonary ligament was dissected.

One-lung ventilation was also performed for the pulmonary sequestration. Thoracotomy was performed via the seventh or eighth ICS in order to approach the abnormal artery in pulmonary ligament at first. One-lung ventilation allowed lower lobe to be easily lifted for the dissection of pulmonary ligament and the ligation of abnormal artery. This abnormal artery was ligated, before ligation of pulmonary vein in order to avoid lung volume expansion.

A rolled vicryl sheet was inserted between the costa during thoracic closure, in order to avoid bony adhesion in some cases. Both the thoracic and subcutaneous tubes were inserted through both ends of wound; therefore, no additional wounds were necessary for tubes.

Results

Thoracotomy was successfully done through from the third and eighth ICS using MSASCI. All of the expected procedures, including pulmonary lower lobectomies, were able to be performed adequately. A good operational field was easily obtained in neonates and infants in comparison to that in elder children. The incision was extended caudally, about 1 cm in only one infant with pulmonary sequestration. Two patients died due to the severe cardiopulmonary anomalies, and one patient with right diaphragmatic hernia showed recurrence and required reoperation using an abdominal approach. The other patient with a right diaphragmatic hernia showed no right lung; therefore, no procedure was performed (exploratory thoracotomy).

Surgical complications included wound disruption in the four cases and transient arm paralysis in the two cases. The wound disruptions were treated by vacuum therapy and healed about 1 week, and the transient arm paralysis

Fig. 1 Operation schema for MSASCI. *M.LD* lattismus dorssi muscle, *N.TL* long thoracic nerve, *M.PM* pectoralis major muscle, *M.SA* serratus anterior muscle, The *numbers* are labeling in the individual ribs.

Axillar skin crease incision
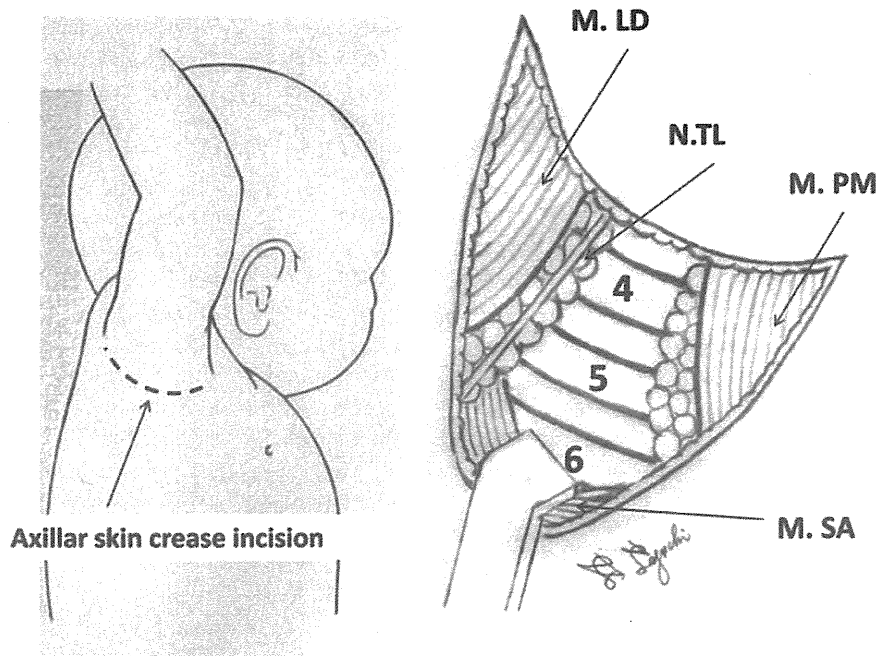
recovered spontaneously in a few weeks. All of the patients showed uneventful postoperative course and achieved excellent motor and aesthetic outcomes after 1 month. The surgical scar was almost hidden by the axillar skin crease in

a year (Figs. 2, 3). So far, there have been no patients showing thoracic deformity, in a relatively short-term follow-up (no more than 4 years). The outcome of each patient is shown in Table 1.
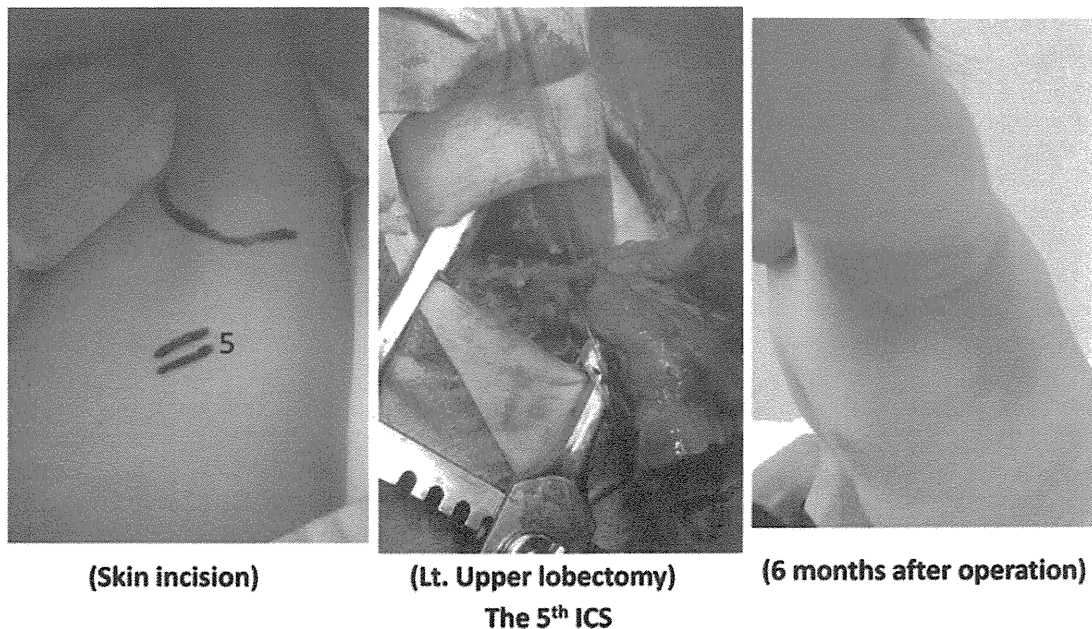

(Skin incision)   (Lt. Upper lobectomy)   (6 months after operation)

The 5th ICS

Fig. 2 Pre, intra, and postoperative appearance of Case 15. Congenital cystic adenomatoid malformation in Lt. upper lobe. *Left* skin incision on the axillar crease. *Middle* Lt. upper lobectomy of lung was

performed through the fifth ICS at 1-month old. *Right* operative wound was almost hidden 6 months after operation
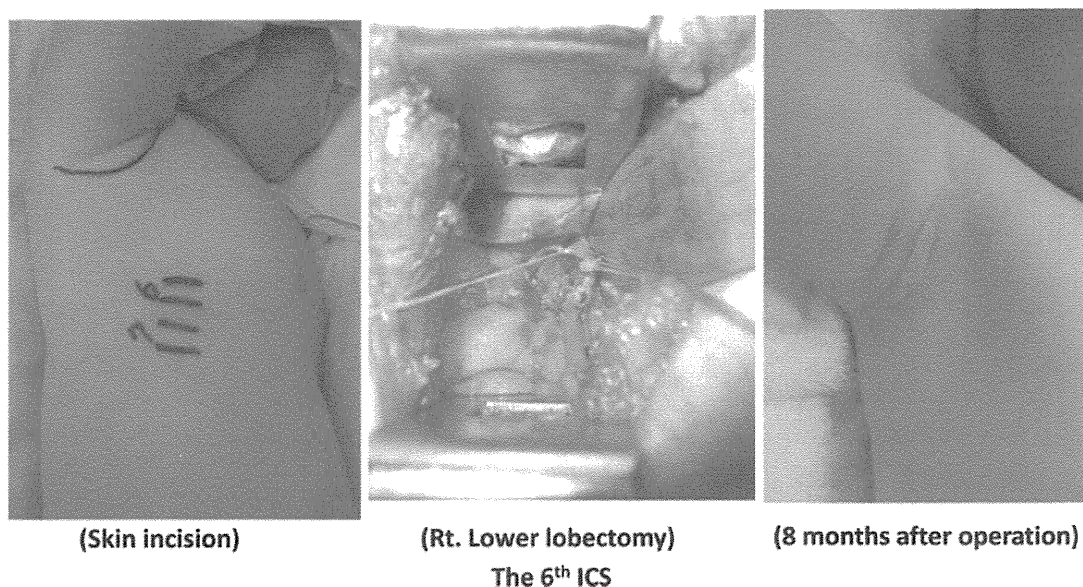
(Skin incision)   (Rt. Lower lobectomy)   (8 months after operation)
The 6th ICS

Fig. 3 Pre, intra, and post operative appearance of Case 17. Intralober lung pulmonary sequestration in Rt. lower lobe. *Left* skin incision on the axillar crease. *Middle* Rt. lower lobectomy of lung was performed through the sixth ICS at 3-month old. *Right* operative wound was almost hidden 8 months after operation

Discussion

Axillary skin crease incision for thoracic surgery was initially reported by Atkinson as "peraxillary approach" for dissection of the upper thoracic and stellate ganglia through the second ICS in adult in 1949 [8]. Bianchi et al. [5] reported using "high axillary skin crease, muscle-sparing to right lateral thoracotomy" for children in 1998. They operated on 29 neonates including 27 esophageal atresia and two patent ductus arteriosus (PDA) through the third or fourth ICS. Kalman and Verebely [6] also reported this approach as "axillary skin crease incision" for thoracotomy of neonates and children in 2002. They performed 17 operations in neonates (8 esophageal atresia, 8 PDA, 1 CCAM) and 9 operations in children (3 neuroblastoma, 1 teratoma, 5 pulmonary operations including lobectomies) through the third or fourth ICS. The oldest patient of this report was a 15-year-old girl with a large teratoma from the anterior mediastinum. They performed five pulmonary operations including one biopsy for histiocytosis, one marsupialization of an inflammatory cyst, one cystectomy of a congenital cyst and two pulmonary resections for bronchiectasia (one S2-3-4 trisegmentectomy on the left side and one middle lobe lobectomy). They concluded that it ensured unrestricted access to the upper two-thirds of the thoracic cavity through the third or fourth ICS. They did not perform any pulmonary lower lobectomies.

These reports indicate that the term MSASCI is appropriate. The approach was extended downward up to the eighth ICS in the current series to perform the expected procedures in all cases, including pulmonary lower lobectomy and intralobular pulmonary sequestration. This technique is feasible for almost all kinds of pediatric thoracic surgery from third to eighth ICS. The appropriate ICS for thoracotomy depends on the target organ. For example, the fourth ICS is used for esophageal atresia, the fifth ICS is for standard pulmonary lobectomy, and the seventh or eighth ICS for pulmonary sequestration. We experienced technical difficulties in patch closure of right diaphragmatic hernia in one case. The medial margin of diaphragmatic defect was difficult to be exposed for suturing, because liver and intestine interfered to the operation field. Right diaphragmatic hernia might not be indication for MSASCI from our restricted experience.

There were initially several complications, such as wound disruption and transient arm paralysis. In 18 out of the 27 patient, thoracotomy was performed below the fourth ICS. The wound disruption occurred in four cases (Cases 5, 7, 9 and 26). These four were operated through fifth, fourth, sixth, and fifth ICS, respectively. Three out of four cases underwent thoracotomy below the fourth ICS. Therefore, downward hyperextension of skin by metal retractor may cause wound disruption. In addition, the case five was extremely premature infant and the modified gestational age at operation was 40 weeks. Cases 7, 9 and 26 were operated in their neonatal period. And the three out of these four cases showed cyanosis in perioperative period due to their congenital heart disease and the subsequent pulmonary hypertension. Therefore, hyperextension of the skin as well as vulnerable factors of each child may cause