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肩腱板断裂患者における臨床像、MRI所見、および病理組織像の関係
－生検筋組織所見に着目して－

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抄　　録

【緒言】肩腱板断裂後の腱板筋には脂肪変性が起こるとされている。これまで、解剖用献体を用いた病理組織学的検討や、動物実験における画像所見と病理組織像の比較検討は行われてきたが、有症状の腱板断裂患者における腱板筋の病理学的特徴や、そのMRI所見、および臨床病態との関係も明らかではなかった。
【目的】肩腱板断裂患者でMRI上みられる脂肪変性所見の病理組織学的特徴およびそれらと術前の臨床像との関係を明らかにすることを目的とした。
【対象と方法】対象は当院で腱板断裂の手術を行った患者41例43肩であった。MRIで断裂の大きさ、脂肪変性の有無（中垣分類）について評価した。また、手術時に棘上筋と棘下筋から針生検で筋組織を採取して病理組織学的に検討し、筋線維間の脂肪浸潤について評価した。病理組織像、MRI所見および術前の臨床像の関係を検討した。
【結果】MRIで脂肪変性を、病理組織像では筋線維間に脂肪細胞の浸潤をそれぞれ一部の例で認めた。棘上筋・棘下筋の双方とも、MRIでの脂肪変性あり群では脂肪変性なし群と比較すると、断裂は大きく、同様に病理組織においても、脂肪浸潤あり群では脂肪浸潤なし群よりも断裂は大きかった。また棘上筋において、MRIで脂肪変性がみられた群では、病理組織像での筋線維間の脂肪浸潤もみられやすく、脂肪変性がみられなかった群では脂肪浸潤もみられにくいという関係があった。
【考察】本研究の病理組織像の検討結果からは、断裂を生じた腱板筋の筋線維間に脂肪浸潤が起こっており、MRI所見として棘上筋の筋腹にみられた脂肪変性と、同部より採取された筋組織にみられた脂肪浸潤の間には有意な関連がみられた。MRIT1強調像でみられる棘上筋内の高信号は、筋線維間の脂肪細胞を表現しているものと考えられた。

キーワード：肩腱板断裂、脂肪変性、病理組織像、脂肪浸潤

【緒　　言】

肩関節は、『忘れられた関節』と称されていた時代もあり[1]、整形外科学の中ではその臨床、研究とも歴史が浅い分野である。肩関節は肩甲骨と上腕骨を結ぶ肩甲上腕関節と、肩甲骨と鎖骨を結ぶ肩鎖関節で構成され、肩峰－上腕骨頭間、肩甲上腕関節周囲には、棘上筋・棘下筋・小円筋・肩甲下筋の各腱からなる回旋筋腱板が存在する[2]。

肩腱板断裂は、中高年にみられる肩関節の有痛性疾患で、薬物療法やリハビリテーションなどの保存的治療のほか、手術治療が行われることも多い[3),4)]。1911年にCodman[5)]が棘上筋断裂の手術例を報告して以来、棘上筋筋腹を周囲より剥離して前進させる方法[6)]や、冷凍乾燥させた腱を移植する方法[7)]が報告され、McLauphlign法に代表される直視下修復術が普及すると、肩腱板断裂に対する治療は1970年代頃より安定した成績が報告されるようになった[8)－13)]。さらに1990年代に入ると、関節鏡視下手術手技の進歩と手術機器の

開発、改良により、関節鏡視下腱板修復術が報告されるようになった[14)−16)]。この術式は創が小さく、三角筋に対する侵襲が少ない点が従来法と比較して有利であり、2000年代になり世界的に広く普及し現在に至っている[17), 18)]。

肩腱板断裂の診断法として、長らく関節造影が行われ、現在もその有用性は失われてはいないが、CT、MRIの出現によって、腱板断裂の診断能力は格段に向上した[19)]。すなわち、CT、MRIによる腱板筋の脂肪変性や筋萎縮の診断と分類がなされるようになり[20), 21)]、加えてMRIによる断裂の大きさ、局在、形態の評価も可能となった[22), 23)]。また、画像検査や献体を用いた研究から、肩腱板断裂を有する症例の中に無症候性の例が存在していることも明らかとなっており[24)−29)]、腱の断裂時や症状出現から受診・確定診断そして手術に至るまでに時間を要してしまう例も報告されている[28)]。このような場合には経過中に腱板筋の筋腹にCTやMRIにおいて脂肪変性が認められることが知られている[20), 21), 30), 31)]。Goutallierら[20)]はCTを用いて腱板筋の脂肪変性の程度を筋－脂肪の比でStage 0から4の５段階に分類し、現在その分類がMRI所見に広く応用されている。また本邦では、中垣ら[21)]がMRIを用いて筋内に入った脂肪の線状像（linear band）の太さ、本数を評価し、Grade 1から3の３段階に分類している。著者ら[32)]は以前、このMRI所見と臨床像、および病理組織像の関係について検討した。本研究では肩腱板断裂患者においてMRI上みられる脂肪変性の病理組織学的特徴およびそれらと術前の臨床像との関係を明らかにすること目的とし、症例数を増やしてさらに検討を行った。

【対象と方法】

対象：当院で2008年から2010年に行われた腱板断裂手術80件の中で、本研究および組織生検に関する説明を行い同意が得られた41例43肩であった。男性30肩、女性13肩、手術時年齢は39歳から80歳で、平均64歳であった。罹病期間は１か月から180か月で、平均23.1か月であった。術前の評価は日整会肩関節疾患治療成績評価基準（以下JOAスコア）を用いて行い、47点から87.5点、平均70.6点であった。手術術式の内訳は、mini-open法による直視下腱板修復術５肩、関節鏡下腱板修復術35肩、大腿筋膜パッチ法による修復術１肩、L'Epicopo変法[33)]による広背筋・大円筋移行術による機能再建術２肩であった。本研究は山形大学医学部倫理委員会において承認されている（平成20年度、承認番号87）。

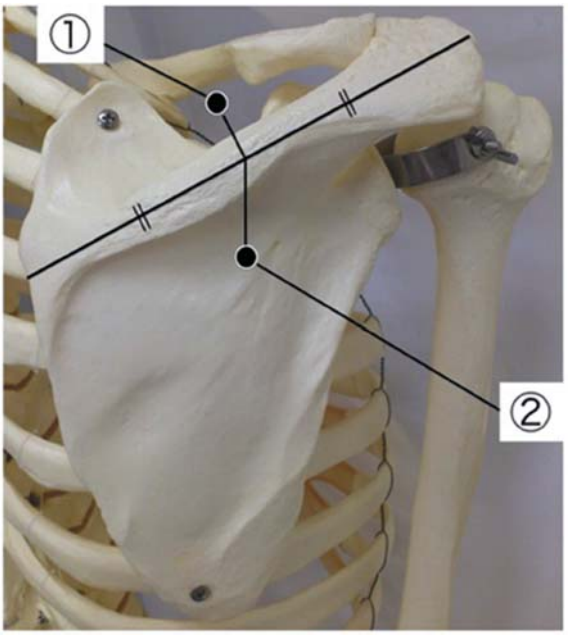

図１．針生検の位置
①棘上筋刺入位置。②棘下筋刺入位置。

MRI所見の検討：MRI検査は術前１週間以内に撮像した。断裂の大きさをT2強調像を用い、縦径、横径のうち大きい方を採用して測定した[22), 34)]。MRI上の腱板筋の脂肪変性は、T1強調像で、中垣分類[21)]（Grade 1：棘上筋筋腹にlinear bandが全く認められない状態、Grade 2：１、２本のlinear bandを認める状態、Grade 3：３本以上のlinear bandか、１、２本の太いlinear bandを認める状態）を用いて棘上筋および棘下筋にも応用して評価した。中垣分類のGrade 2、3を脂肪変性あり群、Grade 1を脂肪変性なし群とした[32)]。これらの評価による画像上の脂肪変性のあり・なしと年齢、罹病期間、術前のJOAスコア、断裂の大きさとの関係について検討した。

病理組織像の検討：全身麻酔下の手術時に、棘上筋・棘下筋からの針生検を行った。針生検は肩甲棘の中点を通る線上で、棘上筋では肩甲棘と鎖骨の中点から棘上窩の中央に向かい、棘下筋では肩甲棘の２㎝下方の点から肩甲骨に垂直に向かって行い、14Gの針生検キット（Bard MONOPTY, C. R. Bard Inc., New Jersey, USA）を用いた[32)]（図１）。検体を１）ホルマリン固定パラフィン包埋切片標本、および２）新鮮凍結切片ホルマリン固定標本とした。１）ではHematoxylin-Eosin（以下H-E）染色のみ行い、２）についてはH-E染色、SudanⅢ染色を行って、病理組織像を光学顕微鏡下に観察した。SudanⅢ染色は、脂溶

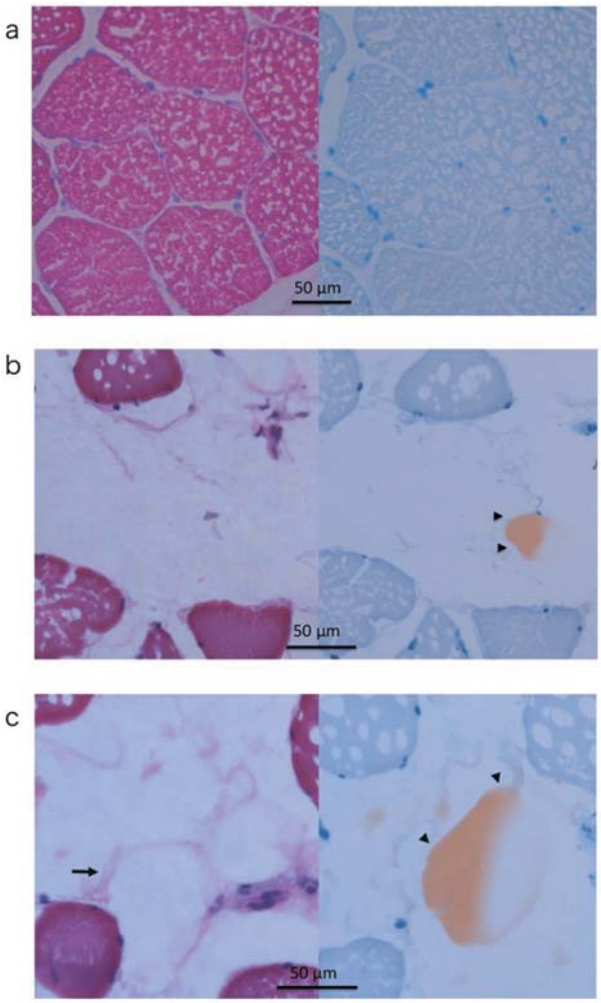

図２．筋線維間の脂肪浸潤の分類（凍結切片）
左H-E染色、右SudanⅢ染色。
a: Grade 0、H-E染色で脂肪細胞が明らかでなく、SudanⅢ染色でも染色されないもの。
b: Grade 1、H-E染色で脂肪細胞がみられてもSudanⅢ染色で染色されないもの、もしくはSudanⅢ染色で染色される部位にH-E染色で脂肪細胞が確認出来ないもの。
c: Grade 2、H-E染色で脂肪細胞が認められ、同部がSudanⅢ染色でも脂肪が染色されるものとした。
矢印は脂肪細胞を示す。矢頭は脂肪の染色部位を示す。

表1: MRI所見

	脂肪変性なし	脂肪変性あり	
中垣分類	Grade 1	Grade 2	Grade 3
棘上筋	15 肩	15 肩	13 肩
	15 肩 (35%)	28 肩 (65%)	
棘下筋	23 肩	11 肩	9 肩
	23 肩 (53%)	20 肩 (47%)	

表2: MRI所見と臨床像の関係；棘上筋

MRI所見 / 臨床像	棘上筋 脂肪変性あり	棘上筋 脂肪変性なし	Mann-Whitney U-test p値
年齢(歳)	66.3 ± 7.5	59.2 ± 10.3	0.082
罹病期間(か月)	30.5 ± 40.2	22.6 ± 32.0	0.454
術前JOAスコア(点)	70.4 ± 9.3	70.9 ± 10.8	0.323
断裂の大きさ(cm)	4.1 ± 1.6	2.3 ± 1.3	< 0.0005 *

*: statistically significant

表3: MRI所見と臨床像の関係；棘下筋

MRI所見 / 臨床像	棘下筋 脂肪変性あり	棘下筋 脂肪変性なし	Mann-Whitney U-test p値
年齢(歳)	64.7 ± 9.1	63.1 ± 9.1	0.271
罹病期間(か月)	27.6 ± 47.2	19.7 ± 26.6	0.304
術前JOAスコア(点)	71.2 ± 10.4	70.1 ± 9.5	0.065
断裂の大きさ(cm)	4.6 ± 1.4	2.5 ± 1.1	< 0.0005 *

*: statistically significant

性色素のSudanⅢを用いた染色液を使用し、組織内脂質を染色する方法である。採取された検体より得られた切片で、筋組織が全く含まれず、病理組織学的検討に適さない検体は除外した。２）の新鮮凍結切片の組織標本を用い、筋線維間の脂肪浸潤を以下のように評価した。Grade 0は、H-E染色で脂肪細胞が明らかでなく、SudanⅢ染色でも染色されないものとした（図２a）。Grade 1は、H-E染色で脂肪細胞がみられてもSudanⅢ染色で染色されないもの、もしくはSudanⅢ染色で染色される部位にH-E染色で脂肪細胞が確認出来ないものとした（図２b）。Grade 2は、H-E染色で脂肪細胞が認められ、同部がSudanⅢ染色でも脂肪が染色されるものとした（図２c）[32]。Grade 1、2を脂肪浸潤あり群、Grade 0を脂肪浸潤なし群とした。以上の病理組織像における脂肪浸潤のあり・なしと年齢、罹病期間、術前のJOAスコア、断裂の大きさおよびMRIでの脂肪変性の評価との関係について検討した。

統計学的解析：Mann WhitneyのU検定とχ^2検定を用い、危険率５％未満を有意差有りとした。

【結　　果】

MRI所見：断裂の大きさは１cmから７cmで、平均3.5cmであった。DeOrioとCofieldの分類[22]を用いる

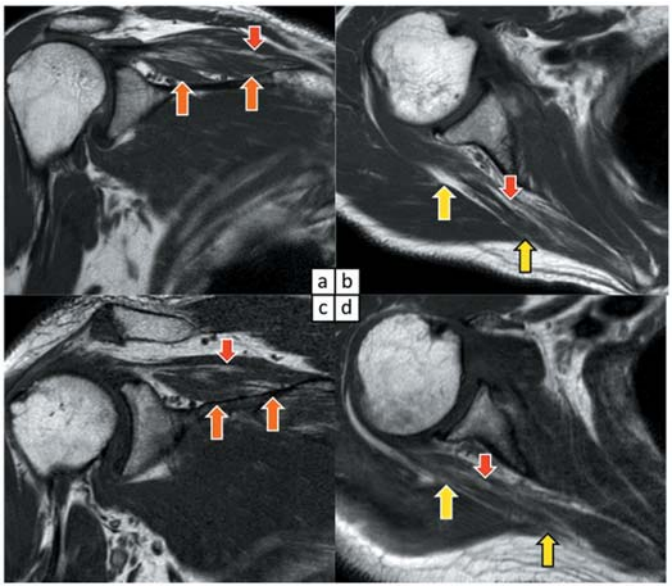

図３．MRI所見　脂肪浸潤進行例
T1強調像（a, c：前額断・棘上筋、b, d：水平断・棘下筋）
a：中垣分類 Grade 3、b：中垣分類 Grade 3、c：中垣分類 Grade 2、d：中垣分類 Grade 2
矢印（橙）は棘上筋を示す。矢印（黄）は棘下筋を示す。矢印（赤）はlinear Bandを示す。

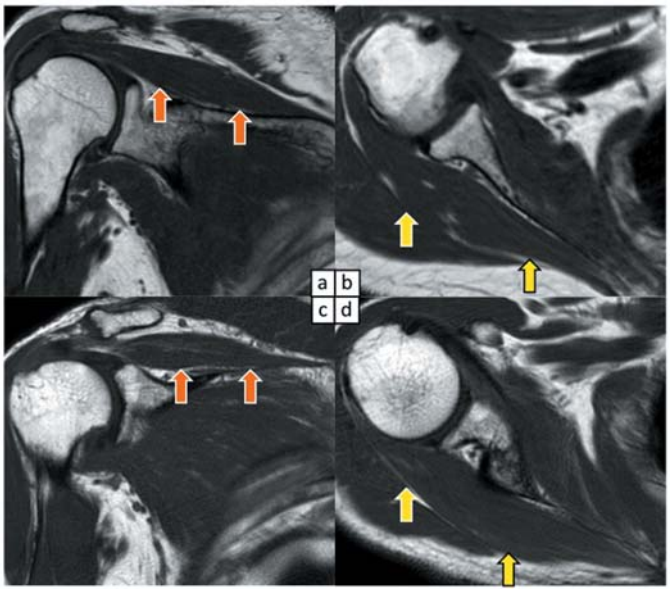

図４．MRI所見　脂肪変性非進行例
T1強調像（a, c：前額断・棘上筋、b, d：水平断・棘下筋）
a：中垣分類 Grade 1、b：中垣分類 Grade 1、c：中垣分類 Grade 1、d：中垣分類 Grade 1
矢印（橙）は棘上筋を示す。矢印（黄）は棘下筋を示す。

と、小断裂（１cm以下）６肩、中断裂（１～３ cm以下）17肩、大断裂（３～５ cm以下）11肩、広範囲断裂（５cmより大）９肩であった。棘上筋における中垣分類による脂肪変性の評価では、Grade 1が15肩、Grade 2が15肩、Grade 3が13肩であり、脂肪変性あり群28肩（65%）、脂肪変性なし群15肩（35%）であった（表１）。棘下筋における中垣分類による脂肪変性の評価では、Grade 1が23肩、Grade 2が11肩、Grade 3が９肩で、脂肪変性あり群20肩（47%）、脂肪変性なし群23肩（53%）であった（表１）。代表的なMRI所見を図３、４に示した。図３a、cの矢印は棘上筋、b、dの矢印は棘下筋で、それぞれ筋腹に高信号の線状像が認めら

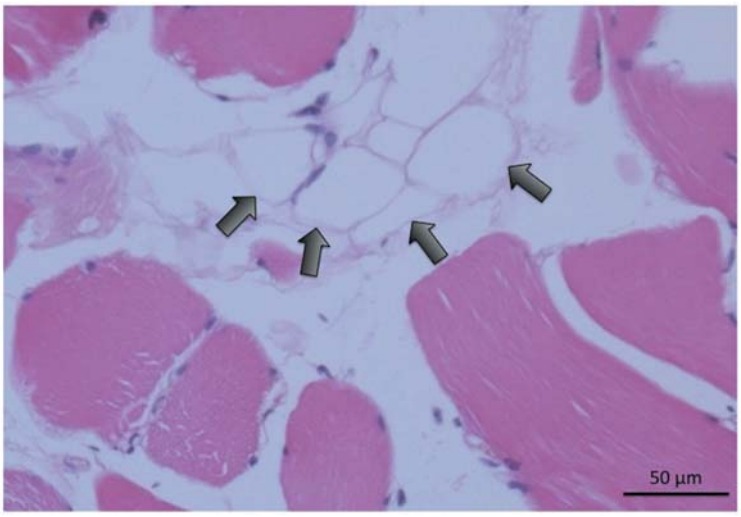

図５．病理組織像
筋線維の離開、筋線維間への脂肪浸潤をみる。矢印は脂肪細胞を示す。ホルマリン固定パラフィン包埋、H-E染色。

表4: 病理組織像と臨床像の関係；棘上筋

病理組織像 / 臨床像	棘上筋 脂肪変性あり	棘上筋 脂肪変性なし	Mann-Whitney U-test p値
年齢(歳)	65.0 ± 6.9	58.5 ± 10.3	< 0.05 *
罹病期間(か月)	19.1 ± 45.3	9.9 ± 8.2	0.249
術前JOAスコア(点)	61.1 ± 9.8	62.1 ± 7.8	0.418
断裂の大きさ(cm)	3.4 ± 1.7	2.3 ± 1.5	< 0.005 *

* : statistically significant

表5: 病理組織像と臨床像の関係；棘下筋

病理組織像 / 臨床像	棘下筋 脂肪変性あり	棘下筋 脂肪変性なし	Mann-Whitney U-test p値
年齢(歳)	61.3 ± 7.8	59.5 ± 10.0	0.050
罹病期間(か月)	20.5 ± 38.0	18.8 ± 33.9	0.341
術前JOAスコア(点)	66.1 ± 7.7	73.3 ± 6.7	0.383
断裂の大きさ(cm)	3.8 ± 1.7	2.4 ± 1.4	< 0.025 *

* : statistically significant

れ、中垣分類Grade 2～3の所見であった。図４a、cの矢印は棘上筋、b、dの矢印は棘下筋で、いずれも筋腹に高信号の線状像は認めず、中垣分類Grade 1と判断された。また、棘上筋、棘下筋におけるMRI所見と臨床像の関係をそれぞれ表２に示した。MRIでの腱板筋の脂肪変性と、年齢・罹病期間・JOAスコアの検討では、棘上筋・棘下筋の双方において、脂肪変性あり群となし群の間に有意差はなかった。MRIでの腱板筋の脂肪変性と断裂の大きさとの検討では、棘上筋・棘下筋の双方において、脂肪変性あり群となし群の間に統計学的有意差を認め（棘上筋：$p<0.0005$、棘下筋：$p<0.0005$）、脂肪変性あり群では脂肪変性なし群よりも断裂は大きかった。

病理組織像：ホルマリン固定、パラフィン包埋切片のH-E染色の標本による検討では、筋線維の変性は明らかではなかったが、一部の例で筋線維間に脂肪細胞が認められた（図５）。凍結切片のH-E染色とSudanⅢ染色を用いた筋線維間の脂肪浸潤の評価では、棘上筋においてGrade 0が12肩、Grade 1が13肩、Grade 2が11肩で、脂肪浸潤あり群24肩（65%）、脂肪浸潤なし群12肩（35%）であった。棘下筋における筋線維間の脂肪浸潤の評価では、Grade 0が14肩、Grade 1が10肩、Grade 2が10肩で、脂肪浸潤あり群20肩（59%）、脂肪浸潤なし群14肩（41%）であった。棘上筋、棘下筋における病理組織像と臨床像の関係をそれぞれ表４、表５に示す。病理組織像での筋線維間への脂肪浸潤の評価と罹病期間、JOAスコアの検討では、棘上筋、棘下筋の双方において、脂肪浸潤あり群となし群の間には有意差はなかった。病理組織像での筋線維間の脂肪浸潤の評価と年齢の検討では、棘上筋において脂肪浸潤あり群の方がなし群と比較して年齢が高く、有意差を認めた（$p<0.05$）。病理組織像での筋線維間の脂肪浸潤の評価と断裂の大きさの検討では、棘上筋・棘下筋の双方において、脂肪浸潤あり群となし群の間に統計学的有意差を認め（棘上筋：$p<0.005$、棘下筋：$p<$

表6: MRI所見と病理組織像の関係；棘上筋

MRI所見 ＼ 病理組織像			棘上筋 脂肪変性あり	棘上筋 脂肪変性なし	χ^2検定 p値
棘上筋	脂肪浸潤	あり	21 肩	3 肩	0.0007 *
		なし	3 肩	9 肩	

*：statistically significant

表7: MRI所見と病理組織像の関係；棘下筋

MRI所見 ＼ 病理組織像			棘下筋 脂肪変性あり	棘下筋 脂肪変性なし	χ^2検定 p値
棘下筋	脂肪浸潤	あり	12 肩	8 肩	0.199
		なし	4 肩	9 肩	

0.025)、脂肪浸潤あり群ではなし群よりも断裂は大きかった。MRIでの腱板筋の脂肪変性と病理組織像での筋線維間への脂肪浸潤の評価では、棘上筋において有意差を認め（p ＝ 0.0007)、病理組織像での脂肪浸潤とMRIでの脂肪変性に関連を認めた（表６)。一方、棘下筋においては有意差を認めなかった（表７)。

【考　　察】

MRI上で脂肪変性が見られた場合、手術の際に、筋の柔軟性や腱板の可動性が低下していることが多く、脂肪変性の有無は手術時の一次修復の可否、術式の選択や術後成績に影響するとされている[35),36)]。この腱板筋の脂肪変性の病理組織像について、中垣ら[37)]は解剖用献体の肩関節を用いた研究を行い、腱板断裂のある腱板筋には病理組織像で筋線維の脂肪変性がみられ、脂肪変性の程度は腱板の退縮の程度に関連すると報告している。一方、Gerberら[38)]は羊を用いた動物実験で、腱板切離を行った後にCTで観察すると、腱板筋には脂肪変性が見られるが、病理組織像では筋線維自体の脂肪変性は明らかではなく、筋線維の間隙に脂肪細胞が認められたと報告している。このように、腱板断裂後の腱板筋には脂肪変性が起こってくるとされてきたが、有症状の腱板断裂患者における腱板筋のMRI所見と病理所見および腱板断裂の臨床像を比較検討した研究はこれまでになく、病理組織像の検討では解剖用献体やヒト新鮮屍体を利用した研究、病理組織像と画像所見との比較検討では動物実験に基づく研究が行われるにとどまっている。

過去の腱板筋の脂肪変性に対するMRIによる評価法としては、Goutallier分類をMRIに応用したものが使用されることが多い。しかし、この方法は本来CTによる評価法で、CTとMRIの相関性は必ずしも明瞭ではなく、３段階程度に簡略化してもなお不十分とする報告がある[39)]。そこで本研究では初めからMRIを用いた中垣の分類で評価することとした。

腱板断裂の大きさについて和田ら[40)]は、棘上筋においてMRIによる中垣分類のGradeが高くなるに従い大断裂の割合が大きくなっていたとしている。本研究では、MRI上の脂肪変性と断裂の大きさの関係をみると、断裂の大きさは脂肪変性が見られた場合に大きくなっていた。また、筋線維間への脂肪浸潤の評価と断裂の大きさの関係をみると、断裂の大きさは脂肪浸潤が見られた場合に大きくなっていた。MRI画像上の脂肪変性とともに、手術時に得られた病理組織での検討でも脂肪浸潤の有無と断裂の大きさに関連があることが示された。すなわち、大きい断裂や断裂の拡大は、腱板断裂後に起こる、画像上の腱板筋の脂肪変性や筋線維間への脂肪浸潤の出現、悪化に影響すると考えられる。

Gerberら[38)]は、羊の腱板切離後の腱板筋の組織を検討し、筋線維の間隙に脂肪細胞が出現・増加すると報告した。本研究では、有症状の腱板断裂手術患者から採取した腱板筋の病理組織標本で筋線維間に脂肪細胞が観察され、棘上筋における術前のMRIでの脂肪変性との間に統計学的に関連が認められた。この棘上筋における結果から、T1強調像での腱板筋の高信号は、病理学的な筋線維間への脂肪細胞の浸潤も反映しているものと考えられた。著者ら[32)]の行った一連の研究により、生体における腱板筋の病理組織像で、初めて筋線維間への脂肪細胞の浸潤を明らかにし、その脂肪浸潤とMRIで観察される脂肪変性との関係も明らかにした。しかし、棘下筋においては統計学的な関連は認められなかった。有意差を認めなかった理由としては、病理組織で筋線維間への脂肪浸潤ありと評価されているにもかかわらず、MRIで腱板筋の脂肪変性なしと評価されている症例数が多いことがあげられる。この結果から、棘下筋における病理組織学的な脂肪浸潤は、MRIでは完全に捉えきれていない可能性があることが考えられた。その理由として、①棘下筋における脂肪浸潤は、棘上筋のそれとは病理組織学的に異なり、MRIでとらえきれない程度の微細な脂肪細胞の浸潤が比較的多く含まれるという可能性、②棘下筋におけ

る脂肪変性がMRIの分類で適切に表現されなかった可能性（中垣の分類は棘上筋を対象としている）が考えられた。一般的に腱板断裂は、棘上筋から発生し棘下筋に及んでいくとされているが、堀ら[41]によると、CTにおける腱板筋の脂肪変性は棘下筋で最も高頻度であり、棘下筋腱を含む棘上筋・棘下筋の断裂や棘上筋・棘下筋・肩甲下筋の３腱の断裂だけではなく、棘下筋腱を含まない棘上筋単独断裂や棘上筋・肩甲下筋腱の断裂でさえも、棘下筋に脂肪変性が認められたと報告している。本研究においても、棘上筋前方の１cm程の小断裂例の病理組織で、棘下筋の筋線維間に脂肪浸潤ありと評価された例や、MRIで棘下筋に脂肪変性ありと評価された例も存在した。また、金谷[42]はマウスを用いた動物実験で、腱断裂と固定による廃用の２つの原因による筋病理組織像を比較し、両群ではtype 1およびtype 2線維の萎縮の程度が異なるなど、筋が使用されなくなった原因によって異なる像を示すと報告している。以上から、棘下筋における脂肪変性または脂肪浸潤においては、棘下筋腱の断裂による変化と、明らかな棘下筋腱断裂がない状態で疼痛などにより肩が使用されないための廃用による変化が混在しており、棘上筋とはやや異なっている可能性を考える必要があるかもしれない。

本研究の限界として、病理組織が針生検での検体である点が上げられる。本研究では手術症例で生体を対象としているため、修復する筋への侵襲を避けこの方法を採用した。そのため一定面積における筋－脂肪組織比などの定量的評価ができていない。また、本来筋全体の脂肪浸潤を正確に評価するのであれば、筋全体か最低限ブロックでの採取が望ましいが、侵襲度の点からは限界がある。

【ま　と　め】

１．肩腱板断裂患者の棘上筋・棘下筋より機能再建術時に組織生検を行い、その病理組織像と臨床像、MRI所見との関係を検討した。

２．棘上筋と棘下筋において、断裂の大きさは、MRIでの脂肪変性および病理組織像での脂肪浸潤がみられた場合に有意に大きくなっていた。大きい断裂や断裂の拡大は、腱板断裂後に起こる筋線維間の脂肪浸潤の有無と程度に影響すると考えられた。

３．棘上筋において、MRIでの脂肪変性がある場合には病理組織像で筋線維間への脂肪浸潤を示す例が多く、脂肪変性がない場合には脂肪浸潤もない例が多くみられ、統計学的に有意であった。MRI T1強調像の高信号は、病理組織像での脂肪細胞の浸潤も反映すると思われた。

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The analysis of the relationship among clinical features, MRI and pathological findings in the patients with torn rotator cuff muscles of the shoulder

— special reference to the findings of biopsied muscular tissue samples —

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ABSTRACT

Purpose : To clarify the pathology of the fatty degeneration on MRI in the patients with torn rotator cuff muscles of the shoulder, and clinical sense of this phenomenon.
Materials : Forty-one shoulders in forty-three patients with rotator cuff tears, treated surgically in our hospital.
Methods : Size of tear and fatty degeneration were evaluated on the MRI using Nakagaki's classification. Needle biopsy was done at the supraspinatus and infraspinatus muscle, and the biopsy organization was evaluated about the fatty infiltration between muscle fibers. We evaluated and analyzed the relationship between the clinical, MRI and pathological findings statistically.
Results : There were fatty degeneration in the MRI, and fat cell infiltration between the muscle fibers. In the supraspinatus and infraspinatus, size of tear was large in the fatty degeneration (+) group and fatty infiltration (+) group. In the supraspinatus, there was a relationship between the fatty degeneration on MRI and fatty infiltration between muscle fibers on pathology.
Conclusion : The fatty degeneration, observed as intramuscular high signal in MRI, was refracted the fat cell between muscle fibers.

Key words : Rotator cuff, Fatty degeneration, Pathological findings, Fatty infiltration

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A comparison of continuous intravenous infusion versus continuous epidural infusion of droperidol for the prevension of post operative nausea and vomiting

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ABSTRACT

Background : The continuous epidural injection (CEPI) of droperidol has been used in Japan for prophylaxis of postoperative nausea and vomiting (PONV). To evaluate the CEPI of droperidol, we compared the efficacy of droperidol given by the CEPI with given by the continuous intravenous injection (CIVI).

Methods : The patients scheduled for gynecological surgery accompanied by epidural analgesia were randomly allocated to an CEPI or CIVI group. In the CEPI group, droperidol (1.25 mg) was injected epidurally at the time of suturing followed a CEPI of droperidol (5 mg in 48ml) at 1 ml/h. In the CIVI group, droperidol (1.25 mg) was injected intravenously at the time of suturing followed a CIVI of droperidol (5 mg in 48ml) at 1 ml/h. The incidence and severity of PONV were evaluated in both groups.

Results : 103 patients in the CEPI group and 102 patients in the CIVI group were included. The incidence of PONV in the first 24 hours (37.9% in the CEPI group and 32.4% in the CIVI group) and the severity of nausea during the first 72 hours were not different significantly between the two groups.

Conclusion : The efficacy of droperidol was not different comparing CEPI with CIVI.

Key words : postoperative nausea and vomiting (PONV), prophylaxis of PONV, droperidol, the continuous epidural injection of droperidol

Background

Appropriate analgesia is important for postoperative pain relief, the prevention of postoperative nausea and vomiting (PONV) and early postoperative recovery[1]. Droperidol has strong antiemetic activity and is administrated for prophylaxis of PONV[2]. An intravenous route of administration is generally recommended for droperidol[3]. The intravenous (IV) injection of droperidol bolus at the end of the surgery is recommended for prophylactic antiemetic therapy[2]. Also, the repeated IV infusion of an antiemetic mixed with an opioid has been performed in the setting of patient-controlled analgesia (PCA)[4, 5].

In contrast to IV administration, the continuous epidural injection (CEPI) of droperidol has been used along with epidural block for postoperative pain relief in Japan[6-8]. It was reported that droperidol given by CEPI was more effective than placebo[6-8].

However, the advantage of the epidural injection (EPI) of droperidol compared with IV administration is not clear. Also, a comparison between EPI and IV injection of a droperidol bolus showed that the IV route was superior to the EPI route for prophylaxis of PONV[9]. We doubted the efficacy of the CEPI of droperidol in Japan. The continuous IV infusion (CIVI) of droperidol or its repeated IV infusion in the setting of PCA may be more effective than CEPI. However, this has not yet been investigated.

We planed this study to evaluate the efficacy of the CEPI of droperidol. We hypothesized that the CIVI of

droperidol would be superior to CEPI for prophylaxis of PONV. To test our hypothesis, we compared the two routes of administration in gynecologic patients, since these patients are at high risk of PONV.

Materials and methods

Patients

This study was approved by the Ethics Committee of Yamagata University, and written informed consent was obtained from all patients. From September 2005 to May 2008, female patients were enrolled at Yamagata University Hospital (Yamagata, Japan). The patients ranged in age from 20~69 years and were in the American Society of Anesthesiologists Physical Status (ASA-PS) category 1 or 2. All patients were scheduled for elective gynecological abdominal surgery under general anesthesia accompanied by epidural analgesia. Patients were excluded based on the following criteria: impossible to communicate sufficiently in Japanese; the use of opioids, antipsychotic drugs, antidepressants, adrenocorticosteroids, antiemetics or antihistamines; pregnancy; diseases of the central nervous system; or a history of convulsions. A 12-lead ECG was obtained in all patients in the month before surgery. Patients with a QTc >0.470 seconds or ventricular premature contractions >6 beats/minutes were excluded.

Protocol

The patients were randomly allocated to an CEPI or CIVI group. The medical staff was blinded to their randomization assignment except for the anesthesiologist in charge of the case. Anesthetic management was the same in each group as follows. Patients were premedicated orally with ranitidine hydrochloride (150 mg) two hours before arrival at the operating room (OR). If necessary, 5~10 mg diazepam was added orally one hour before arrival. On arrival at the OR, a 3-lead ECG, pulse oximeter and noninvasive blood pressure monitor (MP70; Royal Philips Electronics, Amsterdam, Netherlands) were attached to each patient. If invasive blood pressure monitoring was necessary, cannulation of the radial artery was performed after induction of general anesthesia. IV injection of acetated Ringer's solution was also started before the induction of anesthesia. An epidural catheter was inserted at the interspace between Th9 and L2. An anesthesiologist who has two or more years of experience managed the insertion of the epidural catheter. The catheter was aspirated and 2 ml of 0.75% ropivacaine was injected into the catheter to verify appropriate placement of the catheter tip. If no adverse reactions occurred with these two tests, general anesthesia was induced with IV thiopental sodium (3~4 mg/kg) after inhalation of oxygen (O_2, 5 L/min) for several minutes. When patients lost consciousness, inhalation of sevoflurane was started with an FiO_2 of 100%. Vecuronium bromide (0.1 mg/kg) was injected intravenously, and tracheal intubation was performed. After tracheal intubation was completed, mechanical ventilation was started with an FiO_2 of 45-60%. Anesthesia was maintained using sevoflurane (1~3%) and IV fentanyl, and epidural block was performed with ropivacaine. The volume of fluid infusion was adjusted according to the condition of each patient. If necessary, a plasma expander or packed red cells were administered. When systolic blood pressure (SBP) was <80 mmHg, patients were given IV ephedrine hydrochloride (4~8 mg) or methoxamine hydrochloride (1 mg). The need for these vasoconstrictors was based on the judgment of the anesthesiologist in charge. All patients were given an epidural injection of morphine (2 mg) in 5 ml of saline at the beginning of the operation and 10 ml of 0.23% ropivacaine at the time of suturing of the operative wound. After the end of the operation, inhalation of sevoflurane was discontinued. When spontaneous respiration appeared, atropine sulfate (1 mg) and neostigmine (2 mg) were injected intravenously to reverse the effects of vecuronium bromide. The patients were extubated when they woke up and resumed spontaneous respiration. After extubation, the patients left the OR when they were stable based on the judgment of the anesthesiologist in charge. After leaving the OR, the following parameters were monitored: ECG, blood pressure, heart rate, body temperature, oxygen saturation (pulse oximeter), and clinical status.

Droperidol was administered at the time of suturing of the operative wound. In the CEPI group, droperidol (1.25 mg) in 5 ml of saline was injected epidurally at the time of suturing. In addition, a CEPI

of morphine (4 mg), 1% lidocaine (46 ml) and droperidol (5 mg in 2 ml) was started at a rate of 1 ml/h at the time the patient left the OR. This group also received a CIVI of saline (48 ml) at 1 ml/h at the same time as the CEPI. In the CIVI group, droperidol (1.25 mg) in 5 ml of saline was injected intravenously at the time of suturing. In addition, a CEPI of morphine (4 mg), 1% lidocaine (46 ml) and saline (2 ml) was started at a rate of 1 ml/h at the time the patient left the OR. This group also received a CIVI of droperidol (5 mg in 2 ml) and saline (46 ml) at 1 ml/h starting at the same time as the CEPI. The CEPI and CIVI were continued for at least 24 hours in both groups. A disposable infusion pump (Coopdech Syrinjector®, Daiken-iki, Osaka, Japan) was used for both the CEPI and CIVI. The contents of the disposable pumps could not be identified based on appearance. After emergence from anesthesia, the patients were supplemented with an intramuscular injection of pentazocine (15 mg) or anal administration of diclofenac sodium (25 mg) for postoperative pain, and IV injection of metoclopramide (10 mg) for severe PONV. On the first postoperative day, the patients started drinking water and taking oral loxoprofen sodium hydrate (180 mg/day) for pain relief. Standing and walking were also attempted. A physician, who was blinded to the randomization assignment, visited each patient at 6 hours, 24 hours and 72 hours after leaving the OR. This physician evaluated the following parameters: severity of nausea, pain (at rest and with movement) and pruritus; incidence of vomiting; and amount of supplementary pentazocine, diclofenac sodium, and metoclopramide from 0～6, 6～24 and 24～72 hours after leaving the OR. Other complications from 0～72 hours after leaving the OR were also evaluated. For the evaluation of nausea, pain (at rest and with movement) and pruritus, the patients were asked to respond with one of the following five words: “nai” (none), “sukoshi” (little), “tyuugurai” (moderate), “tsuyoi” (severe), or “taerarenai” (unbearable). The results provided a verbal-rating score (VRS) for the severity of each symptom. The evaluation of vomiting, amount of supplementary drugs used and other complications were based on postoperative records and the patient interview. The primary endpoint was the incidence of PONV in the first 24 hours after the operation. It was defined as the fraction of patients that vomited or felt little, moderate, severe or unbearable nausea from 0～24 hours after leaving the OR. Secondary endpoints were the severity of nausea and the incidence of vomiting from 0～6, 6～24 and 24～72 hours after leaving the OR.

Statistical analysis

We considered that the incidence of PONV in the first 24 hours after the operation would be 40% in the CEPI group based on unpublished data and 20% in the IV group based on repeated IV infusion in the setting of PCA[10),11)]. Therefore, we estimated that a sample size >92 was needed to detect a ≥ 20% difference in the incidence of PONV between the two groups (assuming a two-sided α error of 0.05 and 80% power)[12)].

Data values are expressed as means±SD, medians [minimum-maximum] or numbers and percentages. Statistical comparisons between the two groups were performed using an unpaired *t*-test or a chi-square test for patient characteristics, vomiting and the incidence of PONV. The severity of nausea, pain, and pruritus and the amount of supplementary drugs were compared between groups using a Mann-Whitney U test. All analyses were performed with PASW® statistics 18 (SPSS, Chicago, USA). P values < 0.05 were considered significant.

Results

Among the 293 patients enrolled, 71 patients were excluded because of the exclusion criteria or because they declined to participate in the study. After randomization, 17 patients were excluded for the following reasons: eight patients failed to complete the protocol, three patients developed acute illness (one thyroid crisis, one severe bradycardia and one dural puncture), and six patients had unscheduled bowel resection during the surgery that changed the postoperative management. Therefore, 205 patients were included in the final analysis, 103 in the CEPI group and 102 in the CIVI group.

The patient characteristics are shown in Table 1. There were no significant differences between the two

Table 1. Patient characteristics

		CEPI	CIVI
Demographic data	Age (y)	50.0 ± 7.7	50.2 ± 9.0
	Height (cm)	155.4 ± 4.5	156.3 ± 6.1
	Body weight (kg)	56.2 ± 8.0	56.9 ± 9.3
PONV risk factors	Nonsmoker	79 (76.7)	80 (78.4)
	History of PONV or motion sickness	46 (44.7)	48 (47.1)
	Nonsmoker with a history of PONV or motion sickness	36 (35.0)	34 (33.3)
Type of surgery	**Hy**	10 (9.7)	9 (8.8)
	Hy+Ad	29 (28.2)	37 (36.3)
	Hy+Ad+PL	25 (24.3)	25 (24.5)
	Hy+Ad+PL+Om	4 (3.9)	7 (6.9)
	Hy+Ad+PL+Om+PaL	16 (15.5)	7 (6.9)
	oophorectomy	14 (13.6)	10 (9.8)
	others	5 (4.8)	7 (6.9)
Anaesthetic parameter	Duration of surgery (min)	240.5 ± 128.6	225.3 ± 112.9
	Amount of sevoflurane (ml)	82.8 ± 40.8	76.4 ± 37.2
	Amount of fentanyl ($\mu g \cdot kg^{-1}$)	3.3 ± 1.8	3.1 ± 1.8
	Blood loss ($g \cdot kg^{-1}$)	5.1 ± 6.5	5.2 ± 8.3
	Fluid infusion ($ml \cdot kg^{-1} \cdot h^{-1}$)	8.7 ± 2.4	9.3 ± 2.5
	Urination ($ml \cdot kg^{-1} \cdot h^{-1}$)	1.5 ± 0.9	1.7 ± 1.1

Values are means ± SD or numbers (percentages). There were no significant differences between the groups. Hy, hysterectomy; Ad, adnexectomy; Om, omentectomy; PL, pelvic lymphadenectomy; PaL, para-aortic lymphadenectomy, CEPI: CEPI group (n=103), CIVI: CIVI group (n=102)

Table 2. The severity of PONV during the first 72 hours after leaving the operating room.

		0-6 hours		6-24 hours		24-72 hours	
		CEPI	CIVI	CEPI	CIVI	CEPI	CIVI
nausea	none	76 (73.8)	78 (76.5)	76 (73.8)	77 (75.5)	92 (89.3)	89 (87.3)
	little	15 (14.6)	17 (16.7)	8 (7.8)	13 (12.7)	6 (5.8)	5 (4.9)
	moderate	9 (8.7)	4 (3.9)	13 (12.6)	5 (4.9)	2 (1.9)	3 (2.9)
	severe	2 (1.9)	3 (2.9)	5 (4.9)	7 (6.9)	1 (1.0)	1 (1.0)
	unbearable	1 (1.0)	0 (0)	1 (1.0)	0 (0)	2 (1.9)	4 (3.9)
vomiting		17 (16.5)	16 (15.7)	17 (16.5)	19 (18.6)	8 (7.8)	8 (7.8)
Amount of metoclopramide (mg)		0 [0-10]	0 [0-20]	0 [0-30]	0 [0-20]	0 [0-10]	0 [0-20]

CEPI: CEPI group (n=103), CIVI: CIVI group (n=102)
Values are numbers (percentages) or medians [minimum-maximum]. There were no significant differences between the two groups.

groups. The numbers of patients with a PONV risk factor were not significantly different between the two groups (Table 1).

The incidence of PONV in the first 24 hours after the operation was 37.9% in the CEPI group and 32.4% in the CIVI group. There was no significant difference between the two groups (p= 0.496).

The PONV results are shown in Table 2. The respective fraction of patients that replied none, little, moderate, severe or unbearable for the severity of postoperative nausea from 0～6, 6～24 and 24～72 hours after leaving the OR was not significantly different between the two groups. Likewise, the incidence of postoperative vomiting during each of the three time periods was not significantly different between the two groups. The amount of supplemen-

Table 3. The severity of pain during the first 72 hours after leaving the operating room.

		0-6 hours		6-24 hours		24-72 hours	
		CEPI	CIVI	CEPI	CIVI	CEPI	CIVI
Pain at rest	none	50 (48.5)	61 (59.8)	50 (48.5)	55 (53.9)	55 (53.4)	57 (55.9)
	little	43 (41.7)	32 (31.4)	39 (37.9)	32 (31.4)	34 (33.0)	32 (31.4)
	moderate	7 (6.8)	7 (6.9)	9 (8.7)	13 (12.7)	10 (9.7)	13 (12.7)
	severe	2 (1.9)	2 (2.0)	4 (3.9)	2 (2.0)	4 (3.9)	0 (0)
	unbearable	1 (1.0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Pain at movement	none	8 (7.8)	13 (12.7)	1 (1.0)	1 (1)	2 (1.9)	1 (1.0)
	little	47 (45.6)	54 (52.9)	32 (31.1)	33 (32.4)	27 (26.2)	29 (28.4)
	moderate	33 (32.0)	23 (22.5)	48 (46.6)	46 (45.1)	43 (41.7)	41 (40.2)
	severe	13 (12.6)	10 (9.8)	17 (16.5)	20 (19.6)	27 (26.2)	28 (27.5)
	unbearable	2 (1.9)	2 (2.0)	5 (4.9)	2 (2.0)	4 (3.9)	3 (2.9)
Amount of pentazocine (mg)		0 [0-30]	0 [0-15]	0 [0-30]	0 [0-30]	0 [0-15]	0 [0-15]
Amount of dicrofenac (mg)		0 [0-25]	0 [0-25]	0 [0-50]	0 [0-50]	0 [0-75]	0 [0-75]

CEPI: CEPI group (n=103), CIVI: CIVI group (n=102)
Values are numbers (percentages) or medians [minimum-maximum]. There were no significant differences between the two groups.

Table 4. The severity of pruritus during the first 72 hours after leaving the operating room.

		0-6 hours		6-24 hours		24-72 hours	
		CEPI	CIVI	CEPI	CIVI	CEPI	CIVI
Pruritus	none	74 (71.8)	75 (73.5)	50 (48.5)	43 (42.2)	76 (73.8)	70 (68.6)
	little	21 (20.4)	21 (20.6)	36 (35.0)	35 (34.3)	21 (20.4)	23 (22.5)
	moderate	7 (6.8)	5 (4.9)	14 (13.6)	18 (17.6)	4 (3.9)	8 (7.8)
	severe	0 (0)	1 (1.0)	3 (2.9)	6 (5.9)	2 (1.9)	1 (1.0)
	unbearable	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

CEPI: CEPI group (n=103), CIVI: CIVI group (n=102)
Values are numbers (percentages). There were no significant differences between the two groups.

tary metoclopramide used in each group from 0～6, 6～24 and 24～72 hours after leaving the OR ranged from 0～30 mg. The median value was 0 for all time periods in each group, and there were no significant differences between the two groups.

For postoperative pain (at rest and with movement), the respective fractions of patients that replied none, little, moderate, severe or unbearable from 0～6, 6～24 and 24～72 hours after leaving the OR were not significantly different between the two groups (Table 3). The amount of supplementary pentazocine and diclofenac sodium used from 0～6, 6～24 and 24～72 hours after leaving the OR in both groups ranged from 0～30 mg and 0～75 mg, respectively. The median value was 0 for both drugs during all three time periods in both groups, and there were no significant differences between the two groups (Table 3). For pruritus, the respective fraction of patients that replied none, little, moderate, severe or unbearable was not significantly different between the two groups (Table 4).

There were a few other complications that occurred from 0～72 hours after leaving the OR. Nine patients (8.7%) in the CEPI group and seven patients (6.9%) in the CIVI group developed hypotension (SBP <80mmHg). All of these patients recovered with only fluid therapy. The incidence of hypotension was not significantly different between the two groups. In

addition, one transient ischemic attack, one asthmatic attack and two cases of ileus occurred in the CIVI group. Those patients recovered without invasive treatment. One patient in the CEPI group developed restlessness and an extrapyramidal reaction was suspected. The patient recovered after the end of the droperidol injection. There were no other major complications in either group.

Discussion

This study compared CEPI with CIVI of droperidol for the prophylaxis of PONV in patients undergoing gynecologic surgery with continuous epidural analgesia. The incidence of PONV, postoperative pain (at rest and with movement), pruritus, and other complications was not significantly different between the two groups. The efficacy of droperidol was not different comparing CEPI with CIVI. There were no advantages of CEPI over CIVI.

In this study, the dosage of droperidol given by CIVI for the prophylaxis of PONV was based on the dosage recommend for IV PCA (a single bolus of 0.625～1.25 mg during anesthesia followed by an infusion of 0.05～0.1 mg per mg of morphine, as required)[5]. Klahsen, et al. reported that the PCA with a 1 mg IV bolus of droperidol followed by an infusion of 0.04 mg per mg of morphine resulted in 3.9±1.12 mg of droperidol administrated in the first 24 hours postoperatiely[13]. On the other hand, the dosage of droperidol administered by CEPI for the prophylaxis of PONV was reported to be 2.5-5 mg per day[6)-9)], and this was similar to the dosage for CIVI. Therefore, we administrated the same total dose to the patients in the CEPI and CIVI groups to allow a valid comparison between the groups. The dosage of droperidol given to both groups was 3.75 mg in the first 24 hours postoperatively, and this should have been sufficient to prevent PONV.

Recently, the risk factors for PONV in adults were reported. Gan et al. reviewed the risk factors for PONV in adults[14]. They indicated that the well-established risk factors for PONV include female gender, nonsmoking status, history of motion sickness or PONV, intraoperative and postoperative opioid administration, prolonged duration of surgery and the use of volatile anesthetics or neostigmine (>2.5 mg)[14]. These risk factors also apply to Japanese patients[15]. The presence of multiple risk factors also increases the incidence of PONV[16]. Because of the detailed analysis of risk factors for PONV in our study, we believe that our results may be more accurate than the results of previous studies.

Droperidol has antiemetic activity due to the antagonism of dopamine (D_2) receptors at the chemoreceptor trigger zone (CTZ) in the brain stem (area postrema)[17),18)]. Droperidol administered by the epidural route may be absorbed from the epidural space into blood or cerebrospinal fluid (CSF). Droperidol absorbed into blood is delivered to the CTZ via the systemic circulation, whereas droperidol absorbed into CSF is delivered to the CTZ via the CSF circulation[8), 9)].

However, it is uncertain which route of delivery of droperidol to the CTZ is most important. Nakata et al.[8] reported that delivery via the CSF circulation was more important than delivery via the systemic circulation, because the blood concentration of droperidol after bolus epidural injection was only half of that after bolus IV injection[19], and the antiemetic effect of droperidol was similar comparing bolus IV injection with CEPI[8]. In contrast, Sanansilp et al.[9] indicated that absorption into blood was more important, because droperidol is nonpolar and not easily absorbed into CSF. In our study, the incidence of PONV was not different comparing CEPI and CIVI of droperidol. Since droperidol may enhance the effect of analgesics[11] and inhibit epidural morphine-induced pruritus[20], we expected analgesic and antipruritic effects in the CEPI group. However, these effects were not observed. Therefore, we speculate that the antiemetic effect of droperidol administered by CEPI was due to absorption into the systemic circulation, similar to that obtained by CIVI. Namely, the pharmacokinetics of droperidol given by CEPI are similar to the pharmacokinetics of droperidol given by continuous intramuscular injection.

In a previous study, Sanansilp et al.[9] compared epidural injection with IV injection of a single droperidol bolus. They found that IV injection was superior to epidural injection for the prophylaxis of PONV and for antipruritic activity[9]. To account for

the difference between their results and our results, we speculate that the duration of action of droperidol given by bolus epidural injection is shorter than that of droperidol given by bolus IV injection, because the blood concentration of droperidol after bolus epidural injection was only half of that observed after bolus IV injection[19]. However, CEPI should keep the blood concentration of droperidol high enough to prevent PONV. A dose-response relationship has never been established for the prophylaxis of PONV by droperidol in the setting of PCA[4].

This study has several limitations. First, this study was performed at a single institution. Second, the CIVI of droperidol is not used in routine clinical practice for the prophylaxis of PONV. Although the same dose of IV droperidol was administered as that used in the setting of PCA, droperidol in PCA is not constant IV injection. Third, we did not measure any blood concentrations of droperidol in this study.

conclusion

The efficacy of droperidol was not different comparing CEPI with CIVI. The CEPI of droperidol was a useful prophylaxis of PONV for the patients undergoing continuous epidural analgesia.

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MIB-1 Labeling Index (Ki67) of Gastric Type Intraductal Papillary-Mucinous Neoplasms of the Pancreas

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ABSTRACT

Purpose: This study examined the relationship between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological subtypes of intraductal papillary-mucinous neoplasms of the pancreas (IPMN).

Methods: Between 2000 and 2007, we retrospectively evaluated 46 patients who had undergone surgery, were histopathologically diagnosed as IPMN, and in whom immunohistochemical staining was possible.

Results: Histological grades of the 46 IPMNs were adenoma (n = 27), carcinoma in situ (n = 9), and invasive carcinoma derived from IPMN (n = 10). The morphological and immunohistological subtypes were gastric (n = 20), intestinal (n =15), panacreatobiliary (n = 9), and oncocytic (n = 2). The overall MIB-1 labeling index was 8.63% ± 9.16%. The MIB-1 labeling index of the gastric type was 3.99 ± 6.78%, which was significantly less than that of the intestinal (11.83 ± 8.95%) and pancreatobiliary (11.30 ± 10.35%) types. The MIB-1 labeling index of patients with adenoma and the gastric type was less than that for patients with adenoma and the intestinal type (p = 0.04). There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was poor.

Conclusions: gastric type IPMN have a low MIB-1 labeling index, which demonstrates that malignancy of this subtype is lower than that of other subtypes.

Key words : MIB-1 labeling index, Ki67, histological grade, gastric type, intraductal papillary-mucinous neoplasms

Introduction

Intraductal papillary-mucinous neoplasms (lPMNs) are tumors that are classified as true neoplastic cysts of the pancreas. IPMNs are characterized by large quantities of mucous production, opening of Vater's papilla, pancreatic duct dilation, papillomatous proliferation of the pancreatic duct, and poor infiltration. Although prognosis is excellent in noninvasive cases, the postoperative 5-year survival rate of invasive cases is 40%−50%. The male to female ratio is 2:1. IPMNs are common among elderly individuals (mean age for both genders, approximately 65 years). The preferred site of IPMNs is the pancreatic head, which accounts for up to 70% of cases[1].

The concept of an IPMN was first reported by Ohhashi et al[2], who described it as a ''mucin-producing pancreatic tumor.'' Since 1990, this

disease concept has been confirmed worldwide by the Japanese Classification of Pancreatic Carcinoma[3], the Armed Forces Institute of Pathology[4], the International Histological Typing of Tumors of the Exocrine Pancreas by the World Health Organization[5], and by Kimura et al[6-8]. Moreover the International Consensus Guidelines for Management of IPMNs were published in 2006[9]. In recent years, the concept of a new classification of IPMNs, based on immunohistological subtypes, which was revised according to the WHO classification in 2010, has been adopted[11], and the international consensus guidelines of 2012 for the management of IPMN and MCN of the pancreas have been published[10].

Our group, Takasu et al[12] previously reported a retrospective comparative study of the clinicopathological features, degree of malignancy, morphological and immunohistological findings and prognosis of IPMNs. That study divided IPMNs into the following four subtypes: gastric, intestinal, pancreatobiliary, and oncocytic. Furthermore, IPMNs were histopathologically classified as adenoma/borderline (IPMN with low- or intermediate-grade dysplasia), carcinoma in situ (IPMN with high-grade dysplasia), or invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma), in which cancer development was described according to staging. Moreover, Takeshita et al[13] from our group reported that an MIB-1 labeling index (Ki67) could be used as an indicator of the degree of malignancy. However, there has not yet been any study in which the association between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological subtypes was investigated. The present study therefore aimed to examine the relationship between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological IPMN subtypes described above.

Materials and Methods

Patients

Between 2000 and 2007, we retrospectively evaluated 46 patients who had undergone surgery at the Department of Gastroenterological and General Surgery, Yamagata University, Faculty of Medicine, Japan, were histopathologically diagnosed as IPMN, and in whom immunohistochemical staining was possible. Clinical and follow-up information was obtained from patient charts.

Subclassification of IPMNs

The 46 IPMN patients were graded as adenoma/borderline (adenoma, in this paper), carcinoma in situ, or invasive carcinoma derived from IPMN according to their histological grade. This grading corresponded to the WHO IPMN subtype classification[11] of IPMN with low-/intermediate-grade dysplasia, IPMN with high-grade dysplasia, and IPMN with an associated invasive carcinoma, respectively. Adenoma (IPMN with low- or intermediate-grade dysplasia) showed papillary growth, consisted of a higher proportion of columnar cells than the other subtypes, and maintained a proper nuclear arrangement as assessed by hematoxylin and eosin (H-E) staining. Carcinoma in situ (IPMN with high-grade dysplasia) showed a lack of proper nuclear arrangement, enlargement of the nucleus, a definite nuclear pole, and a high level of mitosis. We defined invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma) as cancer cells that infiltrated the basal membrane and invaded interstitial connective tissue.

The 46 cases of IPMN were subclassified into 4 types (Gastric, Intestinal, Pancreatobiliary, and Oncocytic) as described by Furukawa et al[14] on the basis of their morphological features and their immunohistochemical reactivity (MUC1, MUC2, and MUC5AC staining). The samples were first classified on the basis of their H-E stained findings, after which immunohistochemical analysis was performed to confirm the results. When the assessment made on the basis of H-E staining was inconsistent with the immunohistochemicaldata, the H-E stained slides were rechecked. If the H-E data remained inconsistent with the immunohistochemical analysis, the H-E based assessment was used rather than the immunohistochemical based assessment[12].

Immunohistochemical staining

Immunohistological staining was performed using the streptavidin-biotin method. Resected specimens

were fixed with formalin and embedded in paraffin. Thin serial sections were made with a microtome. After deparaffinization, sliced specimens were washed with phosphate-buffered saline. The specimens were then heated three times in a microwave at 900 W for a total of 30 minutes at 100°C. Endogenous peroxidase was blocked with 0.3% H_2O_2. Non-specific staining was blocked by incubating the sections in a solution containing 3% skim milk. The sections were subsequently incubated with primary antibody overnight at 4°C. Next, the sections were incubated with a second biotinylated mouse monoclonal antibody and peroxidase-labeled streptavidin (LSAB kit; Dako, Glostrup, Denmark) for 1 hour. Peroxidase activity was then detected using 3,3'-diaminobenzidine. Finally, counterstaining was performed with hematoxylin. The primary antibodies used were specific for MUC1 (clone Ma695; dilution 1:100) (NovoCastra Laboratories, Newcastle upon Tyne, UK), MUC2 (clone Cep58; dilution 1:200) (NovoCastra Laboratories), MUC5AC (clone CLH2; dilution 1:100) (NovoCastra Laboratories), or the Ki67 antigen (clone MIB-1; dilution 1:120) (Dako, Glostrup, Denmark).

Evaluation of MUC1, MUC2, and MUC5AC staining

Two to four slides were immunohistochemically stained per case. The entire neoplasm on each slide was microscopically examined under low power (×10) and the approximate percentage of positively stained neoplastic cells was calculated. The neoplasms were graded as follows: (-) less than 5% of neoplastic cells positive, (+) 5% to 50% of neoplastic cells positive, and (++) more than 50% of neoplastic cells positive. For invasive carcinoma derived from IPMN, only the noninvasive sites were evaluated: sites of apparent invasion were not assessed.

Evaluation of MIB-1 staining

Two to three slides were immunohistochemically stained per case. More than 5 fields were selected at random and microscopically analyzed. In one particular case, five areas were chosen and analyzed at a higher magnification (×200). More than 2000 tumor cells were countedper case. The MIB-1 labeling index was calculated as the percentage (%) of the total tumor cells that stained positive. In invasive carcinoma derived from IPMN, only the noninvasive sites were evaluated: sites of apparent invasion were not assessed.

All of the pathological and immunohistochemical investigations of IPMNs were performed, and the results were confirmed, by two physicians.

Statistical analysis

Results are expressed as means ± SD (range). Continuous variables were analyzed using Student's *t*-test. Survival was calculated from the date of resection to the date of disease-specific fatality or to the date of censoring at the last follow-up. Cumulative overall survival rates were calculated using the Kaplan-Meier method. Statistical significance was defined as $P < 0.05$. All analyses were carried out using the StatView version 5.0 Software of the SAS Institute, Inc.

Results

Patient clinicopathological characteristics (n = 46) are shown in Table 1. The mean age of the patients (32 males and 14 females) was 67 ± 10 years (range, 47−87). Pancreaticoduodenectomy[15] was performed in 26 patients, distal pancreatectomy with splenectomy in 9, spleen-preserving distal pancreatectomy[16] in 10, and total pancreatectomy in one patient. Histological grade was: adenoma (n = 27), carcinoma in situ (n = 9), and invasive carcinoma derived from IPMN (n = 10). Subtypes, based on morphological features and immunohistochemical reactivity, were as follows: gastric (n = 20), intestinal (n =15), panacreatobiliary (n = 9), and oncocytic (n = 2). The overall MIB-1 labeling index for all patients was 8.6% ± 9.2% (range, 0.34%− 29%). The MIB-1 labeling index (Ki67) of patients with the gastric type was 4.0% ± 6.8%, which was significantly less than that for patients with intestinal or pancreatobiliary types (Figure 1). In patients with the gastric type there were significantly more adenomas observed (n = 17, 86%) than carcinomas in situ (n = 3) or invasive carcinomas derived from IPMN (n = 0) (Table 2). Similar numbers of each histological gradeof tumor were found in the intestinal type. Adenomas and invasive

Table 1. Clinicopathological characteristics of 46 IPMN patients

No.	46
Age (mean ± SD)	67 ± 10
Sex	
Men	32
Women	14
Tumor location	
Head	25
Body and/or tail	20
Whole	1
Macroscopic subtype	
Branch duct type	35
Main duct type	4
Mixed type	7
Operative procedure	
PD	26
DPS	9
SPDP	10
TP	1
Histological grade	
Adenoma	27
Carcinoma in situ	9
Invasive carcinoma derived from IPMN	10
Observation period (mean ± SD)	69 ± 37
Disease-specific fatality (n)	7
Five-year survival rate (%)	84.3%

PD, pancreaticoduodenectomy; DPS, distal pancreatectomy with splenectomy, SPDP, spleen-preserving distal pancreatectomy; TP, total pancreatectomy; Adenoma, IPMN with low- or intermediate-grade dysplasia, adenoma, or borderline; Carcinoma in situ, IPMN with high-grade dysplasia or non-invasive carcinoma; Invasive carcinoma derived from IPMN, IPMN with an associated invasive carcinoma.

carcinomas derived from IPMN were the most common histological grades found in the pancreatobiliary type (both, n = 4). The MIB-1 labeling index (Ki67) of patients with adenoma and the gastric type of IPMN was less than that for patients with adenoma and the intestinal type of IPMN (p = 0.04). There was no significant difference between the MIB-1 labeling index of patients with carcinoma in situ and the gastric type of IPMN and that for patients with carcinoma in situ and the intestinal type of IPMN. The survival curve for all 46 patients with IPMN is shown in Figure 2. The mean observation period was 68.6 ± 36.9 months (range, 6–153 months). There were seven disease-specific fatalities, all of which were invasive carcinomas derived from IPMN, including 1, 4, and 2 patients with intestinal, pancreatobiliary, and oncocytic subtypes, respectively. The 5-year overall survival rate was 84.3%.

The relationship between survival and MIB-1 labeling indices of <10% and ≥ 10% is shown in Figure 3. There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was apparently poor.

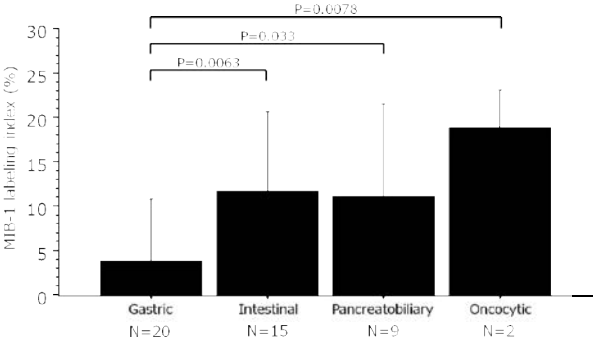

Figure 1. MIB-1 labeling indices of each immunohistological subtype of IPMN

Data are shown as means (thick bars) + standard deviations (thin bars).

The MIB-1 labeling index (Ki67) of patients with the gastric type was significantly less than that for patients with intestinal or pancreatobiliary types.

Table 2. Histological grading and MIB-1 labeling index (Ki67) of IPMNs according to immunohistological subtypes

	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Adenoma				
N	17	6	4	0
MIB-1 labeling index(%)	1.47 ± 1.12 (0.34-4.01)	3.72 ± 3.65 (0.69-9.95)	1.17 ± 0.54 (0.75-1.92)	-
		p=0.04		
Carcinoma in situ				
N	3	5	1	0
MIB-1 labeling index(%)	18.26 ± 9.49 (11.02-29)	15.42 ± 7.68 (4.21-23.21)	11.06*	-
		NS		
Invasive carcinoma derived from IPMN				
N	0	4	4	2
MIB-1 labeling index(%)	-	19.50 ± 6.40 (13-25)	21.50 ± 3.11 (18-25)	16,22*
Total				
N	20	15	9	2
MIB-1 labeling index(%)	3.99 ± 6.78 (0.34-29)	11.83 ± 8.95 (0.69-25)	11.30 ± 10.35 (0.75-25)	16,22*

Adenoma, IPMN with low- or intermediate-grade dysplasia, adenoma, or borderline; Carcinoma in situ, IPMN with high-grade dysplasia or non-invasive carcinoma; Invasive carcinoma derived from IPMN, IPMN with an associated invasive carcinoma; NS, no significant. MIB-1 labeling indexes are expressed as mean ± standard deviation.
* showing actual values.

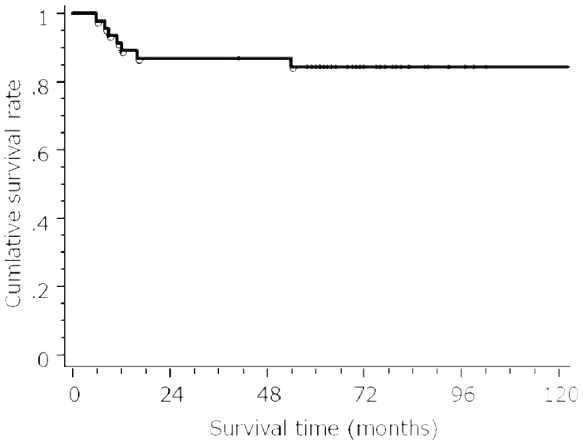

Figure 2. Survival curves of all 46 patients with IPMN
The mean observation period was 68.6 ± 36.9 months, and the 5-year survival rate was 84.3%.

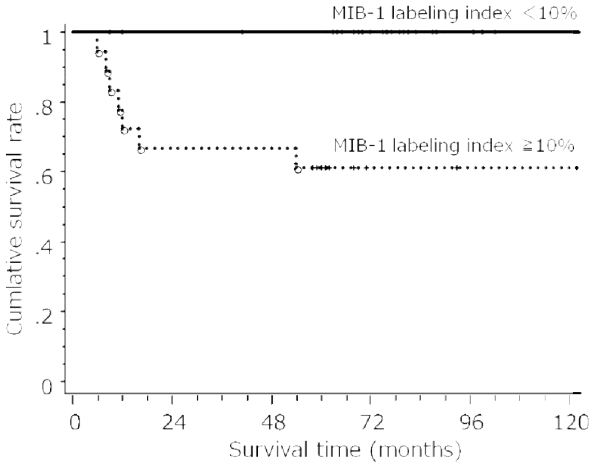

Figure 3. Correlation of survival curves with MIB-1 labeling indices of < 10% and ≥ 10%
There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was poor.

Discussion

Various gastrointestinal cancers are classified according to cell and tissue morphology and a correlation with clinicopathological characteristics and prognosis is acknowledged. Lauren[17] classified gastric carcinoma into diffuse and intestinal types and demonstrated that these types correlated with clinical characteristics. Kimura et al[18] were the first to use the terms intestinal type and pancreatobiliary type in carcinoma of the papilla of Vater, and they reported that cases of the pancreatobiliary type had a worse prognosis than those of the intestinal type.

The following two classification systems were created for IPMNs: Adsay et al[19] divided the condition into intestinal, pancreatobiliary, and null types, whereas Yonezawa et al[20] created two categories: villous dark cell and papillary clear cell types. In a further report by Adsay et al[21], these authors described the concept of intraductal oncocytic papillary neoplasms, in which the papilla, comprising eosinophilic cells, exhibits a complex branching form. In 2005, Furukawa et al[14] reported a consensus study regarding a new IPMN classification that integrated these two schools of thought, in which IPMN was classified into the following four subtypes: gastric, intestinal, pancreatobiliary, and oncocytic. This concept was adopted by WHO as their new classification system in 2010[11]. We classified the 46 patients in our study into four subtypes according to the classification system of Furukawa et al[14]. According to this system, the histopathological subtype of IPMN should first be based on morphological characteristics and then confirmed by immunohistological staining. Our study was based on this concept. When findings from H-E staining differed from those of immunohistological staining, we based the classification on both H-E staining and the pathological findings collected from at least two physicians. However, only a few such cases were found in this study. In our group, the prognosis of patients with the gastric or intestinal types was more favorable than that for patients with the pancreatobiliary type[12]. Moreover, the prognosis of patients with invasive carcinomas derived from IPMN tended to be better for the intestinal type than for the pancreatobiliary type, which may suggest that the former is a slow-growing neoplasm.

IPMN grading for atypia was histopathologically classified into adenoma (IPMN with low- or intermediate-grade dysplasia), carcinoma in situ (IPMN with high-grade dysplasia), or invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma), in which cancer development is described according to staging. Takeshita et al[13] demonstrated that the MIB-1 labeling index, Ki67, was higher for patients with carcinoma in situ than for patients with adenoma; thus, the MIB-1 labeling index was considered as an appropriate indicator of the degree of malignancy. These authors also suggested that when IPMN is diagnosed as carcinoma in situ, it should be surgically removed.

On the basis of these two reports, we examined the relationship between the MIB-1 labeling index, Ki67, which is an indicator of malignancy, and the four different morphological and immunohistological subtypes of IPMN. We found that the MIB-1 labeling index of patients with the gastric type was significantly lower than that of patients with the other subtypes (Figure 1). Moreover, of the 46 patients, those with an MIB-1 labeling index of less than 10% showed no decrease in survival time after surgery (Figure 3). In summary, our findings regarding the MIB-1 labeling index demonstrate that patients with the gastric type, who have a low MIB-1 index, exhibited a lower degree of malignancy than those with other subtypes, who have a higher MIB-1 index, and that their prognosis was good.

Similarly, Furukawa et al[22] also demonstrated that overall prognosis was better for patients with the gastric type of IPMN than for patients with other IPMN subtypes. It has been postulated that gastric type IPMN often displays low- or intermediate-grade dysplasia and that malignant transition occurs less-frequently in patients with gastric type IPMN[10, 11]. In the present study, although adenoma was frequently found in patients with gastric type IPMN, invasive carcinoma derived from IPMN was not found in these patients. On the other hand, some previous studies have shown that patients with invasive carcinoma derived from gastric type IPMN, which often takes the histological finding of tubular adenocarcinoma, have a worse prognosis than patients with invasive carcinoma derived from intestinal type IPMN[22, 23]. In 2002, Adsay et al[26] suggested that MUC2-positive IPMN, i.e. the intestinal type, whose carcinogenesis follows a pathway similar to the adenoma-carcinoma sequence in colorectal cancer, is "indolent" disease, whereas MUC1 positive IPMN, i.e. the pancreatobiliary type, is "aggressive" disease similar to pancreatic adenocarcinoma. In addition, there is increasing evidence that gastric type IPMN shows a significantly higher incidence of KRAS mutations[24], and no incidence of GNAS mutation compared with the

intestinal type[25]. It has been suggested that the carcinogenesis of not only the pancreatobiliary type but also the gastric type of IPMN may be the same as that of pancreatic adenocarcinoma[24), 25)]. In the light of these studies, it is interesting to note that the MIB-1 labeling index of patients with the gastric type differed from that of the intestinal type in this study.

In the present study, no invasive carcinoma derived from IPMN was detected in patients with the gastric type, and the MIB-1 labeling index of this type was significantly less than that of the other subtypes. These results may be due to a difference in histological grade of the neoplasm. However, the MIB-1 labeling index of patients with the gastric type was only less than that of patients with the intestinal type for neoplasms that were graded as adenomas. We concluded that malignancy of the gastric type of IPMN not higher and may be lower than that of other subtypes. Although patients with the gastric type of invasive carcinomas derived from IPMN may have poor prognoses[22), 23)], such cases were not found in this study of 46 cases. We therefore suggest that such cases may be rare and, consequently, more of such cases should be accumulated for further study.

In conclusion, gastric type intraductal papillary mucinous neoplasms have a low MIB-1 labeling index, which demonstrates that malignancy of this subtype is lower than that of other subtypes.

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Current respiratory management for Acute Respiratory Distress Syndrome

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ABSTRACT

Acute Respiratory Distress Syndrome still high has a mortality rate. There are many causes for respiratory failure including sepsis, aspiration, pneumonia, pancreatitis, chest trauma, transfusion, and so on. However, not only respiratory failure, but the mechanical ventilation itself could induce lung injury additionally.

Recently there has been a new definition of ARDS that is based on the clinical findings, time course of onset, and PaO_2/FIO_2 with more than 5 cmH_2O of PEEP. It does not include heart failure and over infusion. Respiratory care for ARDS is going to change, as a result of recent research into respiratory management. In this review we describe respiratory care evidence for ARDS in terms of the Berlin definition, the history of naming ARDS, pathophysiology, etiology, ventilator management that are tidal volume, PEEP, High frequency ventilation (HFO), non-invasive positive pressure ventilation (NPPV), and airway pressure release ventilation (APRV). The physiotherapy of the prone positioning and recruitment maneuver (RM), Extra Corporeal Membrane Oxygenation (ECMO), nitroxide (NO), intravenous muscle relaxants, and so on will be discussed.

Key words : ARDS, Berlin definition, ventilation strategy, respiratory management.

The mortality rate due to Acute Respiratory Distress Syndrome (ARDS) is currently 40%.[1] Although progress has been made in treatments for ARDS, the survival rate after one year has not improved[2]. Ashbaugh[3] First described serious hypoxia-related respiratory failure ARDS in 1967, and Bernard et al.[4] proposed a definition for ARDS in 1994. At the time ARDS was defined as acute onset hypoxemia, with bilateral diffuse shadows on chest X-ray, and not dependent on heart failure. It can be classified into Acute Lung Injury (ALI) and ARDS based on the PaO_2/FIO_2 (P/F) ratio. However, in several clinical studies based on this definition, most treatment strategies, such as artificial ventilation, drug therapy, anti-cytokine therapy, and others, were found to be without a lung protective strategy[5].

In addition, the mortality rate due to ALI and ARDS remained nearly unchanged[6], which indicated that this definition was problematic. ARDS is now referred to as a syndrome, and survival rates are dependent on the primary disease and severity. This includes whether the origin is pulmonary (primary) or extra-pulmonary (secondary). Thus, it was unclear regarding what type of treatment was appropriate.

A new definition for Acute Respiratory Distress Syndrome (ARDS) was proposed in 2011 by the European Society of Intensive Care Medicine[7, 8]. This classified ARDS into three grades based on the P/F ratio: Mild ARDS (P/F = 300-200), Moderate ARDS (P/F = 200-100), and Severe ARDS (P/F/< 100), while on respiratory care with PEEP of > 5 cmH_2O (Table 1).

Thus, the indications for treatment could be demonstrated using many types of respiratory care

Table 1. The Berlin definition[7), 8)]

	Acute Respiratory Distress Syndrome		
Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest Imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation	200<PaO_2/FiO_2≤300 With PEEP/CPAP ≥ 5 cmH_2O	100<PaO_2/FiO_2≤200 With PEEP ≥ 5 cmH_2O	PaO_2/FiO_2≤100 With PEEP ≥ 5 cmH_2O

Onset of timing was stated within one week. Chest imaging and origin of edema were not changed compare with previous definition. However, as the most important points ARDS was classified to three grades by PaO_2/FIO_2 with more than 5 cmH_2O of PEEP. These are Mild, Moderate, and Severe ARDS.

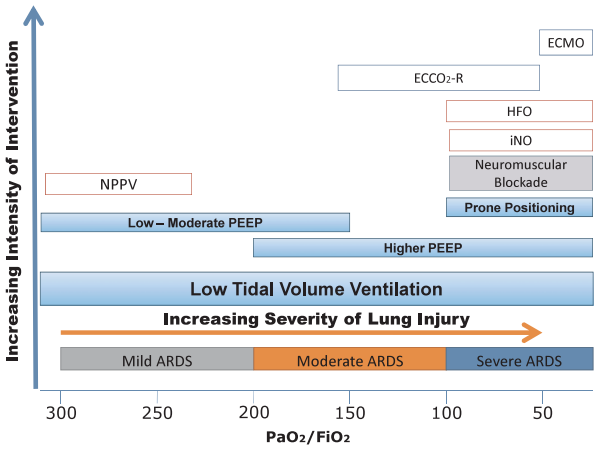

Figure 1. Severity of ARDS by P/F and Intervention.
The respiratory treatment that are based on the evidence is indicated depending on the severity of ARDS. Low tidal volume ventilation is recommended for all grades of ARDS. Low PEEP for Mild to Moderate ARDS and Higher PEEP for Severe ARDS were recommended. NPPV is for Mild ARDS, Prone positioning is for Severe ARDS with high level of recommendation. The others are shown as well with low grade of it.

according to this grade classification. Here, we describe the pathophysiology of ARDS and provide explanations for the indicated respiratory care based on the new advocated definition.

(A) Etiology and pathology of ARDS

Although the cause of ARDS comes from many factors, it is always initiated when an external stimulus, such as endotoxin, activates alveolar macrophages via Toll-like receptors (TLRs). These activated macrophages produce and release cytokines, such as Il-8, which activate neutrophils. These neutrophils attach to a pulmonary blood vessel wall, roll along on a capillary, and then invade through intercellular gaps into interstitial tissue. Leukotrienes, oxidants, PAF, proteases and other mediators are also released from these cells. These mediators decrease surfactant activity, induce alveolar collapse, and increase the permeability of blood vessels and edema in the lungs. They also promote the formation of hyaline films, necrosis of type I cells, cellular apoptosis, collagen production, and clot formation, which results in an inflammatory reaction[9)]. Pulmonary mechanics also worsen and require respiratory management.

(B) Berlin Definition[7), 8)]

The currently used definition of ARDS was first advocated in Berlin, Germany. Respiratory failure with excessive infusion and/or heart failure are excluded for this definition of ARDS. As noted above, ARDS is classified into three categories based on the P/F ratio while performing respiratory management with PEEP of > 5 cmH_2O for respiratory failure within one week after onset (Table 1).

In addition to the abnormal findings on chest X-ray that showed diffuse shadows on both sides, there were increased pathophysiological abnormalities, such as the volume of one minute ventilation, dynamic and static compliance, and the amount of extravascular lung water.

It is particularly noteworthy that they demonstrated an effective respiratory management strategy according to severity based on empirical evidence (Figure 1). By investigating pathological views of the lungs in terms of the classifications in this definition, there is a good relationship between clinical severity and pathological findings[10)]. Some reports[11)] supported that extra-vascular lung water volume and pulmonary blood vessel permeability are good indicators for classifying ARDS.

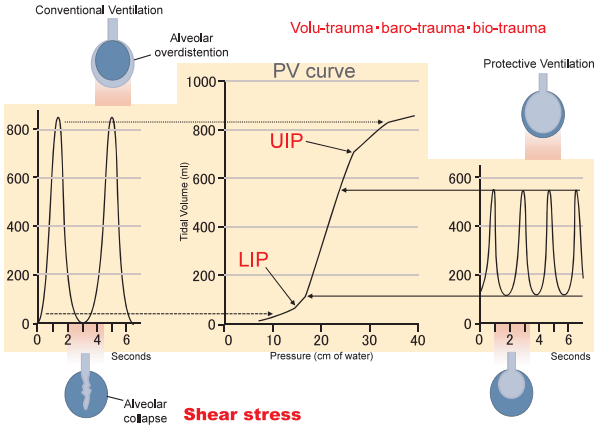

Figure 2. Pressure-Volume curve of the injured lung[10]

The ventilator induced lung injury (VILI) was considered to occur by shear stress with alveolar collapse and opening, or alveolar over distention which induce baro-trauma, volu-trauma and bio-trauma. Protectve ventilation is theoretically that peak inspiratory pressure had better keep less than Upper inflection point and PEEP also should set up at more than Inflection point.

(C) Respiratory management for ARDS

(1) Small Tidal Volume

Conclusion was reached that restrictive ventilation was effective for treating ARDS regardless of severity, as the small tidal volume used for ARDS was demonstrated to improve mortality by the ARDS net in 2000[5]. They discovered that the survival rate increases after the reduction of ventilator-induced lung injury by non-physiological artificial ventilation. In addition they observed that the small tidal volume reduces the over-stretching of alveoli and small airways, which is called volume trauma or barotrauma[12]. This is also called bio-trauma because hyper-extension of the lung induces the release of chemical mediators, such as cytokines, to promote an inflammatory reaction[13]. Furthermore in a separate clinical study, they found that if the peak inspiratory pressure was < 31cmH_2O, the convalescence was not affected regardless of the amount of tidal volume in ARDS patients[14].

(2) PEEP

Even though if low tidal volume is used, if an inappropriate PEEP level is added, lung injury will increase. A representative pressure-volume curve measured during artificial respiration of an ARDS patient is shown in Figure 2. There are two points on the steep curve, which are called the lower inflection point (LIP) and the upper inflection point (UIP)[10]. Lung injury is relieved in terms of a restricted peak inspiratory pressure of < UIP and also using PEEP higher than the LIP. PEEP less than LIP produces shear stress by repeated alveolar collapse and re-opening, and is known to bring about an inflammatory reaction. Although there have been numerous studies since the 1960s regarding the best PEEP level, there is still no consensus regarding the method that provides the most suitable PEEP level in order to improve the survival rate, which was pointed out by Slutsky et al.[15] Maeda et al.[16] performed a randomized controlled trial (RCT) for 987 ARDS/ALI patients with P/F ratios of < 250 and compared a high PEEP group with a low PEEP group. They compared survival rates and other outcomes after randomization for 75 days, but could not find significant differences ($P < 0.18$). Gattinoni et al.[17] described that even if a high PEEP level was applied randomly to indefinite ALI/ARDS patients, the prognosis did not improve. Briel at al.[18] investigated the survival rates of 2,299 ALI/ARDS patients by comparing a High PEEP (HP) group with a Low PEEP (LP) group based on three RCTs. For all of these patients, there was no difference in the survival rate as reflected by 32.9% of the HP group vs. 35.2% of the LP group (CI: 0.86-1.04; $p = 0.25$). However, for 1,892 of these ARDS patients with P/F ratios of < 200, the mortality rate of the HP group (34.1%) was lower than that of the LP group (39.1%). In addition, among 404 ALI patients the mortality rate in the HP group (27.2%) was higher than that in the LP group (19.4%) (CI: 0.98-1.92; $p = 0.07$). These results provided some of the best evidence that PEEP level should be low for mild to moderate ARDS and should be high for moderate to severe ARDS.

(3) Recruitment and Prone Position Management

The principle of recruitment can be explained based on a pressure volume curve (Figure 2). At the beginning, ARDS lungs have low compliance. If the airway pressure increases, then the compliance (⊿V/⊿

P) improve beyond the LIP point. As this pressure increases so does the pulmonary capacity, however, the compliance will remain constant between the LIP and the UIP. However, compliance decreases again after the UIP point. The lung volume at the decreasing part of the curve is greater than that at the increasing part of the curve with the same airway pressure. In other words, the end-expiratory lung volume can be kept greater at a lower PEEP level than that before recruitment. Recruitment seems to prevent lung injury due to keeping alveoli and small airways open. However, this technique does not provide evidence of mortality improvements[19].

It is well known that SaO_2 is improved when a patient moves from a supine to a prone position while undergoing mechanical ventilation. Prone position management for ARDS patients came to be positively adopted in intensive care units. However, Gattinoni et al.[20] tried this prone position strategy for ARDS patients in a prospective study in 2001 and reported that it did not affect the prognosis as compared with the supine position. Several reports were subsequently published, but did not arrive at a consensus. Furthermore, Abrog et al.[21] performed a meta-analysis of five papers regarding prone position therapy for ARDS/ALI patients. These included 713 cases in the prone position and 659 in the supine position. Oxygenation was improved with the prone position, but did not improve mortality.

However, Abrog et al.[22] subsequently added four more papers that included only ARDS patients. This included 862 patients for which prone position ventilation was performed within total 1675 patients. They found no significant differences among seven papers with both ALI and ARDS patients combined. However, prone position management over a long time reduced the mortality in the ICU in only the four latest articles, which were limited to ARDS patients. There were no significant differences in terms of complications between them, including airway occlusion, pulling out catheters, and circulatory complications. According to this report[22], the prone position strategy was certified to be effective for severe ARDS patients. An improved survival rate was demonstrated for 10% to more than 15% of severe ARDS cases who had P/F/ ratios of < 100 when using prone position management[23), 24].

(4) Muscle relaxants

Papazian at al.[25] investigated the effectiveness of muscle relaxants for 1326 ARDS patients in France. These patients were registered after severe ARDS was diagnosed with P/F ratios of < 150 and with PEEP of > 5 cmH_2O. This was a prospective study that compared 177 patients in a muscle relaxant group and 162 patients in a control group. The muscle relaxant of Cisatracrium was administrated at the beginning of artificial ventilation up to an upper limit of use for 48 hours. The mortality rate was significantly lower in the muscle relaxant group than in the control group, with 23.7% vs. 33.3% at 28 days and 31.6% vs. 40.7% at 90 days, respectively. In the muscle relaxant group, there were shorter periods of ventilator-free days and fewer complications involving organ disorders, such as heart failure, liver dysfunction, and renal insufficiency, and fewer blood coagulation disorders. The muscle relaxant group also had fewer instances of barotrauma and pneumothorax, such as ventilator-induced lung injury. However, the severity and frequency of complications involving muscle atrophy and paralysis were the same in both groups. Neto et al.[26] also did a meta-analysis to investigate three RCTs in which muscle relaxants were used for ARDS. This included 431 ARDS patients. They found that the mortality rate was lower in the muscle relaxant group. In addition, the artificial respiration period was shorter, the number of other treatments used was fewer, P/F ratios were higher, and there were fewer instances of barotrauma, such as pneumothorax, as compared with the control group. The complication rates of neuromuscular disease were the same. They emphasized that early administration of a muscle relaxant within 48 hours for severe ARDS patients improved mortality with the same level of complications[26].

Unsynchronized ventilation seems to induce the collapse and hyperextension of the lungs between spontaneous breathing and mechanical ventilation. This is because the trans-pulmonary pressure produced by spontaneous breathing is greater than that produced by forced ventilation in the severe injury lung model. Additionally, it has been shown

that paradoxical breathing (i.e., Pendluft) occurs in the lungs in the case of spontaneous breathing in severe lung injury[27]. For severe ARDS patients, forced ventilation with muscle relaxants was supported from the beginning of respiratory failure for up to two days. However, respiratory care along with observing the trans-pulmonary pressure has not yet become a standard strategy[28], and requires further study.

As evidence, a limited tidal volume strategy has been shown to have a good effect for ARDS. In addition, it has been emphasized that non-spontaneous ventilation with muscle relaxants is useful for those patients with limited ventilation[29]. This was because the relaxant dose administrated was larger in the small tidal group than that used in the control group. In the Surviving Sepsis Campaign 2012[30] it was described that muscle relaxants should be avoided for non-ARDS patients (evidence level 1C). However, muscle relaxants should be administered for severe ARDS patients with P/F ratios of < 150 in the short term of less than 48 hours during the early stage (evidence level 2C).

(5) High Frequency Oscillation (HFO) and Airway Pressure Release Ventilation (APRV)

Again considering a pressure-volume curve, the best means to induce the least amount of stress to the injured lung is ventilation between the LIP and the UIP (Figure 2). The lung compliance in severe ARDS decreases and the slope of the PV curve declines toward the right. Consequently, the distance between the LIP and UIP could possibly shorten. In such a case, High Frequency Oscillation (HFO) becomes the ideal ventilation method, at least theoretically. A few decades ago, many clinical studies of HFO for IRDS were conducted and succeeded in providing evidence for this. HFO is now also used for IRDS of neonates. HFO is set at a frequency (number of vibrations) of 10 HZ from 3 HZ, and with the tidal volume less than the dead space. However, HFO airway pressure is often at 10 cmH_2O higher than the mean airway pressure of conventional ventilation.

Therefore, it is thought that HFO frequently induces hypotension or barotrauma. Sud et al.[31] compared the prognosis of a HFO group and a Conventional group by a meta-analysis that included about 180 ARDS patients in each group. There were no significant differences in the frequencies of complications, such as pneumothorax, hypotension, or obstruction of a tracheal tube. From the first day to the third day, oxygenation was significantly higher in the HFO group than in the control group. In addition, the mortality rate at 30 days was lower in the HFO than in the control group; 73/189. vs. 87/176 ($P < 0.03$). However, the results of the OSCILLATE Trial[32] conducted by a Canadian group and the OSCAR Study[33] conducted in the U.K. were recently reported.

In the OSCILLATE Trial[32], HFOV during the early stage compared with a lung protective strategy with a high PEEP level for moderate-severe ARDS adult patients showed that HFOV increased the mortality rate and did not improve the prognosis. The actual in-hospital mortality rate was 47% in the HFOV group vs. 35% in the CV group, which showed that HFOV deteriorated patients' conditions. Therefore, the plan for 1,200 target patients was cancelled for 548 cases. The HFOV group received more doses of a muscle relaxant and the sedative midazolam. Although the mortality was higher with HFOV for ARDS patients with P/F ratios of > 86, it was almost the same at 42%-43% for those with P/F ratios below this value.

In the OSCAR Study[33], HFOV or CV was used for 795 ARDS adult patients with P/F ratios of < 200 for more than two days. There was no significant difference between both groups in their mortality rates by 30 days, which were 41.7% of 166/398 (HFOV group) and 41.1% of 163/397 (CV group). These results are seemed to require further discussion.

Airway pressure release ventilation (APRV) is CPAP at high pressure under spontaneous breathing while maintaining the lung status at recruitment and is also a ventilation mode for promoting carbon dioxide removal in terms of moving to a low-pressure CPAP for a short time. APRV has been investigated for comparing numerous types of ventilation modes, including PSV, VC-IRV, PCV, s-IMV, and PC-IMV. Those papers emphasized superior points, such as improvements of atelectasis, oxygenation, circulatory distress, airway pressure, and reduced sedative use.

However, Gonzalez[34] compared prognosis between two groups in terms of matching by propensity scores, which involved respiratory failure patients including

234 cases with APRV and 1,228 cases with assist-control ventilation (A/C). APRV was not superior to A/C in terms of factors such as ventilator free days, re-intubation, number of days in the ICU, and in-hospital mortality rates.

(6) NO

Afshri[35] assessed the effectiveness of NO inhalation for ARDS/ALI based on 14 RCTs involving 1,303 patients. They concluded that NO inhalation could not be recommended for hypoxemic respiratory failure patients. Although NO transiently improved oxygenation, it did not result in an increased survival rate. There were no problems with regard to bleeding or met-hemoglobinemia, but its use did result in the development of renal injury that was possibly harmful. Although this was a negative result, if cases could be limited based on strict evaluations of adaptation, it may become a new development in the future.

(7) ECMO

Takeda et al.[36] pointed out the problem that intensivists and staff members in the ICU were not accustomed to using ECMO for ARDS patient during the influenza pandemic outbreak in Japan. Other issues were the materials and the ECMO system used in Japan. In clinical studies, ECMO has been applied not only for H1N1 influenza pneumonia, but also for various types of respiratory failure in foreign countries. It is thought that development of an ECMO system will progress in Japan in the near future[37]. In addition, the Japanese Society of Respiratory Care and the Japan Society of Intensive Care Medicine have begun to register ARDS patient for ECMO therapy. This should contribute to improving the mortality of patients with influenza pneumonia and/or ARDS in Japan.

(8) NPPV

In the Berlin Definition, NPPV was adapted only for Mild ARDS. However, the level of evidence for NPPV use for ARDS patients is not high[38), 39)]. NPPV is thought to prevent Mild ARDS from becoming severe ARDS by starting NPPV during an early stage before any changes are noted on chest X-rays.

Evidence for using NPPV has been accumulating. A high grade of evidence has been provided for acute heart failure (1A)[40), 41)], acute exacerbations of chronic obstructive pulmonary disease (1A)[42)], and respiratory failure due to immunodeficiency (2A)[43)]. Now NPPV is extensively used for postoperative respiratory failure as a treatment and/or for prevention[44)]. For example, there is a high risk of respiratory failure after thoraco-abdominal surgery[45)], lung resection[46)], and other surgeries. Many types of interfaces, such as nasal masks, face masks, full-face masks, and helmets, are sold commercially and their usefulness has increased considerably.

Invasive ventilation with unnecessary tracheal intubation should be reduced by using NPPV. Recently, a trial to classify acute heart failure into five categories was proposed based on the onset mechanism and circulatory conditions[47)].

(I) Crisis of heart failure with blood pressure of > 140 mmHg and diffuse edema in the lungs during the shrinkage period.
(II) Heart failure with blood pressure from 140 to100 mmHg and slight edema in the lungs.
(III) Blood pressure of < 100 mmHg with heart dysfunction and/or cardiac shock.
(IV) Acute coronary syndrome.
(V) Right heart failure.

Identifying those patients who require respiratory management is relatively easy, particularly for those with heart failure and with blood pressure of > 100 mmHg (I) (II) and those with acute coronary syndrome (IV). NPPV should be selected as a first choice for these conditions.

(9) HFNC

Finally, we discuss a recent topic: the oxygen therapy for respiratory failure that is effectively less than that of mild to moderate ARDS. Oxygen therapy is usually provided by using an oxygen mask or a nasal cannula. High Flow Nasal Cannula (HFNC) oxygen therapy is a method for delivering a high volume of gas from a nasal cannula to the nasal cavities[48), 49)].

Nasal cavity mucous membranes are occasionally damaged due to dry gas, and when oxygen is delivered at > 3L/m through a normal nose cannula, nasal

bleeding may be induced. In contrast, HFNC does not dry the respiratory tract and does not slow ciliary movement, as the high volume of gas is sufficiently warmed and humidified. Therefore, epistaxis usually does not occur. Regarding clinical evidence, when it works well, HFNC therapy improves oxygenation, decreases the respiratory rate within one hour, and releaves dyspnea for a mild to moderate respiratory failure patient[48]. As for its physiological effect, this treatment produces a slight PEEP to the upper respiratory tract (3-8 cmH_2O with 30L/min). It has been estimated that a slight PEEP will increase FRC[49] as will a small PEEP. It improves the gas conductivity of the peripheral airway, and it also washes away the gas in the airway of dead space.

It has been noted that patients with HFNC look better than with other treatments, due to the simple treatment with a nasal canula. However, it should be cautioned that hypoxia could occur if the cannula comes out of the nostrils. Level 2C evidence of HFNC has been provided for respiratory failure[30] with sepsis in infants. Clinically, HFNC is thought to provide respiratory management between that of oxygen therapy and NPPV.

Summary

We have described recent respiratory management strategies, including evidence based on the Berlin Definition used for ARDS. We hope that this will contribute to everyday clinical procedures used for treating respiratory failure patients.

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CTで術前診断し得た子宮広間膜裂孔ヘルニアの１例

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（平成26年３月14日受理）

抄　　録

腹部のイレウスの原因に内ヘルニアがあるが、術前に診断することは難しい。今回、われわれは、比較的まれな疾患である子宮広間膜裂孔ヘルニアをCTで術前診断して、手術を行った１例を経験したので報告する。症例は59歳、女性。下腹部痛を主訴に外来を受診した。腹部CT検査で、骨盤内に限局した小腸のループ形成がみられた。子宮と直腸を右側に圧排しており，子宮広間膜裂孔ヘルニアと診断した。外科に入院となり、緊急手術を施行した。開腹したところ、小腸が左子宮広間膜裂孔に入り込んで内ヘルニアとなっていた。嵌頓を解除した後、子宮広間膜に直径約２cmの裂孔を確認し、縫合閉鎖した。嵌頓した小腸は部分切除を行った。本疾患の診断にはCTが有用であり、その所見としては、骨盤内の限局した小腸のループ像と子宮および直腸の圧排が特徴的である。開腹歴のない女性のイレウスにおいては、本疾患も念頭において診療に当たるべきであると考えられた。

キーワード：子宮広間膜裂孔ヘルニア、小腸イレウス

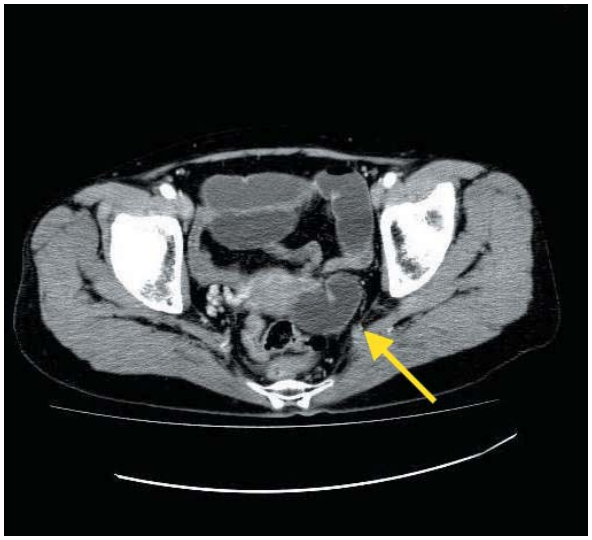
緒　　言

腹腔内の内ヘルニアはイレウスをきたすことが多いが、術前診断に苦慮することも多い。今回、われわれは、比較的まれな疾患である子宮広間膜裂孔ヘルニアをCTで術前診断して、手術を行った１例を経験したので報告する。

症　　例

症例：59歳、女性
主訴：下腹部痛
既往歴：特記事項なし
妊産歴：３妊３産　すべて3800ｇ台の児を自然分娩
現病歴：2012年12月の朝から下腹部痛を自覚し、次第に増強してきたため、救急外来を受診した。
現症：身長165.0cm、体重60.0kg、血圧156/96mmHg、脈拍67/分、整、体温36.7℃、下腹部を中心に強い圧痛あり、苦悶様顔貌。筋性防御なし。手術瘢痕なし。リンパ節腫脹なし。
血液生化学所見：血算、生化学とも異常所見なし。血液ガス分析でもアシドーシスは見られなかった。
腹部CT所見（図１）：骨盤内に拡張した小腸像があり、左卵巣動静脈の尾側でループ形成がみられた。子宮と直腸を右側に圧排しており、子宮広間膜と裂孔を直接確認はできなかったが、子宮広間膜裂孔ヘルニアと診断した。
経過：以上の所見から、左子宮広間膜裂孔ヘルニアと診断し、腹部所見が強かったことから、緊急手術を施行した。
手術所見（図２）：下腹部正中切開で開腹したところ、小腸の拡張がみられ、回盲部から55cmの位置で、小腸が左子宮広間膜に前方から後方に入り込んで内ヘルニアとなっていた。腸管を引き出し、左子宮広間膜に前葉と後葉をともに貫く直径約２cmの裂孔を確認して、縫合閉鎖した。右側の子宮広間膜には裂孔は見られなかった。嵌頓した小腸は色調が悪く、約10cmの部分切除を行った。
術後経過：経過は良好で、第３病日に食事を開始し、第７病日に退院となった。現在まで再発を認めていない。

a



b

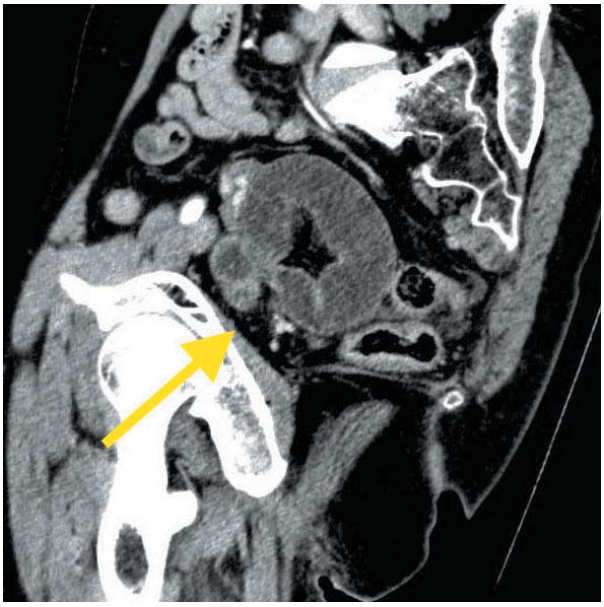
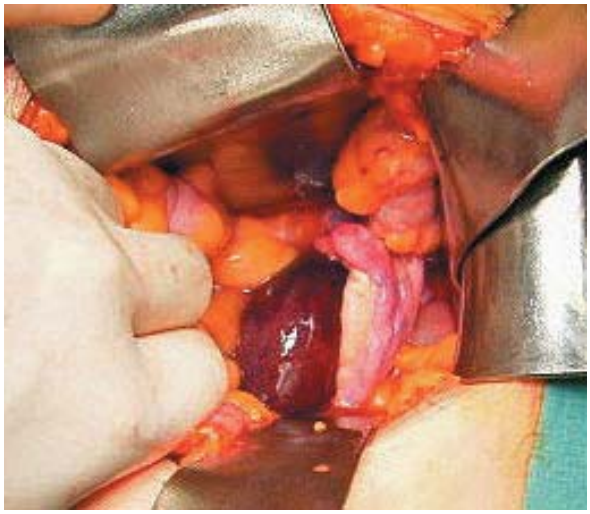


図１．骨盤内に限局した小腸の拡張したループ像がみられ、子宮と直腸を右側に圧排しており子宮広間膜裂孔ヘルニアと診断した。

a



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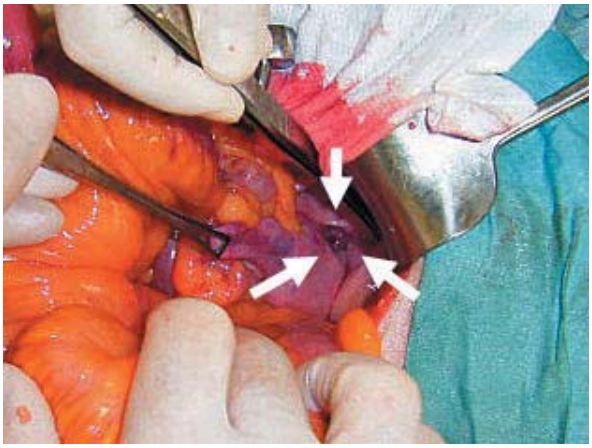

図２．a）回盲部から55cmで、小腸が嵌頓して内ヘルニアになっていた。
b）直径約２cmの左子宮広間膜裂孔（矢印）を確認して閉鎖した。

考　　察

内ヘルニアはイレウス全体の１％以下とされているが、子宮広間膜裂孔ヘルニアは異常裂孔ヘルニアに属し内ヘルニアの0.016%、異常裂孔ヘルニアの１－４％と比較的まれな疾患である[1)]。子宮広間膜裂孔ヘルニアは、子宮広間膜の欠損による異常裂孔をヘルニア門として生じる内ヘルニアである。本症の画像診断において腹部CTが有用であり、Suzukiら[2)]はその所見としては①Douglas窩内に存在する嵌頓した小腸ループ像、②小腸ループによる子宮・S 状結腸・直腸の偏位・圧排像、③怒張した腸間膜血管の患側への集中像を報告している。子宮広間膜は薄い間膜であるため、

CTで直接子宮広間膜と裂孔を確認することは困難であるが、自験例においては、骨盤内に嵌頓した小腸ループ像と、それによる子宮と直腸の圧排像の所見が確認され、術前診断に至っている。

吉村ら[3]は本邦における子宮広間膜裂孔ヘルニアの報告例87例について検討し、術前診断された例はわずか10.4％であったと報告している。1999年以前の正診率が4.5％であったが、2000年以降の正診率は16.2％とやや上昇しており、CT画像の進歩によるものと考察している。また、Kosakaら[4]は、近年のmulti-detector CT（MDCT）とmulti-planar reformatting（MPR）のようなCT機器の進歩により、術前診断能が向上していると報告している。

Huntは[5]、本症を子宮広間膜の前葉および後葉を貫通するfenestra typeと、前葉または後葉の間隙のみを貫くpouch typeに分類している。その成因としては①先天性異常、②妊娠、分娩、手術、重労働等の外力に伴う裂傷によるもの、③加齢に伴う広間膜の弾力性の低下によるもの、④骨盤内の炎症後の組織の癒着や歪みによるものをあげている。谷岡ら[6]は、本邦報告例90例の検討で、79例（88％）はfenestra typeであったと報告している。

自験例は、子宮広間膜の前、後葉をともに貫くfenestra typeであった。3800ｇ台の大きめの児を３回分娩しており、妊娠、分娩の影響による可能性を疑うが、明らかではない。

自験例では左側のみに裂孔がみられ、右側は正常であったが、両側に異常裂孔をみとめた報告もあり[7]、対側の確認は必ず行うべきであると考えられた。

本邦において、90例を超える本症の報告例があるが、本症を保存的加療によって軽快した報告例は見られなかった。術前にイレウス管を挿入し、減圧することで腹腔鏡手術を行った報告例も散見される[1),8),9),10)]。赤松ら[9]はイレウス管等で十分に腸管内減圧が達成できていれば、慎重な手術操作による腹腔鏡手術も可能になり、加えて術前診断がなされていれば腹腔鏡下手術が完遂できる可能性は高まると報告している。自験例では、腹部の圧痛が強く、早期の手術が望ましいと考えられ、受診した当日に開腹手術を選択した。CTにより、術前診断が得られていたことから、下腹部の小開腹のみで完遂することができた。結果として、腸管切除を要する状態であったため、イレウス管による減圧を待たずに手術を行うことで、良好な経過を得ることができた。

結　　語

比較的まれな疾患である、子宮広間膜裂孔ヘルニアをCTにより術前診断して早期手術を行い、良好な経過を得ることができた１例を経験したので報告した。本疾患の診断にはCTが有用であり、その所見としては、骨盤内の限局した小腸のループ像と子宮および直腸の圧排が特徴的である。開腹歴のない女性のイレウスにおいては、本疾患も念頭において診療に当たるべきであると考えられた。

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Yamagata Med J 2014 ; 32(2) : 77-80

A case of internal herniation through a broad ligament defect of uterus diagnosed preoperatively by computed tomography

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ABSTRACT

We report a case of internal herniation through a broad ligament defect of uterus diagnosed preoperatively by computed tomography (CT). A 59-year-old woman presenting with lower abdominal pain was admitted to our hospital. Abdominopelvic CT revealed a dilated small intestinal loop to the left of the uterus and the displacement of the uterus and rectum toward the right side. We diagnosed the patient with internal herniation through a broad ligament defect of uterus and performed emergency surgery. A small intestinal segment was incarcerated in the left uterine broad ligament. Therefore, we released the herniation then detected a defect of the uterine broad ligament, which was about 2 cm in diameter. We sutured the defect and partially resected the small intestine. In this case, CT was useful to diagnose this condition. The characteristic CT appearances of this disease are localized and dilated intestinal loops in the pelvic cavity, and intestinal loops compressing the rectum and the uterus. Therefore, we recommend that this condition be kept in mind in case of female patients presenting with ileus without prior laparotomy.

Key words : broad ligament hernia, small intestine ileus

Yamagata Med J 2014 ; 32(2) : 81-83

A case of major depressive disorder accompanied by multiple somatic delusions

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(*Accepted April 22, 2014*)

ABSTRACT

About 15% of cases of major depressive disorder (MDD) are accompanied by psychotic features, typically as delusions of guilt and hypochondriacal delusions. We report the case of a 55-year-old woman with MDD accompanied by delusions of infestation and body odor, which are characteristic of delusional disorder somatic type (DDST). She developed a major depressive episode that gradually deteriorated. Four months later, she felt that "some liquid" was welling out from skin of her palms, soles and face, and also that she was emitting a foul odor from her body. Treatment with paroxetine at 40 mg/day and olanzapine at 5 mg/day resolved somatic delusions, but some depressive symptoms remained. After addition of mirtazapine 30 mg/day, depressive symptoms were completely resolved. The present report definitively shows that MDD can accompany multiple somatic delusions typically observed in DDST.

Key words : major depressive disorder; somatic delusion; delusional disorder somatic type

Introduction

More than half of patients with delusional disorder somatic type (DDST), which is characterized by somatic delusions such as infestation delusion and delusion of body odor, develop secondary depression[1]. In contrast, only about 15% of cases of major depressive disorder (MDD) are accompanied by psychotic features, typically as delusions of guilt and hypochondriacal delusions[2]. We report herein the case of a patient with MDD accompanied by multiple somatic delusions.

Case Report

The patient was a 55-year-old woman. She consented to this report of her clinical course. Her social and occupational histories were normal. Figure 1 shows the clinical course. In October 2009, she developed depressive mood, diminished interest and pleasure, loss of energy, difficulty concentrating, insomnia, and feelings of worthlessness and guilt. These depressive symptoms gradually progressed. From February 2010, she felt that "some liquid" was welling out from the skin of her palms, soles and face. She felt that her skin was slippery, sticky and becoming thinner. Independent of this feeling, she also felt that she was emitting a foul odor from her body. She demanded that her family members "Burn me to death, because I am emitting a bad smell". Finally, she tried to drown herself in the river, and was admitted to a psychiatric hospital. Trazodone at 100 mg/day and olanzapine at 5 mg/day for three weeks proved ineffective, and she was not eating at all. She was therefore referred to our ward in March 2010.

On examination, she had severe depressive symptoms and multiple somatic delusions, but no other psychiatric symptoms. No hallucinations, disorganized speech, disorganized or catatonic behavior, affective flattening, or alogia were observed. Blood testing and magnetic resonance imaging showed no abnormalities. MDD with psychotic

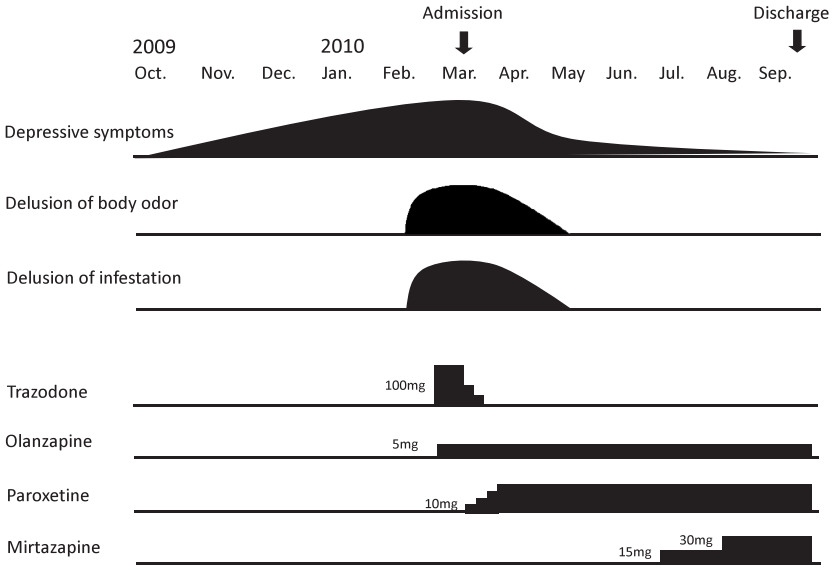

Figure 1. Clinical course of the present case.

features was diagnosed in accordance with the Statistical Manual of Mental Disorders (DSM-IV-TR)[3]. Trazodone was switched to paroxetine at 10 mg/day, while olanzapine was continued. After 4 weeks, the dose of paroxetine was increased to 40 mg/day. Depressive symptoms and somatic delusions then started improving gradually. By day 50, somatic delusions had resolved completely, and she stated that "My depressive symptoms have recovered about 70%". On day 98, mirtazapine at 15 mg/day was added to treat residual loss of energy, and the dose was increased to 30 mg/day after 4 weeks. By day 130, depressive symptoms had resolved completely.

Discussion

The patient in the present case was convinced that liquid was welling out from her skin, which was considered as a delusion of infestation or emanation. She also had a firm belief that she was emitting a foul odor from her body; that is, delusion of body odor. These somatic delusions were preceded by depressive symptoms, and resolved before the disappearance of the depressive symptoms, and so existed only during the major depressive episode. The present report therefore definitively shows that MDD can accompany somatic delusions typically observed in DDST, such as infestation delusion and delusion of body odor. In the literature, another case report has described MDD accompanied by a somatic delusion[4]. However, the somatic delusion in that case was confined to a single theme, with the patient believing that his hands and feet were shorter than usual. This report is thus the first to describe MDD accompanying multiple somatic delusions.

The mechanisms underlying this phenomenon remain unclear, but one possibility is that the somatic delusions developed as an amalgam of feelings of guilt[2] and altered bodily sensations[5] during a major depressive episode. That is, feelings of guilt may lead to misinterpretation of the gestures and comments of others as signs of criticism directed to the self, while unusual bodily sensations may lead to harboring an idea that something is wrong with one's body. A patient with both feelings of guilt and unusual bodily sensations may thus come to believe that they are annoying others by emanating something unpleasant from their body.

In the present case, a switch from trazodone to paroxetine was made due to the ineffectiveness of trazodone and the possible antipsychotic effect of paroxetine[6]. The addition of mirtazapine to paroxetine was because of the reported efficacy of this combination therapy[7]. The present report suggests

the usefulness of the combination of paroxetine, mirtazapine and olanzapine for MDD accompanied by multiple somatic delusions, but this should be confirmed in further studies.

Disclosure of interests

All authors declare that they have no conflicts of interest.

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第30回山形電気生理研究会抄録

Abstracts of the 30th Meeting of Yamagata Electrophysiological Research Group

平成25年12月20日（金）　山形大学医学部　第1 講義室

演題

1．「EMG-Averaging法を用いたヒト橈側手根屈筋から腕橈骨筋への抑制の解析」

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post-stimulus time histogram (PSTH) 法を用いた解析から、ヒト橈側手根屈筋（FCR）と腕橈骨筋（BR）間のⅠ群線維を求心性線維とする寡シナプス性抑制性脊髄反射回路（抑制）の存在が報告されている。しかし、PSTH法は個々の運動ニューロンに対する反射の効果を調べるものであり、同抑制の運動ニューロン群（MNP）に対する効果を調べた報告はない。また、Ⅰ群線維が筋紡錘からのIa線維かGolgi腱器官からのIb線維かの鑑別もなされていない。本研究ではEMG-Averaging（EMG-A）法を用いて、先ずFCRからBRへの抑制のMNPに対する効果について調べた。対象は健常者10名（男性８名、女性２名、21－29歳）の右上肢とした。被験者にBRの最大随意収縮で得られる積分筋電図の振幅（100%）の10%の振幅を示す等尺性収縮を持続させ、その時のBRのEMG-Aを記録しながら、条件刺激としてFCRの電気刺激（ES）と機械的叩打刺激（MS）を行った。また、同じ刺激によりFCRに誘発されるHoffmann（H）波とTendon（T）波も記録した。全ての被験者で、ESとMSによりEMG-Aにそれぞれ潜時16.4±1.4 ms（平均値±標準偏差）と19.9±1.8 ms、持続時間4.8±1.0 msと4.6±1.1 msの谷（抑制、ESで11.7±2.1%、MSで12.3±1.5%の振幅の減少）が誘発された。ESとMSによる抑制の潜時差は、同じ刺激で誘発されるH波とT波の潜時差とほぼ同じであった。以上より、FCRからBRへの抑制のMNPに対する効果が示された。また、この抑制の求心性線維としてIa線維が示唆された。

2．「インスリンによるQ1/E1電流の抑制にPIP$_2$が関与する可能性：Ci-VSPを利用した検証」

大島真悟，永澤悦伸，呉明華，野呂田郁夫，石井邦明（山形大学医学部薬理学講座）

【背景】我々は以前、インスリンの急性投与がKCNQ1/KCNE1（Q1/E1）電流を抑制し、そのシグナルにPI3キナーゼが関与する可能性を報告した。Q1/E1電流の活性にはPIP$_2$（PI3キナーゼによって減少すると考えられる）が必要である事が知られている。【目的】インスリンによるQ1/E1電流の抑制に、PIP$_2$が関与している可能性について検討する。【方法】アフリカツメガエル卵母細胞の発現系を用いて、Q1/E1電流を測定した。また、細胞内PIP$_2$を低下させる目的で、電位感受性ホスファターゼCi-VSPを用いた。さらに、Ci-VSPのホスファターゼ活性変異体であるC363S、G365Aを用いた検討も行った。【結果・考察】インスリン（10^{-6M}）によるQ1/E1電流の抑制は約30%であった。Ci-VSPと共発現した際には、脱分極パルスによってQ1/E1電流が約30%低下したが、それは細胞内PIP$_2$の減少によるものと思われた。その後のインスリン（10^{-6M}）投与による電流抑制は約15%と減弱しており、インスリンの作用にPIP$_2$が関与する可能性が考えられた。また、C363S、G365Aを用いた結果も、それを支持するものであった。

3．「房室結節リエントリー性頻拍と傍His束起源心房頻拍のdouble tachycardiaを呈し、異なる２種類のアプローチでカテーテルアブレーションを行い根治した一例」

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電気生理検査（EPS）により、不整脈のメカニズムを詳細に把握することが可能になり、高周波カテーテル心筋焼灼術（ABL）により根治可能な時代になった。今回、２種類の上室性頻拍（SVT）が併存し、頻拍を繰り返した稀有な一例を経験した。EPSによって正確な診断に至り、異なる２種類のアプローチでABLを行って根治できたため報告する。症例は62歳男性。ホルター心電図で心拍数120 bpmのSVTを頻回に繰り返し、総心拍のうち77.5%が頻拍であった。EPSでは、頻回の上室期外収縮（APC）からSVTが誘発された。SVTの原因は①房室結節リエントリー性頻拍と診断し、右房側からABLした。①の根治後は洞調律を維持できるようになったが、もう一つのSVTが容易に誘発された。頻回のAPCの原因は②His束近傍起源の心房頻拍であった。②の起源は正常伝導路が近く、右房側からの通電が困難であったため、大動脈弁無冠尖より通電して②の根治に成功した。不整脈の開始の原因になる②と、頻拍の維持の原因になる①が併存したため、SVTを繰り返したと考えられた。①②ともに根治することで頻拍は消失した。

4．「代謝型グルタミン酸受容体活性化で誘導する海馬ＣＡ１ニューロンのシナプス可塑性への細胞外ATPの関与－ATPを介するグリアとニューロン機能のcross-talkについて－」

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海馬ニューロンにおいて、ATP（adenosine 5'-triphosphate）とグルタミン酸の放出には、シナプス入力によるシナプス前終末からと、周囲のグリア細胞からのものがある。放出されたグルタミン酸はシナプス後細胞のNMDA（N-methyl-D-aspartate）型受容体ないし代謝型受容体を活性化し、ATPは基質として細胞外リン酸化に作用してこれらグルタミン酸受容体の活性化を増強する。今回我々は、海馬CA1シナプスへの入力刺激を化学物質の投与で置換して誘導したシナプス可塑性について報告する。20秒に一回のモニター電気刺激をNMDAで置換しながらATPないし代謝型グルタミン酸受容体作動薬を海馬スライスに潅流すると、興奮性シナプス後電位（field EPSP）は増大し長期増強（LTP）が誘導された。モニター電気刺激を止めてATPおよび代謝型グルタミン酸受容体作動薬を潅流するとfield EPSPで長期抑圧（LTD）が誘導された。結果、シナプス刺激で放出されるATPはNMDA型受容体をリン酸化してLTP誘導を促進し、周囲のグリアから放出されるATPは代謝型グルタミン酸受容体をリン酸化してLTD誘導を促進することが示唆された。

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実験動物セミナー第24回研究成果発表会抄録

Abstracts of the 24th Seminar of Laboratory Animal Center

2013年12月18日　山形大学医学部視聴覚室

【一般講演１】

血管に対するトリグリセリド作用の基礎的検討

○阿曽吉孝*，山下真里奈**，小野真太郎***，阿部陽平****，
片野由美*，石幡明*（*山形大学医学部看護学科（病態機能），**総合南東北病院，***秋田大学医学部附属病院，****山形大学大学院医学系研究科）

【背景・目的】高中性脂肪血症の血管に与える影響については諸説がある。特に高中性脂肪血症が内皮機能に与える影響については不明な点が多い。そこで、本研究では高中性脂肪血症が血管の弛緩および収縮能力に与える影響をラット摘出大動脈標本を用いて検討した。

【研究方法】実験は山形大学医学部動物実験指針を遵守して行った。５～６ヵ月齢の雄性Fischer344から胸部大動脈を摘出し、内皮無傷標本および除去標本を作製した。標本をコントロール群と高中性脂肪血症（イントラファット1.5%）処置群に分けた。標本を１時間安定させてからアセチルコリン、ニトロプルシドによる弛緩反応、フェニレフリンおよびアンジオテンシンIIに対する収縮反応を測定した。

【結果】内皮無傷標本では高中性脂肪血症処置により、低濃度アセチルコリンに対する弛緩反応が減弱した。また、フェニレフリン累積投与、アンジオテンシンII投与による血管収縮反応は有意に増強した。一方、内皮除去標本ではニトロプルシド、フェニレフリン、アンジオテンシンIIいずれに対しても血管収縮反応に有意差は見られなかった。

【考察】高中性脂肪血症は血管内皮機能障害をおこすことで弛緩反応の減弱、収縮反応の増強を惹起することが示唆された。

【一般講演２】

The HECT-Type Ubiquitin E3 Ligase ITCH Interacts with Thioredoxin-Interacting Protein and Ameliorates Reactive Oxygen Species-Induced Cardiotoxicity

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Background: HECT-Type ubiquitin E3 ligase ITCH is an enzyme which plays a pivotal role in posttranslational modification by ubiquitin proteasomal protein degradation. Thioredoxin-interacting protein (TXNIP) is a negative regulator of thioredoxin system, which is an endogenous reactive oxygen species (ROS) scavenger. In the present study, we focused functional role of ubiquitin E3 ligase ITCH and its interaction with TXNIP to elucidate the mechanism of ROS-induced cardiotoxicity, such as doxorubicin (Dox) and hydrogen peroxide (H_2O_2).

Methods and Results: We confirmed protein interaction between TXNIP and ITCH by immunoprecipitation in cardiomyocyte. Overexpression of ITCH increased proteasomal TXNIP degradation and augmented thioredoxin activity, which may inhibit ROS-induced cardiomyocyte apoptosis in ROS-induced cardiotoxicity. Conversely, knockdown of ITCH by siRNA inhibited TXNIP degradation and demonstrated a subsequent increase in cardiomyocyte apoptosis. Next, we generated cardiac-specific overexpression of ITCH transgenic mouse (ITCH-Tg mice). The myocardium of ITCH-Tg mice had significantly lower expression levels of TXNIP than wild type littermates. ITCH-Tg mice restored an apoptosis in cardiac cells and cardiac dysfunction compared with wild type littermates after Dox injection. Kaplan-Meier analysis revealed that ITCH-Tg mice had higher survival rate than wild type littermates after Dox injection.

Conclusion: We demonstrated for the first time that ITCH targets TXNIP for ubiquitin-proteasome degradation in cardiomyocyte and ameliorates ROS-induced cardiotoxicity through thioredoxin system.

【一般講演３】

ウサギ盲腸内容物を用いた微生物発酵調節因子の探索

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【目的】腸内発酵産物である短鎖脂肪酸（SCFA: short-chain fatty acid: 酢酸、プロピオン酸、n-酪酸）は吸収・輸送されたり、受容体に結合することで認識され、上皮形態を発達させることが示されている。そこで、天然植物抽出物質Xが腸内発酵に及ぼす影響を、ウサギ盲腸内容物を用いた*in vitro*バッチ培養法によって検討した。

【方法】日本白色種ウサギから採取した盲腸内容物を緩衝液で希釈後、２重ガーゼで濾過してイノキュラムとして供試した。イノキュラム、基質および抽出物質Xを加え撹拌し、100%N_2ガスで封入後、37℃ で24ｈ振とう培養した。培養液中の有機酸濃度をHPLC（BTBポストカラム法）にて解析した。

【結果】対照区と比較して高濃度の抽出物質Xは一次発酵産物であるコハク酸濃度を有意に減少させ、逆に乳酸濃度を有意に増大させた。また、二次発酵産物であるSCFA（酢酸、プロピオン酸およびn-酪酸）濃度を有意に減少させた。本研究から、抽出物質Xは高濃度において盲腸微生物発酵を調節することが示された。今後は、食品添加物としての活用を目指して*in vivo*での効果を検討したい。

【一般講演４】

ラット行動学習実験における慢性アルコール投与の影響

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アルコールの慢性投与が、記憶に及ぼす影響（記銘、想起、忘却過程）において不明な点が多く、明らかにされていない。本研究では、アルコールの慢性投与が記憶に及ぼす影響、特に記憶の記銘、想起、忘却においてどのように影響するかについて調べるため古典的条件づけを用い、さらに、運動の協調性を調べるためにRota-rod testを用いて検討した。

Rota-rod testは回転棒上に被験体を載せてから落下するまでの時間や一定時間内に落下した回数を計測することにより運動協調性障害の程度を評価した。

また、学習や記憶の形成のプロセスを検討するためそれぞれの記憶過程の分離に有効的な手法として古典的条件づけがある。古典的条件づけは、

条件づけ、消去過程等のセッションが分離しているため、記憶形成のプロセスの分離が容易であることから古典的条件づけの一種である恐怖条件づけを用いて、記憶の記銘・想起に重点を置いて検討した。

Rota-rod testでは運動協調障害や運動学習の評価を用いて運動学習を検討した。アルコールの慢性的な摂取により、運動学習や平衡感覚、運動協調性にアルコールが影響を及ぼしている可能性がある。恐怖条件づけでは、記憶の獲得と想起のメカニズムについて検討した。条件づけにおいて、群における主効果では有意差が認められず、セッションにおける主効果では有意差が見られ、試行回数が増加するごとに恐怖記憶の獲得ができたことより、恐怖記憶の獲得にアルコールの慢性投与の影響はなかった。急性的なアルコール投与で記銘が低下するという報告があるが、慢性的なアルコール投与では恐怖記憶の記銘ができることが示唆された。消去手続きでは、セッションにおける主効果では試行回数が増すごとにFreezingの割合が減少する傾向が見られた。消去手続き１日目（EXT1）では、Control群に比べてAlcohol群が低い傾向が見られたことから、恐怖記憶の想起に影響があったといえる。

【一般講演５】

T細胞特異的IL-21 isoform過剰発現マウスを用いた新たなアナフィラキシーモデルの確立

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【背景】免疫の過剰応答は、免疫疾患を引き起こす重要な問題の１つである。その中でも、アレルギー性疾患は多様な病態で発症し、その患者も極めて多い。特に、食物アレルギーは、人口の２～６％にのぼり、死に至ることもある重要な疾患である。食物アレルギーには、IgE依存性の他、IgE非依存性の応答が存在するなど、未だに不明な点が多い。

一方、IL-21は、NKT, Th17, 濾胞ヘルパーT細胞から産生されるサイトカインであり、T細胞依存性のB細胞分化機構に重要な役割を担っている。IL-21の生体への投与により、IgGへのクラススイッチが亢進し、一方、IgE産生が抑制されることが知られている。また、抗原感作時にIL-21を投与すると、やはりIgE産生が抑制され、アレルギー反応が抑えられる事が報告されている。

【目的】我々は、IL-21のalternative splicing variantである IL-21 isoformを同定し、解析を進めている。山形大学医学部附属遺伝子実験施設にて、IL-21 isoformをT細胞特異的に過剰発現させたマウス（IL-21iso-Tg）の作出に成功し、これを用いて生体内でのIL-21 isoformの作用を解析してきた。IL-21を投与したマウスと同様に、このマウスでも、血中のIgG量の増加と、IgE量が低下する傾向が認められた。そこで、IL-21iso-TgにおいてもIgG産生亢進・アレルギー反応抑制が生じると予想し、IL-21 isoformの機能解析を試みた。

【方法】オブアルブミン（OVA）を腹腔投与して抗原感作し、３週後にOVAを腹腔または経口経路にて負荷投与した。負荷投与後、体温測定とアナフィラキシースコア採点を行った。また、血中のOVA特異抗体価の測定をELISA法にて行った。

【結果】予想に反し、IL-21iso-Tgでは、野生型マウス（WT）と比較し、負荷投与後１時間以内に体温の低下・死亡に至る個体も認められ、重篤なアナフィラキシー反応であると考えられるマウスが続発した。更にこれらの個体では、投与経路・アジュバントの違いに関わらず、小腸に限局された過剰な充血が認められた。そこで、IgG産生亢進によるアレルギーを想定し、IL-21iso-Tgの血清中の抗OVA抗体の抗体価を測定した。しかし、全体の抗体価はむしろWTより低く、クラス別でもIgG, IgMの量も野生型と同程度であった。

【考察】このIL-21iso-Tgのアナフィラキシー反応は、IgGやIgEを介さない、小腸に限局される病態である可能性がある。これらのことから、IL-21iso-Tgは、IgE非依存性食物アレルギーモデルマウスとして、食物アレルギー発症幾序の解明と新たな治療法の開発に貢献できると考えている。今後、IL-21 isoformの腸管免疫への作用につい解析することで、新たなアトピー素因が同定されるのではないかと期待している。

【一般講演６】

A549非小細胞肺癌細胞の腫瘍創始能維持におけるJNKの特異的な役割

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c-Jun NH_2-terminal kinase（JNK）は近年様々な癌種にて活性の亢進が報告されている。非小細胞肺癌（NSCLC）もJNK活性亢進が認められる悪性腫瘍の一つであるが、NSCLCにおけるJNKの役割、特に*in vivo*におけるその役割については未だ不明な点が多い。本研究において我々は、NSCLC細胞株であるA549細胞においてJNKが腫瘍創始能の維持に重要な役割を果たしていることを見出したので報告する。

A549細胞を*in vitro*において可逆的JNK阻害剤であるSP600125の存在下に培養すると細胞増殖が速やかかつ強力に抑制されたが、予めA549細胞をヌードマウスの皮下に移植し腫瘍体積が200 mm^3を超えた時点でSP600125 を10日間連続で腹腔内投与しても腫瘍増大に対して有意な影響は認められなかった。しかしながら、全く同じプロトコルにてSP600125を腹腔内投与したマウスから薬剤投与終了後皮下腫瘍を取り出し腫瘍細胞の再移植実験を行ったところ、SP600125投与群由来の腫瘍細胞移植では明らかに腫瘍形成が抑制された。また、A549細胞をヌードマウスの皮下に移植した翌日からSP600125を腹腔内投与すると、コントロール群と比較してSP600125投与群の腫瘍形成が抑制された。さらに、*in vitro*で予めSP600125処理もしくはJNK遺伝子をsiRNAにてノックダウンしたA549細胞を各々ヌードマウスの皮下に移植した場合も、SP600125処理群およびJNK遺伝子ノックダウン群共々 *in vivo* SP600125投与実験と同様コントロール群に比して腫瘍形成が抑制された。

これらの結果は、*in vivo*においては、腫瘍細胞自身が発現するJNKの活性が*in vitro*とは異なって細胞の増殖制御そのものには関与せず、むしろ腫瘍細胞の腫瘍創始能の維持に重要な役割を果たしている可能性を示唆している。

【一般講演７】

チタン貪食細胞におけるTLR2及びNLRP3反応系の分子動態解析

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【目的】人工股関節全置換術における無菌性の緩みは未だ克服されていない合併症の一つである。摺動面由来のインプラント摩耗粉はマクロファージに貪食され、異物肉芽腫反応が引き起こされる。それに伴う催炎性サイトカイン過剰産生は、骨溶解を惹起し人工関節の緩みを引き起こす。マクロファージの異物認識反応にはToll様受容体（Toll-like receptor: TLR）やNOD（Nucleotide oligomerization domain）様受容体（NOD-like receptor: NLR）などのパターン認識受容体が関与する。無菌性弛緩人工関節の病態形成にもTLR反応系の一部が関与することが示され、NLR with a pyrin domain 3（NLRP3）反応系が緩みの病態形成に関与する可能性も示唆されている。しかし無菌性弛緩人工関節におけるTLR系の詳細な役割やNLRP3の関与については不明のままである。異物を貪食したマクロファージにおけるTLRとNLRP3を介した催炎性サイトカインの動態について検討した。

【方法】C57BL/6、雌、８～12週齢のマウスより採取した下肢骨から、骨髄由来細胞を培養した。培養細胞は蛍光二重染色、flow cytometoryを用いてマクロファージであることを確認した。マクロファージをチタン粒子（Ti）とリポテイコ酸（LTA）付着チタン粒子（Ti+LTA）で刺激し、TLR2、

NLRP3、TNF-α、IL-1βについてmRNA発現量、各受容体膜表面タンパク発現量、培養上清におけるサイトカイン分泌量を比較検討した。
【結果】Ti、Ti＋LTA群は非刺激群に比べ、TLR2、NLRP3のmRNA、タンパク発現量、およびTNF-α、IL-1βのmRNA発現量が増加した。しかしTNF-α分泌量は増加したが、IL-1βは検出されなかった。
【考察】マクロファージはインプラント摩耗粉の貪食によりTLR2およびNLRP3反応系を介して催炎性サイトカインを分泌し、病原体関連分子パターンにより炎症反応を増強、遷延する可能性が示唆された。IL-1βの不検出は急性炎症を伴わない弛緩人工関節周囲組織の病態に合致した反応と考えられるが、今後、細胞内IL-1βの動態について検討を行う必要がある。

【一般講演８】

ビタミンＣとチオール化合物はアセトアミノフェンの障害作用から肝臓を保護している

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宮田哲***，佐藤英世****，藤井順逸*（*山形大学大学院医学系研究科生化学分子生物学，**産業医科大学第二病理学，***大阪厚生年金病院内科，****山形大学大学院農学系研究科食品応用生命科学）

霊長類などの一部を除いて、ほとんどの哺乳類はグルコースから多段階の反応を経てアスコルビン酸（ビタミンＣ）を合成できる。Aldo-keto還元酵素遺伝子ファミリーの一つAKR1Aはアスコルビン酸合成反応に関わるため、AKR1A欠損（KO）マウスでは野生型の１割程度しかアスコルビン酸を合成できない。一方シスチンはxCTによって取り込まれた後に細胞内でシステインに還元され、グルタチオンなどの合成に用いられる。本研究では、AKR1A-KOマウスとxCT-KOマウスを用いてアセトアミノフェンの肝障害モデルを作製し、アスコルビン酸とチオール化合物が肝障害の誘発にどのように関わるか検討した。さらにアスコルビン酸とチオール化合物のレドックス反応における相互作用を調べるために、AKR1AとxCTをともに欠く二重欠損（DKO）マウスを作製して、あわせて検討した。

まずAKR1A$^{-/-}$マウスとxCT$^{-/-}$マウスを交配してF$_1$（AKR1A$^{+/-}$:xCT$^{+/-}$）マウスを作製し、続いてF$_1$マウスどうしを交配したが、DKOマウスは産まれなかった。そこでアスコルビン酸（1.5 g/L）を投与したところDKOマウスが得られ、持続投与することでDKOマウスどうしの交配でも繁殖が可能となった。

次にWT, xCT-KO, AKR1A-KO, DKOマウスに対するアセトアミノフェンの肝障害について検討した。アセトアミノフェンを腹腔内投与した後、血清ALTとBUN量を測定し、肝障害の程度を推測すると同時に、肝臓の病理学的解析を行った。通常用いられる300 mg/kgアセトアミノフェンの投与では、１日目にいずれの遺伝子型マウスにおいても血清ALTが増加し、３日目にはすべて死亡した。投与量を200 mg/kgにしたところ、WTマウスではわずかに肝障害を認めただけだったが、xCT-KO、AKR1A-KO、DKOマウスでは血清ALTが増加し、激しい肝障害を示した。３日目には、WTマウスは回復していたが、xCT-KOマウスの半数とDKOマウスについてはすべて死亡した。このアセトアミノフェンに対する高い感受性は、アスコルビン酸を投与したAKR1A-KOマウスでは認められなかった。

以上の結果は、アスコルビン酸がアセトアミノフェンによる肝障害からの保護にとって重要なことを示している。また、xCT-KOマウスではシステインの供給量が減る結果、グルタチオン合成量が低下し、アセトアミノフェンに対する感受性が増したと考えられる。本研究により、アスコルビン酸やチオール化合物によってアセトアミノフェンによる肝障害を軽減できる可能性が示唆された。

【一般講演９】

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都合によりにより演題名および抄録の掲載は控えさせていただきます。

査読の御礼

第32巻の発刊に当たっては、以下の方々に査読していただきました。ご多忙中にも拘わらず熱心に査読いただき、誠にありがとうございました。厚く御礼申し上げます。

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（50音順・敬称略）

FACULTY OF MEDICINE
YAMAGATA UNIVERSITY

山形大学紀要（医学）投稿規程

紀要（医学）編集委員会
平成11年３月２日制定
平成12年１月７日改正
平成12年９月５日改正
平成14年11月12日改正
平成16年４月１日改正
平成17年４月19日改正
平成19年３月６日改正
平成20年７月３日改正
平成23年４月１日改正
平成24年２月21日改正

１．名称

本誌の名称は、「山形大学紀要（医学）[Bulletin of Yamagata University（Medical Science）]」（ISSN；0288-030X）とし、文献引用に際しては、通称「山形医学（Yamagata Medical Journal；略称Yamagata Med J）」を用いてもよい。

２．掲載記事および発行

本誌は医学医療の進歩発展に貢献する論文で他誌に発表されていない原著、総説、症例報告、CPC、学会抄録、医学部における学術講演会の要旨等を掲載し、年２回の発刊とし、各々の原稿の締切日は３月１日及び９月１日とする。

３．投稿資格

投稿者は、原則として本学教職員、定年退職した者、現在本学に相当年数勤務している非常勤講師、本学の大学院研究科学生及び研究生とする。

４．掲載の可否

原稿の採否並びに掲載号については山形大学紀要（医学）編集委員会（以下、委員会）に一任のこととする。原著論文については、編集委員会は２名の査読者に審査を依頼する。審査の結果必要ならば、編集委員会は原稿の修正等を求めることができる。

５．投稿論文の提出

本誌への投稿の際には次のものを揃えて、委員長宛に提出する。

１）手紙
２）表紙
３）抄録
４）本文
５）文献
６）表・図版とその説明
７）邦文論文にあっては欧文抄録

表紙を１頁、表・図版とその説明を最後として頁を加える。手紙は１通、他は正１部、副（コピー）２部を提出する。原稿にはＡ４判用紙を用い、原則としてワードプロセッサーを使用する。

邦文は40字×30行とし、平仮名、横書き、現代仮名づかいを用いる。数字は算用数字を用いる。欧文では、必ずタイプを用い、ダブルスペースで、原則として80字×20行とし、３㎝のマージンを空ける。邦文の原著、総説は原則として16,000字以内、症例報告は8,000字以内とし、表・図版は400字と換算する。欧文の場合は、原著、総説は25枚以内、症例報告は10枚以内とする。

査読終了後に投稿論文を収録したフラッシュメモリー、CD-R、またはフロッピーディスク（以下フラッシュメモリー等という）をウイルスの有無を確認の上委員長宛に提出する。フラッシュメモリー等には投稿論文（表・図版の説明を含めてもよい）以外のファイルを収録してはならない。

６．手紙

この論文がこれまでに他誌に掲載されたことがない、または投稿中ではないことを述べた内容を含む。

７．表紙

１）論文名（これには略語を用いてはならない。）
２）ランニングタイトル（邦文25字以内、欧文40字以内）
３）著者名
４）所属教室名（または機関名）
５）論文の連絡者名
６）ワードプロセッサーの機種名、ソフト名（バージョンも記入のこと）、ファイル名を記入する。

８．抄録

邦文においては800字以内、欧文においては200語以内とし、構成は、背景、方法、結果、結論とする。Key wordsを５つ以内付記する。

９．本文

１）構成は、緒言、対象と方法、結果、考察、謝辞とする。
２）測定単位以外の略語は使用しない。ただし、標準的な略語は初めて表示する際に省略元の語句を明示した後に使用してもよい。
３）文献は該当箇所の右肩に片括弧で引用順に記す。
４）表・図は該当箇所に括弧で表示し、図版は印刷に耐えられるものとする。
５）商品名、薬品名は一般名とし、単位、記号は国際単位を用いる。
６）動植物、微生物等の学名は、邦文では片仮名とする。
７）統計処理法を明記する。
８）文部科学省科学研究費補助金等の研究費の出所は謝辞の項に記載する。

10．参照文献

１）引用順に一括する。
２）私信、未発表データ、及び「未発行」または「投稿中」の原稿に対して番号をつけた文献は認めない。
３）雑誌名の省略は、Index Medicus及び医学中央雑誌に従う。
４）著者が６名以内の場合は全員を記載し、７名以上の場合は最初の６名のみを記載して後は「他」または「et al.」とする。
５）記載形式は以下のとおりとする。

例①雑誌

１．楊黄恬，野呂田郁夫，遠藤政夫：メトキサミンの強心作用とPI代謝促進効果．心臓　1994; 26(Suppl. 4)：24-28
２．Endoh M: Physiological and pathophysiological modulation of calcium signaling in myocardial cells. Jpn Circ J 1991; 55: 1108-1117

例②単行書

1．遠藤政夫，安部不二夫：血管平滑筋内皮細胞におけるCaイオンの研究法．江橋節郎編，エクオリン実験法．東京；学会出版センター，1990: 291-301

2．Watanabe T, Shimazaki Y, Saitoh H, Kuraoka S, Ji Wei Zhang, Oshikiri N, et al.: Nutrient blood flow in the canine brain perfused retrogradely during hypothermia. In: Kawashima Y, Takamoto S, eds. Brain Protection in Aortic Surgery. Amsterdam; Elsevier, 1997: 59-69

11. 表・図版

表・図版の説明は本文とは別にまとめる。表・図版・写真は、「図版台紙」に貼り付けするか、「図版台紙」に示された規格に準拠して作成する。

12. 倫理

臨床治験に関しては「ヘルシンキ宣言」、動物を用いた研究は「山形大学動物実験規程」あるいはこれに準ずるものを遵守したものでなければならない。このことを本文中に明記する。

13. 校正

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14. Native Speakerによる校閲

欧文論文及び欧文抄録は著者の責任により論文の提出前にNative Speakerの校閲を受ける。表紙にNative Speakerの「所属・氏名等」を記入する。

15. 著作権

論文を投稿する者は、山形大学に対して、当該論文に関する出版権・複製権・公衆送信権の利用につき許諾するものとする。なお、掲載された論文等は、原則として電子化するものとし、山形大学機関リポジトリに保存し附属図書館ホームページ等を通じてコンピュータ・ネットワーク上に公開する。

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附　則

この規程は、平成19年３月６日から施行する。

附　則

この規程は、平成20年７月３日から施行する。

附　則

この規程は、平成23年４月１日から施行する。

附　則

この規程は、平成24年２月21日から施行し、平成23年７月１日から適用する。

その他の注意事項

１．「投稿申込書」について

各々の原稿の締切日の１か月前（２月１日及び８月１日）までに投稿申込書を提出してください。

２．本学の大学院研究科学生及び研究生の投稿について

「学位論文」及び「本学教職員との共著論文」である場合に投稿が認められます。学位論文については指導教員の承認を得てください。

３．「学会報告」について

別に申合せが定められていますので、新たに投稿を希望される場合は予め医学部事務部学務課図書担当へお尋ねください。

４．「海外ニュース、トピックス等」について

本学部関係の海外研究者の方が、現地での研究の動向（ニュース、トピックス等）を投稿する場合は、

１）邦文：40字×30行で作成の原稿４枚以内

２）欧文：80字×20行で作成の原稿６枚以内

としてください。また、本学における所属講座（責任講座）を明記するようにしてください。

５．査読者について

希望する査読者がいる場合は、３人程度お知らせください。査読者は、学内の方を原則といたします。ただし、希望する方が実際に査読者になるとは限りません。

６．その他不明な点は、医学部事務部学務課図書担当までご照会ください。

編　集　後　記

秘書の笑顔は教授の宝物

山形大学副学部長
山形医学編集委員長　　木　村　　理

スペインのことわざに「女房の笑顔は亭主の宝物」というのがある。日本でもまさにその通りだと思う。古代ではソクラテスは奥さんに怒鳴られた後、やかんの水を浴びせられたとき、「雷の後には大雨が降るものじゃ」と平然としていたと言う。

それはさておき、本題である。これまで自分は秘書に恵まれてきていると思っている。

前任地の東京大学第一外科－第二外科の臓器別再編成で１から２へ異動したときも緑川秘書はついてきてくれた。様々のことに気を利かし、１年３ヶ月で彼女は私を山形大学第一外科教授として送りだした。「わたしはどうしたらいいですか？」がそのときの言葉であるが、２年後輩、東大講師の窪田敬一にゆだねた。彼女はよく働き、窪田君をも獨協医大の教授にした。その後は東大農学部出身のご亭主と結婚し、アメリカに10年住んで３人の子供をもうけ、現在はご主人をテニュアの教授にすべく奮闘中である。見方によっては３人目の教授が彼女から作られることになる。

わたしは「４人目は自分自身だろう」と言った。教授どころか、彼女出身母校の聖心女子大の学長にもなれるのではないかと思う。彼女の東大勤務の時に最も気にしたのは、私が手術でどれだけ疲れていて、今日はどういう機嫌・心持ちだろう、ということだったという。事務的に終わらさなければならない他のことは、二の次の問題だったという。私は毎日の生活・仕事で必死であった。そのことにはまったく気づかなかった。

驚くことに今、自分が還暦をすぎて、いろいろなことが目に入るようになった。山形大学第一外科で教授秘書をしている方はもう15年近くにもなろうか。実によくやってくれる秘書である。仕事の内容には問題ない。そうすると、毎日気持ちよく仕事ができるためには、表題の言葉が１番かな、と思っている。

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